Cognitive Control Mechanisms Revealed by ERP and fMRI: Evidence from Repeated Task-Switching

R. Swainson, R. Cunnington, G. M. Jackson, C. Rorden, A. M. Peters, P. G. Morris, and S. R. Jackson

Abstract

■ We investigated the extent to which a common neural mechanism is involved in task set-switching and response withholding, factors that are frequently confounded in task-switching and go/no-go paradigms. Subjects' brain activity was measured using event-related electrical potentials (ERPs) and event-related functional MRI (fMRI) neuroimaging in separate studies using the same cognitive paradigm. Subjects made compatible left/right keypress responses to left/right arrow stimuli of 1000 msec duration; they switched every two trials between responding at stimulus onset (GO task—green arrows) and stimulus offset (WAIT task—red arrows). Withholding an immediate response (WAIT vs. GO) elicited an enhancement of the frontal N2 ERP and lateral PFC activation of the right hemisphere, both previously associated with the ''no-go'' response, but only on switch trials. Task-switching (switch vs. nonswitch) was associated with frontal N2 amplification and right hemisphere ventrolateral PFC activation, but only for the WAIT task. The anterior cingulate cortex (ACC) was the only brain region to be activated for both types of task switch, but this activation was located more rostrally for the WAIT than for the GO switch trials. We conclude that the frontal N2 ERP and lateral PFC activation are not markers for withholding an immediate response or switching tasks per se, but are associated with switching into a response-suppression mode. Different regions within the ACC may be involved in two processes integral to task-switching: processing response conflict (rostral ACC) and overcoming prior response suppression (caudal ACC). ■

INTRODUCTION

The suppression of a motor response has been associated with specific electrophysiological and neuroimaging effects. Intracranial recordings in monkeys (Sasaki & Gemba, 1986) show that a negative ''N2'' potential is produced by neurons in the lateral prefrontal cortex (PFC) following stimuli which signal a ''no-go'' response. This potential has been interpreted as indicating the decision to suppress a response, or the implementation of that decision, and has also been recorded from frontal scalp electrodes in human event-related potential (ERP) studies (Jackson, Jackson, & Roberts, 1999; Kopp, Mattler, Goertz, & Rist, 1996; Thorpe, Fize, & Marlot, 1996; Jodo & Kayama, 1992; Nativ, Lazarus, Nativ, & Joseph, 1992; Pfefferbaum, Ford, Weller, & Koppell, 1985). Localization of the no-go potential using magnetoencephalography (MEG) indicates that the likely source of the N2 ERP is the bilateral dorsolateral prefrontal–premotor cortex (Sasaki et al., 1996). Event-related functional MRI (fMRI) studies have indicated involvement of the dorsolateral, ventrolateral, and medial PFC in no-go trials, either lateralized to the right hemisphere (Garavan, Ross, & Stein, 1999; Konishi, Nakajima, Uchida, Sekihara, & Miyashita, 1998) or bilaterally (Liddle, Kiehl, & Smith, 2001; Rubia et al., 2001).

These same electrophysiological and neuroimaging measures elicited on no-go trials have been associated in separate studies with the process of ''task-switching.'' Task-switching usually refers to the situation whereby subjects process target stimuli according to a different rule than was used on the previous trial. For instance, a subject may switch from naming digits in their first language to naming in their second language. We have shown previously that switching languages compared with repeating the same language in a digit-naming study led to increased amplitude of the frontal N2. Switching tasks in other contexts has been shown to activate the dorsolateral, ventrolateral, and medial PFC, as well as the parietal cortex (Monchi, Petrides, Petre, Worsley, & Dagher, 2001; Dove, Pollman, Schubert, Wiggins, & von Cramon, 2000; Kimberg, Aguirre, & D'Esposito, 2000; Sohn, Ursu, Anderson, Stenger, & Carter, 2000; Price, Green, & von Studnitz, 1999; Konishi, Nakajima, Uchida, Kameyama et al., 1998). Switching between alternative tasks is held to involve a process of ''suppression'' upon the currently irrelevant task (upon the cognitive representation of the task rule which may be conceived of as the set of stimulus–response mappings for that task; Meuter & Allport, 1999). Thus, the convergence of the

University of Nottingham

imaging data seems to point towards a common neural mechanism being involved in suppression at two different hierarchical levels: the motor response (in no-go) and the cognitive task (in task-switching). Indeed, switching rules in the Wisconsin Card Sort Test (WCST; cards are sorted according to rules based on color, number, or shape of symbols) activated precisely the same region of the right posterior inferior frontal sulcus as was activated for no-go trials (Konishi et al., 1999).

While championing this common neural substrate account of their data, Konishi et al. (1999) speculated that motor set shifting might have contributed to the no-go dominant activity: The motor set to respond immediately would need to be switched off on no-go trials. In doing so, they described a confound which frequently affects both go/no-go and task-switching studies. The first aspect of this confound is that the need to switch motor set is inherent within a task including mixed go and no-go responses: Many no-go trials follow a go trial (and vice versa) and therefore involve switching of the motor set. In addition, there is usually a built-in bias towards switching from go to no-go. Trial ordering is unpredictable, task instructions often emphasize responding quickly on the go trials, and there is often a high ratio of go/no-go trials; all of these features encourage subjects to treat every trial as if it is likely to be a go trial, an expectation which has to be switched from when the stimulus turns out to signal that an immediate response is not required. Switching (potentially at a number of levels, both motor and cognitive) is therefore tightly bound up with such a design. The other side of the problem is that in a switching task such as the WCST, on many or all trials, the response produced to a given stimulus will differ according to which of the tasks is used, that is, stimuli are ''incongruent'' (for example, ''matching to color'' will involve a different motor response from ''matching to number''). The motor response, which is triggered by the irrelevant task set, may itself require suppression. It can be seen then that the usual method of comparing no-go with go trials, and switch with nonswitch trials, is incapable of cleanly isolating the critical factors of each contrast, particularly given the further potential complication of some interaction between response-suppression and task-switching processes. These problems become crucial when examining the possibility of a shared neural mechanism.

The present study was designed to separate completely the requirement for withholding a motor response from that of switching between task sets. To do this, we designed a novel and very simple behavioral paradigm. Subjects switch predictably between two tasks (with two trials of each task in alternating runs): a GO task requiring an immediate response and a WAIT task requiring the response to be withheld until stimulus offset. A mixed block of trials therefore included switch and nonswitch trial types for each of the GO and WAIT tasks. The essence of this design is that it enables us to study neural activity associated with the withholding of a motor response in isolation from that involved in task-switching and vice versa. Thus, activity which is present on WAIT versus GO nonswitch trials will be associated with response withholding but cannot be due to task-switching; that present on switch versus nonswitch trials for the GO task will reflect task-switching but cannot be attributable to withholding a prepotent response. It is important to note here that behavioral studies of task-switching have indicated that under conditions of predictability, and with long preparation intervals, the cost of switching is borne entirely by the first trial in a run of that task (Rogers & Monsell, 1995); thus, we can be confident that our nonswitch trials will not involve task-switching.

A number of previous studies have described a reasonably consistent network of areas involved when subjects switch repeatedly between alternative tasks. These tend to involve the dorsolateral and ventrolateral PFC, the medial PFC including the supplementary motor area (SMA), the pre-SMA and the anterior cingulate cortex (ACC), and the parietal cortex (Monchi et al., 2001; Dove et al., 2000; Kimberg et al., 2000; Sohn et al., 2000; Price et al., 1999; Konishi, Nakajima, Uchida, Kameyama, et al., 1998). It is important to be clear about the type of switch involved in such studies. When switches occur unpredictably, part of the activity measured will relate to the endogenous, or voluntary, switch subsequent to interpreting the task cue (e.g., red stimuli means speak in French). However, behavioral studies have consistently shown that an intriguingly large cost (often in the order of 50–100 msec) is present for switching compared with repeating the same task even without any contribution from the voluntary switch, that is, when the trial ordering is entirely predictable, or the task cue appears well in advance of the target stimulus, and ample time is given before the next target stimulus appears (Meiran, 1996; Rogers & Monsell, 1995). This residual cost seems to indicate that there is an aspect to switching between alternative modes of processing that is driven ''exogenously'' (it requires a target stimulus to be presented) and which no amount of voluntary processing can eliminate in advance of the stimulus. Relatively few studies have investigated the exogenous switch using ERP or event-related fMRI. Kimberg et al. (2000) identified a network of regions including the SMA, thalamus, occipital cortex, right parietal cortex, and insula, which was more active on switch than nonswitch trials, where switches occurred predictably. Only one area, the left superior parietal lobule, was active solely on switch trials. Sohn et al. (2000) isolated the stimulus-driven switch component on predictable ''foreknowledge'' trials: Upon presentation of the target in this condition, there was switch-related activation in the posterior cingulate (BA 31) and occipital cortex. Both the Kimberg et al. and Sohn et al. studies used a digit- and letter-judgement paradigm, in which two possible responses applied to both tasks—whatever the direction

of the switch, then, a switch trial would be likely to involve both suppression and facilitation of responses. The GO/WAIT paradigm used in the current study allows us to investigate separately those processes of the exogenous switch involved in switching to response withholding and switching to immediate responding. We have previously used ERPs to investigate the temporal course of neural activity involved with exogenous task-switching (Jackson, Swainson, Cunnington, & Jackson, 2001). In that study, subjects switched every two trials between their first and second languages when naming colored digits (color indicating language to be used). We identified two ERP components associated with switch trials in comparison to nonswitch trials: an increased frontal N2 and a prolonged parietal positivity. The language-switching study required responses to be withheld until stimulus offset (to avoid contamination of ERPs with vocal response artifacts) and its incongruent stimuli meant that any trial might have involved suppressing the alternative irrelevant response. The current GO/WAIT design will allow us to investigate whether these components only apply to the switch versus nonswitch contrast when a response must be withheld (the WAIT task) or whether they are also evident with immediate responding (the GO task).

RESULTS

Behavioral Results

Behavioral data from the ERP and fMRI studies are shown in Figure 1A and B, respectively. There was a significant switch cost (switch vs. nonswitch trials) present in the response times (RTs) on GO trials in both studies [ERP: $F(1,17) = 21.0$; $p < .001$; fMRI: $F(1,11) = 38.3$; $p < .001$]. In addition, RTs were significantly longer on nonswitch than on pure trials [ERP: $F(1,17) = 6.79$; $p = .018$]. Error rates for the GO task were extremely low and did not differ significantly between switch and nonswitch trials in either study.

Performance in the WAIT task was measured in terms of the proportion of early responses (i.e., trials on which the response was made before stimulus offset); these were analyzed nonparametrically using the Wilcoxon signed-rank test. Although more errors were made on switch than on nonswitch, this difference did not reach significance in either study [ERP: $z = 1.44$; $p = .15$; fMRI: $z = -1.16$; $p = .25$]. There were significantly more early responses made on nonswitch than on pure trials [ERP: $z = 2.65$; $p = .008$]. The predictable nature of the trial order, together with the instruction to subjects to minimize errors, probably accounts for the low sensitivity of this measure to the task-switching process on the WAIT task.

ERP and fMRI Results

We will first describe the results from the analysis of previously identified "markers" of response suppression—the frontal N2 ERP component and the lateral PFC activation—both of which have also been observed when subjects switch between alternative task sets. This

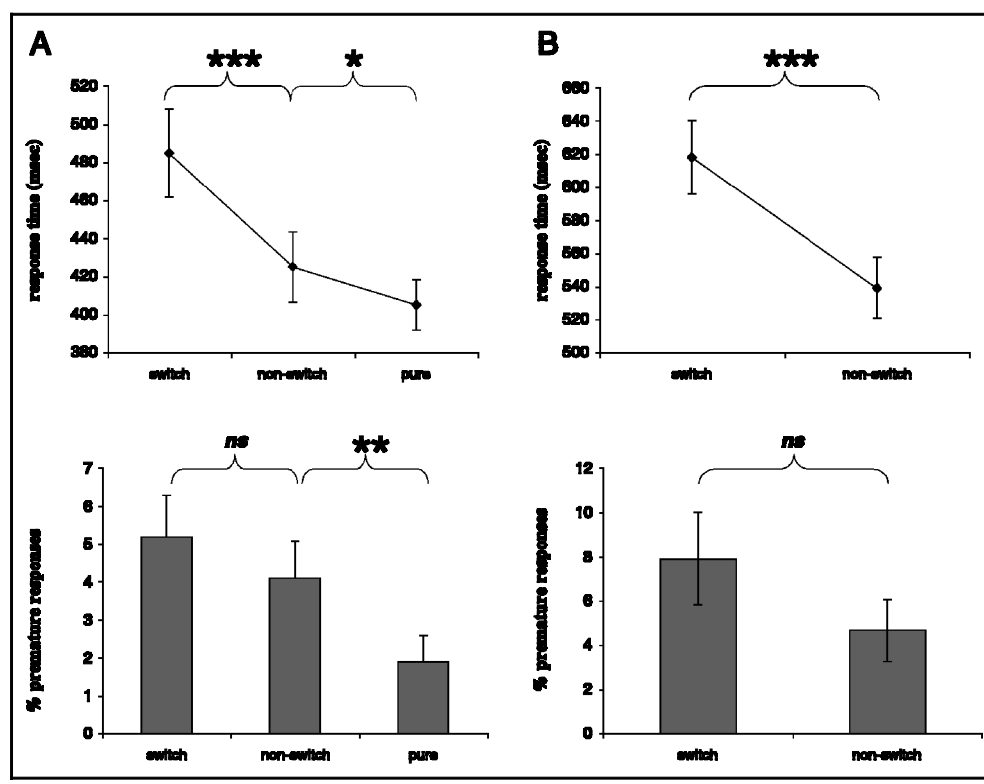

Figure 1. Behavioral data. (A) ERP study; (B) fMRI study. Line graphs show mean response time for correct responses in the GO task. Bar graphs show percentage of trials in the WAIT task on which responses were premature (i.e., made before stimulus offset). Error bars show standard error of the mean. Asterisks indicate level of significance for particular contrasts: ***$p < .001$; **$p < .01$; *$p < .05$; *ns* not significant, $p > .05$.

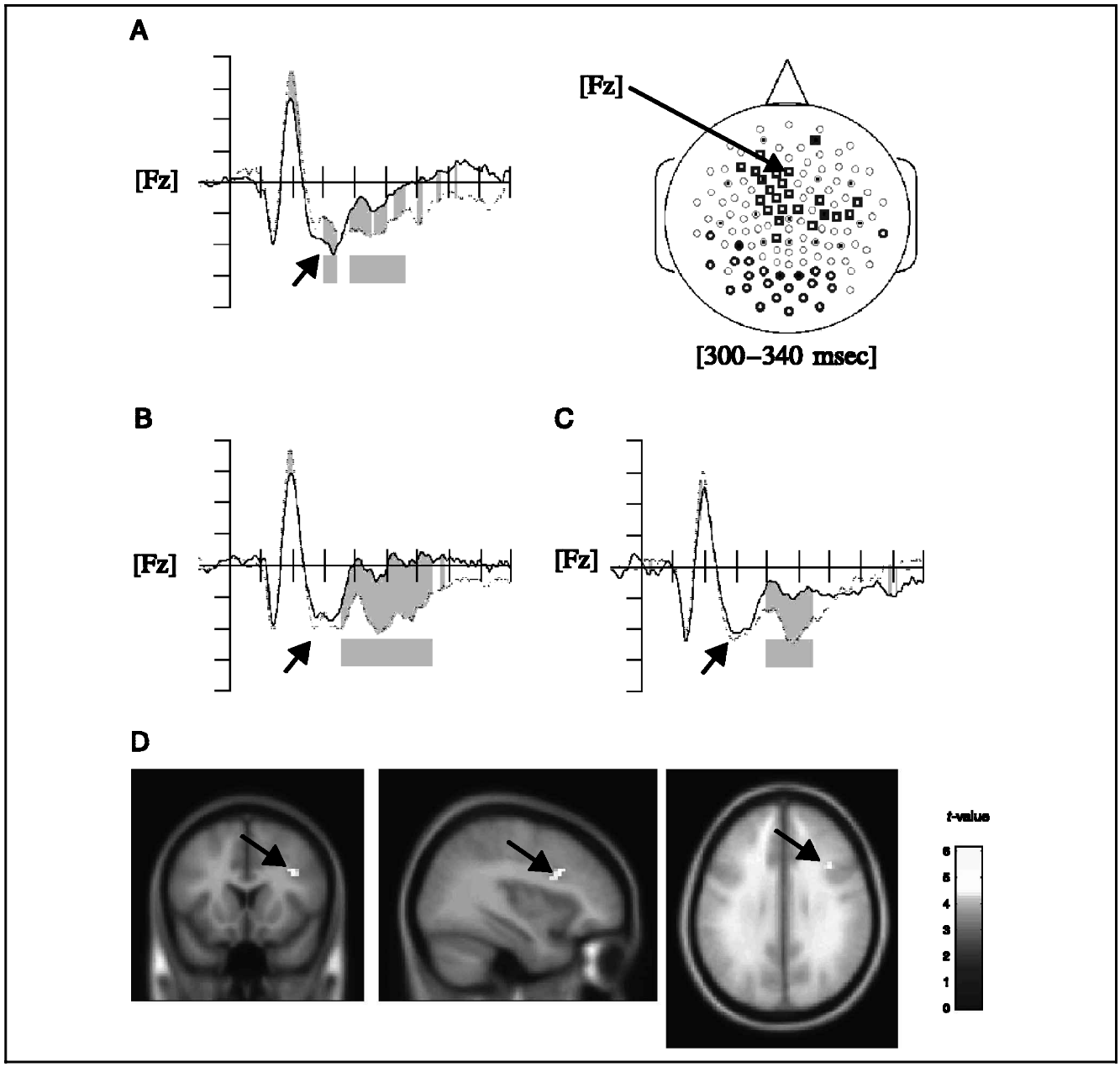

Figure 2. Frontal N2 and lateral PFC activations in WAIT versus GO contrasts. (A) Left: Grand average waveforms from WAIT (solid) and GO (dotted) ''switch'' trials over the Fz site (sensor 11). Shaded areas between waveforms show samples with a significant ($p < .05$) WAIT versus GO potential difference; shaded blocks below waveforms show runs of consecutive significance. Arrow indicates the N2 component. Right: Topography of the WAIT versus GO effect on switch trials over the 300–340 msec time range. Squares indicate that the WAIT waveform is significantly ($p < .05$) more negative than GO; circles show that it is significantly more positive. (B) Grand average waveforms from WAIT (solid) and GO (dotted) ''nonswitch'' trials at Fz. (C) Grand average waveforms from WAIT (solid) and GO (dotted) ''pure'' trials at Fz. (D) fMRI activation in the right inferior frontal sulcus for WAIT versus GO ''switch'' trials.

first analysis addressed the hypothesis that these are markers for the psychological functions of withholding a response and/or task-switching per se, as opposed to indexing the more specific function of switching to a mode of response withholding. Thus, WAIT trials were compared with GO trials to assess response withholding under different task-switch conditions: switch, nonswitch, and (in the ERP study) pure trial types; in addition, switch trials were compared with nonswitch trials under different response-withholding conditions: the WAIT and GO tasks.

Response Suppression Markers

WAIT versus GO

Based upon the findings of previous studies (Jackson et al., 1999, 2001), we examined the shape of the frontal N2 component at the Fz site [sensor 11]. The waveforms

from switch, nonswitch, and pure trials are shown in Figure 2A–C; the N2 component is indicated by arrows. On the basis of previous data, it was expected that the peak of the N2 would occur at around 300–320 msec after stimulus onset and visual analysis of the grand average data confirmed this. On switch trials, the N2 component for WAIT was significantly more negative than that for GO over the consecutive time range 300–340 msec (Figure 2A, left). A 40-msec time window centered at 320 msec was used to plot the topography of the effect, which showed a left fronto-central distribution (Figure 2A, right). There was no difference in the amplitude of the N2, however, on nonswitch or pure trials (Figure 2B and C). For completeness, ANOVAs were also carried out using the mean voltage data over the 40-msec window centered on 320 msec. There was a significant Task × Trial type interaction, $F(1,17) = 5.80$, $p = .03$, due to a significantly greater amplitude of the N2 on WAIT than on GO switch trials, $t(17) = 3.50$, $p = .003$.

The fMRI data for the WAIT versus GO contrast on switch trials showed activation within the right dorsal PFC [BA 44/9; $x = 36$, $y = 15$, $z = 30$; Z score = 4.14], lying within the inferior frontal sulcus (Figure 2D). There were no areas of significant activation for the WAIT–GO contrast on nonswitch trials.

Switch versus Nonswitch

The frontal N2 was again examined at the Fz site [sensor 11]. Figure 3A (left) shows that on WAIT trials, the latter part of the N2 was significantly enhanced for switch compared with nonswitch trials; this was consecutively significant over the 364–412 msec time range. Because this effect occurred at the latter part of the N2 wave rather than its peak, the a priori time range (300–340 msec) was not appropriate to define its topography. Instead, data were collapsed over the 360–400 msec period; the topography of sensors showing a significant switch versus nonswitch effect is shown in Figure 3A

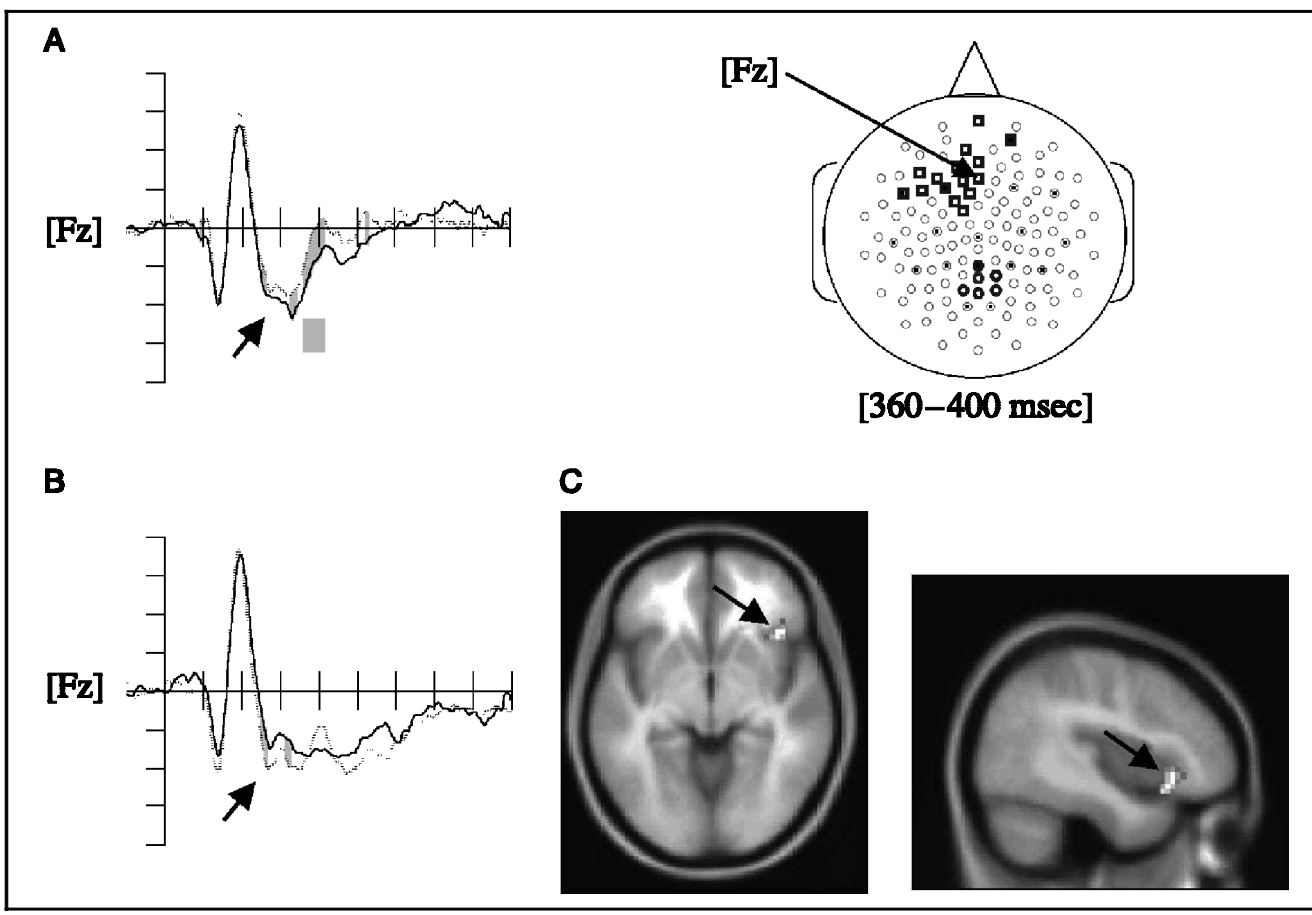

Figure 3. Frontal N2 and lateral PFC activations in switch versus nonswitch contrasts. (A) Left: Grand average waveforms from switch (solid) and nonswitch (dotted) WAIT trials over the Fz site (sensor 11). Shaded areas between waveforms show samples with a significant switch versus nonswitch potential difference; shaded blocks below waveforms show runs of consecutive significance. Arrow indicates the N2 component. Right: Topography of the WAIT versus GO effect on switch trials over the 360–400 msec time range. Squares indicate that the switch waveform is significantly more negative than nonswitch; circles show that it is significantly more positive. (B) Grand average waveforms from switch (solid) and nonswitch (dotted) GO trials at Fz. (C) fMRI activation in the right inferior frontal gyrus for switch versus nonswitch WAIT trials.

(right) and has a similar left fronto-central distribution to that described above for WAIT versus GO on switch trials. As Figure 3b shows, there was no increase in the frontal N2 for switching in the GO task. Again, for completeness, an ANOVA was run on the mean voltage data over the 40-msec window centered at 380 msec. This showed a main effect of task, such that GO trials were significantly more negative than WAIT trials over this time period. Additionally, there was a significant Task × Trial type interaction, $F(1,17) = 4.32$, $p = .05$. A significant effect of trial type—a greater negativity on switch trials—was present only for the WAIT task, $t(17) = -3.23$, $p = .002$.

The fMRI data revealed activation in the right inferior frontal gyrus [BA 47; $x = 42$, $y = 24$, $z = -6$; Z score = 4.18] on switch versus nonswitch WAIT trials (see Figure 3c). This region is inferior to that in the inferior frontal sulcus described above for the WAIT versus GO contrast on switch trials. No voxels within the lateral PFC were activated for the switch versus nonswitch contrast in the GO task.

To summarize, the increases in frontal N2 amplitude and lateral PFC activation were observed only for switch WAIT trials (versus either switch GO trials or nonswitch WAIT trials). Neither was observed for response withholding in the absence of switching (WAIT vs. GO on nonswitch trials) or for switching in the absence of response withholding (switch vs. nonswitch on GO trials). This argues strongly against these measures being generalized ''markers'' of either response withholding or task-switching.

We will now describe the results of the more detailed examinations of ERP and fMRI task-switching effects (i.e., switch vs. nonswitch trials) which were carried out separately for the WAIT and GO tasks. As described below (Methods), these effects were identified from an initial analysis of significant effects at all 129 sensors as well as at selected 10–10 equivalent sensors, as shown in Figure 4.

Task-Switching in the WAIT Task

Figure 4A shows that, in addition to the increased negativity in the later part of the frontal N2 described above (shown by right-pointing arrow), switching to a mode of response withholding in comparison with repeating withholding led to increased positivity in the waveforms recorded over parietal sensors between roughly 500 and 800 msec poststimulus (shown by left-pointing arrows). Samples were collapsed over this time range to produce the central-parietal topography shown in Figure 5A (left). Sensor Pz lies within this cluster of significant sensors; its waveform, shown in Figure 5A (right), showed a consecutively significant increase in positivity between 364 and 408 msec and between 480 and 780 msec poststimulus. The fMRI activations are shown in Figure 5B; in addition to the inferior frontal gyrus activation described above, the pre-SMA [BA 6; $x = 0$, $y = 9$, $z = 51$; Z score = 4.72; right-pointing arrows] and the right anterior cingulate [BA 24/32; $x = 3$, $y = 33$, $z = 24$; Z score = 4.37; left-pointing arrows] were significantly activated for switch versus nonswitch trials in the WAIT task.

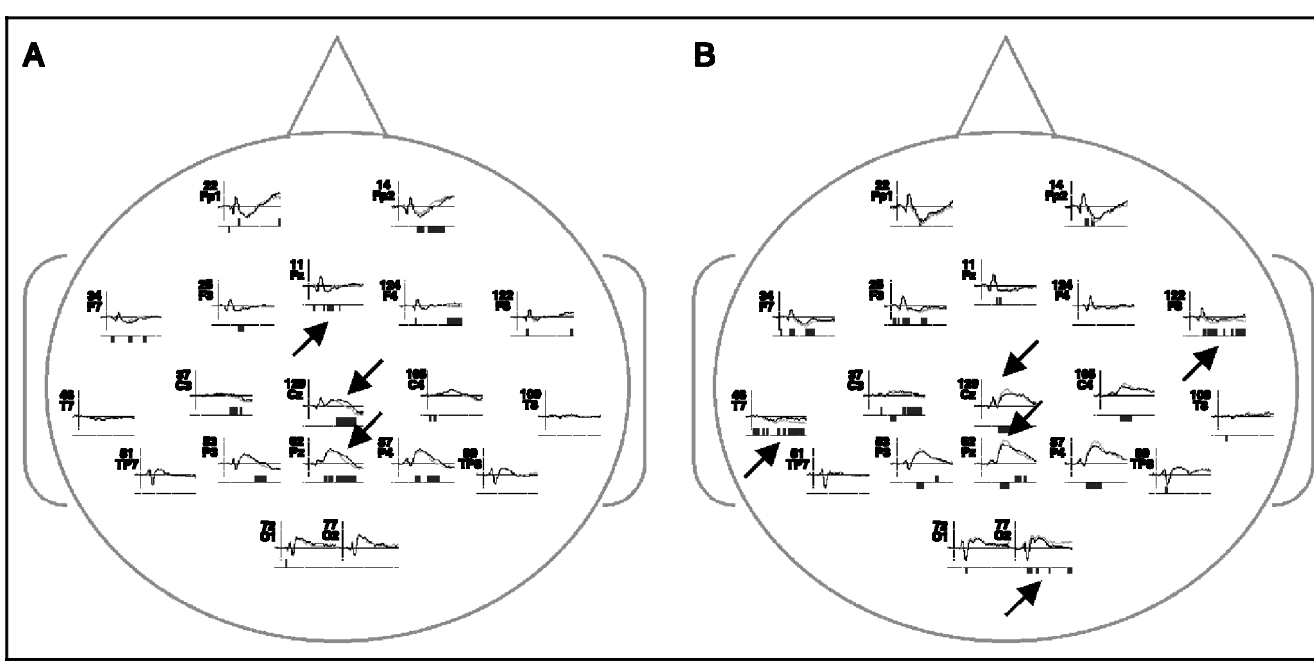

Figure 4. ERP task-switch effects in the WAIT and GO tasks. (A) WAIT task; (B) GO task. Grand average waveforms for switch (solid) and nonswitch (dotted) trials over selected 10–10 equivalent sensors. Bars beneath show individual time points with significant difference between conditions: below bar = switch is more negative than nonswitch; above bar = switch is more positive than nonswitch. Arrows show effects discussed in text.

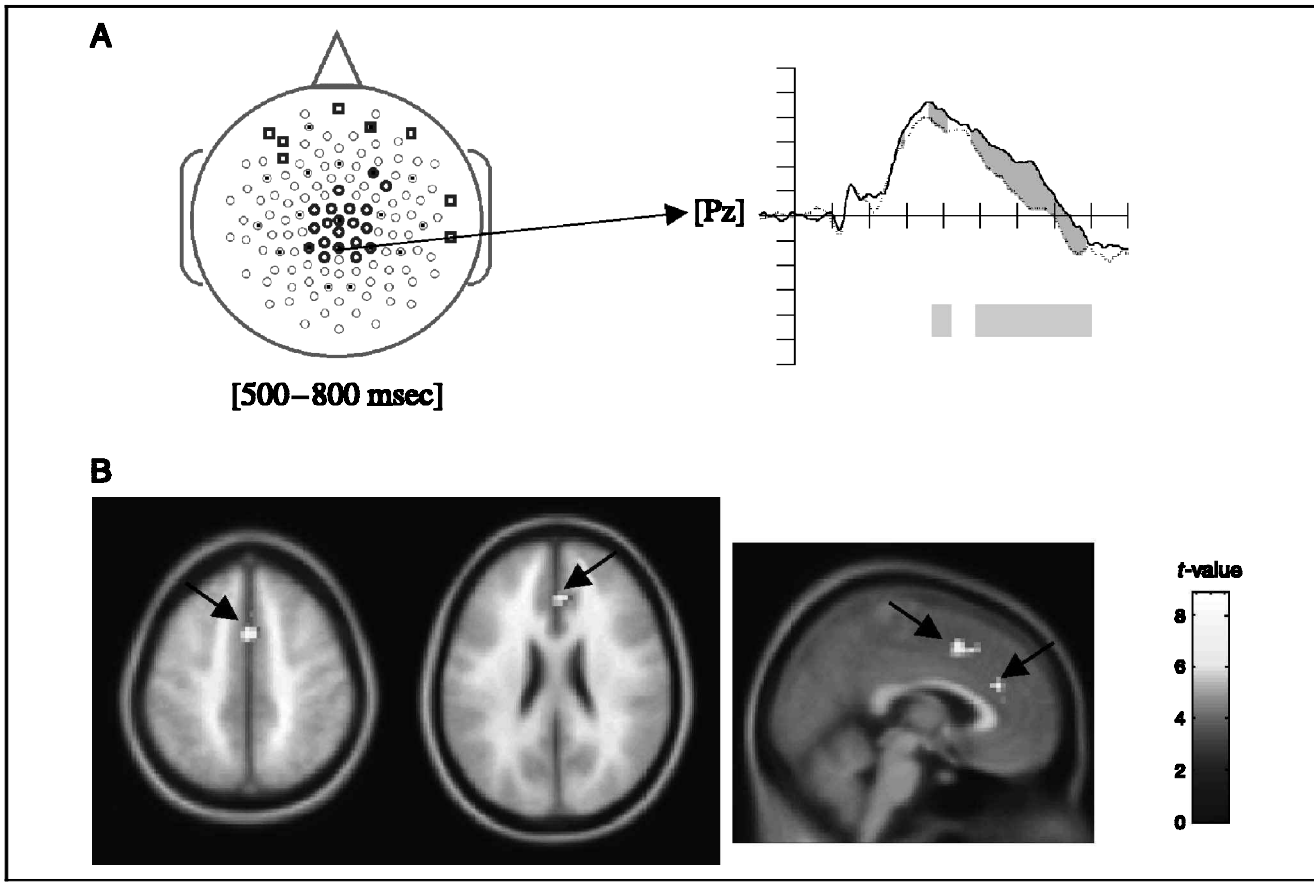

Figure 5. ERP and fMRI task-switch effects in the WAIT task. (A) Left: Topography of the switch versus nonswitch effect on WAIT trials over the 500–800 msec time range. Squares indicate that the switch waveform is significantly more negative than nonswitch; circles show that it is significantly more positive. Right: Grand average waveforms from switch (solid) and nonswitch (dotted) WAIT trials over the Pz site (sensor 62). Shaded areas between waveforms show samples with a significant switch versus nonswitch potential difference; shaded blocks below waveforms show runs of consecutive significance (see Figure 3A for topography and waveforms of the frontal N2 effect). (B) fMRI activations in pre-SMA (right-pointing arrows) and rostral ACC (left-pointing arrows) for switch versus nonswitch WAIT trials (see Figure 3B for activation in the right inferior frontal gyrus).

Task-Switching in the GO Task

Two ERP effects were identified for the comparison of switching to a mode of immediate responding compared with repeating immediate responding. As shown in Figure 4B (right-pointing arrows), switch and nonswitch conditions diverged significantly for much of the epoch over sensors including bilateral fronto-temporal and occipital scalp sites. The topography of the effect was examined at a number of points throughout this epoch and found to be consistent between 200 and 900 msec poststimulus; therefore, data were collapsed over that entire 700-msec interval to define the topography shown in Figure 6A (left). Over the bilateral fronto-temporal scalp, the amplitude of waveforms was significantly less negative on switch trials than on nonswitch trials; the effect showed the opposite polarity over the right occipital scalp. Site T7 (sensor 46) exemplifies the effect: As shown in Figure 6A (right), switch and nonswitch waveforms gradually diverged to become significantly different over the consecutive time range 612–868 msec.

Between roughly 300 and 500 msec, switch trials produced lower amplitude positivity than nonswitch trials over the middle central scalp (see Figure 4B, left-pointing arrows). Collapsing samples over this interval produced the topography of the effect, shown in Figure 6B (left). At the Pz site (sensor 62), the effect was consecutively significant over the 336–448 msec time range, as shown in Figure 6B (right).

Two fMRI loci were significantly active for switching to, compared with repeating, immediate responding: the right anterior cingulate [BA 24/32; $x = 9$, $y = 15$, $z = 30$; Z score = 4.28] (see Figure 6c) and the right cuneus [BA 18; $x = 21$, $y = -87$, $z = 9$; Z score = 4.18].

DISCUSSION

This study employed the convergent methodologies of ERP and event-related fMRI to investigate neural activity associated with withholding an immediate response and with switching between task sets. We examined two measures which have been proposed to index the suppression of a motor response and which have also been observed for task-switching: increased amplitude of the frontal N2 electrical brain potential and increased

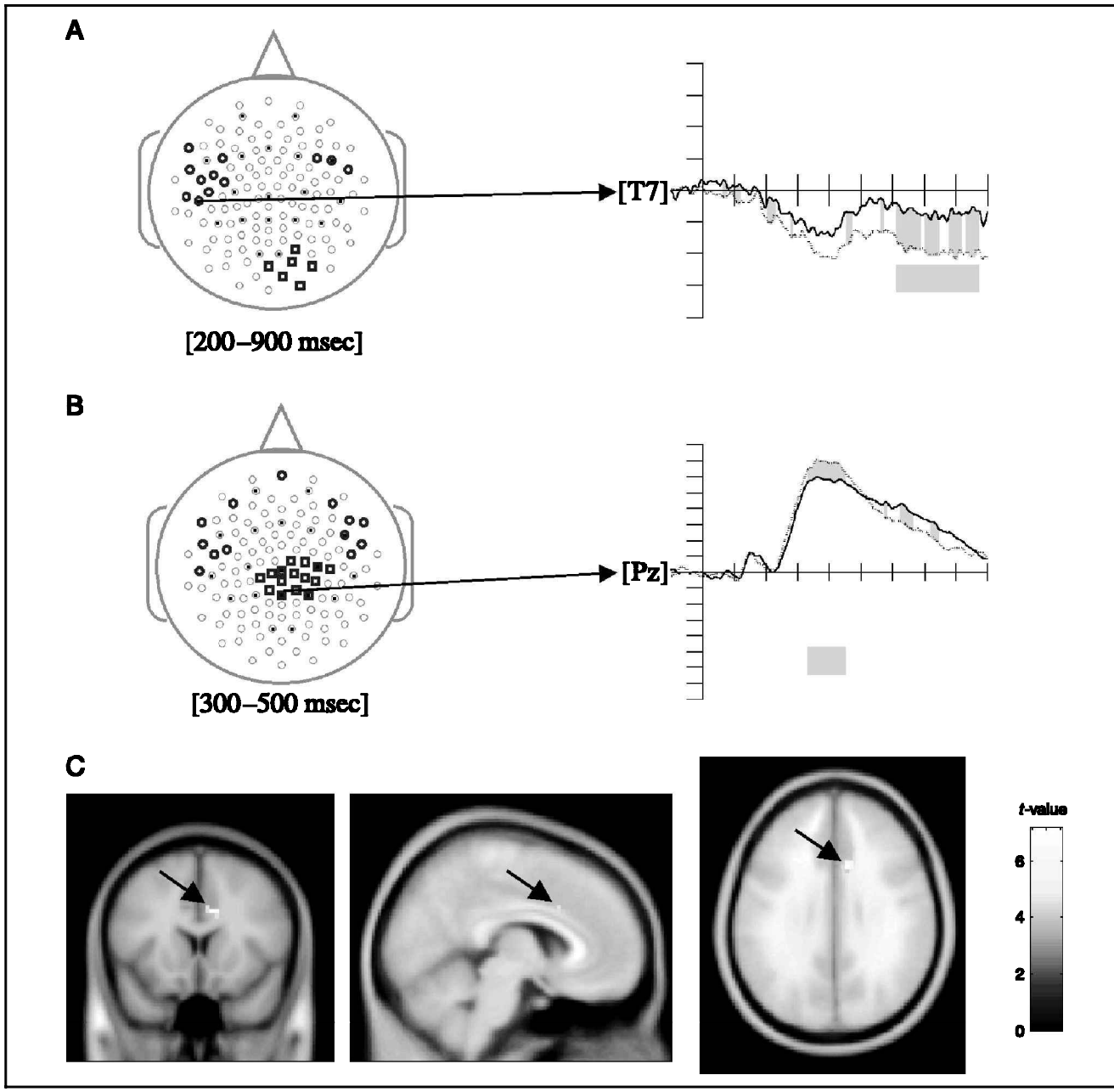

Figure 6. ERP and fMRI task-switch effects in the GO task. (A) Left: Topography of the switch versus nonswitch effect on GO trials over the 200–900 msec time range. Squares indicate that the switch waveform is significantly more negative than nonswitch; circles show that it is significantly more positive. Right: Grand average waveforms from switch (solid) and nonswitch (dotted) GO trials over the T7 site (sensor 46). Shaded areas between waveforms show samples with a significant switch versus nonswitch potential difference; shaded blocks below waveforms show runs of consecutive significance. (B) Left: Topography of the switch versus nonswitch effect on GO trials over the 300–500 msec time range. Right: Grand average waveforms from switch (solid) and nonswitch (dotted) GO trials over the Pz site (sensor 62). (C) fMRI activations in caudal ACC for switch versus nonswitch GO trials.

blood flow in the lateral PFC. The results showed clearly that neither marker was associated with either task set switching or response withholding per se. Instead, both were seen specifically for switching to a mode of response withholding. In addition, the timing and location within the brain of neural activity associated with switching to (as opposed to repeating) a task was shown to differ according to whether the task required an immediate or a delayed response.

The paradigm used in these studies was very simple: Subjects made compatible left or right button presses to colored arrows, with the task switching on every second trial between GO (respond immediately) and WAIT (withhold response until stimulus offset). Nevertheless, significant and substantial behavioral costs of switching task were evident in both the ERP and fMRI studies, comparable to those observed in more complex paradigms. The switch cost was calculated by subtracting the

RT on trials where a task was repeated (nonswitch trials) from that on which the task was switched (switch trials) relative to that used on the previous trial. The costs measured 60 and 80 msec in the ERP and fMRI studies, respectively, in each case comprising around a 14% increase upon the nonswitch baseline RT. The predictable trial order and long response–stimulus interval allowed subjects the opportunity of voluntarily preparing for a task in advance of the target stimulus; thus the switch costs obtained constituted the ''residual switch cost,'' which remains despite endogenous, or voluntary, preparation (Rogers & Monsell, 1995). It is notable that the proportional size of the cost was no larger in the ERP study, with around a 2-sec preparation interval, than in the fMRI study, with an 8-sec delay between trials. This is consistent with the notion that the residual switch cost reaches asymptote after about 1 sec, beyond which the endogenous mechanism of switching is unable to prepare further for the change in task (Rogers & Monsell, 1995).

One of the main aims of the study was to assess the extent to which neuroimaging ''markers'' of response suppression, also seen in task-switching, were generally applicable to either the situation of withholding an immediate response or switching.

Withholding an immediate response (comparison of WAIT vs. GO tasks) was shown clearly to differ according to whether this involved switching to, or repeating, the motor response set used on the directly preceding trial. The ERP data showed a significant increase in negativity of the frontal N2 component on WAIT compared with GO switch trials. This effect was entirely absent, however, on nonswitch trials, as it was on the pure trials (in which there was no requirement to switch between the two rules, and hence presumably very little interference between the immediate and delayed response sets). The fMRI data converged with the ERP results: A locus in the lateral PFC (areas 9/44) was activated for the WAIT versus GO contrast on switch trials while no areas were activated for the same contrast on nonswitch trials. The coordinates of this response suppression effect [36, 15, 30], here shown to be specific to the situation of switching to withheld responding, are close to those reported by Konishi et al. (1999: [41, 16, 19]), also within the right inferior frontal sulcus, to be active for the suppression of a response on no-go trials. The implication of these data is that the neural processes underlying the withholding of an immediate response depend critically on the nature of the preceding trial. The ERP and fMRI data are quite consistent with the time course (around 300 msec) and brain source (lateral PFC) of response suppression reported previously for no-go trials; our data suggest that the previous findings, which collapsed over switch and nonswitch types of no-go trial, may have masked an important difference between these types of trial.

Task-switching (switch versus nonswitch trials) within a task requiring response withholding (the WAIT task) elicited enhancement of the latter part of the N2 as well as activation of the right inferior frontal gyrus in the ventrolataral PFC. Neither measure, however, was observed for switching within a task which required no response withholding (the GO task), leading us to conclude that they are not associated in a general way with switching between alternative task sets, but more specifically with switching to a mode of response withholding. The presence of the N2 difference between switch and nonswitch trials is analogous to the residual switch cost seen behaviorally. Despite there being ample opportunity for advance preparation for a switch of tasks, presentation of a stimulus on a switch trial elicited neural activity associated with actively suppressing the response which applied to the previous task.

A second aim of this study was to add to our current knowledge of the brain imaging correlates of task-switching. There were activations within the ACC for both types of switch, but their locations dissociated within the ACC according to the direction of the switch: an anterior locus for switching to (relative to repeating) response withholding and a posterior locus for switching to (relative to repeating) immediate responding. This anterior–posterior division is consistent with the dissociable roles of two regions within the ACC (Picard & Strick, 2001). The anterior zone of the rostral cingulate (RCZa; between roughly 15 and 31 mm anterior to the vertical plane of the anterior commisure) is associated with conflict situations (e.g., in a stop-signal task) where a prepared response must be suppressed. (In the stop-signal paradigm (see Logan, 1994), the imperative stimulus is followed on some trials by a signal to stop, that is, to abort the response. The longer the delay between the imperative and stop signals, the less likely it is that the initiated response will be successfully aborted). The site of the rostral ACC proposed by Picard and Strick roughly fits our activation at $y = 33$ for switching within the WAIT task, where the need to switch to response withholding, compared with repeating delayed responding, is likely to generate conflict with the preceding task rule of immediate responding. In fact, activation this far anterior is on the border with the more anterior ''affective'' ACC regions which extend in front of and below the genu of the corpus callosum and are associated with emotional processing (Bush, Luu, & Posner, 2000). The need to suppress a response, which is particularly strongly triggered on a switch WAIT compared with a nonswitch WAIT trial, is likely to also be associated with a degree of stress or arousal, a strong predictor of ACC activation (Paus, 2001). The posterior zone (RCZp; between the vertical planes at the anterior commisure and 15 mm anterior to it) has been more closely associated with high response selection demands (Picard & Strick, 2001), consistent with the need to respond appropriately and quickly with the left or right hand on a GO trial. The findings of Ruff, Woodward, Laurens, and Liddle (2001) that nearby regions of ACC/pre-SMA are activated for

reverse Stroop trials within a switching paradigm led those authors to postulate a role for this region in overcoming prior suppression. The time taken to overcome prior suppression of task-specific processes has been suggested to underlie part of the switch costs when switching back to a more habitual task (Meuter & Allport, 1999). A clearly analogous situation is that of switching back to immediate responding in our GO/WAIT paradigm and this may explain the presence of activation in relatively posterior ACC for switching in the GO task.

Two regions were activated for switching to withheld responding but not for switching to immediate responding: ventrolateral PFC and pre-SMA. Both of these regions have been shown to be active on no-go trials (Rubia et al., 2001; Garavan et al., 1999) and they have also been associated with learning or performing according to arbitrary stimulus–response rules (Sakai et al., 1999; Rushworth & Owen, 1998). Monchi et al. (2001) showed activation of BA 47/12 (ventrolateral PFC) following negative feedback in the WCST (i.e., at the time of a switch between task rules). Our data may indicate therefore that the activity of these regions on no-go trials may reflect retrieval of the no-go "rule" or the response set for suppression, particularly on those no-go trials which follow go trials.

It is of note (we are grateful to an anonymous reviewer for pointing this out) that the medial frontal areas activated in our paradigm can be considered motor association areas, with connections either directly, or via other motor association areas, to the spinal cord. Thus, they are both well placed to carry out functions such as response suppression relevant to switching in the current paradigm. Although we have stressed the roles of both the pre-SMA and rostral ACC in terms of relatively abstract cognitive function, it may be worth considering that this was a paradigm in which the switch was very much between "response" sets. (A specification of the entire task schema would of course include stimulus features—i.e., color of the arrow—as well as response features, but it is probably fair to say that the emphasis of the task demands was at the level of response.) In an alternative paradigm, in which, say, it is the perceptual features of stimulus input between which attention must be switched (e.g., color vs. meaning of a written word in a Stroop task), the particular areas activated for switching may involve other, possibly more posterior, cortical areas. The degree to which particular areas activated for switching are task-specific is an important one and certainly deserves further study. Indeed, the current study has shown specificity of activation to either the GO or the WAIT task in areas already known to be involved in task-switching (including the lateral PFC and ACC), demonstrating a considerable degree of task specificity in the functioning of executive control systems.

ERP studies of task-switching are particularly few in number as yet. Two studies have isolated stimulus-locked ERPs related to exogenous (stimulus-driven) task-switching. Lorist et al. (2000) identified a decrease in parietal positivity on switch trials, present over much of the 1-sec poststimulus epoch. We have previously used a language-switching paradigm (Jackson et al., 2001) in which subjects named digits in either their first or second language according to a color rule, with language switches occurring predictably on every second trial. Two ERPs were identified in that study, both of which have been replicated here for switching within the WAIT task. Firstly, the N2 wave over the left frontocentral scalp was prolonged on switch compared with nonswitch trials, with an almost identical latency and topography in both studies. The effect was not apparent for the GO task, which required immediate responses. Nor was it apparent in a study of receptive language-switching requiring an immediate parity (odd/even) judgment of number words presented in the subject's first or second language and which presumably involved no response suppression (Jackson, Swainson, Mullin, Cunnington, & Jackson, in press). The N2 effect for task-switching therefore appears to be specific to the situation where a response must be withheld, possibly reflecting active "top-down" suppression of an immediate and/or prepotent response. It is important to note that ERPs in the digit-naming task, like the WAIT task in the current study, were taken from trials in which the response had to be delayed until stimulus offset. It is possible that the increased N2 associated with task-switching is only evident under delayed-response conditions; this hypothesis is currently under investigation. A second switching effect present with similar latency and topography in both the WAIT task and the previous digit-naming task was a sustained increase in the magnitude of the late positivity over the central and parietal scalp. This may reflect a process of reconfiguration of stimulus–response mappings where these differ for the two tasks. In the language-switching (digit-naming) study and in the present study, each task uses differently colored stimuli and therefore different mappings of a perceptual template onto an appropriate response. Close examination of Figure 4B shows that this effect was present also for the GO task (see sensor 62, Pz); it was not, however, examined in further detail because the very different RTs to switch and nonswitch GO trials may have differentially affected the later parts of the waveform. The effect was entirely absent in the parity-judgement language-switching study (Jackson et al., in press); that paradigm used no color–task rule, hence, there was no need for reconfiguration of stimulus-to-responses mappings required upon the change in appearance of the stimuli.

Two novel ERP effects of task-switching were identified from the contrast of switch with nonswitch trials on the GO task (i.e., for task-switching in the absence of any response-withholding demands). Firstly, a clear and sustained positivity was seen over bilateral fronto-temporal

sites for most of the epoch, with occipital sites showing the same effect with the opposite polarity. The prolonged, gradually increasing pattern of this effect suggests that it was not stimulus-driven. Rather, it seems likely that a negativity such as the contingent negative variation (CNV) was present prior to stimulus presentation on GO switch trials, reflecting increased effort and readiness for speeded evaluation of the imperative stimulus. A CNV effect would not be visible in baseline-corrected waveforms, but would have both swamped the negative stimulus-locked deflections of the subsequent part of the switch waveform (Walter, Cooper, Aldridge, McCallum, & Winter, 1964) and resolved upon stimulus presentation, resulting in an apparently stimulus-driven positivity which increased towards the end of the epoch (see Figure 6a, right). No such effect resembling CNV resolution was evident for switching within the WAIT task, presumably because speeded evaluation of the stimulus would be unhelpful on that task. A second effect of switching in the GO task was clearly stimulus-locked. Its latency and scalp distribution match those of the parietal P3b potential. This is a positive ERP component with a posterior-parietal scalp distribution occurring roughly between 300 and 600 msec following stimulus onset. It is evoked by stimuli to which some type of response should be made. A perceptual/central cognitive role for the P3b is suggested by its tendency to be modulated by factors such as task-relevance or probability of occurrence of a stimulus, but not by the difficulty of response selection (e.g., stimulus–response compatibility; see Kok, 2001, for a review). Its amplitude has recently been postulated to reflect the strength of a matching process between a stimulus and an internal ''template'' of the target stimulus (Kok, 2001). We suggest that strengthening of the template by any match with an actual stimulus may form at least part of the exogenous switch process by improving subsequent stimulus evaluation. It would explain the increased P3b ERP as well as better behavioral performance on subsequent nonswitch trials. Such a mechanism may also help to account for the pattern of nonswitch ''benefits'' seen in the predictable language-switch paradigms of Jackson et al. (2001, in press). An increased P3b amplitude was not apparent in the data from the WAIT although a similar priming of task-related stimulus evaluation would be expected to apply regardless of the timing of response. The effect may have been simply less visible in the averaged ERPs for the WAIT task: Because of the lack of time constraints in that task, the neural processes underlying the effect may have occurred over a longer and more variable time scale from trial to trial. Lorist et al. (2000) have previously reported an increased positivity over Pz for task-repetition trials in a predictable color- versus letter-identity judgment paradigm, albeit a much more sustained effect than in the present data for the GO task. They also proposed that their effect may indicate increased efficiency of stimulus evaluation on nonswitch trials, while also suggesting that switch trials may simply be more difficult, a factor known to affect the size of the P3 potential.

In summary, we have demonstrated the specificity of two neuroimaging ''markers'' of response suppression—the frontal N2 ERP and lateral PFC activation—to the situation of switching to a mode of withholding an immediate response rather than more generally to either withholding or switching. The presence of these effects in a paradigm with predictable switches between tasks and large intertrial intervals links them closely with the behavioral features of the residual switch cost. In addition, we have shown that rostral and caudal regions within the anterior cingulate appear to be involved respectively in switching to withheld and to immediate responding. Finally, we have replicated the finding of two ERP components involved in switching in a delayed-responding task (amplifications of the frontal N2 and parietal late positivity) and identified two new components (fronto-temporal/occipital CNV resolution and amplification of the parietal P3b) associated with switching on an immediate-response task.

METHODS: ERP STUDY

Subjects

Nineteen healthy right-handed subjects took part in the ERP study. The data from one of these had to be excluded because of very high amplitude alpha-frequency activity (see ERP analysis below), leaving a total of 18 subjects aged between 18 and 36 years (mean ± standard deviation: 24.9 ± 5.7 years). One subject also took part in the fMRI study. All subjects provided written informed consent.

Procedure

Subjects' EEG was measured continuously during performance of the behavioral task in a single session. Subjects viewed stimuli projected onto a screen from a distance of 2.2 m. Stimuli were colored left- or right-pointing arrows, presented one at a time in the center of the screen. Arrow stimuli (dimensions 20 cm × 15 cm max), colored either red or green (these being isoluminant), were presented against a dark blue background for high definition in a dimmed room.

The subject's objective was to press a button with their left index finger for a left-pointing arrow or their right index finger for a right-pointing arrow; the left and right buttons were 10 cm apart on a single button-box, and a comfortable distance in front of the subject. Subjects were instructed to respond immediately upon stimulus onset for green arrows (''GO'' trials) and to respond immediately upon stimulus offset for red arrows (''WAIT'' trials). They were asked to respond as quickly as possible in both conditions, while minimizing errors.

On all trials, stimuli were presented for a fixed interval of 1000 msec, with a fixation cross being presented between stimuli. On GO trials, the next stimulus appeared randomly at a variable interval of 1500–2500 msec after offset of the previous stimulus and on WAIT trials, the interval between stimulus offset and the next stimulus onset was equal to RT plus 1500–2500 msec.

All subjects received three practice blocks of trials in a fixed order to introduce the different response rules (GO and WAIT) and the types of blocks used for the main experiment. First, a block of 32 GO trials (pure GO block), then 32 WAIT trials (pure WAIT block), then 32 trials in a mixed block using a two-trial alternating runs procedure, starting with two GO trials (i.e., GO GO WAIT WAIT GO etc.). Thus, a switch between tasks (GO/WAIT response rules) was required on every second trial. Subjects were made fully aware of this predictable sequence. The experimental trials then followed, with 12 blocks of 32 trials, in the order MIXED MIXED GO MIXED MIXED WAIT GO MIXED MIXED WAIT MIXED MIXED for nine subjects and the reverse order for the remaining nine subjects. A 15-sec break was given after every 32 trials. This resulted in there being 64 trials given for each of the conditions: pure GO, pure WAIT, nonswitch GO, nonswitch WAIT, switch GO, and switch WAIT.

ERP Recording and Data Reduction

High-density ERPs were recorded from each participant using a 128-channel geodesic sensor net coupled to a high input impedance amplifier (Tucker et al., 1994). EEG was continuously recorded and digitized at 250 Hz. Wherever possible, impedances were reduced to <50 KΩ prior to recording; where this level could not be attained by adjusting or rewetting the sensor with electrolyte solution, and where this led to noisy recordings, that channel was excluded before analysis. The continuous EEG was then segmented into 1-sec epochs time-locked to the onset of each visual stimulus, commencing 100 msec prior to stimulus onset. Samples were low-pass filtered with a cutoff frequency of 45 Hz. Trials with incorrect responses were rejected prior to averaging. These included trials where the wrong key was pressed, or where the response was not within the allowed time range of 200–1000 msec after stimulus onset for GO trials and 1000–2000 msec after stimulus onset for WAIT trials. In addition, trials containing eye movement artefacts (i.e., an EOG channel difference greater than 70 μV) and trials containing more than 10 bad channels (channels with voltage amplitudes over 200 μV or a change in amplitude between adjacent samples of more than 100 μV) were rejected prior to averaging. Channels that were bad for more than 25% of trials for a given participant, or where visual inspection revealed a bad recording, were excluded from all analyses. Three or fewer channels per subject were rejected in all. The average number of trials retained per subject was 84% (range 45–96%). ERPs were average reference transformed off-line [i.e., each channel shows the difference between its voltage and that of the average of all other channels (after first excluding bad channels)]. The epoch was baseline corrected using data from the 100 msec prior to stimulus onset.

ERP Data Analysis

The N2 ERP was examined at the midline frontal scalp site (Fz; sensor 11 in the EGI system), this location being determined a priori from previous studies (Jackson et al., 1999, 2001). Planned contrasts were run between the waveforms from the experimental conditions. To test for significance of each effect and to determine its time course, t tests between the two conditions of interest were run on the data from the Fz sensor at each time sample. Because of the large number of comparisons made in this way, a criterion of ''consecutive significance'' was set when determining the actual time course of the effect: at least 10 consecutive samples indicated start of a run of consecutive significance; a run ended only when followed by a run of at least 10 consecutive nonsignificant samples. This method is based upon that of Rugg et al. (1993) and used by Jackson et al. (2001). The topography of an experimental effect upon the N2 was determined by collapsing data over the relevant time range (where appropriate, this time range was the 300–340 msec window determined a priori from previous studies together with examination of the grand average data) and testing the difference between conditions with a t test at each of the 129 sensors. All t tests were two-tailed with a significance level of $p < .05$. To complete the analysis, ANOVAs were additionally run on the data, with the two repeated-measures factors of task (GO vs. WAIT) and trial type (switch vs. nonswitch). These were run using the average voltage over the time window of interest.

The starting point for the data-driven analyses of further ERP effects of task-switching was to plot the grand average waveforms for the switch and nonswitch conditions over selected sensors corresponding closely to commonly used sites in the 10–10 system (Luu & Ferree, 2000; see Figure 4). T tests were carried out at each time point in order to identify the approximate time ranges over which the conditions differed significantly at these sites (shown as gray bars below waveforms in Figure 4), as well as at all 129 sites (not shown) in order to confirm that the effect identified was present over more than one sensor. This allowed identification of the approximate time range of a significant effect. Data were collapsed over the identified time range and analyzed by t test for each of the 129 sensors in order to identify the scalp topography of the effect (see, e.g., Figure 5A). Waveforms were plotted from a sensor demonstrating the effect (i.e., one of those identified in the topographic analysis); this

was chosen to be one of those equivalent to a commonly used 10–10 site (i.e., one of those shown in Figure 4) in order to aid comparison with other studies. A method of testing consecutive significance between waveforms was applied, as described above.

METHODS: fMRI STUDY

Subjects

Twelve healthy right-handed volunteers, aged between 18 and 36 years (mean ± standard deviation: 24.5 ± 6.3 years), participated in the study. One of these subjects also took part in the ERP study. All subjects provided written informed consent.

Procedure

Participants were scanned in one continuous measurement session of approximately 15 min duration. Throughout the scanning session, visual stimuli were presented via a video projector on a back-projection screen at the foot of the scanner bed and subjects wore prism glasses which allowed full binocular vision of the screen and stimuli while lying inside the scanner. Participants also kept their index fingers of each hand on left and right microswitches mounted on a single response box positioned on the lower abdomen in the midline of their body. A PC computer recorded the precise timing of button presses together with the timing of the acquisition of the first slice in each image volume from the MR scanner.

Initially, a white central fixation cross was presented for a duration of 25 sec, providing time for saturation scans to allow the signal to reach equilibrium, and also providing an initial baseline resting period. Following this, visual stimuli consisting of single arrows were presented consecutively at the central fixation position. All arrows were presented for a duration of 1000 msec at a rate of one every 8000 msec. The white fixation cross was always redisplayed during the interstimulus interval.

The task was exactly the same as that for the ERP study except that speed of response (following stimulus offset) was not emphasized for the WAIT task and arrows were presented once every 8 sec to allow stimulus-triggered BOLD signal changes to return towards baseline between trials; in addition, only mixed blocks (two-trial alternating runs of GO and WAIT tasks), with no pure blocks, were presented.

Every 16 trials (approximately every 2 min), a brief rest interval of 30 sec duration was given to allow participants a break in concentration. This was indicated by presentation of the word ''Rest'' at the central fixation position. At the end of the rest period, the fixation cross was again displayed for 8000 msec before presentation of the next stimulus.

All participants practiced the task while lying in the scanner for 32 trials (approximately 5 min) immediately before beginning the experiment. During the fMRI acquisition, 96 arrows in total were presented (24 trials of each of the four event types).

Image Acquisition

Imaging was performed at the University of Nottingham Magnetic Resonance Centre using a 3-Tesla magnet (Oxford Magnet Technology), custom-built head gradient set and birdcage quadrature RF coil. Continuous T2* echo-planar images were acquired consisting of 16 contiguous sagittal slices covering most of the brain (8-mm slice thickness; 128 × 128 voxels at 3.0 × 3.0 mm resolution; volume repetition time TR = 2992 msec; echo time TE = 26 msec). A single run of 300 continuous whole brain images (15 min duration) was obtained, of which the first three volumes were discarded to allow for equilibration of T1 saturation effects. The difference between the scanning repetition time and the task interstimulus interval (a ratio of approximately 3:8) gave an effective sampling rate of the hemodynamic response over repeated task events of approximately 1 Hz.

Data Analysis

Image preprocessing and statistical analysis were performed using SPM99 (Friston et al., 1995). The sagittal image volumes were first corrected for differences in the timing of acquisition between slices, using a sinc interpolation in time to shift time courses relative to the acquisition time of the middle slice (slice 8). Images were then reoriented into axial slices, realigned to the first image of each time series using a six-parameter linear transformation and resliced using sinc interpolation. A mean EPI image generated from each realigned time series was spatially normalized, using a nonlinear transformation, to the standard EPI template image based on the Montreal Neurological Institute reference brain in the reference system of Talairach and Tournoux (1988). All functional images were then resliced to 3 × 3 × 3 mm voxels according to the resulting spatial normalization parameters, and spatially smoothed with an 8-mm full-width half-maximum isotropic gaussian kernel.

Image data for each participant were analyzed individually at the first level using the general linear model as implemented in SPM99. Trials were classified according to five event types: Go–Switch stimuli, Go–Nonswitch, Wait–Switch, Wait–Nonswitch, and Errors on Wait trials. Errors on Go trials were not separately modeled as they occurred so rarely (only four subjects each showed single errors of this type). Hemodynamic responses to the stimulus onset for each of these five event types were modeled with a canonical hemodynamic response function and its first-order temporal derivative (Josephs, Turner, & Friston, 1997). The temporal derivative was included in the model in order to accommodate small

deviations in the timing of hemodynamic response onsets (Friston, Fletcher, Josephs, Holmes, & Rugg, 1998). Rest intervals were modeled with a standard box-car function convolved with a hemodynamic response function, covering the periods of presentation of the "Rest" message. A high-pass filter with 64 sec cutoff was applied to filter low-frequency noise. Contrast images, representing the difference in parameter estimates of the height of canonical responses for modeled event types, were generated for comparisons of Switch versus Nonswitch trials for red arrows (Wait responses) and for green arrows (Go responses), respectively, and Wait versus Go responses for Switch trials. The first set of contrasts examined activation associated with switching of response sets, while the last contrast examined activation associated with inhibition of responses per se.

For group analysis, contrast images for all 12 participants were entered into a second level (random effects) analysis. Voxel-wise single-sample t tests were used to generate statistical parametric maps for each contrast. Significant activation was defined as regions with a cluster-level probability of $p < .05$ (clusters of four or more contiguous voxels below the threshold of $p_{\text{uncorrected}} < .0001$). For visualization, regions with significant peak activations were thresholded at $p_{\text{uncorrected}} < .001$ and overlayed on the mean 152-brain T1-weighted image of the Montreal Neurological Institute.

Acknowledgments

This work was supported by a BBSRC grant to G. M. J. and C. R., a Wellcome Trust grant to S. R. J. and G. M. J., and an MRC program grant to P. G. M. R. S. was supported by a Leverhulme Trust Special Research Fellowship and R. C. by a University research award to S. R. J.

Reprint requests should be sent to Dr. Rachel Swainson, School of Psychology, University of Nottingham, Nottingham NG7 2RD, UK, or via e-mail: rachel.swainson@nottingham.ac.uk.

The data reported in this experiment have been deposited in The fMRI Data Center (http://www.fmridc.org). The accession number is 2-2003-113DJ.

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