

BEHAVIORAL NEUROSCIENCE

Prefrontal and midline interactions mediating behavioural control

Catherine Fassbender,¹ Robert Hester,² Kevin Murphy,¹ John J. Foxe,³ Deirdre M. Foxe³ and Hugh Garavan^{1,3}¹School of Psychology and Institute of Neuroscience, Trinity College Dublin, Dublin 2, Ireland²Queensland Brain Institute and School of Psychology, University of Queensland, St Lucia, Qld, Australia³Cognitive Neuroscience & Schizophrenia Program, Cognitive Neurophysiology Laboratory, Nathan Kline Institute for Psychiatric Research, Orangeburg, NY, USA**Keywords:** anterior cingulate cortex, cognitive control, dorsolateral prefrontal cortex, fMRI, human, pre-supplementary motor area

Abstract

Top-down control processes are thought to interact with bottom-up stimulus-driven task demands to facilitate the smooth execution of behaviour. Frontal and midline brain areas in humans are believed to subserve these control processes but their distinct roles and the interactions between them remain to be fully elucidated. In this functional magnetic resonance imaging (fMRI) study, we utilized a GO/NO-GO task with cued and uncued inhibitory events to investigate the effect of cue-induced levels of top-down control on NO-GO trial response conflict. We found that, on a within-subjects, trial-for-trial basis, high levels of top-down control, as indexed by left dorsolateral prefrontal activation prior to the NO-GO, resulted in lower levels of activation on the NO-GO trial in the pre-supplementary motor area. These results suggest that prefrontal and midline regions work together to implement cognitive control and reveal that intra-subject variability is reflected in these lateral and midline interactions.

Introduction

Botvinick, Carter, Cohen and colleagues have theorised that the prefrontal cortex (PFC) and anterior cingulate cortex (ACC) work together to implement cognitive control (Cohen *et al.*, 2000; Botvinick *et al.*, 2001). They maintain that the ACC serves as a conflict monitor, detecting when two competing response pathways are simultaneously activated and feeding this information back to the PFC in order to increase levels of top-down control or selective attention. Increasing top-down control leads to a decrease in conflict by focusing attention on the relevant and away from the irrelevant dimensions of a task.

Successful task performance relies upon monitoring behaviour, comparing outcomes with internal goals and using these internal calculations to guide behaviour change when performance is deemed below par. The lateral PFC has been implicated in maintaining representations of the task set or rules defining appropriate stimulus-response mappings used in decision-making or execution of behaviour (see Miller & D'Esposito, 2005 for a review). It is also thought to maintain internal goals and to bias attentional resources toward relevant dimensions of a task (Cohen *et al.*, 2000). Midline structures are thought to monitor performance for errors or the possibility that errors are likely to occur (Brown & Braver, 2005; Magno *et al.*, 2006), as in the situation of high response conflict. Rostral areas of the ACC may be responsible for error processing, whereas more dorsal, caudal

parts of the ACC extending into the pre-supplementary motor area (SMA) may be concerned with the detection of response conflict (Ullsperger & von Cramon, 2001; Garavan *et al.*, 2003; Hester *et al.*, 2004a). Hence it follows that the lateral PFC and midline regions should interact during task performance (Cohen *et al.*, 2000; Botvinick *et al.*, 2001). Consequently, observing control-conflict inter-relationships between cortical areas would progress our understanding of both where and how control processes are instantiated in the brain.

Although hypothesized and central to models of cognitive control, prefrontal/midline interactions have not yet been empirically demonstrated on a within-subject, trial-for-trial basis. Although associations have been found between the PFC and ACC in response conflict resolution (MacDonald *et al.*, 2000; Badre & Wagner, 2004; Fincham & Anderson, 2006), studies have not examined how changing levels of conflict on a trial-by-trial basis affected the relationship between these regions. We utilized data from a previous GO/NO-GO study (Hester *et al.*, 2004b), in which half of the NO-GO events were cued and half were uncued. By examining activity during the preparatory period between the cue and the NO-GO, we sought to identify the mechanisms involved in marshalling top-down attentional control to prepare for the inhibition and, critically, to determine how this attentional control affected conflict-related levels of midline activity produced on the NO-GO trial. Being interested in the dynamic between the PFC (Frith & Dolan, 1996; Brass & von Cramon, 2002; Garavan *et al.*, 2002) and midline areas (Carter *et al.*, 1998; Botvinick *et al.*, 1999; Ullsperger & von Cramon, 2001) associated with behavioural control, our functional analyses focused on cued correct inhibitions and the cue period prior to these correct events, which also

Correspondence: Dr H. Garavan, ¹School of Psychology and Institute of Neuroscience, as above.

E-mail: hugh.garavan@tcd.ie

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enabled us to focus on conflict uncontaminated by any other error-specific processes (Garavan *et al.*, 2003).

Materials and methods

Subjects and experimental design

All participants provided written, informed consent and were paid for their participation. The Institutional Review Board of the Nathan Kline Institute, where the MRI scans were acquired, approved all procedures which were in compliance with the Declaration of Helsinki. Fifteen right-handed participants (10 female, mean age 30 years, range 23–40 years) were required to respond by button press to a series of alternating letters X and Y presented at 1 Hz. Each letter was on-screen for 900 ms followed by a 100 ms blank screen. Participants were required to inhibit their response when the alternating sequence was broken (i.e. when two Xs or two Ys were presented in succession; participants would respond to all stimuli except the fifth in the sequence X Y X Y Y X) (Garavan *et al.*, 2002). A cue (a letter with a strikethrough, e.g. X or Y) was presented from two to seven letters (seconds) in advance of half of the NO-GO trials (e.g. participants would respond to all letters except the last but including the cue letter in the following sequence X Y X Y X Y X X). Prior to scanning, participants were informed of the relationship between the cue and an impending NO-GO stimulus. For any given cue, participants did not know the duration of the period between the cue and the coming NO-GO trial. In total, the task comprised 40 cued NO-GO, 40 uncued NO-GO and 1096 GO trials, with the cued and uncued NO-GO stimuli pseudo-randomly interspersed throughout the GO trials.

Imaging parameters

Scanning was performed on a 1.5 T Siemens VISION scanner in which foam padding was used to restrict head movements. Contiguous high-resolution, T₁-weighted magnetization prepared rapid gradient echo slices were acquired for each participant (slice thickness, 1 mm; field of view, 256 mm) to enable subsequent anatomical localization and spatial normalization. Functional images were single-shot, T2*-weighted, echo planar imaging sequences. Contiguous 5 mm sagittal slices were acquired for each participant covering the entire brain (TR, 2000 ms; TE, 50 ms; 64 × 64 mm matrix size; field of view, 256 mm). Stimuli were presented using an IFIS-SA stimulus-delivery system (MRI Devices Corp., Waukesha, WI, USA), which was equipped with a 640 × 480 LCD screen, which was mounted on the head coil and was directly in the participant's line of vision. E-prime (Psychology Software Tools Inc.) presented and recorded the participants' responses.

Image analyses

All analyses were conducted using AFNI software (Cox, 1996) (<http://afni.nimh.nih.gov/afni>). Images were time-shifted using Fourier interpolation to correct for differences in slice acquisition time, motion-corrected using three-dimensional volume registration (least squares alignment of three translational and three rotational parameters) and edge-detected by removing any activation outside the brain. The first five and last two volumes were excluded from further analysis. As no participant displayed significant residual motion, data from all 15 participants were included. A mixed regression analysis was employed whereby cue-period activation was calculated in a block-design manner as a percentage change score relative to tonic, task-related activity and four separate impulse response functions were calculated for event-related activity associated with cued and uncued

inhibitions and commission errors. Although we were specifically interested in activation for correct inhibitions and the cue periods that preceded them, the inclusion of the additional event-related regressors served to account for the variance associated with these events. Varying the duration of the cue periods (from 2 to 7 s) enabled us to separate cue-period activation from the event-related NO-GO activation. Two separate cue-period regressors were identified, one for cue periods that preceded successful inhibitions and one for cue periods that preceded commission errors. Here, we will discuss activations associated only with correct inhibitions and the cue periods that preceded them.

Assessment of prefrontal and midline interactions

The intra-individual analyses were restricted to the cue periods prior to correct inhibitions and the correct inhibitions themselves. As described below, the initial regression analysis identified bilateral activation in the dorsolateral PFC during the cue period prior to an inhibition (see Fig. 1 and Hester *et al.*, 2004b). These activated areas provided functionally-defined regions for subsequent analyses. For each participant, we categorized activation in the left dorsolateral PFC region during the cue period as either high or low based on a split-half comparison of the mean activity levels for all cue periods prior to a correct inhibition for that participant. Trials during which there was greater activation during the cue period in the left dorsolateral PFC were categorized as high-control cue periods, whereas trials that displayed lower activation during the cue were classified as low-control cue periods. Based on this ranking, the subsequent event-related successful inhibitions were then categorized as high- or low-control events, i.e. successful inhibitions (STOPS) that followed cue periods with relatively high activation in the left dorsolateral PFC were denoted high-control STOPS. Conversely, the STOPS that followed cue periods with relatively low activation in the left dorsolateral PFC were denoted low-control STOPS.

Although the relationship between fMRI activation and prefrontal efficiency is not unambiguous (e.g. does greater activation reflect more control or more inefficient control?), greater activation has consistently been associated with better performance for response preparation (Sakai & Passingham, 2003; Hester *et al.*, 2004b; Fassbender *et al.*, 2006). When subjects are given the opportunity to prepare an upcoming response, activation is usually noted in task-appropriate areas (Fassbender *et al.*, 2006). In addition, when subsequent correct responses are examined, activation to cued correct responses is usually greater than to uncued correct responses (Hester *et al.*, 2004b). Moreover, trials exhibiting the greatest degree of post-error behavioural adjustment were also associated with increased activity in the dorsolateral PFC (Garavan *et al.*, 2002). Overall therefore, more activation in the PFC might be taken as indicative of greater preparedness for an upcoming response or greater levels of attentional control.

A new multiple regression analysis calculated the event-related activity associated with the separate high-control and low-control STOP regressors. This analysis included all of the same regressors as the initial general linear model with the single change being that the previous event-related regressor for successful cued STOPS was separated into two new regressors, one for low-control STOPS and one for high-control STOPS (see Fig. 2).

A non-linear regression program determined the best-fitting gamma-variate function for the impulse response functions (Cohen, 1997; Murphy & Garavan, 2005). The area under the curve of this gamma-variate function was expressed as a percentage of the area under the baseline, with the baseline representing the ongoing tonic

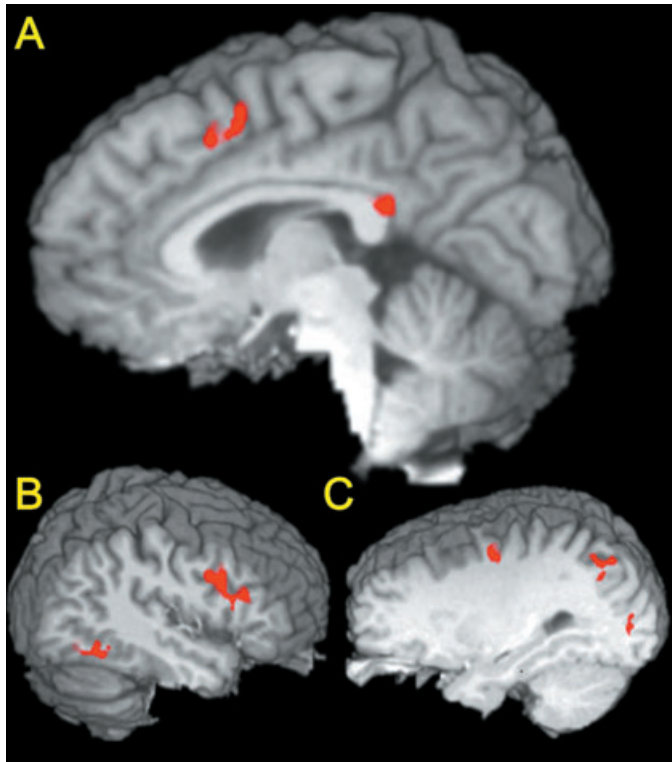


FIG. 1. Areas activated during cue periods prior to a correct response. Activated areas include the pre-SMA (A) (Talairach, $x = 2$, $y = 10$, $z = 46$), right (B) (41, 14, 27) and left (C) (-28, -7, 48) dorsolateral PFC as well as the left parietal, occipital and right temporal areas.

or GO-trial task-related activity. The percentage area under the curve (event-related activation) and percentage change score (cue-period activation) maps were then warped into standard Talairach space (Talairach & Tournoux, 1988) and spatially blurred using a 3 mm isotropic root mean square Gaussian blur. Statistical t -tests against the null hypothesis of no percentage activation change were performed separately for each of the event-related (successful STOP) and block (cue period prior to successful STOP) periods of interest, with a voxel-wise threshold of $P = 0.001$ ($t = 4.14$) and a cluster-size criterion of 142 μL , which resulted in a 5% probability (corrected) of an activation cluster exceeding the imposed threshold by chance. This produced separate activation maps for the high- and low-control STOPS. These thresholded activation maps were then combined such that a voxel was included if it was significant in either map (i.e. a union of the two significant activation maps), resulting in one STOP activation map. The mean activation was then calculated for each of the resulting functionally defined regions. Finally, to assess the specific importance of the left dorsolateral PFC in this type of attentional control, identical analyses were performed based on cue-period activation in the right dorsolateral PFC.

Results

Performance

Cues improved performance (20% NO-GO commission errors with cues, 40% without cues; $t_{14} = 4.155$, $P < 0.001$) and slowed reaction time during the cue period when measured relative to comparable periods prior to uncued NO-GO trials (370 vs. 340 ms; $t_{14} = 4.155$, $P < 0.001$).

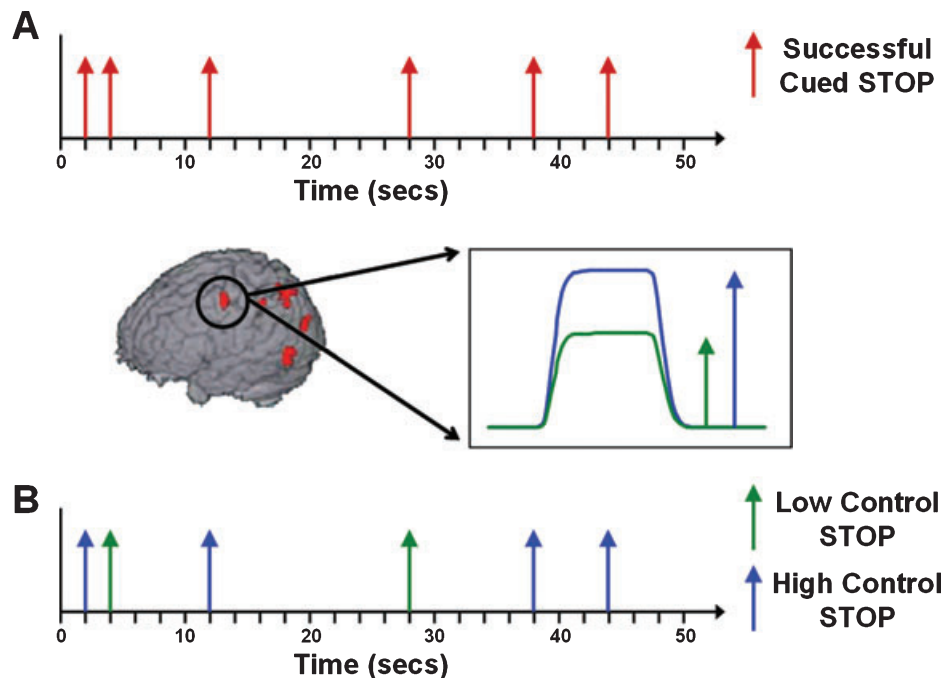


FIG. 2. Method of defining high- and low-control STOP events. (A) Regressor for cued successful STOPS during the initial analysis. As shown in B, activations during the cue period in the left dorsolateral PFC were divided into low activations (or low-control cue periods) (represented by the green curve) and high activations (or high-control cue periods) (represented by the blue curve). Successful STOPS from the original regressor (A) were then classified as high- or low-control STOPS based upon the cue period immediately preceding them, as shown in B. Therefore, the blue arrows represent STOPS that were preceded by high-control cue periods and are high-control STOPS, whereas the green arrows represent STOPS that were preceded by low-control cue periods and are low-control STOPS.

Cue and STOP-related activation

A number of areas, including the pre-SMA (activation was superior to the cingulate gyrus and anterior to the anterior commissure) (Picard & Strick, 1996) and left and right dorsolateral PFC (see Fig. 1 for areas and their coordinates), were activated during the cue periods preceding STOPS. The event-related analyses revealed activation in a number of areas including bilateral activation of the middle frontal gyrus, inferior parietal lobule, middle temporal gyrus, thalamus and right insula for cued and uncued STOPS. Although there was substantial overlap between activation maps for cued and uncued STOPS, pairwise *t*-tests revealed a general pattern wherein cues increased STOP-related activity (see Hester *et al.*, 2004b).

Intra-individual analysis

The high- and low-control STOP analysis, based on the left dorsolateral PFC categorization of cue periods, revealed two midline activations, one in the pre-SMA extending into the SMA and one in the SMA proper (Fig. 4A(i)). There was significantly lower activation in the pre-SMA for high-control relative to low-control STOPS ($t_{14} = 2.28$, $P < 0.04$), which is the expected pattern if higher levels of control lead to reduced levels of response conflict (Botvinick *et al.*,

2001). Activation in the SMA region did not differ between high- and low-control STOPS. The comparable analysis based on the right dorsolateral PFC cue-period categorization revealed an activated region in the ACC (Fig. 4B(i)) but this activation did not differ between high- and low-control STOPS.

Although there was no above-threshold activation in the ACC for the left hemisphere split, we were interested in examining any possible relationship between the ACC and PFC due to the importance given to the ACC by previous findings and theory (Botvinick *et al.*, 1999, 2001). Thus, the voxel-wise threshold for the STOP activation map was lowered to $P < 0.005$, revealing two ACC regions (Fig. 4A(ii)). These ACC regions did not differ between low- and high-control STOPS. To test for regional dissociations we combined the two left hemisphere categorization maps (the original map revealing regions in the pre-SMA and SMA, and the lower threshold map revealing two ACC regions). A 2 (high- vs. low-control) $\times$ 2 (pre-SMA vs. ACC) ANOVA was performed for each of the two ACC regions. As shown in Fig. 3A, both Region and Region $\times$ Control interactions were significant for both ANOVAs (Fig. 3A, rostral ACC: Region, $F_{1,14} = 18.98$, $P < 0.001$; Region $\times$ Control, $F_{1,14} = 4.95$, $P < 0.04$; Fig. 3A, caudal ACC: Region, $F_{1,14} = 7.48$, $P < 0.02$; Region $\times$ Control, $F_{1,14} = 8.5$, $P < 0.01$). Newman-Keuls *post-hoc* tests revealed that, for the first comparison, the high/low-control effect was present only in the pre-SMA (pre-SMA low vs. pre-SMA high, $P < 0.006$) and, for both comparisons, pre-SMA activation in the low-control condition was greater than ACC activation in both the low- and high-control conditions (rostral ACC: pre-SMA low vs. ACC low, $P < 0.002$; pre-SMA low vs. ACC high, $P < 0.004$; caudal ACC: pre-SMA low vs. ACC low, $P < 0.007$; pre-SMA low vs. ACC high, $P < 0.04$).

Lowering the threshold for the right hemisphere split map revealed two additional midline areas, both in the SMA (Fig. 4B(ii)). High-control STOPS produced significantly greater activation in the more caudal region only ($t_{15} = -2.84$, $P < 0.01$). As above, we combined the two right hemisphere categorization maps. A 2 (high- vs. low-control) $\times$ 2 (ACC vs. SMA) ANOVA was performed for each of the two SMA regions (Fig. 4B). In the more rostral SMA region, there was a main effect of region with the SMA being more active than the ACC (Fig. 4B; $F_{1,14} = 8.97$, $P < 0.01$) but there was no interaction. Conversely, only the Region $\times$ Control interaction was significant for the more caudal SMA region (Fig. 4B; $F_{1,14} = 11.29$, $P < 0.005$) driven by greater activity in the SMA for high-control relative to low-control STOPS as mentioned above.

Discussion

These results support the theory that the lateral PFC and midline regions work in concert in implementing cognitive control. Using a GO/NO-GO task we demonstrate that increased activity in the lateral PFC results in a decrease in conflict-related activity in the pre-SMA on a trial-for-trial, within-subjects basis. The results show that trials that were preceded by cue periods of relatively high left prefrontal activation, indicative of high levels of control, displayed lower amounts of conflict-related activation than those that were preceded by low-control periods. Moreover, these interactions were observed for the pre-SMA and not the ACC (Botvinick *et al.*, 1999; Cohen *et al.*, 2000), consistent with a conflict-error distinction between these two areas (Ullsperger & von Cramon, 2001; Hester *et al.*, 2004a).

It is interesting to note that this study did not find any support for the involvement of the ACC in cognitive control during conflict trials in this task. Our original work utilizing this same data set (Hester *et al.*, 2004b) demonstrated robust error-related activity in the ACC to errors (see Fig. 5). Here, we found no evidence for a conflict role of the ACC,

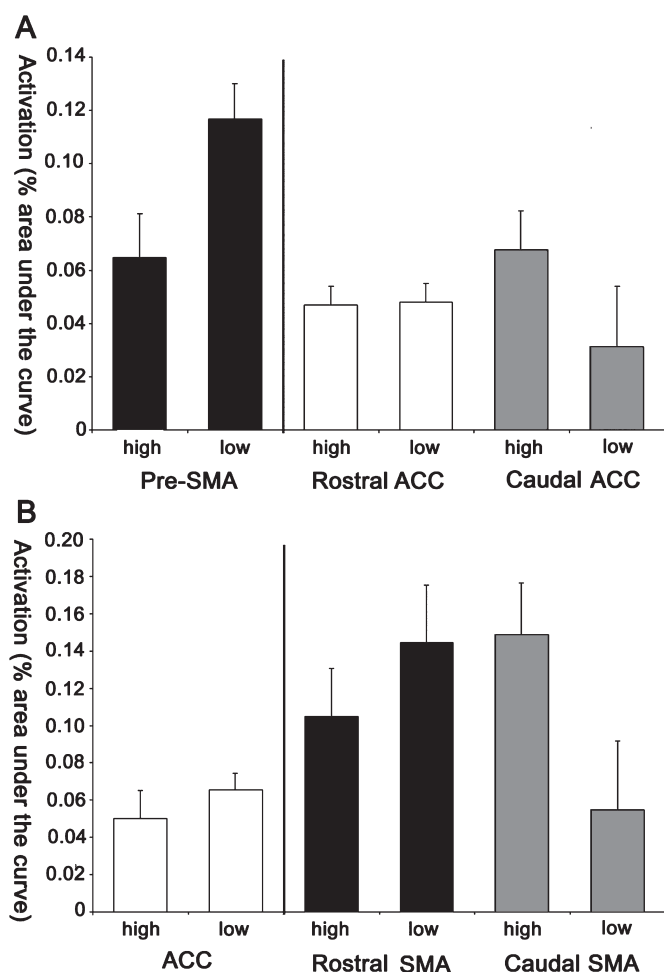


FIG. 3. (A) Mean activation in the pre-SMA, rostral ACC and dorsal ACC for high- and low-control events as defined by the left dorsolateral PFC. (B) Mean activation in the ACC, rostral SMA and caudal SMA for high- and low-control events defined by the right dorsolateral PFC.

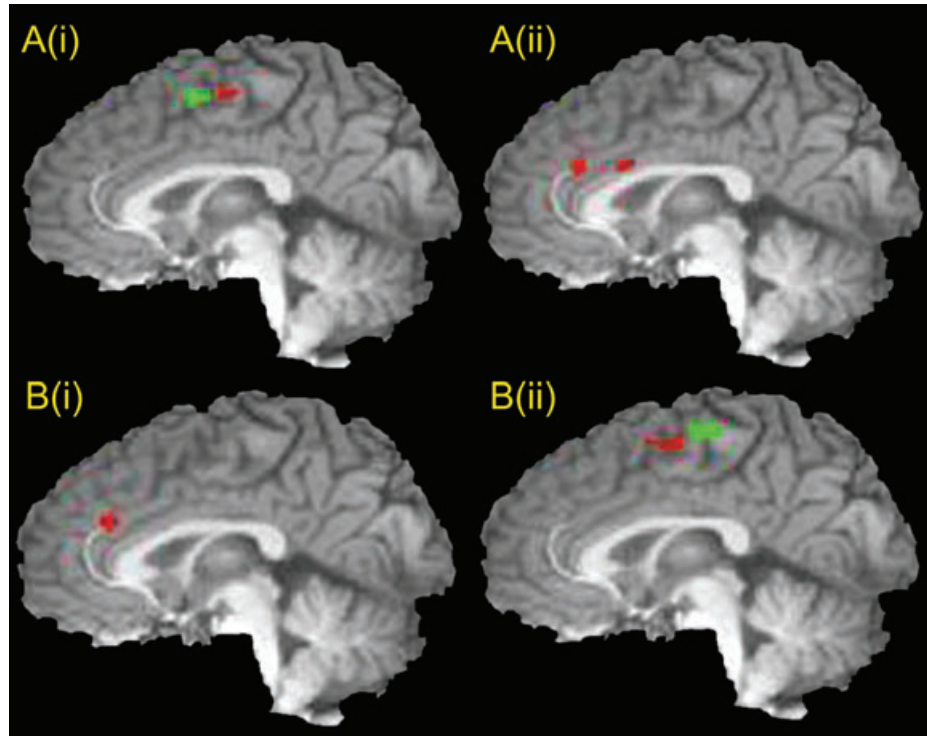


FIG. 4. Correct inhibition activations from the left dorsolateral PFC split [A; (i): pre-SMA (0, 1, 58), SMA (1, -11, 59); (ii): rostral ACC (-2, 30, 28), caudal ACC (1, 13, 26)] and from the right dorsolateral PFC split [B; (i): ACC (-2, 31, 26); (ii): rostral SMA (1, -3, 60), caudal SMA (1, -18, 65)]. Areas in which activation differed significantly between high- and low-control conditions are displayed in green.

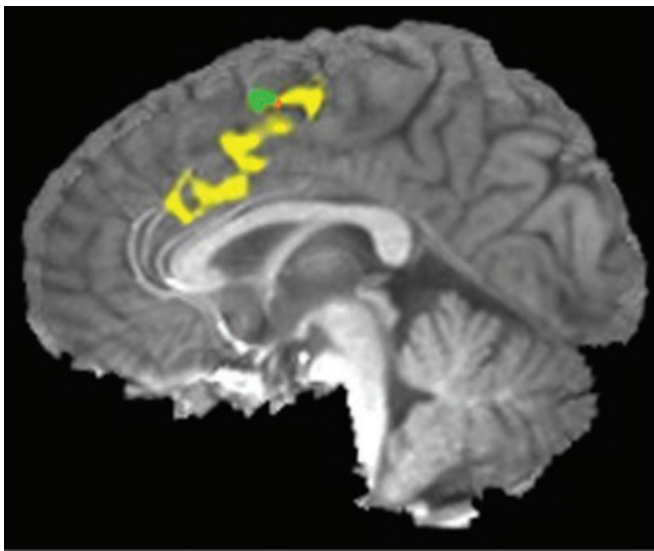


FIG. 5. An area activated during errors in this task (from Hester *et al.*, 2004b), including the ACC extending into the dorsal ACC, is represented in yellow. The pre-SMA, implicated in response conflict monitoring in this study, is displayed in green. Orange represents the small area of overlap in pre-SMA between the two clusters. We found no evidence for any conflict-related activity in the ACC, even at a liberal threshold.

even at a more liberal threshold. Although pre-SMA rather than ACC involvement in response conflict has been a consistent finding from our previous studies (Garavan *et al.*, 2002, 2003; Fassbender *et al.*, 2004; Hester *et al.*, 2004a), a review of medial PFC involvement in performance monitoring neither supported nor negated an anatomical dissociation between error detection and conflict monitoring (Ridder-

inkhof *et al.*, 2004). One interesting observation made in this review was that activations associated with pre-response conflict tended to be located more often in the dorsal/caudal ACC extending into Brodmann areas 8 and even 6. It may be that studies that involve strong pre-potent response tendencies that invoke large degrees of response conflict, such as the GO/NO-GO tasks often utilized in our studies, may result in stronger activity in motor-related areas such as the pre-SMA. Response conflict on GO/NO-GO tasks between the pre-potent GO responses and the unpredictable requirement to withhold responding upon presentation of the NO-GO stimulus has been suggested in a number of studies in humans (Braver *et al.*, 2001; Jones *et al.*, 2002; Garavan *et al.*, 2003; Nieuwenhuis *et al.*, 2003) and primates (Stuphorn *et al.*, 2000). More cognitive or 'higher-order' conflicts related to negative feedback or post-response conflict, which involve recognition that an incorrect response has just been made, may not trigger such a strong response in motor-related areas.

The maintenance of task goals and rules in working memory is an important aspect of task execution and problem solving. The dorsolateral PFC has been implicated in these working memory processes and, more specifically, a number of studies have suggested that the maintenance of representations or task set is subserved by the left lateral PFC (Frith & Dolan, 1996; MacDonald *et al.*, 2000; Garavan *et al.*, 2002; Ruchow *et al.*, 2002). Similarly, Ruchow *et al.* (2002) noted left prefrontal activation associated with negative feedback and suggested that it may have reflected an adjustment of rules or strategy following an error. Although an association between the left lateral PFC and task-set maintenance has been previously reported, the left lateral PFC region that we observed in this task was quite caudal extending into the premotor area, suggesting that this activity may code for the upcoming motor inhibition (Pochon *et al.*, 2001; Schubotz & von Cramon, 2002a). Schubotz & von Cramon (2002a,b) have suggested that the lateral premotor cortex is involved

not only in the execution of complex motor schemes but also in planning to carry them out. Brass & von Cramon (2002, 2004) also found a very posterior portion of the left dorsolateral PFC, the inferior frontal junction, to be involved in task preparation.

It is worth noting that our results reveal only that an increase in activity in the lateral PFC was followed by a decrease in subsequent conflict-related activity. The PFC could feasibly have exerted an indirect influence on the pre-SMA resulting in decreased levels of conflict. It is possible that some other prefrontal operation during the cue period resulted in this reduced conflict-related activity. A recent study suggests that the dorsolateral and medial PFC are involved in dynamic adjustments in speed-accuracy trade-offs (van Veen *et al.*, 2008) and these dynamic adjustments are likely to be related to the interactions reported here. However, we believe that adjustments in speed or accuracy do not adequately account for the pattern of results in the present study. van Veen *et al.* (2008) suggest that the dorsolateral PFC increases baseline activity in the medial PFC under conditions where speed is stressed over accuracy, whereas increased activity in the dorsolateral PFC was associated with slower responding and increased accuracy in our paradigm (Hester *et al.*, 2004b). Furthermore, whereas van Veen *et al.* (2008) report an increase in sustained levels of activity in a broad network of regions including the bilateral dorsolateral PFC and the medial wall of the PFC when speed is emphasized, our data suggest a dissociable effect of top-down control on the medial PFC. We find that the left but not right lateral PFC correlates with activity in the pre-SMA but not the ACC. Given the lateral PFC's involvement in task-set maintenance, task and motor preparation, and response correction, we argue that our results are supportive of the hypothesis that the PFC and midline regions work together to implement cognitive control.

In contrast to the inverse relationship between the left dorsolateral PFC and pre-SMA, greater cue-period right dorsolateral PFC activation was associated with greater SMA activity. Previously, we have observed SMA involvement on both GO and NO-GO trials, whereas pre-SMA activity was restricted to inhibitions (Garavan *et al.*, 1999). Perhaps, whereas greater left prefrontal control reduces pre-SMA conflict-related activity, greater preparation in the right PFC, which previous data suggest is central to response inhibition (Kawashima *et al.*, 1996; Garavan *et al.*, 1999; de Zubizaray *et al.*, 2000), yields increased motor inhibition-related activity in the SMA. This pattern of results suggests quite distinct functional roles for the pre-SMA and SMA proper.

Conclusion

These results demonstrate that it is possible to observe the interactions of distinct cortical areas, performing different functions in an interactive, dynamic way in the service of smooth behavioural control. The results illuminate how top-down, attentional resources that implement cognitive control might reduce bottom-up, stimulus-driven conflict.

Acknowledgements

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Abbreviations

ACC, anterior cingulate cortex; PFC, prefrontal cortex; SMA, supplementary motor area.

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