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Neural Evidence for Dissociable Components of Task-switching

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The ability to retrieve and flexibly switch between task rules is seen as an important component of cognitive control. It is often assumed that lateral prefrontal cortex (latPFC) is important for switching between rules. However, activation associated with rule-switching is less reliably observed in latPFC than in medial PFC (specifically, pre-supplementary motor area). In this study, we tested the hypothesis that medial PFC is important for reconfiguration of task sets, whereas latPFC is important for retrieving, maintaining and implementing relevant rules (i.e. rule representation). Twenty young adults participated in a functional magnetic resonance imaging study in which they determined the correct response to a target stimulus on the basis of an instructional cue. For bivalent targets, the appropriate response depended on the currently relevant rule. In contrast, univalent targets were always associated with the same response. Brain regions of interest were characterized according to their responsiveness to bivalent and univalent targets, on both rule-switch and rule-repetition trials. The data support the hypothesis that rule representation and task-set reconfiguration are separable cognitive processes, associated with dissociable neural activation in latPFC and medial PFC, respectively. Activation profiles of posterior parietal cortex, basal ganglia and rostrolateral PFC are also examined and discussed.

Keywords: context, goal, pre-SMA, reconfiguration, rule, task set, task switching, VLPFC

Introduction

To produce meaningful behavior in a rapidly changing environment, one must be able to retrieve and flexibly switch between appropriate rules for behavior. This ability to adjust behavior on the basis of changing task requirements is seen as an important aspect of cognitive control (Allport *et al.*, 1994; Meiran, 1996; Monsell, 2003; Bunge, 2004). Flexible task performance has been extensively studied in the task-switch paradigm, in which subjects rapidly switch between two or more reaction time (RT) tasks that are typically performed on a set of stimuli. Switching between tasks (or, strictly speaking, switching between specific rules of a task) is usually associated with a sizeable decrement in performance. Two types of switch-related performance decrements have been characterized. Mixing costs refer to the decrement in performance on mixed-task blocks relative to blocks of trials involving a single task (Los, 1996), and switch costs refer to the decrement in performance associated with switching tasks within a mixed task block versus repeating tasks in a mixed-task block (Meiran, 1996). Additionally, different aspects of switching can be investigated by manipulating the delay between consecutive trials, or by manipulating task difficulty. These manipulations have revealed that separable cognitive functions contribute to the ability to flexibly switch between different rules, but the exact mechanisms contributing to switch costs remain under debate (e.g. Meiran, 1996; Mayr and Kliegl, 2000; Logan and Bundesen, 2003; Monsell, 2003; Wylie and Allport, 2003).

Rule retrieval, or activation of the currently required task set, is presumed to be an important component of task-switching (Mayr and Kliegl, 2000). However, behavioral studies have consistently found that switching to rules involving stimuli that have two response meanings (*bivalent* stimuli) is more effortful than switching to rules involving stimuli that have single response meanings (*univalent* stimuli) (Meiran, 2000; Monsell, 2003). This pattern of findings suggests that switch costs do not merely result from effort associated with activation of a previously relevant rule. Rather, switch costs also appear to be associated with the need to override the previously relevant stimulus–response (S-R) association. We refer to the latter process as 'task-set reconfiguration'. Thus, these findings suggest that different cognitive mechanisms may underlie rule representation (i.e. the ability to actively retrieve and/or select a currently relevant rule), and task-set reconfiguration (i.e. the ability to override and reconfigure the previously activated task set when a new external stimulus is presented).

Neuroimaging methods may allow us to examine the possible dissociability of underlying mechanisms associated with rule representation and task-set reconfiguration. To date, most neuroimaging studies of cognitive control (for reviews, see Miller and Cohen, 2001; Wagner *et al.*, 2004) have focused on either the neural substrates of task-switching (Sohn *et al.*, 2000; Dreher and Berman, 2002; Rushworth *et al.*, 2002; Braver *et al.*, 2003) or rule representation (Brass and von Cramon, 2002; Braver and Bongiolatti, 2002; Bunge *et al.*, 2003; Sakai and Passingham, 2003), but have not attempted to dissociate rule representation and task-set reconfiguration. Therefore, the question of whether the putative cognitive processes mentioned above are carried out by distinct brain regions has not yet been explicitly addressed. A review of these studies suggests that rule representation and task-set reconfiguration may indeed be neurally separable.

Prior neuropsychological and neuroimaging studies have considered lateral prefrontal cortex (latPFC) to be important for task-switching. Neuropsychological studies indicate that patients with damage to latPFC perseverate on previously relevant rules in the Wisconsin Card Sorting Task (WCST) (Milner, 1963; Stuss *et al.*, 2000; Barcelo and Knight, 2002). However, the WCST is a complex task, and therefore it is difficult to know which cognitive function is impaired in latPFC patients. Moreover, one study found that it was medial PFC, rather than latPFC, that was most consistently associated with perseverative errors on the WCST (Stuss *et al.*, 2000).

Using more straightforward task-switching paradigms, several neuroimaging studies have shown that latPFC is more active on task-switch than task-repetition trials (Dove *et al.*, 2000; Sohn *et al.*, 2000; Dreher and Berman, 2002; Sylvester *et al.*, 2003). However, several neuroimaging studies have failed to show robust differences in latPFC activation between task-switch and task-repetition trials, and instead indicate that this region is transiently activated at the onset of both task-switch and task-repeat trials (Dreher and Berman, 2002; Braver *et al.*, 2003).

LatPFC has been implicated more generally in rule retrieval in both non-human primates (for reviews, see Murray *et al.*, 2000; Passingham *et al.*, 2000) and humans (Brass and von Cramon, 2002, 2004; Bunge *et al.*, 2003). These studies show that ventrolateral prefrontal cortex (VLPFC) — which has been implicated in semantic memory retrieval (Poldrack *et al.*, 1999) and working memory (Wagner *et al.*, 2001) — is active when individuals retrieve rule meanings and keep rules on-line over several seconds. Thus, VLPFC is involved in rule retrieval and maintenance, which may explain why in some studies it is more active on task-switch than task-repeat trials, since it is necessary to retrieve a less recently used rule when the task changes.

In contrast to latPFC, medial PFC [which includes pre-supplementary motor area (pre-SMA), supplementary motor area (SMA) and cingulate motor area] and superior parietal cortex have been consistently engaged during task-switching (for review, see Paus, 2001; Rushworth *et al.*, 2002; Wager *et al.*, 2004). Transcranial magnetic stimulation of medial PFC or parietal cortex leads to enhanced switch costs (Rushworth *et al.*, 2001), and a number of neuroimaging studies have shown greater activation in these regions on switch than repeat trials (Braver *et al.*, 2003). In addition to medial PFC and parietal cortex, the basal ganglia have also been implicated in task-switching (Sohn *et al.*, 2000; Aron *et al.*, 2003; Cools *et al.*, 2004). These motor-related structures may be involved in overriding inappropriate responses or task sets (i.e. task-set reconfiguration) when switching between tasks (Picard and Strick, 2001; Rushworth *et al.*, 2004), whereas latPFC, in particular VLPFC, is likely to be involved at a more abstract level to retrieve the currently relevant S-R association.

The goal of the current study was to determine whether flexible rule use can be neurally dissociated into two component processes: rule representation and task-set reconfiguration. Specifically, we sought to test the predictions that pre-SMA, parietal cortex and the basal ganglia would be implicated in task-set reconfiguration, whereas latPFC activation would be better characterized as relating to rule representation. We were also interested in characterizing contributions to flexible rule use by rostrolateral prefrontal cortex (RLPFC), a region that has been implicated in the representation of high-level rules (Bunge *et al.*, 2003) and task sets (Sakai and Passingham, 2003).

Subjects were trained to respond to three different rules with manual button presses. One of the rules was associated with univalent targets (stimuli which were associated with the same response on every trial). Two other rules were associated with bivalent targets (stimuli which were associated with different responses, depending on the rule) (Brass *et al.*, 2003). These different rule types will be referred to in the text as univalent or bivalent rules, in accordance with the prior behavioral literature, although it is important to note that all three rules require a choice between two responses.

Bivalent trials were assumed to tax rule representation more strongly than univalent trials, because they require retrieval of the *currently relevant* S-R mapping associated with a target stimulus, rather than simply a *fixed* S-R mapping. Additionally, rule switch trials were assumed to tax task-set reconfiguration more strongly than rule repetition trials. To distinguish between brain regions involved in rule representation and task-set reconfiguration, however, it is necessary to take into consideration interactions between these two processes. Prior behavioral studies have shown that task-switching results in worse performance when subjects switch to a bivalent rule than to a univalent rule, because switching to a bivalent rule involves reconfiguration of a prior task set (Meiran, 2000; Monsell, 2003). Conversely, performance on a given rule type is best when subjects need not switch between rules frequently (Los, 1996; Monsell, 2003; Wylie and Allport, 2003). We posited that a region involved in rule representation should be consistently modulated by rule complexity (Bunge *et al.*, 2003; Bunge, 2004), showing greater activation for bivalent trials than univalent trials — not only on rule switch trials, but also on rule repetition trials. Further, we posited that such a region should be more active on rule switch than rule repetition trials, because of the need to retrieve a less recently accessed rule. By the same token, we posited that a region involved in task-set reconfiguration should be more active on bivalent rule switches than bivalent rule repetitions. We further posited that such a region would be more strongly engaged by bivalent than univalent rule switches, because of the need to override previously relevant S-R associations when switching to a bivalent rule. We predicted that VLPFC would exhibit a pattern consistent with a role in rule representation, and pre-SMA with task-set reconfiguration. The basal ganglia and superior parietal cortex were also predicted to play a role in task-set reconfiguration.

The rules were first presented in a blocked design and then in a mixed design. The inclusion of a blocked scan served three purposes. First, the blocked design served as a baseline for examining which brain regions were involved in applying the required rules even when rule retrieval and switch requirements were minimized. By comparing activation between the mixed and blocked designs, we were able to assess the neural equivalent of 'mixing costs'. Second, because subjects always began with the blocked design, it allowed them to practice the rules extensively. As such, we expected the rules to be better learned by the time the mixed scans began. Finally, we sought to determine whether RLPFC would be more active during application of the bivalent rule learned second relative to the bivalent rule learned first, as we had previously found in an event-related functional magnetic resonance imaging (fMRI) study (Bunge *et al.*, 2003). A well-controlled replication of this earlier observation would be taken as evidence that RLPFC represents higher-order rules, such as 'rule B is the *opposite* of rule A'.

Materials and Methods

Subjects

Twenty-one paid volunteers were recruited from the University of Davis. Twenty healthy right-handed volunteers (14 females, 6 males) were included in the study. One subject was excluded due to equipment malfunction. subjects' consent was obtained according to the Declaration of Helsinki and the study was approved by the Internal Review Board at the University of California at Davis.

Tasks

Prior to scanning, subjects learned to associate each of three visual cues with a set of S-R associations (see Fig. 1). Subjects used the index and

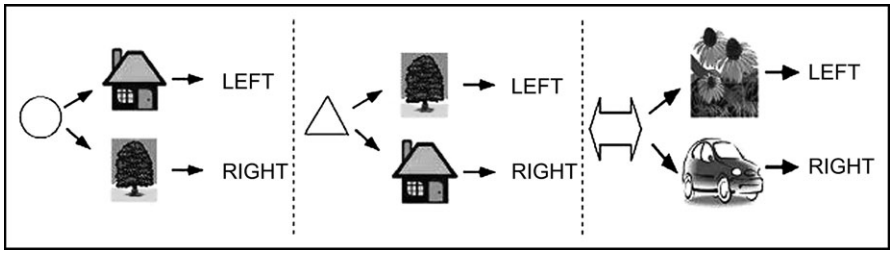

Figure 1. The three rule types are depicted here. During scanning, subjects viewed an instructional cue (a circle, triangle or double arrow) for 1 s. After a 0.5 s delay, a target stimulus, such as a picture of a house, was presented for 2.5 s. The target required a left- or right-button response, depending on the relevant S-R association learned prior to scanning. The order in which rules were learned was counterbalanced across individuals but kept fixed during the experiment.

middle fingers of their left hand to respond. The task involved a visual cue that instructed the subject which rule to use, followed by a target stimulus that required a left- or right-button response. The cue could be a circle, a triangle or a bidirectional arrow. The circle cue could be followed by a house or a tree, and subjects were instructed to respond with a left-button press to the house and with a right-button press to the tree. The triangle cue could also be followed by a house or a tree, but for this cue the S-R mapping was reversed; the house was associated with a right-button response and the tree with a left-button response. The arrow cue could be followed by a flower or a car; the former was associated with a left-button response and the latter with a right-button response. Thus, the circle and triangle rules were considered bivalent rules, because the appropriate responses to the targets depended on which rule was currently in effect. In contrast, the arrow rule was considered a univalent rule, because each target was associated with a specific response. Trials were 4 s long, and had the following structure: a cue was presented for 1 s, followed by a 0.5 s delay (blank screen), and then by the target. The presentation of the target was response-terminated, but responses had to be given within 2.5 s. When the response was given within the 2.5 s response time window, the target was replaced by a fixation cross for the length of the trial. Before the scan, each of the rules was practiced separately for 15 trials, and subjects performed one practice block of 90 trials in which the rules were intermixed.

Data Acquisition

In the first scan, subjects performed a block of 90 trials (30 trials per rule) in which the rules were presented in blocks of 15 trials, separated by 20 s of fixation (60 s of trials, 20 s fixation, 60 s of trials, 20 s fixation, etc.). The order of conditions in the blocked task was counterbalanced across subjects. Subsequent to the blocked scan, subjects participated in three mixed scans. Over the course of the three event-related scans, subjects performed a total of 270 experimental trials in which the three rules were mixed (90 trials for each rule, equally distributed across the three scans). Each condition included an equal number of response repetitions and response switches. Each subject performed 60 bivalent rule repetitions, 60 bivalent-to-bivalent rule switches, 60 univalent-to-bivalent switches, 30 univalent rule repetitions and 60 bivalent-to-univalent switches. There were an equal number of trials of each type requiring left-button and right-button responses. 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 fixation lasting between 2 and 8 s, jittered in increments of 2 s, were interleaved with the experimental trials as determined by the optimization program.

Scanning was performed with a standard whole-head coil on a 1.5 T GE scanner at the UCD Imaging Research Center. Functional data were acquired using a gradient-echo echo-planar pulse sequence (T_R = 2 s, T_E = 40 ms, 24 axial slices, 3.44 × 3.44 × 5 mm, 0 mm inter-slice gap, 235 volumes per run). Prior to each scan, four volumes were discarded to allow for T_1-equilibration effects. High-resolution (1.2 mm thick sagittal slices) T_1-weighted anatomical images were collected. Head motion was restricted using a pillow and foam inserts that surrounded the head. Visual stimuli were projected onto a screen that was viewed through a mirror.

fMRI Data Analysis

Data were preprocessed using SPM2 (Wellcome Department of Cognitive Neurology, London). Images were corrected for differences in timing of slice acquisition, followed by rigid body motion correction. Structural and functional volumes were spatially normalized to T_1 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 2 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 on individual subjects' data using the general linear model in SPM2. The fMRI time series data were modeled by a series of events convolved with a canonical hemodynamic response function (HRF). The cue of each trial was modeled as an event. Error trials were modeled separately, and were excluded from the analyses. The correct trial functions were used as covariates in a general linear model, along with a basic 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 canonical HRF for each condition were used in pairwise contrasts. 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 were considered significant if they consisted of at least 10 contiguous voxels that exceeded an uncorrected threshold of $P < 0.001$.

Region-of-interest (ROI) analyses were performed to further characterize rule sensitivity of five *a priori* predicted regions. ROI analyses were performed with the Marsbar toolbox in SPM2 (Brett *et al.*, 2002; http://marsbar.sourceforce.net/). ROIs that spanned several functional brain regions were subdivided by sequentially masking the functional ROI with each of several anatomical Marsbar ROIs. The contrast used to generate functional ROIs was that of bivalent rules versus fixation (full list of coordinates available upon request). This contrast was chosen instead of the more general contrast of all rules versus fixation because there were large differences in activation between the bivalent and univalent rules, and therefore not all our regions of interest could be identified from that more general contrast. For all ROI analyses, effects were considered significant at an α of 0.05. For each ROI, the center of mass is reported.

Results

Behavioral Data

Two sets of ANOVAs were performed: one for the blocked task and one for the mixed task. For the blocked task, Rule Type (bivalent, univalent) ANOVAs for accuracy and RTs revealed that subjects were less accurate and slower on bivalent than univalent trials [accuracy: M = 0.8 versus 0.2%; $F(1,19) = 6.78$; $p < 0.05$; RTs: M = 604 versus 547; $F(1,19) = 17.85$, $P < 0.001$]. Additional ANOVAs revealed that there were no differences in accuracy or RTs for bivalent trials that were learned first

compared to bivalent rules that were learned second (both *F*s < 1).

For the mixed task, ANOVAs were conducted to examine the effects of Rule Type (bivalent, univalent) and Rule Switch (rule repetition, rule switch). A 2 (Rule Type) × 2 (Rule Switch) ANOVA for accuracy resulted only in a main effect of Rule Type [$F(1,19) = 20.60$; $P < 0.001$], showing that subjects made more errors when responding to bivalent than univalent rules (mean = 2.7 versus 0.5%, SD = 0.2%), but there was no main effect of switching on accuracy (see Fig. 2). For RTs, a 2 (Rule Type) × 2 (Rule Switch) ANOVA revealed main effects of Rule Type [$F(1,19) = 21.38$; $P < 0.001$] and Rule Switch [$F(1,19) = 15.60$; $P < 0.001$], and a significant Rule Type × Rule Switch interaction [$F(1,19) = 4.88$; $P < 0.05$]. Follow-up ANOVAs showed that switching to a bivalent rule was associated with RT slowing relative to repeating a bivalent rule [$F(1,19) = 12.98$; $P < 0.005$]. In contrast, the difference in RT for switching to a univalent rule compared to repeating a univalent rule failed to reach significance [$F(1,19) = 4.24$; $P = 0.06$; see Fig. 2].

Two additional sets of analyses were performed to further probe performance on bivalent rule switch trials. First, the bivalent rule switch trials were subdivided according to whether they were preceded by a bivalent rule or by a univalent rule. These analyses revealed that the identity of the prior rule did not affect either accuracy or RTs for responses on bivalent switch trials (both *F*s < 1). Second, additional analyses were performed to examine whether there were performance differences on bivalent switch trials when switching versus repeating *responses* (left or right button press). With respect to accuracy, a 2 (Rule Repetition, Rule Switch) × 2 (Response Repetition, Response Switch) analysis revealed no effect on accuracy of either Rule Switch [$F(1,19) = 3.57$, $P = 0.08$] or Response Switch trials [$F(1,19) = 3.89$, $P = 0.07$; interaction: $F(1,19) = 2.71$, $P = 0.12$]. With respect to RTs, this analysis revealed only a main effect of Rule Switch [$F(1,19) = 13.28$; $P < 0.005$], but no effect of Response Switch [$F(1,19) = 3.63$; $P = 0.08$], and no Rule Switch × Response Switch interaction ($F < 1$).

These results indicate, first, that bivalent rules were associated with worse performance than univalent rules, both when rules were repeated and when they were switched. Second, switching to a bivalent rule resulted in worse performance compared to repeating a bivalent rule, whereas switching to a univalent rule was not significantly more effortful than repeating a univalent rule. Finally, the decrement in performance when switching to a bivalent rule was associated with switching task set (i.e. the relevant set of S-R mappings) and not with switching responses.

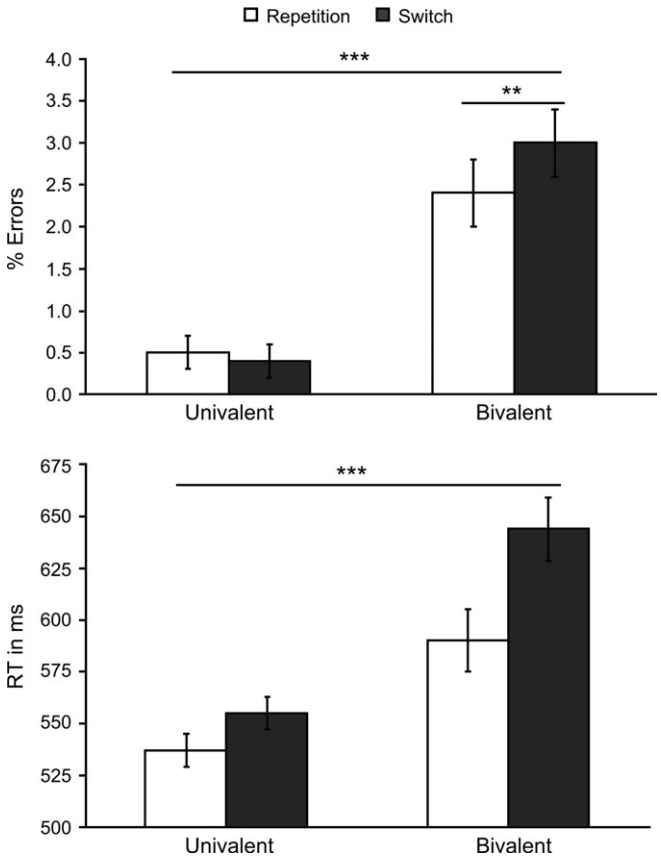

Figure 2. RTs and accuracy are plotted separately for univalent and bivalent rules, for both rule repetitions and rule switches. RTs are shown for correct responses only. Subject performed worse on bivalent than on univalent trials, and showed switch costs associated with switching to bivalent rules but not with switching to a univalent rule. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

fMRI Results: Rule and Switch Effects

Blocked Task

Although there were minimal differences in performance between bivalent and univalent rules in the blocked task, a comparison of these rule types revealed greater activation for bivalent rules in right middle frontal gyrus (BA 9), left caudate nucleus and bilateral anterior cingulate cortex (BA 32). These regions are likely to be important for response selection under conditions in which the target stimulus has been associated with different responses, depending on the rule. VLPFC, which has been implicated in rule retrieval, was not modulated by rule type during performance of the blocked task. This finding was expected; retrieval demands were minimal in the blocked task because subjects applied the same rule 30 times sequentially within a block of trials.

Mixed Task

Rule Type (bivalent > univalent) in the mixed task was associated with activation of left anterior and posterior VLPFC (BA 45/47, 44), bilateral anterior insula, dorsolateral PFC (DLPFC; BA 9), left RLPFC (BA 10), pre-SMA/SMA (BA 6), primary motor cortex (BA 4), and bilateral inferior and superior parietal lobule (BA 7, 40) (Fig. 3, Table 1). In the left hemisphere, both anterior and posterior VLPFC were active. Thus, at first glance, there appeared to be a bigger effect of rule type on brain activation in the mixed scans than the blocked scans, consistent with behavioral results showing that rule retrieval is taxed more heavily on mixed than blocked trials. This observation was borne out by ROI analyses, as discussed below.

The effects of rule-switching were examined separately for bivalent and univalent trials (see Fig. 3; Table 2). Univalent switches versus repetitions were associated with activation of left lateral superior frontal gyrus (BA 6) and right visual association cortex (BA 18). Bivalent switches versus repetitions were associated with increased activation of bilateral DLPFC (left BA 9, 46; bilateral BA 8), pre-SMA/SMA (BA 6), and bilateral superior and inferior parietal lobules (BA 7, 40).

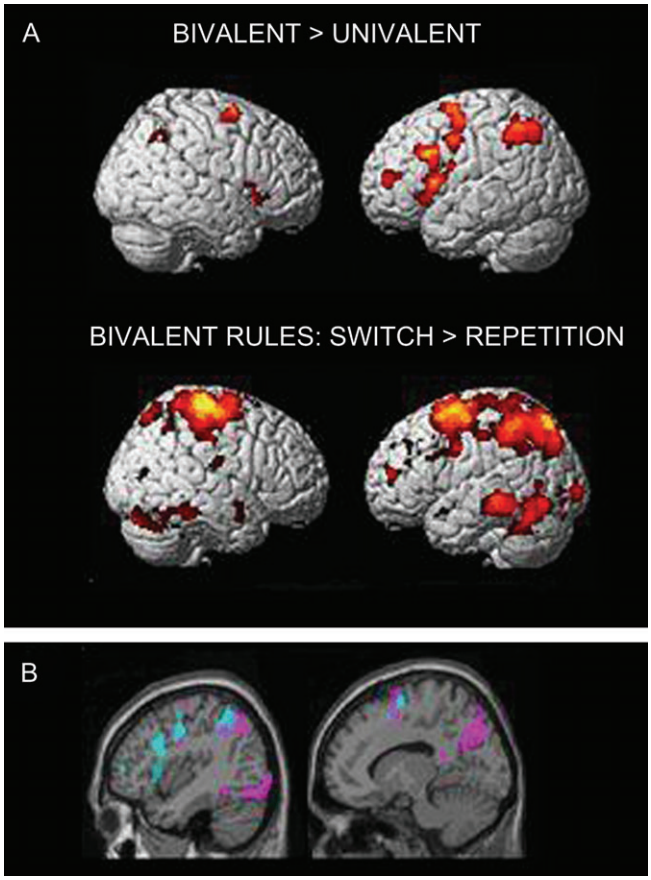

Figure 3. Whole-brain activation associated with rule representation (bivalent > univalent rules) and task set reconfiguration (bivalent rule switches > bivalent rule repetitions) is shown in (*A*), and the overlap between activations is shown in (*B*). Regions displayed in cyan were more active for bivalent rules than for univalent rules. Rule-related activation was observed in left VLPFC (BA 45/47, 44), insula, RLPFC (BA 10), anterior cingulate cortex (BA 32), pre-SMA/SMA (BA 6), and superior (BA 7) and inferior (BA 40) parietal cortex. Regions displayed in magenta were more active for bivalent switching compared to bivalent repetitions. Switch-related activation was observed in pre-SMA/SMA (BA 6), DLPFC (BA 9/46), RLPFC (BA 10), superior (BA 7) and inferior (BA 40) parietal cortex, and inferior, middle and superior temporal cortex (BA 20/38). Overlap activation in pre-SMA/SMA and superior parietal cortex appears in blue.

ROI Analyses

At first glance (Fig. 3), it appears that rule type and rule-switching both recruit pre-SMA/SMA and parietal cortex, whereas rule type additionally recruits VLPFC (Fig. 3). To examine the relative contribution of these regions to rule representation and task-set reconfiguration, ROI analyses were performed for VLPFC, pre-SMA/SMA and superior parietal cortex. Additional ROIs were located in the caudate nucleus and RLPFC. All ROIs were left-lateralized because the whole-brain comparisons revealed more left- than right-hemisphere activation in these regions, and because our prior work had suggested a stronger role for left than right PFC in the representation of similar rules (Bunge *et al.*, 2003).

Ventrolateral versus Medial PFC

We examined effects of rule representation and task set reconfiguration in VLPFC and pre-SMA/SMA with a 2 (Rule Type) × 2 (Rule Switch) ANOVA for each region. VLPFC exhibited a main effect of Rule Type [$F(1,19) = 20.31$; $P < 0.001$] and a main effect of Rule Switch [$F(1,19) = 7.08$;

Table 1
Regions implicated in bivalent rule use in blocked and mixed tasks

Bivalent–univalent Region of activation	~BA	*x*	*y*	*z*	*Z*-score
Blocked task					
R DLPFC	9	18	28	30	3.45
L caudate		−22	−28	22	3.35
L cingulate gyrus	32	−2	20	36	3.18
R anterior cingulate	32	20	34	6	3.35
Mixed task					
Lateral PFC					
L DLPFC	9	−38	16	30	4.44
L VLPFC/insula	44/45	−44	16	10	4.19
R DLPFC	9	14	28	30	3.41
R VLPFC/insula	47	34	24	−2	3.88
L middle frontal gyrus	6	−32	−4	54	4.42
L precentral gyrus	6	−40	−8	40	3.88
R superior frontal gyrus	6	24	2	64	4.32
R middle frontal gyrus	6	26	−2	46	3.56
L RLPFC	10	−36	52	12	3.73
Cingulate gyrus					
L cingulate gyrus	32	−4	20	42	3.16
R cingulate gyrus	31	24	−48	22	5.39
Medial PFC					
L pre-SMA/SMA	6	−4	8	60	5.45
R pre-SMA/SMA	8	10	16	46	4.11
Parietal cortex					
L superior parietal lobule	7	−30	−58	46	4.38
L inferior parietal lobule	40	−40	−44	44	4.29
R inferior parietal lobule	40	34	−56	40	3.67

Table 2
Regions implicated in univalent switching and bivalent switching

Univalent switches–repetitions Region of activation	~BA	*x*	*y*	*z*	*Z*-score
L middle frontal gyrus	6	−22	−2	42	3.65
R middle occipital gyrus	18	38	−82	−10	3.56
Bivalent switches−repetitions					
Lateral PFC					
L VLPFC	45/46	−32	30	16	3.37
L DLPFC	9	−14	48	34	3.3
L DLPFC	9	−32	36	38	3.23
L middle frontal gyrus	6	−28	−6	52	4.66
R precentral gyrus	6	42	−8	32	3.19
L RLPFC	10	−26	36	20	4.4
Medial PFC					
L superior frontal gyrus	6	−12	8	60	5.41
R pre-SMA/SMA	6	4	2	62	4.8
L pre-SMA/SMA	6	−8	−16	66	4.73
Parietal cortex					
L superior parietal lobule	7	−32	−52	52	4.83
R precuneus	7	18	−60	50	4.66
L sub-gyral	7	−24	−42	2	4.55
L precuneus	7	−6	−62	34	4.51
L inferior parietal lobule	40	−42	−42	42	4.39
Temporal cortex					
L inferior temporal gyrus	20	−62	−40	−16	3.82
L middle temporal gyrus	20	−48	−32	−8	4.66
L superior temporal gyrus	38	−38	8	−16	4.92
R fusiform gyrus	20	48	−34	−18	4.39
R middle temporal gyrus	21	62	0	−12	3.84
Somatomotor cortex					
L postcentral gyrus	3	−58	−22	42	3.73
R postcentral gyrus	3	26	−30	64	5.3
R precentral gyrus	4	32	−30	54	4.87
L caudate, head and tail		−13	7	13	3.88

$P < 0.05$], but no Rule Type × Rule Switch interaction. *Post hoc* comparisons confirmed that VLPFC was more active for bivalent than for univalent trials on both rule repetition and rule switch trials [$F(1,19) = 8.49$, $P < 0.01$ and $F(1,19) = 27.48$, $P < 0.001$ respectively]. Like VLPFC, pre-SMA/SMA exhibited a main effect of Rule Type [$F(1,19) = 15.83$; $P < 0.001$] and a main effect of Rule Switch [$F(1,19) = 18.43$; $P < 0.001$]. However, unlike VLPFC, pre-SMA/SMA exhibited a Rule Type × Rule Switch interaction [$F(1,19) = 5.62$; $P < 0.05$]. *Post hoc* comparisons revealed that this region was more involved when switching to a bivalent rule compared to repeating a bivalent rule [$F(1,19) = 28.00$; $P < 0.001$]. In contrast, pre-SMA/SMA was not more active for switching to a univalent rule compared to repeating a univalent rule ($F < 1$); nor was it more active for bivalent than univalent trials when rules were repeated ($F < 1$).

A direct comparison of the VLPFC and pre-SMA/SMA profiles was performed with a 2 (ROI) × 2 (Rule Type) × 2 (Rule Switch) ANOVA. This analysis confirmed that these regions had significantly different activation profiles [ROI × Rule Type × Rule Switch interaction: $F(1,19) = 7.45$; $P < 0.05$]. Follow-up comparisons showed that pre-SMA/SMA was sensitive to Rule Type only on rule switch trials, whereas VLPFC was sensitive to Rule Type on both rule switch and rule repetition trials (Fig. 5). Thus, only VLPFC showed a consistent effect of Rule Type. Both regions were activated by bivalent rule switches versus repetitions [$F(1,19) = 21.70$, $P < 0.001$), but not by univalent rule switches versus repetitions [$F(1,19) = 0.65$, $P = 0.43$]. However, the bivalent rule switch effect was larger for pre-SMA/SMA than for VLPFC [ROI × Switch: $F(1,19) = 15.78$; $P < 0.001$; see Fig. 5].

To examine whether pre-SMA/SMA activation for switching to bivalent rules was associated with changing task sets or increased response competition, a 2 (Rule Switch, Rule Repetition) × 2 (Response Switch, Response Repetition) ANOVA was performed. This comparison resulted in a main effect of Rule Switch, as above [$F(1,19) = 7.07$, $P < 0.01$], but no effect of Response Switch ($F < 1$), suggesting that pre-SMA/SMA is preferentially engaged when switching to a new bivalent *rule*, rather than to a new *response*. Further, no other ROI showed a significant Response Switch effect.

Basal Ganglia

In the whole-brain analysis, left caudate nucleus was more active when switching to a bivalent rule compared to repeating a bivalent rule. This result was followed up by a 2 (Rule Type) × 2 (Rule Switch) ANOVA for the ROI of left caudate (see Fig. 4). This analysis resulted in main effects of Rule Type [$F(1,19) = 7.01$; $P < 0.05$] and Rule Switch [$F(1,19) = 4.89$; $P < 0.05$], and a significant interaction [$F(1,19) = 8.34$; $P < 0.01$]. Follow-up comparisons showed that the left caudate was more active on bivalent rule switch versus repetition trials [$F(1,19) = 11.84$; $P < 0.005$], whereas there was no difference in caudate activation for univalent rule switch versus repetition trials ($F < 1$). These results show that left caudate nucleus, like left pre-SMA/SMA, is involved in switching between tasks, but not rule representations. A 2 (ROI) × 2 (Rule Type) × 2 (Rule Switch) ANOVA comparing activation for pre-SMA/SMA and caudate resulted in ROI × Rule Type [$F(1,19) = 7.68$, $P < 0.05$] and ROI × Rule Switch [$F(1,19) = 5.04$, $P < 0.05$] interactions. These interactions showed that increased activation associated with Rule Type (bivalent > univalent) and Rule Switch (switch > repetition) was larger for pre-SMA/SMA than for the caudate. However, both pre-SMA/SMA and the caudate nucleus showed a distinct pattern from VLPFC, lending support to the hypothesis that task-switching comprises neurally dissociable sub-processes.

Superior Parietal Cortex

In an additional set of ROI analyses, we assessed the activation patterns in left superior parietal cortex (Fig. 4) and its relation to VLPFC and pre-SMA/SMA. The whole-brain contrasts revealed that superior parietal cortex was strongly modulated by both rule type and rule-switching. A 2 (Rule Type) × 2 (Rule Switch) ANOVA for superior parietal cortex resulted in main effects of Rule Type [$F(1,19) = 16.68$; $P < 0.001$] and Rule Switch [$F(1,19) = 16.81$; $P < 0.001$], but no interaction [$F(1,19) = 2.59$; $P > 0.10$]. Thus, superior parietal cortex was implicated in both rule representation and rule-switching. When comparing ROI activity for rule repetitions only, parietal cortex was significantly more active for bivalent than univalent rule repetitions. Parietal cortex was not functionally dissociable from either VLPFC or pre-SMA/SMA (both Fs < 1), even though these latter regions were dissociable from one another. This finding suggests that superior parietal cortex works together with both VLPFC and pre-SMA/SMA to retrieve and switch between rules.

An additional 2 (ROI) × 2 (Rule Type) × 2 (Rule Switch) ANOVA comparing activity in superior and inferior parietal cortex revealed only a 2 (ROI) × 2 (Rule Switch) interaction [$F(1,19) = 4.66$, $P < 0.05$]. This interaction indicates that switch-related activation in superior parietal cortex was larger (4.8 versus 3.4) than in inferior parietal cortex (4.3 versus 3.2), but there was no interaction involving Rule Type [$F(1,19) = 1.42$, $P = 0.25$]. Thus, superior parietal cortex was more strongly implicated in rule-switching than inferior parietal cortex, but both regions contributed to rule representation.

Learning Rules: VLPFC and RLPFC

In a final set of ROI analyses, we focused on the role of VLPFC and RLPFC in learning S-R rules (Fig. 6). RLPFC showed a similar pattern of activation to VLPFC (Fig. 3), and a cross-region ANOVA confirmed that there were no significant differences between the two regions' profiles ($F < 1$). We compared activation in these regions for bivalent rules that were learned first compared to bivalent rules that were learned second, in both the blocked task and the mixed task. The 2 (Task) × 3 (Bivalent learned first, Bivalent learned second, Univalent) ANOVA for VLPFC resulted in main effects of Task [$F(1,19) = 37.12$; $P < 0.001$] and Rule [$F(2,38) = 11.47$; $P < 0.001$], and a significant interaction [$F(2,38) = 5.97$; $P < 0.01$]. *Post hoc* comparisons focused on the difference in activation for bivalent rules that were learned first and bivalent rules that were learned second, separately for the blocked and the mixed tasks. For the blocked task, the 2 (Rule) ANOVA revealed greater VLPFC activation for the bivalent rule that was learned second than for the bivalent rule that was learned first [$F(1,19) = 9.01$; $P < 0.01$], but this difference was absent in mixed task ($F < 1$). The same pattern was observed for RLPFC, showing a significant Rule effect in the blocked task [$F(1,19) = 5.39$; $P < 0.05$], but not in the mixed task ($F < 1$). Thus, the performance benefit for the rule learned first was abolished in the later scans. These results replicate our prior findings involving a different task (Bunge *et al.*, 2003), and are consistent with the hypothesis that both VLPFC and RLPFC are involved in learning and using rules.

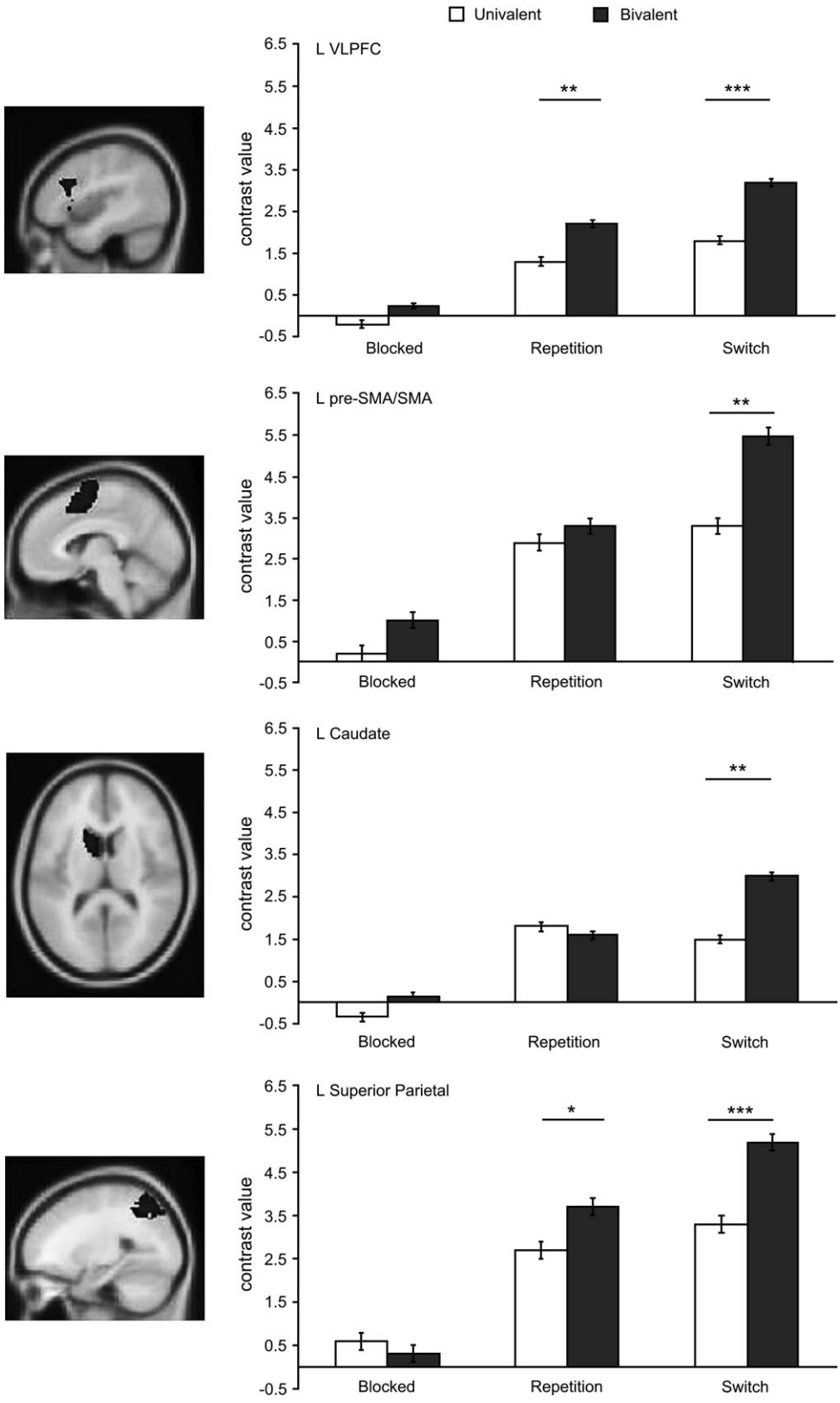

Figure 4. Plotted here are the activation profiles for ROIs identified by the whole-brain contrast of bivalent rules > fixation ($P < 0.001$). These ROIs included anterior VLPFC (BA 45; coordinates –43, 21, 23), pre-SMA/SMA (BA 6; coordinates –5, 3, 59), superior parietal cortex (BA 7; coordinates –24, –65, 52) and caudate nucleus (coordinates –13, 7, 13). Error bars depict an estimate of within-subject standard error. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

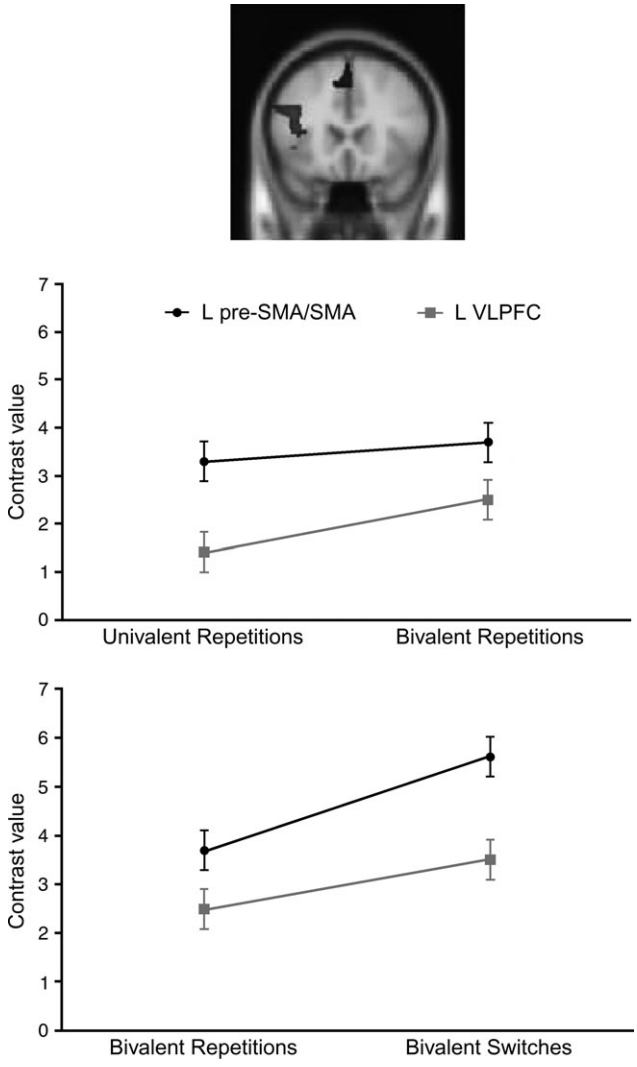

Figure 5. A direct comparison of the VLPFC and pre-SMA/SMA ROIs featured in Figure 4 is shown here. VLPFC was sensitive to rule representation (bivalent switches > univalent switches *and* bivalent repetitions > univalent repetitions), whereas pre-SMA/SMA was more sensitive to task set reconfiguration (bivalent switches > bivalent repetitions). *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

Discussion

In the present study, we used fMRI to distinguish between two component processes involved in flexible rule performance: rule representation and task-set reconfiguration. We focused on several brain regions that have been associated with either or both of these functions in prior studies, namely VLPFC, pre-SMA/SMA, parietal cortex, RLPFC and the basal ganglia. As discussed below, these regions appear to work together to learn, retrieve, implement and switch between task rules. However, the activation profiles of several of these regions were sufficiently different as to provide clues regarding their distinct contributions.

Performance

The behavioral effect of increased RTs for bivalent rules is consistent with the idea that selecting appropriate responses for targets that have bivalent meanings is an effortful, time-consuming process. A key feature of the bivalent rules was that the actions related to the targets were dependent on the task cues, whereas for univalent rules the actions associated with each target were uniquely specified (see also Bunge *et al.*, 2003). When these rules were applied in separate blocks, there were minimal performance differences between bivalent and univalent rules. In contrast, when the rules were presented in mixed blocks, bivalent rules were associated with significantly worse performance. In these mixed blocks, bivalent rules required controlled rule implementation because subjects had to retrieve the relevant S-R mapping and had to resolve interference between competing S-R mappings, rather than applying a single set of mappings. It should be noted that the mixed task was always presented after the blocked task. However, previous studies examining mixing costs in which task blocks were counterbalanced found very similar patterns of results (e.g. Los, 1996).

Rule-switching was associated with a greater increase in RT for bivalent than for univalent rules. This result is consistent with the theoretical framework outlined by Meiran (2000; see also Meiran and Gottler, 2001). According to this theory, switch costs result from a process labeled 'retroactive response-set adjustment' (Meiran, 2000; Meiran and Gottler, 2001). This term refers to post-response (retroactive) modulation of the strength of association between a particular response and a particular task when stimuli and responses are bivalent (i.e. when both tasks involve the same stimuli and responses). Meiran's theory proposes that effects of retroactive response set adjustment largely account for 'residual switch costs', which refers to the costs of switching that cannot be diminished by longer preparation times. Given that the current design used relatively long preparation times (1500 ms), it is likely that this study examined residual switch costs.

In the current design, a univalent switch trial was always preceded by a bivalent rule, whereas a bivalent switch trial could be preceded by a univalent rule or by the other bivalent rule. In future research, this potential confound could be solved by adding a second univalent rule to the design. However, the cost of switching to a bivalent rule was similar when this rule was preceded by a univalent or a bivalent rule, for both performance and involved brain regions, suggesting that the identity of the *previously* applied rule has minimal effects on performance and brain activity.

In this study, as in prior behavioral studies, switch costs were not significant when switching to univalent rules, although they tended towards significance. This finding suggests that switch costs are primarily related to task set reconfiguration when a previously activated S-R mapping must be overridden (Meiran, 2000; Hommel and Eglau, 2002), rather than simply being related to the requirement to activate a less recently used rule (Mayr and Kliegl, 2000; Monsell, 2003). In summary, we observed consistent performance changes associated with both rule representation and rule switch manipulations. These behavioral findings provide the context for understanding the functional and neural dissociation of rule representation and task set reconfiguration.

Ventrolateral PFC Involvement in Rule Representation

An initial comparison of blocked versus mixed tasks showed that VLPFC was sensitive to rule type when the different rules were intermixed, but not when they were presented in separate blocks. However, ROI analyses showed that VLPFC as well as

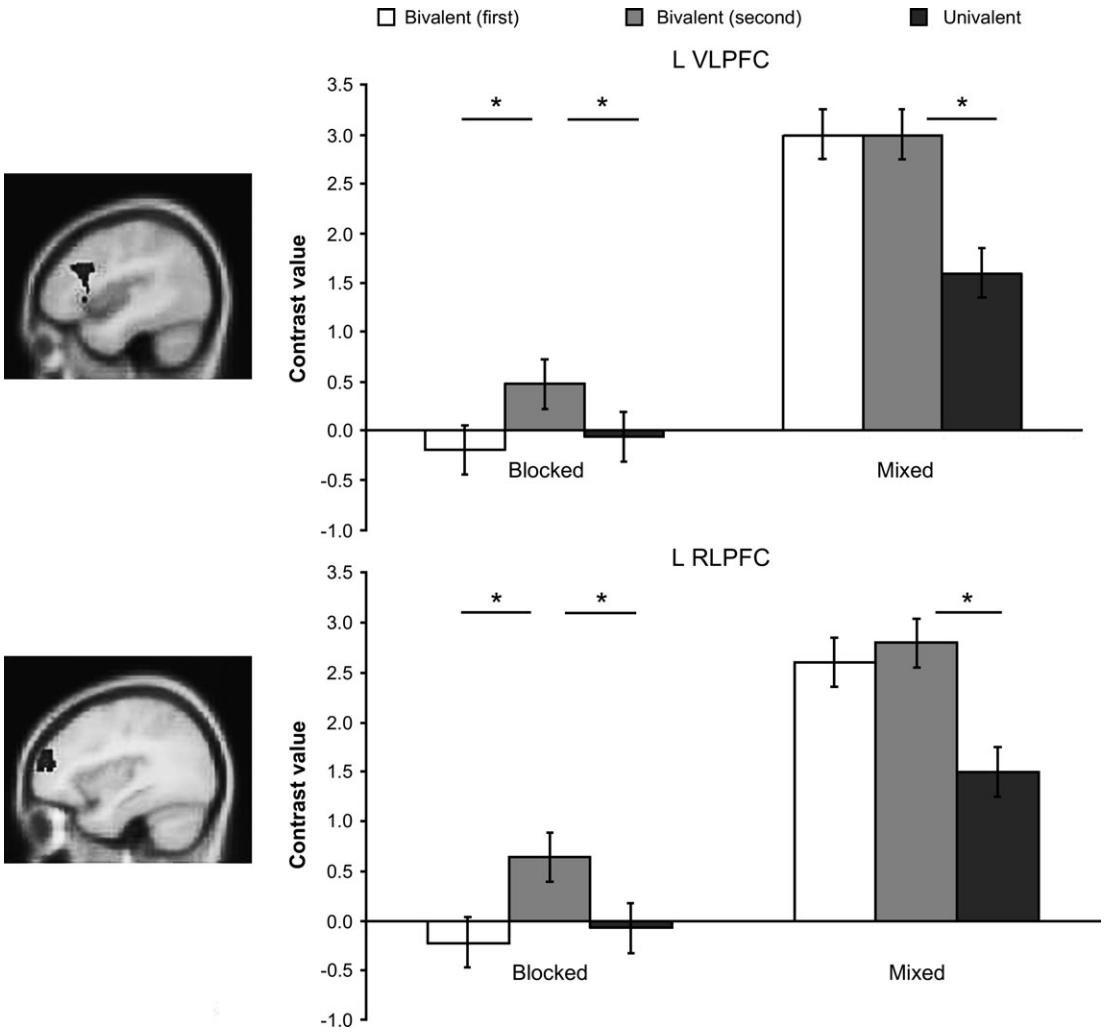

Figure 6. Learning-related modulation of PFC activation is illustrated here. Activation is plotted for VLPFC (same region as in Fig. 4) and RLPFC (BA 10; –34, 52, 22) for bivalent rules learned first and second, as well as univalent rules, across blocked and mixed tasks. Error bars depict an estimate of within-subject standard error. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$.

RLPFC were modulated by rule type in the blocked task, in that these regions were more strongly recruited in response to the bivalent rule learned second relative to the other rules. Thus, these results suggest that VLPFC and RLPFC are important for learning and retrieving S-R associations.

ROI analyses further revealed that VLPFC was more active when switching to bivalent rules compared to repeating bivalent rules. This finding is consistent with the prior fMRI studies that have identified VLPFC for task-switch contrasts (Dove *et al.*, 2000; Sohn *et al.*, 2000, Dreher and Berman, 2002; Sylvester *et al.*, 2003). However, the response profile for this region — which was modulated by rule type even on rule repetition trials — is more parsimoniously explained by a role in rule representation. This finding is consistent with prior studies that have focused on the role of VLPFC in learning and retrieving cue–response associations, or *conditional visuomotor rules* (Toni and Passingham, 1999; Murray *et al.*, 2000; Toni *et al.*, 2001), as well as more complex rules (Brass and von Cramon, 2002; Bunge *et al.*, 2003). The present results are further consistent with studies showing that latPFC neurons exhibit sustained delay-period activity that is sensitive to specific conjunctions between stimuli and responses (Asaad *et al.*, 1998) or to specific rules (Asaad *et al.*, 2000), and that latPFC (including both VLPFC and DLPFC) is important for holding a goal in mind in the presence of interference (Shallice and Burgess, 1991; Chao and Knight, 1995; Miller *et al.*, 1996; Bunge *et al.*, 2001; Sakai *et al.*, 2002). Further, Brass and von Cramon (2002) showed that VLPFC is involved in selecting appropriate rules for the current task set even when there are no response requirements (i.e. on catch-trials in which a cue appears but is not followed by a target; see also Donohue *et al.*, 2005). Thus, a large body of evidence implicates VLPFC in the ability to use instructional cues to select relevant sets of responses.

Left RLPFC, which had a similar response profile to left VLPFC, has been associated with rule representation in a number of neuroimaging studies (Burgess *et al.*, 2001; Braver *et al.*, 2003; Bunge *et al.*, 2003; Sakai and Passingham, 2003). Indeed, one brain imaging study implicated this region in the acquisition of artificial grammar rules (Strange *et al.*, 2001). Bunge *et al.* (2003) previously observed more RLPFC activity for one rule involving a set of S-R mappings than for either another rule with the opposite S-R mappings that had been learned first, or a rule for which a given cue stimulus designated a fixed response. The current finding that RLPFC is more involved when applying the bivalent rule learned second in the blocked task but not

in the mixed task replicates and extends previous findings in the mixed rule task by Bunge *et al.* (2003), by suggesting that this effect diminishes with practice. However, the interpretation of this pattern of results is tentative, because the blocked task always occurred prior to the mixed task. RLPFC and VLPFC have been shown to work closely together during rule maintenance, especially during maintenance of a rule that is the opposite of a more strongly represented rule (see Sakai and Passingham, 2003).

Pre-SMA/SMA Involvement in Task-set Reconfiguration

The whole-brain analyses suggested that pre-SMA/SMA, but not VLPFC, was preferentially recruited when switching to a bivalent rule. The ROI analyses revealed that VLPFC also played a role in task-set reconfiguration (bivalent switch > bivalent repetition), but a cross-region comparison showed that VLPFC was less strongly modulated by switch demands than was pre-SMA/SMA. These results indicate a relatively more important contribution of pre-SMA/SMA than VLPFC to task-set reconfiguration, consistent with previous neuroimaging studies (Rushworth *et al.*, 2001; Brass and von Cramon, 2002; Wager *et al.*, 2004). That pre-SMA/SMA was differentially engaged by bivalent rule switches relative to all other conditions suggests that this region is most likely involved in overcoming interference from the previously activated task set, rather than simply in switching to any new set of S-R mappings. Similarly, Brass and von Cramon (2004) recently showed that pre-SMA is engaged when cue changes indicate a change in task independently of whether or not the task is executed. Importantly, in their study, pre-SMA/SMA was similarly active for cue switches as for task switches. The current study did not attempt to dissociate between task preparation and task execution, but this would be an important direction for future research. Our finding is also consistent with prior claims that pre-SMA is necessary when the set of relevant rules is changed (Paus, 2001; Picard and Strick, 2001; Rushworth *et al.*, 2004).

Basal Ganglia Sensitive to Bivalent Rule Switches

As with left pre-SMA/SMA, dorsal and ventral parts of left caudate nucleus were more active for bivalent rule switches than for bivalent rule repetitions. Importantly, the caudate was not differentially engaged for bivalent compared to univalent rule repetitions or for univalent rule switches compared to univalent rule repetitions. Previous brain imaging studies on rule-learning have indicated that the dorsal striatum (dorsal caudate and putamen) are involved in feedback-based rule-learning (Poldrack *et al.*, 2001; Toni *et al.*, 2002) and reversal learning (Stern and Passingham, 1995; Rogers *et al.*, 2000; Cools *et al.*, 2002). The correspondence between pre-SMA/SMA and caudate activation observed in this study is consistent with the fact that the basal ganglia receives frontal inputs and projects to premotor areas (Haber *et al.*, 2000; Strick, 2004). In the present study, the caudate nucleus and VLPFC were functionally dissociable, the former being most sensitive to bivalent rule switches and the latter being sensitive to rule representation in general. This result is analogous to a prior study showing that the ventral striatum responded to object switching (changing S-R mappings) but not to switching between simple rules, whereas latPFC responded to all types of switching (Cools *et al.*, 2004). Further, patients with Huntington's disease, an inherited neurodegenerative disorder affecting the basal ganglia, have difficulty switching to a new rule when the appropriate response is the same as on the prior trial (Aron *et al.*, 2003). Together, these findings are consistent with the hypothesis that the basal ganglia, like pre-SMA/SMA, operate on lower-level, motor-related associations between specific stimuli and responses, and therefore play a crucial role in overriding previous S-R associations when switching between tasks, whereas latPFC exerts a more general role in working with different types of rule representations.

Parietal Cortex Involved in Both Rule Representation and Task-set Reconfiguration

Left superior parietal cortex was sensitive to both rule type (bivalent > univalent) and rule-switching (switching > repetitions). This region failed to differentiate between bivalent and univalent switches, suggesting that it is involved whenever there is a need to switch S-R mappings (see also Wager *et al.*, 2004). The trend towards an RT switch cost for univalent rules may be associated with the need to remap the relevant S-R associations, a function purportedly subserved by parietal cortex (Brass and von Cramon, 2004). Superior parietal cortex was also more active for bivalent than for univalent rules, independent of rule switches or repetitions, suggesting that parietal cortex is involved when there is a need to control sets of S-R associations. These results are generally consistent with previous studies, suggesting that this region represents sets of possible responses (Sohn *et al.*, 2000; Bunge *et al.*, 2002; Brass and von Cramon, 2002, 2004; Braver *et al.*, 2003; Rushworth *et al.*, 2004).

Conclusion

As hypothesized, the results suggest that VLPFC is associated with rule representation, whereas pre-SMA, together with SMA, is more associated with task set reconfiguration. Additional analyses revealed that RLPFC showed a similar pattern to VLPFC, whereas the basal ganglia showed a similar pattern to pre-SMA/SMA. Parietal cortex was modulated by both rule type and task set reconfiguration, with superior parietal cortex showing a particularly strong response to task set reconfiguration. Thus, rule representation and task set reconfiguration appear to be interdependent but separable processes, and the frontal, parietal and subcortical regions examined here contribute differentially to these processes. Interestingly, developmental studies in our laboratory show that task set reconfiguration develops earlier in childhood than rule representation (Crone *et al.*, 2004a,b). We are currently characterizing the developmental timecourse of functional changes in VLPFC, pre-SMA/SMA and the other regions reported here, to further test the dissociability of rule representation and task set reconfiguration.

Notes

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