The Regulation of Cognitive Control following Rostral Anterior Cingulate Cortex Lesion in Humans

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Abstract

■ The contribution of the medial prefrontal cortex, particularly the anterior cingulate cortex (ACC), to cognitive control remains controversial. Here, we examined whether the rostral ACC is necessary for reactive adjustments in cognitive control following the occurrence of response conflict [Botvinick, M. M., Braver, T. S., Barch, D. M., Carter, C. S., & Cohen, J. D. Conflict monitoring and cognitive control. *Psychological Review, 108,* 624–652, 2001]. To this end, we assessed 8 patients with focal lesions involving the rostral sector of the ACC (rACC patients), 6 patients with lesions outside the frontal cortex (non-FC patients), and 11 healthy subjects on a variant of the Simon task in which levels of conflict were manipulated on a trial-by-trial basis. More specifically, we compared Simon effects (i.e., the difference in performance between congruent and incongruent trials) on trials that were preceded by high-conflict (i.e., incongruent) trials with those on trials that were preceded by low-conflict (i.e., congruent) trials. Normal controls and non-FC patients showed a reduction of the Simon effect when the preceding trial was incongruent, suggestive of an increase in cognitive control in response to the occurrence of response conflict. In contrast, rACC patients attained comparable Simon effects following congruent and incongruent events, indicating a failure to modulate their performance depending on the conflict level generated by the preceding trial. Furthermore, damage to the rostral ACC impaired the posterror slowing, a further behavioral phenomenon indicating reactive adjustments in cognitive control. These results provide insights into the functional organization of the medial prefrontal cortex in humans and its role in the dynamic regulation of cognitive control. ■

INTRODUCTION

Many views of cognition posit the existence of executive or supervisory control mechanisms that guide and flexibly adapt behavior to current goals or intentions (e.g., Umiltà, 1988; Baddeley, 1986; Norman & Shallice, 1986; Shiffrin & Schneider, 1977). Cognitive control is mainly exerted when we need to ignore interfering stimuli, or overcome prepotent responses, particularly in novel and complex tasks. A number of theories have been proposed for how executive control might achieve this (Miller & Cohen, 2001; Desimone & Duncan, 1995; Cohen & Servan-Schreiber, 1992). Recently, however, the debate has centered on how the cognitive system determines the need to recruit cognitive control, and dynamically regulates its influence on processing. It is argued that adjustments of top-down control occur online on the basis of the amount of conflict induced by competing stimuli or responses. One prominent theory (Botvinick, Cohen, & Carter, 2004; Botvinick, Braver, Barch, Carter, & Cohen, 2001) proposes that the medial frontal cortex (MFC), particularly the anterior cingulate cortex (ACC), constantly monitors for response conflicts in information processing, triggering other systems (housed in the lateral prefrontal cortex [PFC]) to implement strategic processes when conflict occurs. Although the MFC has been consistently implicated in situations demanding such performance-monitoring activity (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004), uncertainties remain regarding which specific subarea within the MFC is essential for this process (see Rushworth, Kennerley, & Walton, 2005).

Neuroanatomical studies reveal that the medial surface of the human frontal lobe is highly differentiated in terms of cytoarchitecture and connectivity with other brain regions (Picard & Strick, 1996). The ACC, in particular, can be parsed into two major subdivisions. Firstly, the rostral ACC, which lies anterior and ventral to the genu of the corpus callosum, and has dense projection to limbic areas, including the orbito-frontal cortex, insula, and amygdala (Öngür & Price, 2000). Secondly, the dorsal ACC, which is located above the corpus callosum, and connects with the lateral PFC and motor systems (Luppino, Rozzi, Calzavara, Matelli, 2003; Paus, 2001). Based on evidence from functional imaging studies, it has been suggested that the rostral and dorsal subregions of the ACC subserve distinct affective

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and cognitive functions, respectively (Allman, Hakeem, Erwin, Nimchinsky, & Hof, 2001; Paus, 2001; Bush, Luu, & Posner, 2000).

Consistent with this hypothesis, several functional neuroimaging studies have demonstrated enhanced activity in the dorsal ACC during a variety of cognitively demanding tasks, specifically those involving response conflict, such as the Stroop, the Eriksen, the go/no-go, and Simon tasks (for a review, see Botvinick et al., 2004; Rushworth, Walton, Kennerley, & Bannerman, 2004; Paus, 2001). However, despite the ubiquity of the dorsal ACC activation in functional studies, lesion data do not convincingly implicate this brain region in the detection and resolution of response conflict (Baird et al., 2006; Swick, & Jovanovich, 2002; Swick & Turken, 2002; Stuss, Floden, Alexander, Levine, & Katz, 2001; Vendrell et al., 1995). Notably, executive functions and performance monitoring can be entirely normal despite severe damage of the dorsal ACC (Fellows & Farah, 2005; Critchley et al., 2003).

The rostral ACC and the adjoining PFC, by contrast, have been primarily implicated in the evaluation of emotional and reward-related information (Phillips, Drevets, Rauch & Lane, 2003a; Whalen et al., 1998; Devinsky, Morrell, & Vogt, 1995), and the way in which this information guides decision making (Bechara, Tranel, & Damasio, 2000). Humans with lesion including these prefrontal regions have been typically described as apathetic and unconcerned when committing errors (Eslinger & Damasio, 1985), and demonstrate abnormal control of autonomic arousal states (Critchley, 2005). Moreover, functional abnormalities in the rostral ACC have been reported in patients suffering from psychiatric illness, such as schizophrenia and mood disorders (Laurens, Ngan, Bates, Kiehl, & Liddle, 2003; Phillips, Drevets, Rauch & Lane, 2003b; Drevets et al., 1997).

However, the affective–cognitive parcellation of the ACC remains a contentious subject, and a substantial body of evidence suggests that each region may not be functionally exclusive (Critchley, 2005; Davis et al., 2005; Eisenberger & Lieberman, 2004). For example, several electrophysiological studies have suggested that the error-related negativity (ERN), a scalp potential commonly taken as an index of performance monitoring (Falkenstein, Hohnsbein, & Hoormann, 1991), engages both the ''affective'' rostral and ''cognitive'' dorsal portions of the ACC (Luu, Tucker, Derryberry, Reed, & Poulsen, 2003; Luu, Flaisch, & Tucker, 2000). Moreover, a number of brain imaging studies have revealed the involvement of both subdivisions of the ACC in processing conflicts between different information processing pathways (Wager, Jonides, Smith, & Nichols, 2005; Dreher & Grafman, 2003; Menon, Adleman, White, Glover, & Reiss, 2001; Kiehl, Smith, Hare, & Liddle, 2000). Interestingly, in control demanding tasks, the dorsal ACC activity increases while the rostral ACC activity decreases, implying close functional interconnection between ACC subregions in the regulation of cognition (Polli et al., 2005; Bush et al., 1998; Drevets & Raichle, 1998).

Although the results of these studies suggest that a role in executive processes extends to the rostral portion of the cingulate, it is currently unclear whether this brain structure is *essential* for those functions. Thus, functional imaging studies can suggest merely the involvement of a brain region in a functional system, but cannot confirm whether an individual component is necessary for normal functioning. To date, only few neuropsychological studies have explicitly looked at compensatory adjustments in control following cingulate damage (Fellows & Farah, 2005; Swick & Jovanovich, 2002). None of these studies have focused on the rostral sector of the ACC. Nor have they confirmed whether the ACC performs an essential role in conflict monitoring and on-line mobilization of cognitive control.

In this study, we evaluated whether the rostral ACC is necessary for the on-line modulation of control process depending on the strength of response conflict. To investigate this, 8 patients with damage to the rostral ACC and the adjacent medial PFC (rACC patients), 6 patients with lesions outside the frontal lobe (non-FC patients), and 11 healthy control subjects were tested on a version of the Simon task in which levels of conflict and cognitive control were manipulated on a trial-by-trial basis.

Using the Simon task (Simon, 1969), it is possible to study how the cognitive system handles conflicts between competing task dimensions. In this paradigm, subjects must respond with a left or right keypress based on the color (or shape) of a stimulus that is randomly presented to the left or right of fixation. Although this stimulus location is irrelevant for the task, reaction times (RTs) are faster and error rates are lower when the stimulus and response location correspond (congruent trials), than when they do not (incongruent trials). Interference (or Simon) effects (e.g., the difference in performance between congruent and incongruent trials) are usually explained in terms of conflict between two parallel routes of response selection (Kornblum, Hasbroucq, & Osman, 1990). Typically, it is argued that there is an indirect route that determines the correct response on the basis of the relevant stimulus feature (e.g., color), and a direct route that automatically primes the response corresponding to the position of the stimulus. Thus, if stimulus position and correct response do not match (e.g., left-sided stimulus requires right-sided response), a response conflict arises, and the resolution of this conflict delays response execution.

Critically, recent findings on the Simon task strongly indicate that the prior context influences the size and sign of the interference effects in subsequent trials. More specifically, it has been reported that the Simon effect decreases (Wuhr & Ansorge, 2005), disappears (Stürmer, Leuthold, Soetens, Schröter, & Sommer, 2002), or even reverses (Hommel, Proctor, & Vu, 2004) when the pre-

vious trial (trial $n-1$) is incongruent, compared to when trial $n-1$ is congruent. Similar sequential effects have also been demonstrated for other conflict tasks, such as the Stroop and Eriksen task (Egner, & Hirsh, 2005; Kerns et al., 2004; Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; Gratton, Coles, & Donchin, 1992). According to the conflict monitoring hypothesis (Botvinick et al., 1999, 2001), these sequential dependencies of interference effects can be readily interpreted as an example of task-induced regulation of control. On this view, whenever a conflict is detected, compensatory adjustments take place, and more control is allocated to a particular task. The purpose of these adjustments is to eliminate, or at least reduce, the influence of the irrelevant information, hence, an overall reduction of the interference effect results. Some authors, however, have challenged this account, suggesting that adjustments effects are completely confounded with the presence of stimulus–response repetitions in successive trials, and therefore, can be explained by bottom-up, binding, or priming effects (Hommel et al., 2004; Mayr, Awh, & Laurey, 2003; Notebaert, Soetens, & Melis, 2001). Several recent studies, on the other hand, controlled for such stimulus or response repeats and still observed sequential modulations, making it difficult to attribute these effects entirely to perceptual or motor priming (Ullsperger, Bylsma, & Botvinick, 2005; Wuhr & Ansorge, 2005; Kerns et al., 2004).

The Simon paradigm elicits a sufficient number of errors to allow examination of another indicator of conflict-mediated adjustments in control, posterror slowing. This phenomenon refers to the fact that participants performing speeded response tasks tend to slow down following the occurrence of errors (Laming, 1968; Rabbitt, 1966). According to the conflict monitoring model, errors are frequently associated with a high degree of response conflict. This is a consequence of the competition between the just executed incorrect response and the (posterror) activation of the correct response resulting from continued processing of the stimulus (Yeung, Botvinick, & Cohen, 2004; Botvinick et al., 2001). Following errors, activation of the conflict-related control process tends to shift the system toward a more conservative strategy, producing slower but more accurate responding in subsequent trials. Here, as in the case of sequential effects, conflict monitoring provides crucial information in regulating cognitive processing based on an ongoing evaluation of performance.

Such trial-by-trial sequential modulation of interference effect and posterror slowing provides an excellent means of investigating reactive, conflict-triggered adjustments in top-down control in patients with rostral ACC lesions. Accordingly, we directly compared Simon effects following congruent and incongruent trials. If the rostral ACC provides adaptability in performance according to changing task demands, then strategic modulation of the Simon interference effect depending on the nature of the preceding trial (congruent vs. incongruent) should not be seen in rACC patients. By contrast, normal participants and non-FC patients would be expected to show a significant decrease of the Simon interference effect after incongruent compared to congruent trials. Moreover, rostral ACC damage is expected to result in reduced adjustments (slowing) of the response generation process after commission of errors.

METHODS

Participants

Three groups of subjects participated in the study: (a) a group of patients with focal lesions centered on the rostral ACC and the adjoining ventromedial PFC (rACC group, $n = 8$, mean age = 55 years, $SD = 6.1$); (b) a control group of patients with focal damage sparing the frontal cortex (non-FC group, $n = 6$, mean age = 66.8 years, $SD = 8.1$); and (c) a control group of healthy subjects ($n = 11$, mean age = 53.4 years, $SD = 7.7$), age, education, and sex ratio matched with the ACC group.

Brain-damaged patients were recruited from the Centre for Studies and Research in Cognitive Neuroscience in Cesena. They were selected on the basis of the location of their lesion evident on computed tomography (CT) or magnetic resonance imaging (MRI) scans. In rACC patients, lesions were the result of a ruptured aneurysm of the anterior communicating artery. Included patients were those who had lesion restricted to the rostral portion of medial surface of the frontal lobe, and with no other diagnosis likely to affect cognition or interfere with the participation in the study (e.g., significant psychiatric disease, alcohol misuse, history of cerebrovascular disease, focal neurological examination). In no case did patients selected for the study contain lesions extending into the lateral PFC. Lesions were traced from CT or MRI scans on standard templates (Damasio & Damasio, 1989) by a neurologist. Figure 1 shows the extent and overlap of the brain lesions in the rostral ACC group. The Brodmann's areas affected in this group were areas 10, 12, 32, 24, with region of maximal overlap occurring in Brodmann's areas 32 and 24a–c (i.e., the rostral portion of the ACC), where all cases had lesions.

As for non-FC patients, their lesions were the result of infarction or the removal of a meningioma (1 patient) involving the cerebral cortex outside the frontal lobe, mostly in the medial and lateral temporal lobe ($n = 5$). The Brodmann's areas affected in this group were areas 21, 22, 28, 36, 37, 38, 39.

Patients were not receiving psychoactive drugs at the time of testing, and were all more than a year postonset. They gave informed consent to participate in the study according to the Declaration of Helsinki (International Committee of Medical Journal Editors, 1991) and the Ethical Committee of the Department of Psychology, University of Bologna. Table 1 shows demographic data,

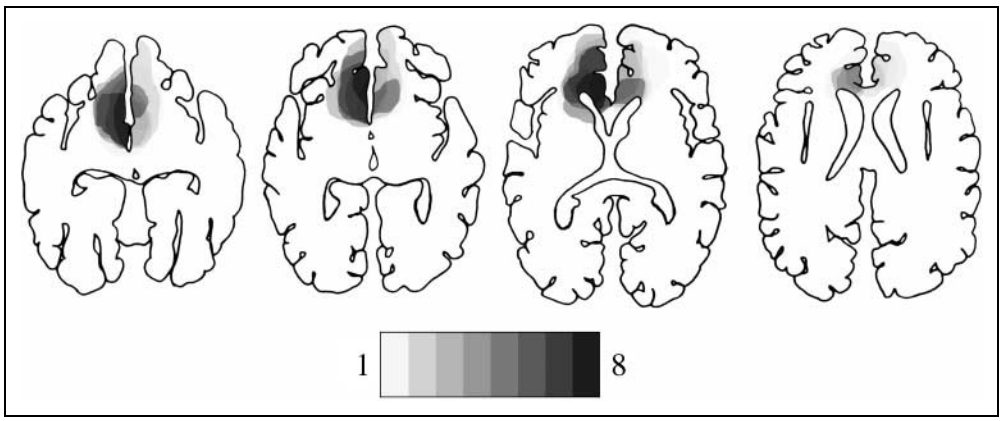

Figure 1. Location and degree of overlap of brain lesions. The figure shows the lesions of the eight subjects with rostral ACC lesion. Lesions are projected on the same four axial templates following the method developed by Damasio and Damasio (1989). Progressively darker shades denote the degree to which lesions involve the same brain regions, as indicated in the legend.

Table 1. Demographic, Clinical, and Lesion Data of the Two Patient Groups

	Sex	*Age at Test (Years)*	*Education*	*Side of Lesion*	*Etiology*	*Description of Lesion*	*MMSE Score*
Rostral ACC Patient							
1	M	49	8	L	AcoA Aneurysm	Rostral ACC VmPFC	26
2	M	56	13	B	AcoA Aneurysm	Rostral ACC VmPFC	27
3	M	56	13	R	AcoA Aneurysm	Rostral ACC VmPFC	24
4	F	62	8	L	AcoA Aneurysm	Rostral ACC VmPFC	24
5	F	52	19	B	AcoA Aneurysm	Rostral ACC VmPFC	27
6	M	66	5	L	AcoA Aneurysm	Rostral ACC VmPFC	23
7	F	53	8	R	AcoA Aneurysm	Rostral ACC VmPFC	23
8	M	46	8	R	AcoA Aneurysm	Rostral ACC VmPFC	24
Non-FC Patient							
1	M	58	13	R	Infarction	Mesial Temporal	25
2	F	75	10	R	Infarction	Temporal Parietal	23
3	F	61	5	L	Infarction	Lateral Temporal	–
4	F	82	5	R	Tumor	Mesial Temporal	23
5	F	77	8	R	Infarction	Temporal pole	24
6	M	58	8	L	Infarction	Insula Basal ganglia	26

M = male; F = female; L = left; R = right; B = bilateral; ACoA = Anterior Communicating Artery; ACC = Anterior Cingulate Cortex; VmPFC = Ventromedial prefrontal cortex; MMSE = Mini-Mental State Examination.

lesion side, etiology, lesion description, as well as the Mini-Mental Status Examination score (MMSE; Folstein, Robins, & Helzer, 1983) for each patient.

Normal participants were healthy volunteers who were not taking psychoactive medication and were free of current or past psychiatric or neurological illness as determined by history. Normal controls scored at least 28 out of 30 on the MMSE. There were no significant differences between ACC patients and normal controls on the measured demographic variables ($p > .7$ in all cases).

Stimuli and Apparatus

In each experiment, stimuli were displayed on a 21-in. color VGA monitor (1024 × 768 spatial resolution, 16 color bit) situated on a table top. An IBM-compatible Pentium IV computer, running E-Prime software (Schneider, Eschman, & Zuccolotto, 2002), controlled the presentation of stimuli, timing operation, and data collection. The subjects were seated approximately 60 cm away from the screen. All stimuli were presented on a black background. A fixation display, consisting of a central fixation cross (subtending 0.4° × 0.4°) was present for the entire duration of the trial, except during the intertrial interval (ITI). The central cross was positioned at eye level, along the subjects' midline. Target stimuli were green or red circle outlines (4.5° in diameter), indicating left or right responses, respectively. Each target stimulus appeared approximately 6° either on the left or right of central fixation. Responses were made by pressing the ''Alt'' key (on the left side of the keyboard) with the index finger of the left hand if a green circle was presented, and the ''Ctrl'' key (on the right side of the keyboard) with the index finger of the right hand, if a red circle was shown.

Procedure

All experiments took place in a dimly lit room. Subjects were seated in front of the computer, which presented the task instructions. These were also summarized by the experimenter, after subjects had read them, to ensure that they had been understood.

Sequences of two consecutive trials were created, somewhat arbitrarily, by increasing the ITI after every second trial. In each sequence, the first trial was treated as the prime or ''previous trial,'' and the second trial as the probe or ''current trial.'' This procedure allowed us to connect previous and current trials as closely as possible, and to prevent effects of a trial sequence from influencing the processing of the following ones.

When target stimuli appeared, participants were required to press the key corresponding to the color of the circle, while ignoring the physical location of the target stimuli. At the beginning of each trial sequence, the fixation display appeared for 1000 msec, acting as a warning signal. Then, the first target stimulus (S1) was presented until one of the keys was pressed (R1), or 3000 msec had elapsed, whichever occurred first. Following a fixed interval of 1000 msec, the second target stimulus (S2) was shown for up to 3000 msec until a response (R2) was given. This started an ITI of 2000 msec during which the screen was blank. If participants responded with the wrong key, or were slower than 3000 msec after S1 or S2, it was considered respectively an error or omission. No feedback was given, and omission and error trials were not repeated.

Target stimuli were presented randomly in the left and right visual space with equal probability, such that the side of the first stimulus did not predict the location of the second stimulus. The participants were informed that there was no relationship between the S1 and S2 stimuli, and were instructed to respond as quickly as possible while maintaining high levels of accuracy.

Design

Each participant received one practice block and two experimental blocks in two separate sessions. Every block was composed of four repetitions of 16 randomly intermixed unique trial sequences, resulting from the factorial combination of two S1 positions (left vs. right), × two R1 locations (left vs. right, correlated with S1 color), × two S2 positions (left vs. right), × two R2 locations (left vs. right, correlated with S2 color). Congruent and incongruent trials were in equal proportion. Trial sequences were classified according to the congruency of the previous and current trial, generating four equiprobable trial sequences: congruent–congruent (C–C), congruent–incongruent (C–I), incongruent–congruent (I–C), and incongruent–incongruent (I–I). The dependent variables were RTs (msec) and error rates. When necessary, multiple comparisons were conducted using the Newman –Keuls test. The level of significance was set to $p < .05$ for all analyses.

RESULTS

Response times exceeding the range of 150–2000 msec were discarded from analysis. This cutoff procedure resulted in the exclusion of 2% of responses for normal controls, and 3.8% and 4.1% for the rACC patients and the non-FC patients, respectively. This outlier analysis was done prior to all statistical analyses in all experiments for previous and current trial RTs, and therefore will not be mentioned again below. Of the remaining data, correct median RTs and percentages of errors were computed for each group of participants in each condition of the previous and current trial.

We first tested whether the three participant groups differed on overall task performance through a two-factorial analysis of variance (ANOVA) on correct RTs, with congruency (congruent and incongruent) as a within-subject factor, and group (normal controls, rACC

patients, and non-FC patients) as a between-subject factor, pooling over previous and current trials. The main effect of congruency and group were both significant [$F(1,22) = 130.4$, $p < .0001$, and $F(2,22) = 17.8$, $p < .0001$, respectively]. Of particular relevance, the effect of congruency interacted with group [$F(2,22) = 6.1$, $p < .007$], reflecting a smaller Simon effect (e.g., incongruent minus congruent RTs) in normal controls (31 msec) relative to both non-FC (47 msec) and rACC patients (65 msec). However, the Simon effect did not differ between patient groups [$F(1,12) = 1.6$, $p = .2$]. Likewise, the Simon effect in error rate was significantly higher in non-FC (1.1%) and rACC patients (1.3%) than in healthy participants [0.4%; $F(2,22) = 6.7$, $p < .005$], but the two patient groups did not differ ($p = .5$).

Previous Trial

For previous trials, a two-factorial ANOVA, with congruency (congruent and incongruent) as a within-subject factor, and group (normal controls, rACC patients, and non-FC patients) as a between-subject factor, was conducted on the RT data. The main effect of group was significant [$F(2,22) = 10.04$, $p < .001$]. Thus, normal control participants displayed significantly faster RTs (561 msec) than did rACC (678 msec) and non-FC patients (726 msec; $p < .007$ in all cases). However, no significant differences were observed between patient groups ($p > .05$). There was also a significant main effect of congruency [$F(1,22) = 49.36$, $p < .001$], with faster RTs on congruent (623 msec) than incongruent trials (686 msec), confirming the presence of the basic Simon effect. The interaction between group and congruency was not significant [$F(2,22) = 1.82$, $p = .20$].

Error rates followed a similar pattern. There was a significant main effect of group [$F(2,22) = 7.23$, $p < 0.003$], a significant effect of congruency [$F(1,22) = 30.5$, $p < .001$], and no interaction between group and congruency [$F(2,22) = 2.2$, $p = .12$].

Current Trial

Incorrect RTs of the current trial, as well as RTs following an error in the previous trial, were excluded from further analyses. The remaining RTs (see Figure 2, left panel) were subjected to a three-factorial ANOVA, with previous

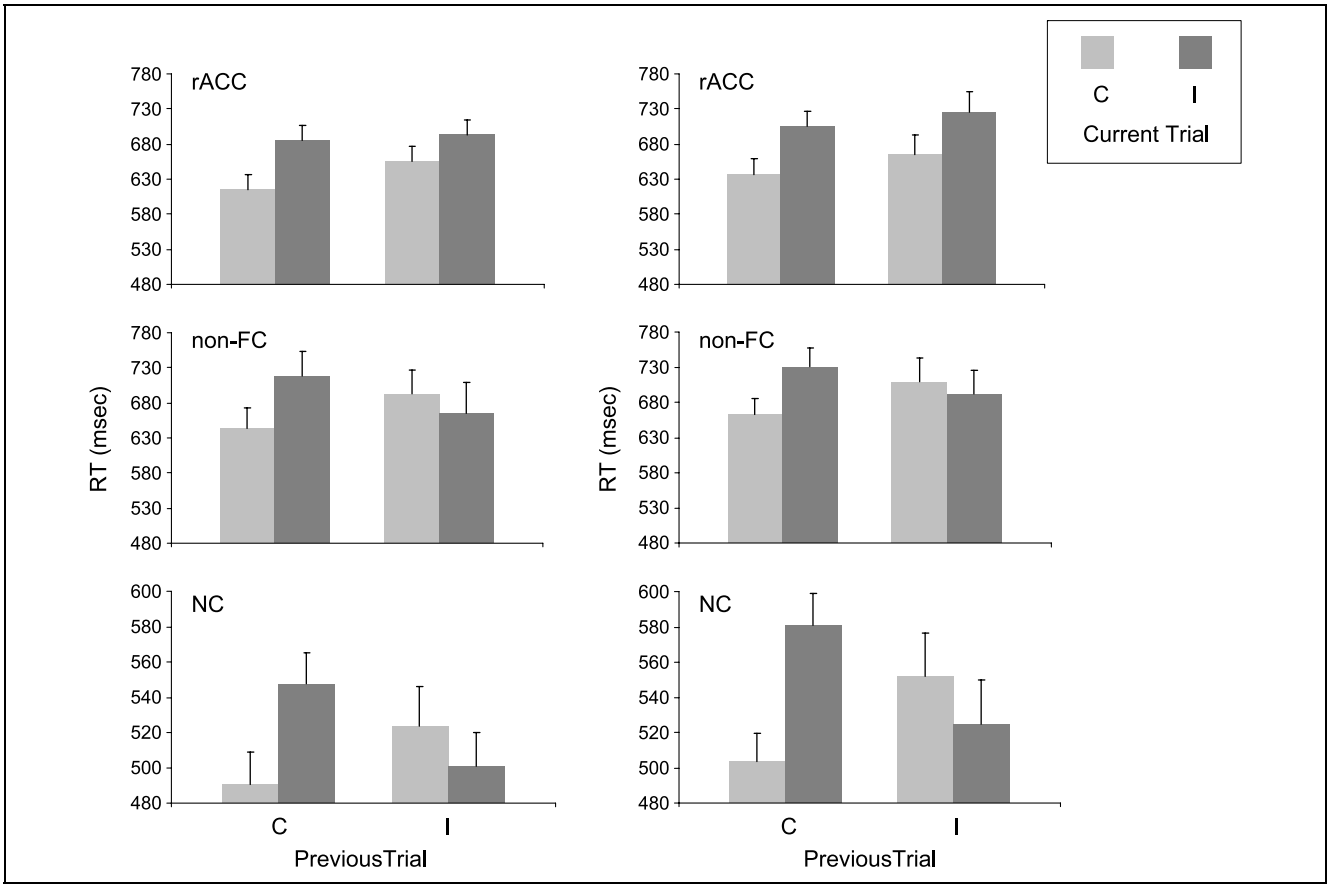

Figure 2. Mean reaction times for congruent (C) and incongruent (I) current trials, reported separately for trials coming after congruent (Previous C) and incongruent trials (Previous I) in the three participant groups (rACC = rostral anterior cingulate patients; non-FC = nonfrontal patients; NC = normal controls). Error bars show standard error of the mean. Left panel depicts data from all current trials. Right panel depicts data from 50% of current trials in which neither color of stimuli nor responses of the preceding trials were repeated.

congruency (congruent and incongruent) and current congruency (also, congruent and incongruent) as within-subject factors, and group (normal controls, rACC patients, and non-FC patients) as a between-subject factor.

The main effect of group was significant [$F(2,22) = 17.15$, $p < .0001$], with normal controls responding faster (516 msec) than either group of patients (671 and 659 msec, for non-FC and rACC patients, respectively). There was also a main effect of current congruency [$F(1,22) = 82.67$, $p < .0001$], reflecting shorter RTs on congruent (584 msec) than on incongruent trials (619 msec; e.g., standard Simon effect). The effect of previous congruency was not significant [$F(1,22) = 1.01$, $p = .3$].

Of particular interest in the present context were the sequential influences of the Simon effect from a previous trial. The analysis revealed that the interaction between previous congruency and current congruency was significant [$F(1,22) = 59.41$, $p < .0001$], and its details were consistent with the conflict adaptation effect. Thus, the Simon effect (e.g., incongruent minus congruent RTs) was large after congruent trials (68 msec) but tended to become negative after incongruent trials (−4.5 msec). There was also a significant interaction between group and current congruency [$F(2,22) = 9.33$, $p = .001$].

Of most importance for the present purposes, however, there was a significant three-way interaction between group, previous congruency, and current congruency [$F(2,22) = 5.00$, $p < .01$], suggesting that the sequential modulation of the Simon effect differed across groups. This interaction was further explored with two-way ANOVAs performed separately on RTs from each group of participants. Significant interactions between previous congruency and current congruency were noted for normal controls [$F(1,10) = 33.93$, $p < .0001$] and non-FC patients [$F(1,5) = 74.33$, $p < .001$], but not for the rACC group [$F(1,7) = 3.11$, $p = .12$]. Planned comparisons revealed that the Simon effect was significantly larger following congruent trials than following incongruent trials in normal control participants (57 msec vs. −23 msec) and non-FC patients (76 msec vs. −28 msec), but not in rACC patients (70 msec vs. 38 msec).

Error percentages (shown in Table 2) were also subjected to a three-way ANOVA. The main effect of group was significant [$F(2,22) = 20.02$, $p < .0001$]. Normal controls tended to produce fewer errors (1%) than both non-FC (2.4%) and rACC patients (2.2%). The significant main effect of current congruency [$F(1,22) = 43.47$, $p < .0001$] indicated a Simon effect in error rates, with fewer errors on congruent trials (1.5%) than on incongruent ones (2.4%). Moreover, the significant interaction between previous congruency and current congruency [$F(1,22) = 22.15$, $p < .0001$] signaled a sequential modulation of the Simon effect. In particular, a significant Simon effect in error percentages occurred after congruent trials (1.7% of accuracy difference between incongruent and congruent trials) but not after incongruent trials (0.1%). The three-way interaction was not significant [$F(2,22) = 3.0$, $p = .07$]. Nevertheless, for completeness, we also conducted planned comparisons of the sequence effect for each individual group of participants. We found a reliable sequential modulation of the Simon effect in normal controls [1.2% vs. −0.5% of error rate difference after congruent vs. incongruent trials, respectively; $F(1,10) = 8.05$, $p < .01$] and non-FC patients [2.3% vs. −0.3%; $F(1,5) = 11.03$, $p < .02$], but not in rACC patients [1.6% vs.1.1%; $F(1,7) = 3.50$, $p = .1$]. Therefore, accuracy data corroborated the RT data.

Table 2. Mean Percentages of Errors for Congruent (C) and Incongruent (I) Current Trials, Reported Separately for Trials Coming after Congruent (Previous C) and Incongruent Trials (Previous I) in the Three Participant Groups

	Previous C		*Previous I*	
Group	*Current C*	*Current I*	*Current C*	*Current I*
rACC	1.5	3	1.7	2.9
non-FC	1.3	3.7	2.5	2.1
NC	0.6	1.8	1.1	0.6

rACC = rostral anterior cingulate patients; non-FC = nonfrontal patients; NC = normal controls.

Repetition Priming vs. Conflict Adaptation

As already noted in the Introduction, it is controversial whether sequential modulation of interference effects truly reflect task-induced variations in top-down control, or depend on bottom-up repetition priming effects. Recently, Mayr et al. (2003) demonstrated (in an Eriksen flanker task) that when trial repetitions were excluded from the data analysis, there was no reduction of the interference effect after incongruent trials. They noted that subjects may be faster on incongruent trials preceded by incongruent trials (I–I) than on incongruent trials preceded by congruent trials (C–I) because half of the I–I transitions but none of the C–I transitions involved exact stimulus (and thus response) repetitions. Therefore, they suggested that the substantial RT benefits observed after incongruent trials may simply reflect repetition priming, rather than adaptation of top-down control. Given these considerations, it is important to explore whether our results can be accounted for in terms of repetition priming. To this end, 50% of the C–C and I–I sequences that involved complete repetitions (e.g., sequences in which stimulus color, stimulus position, and the response repeat), and 50% of the C–I and I–C that involved partial repetitions (e.g., sequences in which stimulus color and response repeat, while stimulus position changes) were eliminated from the dataset (see Figure 2, right panel). Additional analyses focusing on the sequential modulations of the Simon effect were

then performed on the remaining RTs. As before, the analyses showed significant interactions between previous congruency and current congruency for normal controls [$F(1,10) = 21.71, p < .001$] and non-FC patients [$F(1,5) = 21.43, p < .005$], but not for the rACC group [$F(1,7) = 0.14, p = .7$]. These interactions signaled that a pronounced, positive Simon effect was present following congruent trials, but it reversed following incongruent trials in normal controls (77 msec vs. −27 msec) and non-FC patients (68 msec vs. −17 msec). By contrast, a robust Simon effect occurred in rACC patients, regardless of congruency of previous trial (68 msec vs. 61 msec, following congruent vs. incongruent trials, respectively).

Posterror Slowing

To test the prediction that rACC patients are impaired in posterror slowing, we performed an ANOVA with group as a between-subject factor, and trial (trial after error and trial after correct response) as a within-subject factor. The normal control group was limited to those participants who made more than three errors ($n = 9$). For all groups, correct responses on trials following errors were slower than following correct trials [$F(2,20) = 20.3, p < .001$]. Most importantly, there was a significant interaction between group and trial [$F(2,20) = 3.94, p < .003$]. Planned comparisons revealed that normal controls and non-FC patients exhibited a sizeable, significant posterror slowing (76 msec, $p < .001$, and 63 msec, $p < .003$, respectively). In contrast, rACC patients showed a nonsignificant posterror slowing (8 msec, $p = .6$).

DISCUSSION

The role of the more rostral aspect of the medial PFC in executive processes is not well understood. Classical neurological evidence suggests that patients with lesion involving this region appear to be intellectually unimpaired, and demonstrate apparently normal performance on a host of neuropsychological measures (Teuber, 1964; Rylander, 1947). More recent studies have essentially confirmed these early observations (Bechara et al., 2000; Eslinger & Damasio, 1985), but they also demonstrate that some of these patients show behavioral deficits on difficult, attention-demanding tasks (Burgess, Veitch, de Lacy Costello, & Shallice, 2000). In the present study, we examined whether the rostral ACC and the adjoining medial PFC is necessary for rapid, on-line adjustments in cognitive control, following the occurrence of response conflict. Specifically, subjects were tested in a variant of the Simon task in which interference effects were measured as a function of conflict level of the preceding trial. Less interference was expected following events associated with response conflict, arguably due to increased focusing of top-down control. The performance of individuals with focal damage to the rostral ACC was compared with that of age-matched normal controls and patients who had brain damage outside the frontal lobe.

Our neuropsychological data provide compelling new evidence that the rostral ACC is critical for the dynamic regulation of cognitive control. Rostral ACC patients failed to appropriately modulate their performance in response to the amount of conflict generated by the task, showing a sizeable Simon interference effect not only after congruent trials (which do not induce response conflict) but also after incongruent trials (which induce response conflict). By contrast, both healthy controls and non-FC patients showed abolition of interference effects following incongruent events, thus revealing that they were able to actively monitor their performance and use this information to intensify the cognitive control allocated to the task.

Because the two patient groups had comparable interference effects after the occurrence of congruent trials, as well as on $n-1$ (or previous) trials, it appears unlikely that the inefficiency of rACC patients after incongruent trials can be explained entirely by group differences in mental effort or motivation. Moreover, control analyses suggested that group differences in the sequential modulation of the Simon effect cannot be attributed to low-level priming effects from one trial to the next (Mayr et al., 2003), but truly reflect differences in compensatory adjustments of cognitive control (Wuhr & Ansorge, 2005; Kerns et al., 2004; Stürmer et al., 2002). Indeed, our pattern of results persists even when repetition of identical stimuli (and responses) in trial sequences was excluded from analysis. Finally, both healthy participants and non-FC patients tended to adopt a more cautious response mode after errors. This was not the case for rACC patients, who exhibited a near absence of posterror slowing. Together, these findings reinforce the proposal, put forth by Botvinick et al. (2001), that both postconflict and posterror compensatory adjustments in performance may depend on a single functional mechanism.

These results have several implications for theories of executive control and ACC function. We first discuss how rostral ACC damage can disrupt context-sensitive control adjustments. Cognitive theorists distinguish between two executive functions involved in the flexible modulation of control: an evaluative function, which *detects* conflict between competing behavioral responses, and a strategic function, which *implements* control adjustments for conflict reduction. According to one perspective (the conflict monitoring hypothesis, Botvinick et al., 2001), the ACC plays a critical role in conflict and error monitoring, but it is not responsible for the allocation of control. Conversely, the selection for action hypothesis (Posner & DiGirolamo, 1998; Posner & Petersen, 1990) maintains that the ACC implements cognitive control directly by biasing or selecting task-relevant responses against strong habitual behaviors. It is difficult, however,

to adjudicate between these two alternative views based on current lesion data. This is because impairments of either evaluative or strategic processes would result in the same pattern of behavioral effects, namely, lack of context-dependent adjustments in behavior. It is important to note, however, that the selection for action hypothesis would predict that rACC patients should exhibit performance decrements in *all* incongruent conditions, irrespective of previous context, due to difficulties in overcoming task-irrelevant, prepotent responses. Our behavioral findings do not support such a prediction. When compared to non-FC patients, the rACC group did not display greater interference effects and/or higher error rates in incongruent trials that were preceded by congruent ones. This seems to suggest that the rostral ACC itself does not contribute to attentional allocation. Accordingly, both behavioral and imaging studies have shown that the lateral PFC is most critical in processing response selection via top-down control of other brain regions (Egner & Hirsh, 2005; Kerns et al., 2004; Gehring & Knight, 2002; Miller & Cohen, 2001; Vendrell et al., 1995). Instead, the current observations fit more closely with a conflict monitoring view, according to which ACC lesions would specifically impair the patients' ability to shift toward more focused or conservative behavior on the basis of an evaluation of their own performance.

As previously discussed, and in contrast to the dorsal ACC and its association with cognitive activity, the rostral ACC and adjacent areas have been identified primarily with emotional, motivational, and reward-related processing (Bush et al., 2000; Devinsky et al., 1995). The current data, however, challenge this view by demonstrating that the rostral, ''affective'' ACC is also critically involved in the ongoing adjustment of cognitive control. This suggests that a functional separation of the rostral and dorsal ACC along emotional versus cognitive lines may be an oversimplification. Neuroimaging studies showing activation within the dorsal ACC (the alleged cognitive division) in response to emotional and painful stimuli also argue against a clear-cut functional segregation within the ACC and the medial PFC (Rainville, 2002; Ploghaus et al., 1999).

In the majority of previous imaging studies, the response associated with cognitive conflict has been localized to the dorsal ACC. However, the present findings suggest that other regions in the frontal cortex may be critical for determining when cognitive control is needed (Swick & Turken, 2002; Gehring & Knight, 2000). Consistent with our results, recent research has suggested that the conflict-dependent activation may lie rostrally within the ACC (Milham & Banich, 2005). Moreover, several authors emphasize the role of the rostral ACC in processing errors and monitoring the outcomes of actions (Nieuwenhuis, Slagter, Alting von Geusau, Heslenfeld, & Holroyd, 2005; Braver, Barch, Gray, Molfese, & Snyder, 2001; Kiehl et al., 2000). Also consistent with this evidence, patients with damage to the ventromedial PFC, including the rostral ACC, show reduced error-related brain potentials while responding in a flanker task, which suggests a close relation between performance monitoring, as reflected by the ERN, and the rostral ACC (Stemmer, Segalowitz, Witzke, & Schönle, 2003). Thus, current data and previous physiological and neuropsychological findings converge in indicating that a role in conflict processing and cognitive control extends to the rostral region of the ACC.

One may then ask what the specific role of the rostral ACC in conflict processing and control might be. Multiple evidence suggests that rostral ACC is responsive to a variety of emotional signals (such as errors, negative feedback, pain, and monetary loss) that predict negative outcome, unless the level of cognitive control is appropriately intensified (Aston-Jones & Cohen, 2005). Although a characterization of the rostral ACC as a purely ''emotional'' sector is clearly inappropriate, it seems plausible to suggest that this area is involved in mediating the interaction between cognitive functioning and affective, motivational, and autonomic processes necessary for the guidance of adaptive behavior (Critchley, 2005; Simpson, Drevets, Snyder, Gusnard, & Raichle, 2001; Bechara et al, 2000; Drevets & Raichle, 1998). Thus, when lapses in performance are detected, signals from rostral ACC can activate both affective and cognitive systems, perhaps via prominent cingulate connections with the amygdala and brainstem nuclei, such as the *locus coeruleus*. Recent findings suggest that the locus coeruleus, in addition to its role in arousal, can have precise effects in regulating higher-level cognitive functions, for instance, by enhancing task-specific control mechanisms in the PFC. This pathway, possibly complemented by direct projections from the dorsal ACC to the PFC, may ensure rapid change in behavior according to emergent demands (Aston-Jones & Cohen, 2005).

The observed impairment of dynamic adjustment in cognitive control is highly consistent with the well-known effects of medial prefrontal lesion, which typically causes patients to suffer from behavioral rigidity and perseveration (Robbins, 2005; Fellows & Farah, 2003). On this view, perseveration may result from the patients' inability to modify their behavior in response to an evaluation of their own performance, due to a failure in detecting internal stimuli (e.g., conflict) that predict unfavorable outcomes.

The current findings also have direct implications for our understanding of the nature several psychiatric disorders. For instance, the disordered monitoring and regulation of self-generated behavior in schizophrenia bears some striking similarities with the cognitive deficits evidenced in ventromedial PFC patients (Cohen, & Servan-Schreiber, 1992). Consistent with this, neuroimaging studies have suggested that schizophrenic patients demonstrate relative underactivity in the rostral ACC associated with impaired performance in conflict

tasks (Laurens et al., 2003; Carter, Mintun, Nichols, & Cohen, 1997). Another relevant example comes from the strong correlation between obsessive–compulsive disorders (OCD) symptoms and the presence of hyperactivity in the rostral ACC and medial PFC. Although these findings were initially interpreted as a nonspecific result of increased anxiety, more recent studies have shown that a dysfunctional conflict monitoring system is a critical aspect of OCD (Ursu, Stenger, Shear, Jones, & Carter, 2003), which might explain why OCD patients experience the need to monitor and correct their actions repeatedly (Pitman, 1987).

In summary, we report that the rostral ACC and the adjacent ventromedial PFC play a crucial role in conflict monitoring and on-line, plastic adjustment of performance. These findings have important implications for the anatomy of cognitive control, as well as for our understanding of medial frontal functions. Thus, our results impact on the simple scheme of the ACC divided into rostral ''emotion'' and dorsal ''cognition'' parts. The data also highlight the importance of lesion studies for establishing cognitive neuroanatomy, given that the rostral ACC lies outside the regions commonly activated in functional imaging studies of control. Finally, the present findings appear compatible with the view wherein the rostral ACC is involved in the mechanisms by which mental processes are integrated by emotional signals. This proposal is, of course, speculative, and further research will be needed to directly evaluate its merit.

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