

## On the Programming and Reprogramming of Actions

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**Actions are often selected in the context of ongoing movement plans. Most studies of action selection have overlooked this fact, implicitly assuming that the motor system is passive prior to presentation of instructions triggering movement selection. Other studies addressed action planning in the context of an already present motor plan, but focused mostly on inhibition of a prepotent response under fierce time pressure. Under these circumstances, inhibition of previous motor plans and selection of a new response become temporally intermingled. Here, we explore how the presence of earlier motor plans influences cerebral effects associated with action selection, separating in time movement programming, reprogramming, and execution. We show that portions of parietofrontal circuits, including intraparietal sulcus and left dorsal premotor cortex, are systematically involved in programming motor responses, their activity being indifferent to the presence of earlier motor plans. We identify additional regions recruited when a motor response is programmed in the context of an existing motor program. We found that several right-hemisphere regions, previously associated with response inhibition, might be better characterized as involved in response selection. Finally, we detail the specific role of a right precentral region in movement reprogramming that is involved in inhibiting not only actual responses but also motor representations.**

**Keywords:** fMRI, inhibition, motor intention, motor preparation, response switching

### Introduction

Several studies have addressed the issue of how the goal of an action, the relevant effector, and timing information are integrated into an appropriate motor plan (Toni et al. 2001; Andersen and Buneo 2002; Thoenissen et al. 2002; Hesse et al. 2006; Rushworth and Taylor 2006). This issue has been mainly addressed by assuming that the brain is an input-output device that processes sensory material to generate motor responses; this reflex-like process being set in motion by the presentation of a sensory trigger (Glimcher 2003). However, it is known that motor areas are affected by preparatory processes (Crammond and Kalaska 2000), and visual areas are affected by expectations (Engel et al. 2001), as well as ongoing intrinsically generated activity (Kenet et al. 2003). Accordingly, it has been suggested that it might be more appropriate to consider the brain as mainly driven by its own self-sustained internal dynamics (Friston 2005), and by occasional samples of the environment (Bullier 2001; VanRullen and Koch 2003).

These considerations imply that actions are often selected in the context of ongoing preparatory activity for potential responses (Thoenissen et al. 2002). There have been several studies on the planning of actions in the context of an already

present motor plan, and these studies have used countermanding, go/no-go, and stop tasks (Garavan et al. 1999; Curtiss et al. 2005; Li et al. 2006). The focus of these types of studies has been on the mechanisms supporting movement inhibition, and a number of studies have implicated a predominantly right-lateralized cerebral circuit, involving the right inferior frontal gyrus (Garavan et al. 1999; Aron et al. 2004), the right inferior parietal cortex (Garavan et al. 1999; Liddle et al. 2001), the presupplementary motor area (pre-SMA; Nachev et al. 2005), and the striatum (Vink et al. 2005).

However, inhibition of a prepotent response, under fierce time pressure, is likely to be accompanied by other concurrent phenomena, such as the selection of a new motor plan, and the implementation of the new response. Previous studies have accounted for these effects by relying on subtractive methods (Donders 1969), that is, by assuming that they add linearly, but this assumption is unlikely to hold (Sternberg 1969; Friston, Price, et al. 1996). Furthermore, putting time pressure on movement selection at the time of reprogramming motor actions is likely to emphasize response conflict, due to the presence of multiple motor programs competing for access to the execution system (Botvinick et al. 2001; Nieuwenhuis et al. 2003), rather than capturing the interplay between an external instruction and the intrinsic dynamic of the brain. In the current study we circumvent this problem by employing an experimental design that allows the partitioning of variance related to different within-trial events in separate regressors.

In this study we explore how the presence of earlier motor plans influences cerebral effects associated with action selection and preparation, separating in time the original movement programming, the movement reprogramming, and the actual movement execution. We address this issue in the context of arbitrary combinations of instructions and movements, that is, flexible mappings that do not need to rely on spatially or temporally congruent sensorimotor associations (Passingham 1993; Passingham et al. 1998; Wise and Murray 2000).

### Materials and Methods

#### Participants

Eleven right-handed volunteers (3 males, age range 19–29 years) with normal or corrected-to-normal vision participated in this study. Participants gave written informed consent according to institutional guidelines of the local ethics committee (CMO region Arnhem-Nijmegen, Netherlands) and were paid 20 euros for their participation.

#### Experimental Setup

During the scanning session, participants lay supine in the scanner. Head movements were minimized by an adjustable padded head holder. Visual stimuli covered a visual angle of approximately 6° and were projected

onto a mirror above the participants' heads. Motor responses were recorded via a magnetic resonance-compatible keypad (MRI Devices, Waukesha, WI), positioned on the right side of the participant's abdomen. Stimulus presentation and response collection were controlled by a computer running Presentation 0.81 (Neurobehavioral Systems, San Francisco, CA).

### Behavioral Procedure

The experiment consisted of a training session (45 min) and a scanning session (1 h, including acquisition of structural scan). During the training session, participants were first trained on a delayed response task on trials with the following structure (Fig. 1*B*—NORMAL trials). Participants were presented with 1 of 4 visual shapes at the center of the screen (instruction cue [IC<sub>normal</sub>]). Two shapes instructed one response (flexion-extension of the index finger of the right hand), the other 2 shapes instructed another response (flexion-extension of the middle finger of the right hand—Fig. 1*A*). After the IC<sub>normal</sub> was displayed for 300 ms, it was replaced with a central fixation cross, which remained on screen for the duration of the trial. Following a variable delay (1000–5000 ms) a tone (trigger cue [TC<sub>normal</sub>], 300 ms) instructed the participants to provide the response specified by the IC<sub>normal</sub>. Visual feedback, consisting of a green "V" or a red "X," was presented for 200 ms immediately after the response. The visual feedback allowed the participants to learn the appropriate stimulus-response mappings by trial and error. Participants were required to execute the instructed response as fast as possible following the TC<sub>normal</sub>. If participants did not respond within an 800-ms deadline, a "too late" feedback was presented. This procedure ensured that on these trials the participants prepared the response during the variable delay.

Following 40 trials of this type, we introduced neutral trials, in which the IC<sub>neutral</sub> (a question mark) did not specify the movement to be executed in that trial. In this condition, the shape instructing the correct response was presented simultaneously with the tone trigger (TC<sub>neutral</sub>—Fig. 1*C*). This procedure ensured that the participants were discouraged from preparing a response during the variable delay.

Following 40 practice trials, we introduced SWITCH trials. These trials were identical to NORMAL trials, except that during the variable delay a new IC (IC<sub>switch</sub>, Fig. 1*D*) could have been presented (300 ms). Presentation of the IC<sub>switch</sub> instructed the participants to discard the instruction provided by the IC<sub>normal</sub> (at the beginning of that trial) and prepare the response specified by the IC<sub>switch</sub>. The trial distribution was

such that NEUTRAL and SWITCH trials occurred on approximately 15% of the trials each. Furthermore, on approximately 15% of the SWITCH trials, multiple switches occurred (Fig. 1*E*).

Following an additional 192 practice trials, participants entered the scanner. During the scanning session, they performed 225 trials of the same task as performed during the last phase of the practice, except that performance feedback was no longer provided. Participants were told before the experimental session that there would be no more feedback but that the task instructions were the same. Because there was no feedback, participants did not receive too late feedback for slow responses. Therefore, unknown to the participants, no reaction time (RT) deadline was enforced during the scanning session. An extensive range of variable delays between ICs and TCs (see Experimental Timing) ensured that the participants were ready to respond at any time after the presentation of the instruction cue (Toni, Thoenissen, et al. 2002). Furthermore, by presenting the IC<sub>switch</sub> at unpredictable moments during a small (15%) percentage of the trials, we ensured that it was advantageous for the participants to prepare a response whenever possible. Crucially, by comparing the RTs evoked by normal and neutral trials during the scanning session, we could determine whether participants complied with our expectations and prepared their response when possible.

### Behavioral Data Analysis

Mean response times for correct trials (RT) and percent correct (PC) trials measured during the scanning session were analyzed separately and considered as dependent variables in a repeated-measures analysis of variance (ANOVA). Participants were considered as a random factor. The alpha-level was set at  $P = 0.05$ , univariate approach, Greenhouse-Geisser corrected.

### Image Acquisition

Images were acquired using a 3T Trio scanner (Siemens, Erlangen, Germany). Blood oxygen level-dependent (BOLD) sensitive functional images were acquired using a single-shot gradient echo-planar imaging (EPI) sequence (time repetition/time echo 2.430 s/40 ms, 33 transversal slices, ascending acquisition, voxel size 3.5 × 3.5 × 3.5 mm). Following the experimental session, structural images were acquired using an MP-RAGE sequence (time repetition/time echo/time to inversion 2.3 s/3.93 ms/1100 ms, voxel size 1 × 1 × 1 mm).

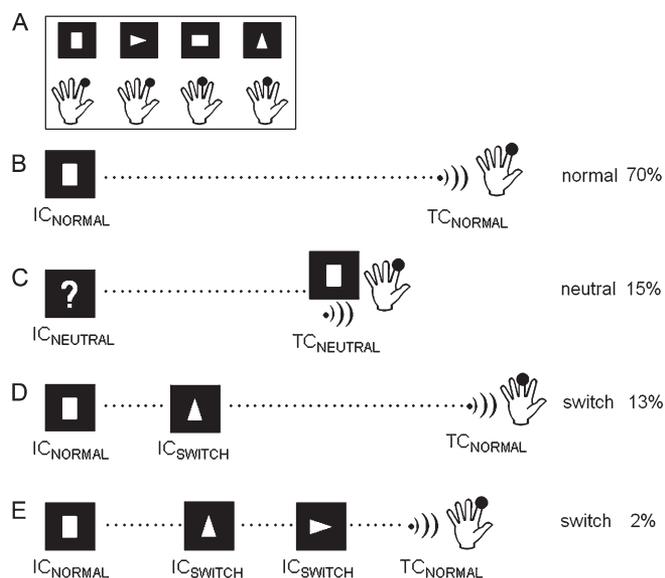
### Experimental Timing

Delays between ICs and TCs, both within and between trials, varied between 1.5 and 16 s (right-skewed distribution), such that the occurrence of trial events and onsets of functional magnetic resonance imaging (fMRI) volumes were not synchronized. This procedure enabled us to homogeneously characterize the hemodynamic responses at a finer temporal resolution than the actual time repetition (Josephs et al. 1997; Price et al. 1999) and to characterize the BOLD responses evoked by different events within the same trial (Toni et al. 1999; Mars et al. 2005). Prior to the experiment, simulations were run to determine the optimal range and distribution of delay lengths and trial order, such that the correlations between the different model regressors was sufficiently low to enable a reliable estimation of the hemodynamic responses. The same distributions were used for determining the interstimulus interval between all different types of stimulus events during the whole experiment.

This approach relies on the assumption that the BOLD responses to subsequent events summate in an approximately linear fashion. Although there is evidence that this assumption holds in the visual cortex (see Rosen et al. 1998 for a review), the extent to which this assumption holds has not been established for the entire cortex. However, our average stimulus-onset asynchrony was more than 5 s for each participant, which is above the 3–4 s that is considered to mark the boundary between linear and nonlinear regimens of the neurovascular couplings to successive events (Vazquez and Noll 1998).

### Image Analysis and Statistical Inference

Functional data were preprocessed and analyzed using SPM2 (statistical parametric mapping, <http://www.fil.ion.ucl.ac.uk/spm>). The first 5 volumes of each participant's data set were discarded to allow for  $T_1$



**Figure 1.** Experimental task. (*A*) Stimulus–response mappings learned during the training session prior to the scanning session. During the scanning session, trials from the normal (*B*), neutral (*C*), and switch (*D*, *E*) condition were presented randomly intermixed. Visual stimuli were presented for 300 ms each. During the variable delay intervals, a fixation cross was presented. An auditory trigger cue signaled participants to execute the instructed response.

equilibration. The image time series were spatially realigned using a sinc interpolation algorithm that estimates rigid-body transformations (translations and rotations) by minimizing head movements between each image and the reference image. The time series for each voxel were realigned temporally to acquisition of the middle slice. Subsequently, images were normalized onto a custom Montreal Neurological Institute (MNI)-aligned EPI template (based on 28 male brains acquired on the Siemens Trio scanner at the F.C. Donders Centre) using both linear and 16 nonlinear transformations and resampled at an isotropic voxel size of 2 mm. Finally, the normalized images were spatially smoothed using an isotropic 8-mm full-width-at-half-maximum Gaussian kernel. Each participant's structural image was spatially coregistered to the mean of the functional images and spatially normalized using the same transformation matrix as applied to the functional images.

The fMRI time series were analyzed using an event-related approach in the context of the general linear model. Statistical models for each participant's data included separate regressors for the different instruction cues ( $IC_{\text{normal}}$ ,  $IC_{\text{neutral}}$ ), trigger cues ( $TC_{\text{normal}}$ ,  $TC_{\text{neutral}}$ ), and switch cues ( $IC_{\text{switch}}$ ). Thus, we created separate regressors for individual trial events, rather than creating regressors modeling activity during whole trials simultaneously. Thus, our statistical model does not capture variance resulting from all events within trials of different conditions, but rather variance due to different events within any one trial. This approach does not rely on the assumption that there are no interactions between the component of interest and the other task-related neural processes (Friston, Price, et al. 1996). Incorrect responses and trials in which no response occurred were taken into account in separate regressors. Each of these functions was then convolved with a canonical hemodynamic response function and its temporal derivative (Friston et al. 1998) and downsampled at each scan in order to generate regressors modeling the main effects described above. Separate covariates including trials with incorrect or missing responses, head-related movements (as estimated by the spatial realignment procedure) and their first derivatives, and a constant term over scans were also considered in the model. Furthermore, we also included terms describing the average white matter intensity and cerebrospinal fluid intensity as extracted from the EPI time series following a standard segmentation procedure. These regressors were meant to capture scan-by-scan variations in global signals unconfounded by task-related BOLD changes (Verhagen L, Grol MJ, Dijkerman HC, Toni I, unpublished data). Data were high-pass filtered (cut-off 500 s) to remove low-frequency confounds, such as scanner drifts.

The statistical significance of the estimated evoked hemodynamic responses was assessed using *t*-statistics in the context of a multiple regression analysis. Contrasts of the parameter estimates for the main effects of all correct trial events were calculated and entered into a 1-way, repeated-measures ANOVA treating subjects as a random variable (Friston et al. 1999) and correcting for nonsphericity at each voxel. We report the results of a random-effects analysis, with inferences drawn at the voxel level, corrected for multiple comparisons using the familywise error correction ( $P < 0.05$ ) (Friston, Holmes, et al. 1996). The effective degrees of freedom of the error term took into account the temporal autocorrelation of the data (Friston et al. 1995).

We isolated both differential hemodynamic responses (indicated by “>”) and common hemodynamic responses (indicated by “∩”). The differential effects were identified by testing the null hypothesis that there was no effect in the statistical parametric map (SPM) of the *t*-statistics describing the difference between the variance explained by 2 given regressors (*t*-contrasts). The common responses were identified by testing the null hypothesis that there was no effect in any of the 2 constituent SPMs (Nichols et al. 2005). Specifically, we assessed the spatial distribution of the following effects.

- We isolated responses evoked by selecting a motor response on the basis of a visual instruction cue. These constraints were implemented in the following contrast:  $[(IC_{\text{normal}} > 0) \cap (IC_{\text{switch}} > 0) \cap (TC_{\text{neutral}} > 0)]$ .
- We isolated responses evoked by selecting a motor response in the context of ongoing preparatory activity, over and above the responses evoked by selecting a response per se. These constraints were implemented in the following contrast:  $IC_{\text{switch}} > IC_{\text{normal}}$ .

We then controlled for a series of potential confounds by limiting the search of effect within the effects revealed by other contrasts. To control for potential effects of differential frequency of  $IC_{\text{switch}}$  and  $IC_{\text{normal}}$ , the effects isolated by our contrast were masked by the contrast  $IC_{\text{switch}} > IC_{\text{normal}}$ . Because the  $IC_{\text{neutral}}$  and  $IC_{\text{switch}}$  are equally frequent, any differential activation identified by this masking contrast cannot be due to a frequency effect.

To further ensure that the effects isolated by the contrast were confined to regions specifically interested in movement selection, we also masked by the contrast  $[(TC_{\text{neutral}} > IC_{\text{neutral}}) > (TC_{\text{normal}} > IC_{\text{normal}})]$ . This mask identifies cerebral voxels involved in selecting a movement following presentation of a visual instruction ( $TC_{\text{neutral}}$ ,  $IC_{\text{normal}}$ ), over and above the presentation of a visual (noninformative) stimulus ( $IC_{\text{neutral}}$ ), as well as the presentation of auditory cues and the execution of the response ( $TC_{\text{normal}}$ ).

- Finally, to distinguish reprogramming effects from increased attention to action, effect *b* was masked by  $IC_{\text{switch}} > TC_{\text{neutral}}$ . This mask identifies cerebral voxels involved in reprogramming a movement ( $IC_{\text{switch}}$ ), over and above the increase attention to action that can arise when selecting a response under time pressure ( $TC_{\text{neutral}}$ ).

The masking procedures outlined above identify voxels involved in the contrast of interest over and above the effects in the masks. With this procedure, the search space of the contrast is constrained to those voxels that conform to a series of desired characteristics (as indicated by the mask) that might not be captured by a single contrast between explanatory variables of the design matrix. The presence of the mask does not alter the *P* value of the contrast of interest but only allows those voxels that show a significant effect in the masking condition to be displayed in the contrast of interest.

### Anatomical Inference

Anatomical details of significant signal changes were obtained by superimposing the SPMs on the structural images of each participant in MNI space. The atlas of Duvernoy et al. (1991) was used to identify relevant anatomical landmarks. When applicable, Brodmann areas were assigned on the basis of the SPM Anatomy Toolbox (Eickhoff et al. 2005), that is, the anatomical position of our significant clusters and local maxima was formally tested against published 3-dimensional probabilistic cytoarchitectonic maps.

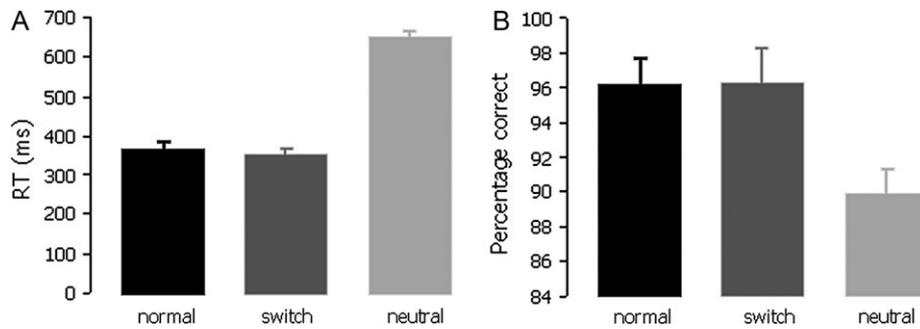
## Results

### Behavioral Results

Behavioral data obtained during the scanning session are summarized in Figure 2. Separate ANOVAs on the reaction times on correct trials (RT) and the percent correct (PC) revealed an effect of task condition on both the RT ( $F_{2,20} = 338.7, P < 0.001$ ) and PC ( $F_{2,20} = 12.2, P = 0.004$ ). Planned paired *t*-tests revealed that reaction times were longer and PC was lower in the neutral conditions, whereas behavior on the normal and switch trials was identical, both with respect to RT ( $t_{10} = 1.7$ , not significant [NS]) and PC ( $t_{10} = -0.2$ , NS). These data indicate that participants were similarly prepared to respond in the normal and switch conditions, whereas, as predicted, no preparation was possible in the neutral condition.

### Imaging Results—Programming Actions

All imaging results are listed in Table 1. We first identified regions showing consistent responses evoked by selecting a motor response on the basis of a visual instruction cue [contrast *a*,  $(IC_{\text{normal}} > 0) \cap (IC_{\text{switch}} > 0) \cap (TC_{\text{neutral}} > 0)$ ]. This effect was confined to the ventral visual pathway (bilaterally), the posterior parietal cortex, the left precentral gyrus, and the mesial superior frontal gyrus. Formal tests against published probability maps (Eickhoff et al. 2005) indicated that 94% of the left precentral cluster falls within the probabilistic boundary



**Figure 2.** Behavioral data. Reaction times for correct trials (A) and PC responses (B) in the 3 experimental conditions, obtained during the scanning session. Error bars reflect  $\pm$  standard error of the mean.

**Table 1**

Imaging results

Anatomical region	MNI coordinates			<i>t</i> value
	<i>x</i>	<i>y</i>	<i>z</i>	
$(IC_{normal} > 0) \cap (IC_{switch} > 0) \cap (TC_{neutral} > 0)$				
Frontal lobes				
Left superior frontal sulcus	-30	-8	64	7.43
Mesial superior frontal gyrus	0	8	52	7.09
Parietal cortex				
Left anterior intraparietal sulcus	-44	-38	44	9.46
Left posterior intraparietal sulcus	-26	-62	40	7.06
Right posterior intraparietal sulcus	32	-54	44	6.27
Occipital/temporal				
Right ventral visual pathway	34	-48	-30	9.46
Left ventral visual pathway	-40	-62	-30	6.08
$IC_{switch} > IC_{normal}$ masked by $(IC_{switch} > IC_{neutral}) \cap (TC_{neutral} > IC_{normal}) > (TC_{normal} > IC_{normal})$				
Frontal lobes				
Left frontal operculum/insula	-42	20	-10	7.16
Right inferior frontal gyrus	60	18	2	7.76
Right precentral gyrus*	42	0	42	6.69
Right insula	32	20	-16	6.69
Parietal cortex				
Left supramarginal gyrus	-52	-48	40	7.15
Right supramarginal gyrus/inferior parietal lobule	54	-44	48	8.98
Subcortical				
Caudate nucleus	16	-4	6	5.99

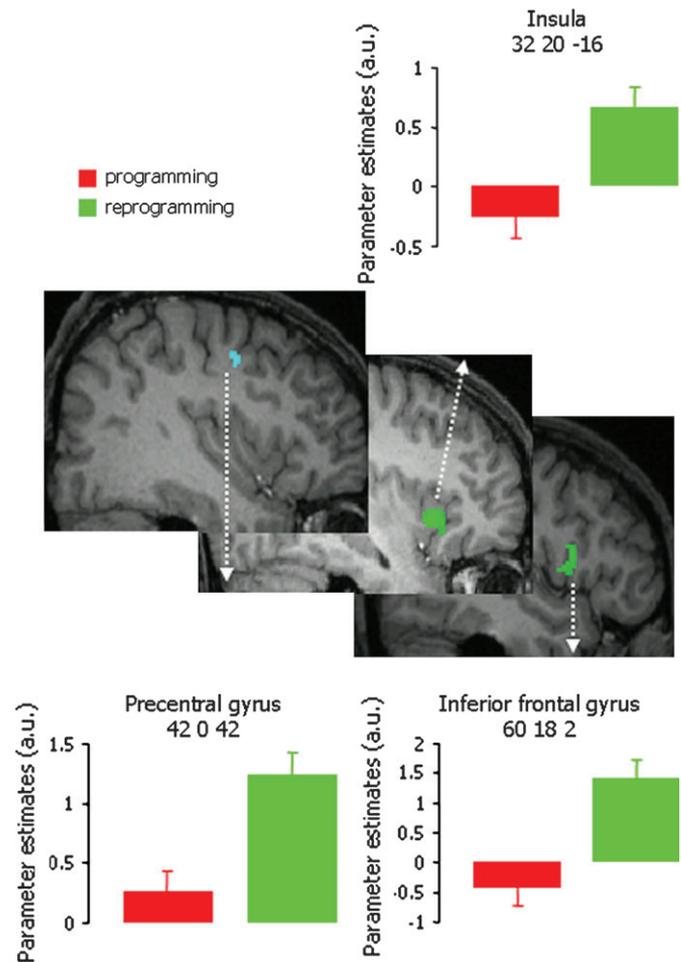
Note: Anatomical specification, MNI coordinates, and *t* values of clusters identified by the programming and reprogramming contrasts. The cluster labeled with asterisk survives further masking by the contrast  $IC_{switch} > TC_{neutral}$ .

of BA6, and we could label it as dorsal premotor cortex. The cluster in the mesial superior frontal gyrus also falls within BA6 (probability 70%), and we could label it as pre-SMA (Picard and Strick 1996).

Figure 4 illustrates how the 3 parietal clusters were located in both the superior and inferior portion of this region (viz., in the left anterior and posterior intraparietal sulcus and in the right posterior intraparietal sulcus). These regions responded whenever a movement needed to be selected, that is,  $IC_{normal}$ ,  $IC_{switch}$ , and  $TC_{neutral}$ .

### Imaging Results—Reprogramming Actions

Regions specifically activated in response to the switch cues, over and above the effects associated with the instruction cues, are listed in Table 1 (contrast *b*,  $IC_{switch} > IC_{normal}$ ). In the right hemisphere, there were clusters around the right insula (extending into the right inferior frontal gyrus), in the right inferior frontal gyrus (assigned to BA44/45; Amunts et al. 1999) and in the right precentral gyrus (BA6 border—Fig. 3). On the



**Figure 3.** Imaging data—right frontal cortex. Anatomical location (SPM[*t*]s of the contrasts detailed in Table 1, overlaid on spatially normalized anatomical sections of 1 participant) and parameter estimates ( $\pm$ 90% confidence interval boundary) of right frontal clusters activated during reprogramming. The cluster in cyan is the only cluster surviving a more constrained contrast ( $IC_{switch} > TC_{neutral}$ , see main text for details).

left side, a cluster was found along the left inferior frontal gyrus, extending into the left insula. Additionally, the left supramarginal gyrus and the right supramarginal gyrus and inferior parietal lobule were also activated preferentially in response to the switch cues.

Given that, following the presentation of  $IC_{switch}$ , the participants needed to select and potentially execute a response

within a short period of time, it could be argued that the activity of the regions identified by contrast *b* was a mixture of switch-related effects and increased attention to action associated with selecting a response under time pressure. To disambiguate this mixture of effects, we masked contrast *b* with ( $IC_{\text{switch}} > TC_{\text{neutral}}$ ). Following this additional constraint, only a right precentral cluster (42 0 42) revealed a specific switch-related effect (Fig. 3).

We did not find any regions that showed more activation in response to the informative instructional cues ( $IC_{\text{normal}}$ ) than in response to the switch cues ( $IC_{\text{switch}}$ ).

## Discussion

We isolated cerebral activity evoked by selecting a movement in the context of an already present motor plan while controlling for the effects of processing sensory instructions, executing motor responses, and the nonlinear interactions (e.g., response conflict) that could arise when these processes occur in close temporal proximity.

We confirm the involvement of a distributed parietofrontal system in preparing motor responses (Toni et al. 2001; Rushworth et al. 2003), showing that portions of intraparietal and dorsal precentral cortex are fundamental for selecting responses on the basis of a sensory trigger according to arbitrary visuomotor associations. Crucially, we also illustrate how the contribution of these parietofrontal circuits is embedded in a larger cerebral network when a new motor program needs to be selected in the context of ongoing preparatory activity for potential responses.

### Behavioral Performance

Behavioral data indicate that our design was successful in inducing the participants to prepare a motor response after receiving an instruction. Participants responded faster and more accurately on normal and switch trials than on trials where they could not prepare the response in advance of the trigger cue (neutral trials). Because the participants could not predict the temporal occurrence of the trigger cue that followed the presentation of a switch cue and given that participants' responses during normal and switch trials were indistinguishable, we infer that the switch cue induced the participants to abort the ongoing preparatory process and to select a new motor program. Furthermore, because participants are equally prepared at the time of the trigger cue in both switch and normal trials, this justifies modeling the activity associated with the trigger cues in these 2 trial types in a single regressor ( $TC_{\text{normal}}$ ).

### Frontal Cortex

We found that specific portions of the left dorsal precentral cortex and pre-SMA were similarly activated following the presentation of visual cues specifying the selection of a particular response. These regions revealed the same activity when a movement program was established at the time of movement execution ( $TC_{\text{neutral}}$ ), long before movement execution ( $IC_{\text{normal}}$ ), or in the context of an ongoing preparatory process ( $IC_{\text{switch}}$ ). In other words, the left dorsal precentral cortex was active every time an action needed to be selected. This finding confirms and extends previous reports on the role of dorsal premotor cortex in humans (Toni, Shah, et al. 2002; Amiez et al. 2006), namely, the transformation of a visual instruction cue into the associated movement, according to a learned,

arbitrary rule. Here, we further illustrate the crucial contribution of this region to the visuomotor transformation, its activation being indifferent to the presence of an ongoing motor plan ( $IC_{\text{switch}}$ ) or to the need to respond under time pressure ( $TC_{\text{neutral}}$ ).

The presence of robust pre-SMA activity during each instance in which a motor response had to be programmed indicates that this region is not exclusively engaged during the inhibition of an ongoing response following a "stop" cue (Kelly et al. 2004; Nachev et al. 2005). Rather, pre-SMA is engaged at a higher level of motor programming, dealing with the rules that convert sensory material or intentions into the associated movements (Bunge 2004; Rushworth et al. 2004; Mars et al. 2005). However, given the structure of our task, it could be argued that the effects observed in the pre-SMA are related to task switching (Rushworth et al. 2002; see Lau et al. 2006 for a similar concern). Namely, on approximately half the trials, the instruction cue specified a response that was different from the response executed on the previous trial. It has been shown that in speeded response tasks participants might sometimes adopt a strategy to commit to a certain response even before any explicit instruction has been provided (Gratton et al. 1988). In principle, it is possible that participants might have opted to select the same response provided in the previous trial, even before the presentation of the  $IC_{\text{normal}}$ . In this scenario, the  $IC_{\text{normal}}$  might have included a reprogramming component. To exclude this possibility, we performed a further analysis in which we created a new statistical model for each participant in which the  $IC_{\text{normal}}$  regressor was split up in 2 separate regressors: one capturing  $IC_{\text{normal}}$  cues that specified the same response as executed on the previous trial and one capturing  $IC_{\text{normal}}$  cues that specified another response than was executed on the previous trial. As indicated by the group beta weights, there were no differences in activity between these 2 event types, indicating that our results are not confounded by a switch of task context on certain ICs.

Other frontal regions, mainly localized in the right hemisphere, were particularly responsive at the time the  $IC_{\text{switch}}$  was presented (Fig. 3), that is, during the abortion of the ongoing motor plan and the selection of a new response. A number of these regions where originally identified in the literature as belong to an "inhibition network" consisting of right frontal and right inferior parietal regions (Garavan et al. 1999). Subsequent studies have tried to distinguish the specific contribution of each of these regions in the wider area of cognitive and action control (e.g., Garavan et al. 2003, 2006; Hester et al. 2004; Rubia et al. 2006). The current study allows us to characterize the contribution of these regions to canceling the ongoing motor plan and selecting a new response by formally comparing the responses evoked during  $IC_{\text{switch}}$  and during  $TC_{\text{neutral}}$  (where selection but not inhibition was likely to occur). We found that a majority of these right frontal clusters were also activated following the presentation of  $TC_{\text{neutral}}$  (Table 1, Fig. 3). This finding indicates that these right frontal regions are not specifically involved in inhibition of the current motor plan. Rather, these regions might intervene to support an altered response selection process (Norman and Shallice 1986). This might be the case when a response must be selected in the context of a current motor plan (following  $IC_{\text{switch}}$ ) or when a response has to be selected under fierce time pressure (following  $TC_{\text{neutral}}$ ).

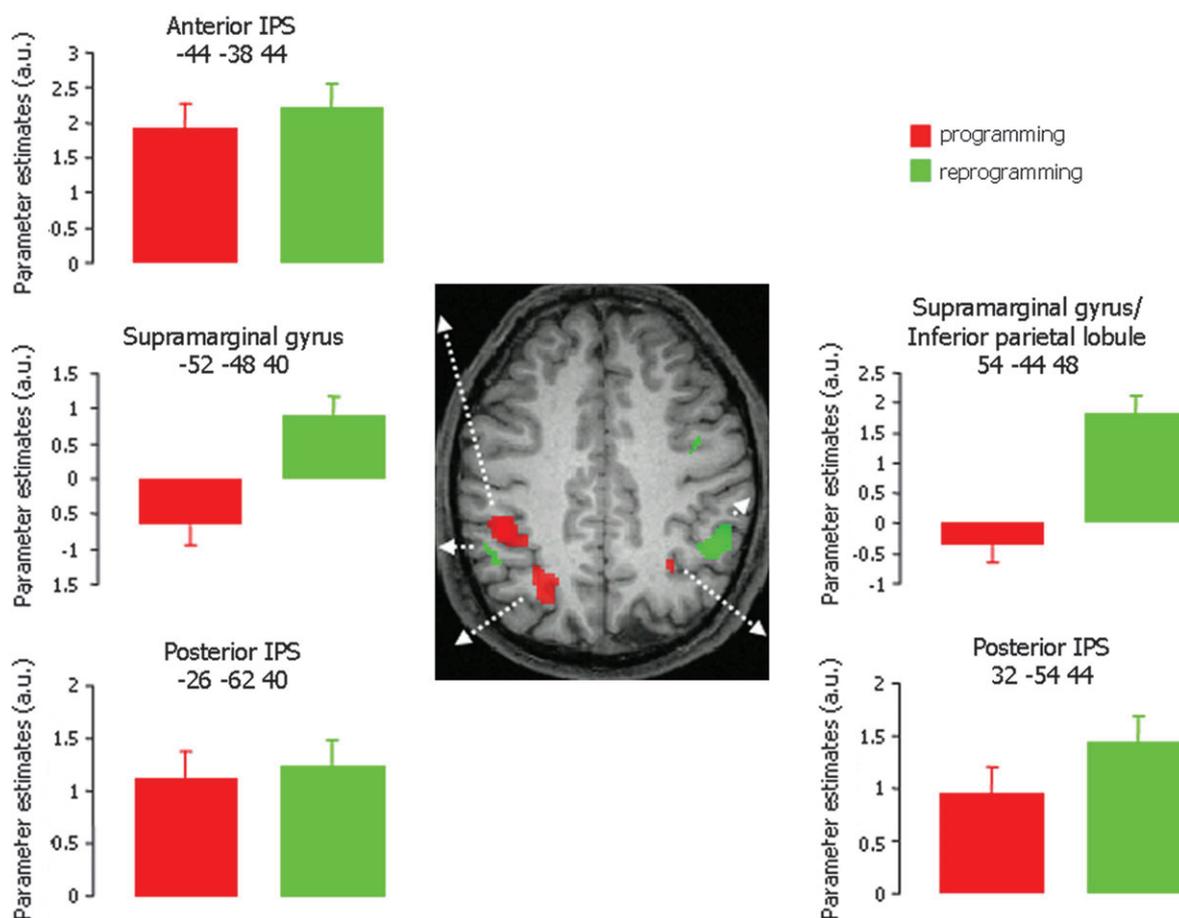
In line with previous work, we also found specific inhibitory responses in the right frontal lobe. There was stronger activity during IC<sub>switch</sub> than during TC<sub>neutral</sub> near (<10 mm) a middle frontal region previously associated with movement inhibition (Garavan et al. 1999). This finding is consistent with the suggestion that this general region is involved in response inhibition (Garavan et al. 1999). However, here we show that this specific inhibitory effect is localized along the precentral gyrus (i.e., premotor cortex) and not in the middle frontal gyrus (i.e., prefrontal cortex). This result fits with previous reports detailing a macroscopic spatial segregation between neuronal clusters involved in mediating suppression and facilitation of neuromuscular responses (Strafella and Paus 2001; Thoenissen et al. 2002). Furthermore, here we show that the inhibitory role of this precentral region is not confined to the execution of a response, but extends to its mental representation, that is, to a motor program held online.

On the left side, we observed a large cluster of activation between the insula and the inferior frontal gyrus. This region was activated in response to both IC<sub>switch</sub> and TC<sub>neutral</sub>. Because the stimulus-response mappings used in the task were well learned and given the corresponding lack of activity following the presentation of IC<sub>normal</sub>, the effects observed at IC<sub>switch</sub> and TC<sub>neutral</sub> are unlikely to be related to the “learning” of arbitrary stimulus-response associations (Passingham et al. 2000). Rather, our findings appear consistent with the role of this region in

selecting the relevant stimulus-response association among a set of ongoing possibilities (Rushworth et al. 2005).

### Parietal Cortex

Whenever a movement had to be selected, there was activity in the posterior intraparietal sulcus, irrespective of whether a motor program was already in place or not. This finding is reminiscent of earlier studies showing activation of posterior parietal cortex during the selection and maintenance of movement representations, independently from the likelihood of their execution (Andersen and Buneo 2002; Thoenissen et al. 2002). Our results also fit with previous fMRI studies showing increased activation of the left parietal cortex when motor sets are changed (Rushworth, Krams, et al. 2001) and transcranial magnetic stimulation (TMS) studies of the left supramarginal gyrus showing interference with the redirection of motor attention (Rushworth, Ellison, et al. 2001). However, these earlier studies did not directly address the question of whether the reprogramming of a motor plan is associated with reactivation of the same posterior parietal regions involved in the initial action selection or with activation of additional clusters. Our results point to the latter scenario: In addition to the parietal regions involved in motor programming, we have isolated an additional region along the left supramarginal gyrus that is specifically recruited during motor reprogramming.



**Figure 4.** Imaging data—parietal cortex. Anatomical location (SPM[t] s of the contrasts detailed in Table 1, overlaid on spatially normalized anatomical sections of 1 participant) and parameter estimates ( $\pm 90\%$  confidence interval boundary) of parietal clusters activated during motor programming (red) and reprogramming (green).

## Hemispheric Lateralization

This study was not designed to explicitly address issues of hemispheric lateralization in movement selection and motor inhibition. For instance, we studied right-handed subjects, asking them to respond with their dominant hand. Yet, it is difficult to avoid noticing that our results point to a left-hemisphere dominance for movement selection, and a right-hemisphere dominance for reprogramming instructed responses. These findings are consistent with previous reports on the dominant role of the left hemisphere in the selection and preparation of arbitrary visuomotor associations (Rushworth, Krams, et al. 2001; Schluter et al. 2001) and a right-hemisphere dominance in inhibitory control (Garavan et al. 1999; Aron et al. 2004). Our results indicate that these right-hemisphere regions are more likely to be involved in response selection processes than in the inhibition of ongoing movements (Fig. 4).

Furthermore, it is possible to speculate that the lateralization pattern observed in this study reflects the different characteristics of selecting and reprogramming an instructed response from a limited set of possible movements. In the current task, whereas the initial movement selection needed to rely on the prelearned and arbitrary mappings between stimuli and responses (Fig. 1), the reprogramming might have relied on a spatial strategy, that is, the selection of the alternative response to the one currently on hold. This hypothesis would predict that the right-hemisphere dominance in reprogramming would disappear once the task would not allow for such a spatial strategy, using, for instance, a larger number of potential responses or nonspatial responses (Brasted et al. 2003).

## Conclusions

In this study, we examined how the presence of existing motor plans affects cerebral activity related to the programming (i.e., selection and preparation) of voluntary actions. We have argued that this experimental setting is more likely to capture the interplay between sensory instructions and the intrinsic dynamic of the brain than a typical stimulus-response paradigm (Fitts and Peterson 1964). We show that portions of parieto-frontal circuits involved in selecting and preparing a motor response on the basis of a visual instruction cue are indifferent to the ongoing activity related to the presence of earlier motor plans. This finding points to the obligatory nature of their involvement in the visuomotor process, at least in the context of the arbitrary stimulus-response mappings used in this study. Furthermore, we identified a number of regions that are additionally recruited when a motor response has to be programmed in the context of an existing motor program. Among these regions, we found that several right-hemisphere areas, previously associated with inhibition of an ongoing motor plan, might be better characterized as being involved in response selection. Finally, we detail the specific role of a right precentral region in movement reprogramming that may involve inhibition not only of actual responses but also of motor representations.

## Notes

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