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Rule-Selection and Action-Selection have a Shared Neuroanatomical Basis in the Human Prefrontal and Parietal Cortex

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The human capacity for voluntary action is one of the major contributors to our success as a species. In addition to choosing actions themselves, we can also voluntarily choose behavioral codes or sets of rules that can guide future responses to events. Such rules have been proposed to be superordinate to actions in a cognitive hierarchy and mediated by distinct brain regions. We used event-related functional magnetic resonance imaging to study novel tasks of rule-based and voluntary action. We show that the voluntary selection of rules to govern future responses to events is associated with activation of similar regions of prefrontal and parietal cortex as the voluntary selection of an action itself. The results are discussed in terms of hierarchical models and the adaptive coding potential of prefrontal neurons and their contribution to a global workspace for nonautomatic tasks. These tasks include the choices we make about our behavior.

Keywords: action, adaptive coding, fMRI, prefrontal cortex, rule, selection

Introduction

The regulation of human behavior is critical to our success as individuals and as a species. It is widely thought to depend on a hierarchy of cognitive and motor processes (Norman and Shallice 1980) that are often associated with the frontal lobes. In this hierarchy, actions are subordinate to the rules that govern them, and they may therefore have a distinct neuroanatomical basis. Based on the integration of results from behavioral studies, neuroimaging, and primate physiology, it has been proposed that the encoding of pertinent rules in prefrontal cortex may "guide the flow of activity along neural pathways that establish the proper mappings between inputs, internal states, and outputs needed to perform a given task" (Miller and Cohen 2001). A recent influential model posits *spatially distributed* layers of such control, including stimulus response mappings in premotor cortex that are modulated by contextual control processes that are represented in caudal lateral prefrontal cortex (Koechlin et al. 2003). The contextual control processes are themselves modulated by broader "episodes" or behavioral rules mediated by lateral prefrontal cortex (Koechlin et al. 1999, 2003). Such distributed hierarchical models conflict with the concept of a "global workspace" that includes frontal and parietal cortex for multiple cognitive processes (Dehaene et al. 1998). These global workspace models are supported by neuroimaging and neurophysiological data, including the adaptive properties of cortical neurones under multiple tasks (Duncan 2001).

These 2 models make distinct predictions about the neuroanatomical distribution of processes related to different levels of the cognitive hierarchy. In contrast with distributed hierarchical models, adaptive coding models do not predict spatially separated regions of activation for processes at different levels of the hierarchy. This can be tested with functional magnetic resonance imaging (fMRI). We also sought to extend the models to the context of voluntary behavior. Both models are supported by animal literature (without reference to volition) and human studies based on cued tasks. Yet one of the important functions of the prefrontal context is in volitional control of behaviors (Norman and Shallice 1980; Frith et al. 1991; Passingham 1993; Frith 2000; Lau et al. 2004; Rowe et al. 2005). This is therefore an important context within which to study rule-based behaviors. In addition, the role of the parietal cortex is unclear. Although it is a component of the "global workspace" (Dehaene et al. 1998), hierarchical models have often overlooked it. This is not a necessary limitation and one might predict parallel hierarchies in parietal cortex based on the frequent coactivation of parietal and frontal regions in tasks of cognitive control (Duncan and Owen 2000; Duncan 2006); similar properties of parietal and prefrontal neurons in tasks of working memory and cognitive control (Chafee and Goldman-Rakic 1998, 2000; Nieder and Miller 2004; Stoet and Snyder 2004); and the reciprocal interactions between parietal and prefrontal regions in nonhuman primates (Cavada and Goldman-Rakic 1989) (see also the Cocomac database, Stephan et al. 2001).

To study the neural basis of the cognitive hierarchy pertaining to voluntary action, we developed a novel task which used rules to determine specific manual responses to subsequent visual stimulus arrays. These rules were sometimes chosen by the subjects themselves and sometimes specified to them, in advance of the response arrays. The difference between chosen and specified rules defines "rule-selection." Responses were also sometimes chosen by subjects in the absence of a prior rule, and sometimes a specific response was specified to them. The difference here defines "action-selection." Two versions of the task were used. The first had a complex design, enabling inferences about the generalization of rule-selection. The second experiment used a simpler factorial design with less task switching and no incongruence between rule and response options. We hypothesized that rule-selection would be superordinate to response or action-based processes in parietal and prefrontal cortex. Specifically, we predicted that rule-selection would be mediated by frontopolar or rostral lateral prefrontal cortex and interconnected parietal cortex, whereas action-selection would be mediated by caudal lateral prefrontal cortex, premotor regions and their parietal connections.

Materials and Methods

Subjects and Task

Data from 2 new experiments (1 and 2) are presented, plus selected re-analyzed data from a previous study for comparison (experiment 3) (Rowe *et al.* 2005). Experiment 1 included 20 subjects (aged 19–40 years, mean 26 years, 10 men) and experiment 2 included 16 subjects (aged 19–37, mean 25 years, 8 men). MRI data from 2 subjects in experiment 1 were discarded prior to analysis because of technical problems. Subjects were all right handed, with no neurological history, no current psychiatric illness, and took no regular medication. The experiments had received a favorable opinion from the Cambridge Research Ethics Committee and all subjects gave written informed consent.

Experiment 1

Subjects were scanned during performance of a rule-based response selection task (see Fig. 1). Apart from null trials, each trial lasting 4.25 s followed a similar format: a rule cue for 1 s (width ~2°), blank screen interval for 1 s, response cue for 1 s (width ~4°) during which a response may be made, and an interval of 1.25 s in which a late response could also be made (see Fig. 1).

In this first experiment, we wanted to make inferences about the generalization of rule-selection, across 2 rule modalities—color and height. We also wanted to study action-selection without reference to one of these rules. Lastly, we wanted to study the effects of different numbers of response options on neural activity, whether choosing the response according to a rule or not. This complexity had been a point of criticism during external peer review of the proposed study protocol, but we felt that each condition was necessary in the first instance and a simpler design was planned for experiment 2.

For experiment 1 there were 8 possible trial types as defined by the first cue (rule cue). For each of these, there were 3 possible events types defined by the second cue. Table 1 summarizes the trial types according to variation in the first and second cues. From the first cue (rule cue) the 8 trial types included 1) that the rule was to respond according to the highest stimulus in the response cue set, 2) that the rule was to respond to the lowest stimulus in the response cue set, 3) to choose a rule based on height, that is to say to choose to respond according to the highest stimulus, or choose to respond to the lowest stimulus, and "to have this rule ready in mind just as if you had been told the rule," 4) that the rule was to respond according to the lightest stimulus in the response cue set, 5) that the rule was to respond according to the darkest stimulus in the response cue set, 6) to choose a rule based on color, that is to say to choose to respond according to the lightest stimulus, or choose to respond to the darkest stimulus, 7) that there was no-rule, and to "just wait for the response cue to appear before choosing a circle to respond to," and lastly 8) null events that lasted 4.25 s appearing identical to the interstimulus interval screen, with a central low contrast "+" to orient subjects to the center of the screen, but without the stipulation to maintain fixation. Although the stimulus onset asynchrony was 4.25 s, including a blank screen that acted as an intertrial interval, the presence of null events varied the subjects' experience of the time from onset of one rule cue to the onset of the next rule cue. Null events enable one to contrast "all trials versus baseline" and vary the pacing of other trial types during a long experiment.

The response cue had 1, 2, or 4 circles in 4 columns, aligned closely in central vision. The circles differed in height and shade of gray, such that no 2 stimuli had the same height or the same color. Responses were made by pressing a button with the right hand fingers, with each finger corresponding intuitively to 1 of the 4 columns.

Subjects were pretrained at first with blocks of 8 trials defined by rules 1 and 2, then 8 trials defined by rules 4 and 5, then 18 trials defined by rules 3, 6, and 7, and then 28 trials intermixed using any rule type, with accuracy feedback and with as much time as required per trial to understand and practice the rules and response patterns. They were then pretrained on a block of 56 trials with all response types, with no feedback, intermixed, and at the rate of 1/4.25 Hz, similar to the scanned protocol. In the scanner, subjects performed 220 active trials (40 with choice of color rule, 40 with choice of heights rule, 40 with specified color rule, 40 with specified heights rule, 60 with no-rule) divided evenly across the 3 response cue conditions (73 trials with 1 circle, 73 trials with 2 circles and 74 trials with 4 circles). Active trials were interspersed with 80 null events.

Experiment 2

For the second experiment, we used a simpler 2 × 2 factorial design, using the key rule conditions from experiment 1 (selection or specification of a height based rule) and 2 types of response cues (1 or 4 circles). This simpler design would allow us to replicate rule-selection effects, without interactions with the frequent task switching required in experiment 1 or the effects of incongruence when 2 circles are presented. Subjects performed a simplified version of experiment 1, using only height-based rules (1–3 above), not color based (4–6) nor rule 7. After similar pretraining, subjects were scanned during 140 active trials with 70 null events. Forty trials had 1 circle in the response cue, 100 had 4 circles, divided equally between trials of chosen and specified rules.

Experiment 3

Data from a previously published study of action-selection are also shown (Rowe *et al.* 2005) for direct comparison with the current action-selection contrasts. These data were obtained on a different scanner, but normalized to the same template in MNI space. They key conditions required subjects to choose to press a button with 1 of the 4 fingers of the right hand, or to press the button specified by an arrow cue.

The presentation of data was controlled using E-prime 1.1 software (www.pstnet.com) in Windows XP (www.microsoft.com). Reaction times (RT) to presentation of the response cue were recorded and

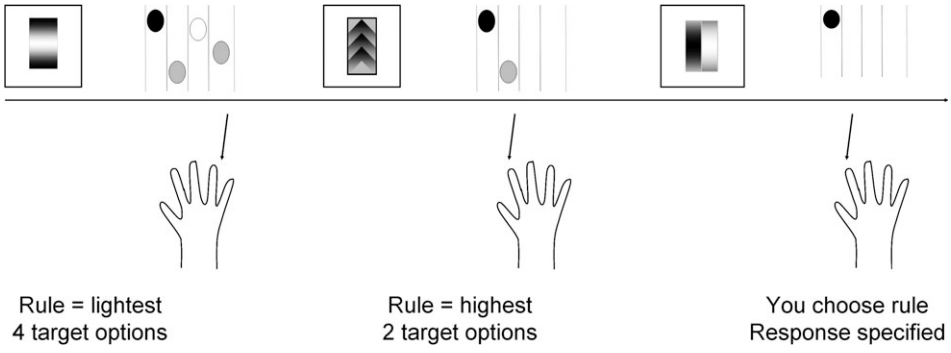

Figure 1. Three example trials from the task used in experiment 1, each including a rule cue, a response cue, and a button press response. The rule cue would indicate whether the response could be chosen (within either heights or color modality) or was specified or that there was no-rule and subjects should wait until the response cue before choosing a response. The response cue had either 1 target (thereby specifying the response) or more than 1 enabling response selection according to the rule (chosen or specified) or free response selection (after no-rule cues). Stimulus onset asynchrony is 4.25 s. Null trials looked like the background screen, introducing a variable interval between active trials. For experiment 2, only height based rules were used, with 1 or 4 targets.

Table 1
Summary of trial types in experiments 1 and 2

First cue: defines rule (±modality)	Second cue: defines action
Specified: 1, 2 (height)	Apply rule: 4 targets
	Apply rule: 2 targets
	Rule irrelevant: 1 target specified
Specified: 4, 5 (color)	Apply rule: 4 targets
	Apply rule: 2 targets
	Rule irrelevant: 1 target specified
Choose: 3 (height)	Apply rule: 4 targets
	Apply rule: 2 targets
	Rule irrelevant: 1 target specified
Choose: 6 (color)	Apply rule: 4 targets
	Apply rule: 2 targets
	Rule irrelevant: 1 target specified
No-rule: 7	Choose action: 4 targets
	Choose action: 2 targets
	Specified action: 1 target
Null event: 8	Null

Note: The left hand column numbers refer to the rule cue types listed in the methods section. Heights were used in both experiments 1 and 2, but colors only in experiment 1.

analyzed in SPSS 11.0 (SPSS, Inc., Chicago, IL) using planned repeated measures analysis of variance (ANOVA). Within-subject factors included modality of rule and type of rule (selected, specified or no-rule) and number of response cue targets (1, 2, or 4). A post hoc analysis of RT in the 2-target conditions of experiment 1 distinguished trials according to the congruency between the rule and the correct response. For example, if the rule required the highest target to determine the response, the highest target might be at the top of the display (congruent), in the upper half of the display but not the highest possible position (semi congruent) or in the lower half of the display (incongruent).

MRI Data Acquisition and Analysis

The Medical Research Council Cognition and Brain Sciences Unit's Siemens Tim Trio 3-T MRI scanner was used. fMRI used blood oxygen level-dependent (BOLD) sensitive T_2^*-weighted echo planar images (time repetition [TR] 2000 ms, time echo [TE] 30 ms, flip angle [FA] 78°) with 32 slices, 3.0 mm thick, in-plane resolution 3 × 3 mm, with slice separation 0.75 mm, in sequential descending order. Six hundred and fifty images were acquired for each subject in experiment 1, the first 5 of which were discarded to allow for steady-state magnetization. Subjects also underwent high resolution magnetization prepared rapid gradient echo (MP-RAGE) scanning (TR 2250 ms, TE 2.99 ms, FA 9°, inversion time 900 ms, 256 × 256 × 192 isotropic 1 mm voxels) and single volume turbo spine echo (TR 5060 ms, TE 102 ms, FA 140, 28 × 4 mm slices) for the purposes of normalization of images, localization of activations on individual and group brains, and assurance of structural normality. Occasional movement events and radiofrequency artifacts in other subjects were accommodated by scan specific regressors in the subject specific first level general linear models, to reduce the effects of spikes or movements on the estimation of parameters for the effects of interest. These scans were detected by in-house image diagnostic software (typically 0–5 scans).

Data analysis used Statistical Parametric Mapping 5 (SPM5) software (http://www.fil.ion.ucl.ac.uk/spm) in Matlab 7 environment (R14, Mathworks, CA). fMRI data were converted from DICOM to NIFTII format, spatially realigned to the first image to produce a mean image and 6 rigid body motion parameters (Friston et al. 1995). The mean fMRI volume and MP-RAGE were coregistered using mutual information, and the MP-RAGE segmented and normalized to the Montreal Neurological Institute (MNI) T_1 template in SPM by linear and nonlinear deformations (Ashburner and Friston 1999, 2005). The normalization parameters were then applied to all spatiotemporally realigned functional images, the mean and structural images, prior to spatial smoothing of fMRI data with an isotropic Gaussian kernel with full width half maximum 10 mm.

First level Statistical Parametric Modeling for each subject in experiment 1 used a general linear model with regressors of interest that included each of the 15 trial types shown in the summary Table 1, except null events. Modeling of experiment 2 at the first level was formally similar to experiment 1, but included only the appropriately reduced number of rule types and response cue types.

Second level models (random effects) for each contrast of interest were made using images of the differences between parameter estimates for trial types in a contrast in a one-sample *t*-test. Given the similar design of first level analyses, this 2 step approach is equivalent to a mixed effects analyses incorporating within and between subjects variance. SPM{*t*}maps were generated each of the effects of interest, thresholded as standard such that the false discovery rate (FDR) was 0.05 (Genovese et al. 2002) for each map. This standard threshold was used to give equivalent confidence in the suprathreshold voxels, even though the absolute *t*-threshold may differ. In view of our hypotheses regarding activations in the prefrontal cortex, we also corrected for multiple comparisons within an anatomically defined prespecified prefrontal cortex region of interest ("prefrontal ROI"). In the absence of probabilistic cytoarchitectonic maps of prefrontal cortical regions in standard anatomic space, we built a ROI beginning with all the frontal lobe and then excluding Brodmann areas 6, 44, 45 as defined in MNI space from cytoarchitectonically characterized brains (Amunts et al. 2004); and excluding voxels that were both inferior to and posterior to the genu of the corpus collosum; and excluding voxels posterior to $y = 0$. This leaves Brodmann areas 8, 9, 10, 24, 32, 46, and 47 in the prefrontal ROI. MRIcro software was used to construct this ROI (http://www.mricro.com) (Rorden and Brett 2000). For some contrasts we reduce the thresholds to $P < 0.001$ or 0.01 uncorrected because of negative results at standard thresholds. These instances are indicated in the text but in general they are used to reduce type II error for key contrasts.

Results

Behavioral Results

Behavioral data are shown in Figure 2. There was no overall effect of rule-selection on RT in experiment 1 or 2 (Expt. 1: specified rule: mean = 935.4 ms, SE = 24.65; chosen rule: mean = 920.6 ms, SE = 24.5; no-rule: mean = 920.8ms, SE = 23.6; $F_{2,38}$ = 0.97, $P > 0.05$; Expt. 2: specified rule: mean = 878.0, SE = 36.5; chosen rule: mean = 875.3, SE = 35.5; $F_{1,15} = 0.22$, $P > 0.05$). For both studies there was a significant effect of the number of targets on RT (Expt. 1: One target: mean = 872.4 ms, SE = 107.9; Two targets: mean = 960.08 ms, SE = 22.38; four targets: mean = 944.32 ms, SE = 24.77; $F_{2,38} = 56.53$, $P < 0.0$; Expt. 2: one target: mean = 851.4, SE = 34.3; four targets: mean = 902.0, SE = 36.4; $F_{1,15} = 27$, $P < 0.05$). In experiment 1, when 2 targets were presented RT was longest. Post hoc paired *t*-tests confirmed differences in RTs between 1 and 2 targets ($t_{(19)} = -11$, $P < 0.01$), 1 and 4 targets ($t_{(19)} = -7.2$, $P < 0.01$), and 2 and 4 targets ($t_{(19)} = 2.4$, $P < 0.05$). The only significant interactions were in experiment 2, between rule type and number of targets ($F_{1,15} = 6.4$, $P < 0.05$).

A second repeated measures ANOVA for experiment 1 investigated the effects of rule-selection (either specified or freely chosen) based on height or color. There were longer RTs for specified rules ($F_{1,19} = 5.0$, $P < 0.05$) but no effect of modality ($F_{1,19} = 1.2$, $P > 0.05$). There was also an effect of the number of targets ($F_{2,38} = 57.0$, $P < 0.01$) and a significant interaction was between modality and number of targets ($F_{2,38} = 14.5$, $P < 0.01$). This interaction is driven by the color rule for which RTs were slower when 2 targets were presented for both the rule specified and rule chosen conditions (see Fig. 2). One reason that RTs are faster in the 4 compared with 2 target condition for color (as confirmed by a post hoc paired *t*-test ($t_{(19)} = 4.5$, $P < 0.01$) is that in the 4 target condition all 4 colors (black, dark-gray, light-gray, and white) were present: the

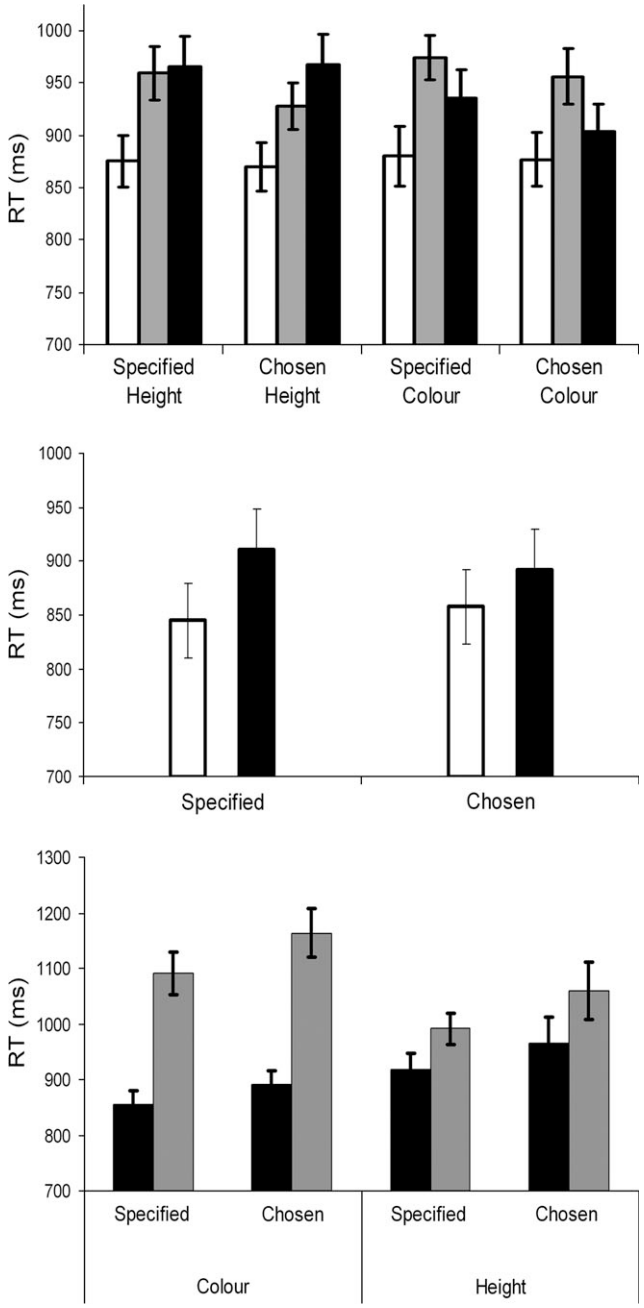

Figure 2. Top: The mean RT (±SE) for experiment 1, according to rule type (specified vs. chosen) and modality (height vs. color) and number of targets in the response cue (white1; gray2; black 4). Middle: The mean RT (±SE) for experiment 2 according to rule type and number of targets (white1; black 4). Bottom: RT (±SE) for trials with congruent (black) versus incongruent (gray) targets for each rule type and modality.

darkest was black and the lightest white, this cue may have facilitated participants' responses. For the height based tasks and no-rule conditions there was no difference in RT between 2 and 4 targets ($t_{(19)}$ = –1.6, P> 0.05; $t_{(19)}$ = 1.3, P > 0.05, respectively).

A post hoc ANOVA of RT in experiment 1 for trials with 2 response targets confirmed a main effect of congruency ($F_{1,15}$ = 14.5, P < 0.005) and rule type ($F_{1,15}$ = 8.1, P < 0.05) but no effect of modality ($F_{1,15}$ = 0.4, nonsignificant [ns]) as shown in Figure 2. The effect of congruency interacted with modality, being greater for color based tasks ($F_{1,15}$ = 21, P < 0.001) and did not interact with rule type ($F_{1,15}$ = 0.1, ns). There was no 3-way interaction ($F_{1,15}$ = 0.3, ns).

Specified rules were balanced within both color and height domains. Color-based rule choices were for lightest in 44% (SE 4.9) of trials and darkest in 56% (SE 4.9) of trials (chi-squared for distribution of responses 3.0, df 1, P = ns). The height-based rule choices were overall for highest in 47% (SE 4.4) of trials and lowest in 53% (SE 4.4) of trials (chi-squared for distribution of responses 6.1, df 1, P < 0.05) suggesting a small bias toward choosing the "lowest" rule. Specified actions were balanced across all fingers. Chosen actions were for index finger in 27% (SE 1.6), middle finger in 26% (SE 1.0), ring finger in 22% (SE 1.2), and little finger in 25% (SE 1.1). Chi-squared test for distribution of selected actions 7.2, df 3, P 0.07, suggesting a trend bias against selection of ring finger responses.

Principal Neuroimaging Results

Trials in which there was rule-selection in experiments 1 and 2, compared with trials in which the rule was specified, were associated with greater activation of dorsal, ventral, and polar frontal cortex, together with supramarginal parietal cortex, as shown in Figure 3*A,D* (details in Table 2). Activation was neither greater than nor less than that associated with action-selection, at thresholds P < 0.05 (FDR corrected in whole brain or corrected within the prefrontal ROI reduced search volume) or at P < 0.01 (uncorrected), shown as the blank difference image in Figure 3*C*.

Action-selection can be defined in terms of the choice between action alternatives in the absence of a specified rule. This selection process was associated with activation of frontopolar, dorsal-lateral, and ventral-lateral prefrontal cortex, bilaterally and supramarginal parietal cortex, similar to rule-selection as shown in Figure 3*B* were identified from experiment 1 by the *t*-contrast for trials of 2 or 4 targets versus 1 target, in the context of no-rule having been specified (see Table 1) (FDR P < 0.05). Action-selection related activations were identified from experiment 3 by the contrast of free-selection of action versus specified actions, illustrated in Figure 3*E* (FDR P < 0.05). Details are given in Table 2. Note that for frontal and lateral parietal regions associated with rule-selection there is a corresponding cluster of activated voxels for action-selection, in one or both rule-selection tasks.

The selection of actions can also be described in terms of selection between a number (n > 1) of possible response options when a prevailing rule needs to be applied. Voxels shown in Figure 3*F* are associated with this type of selection and were identifiable in experiment 1 by the *t*-contrast for trials of 2 or 4 targets versus 1 target, in the context of a rule having been either specified or chosen freely (see Table 1). The pattern is quite different from action-selection in the absence of a rule (Fig. 3*B,E*).

The effects of modality were also studied. There was no main effect for color versus heights or vice versa, in experiment 1 (FDR P < 0.05). The effects of selection or choice may in principle vary with modality, causing an interaction between modality and selection. No significant activations were identified in experiment 1 at FDR P < 0.05 (corrected within whole brain or the prefrontal ROI), but rule-selection was associated with greater activations in color based tasks at reduced threshold (P < 0.001 uncorrected) in bilateral prefrontal cortex at 22, 40, 32 (t = 5.05) and –32, 44, 6 (t = 4.41).

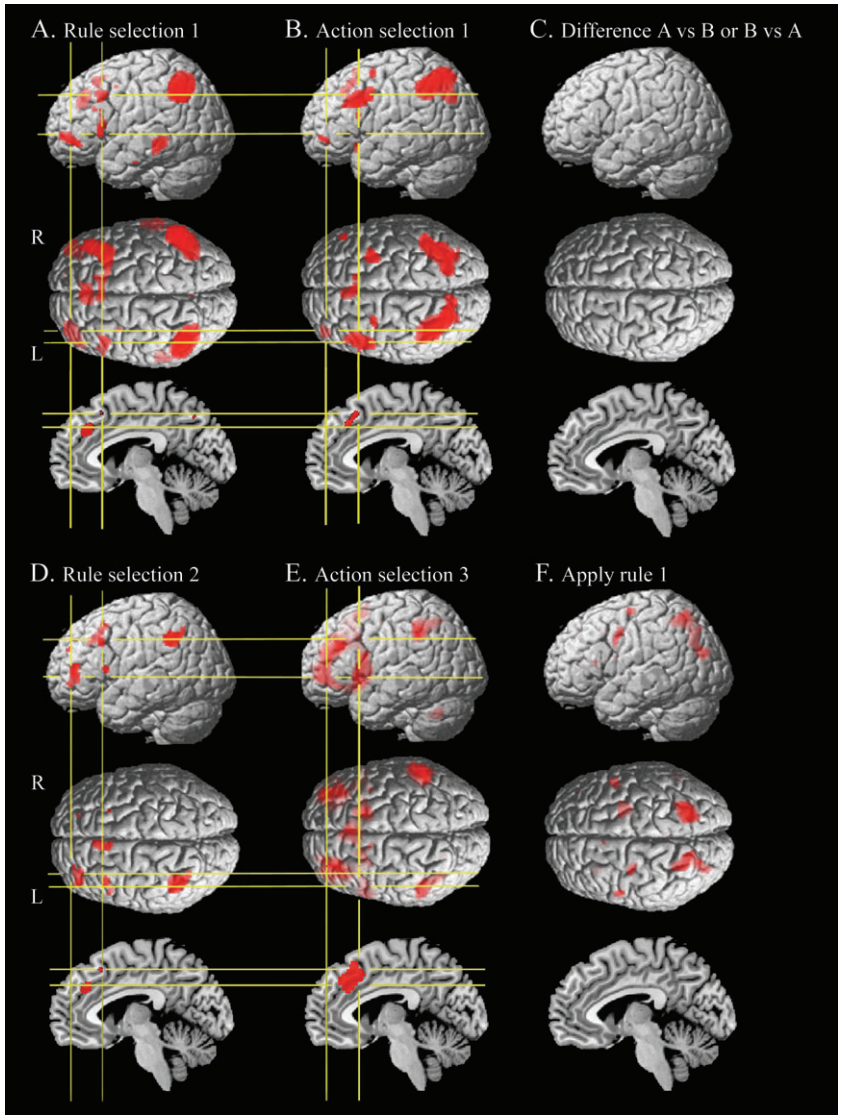

Figure 3. (*A*) SPM{*t*} map thresholded at FDR $P < 0.05$ for choose versus specified rule trials in experiment 1, averaging across color and height modalities and types of second cue (see Table 1) (*B*) SPM{*t*} map thresholded at FDR $P < 0.05$ for action-selection versus specification in experiment 1 (choose action vs. specified action trials in Table 1) (*C*) SPM{*t*} emphasizing that rule-selection in (*A*) and action-selection in (*B*) did not differ from each other by *t*-tests at either FDR $P < 0.05$ or at the liberal threshold of $P < 0.01$ uncorrected. (*D*) SPM{*t*} at uncorrected threshold $P < 0.001$ for rule-selection versus specification from experiment 2, averaging across all types of second cue (see Table 1). Correction to $P < 0.05$ within a frontal ROI is indicated in Table 2. (*E*) SPM{*t*} FDR $P < 0.05$ for action-selection versus specification from experiment 3 (cf. choose action vs. specified action trials in Table 1) (*F*) SPM{*t*} FDR $P < 0.05$ for the application of a current rule to the selection among 2 or 4 targets versus a single target in experiment 1 (apply rule vs. irrelevant to specified response in Table 1). Note the absence of prefrontal cortical activations in comparison to free-selection of actions in (*B*). The SPM{*t*}s are rendered on the SPM5 canonical T_1 brain volume in MNI space. Yellow lines are overlaid to assist comparison of the dorsal- and ventral-prefrontal activations in (*A*), (*B*), (*D*), and (*E*). The sagittal slice is at $x = -5$ mm.

We compared trials in which rules were selected with trials in which actions were selected. Rule-selection versus action-selection was associated with no activation difference at threshold FDR $P < 0.05$. At $P < 0.001$ uncorrected there were 2 foci of differential activation in the temporal lobe (50, –4, 8, $t = 4.94$, cluster 50 voxels; 68, –46, 8, $t = 4.31$, 53 voxels) and 1 at the parieto-occipital junction (42, –74, 40, $t = 4.60$, 32 voxels). There were no significant activations within the prefrontal ROI at threshold FDR $P < 0.05$. When comparing action-selection versus rule-selection, there was no difference at FDR $P < 0.05$. At $P < 0.001$ uncorrected, a cluster is revealed in the corpus collosum (–6, 2, 24, $t = 4.19$, 13 voxels) but this is likely to be a false positive. There were no voxels of significant difference within the prefrontal ROI at threshold FDR $P < 0.05$.

To illustrate the similarity between rule-selection and action-selection, we performed the contrast "all-selection versus all-specified." We chose 6 regional peaks from this contrast in prefrontal and parietal cortex (see Table 3 for further details and Fig. 4) and show separately in Figure 4 the BOLD signal change for the contrasts "rule-selection versus rule-specification" and "action-selection versus action-specification." Not only are the peaks of activation very similar for the rule and action contrasts (Fig. 3*A*,*B*), but in these regions the magnitude of effect is similar. This new contrast, shown in Figure 5, overlaps extensively with Figure 3*A*,*B* as expected.

Table 2

Regions of significant cerebral activation associated with rule-selection (vs. rule-specification) and action-selection (vs. action specification)

	Rule-selection (experiment 1)		Rule-selection (experiment 2)		Action-selection (experiment 1)		Action-selection (experiment 3)	
	t	*x*, *y*, *z* (mm)	*t*	*x*, *y*, *z* (mm)	*t*	*x*, *y*, *z* (mm)	*T*	*x*, *y*, *z* (mm)
Regions activated in association with rule-selection and action-selection								
Rostral PFv (47) $y > 40$	5.21	−34 52 −6	4.6*	−30 48 −6	4.57	−42 50 −6	5.10	−36 52 −2
	4.96	−48 44 −8	4.25*	−34 52 −4	3.84	−36 54 −2	6.61	36 52 16
	5.32	36 44 −12	4.47*	−40 46 10	—	—	4.14	34 48 −2
	4.64	44 50 −8	—	—	—	—	3.8	40 50 −8
	3.89	16 58 −4	—	—				
Rostral PFd (10/46), $y > 40$	—	—	4.08*	−26 50 30	—	—	9.92	−32 44 22
	—	—	3.76*	22 46 28	—	—		
Mid PFd (9/46),$18 < y < 40$	4.64	44 34 34	4.39*	−40 20 34	5.26	−46 20 30	15.2	−40 36 30
	3.96	−46 18 36	—	—	4.02	50 28 35	7.42	42 40 32
Caudal PFd (8, 9), $y < 18$	5.70	38 16 48	3.76*	26 16 58	4.91	32 6 50	7.44	18 14 58
	3.72	−36 6 46	—	—	4.82	−54 8 36	3.82	40 8 54
					4.49	−32 4 58		
Caudal PFv (45)	3.60	−52 26 26	—	—	—	—	4.77	42 22 24
	—	—	—	—	—	—	5.18	44 38 −8
Caudal PFv (44)	4.37	−50 20 6	4.70	−52 16 10	4.09	−34 16 −9	4.89	52 16 −6
	3.62	−54 18 16	—	—	4.02	−58 14 23	—	—
Medial frontal cortex	4.08	−6 22 50	4.79*	−8 16 50	4.34	−2 24 48	8.38	−8 20 44
	4.67	2 36 34	4.35*	−6 24 40	4.05	−6 28 42	6.13	2 26 40
	4.58	−8 36 30	—	—	3.89	12 16 63	5.74	−4 36 40
Parietal SMG	6.42	−46 −58 48	3.97	−38 −56 44	5.93	−36 −52 48	12.79	54 −44 50
	5.60	−50 −54 40	—	—	5.65	−40 −44 42	8.71	−56 −40 42
	6.37	52 −58 46	—	—	5.61	−28 −64 52	4.47	−44 −58 54
	5.76	44 −64 50	—	—	4.56	42 −46 48	—	—
Parietal IPS	—	—	6.49	−40 −48 36	5.2	36 −54 52	—	—
	—	—	3.96	−36 −58 46	5.8	26 −68 58	—	—
Regions activated only in association with rule-selection								
Middle temporal gyrus	4.76	−56 −36 −14	—	—	—	—	—	—
	4.74	−62 −36 −6	—	—	—	—	—	—
	4.58	64 −30 −10	—	—	—	—	—	—
	4.08	58 −30 −16	—	—	—	—	—	—
	4.01	56 −8 −28	—	—	—	—	—	—
Inferior temporal gyrus	4.49	66 −16 −20	—	—	—	—	—	—
Medial parietal cortex	3.58	−2 −64 42	—	—	—	—	—	—

Note: FPC = frontopolar cortex. PFd = dorsal-lateral prefrontal cortex. PFv = ventral-lateral prefrontal cortex (suggested Brodmann areas in brackets). Values are significant at FDR $P < 0.05$ for experiments 1 and 3. For experiment 2, clusters are shown at threshold $P < 0.001$ uncorrected with an asterisk indicating corrected significant $P < 0.05$ within the ROI. This ROI included the prefrontal cortex bilaterally (areas 8, 9, 23, 32, 46, 47, 10).

Replication and Overlap of Imaging Results

Table 2 and Figure 3*A*,*B* and *D*,*E* suggest considerable similarity between the significant activations associated with rule- and action-selection, there were some differences in the thresholded SPM{*t*} images. The question arises whether these differences reflect true differences in the patterns of neuronal activation for rule- and action-selection; the result of type II errors; or the effects of different sampling from the general population for our 3 experiments.

We adopted several approaches to clarify these issues. First, we asked whether the reduced number of frontal activations for rule-selection in experiment 2 (Fig. 3*B* vs. *A*, Table 2) may have resulted from reduced sensitivity. We constructed a symmetrical ROI, including the prefrontal cortical areas 8, 9, 10, 24, 32, 46, and 47. We then corrected the statistical inferences for rule-selection in experiment 2 for multiple comparisons (family wise error $P < 0.05$) within this reduced search volume. The results are presented in Table 2 with asterisks to indicate corrected significance. The mid and rostral lateral prefrontal cortical activations for rule-selection in experiment 2 were significant when corrected for multiple comparisons within this ROI. The interaction between modality and selection processes in experiment 1 suggests that heights based rule-selection were associated with less prefrontal activation than color rule-selection. This may partially account for the reduced activations in experiment 2, which used only heights based rules.

Second, we formally compared rule-selection with action-selection in experiment 1 (although note that the action-selection was nested in nonrule-selection trials so these are not orthogonal in a factorial design). We found no difference between rule-selection and action-selection or vice versa at FDR $P < 0.05$. There was still no difference even at the very reduced threshold of $P < 0.01$ uncorrected (Fig. 3*C*). This argues against a difference, although is not of course proof that there is no absolute difference.

Third, we sought regions activated with rule-selection in experiment 1 that were not associated with action-selection (contrast: rule-selection FDR $P < 0.05$ exclusively masked by action-selection $P < 0.05$ uncorrected), and vice versa. No such voxels were found, indicating that each voxel associated with rule-selection was also associated with action-selection, and vice versa, even if only at a lower threshold.

Discussion

The selection of rules to govern future behaviors was associated with activation of dorsal- and ventral-lateral prefrontal cortex, medial frontal cortex, and supramarginal gyrus in 2 separate experiments. The selection of action was associated

with a very similar pattern of activations in prefrontal and parietal cortex. Action-selection related activations in experiment 1 were also similar to previous reports of action-selection, including experiment 3, which had used paradigms that did not include choices about rules.

The choice between actions has been shown to activate dorsolateral prefrontal cortex whether it is a simple hand movement (Frith et al. 1991; Hyder et al. 1997; Spence et al. 1997; Lau et al. 2004; Rowe et al. 2005), tongue movement (Spence et al. 1998), spoken word (Frith et al. 1991), or complex movement like line drawing (Jueptner et al. 1996). It has been proposed that it is the neuronal ensemble representing the target of action that is selected (Rowe et al. 2005). A candidate region for these ensembles is the premotor cortex in which action-target representations exist (Alexander and Crutcher 1990; Shen and Alexander 1997; Kakei et al. 1999; Graziano et al. 2002). We suggest that prefrontal and/or parietal afferents to premotor cortex bias competition between such action representations like the top-down biases in the visual system reported at neuronal and systems levels (Desimone and Duncan 1995; Brefczynski and DeYoe 1999; Barcelo et al. 2000). Our key question was whether the selection of rules operated by a separate or similar mechanism.

Trials requiring rule-selection also activated dorsal- and ventral-prefrontal cortex over and above the trials with 3 specified rules. Neurons in these regions are capable of encoding different contextually appropriate abstract rules in electrophysiological studies (Wallis et al. 2001; Wallis and Miller 2003a) and these are candidate neurons to mediate the rule-selection effects shown. Rule-selection activation was also seen in the caudal prefrontal cortex, which has previously been shown in human studies to be sensitive to the "context" of rule-based tasks (Koechlin et al. 2003) and the retrieval and maintenance of rules (Bunge et al. 2003). This latter study also showed temporal cortex activation with rule tasks, corresponding to

Table 3

Regions of signification differential activation for the contrast "all-selection trials versus all-specified trials" in experiment 1 collapsed across action and rule events for both modalities, at threshold FDR $P < 0.05$, corresponding to Figure 5

Region	*t*	*x*, *y*, *z* (mm)
Rostral PFv (47), $y > 40$	5.17	−34 48 −6**
	5.08	−42 50 −6
	4.86	−32 50 −4
	3.63	40 50 −8
Mid PFd (9/46), $18 < y < 40$	4.61	50 32 30
	3.56	−58 20 2
Caudal PFd (8,9), $y < 18$	5.56	−34 4 58**
	4.55	36 8 54
	3.34	−46 10 48
Caudal PFv (45)	5.85	−48 22 32**
	3.98	54 24 2
Caudal PFv (44)	4.12	−50 18 6**
	4.47	−50 18 18
Medial frontal cortex	4.77	2 20 50**
	4.56	12 20 58
	4.53	−6 32 38
Frontal operculum	4.60	−34 20 −14
Parietal cortex	6.52	−32 −62 56**
	5.98	44 −64 50
	5.71	50 −58 58
	5.27	−48 −58 40
Medial parietal cortex	4.48	−12 −70 58
	4.41	−6 −66 46
Middle temporal gyrus	4.33	−66 −36 −6

Note: Effects sizes at the peaks marked ** are illustrated in Figure 4. For frontal regions, the corresponding Brodmann area is suggested based on anatomical landmarks (8, 9, 46, 47) or probabilistic cytoarchitectonic maps (44, 45).

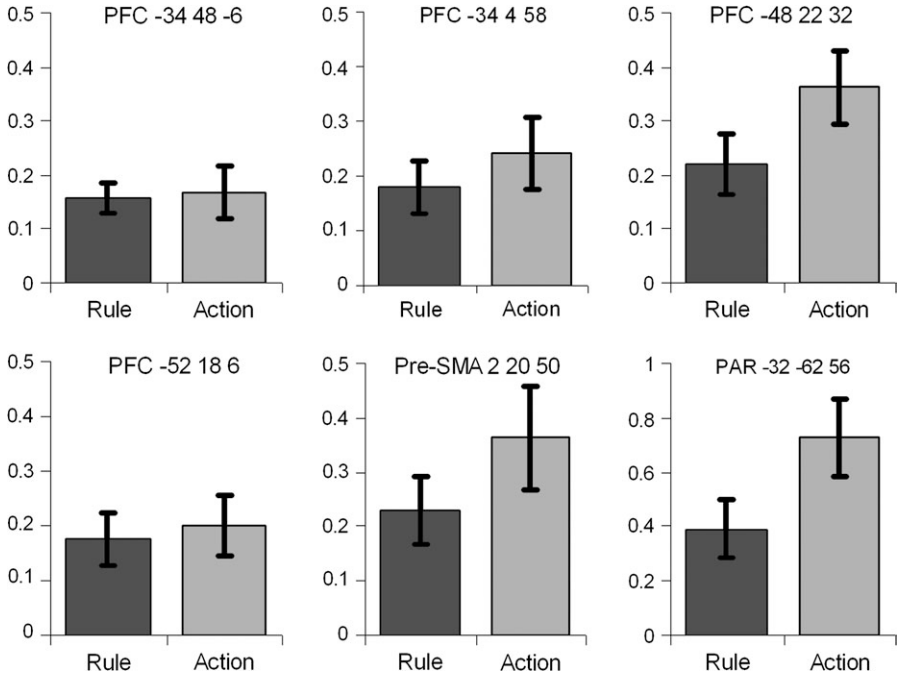

Figure 4. Difference in BOLD signal change (%) between trials in which rules were chosen and rules were specified (black bars, "Rule," cf. Fig. 3*A*) and between trials in which actions were chosen and actions were specified (gray bars, "Action," cf. Fig. 3*B*). Data are presented from 6 voxels, identified as local peaks of activation difference in the contrast "all-selected versus all-specified" (see Fig. 5 that overlaps extensively with Fig. 3*A*,*B*). Coordinates are given in standard anatomic space (MNI template). Despite the slight variation in height of the bars, the contrast of "[action-selection versus action-specification] versus [rule-selection versus rule-specification]" was not significant in any of these regions (see Fig. 3*C* and Results). PFC = prefrontal cortex, PAR = parietal cortex.

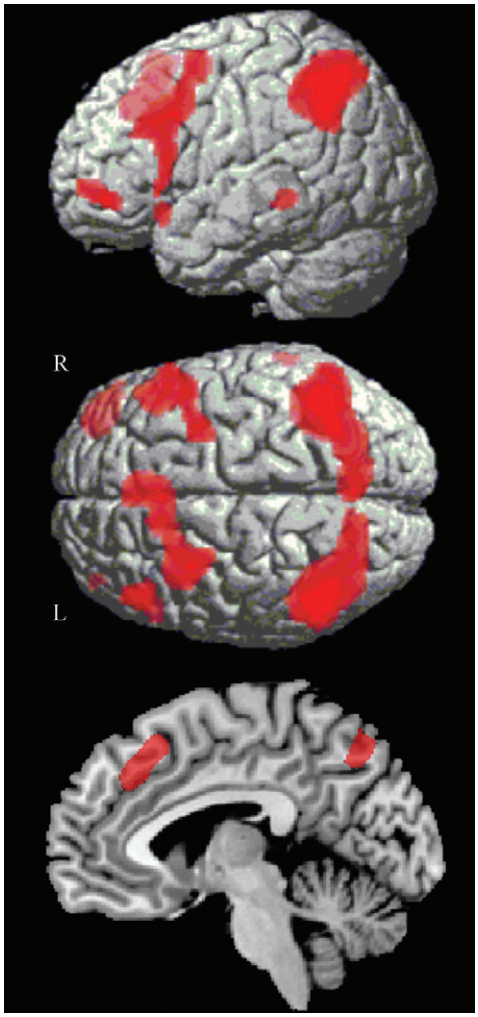

Figure 5. SPM{t} map thresholded at FDR $P < 0.05$ for the contrast of "selection" versus "specified" trials in experiment 1, averaging across rule and action based trials, and across color and height modalities, rendered on the SPM5 canonical T_1 brain volume in MNI space.

the temporal regions associated with "rule-selection versus rule-specification" and "rule-selection versus action-selection" in our experiment 1. The frontal and temporal activations may nonetheless differ in their functional significance. For example, it has been suggested that the frontal cortex mediates rule-selection in contrast to posterior representations of rule meaning (Bunge et al. 2003; Donohue et al. 2005). This distinction is consistent with our data, but our paradigm was not designed to test this latter hypothesis further. Rules are also encoded by neurons more caudally in premotor cortex (Wallis and Miller 2003b) and interactions have been demonstrated between frontopolar cortex and the rostral margin of premotor cortex during the maintenance of readiness of specific rules (Sakai and Passingham 2006). We found caudal prefrontal activations close to the rostral margin of premotor cortex associated with rule-selection (Wallis and Miller 2003; Sakai and Passingham 2006) leaving open the possibility that this region is homologous between studies despite the different anatomical terminology across studies.

Both rule-selection and action-selection were associated with activation of medial frontal cortex, including pre-supplementary motor area (pre-SMA) and dorsal anterior cingulate. These regions have been reported in earlier studies of voluntary action-selection (Frith et al. 1991; Hyder et al. 1997; Lau et al. 2004; Haynes et al. 2007) and rule encoding (Dosenbach et al. 2006). When choosing between rules and actions in the current study there are no "right" or "wrong" choices. It is unlikely therefore that the activity we identify reflects cingulate function connected to error detection (reviewed Rushworth et al. 2007). However, there still is a potential conflict between equipotent rules or actions that requires resolution for the choice to be made. Such decision uncertainty or response conflict is consistently associated with activation of the pre-SMA and dorsal cingulate, spanning the medial frontal regions identified in the current study (Ridderinkhof et al. 2004). Moreover, the resolution of conflict leading to the selection of a subsequent response is associated with an interaction between the dorsal anterior cingulate and the lateral prefrontal regions (Kerns et al. 2004; Liston et al. 2006). Such an interaction may support the lateral frontal activations also seen in the current study.

It has been proposed that the pre-SMA selects between actions and between the rules for selection of actions based on expected outcomes (Rushworth et al. 2004). This is evident when rules or response sets must be changed during neuroimaging studies (Brass and von Cramon 2002; Rushworth et al. 2002) or following medial frontal lesions (Rushworth et al. 2002, 2003). However, in the current study, the specification of rules and actions also required switching between response sets and between rule sets. This suggests that in the current study, the medial frontal activations are attributable to the selection process that requires resolution of conflict between several equipotent responses, rather than the switch of action or rule per se. Indeed, the effects of repetitive transcranial stimulation of dorsal medial prefrontal cortex suggest that the pre-SMA may be necessary to resolve conflict between responses (Taylor et al. 2007), including the conflict that arises when there are ambivalent responses, as in the free-selection of actions.

Although the current study was motivated by accounts of prefrontal cortical function, we also found coactivation of parietal cortex with selection. Activation of the supramarginal gyrus has been noted before with free-selection of responses (Rowe et al. 2005; Wiese et al. 2005) as has adjacent intraparietal cortex (Frith et al. 1991; Hyder et al. 1997; Lau et al. 2004). Together with medial and lateral prefrontal cortical areas above, these areas are activated with many cognitive demands (Duncan and Owen 2000; Duncan 2001, 2006) resembling a distributed "workspace" (Dehaene et al. 1998). However, coactivation does not prove a similar function in separate regions. Despite the neurophysiological similarities between these regions (Chafee and Goldman-Rakic 1998, 2000; Nieder and Miller 2004; Stoet and Snyder 2004) there is some evidence of dissociation of functions in cognitive control. For example, the medial prefrontal cortex, but not lateral prefrontal cortex or parietal cortex, may be more associated with decision making in the face of uncertainty (Grinband et al. 2006). In addition, the parietal cortex and medial frontal cortex have subtly different roles when there is conflict between stimulus based responses (Kerns et al. 2004; Liston et al. 2006) even though both influence lateral prefrontal cortex for subsequent decisions.

Our main aim was to test the hypothesis that rule-selection and action-selection have spatially distinct activations in lateral

prefrontal cortex. Specifically, we proposed that rule-selection be mediated by more rostral lateral prefrontal cortex and interconnected parietal cortex, whereas action-selection be mediated by more caudal prefrontal cortex, premotor regions and their parietal connections. Our data do not support this hypothesis, even if we reduce the statistical thresholds to look for weak evidence of spatially distributed differences between rule- and action-selection in the frontal cortex.

An alternative explanation supported by our data is that the same neurons and the same regions adapt their function for different tasks, including both rule-selection and action-selection. The adaptive coding model of prefrontal cortical function (Duncan 2001) emphasizes the ability of neurons to encode specific objects (rules, actions, percepts) within one context, but to be able to change to encode other specific objects (rules, actions, percepts) in another context (Rao et al. 1997; Freedman et al. 2001). Because premotor and prefrontal cortical neurons in monkeys can encode both abstract rules and specific actions, in separate studies, it is possible that individual neurons can encode either rules or actions according to the current task demands. Duncan's hypothesis can also be extended to the parietal cortex, which in imaging and neuropsychological studies has similar roles to prefrontal cortex in a distributed network for multiple cognitive tasks (Dehaene et al. 1998) despite the electrophysiological differences in response to lesions or cooling (Quintana et al. 1989; Fuster 1997). This is again supported by our results, with similar activations of supramarginal parietal cortex in rule- and action-selection.

Similar imaging results would be obtained if the rostral and caudal regions each contain a balance of intermixed rule-, action-, and both-selective cells, analogous to the rule-, object-, and both-selective neurons across monkey prefrontal cortex (Wallis *et al.* 2001). Our paradigm is not able to exclude this latter possibility, although adaptation paradigms with fMRI might in principle be able to do so. However, at a regional or systems level our data support the hypothesis that the prefrontal cortex and the supramarginal gyrus are capable of adapting their function according to the demands of both rule-selection and action-selection. This implies that even functions that may be considered to be hierarchically organized in cognitive terms (Norman and Shallice 1980; Miller and Cohen 2001) like selection of rules for action and selection of actions themselves, are not necessarily organized with a corresponding large scale spatial hierarchy across prefrontal regions.

The rostral, caudal, and medial prefrontal regions showed similar activation for rule-selection and action-selection. The parsimonious explanation is that these diverse regions have a common function or adapt functions in line with each other, perhaps supported by adaptive coding properties of neurons in each area. However, the reasons for overlap between action- and rule-selection in each area may be different. The contrast between selection and specified trials we have examined could include several cognitive processes including conflict detection (Kerns et al. 2004; Ridderinkhof et al. 2004), set-switching (Brass and von Cramon 2002; Rushworth et al. 2002, 2003), and selection of responses by provision of top-down bias between competitive effectors (Rowe et al. 2005). These processes in addition to adaptive coding may account for overlap in some areas but not others.

In view of the previous reports of prefrontal rostro-caudal functional gradients (Koechlin et al. 2003; Koechlin and Jubault 2006) we must consider other possible explanations of our results. First, that subjects may have performed a similar task despite different instructions. This is not supported by behavioral or imaging data. The RTs across different modalities and different target numbers were the same for specified and chosen rules. More importantly, the effects of congruency indicate that by the time of target presentation, a rule had been chosen and subjects did not "wait and see" when they were asked to choose a rule at the first cue. Had subjects merely waited for targets to appear, the congruency effect on RT would not be the same for the chosen and specified conditions, as was the case. One might argue conversely that when no-rule was specified, subjects nonetheless chose a rule and applied this when the response cue appeared. However, they had no means of knowing how many targets would appear with the response cue. In addition, one can see from Figure 3*F* versus Figure 3*A* or Figure 3*B* that the choice of a target by application of a rule is very different in its neural correlates from selection of a rule to guide later actions. Furthermore, the argument that subjects had selected a rule in advance even on nominal no-rule trials could not easily be applied to experiment 3 or other action-selection studies which made no reference to rule choices in training or scanning. Therefore, although free-selection of actions may be made with some frame of reference, this frame of reference is not the rules systems used in the other trials in these paradigms.

Second, that there may be a spatially distributed hierarchy, but one that we have not been able to demonstrate. This might arise if the hierarchy had complex temporal dynamics. For example, there is electrophysiological evidence that rule signals in premotor populations can occur *earlier* than in prefrontal cortex (Wallis and Miller 2003) undermining the concept of a simple spatially distributed hierarchy with a rostro-caudal gradient of influence. It is possible therefore that rule-selection has a rostro-caudal flow of influence, but this is matched in action-selection by a caudal–rostral flow if information about the selected actions. With the resolution of MRI, rule- and action-selection would then appear similar. Other neuroimaging methods with superior temporal resolution like magnetoencephalography or event-related potential would be required to explore this alternate hypothesis.

We may also have had insufficient power to detect a spatially distributed hierarchy. The similarity of different SPM{*t*} results is indicated partly by the colocalization of regional activations, but also the similarity of magnitude of effects, for example lack of difference between different images such as Figure 3*C*. The latter calls into question the power of the study to detect activations and activation differences. We believe that our study had good power to detect differences, based on simulation and empirical studies of cognitive and motor tasks, given the relatively large group of 20 subjects; a secondary threshold of $P < 0.001$ uncorrected; the low intersubject variance afforded by young healthy volunteers; smoothing at 10 mm, and magnitudes of BOLD differences between 0.25% and 0.5% as shown in Figure 4 (Desmond and Glover 2002; Murphy and Garavan 2004; Mumford and Nichols 2007; Thirion et al. 2007). However, we prioritized control of type I error over control of type II error and acknowledge the possibility of false negative results.

Could our difficulty showing a spatially distributed hierarchy be because we used fully intermixed event-related designs in

experiments 1 and 2? Event-related and block designs have different implications for selection processes and different requirements for optimal model efficiency. In event-related designs the choice of action, its preparation, and execution are temporally aligned. In contrast, block designs allow selection and preparation of responses in advance. There are in addition hybrid event/block designs (Braver et al. 2003; Dosenbach et al. 2006) that can distinguish sustained activations from transient events, event within the same region. For example, during rule-based tasks with their correct/incorrect answers, the medial and lateral prefrontal cortex (but not parietal cortex) show a combination of sustained activity during task-blocks but also phasic responses to error events (Dosenbach et al. 2006). By allowing repeated responses of a similar type (say action-selections rather than rule-selections) block designs may encourage the monitoring of recent responses and making choices weighted in relation to these recent events. In block designs, it has been shown that tonic rather than phasic models are better predictors of lateral prefrontal cortical activation (Wiese et al. 2005) and seem to be more sensitive. In related studies of choice of "when" to move a finger, rather "which" finger, block designs have also shown activation of lateral prefrontal cortex (Jahanshahi et al. 1995; Jenkins et al. 2000). In contrast, a sparse event-related design of repeated choice trials did not identify phasic activations of prefrontal cortex associated with choice (Wiese et al. 2004) perhaps because of sustained monitoring processes between trials. Experiment 3 (Rowe et al. 2005) had used a block design but with shorter intervals (4 s). It would be possible to present rule-selection trials in predictable blocks. We predict that some of the selection related activation would in that case become dissociated from the rule cues in this case and different models needed to optimally analyze the data. However, our model was appropriate for the type of event-related design used, and we suggest that the intermixed event types reduced selection in advance of trials.

In summary, our data did not support spatially distributed hierarchies in parietal and prefrontal cortex, mediating the selection of rule- then action-representations. In the context of rules and actions underlying voluntary behaviors our data support the alternative hypothesis that the adaptive coding properties of neurons in prefrontal and parietal cortex result in similar patterns of brain activations for rule-selection and action-selection. This could be tested in future using the higher temporal resolution of magnetoencephalography to detect differences between the rostral and caudal prefrontal loci, looking for a reversal of gradient between action and rule-based selection tasks.

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Notes

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