Strategic Modulation of Cognitive Control

Ovidiu V. Lungu[1,2], Tao Liu[1,2], Tobias Waechter[1,2], Daniel T. Willingham[3], and James Ashe[1,2]

Abstract

■ The neural substrate of cognitive control is thought to comprise an evaluative component located in the anterior cingulate cortex (ACC) and an executive component in the prefrontal cortex (PFC). The control mechanism itself is mainly local, triggered by response conflict (monitored by the ACC) and involving the allocation of executive resources (recruited by the PFC) in a trial-to-trial fashion. However, another way to achieve control would be to use a strategic mechanism based on long-term prediction of upcoming events and on a chronic response strategy that ignores local features of the task. In the current study, we showed that such a strategic control mechanism was based on a functional dissociation or complementary relationship between the ACC and the PFC. When information in the environment was available to make predictions about upcoming stimuli, local task features (e.g., response conflict) were no longer used as a control signal. We suggest that having separate control mechanisms based on local or global task features allows humans to be persistent in pursuing their goals, yet flexible enough to adapt to changes in the environment. ■

INTRODUCTION

The neural basis of cognitive control, the processes underlying the executive control of behavior, is a major focus of cognitive neuroscience. Although there is general agreement that the prefrontal cortex (PFC) is the principal structure involved in executive control (Fuster, 2002; Miller & Cohen, 2001), there has been much debate as to how and when cognitive control is recruited and how it operates.

One prominent theory of cognitive control, the conflict monitoring hypothesis, holds that cognitive control is recruited when there are conflicts in information processing that lead to error-prone situations (MacDonald, Cohen, Stenger, & Carter, 2000; Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; Carter et al., 1998). However, there continues to be debate as to exactly what aspect of stimuli is important: processing conflict (Botvinick et al., 1999; Carter et al., 1998), error likelihood (Brown & Braver, 2005), or the consequences of an action (Nachev, Rees, Parton, Kennard, & Husain, 2005; Walton, Devlin, & Rushworth, 2004; Matsumoto, Suzuki, & Tanaka, 2003; Stuphorn, Taylor, & Schall, 2000). Response conflict theory proposes that conflict is but one of the signals triggering strategic adjustment in behavior (Botvinick, Cohen, & Carter, 2004; Botvinick, Braver, Barch, Carter, & Cohen, 2001). Studies done within this framework have shown that high levels of conflict in the current trial result in the activation of the anterior cingulate cortex (ACC), which are followed by subsequent adjustments in performance associated with engagement of the PFC (Botvinick et al., 2004; Kerns, Cohen, MacDonald, et al., 2004). In addition, recent data suggest that the cognitive control mechanisms in the Stroop and similar tasks are local in nature (Egner & Hirsch, 2005a, 2005b; Weissman, Giesbrecht, Song, Mangun, & Woldorff, 2003) in that they are based on transient amplification of task-relevant information. Taken together, these findings imply that the control mechanism used in Stroop-like tasks has an ''on-line'' property to the extent that the physical presence of incongruent stimuli is needed for the control to emerge.

However, another way to achieve cognitive control would be via a strategic, top–down mechanism, based on global task features, that ignores the local aspects of the task. Such mechanism would use long-term predictions about the environment as a control signal; in other words, it would use expectations about upcoming stimuli rather than information about immediate processing conflict or the outcome of the current actions. Humans are well equipped to detect and use sequential or statistical regularities in the environment (Huettel, Mack, & McCarthy, 2002; Hunt & Aslin, 2001), and both the PFC and the ACC have been shown to be sensitive to expectancy effects (Kerns, Cohen, Stenger, & Carter, 2004; Durston, Thomas, Worden, Yang, & Casey, 2002). Moreover, the ACC has been shown to be sensitive to both global and local features of behavior (Weissman et al.,

[1]Veterans Affairs Medical Center, Minneapolis, [2]University of Minnesota, [3]University of Virginia

2003), and activity in the PFC shifted from transient to sustained activity during a temporally extended decision-making task (Yarkoni et al., 2005). All these findings seem to point to the involvement, under specific circumstances, of the ACC and PFC in a strategic control mechanism based on ignoring the local and amplifying the global features of the task.

Thus, if the brain were to exert cognitive control based on a strategic mechanism, one would predict behavioral improvement in addition to increased activity in the PFC during trials that were consistent with subjects' expectancies, reflecting a top-down support process, similar to that found in temporally extended decision making (Yarkoni et al., 2005). The motivation for the current study was to determine the neural substrate of such a system and to examine how it might affect the interactions between the ACC and the PFC. In particular, we were interested in whether the ACC would also react to local or global task features.

METHODS

We used a spatial stimulus–response compatibility (SRC) task in which, as in previous studies (Vu & Proctor, 2004; Marble & Proctor, 2000; de Jong, 1995), participants were presented with compatible and incompatible trials. We manipulated the frequency of the trial types such that subjects could, or could not, form predictions about upcoming events. When the frequency of compatible and incompatible trials was the same and subjects could not predict the type of the next stimulus, we expected that cognitive control would be based on local features, namely, response conflict (MacDonald et al., 2000; Botvinick et al., 1999; Carter et al., 1998). However, when the two types of trials were unequally distributed, we expected subjects to implement control based on the frequency information about the stimuli and, thus, to use a strategic control mechanism based on global task features. The participants had to respond via a button press to stimuli appearing at one of two locations on the screen, using a compatible or incompatible stimulus–response (S-R) mapping rule, based on stimulus color (blue, yellow) and location (left, right). For example, for the blue stimuli, subjects pushed the same-side button (left button for left location, right button for right location), whereas for the yellow stimuli, they pushed the opposite-side button. This rule ensured a direct-mapping response for one type of stimulus (compatible trials, low response conflict) and a crossed-mapping response for the other one (incompatible trials, high response conflict). During functional imaging, the subjects performed two experimental runs, each containing six blocks of trials. The distribution of trials in the first and last blocks in each run were pseudorandom in that the two types of S-R mappings (compatible and incompatible) were evenly distributed (50–50). The middle four blocks in each run were called probabilistic and the S-R mappings were distributed 80–20 (in one run, the compatible S-R mapping was presented 80% of the time; in the other run, the incompatible S-R mapping was presented 80% of the time). Thus, in these blocks, the stimuli differed in terms of both their compatibility and their frequency. Motor responses (left vs. right finger) and stimulus locations on the screen (left vs. right side) were equally distributed in all blocks. As mentioned above, we expected that neural activity in the random blocks would reflect a cognitive control mechanism based on response conflict (local feature), whereas in probability blocks it would reflect a control mechanism based on subjects' expectancies (global feature).

Subjects

Eight volunteers (4 women; median age 22 years, age range 20–38 years) participated as normal subjects in the functional magnetic resonance imaging (fMRI) experiment in exchange for fixed monetary rewards. All subjects were right-handed and did not have any neurological history. The study was approved by the University of Minnesota Institutional Review Board. Data from one female participant was excluded from analysis because she moved more than 3 mm during the experiment. Therefore, the results reported here are from the remaining 7 subjects (14 experimental runs, 2 runs per subject, acquired in the same experimental session).

Behavioral Task

Stimuli were presented to the participants on a screen via a video projector from a room adjacent to the magnet. Subjects were positioned supine in the magnet, with a response box on their chest. They saw the screen through a mirror attached to the receiver coil. On the screen, they saw two circular lights set in a dark brown background. The lights were discs 2 cm in diameter and their centers were 9 cm apart, equivalent to a visual angle of approximately 4.3°. Subjects made motor responses on a push-button pad by using the index and middle fingers of their dominant hand. The blue and yellow lights appeared in either the left or the right location and were illuminated separately. Subjects made a motor response based on the color and location of the light, using the following rule: when the light was blue, subjects pushed the same-side button (left button for left location, right button for right location); when the light was yellow, they pushed the opposite button (left button for right location, right button for left location). This rule ensured a direct-mapping response for the blue stimuli and a crossed-mapping response for the yellow ones. Lights were turned off immediately following a correct response; otherwise, they were illuminated for 1200 msec after which they were turned off automatically. When subjects pushed the wrong button, the lights stayed on the screen until the

correct choice was made or the 1200 msec had elapsed. This procedure ensured visual feedback for correct responses. Stimulus onset asynchrony was 1500 msec. A LabVIEW 6.1 program controlled the presentation of the lights and recorded the reaction time and accuracy of each response. Six blocks of 40 stimuli were presented in each experimental run. The first and last blocks were pseudorandom, where the two types of stimuli (blue and yellow) were distributed 50–50. The middle four blocks were probabilistic, where one color was more frequent than the other one by a ratio of 4 to 1. Each subject was exposed to two experimental runs, one in which the blue color was more frequent in the probability blocks and another in which the yellow color was more frequent. The order of these runs was counterbalanced between subjects. There was a 30-sec break before and after each block of stimuli.

Imaging Parameters of the fMRI Experiment

A 3-T MAGNETOM Trio Whole Body MR System (Siemens Medical Systems, Erlangen, Germany) was used for image acquisition. Before the fMRI runs, 144 or 160 (depending on the subject's head width) FLASH structural images were acquired in slices of 1-mm thickness in the sagittal plane (256 × 256 mm) yielding a spatial resolution of 1 × 1 × 1 mm for the anatomical volume. Then, a whole-brain fMRI was performed using an echo-planar imaging sequence measuring blood oxygenation level dependent (BOLD) signal. Thirty functional slices per volume were acquired for all subjects in all runs. These slices had a thickness of 3 mm and they were acquired in the transversal plane (matrix size 64 × 64), in a field of view of 192 × 192 mm, with a 1-mm gap between them to avoid cross talk. Therefore, the spatial resolution of functional images was 3 × 3 × 3 mm. A complete scan of the whole brain was acquired with 3750-msec repetition time, 35-msec echo time, and 90° flip angle; 152 volumes were measured during each functional run.

Preprocessing of fMRI Data

Brain Voyager (Brain Innovation B.V., Maastricht, the Netherlands) software was used to preprocess and analyze the fMRI data. The functional bidimensional images of every subject were preprocessed to correct for motion artifacts (movements less than 3 mm in any plane), for differences in slice scan time acquisition, and for temporal linear trends. We had to exclude one subject whose movements were greater than 3 mm. The functional images were used to reconstruct the 3-D functional volume for every subject and every run. Spatial smoothing of functional data was performed using a Gaussian full width at half maximum kernel of 7 mm. The 3-D functional volume was subsequently aligned with the corresponding 3-D anatomical volume and both were normalized to standard Talairach space (Talairach & Tournoux, 1988).

Statistical Analysis of fMRI Data

We used a rapid event-related design for our experiment, analyzing the correct trials only. Each behavioral event (1500 msec) was classified according to its dominant frequency in the probability blocks and whether the preceding stimulus was of the same or a different type. This yielded four predictors per type of block per experimental condition. These predictors were entered as fixed factors in a first stage of analysis, and then a multisubject general linear model (GLM), with subjects as random effects, was used in the second stage of analysis (Penny & Holmes, 2003), using the standard procedure implemented in Brain Voyager software. The statistical parameters of this model were computed voxelwise for the entire brain and activation maps were computed for various contrasts between the predictors. The criteria used for displaying the activation maps were a cluster size of at least 100 adjacent isometric voxels (resolution 1 × 1 × 1 mm) and a statistical threshold of $p < .005$ (uncorrected) for each voxel in this cluster. The general method of analyzing the imaging data was as follows: Regions of interests (ROIs) were identified using main contrasts (e.g., more frequent vs. less frequent trials) and the abovementioned statistical and spatial thresholds. Then, the estimates of the multisubject GLM computed by Brain Voyager for these regions were further analyzed using SPSS (SPSS Inc., Chicago, IL) to assess the changes in BOLD signal for other conditions. This approach is similar to that used by Carter et al. (2000) when further analysis of activation in the ACC was performed separately for Scan 3.

In our study, subjects performed two runs (A and B) as a measure of counterbalancing the type of stimulus that was more or less frequent during the probability blocks, rather than comparing the two runs with each other. Our primary goal was to find what was common for both of them (e.g., the effect of frequency regardless of stimulus compatibility or the effect of stimulus compatibility regardless of stimulus frequency), and not to compare or contrast run A with run B. Therefore, we considered 14 runs for analysis of behavioral and imaging data.

RESULTS

Behavioral Performance

In the random blocks, compatible and incompatible stimuli were evenly distributed. Therefore, there was no way for subjects to predict the next trial. Figure 1A shows the reaction time (RT) for correct trials across

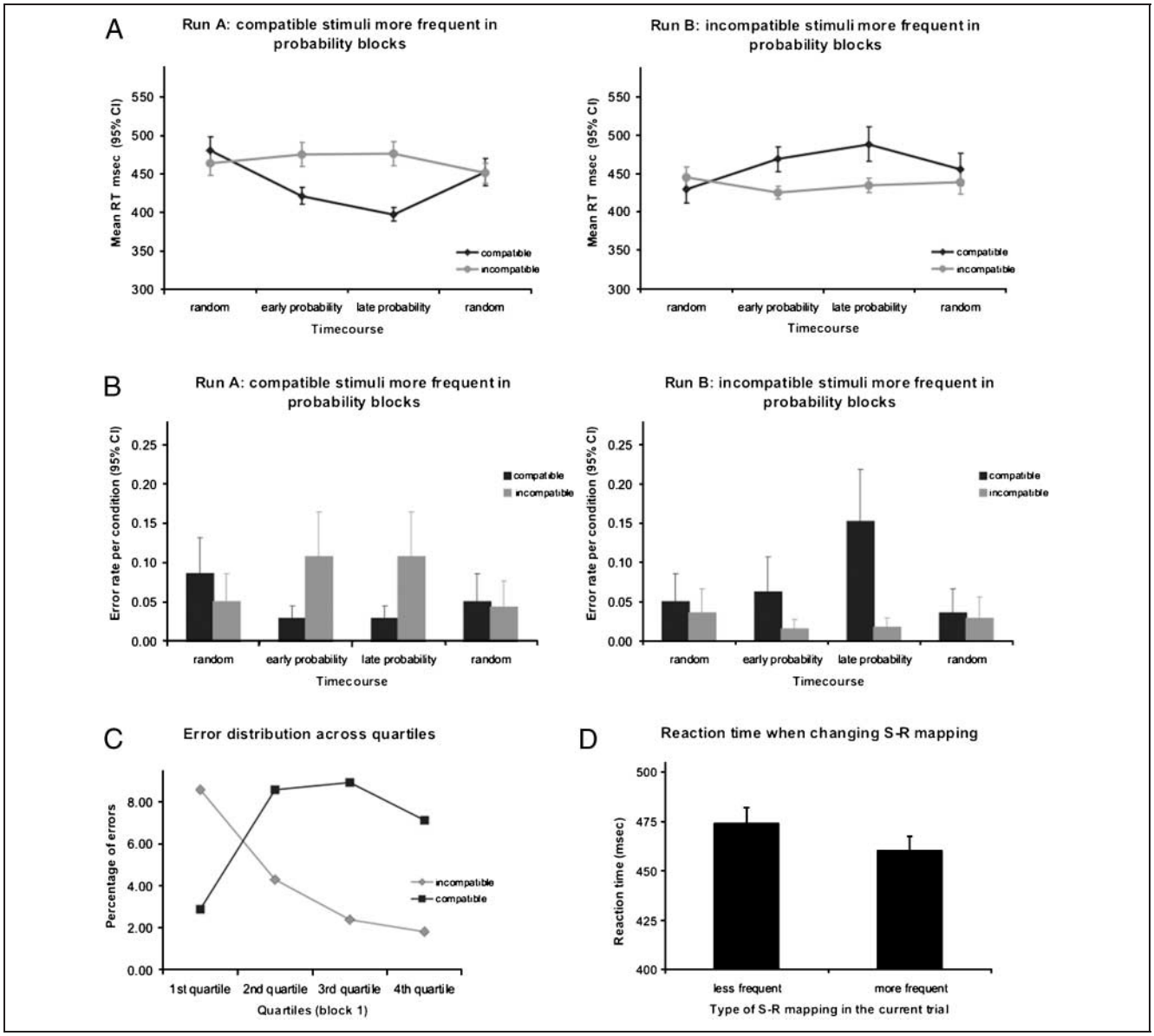

Figure 1. (A) Reaction time across blocks, in the two experimental runs. (B) The error rate per condition in the two experimental runs. (C) Error rate for the compatible and incompatible trials in each quartile of the first random block. (D) Reaction time for trials in probability blocks in which there was a change in S-R mapping.

blocks, separately for each experimental run. The difference in RT between incompatible and compatible trials did not reach significance, $t(13) = 0.904$, $p = .36$, as assessed by a contrast that had the experimental runs as random effects. The lack of a difference in RT is not especially surprising given that previous studies mixing compatible and incompatible S-R mappings in equal proportion (Vu & Proctor, 2004; Marble & Proctor, 2000; de Jong, 1995) also failed to find a spatial compatibility effect on RT. In the same line, increasing the percentage of colored words relative to neutral words reduced the interference effect in the Stroop task (Tzelgov, Henik, & Berger, 1992). Moreover, a series of experiments using SRC tasks (de Jong, 1995) showed that the apparent absence of the compatibility effect was due to suppression of the compatible mapping rule. Therefore, the lack of a difference in RT reflects control implementation similar to that present in the Stroop task (i.e., overcoming a prepotent response). Further evidence for adaptation in this condition comes from examining the distribution of errors across quartiles in the first block of each run (Figure 1C). The percentage of errors for incompatible trials tended to decrease over time in the first random block, whereas those for compatible trials showed the opposite pattern. A series of chi-square tests was used to show these trends. The tests assessed the distribution of errors and correct responses for each type of stimulus (compatible vs. incompatible) in the last three quartiles. The cutoff for these tests was chosen to be the distribution of

errors and correct responses in the first quartile for the corresponding type of stimulus. In this way, the distribution of each subsequent quartile was compared with that of the first, separately for each type of stimulus. The results of these chi-square tests are shown in Table 1.

In probability blocks, the RT to the most frequent stimuli (regardless of their S-R mapping) was significantly shorter than that of the less frequent stimuli, $t(13) = 10.92$, $p < .001$, for both experimental runs combined. This finding suggests that in probability blocks, stimulus frequency and not stimulus compatibility influenced RT. Figure 1B shows the error rate for each type of stimulus in random and probability blocks (grouped as early and late), for each experimental run. Although the error rates in the random blocks were the same for both compatible and incompatible stimuli, $t(13) = 1.713$, $p = .11$, for both runs combined, there was an opposite speed–accuracy trade-off effect in the probability blocks, $t(13) = 3.214$, $p = .007$, for both runs combined. In other words, the most frequent stimuli elicited lower error rates in spite of the associated short RT as opposed to the less frequent stimuli for which both the error rates and the RT were higher.

It is possible that the phenomenon of task switching will confound the interpretation of the results in the different blocks. The probability blocks contained fewer task switches (changes in S-R mapping from one trial to the next) and more task repetitions than did the random blocks. Thus, one might consider that differences in RT between frequent and less frequent stimuli in the probability blocks were due to the repetition of the S-R mapping rather than to a long-term predictive process. To rule out such a possibility, we analyzed, in the probability blocks, trials in which a task switch occurred. By design, switching from a less frequent S-R mapping to a more frequent one occurred as often as the opposite switch. If the subjects used a global predictive strategy, then they should be faster when switching from less frequent S-R mapping to the more frequent one than vice versa. Indeed, that was the case (Figure 1D), and the difference in RT between the two types of switches was significant, $t(13) = 3.201$, $p < .007$ for both runs combined. Again, the behavioral adjustment appears to have been related to stimulus frequency, regardless of stimulus compatibility, which supports the idea that subjects used a global, anticipatory strategy to implement control in these blocks.

Table 1. Chi-square Tests Showing that the Distribution of Correct Responses and Errors in Subsequent Quartiles of the First Random Block Differed from That of the First Quartile

	Distribution of Correct Responses and Errors (%)	*χ^2 Test (df = 1)*
Compatible S-R mapping		
First quartile (target distribution)	97.1–2.9	N/A
Second quartile	91.4–8.6	$\chi^2 = 8.235$ ($p = .004$)
Third quartile	91.1–8.9	$\chi^2 = 7.438$ ($p = .006$)
Fourth quartile	92.9–7.1	$\chi^2 = 5.559$ ($p = .018$)
Incompatible S-R mapping		
First quartile (target distribution)	91.4–8.6	N/A
Second quartile	95.7–4.3	$\chi^2 = 1.641$ ($p = .200$)
Third quartile	97.6–2.4	$\chi^2 = 4.108$ ($p = .040$)
Fourth quartile	98.2–1.8	$\chi^2 = 3.290$ ($p = .070$)

Imaging Results

Random Blocks

In the first random blocks of both experimental runs, three regions in the ACC were found to be significantly activated when contrasting the BOLD signal of incompatible with that of compatible trials (Table 1). One of these regions, the left dorsal ACC (−1, 22, 32; Brodmann's area [BA] 32) was spatially close to regions found to be more activated by incongruent than congruent trials in the Stroop task (Peterson et al., 1999), to respond more to incompatible than to compatible trials in the Flanker task (Botvinick et al., 1999), and to be more active during inappropriate than during appropriate responses in a missing letter task (Kerns, Cohen, Stenger, et al., 2004). Thus, this area is the closest, spatially, to other areas found to be activated in experiments supporting the response-conflict theory. These previous studies localize the evaluative component of cognitive control in the dorsal ACC. The other two ACC regions, both in the ventral ACC, were spatially close to areas found to be activated by incongruent trials in the Stroop task (Peterson et al., 1999), or by an interaction between task speed and stimulus congruency (Matthews, Paulus, Simmons, Nelesen, & Dimsdale, 2004). These activations support the involvement of other parts of the ACC in response to evaluative demands in the task. The same contrast between incompatible and compatible stimuli in random blocks also activated a network of frontal, temporal, and parietal areas (Table 2 and Figure 2A), with a very strong activation (1135 voxels, 1 × 1 × 1 mm) in the right middle frontal gyrus encompassing BA 9/46 (45, 2, 36). This frontal area is spatially close to regions found to be sensitive to context (Koechlin, Ody, & Kouneiher, 2003), to maintenance in working memory (Rypma, Prabhakaran, Desmond, Glover, & Gabrieli, 1999), to changing the attended dimensions in a computerized variant of Wisconsin Card Sorting Task (Konishi et al., 2002), and to task switching (Dove, Pollmann, Schubert, Wiggins, & von Cramon, 2000).

Table 2. Regions Activated by Contrasting the Activity in the Incompatible (Crossed S-R Mapping) with the Compatible Trials (Direct S-R Mapping) in the First Random Blocks of Both Experimental Runs

	Talairach Coordinates			
Region (BA)	*x*	*y*	*z*	*Voxels*
Middle frontal gyrus (6)	36	5	56	112
Middle frontal gyrus (9/46)	45	2	36	1135
Anterior cingulate gyrus (24)	2	39	−3	238
Anterior cingulate gyrus (32)	−1	22	32	287
Anterior cingulate gyrus (24)	−7	21	23	127
Posterior cingulate gyrus (23/30)	4	−52	11	233
Inferior parietal lobule (40)	59	−37	27	505
Precuneus (7)	7	−53	36	109
Cuneus (19)	−15	−83	33	103
Superior occipital gyrus (19)	26	−72	36	437
Superior temporal gyrus (22)	−48	−40	14	137
Middle temporal gyrus (21)	54	−50	7	982
Middle temporal gyrus (39)	41	−75	24	213
Middle temporal gyrus (21)	−51	−52	7	1689
Insula	−34	8	15	262
Caudate nucleus	16	−19	20	148
Putamen	−27	17	3	166
Cerebellum	38	−44	−22	222

The statistical threshold for all voxels in these regions was $t(13) \geq 3.3725$, $p < .005$. Voxels reported here have a resolution of 1 × 1 × 1 mm and only regions of at least 100 contiguous voxels are presented. Coordinates show the mass center of each region.

The change in BOLD signal for both compatible and incompatible stimuli in the first random blocks in dorsal ACC (BA 32) and middle frontal gyrus (BA 9/46) is shown in Figure 2B and C. A detailed analysis of the change in BOLD signal in the ACC showed not only that the activation was significantly higher for incompatible stimuli compared with compatible ones, $t(13) = 4.867$, $p < .001$, but also that it was significantly higher than baseline, when incompatible trials followed the compatible trials, $t(13) = 4.224$, $p = .001$, but not when incompatible trials were preceded by other trials of the same type, $t(13) = 1.667$, $p = .119$. The same analysis performed for the region in the right middle frontal gyrus (BA 9/46) revealed that activation in this area was higher for incompatible trials than for the compatible ones, $t(13) = 7.313$, $p < .001$. Unlike the ACC, the BOLD signal in the PFC for incompatible trials was higher than baseline when they were preceded either by compatible, $t(13) = 5.618$, $p < .001$, or incompatible trials, $t(13) = 2.926$, $p = .012$. Again, these results are consistent with studies supporting the response-conflict theory (Kerns, Cohen, MacDonald, et al., 2004; MacDonald et al., 2000; Botvinick et al., 1999). Consequently, the ACC was more active when incongruent stimuli followed congruent ones, signaling the need for control implementation. The PFC was more active for incongruent trials regardless of the type of stimulus preceding them, which suggests that control implementation activity, once triggered, persisted as long as the incongruent trials were present. Unlike the PFC, ACC activity diminished for incongruent trials following other incongruent trials, because control implementation module was already activated. This finding supports the role of the ACC as a trigger of executive control and an evaluator of the need for control; once control is effectively implemented, there is no need for further control.

Probability Blocks

In the probability blocks, one type of S-R mapping was more frequent than the other. If subjects used this frequency information when implementing control in the task, then one should see cingulate and prefrontal areas activated using a contrast in which the stimuli were grouped on the basis of the frequency of the S-R mapping (regardless of stimulus compatibility). Indeed, regions in the cingulate, premotor, motor, parietal, and temporal cortex were activated more by the less frequent stimuli, whereas areas in the PFC were activated more by the most frequent stimuli (Table 3 and Figure 3A). Specifically, in the frontal cortex, three areas were more active during the most frequent trials: one in the left presupplementary motor area (pre-SMA) (BA 6) and two in the medial PFC, the right and left superior frontal gyrus (BA 9). The opposite contrast, between the less frequent and most frequent trials, activated a region bilaterally in the caudal ACC (BA 24), which was part of a bigger activated network spanning from left motor and premotor cortices to cingulate cortex and adjacent parietal region (Figure 3A).

Therefore, changes in stimulus frequency that allowed subjects to anticipate in the long run the type of upcoming trial had an effect, albeit in opposite directions, on the ACC and PFC. The ACC was activated more by the less frequent stimuli, suggesting that it was sensitive to a different type of conflict, based on stimulus frequency information (global or strategic level), and not on stimulus compatibility (local level). Prefrontal regions were more activated by the most frequent stimuli, suggesting a putative goal-setting function, consistent with a global and sustained control strategy. The fact that regions in the prefrontal and cingulate cortex were activated by opposite contrasts indicates that the control mechanism in this behavioral context was

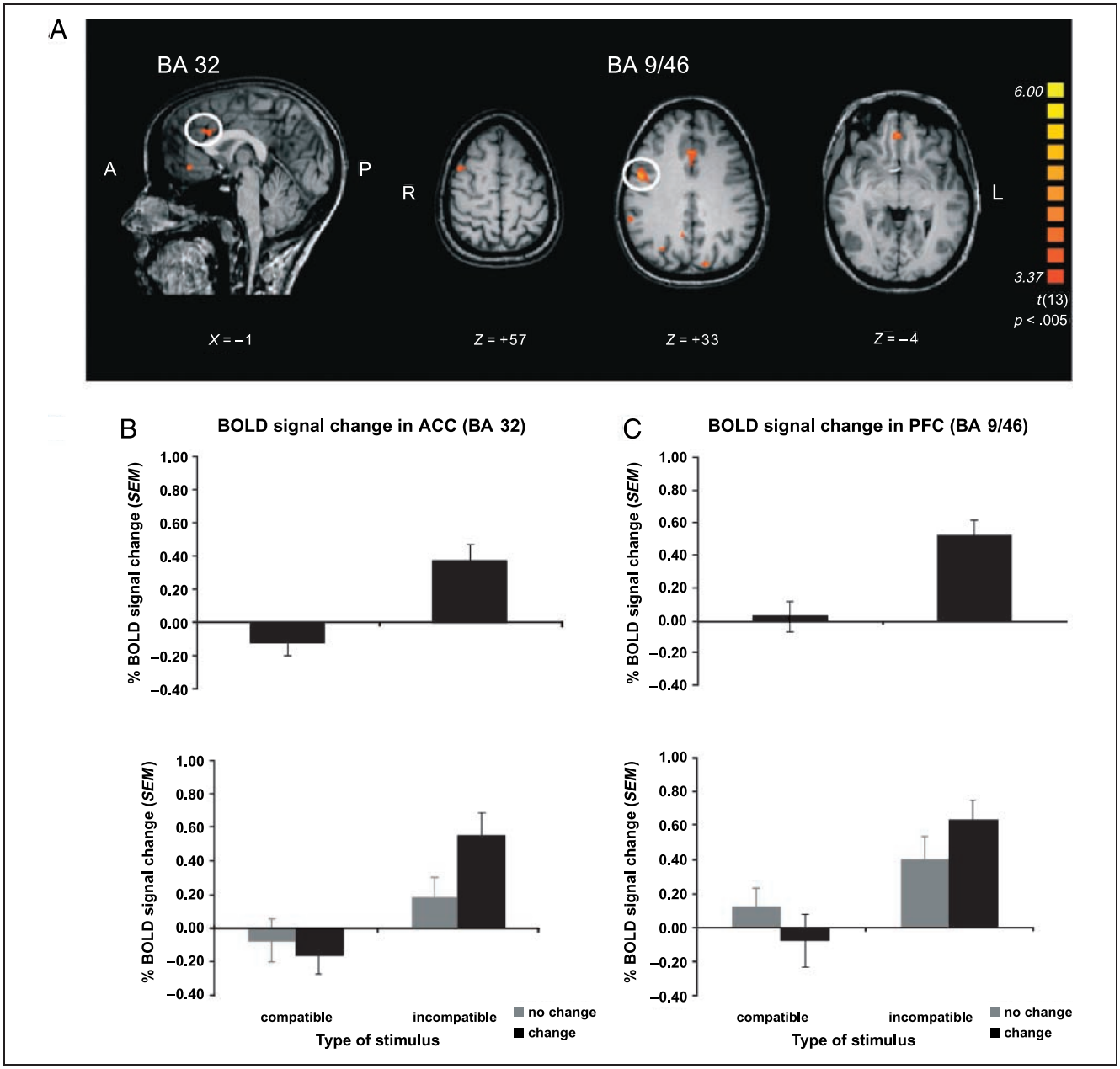

Figure 2. (A) Areas activated by the contrast *incompatible S-R mapping > compatible S-R mapping* in first random blocks. (B) The change in BOLD signal in area BA 32 for compatible and incompatible stimuli (top) and for compatible and incompatible stimuli as a function of the type of previous stimulus (bottom). (C) The change in BOLD signal in area BA 9/46 for compatible and incompatible stimuli (top) and for compatible and incompatible stimuli as a function of the type of previous stimulus (bottom).

different from that proposed by the response-conflict theory (MacDonald et al., 2000; Botvinick et al., 1999; Carter et al., 1998).

Further analysis of the BOLD signal in the prefrontal area showed that the most frequent stimulus yielded more activation than the less frequent ones in probability blocks (first graph in Figure 3B), $t(13) = 4.783$, $p < .001$. This was especially true when a trial from the most frequent stimulus category followed one from the less frequent group (second graph in Figure 3B), $F(1,13) = 10.432$, $p = .007$. The same pattern of activity was maintained regardless of stimulus compatibility, as may be seen in the third graph in Figure 3B, which shows the activation in both experimental runs. This prefrontal area in the left superior frontal gyrus (−8, 39, 51; BA 9) is spatially close to a region found to be sensitive to the preceding context in a go/no-go task (Durston et al., 2002), which is consistent with the strategic role we attribute to it.

A converse pattern of activation was seen in the caudal region of the ACC (−2, −4, 48; BA 24) that was more activated by the less frequent stimuli than by the most

Table 3. Regions Activated by Contrasting the Activity in the More Frequent Trials (Regardless of Their S-R Mapping) with Activity in the Less Frequent, in the Probability Blocks of Both Experimental Runs

	Talairach Coordinates			
Region (BA)	*x*	*y*	*z*	*Voxels*
80% Stimuli > 20% stimuli				
Right superior frontal gyrus (9)	13	37	54	119
Left superior frontal gyrus (9)	−8	39	51	530
Left superior frontal gyrus (6)	−22	14	58	262
Middle temporal gyrus (21)	−51	−29	−10	135
Middle occipital gyrus (19)	18	−86	17	126
20% Stimuli > 80% stimuli				
Premotor cortex (6)	54	−2	8	142
Precentral gyrus (4/6)	22	−14	46	533
Primary motor cortex (4)	−5	−22	71	185
Cingulate gyrus (24)	−21	−8	35	148
Precuneus (7)	3	−55	44	166
Inferior parietal lobule (40)[a]	−34	−32	44	21,201
Precuneus (7)	−2	−58	63	487
Superior parietal lobule (7)	−31	−43	62	323
Superior temporal gyrus (22)	−46	0	−1	427
Middle temporal gyrus (37)	49	−53	−1	314
Middle temporal gyrus (21)	48	−10	−5	614
Middle occipital gyrus (19)	−42	−66	−9	1976
Thalamus	−14	−18	12	1104
Brain stem	−4	−15	−25	152
Putamen	14	9	5	936
Caudate nucleus	−12	10	4	212
Insula	35	12	17	855
	33	2	0	173
	−34	7	17	2203
Cerebellum	39	−36	−25	292
	34	−55	−23	127
	14	−54	−11	1479
	−35	−45	−22	1930

The statistical threshold for all voxels in these regions was $t(13) \geq 3.3725$, $p < .005$.

[a]This region also extends anterior to sensorimotor and premotor areas (BA 1, BA 2, BA 3, BA 4 and BA 6) and ventrally to cingulate cortex (BA 24).

frequent ones (first graph in Figure 3C), $t(13) = 7.532$, $p < .001$. There was also a significant interaction effect between stimulus frequency and the change in type from the previous stimulus (second graph in Figure 3C), $F(1,13) = 19.391$, $p = .001$. This shows that the BOLD signal for less frequent stimuli was higher following a more frequent stimulus than when it was preceded by another less frequent stimulus. It can also be seen that, regardless of stimulus compatibility, the less frequent stimuli were associated with more activation in this region of caudal ACC, and this effect persisted even when the incongruent stimuli were the trials with the higher frequency (Figure 3C). The activated portion of caudal ACC is spatially close to areas found to be involved in successful inhibition of response in a go/no-go task (Garavan, Ross, Murphy, Roche, & Stein, 2002) or during presentation of targets requiring a nonprepotent response in a cued S-R incompatibility task (Barber & Carter, 2005).

Activation over Time

To better understand the roles played by the ACC and PFC during this strategic cognitive control, we examined changes in activation in these regions over time, in the probability blocks (Figure 4).

The ACC, motor, premotor, and parietal areas became sensitive to stimulus frequency in the first probability block, within less than 2 min from the beginning of the experimental run (Figure 4A), then this activation decreased over time (Figure 4C, right). By contrast, areas in the PFC became activated by stimulus frequency only after the first probability block (Figure 4B), as there was no significant difference in activation between the more and less frequent trials in Block 1 (Figure 4C, left). This suggests that regions in the ACC were sensitive to rapid changes in the task context, whereas the sustained control strategy developed in the PFC at a slower pace over time.

We were also interested in the issue of a control trigger. If we are to eliminate the idea of the homunculus from theories of control, we need to specify the modulatory signal and the mechanism by which control is triggered. For example, the response conflict theory considers the amount of conflict in a given trial as the control signal and the sensitivity of the ACC to response conflict as the control mechanism. Although our experiment was not designed to specifically identify the control trigger in cases of strategic control, we can explore this issue by analyzing the changes in activation during transition from the random to the first probability block; six regions showed increases in activation during this transition (Table 4). Of these, the bilateral pre-SMA and superior frontal gyrus (BA 9) showed increases in activity when comparing the more frequent trial type in the first probability block with trials of the same type in the first

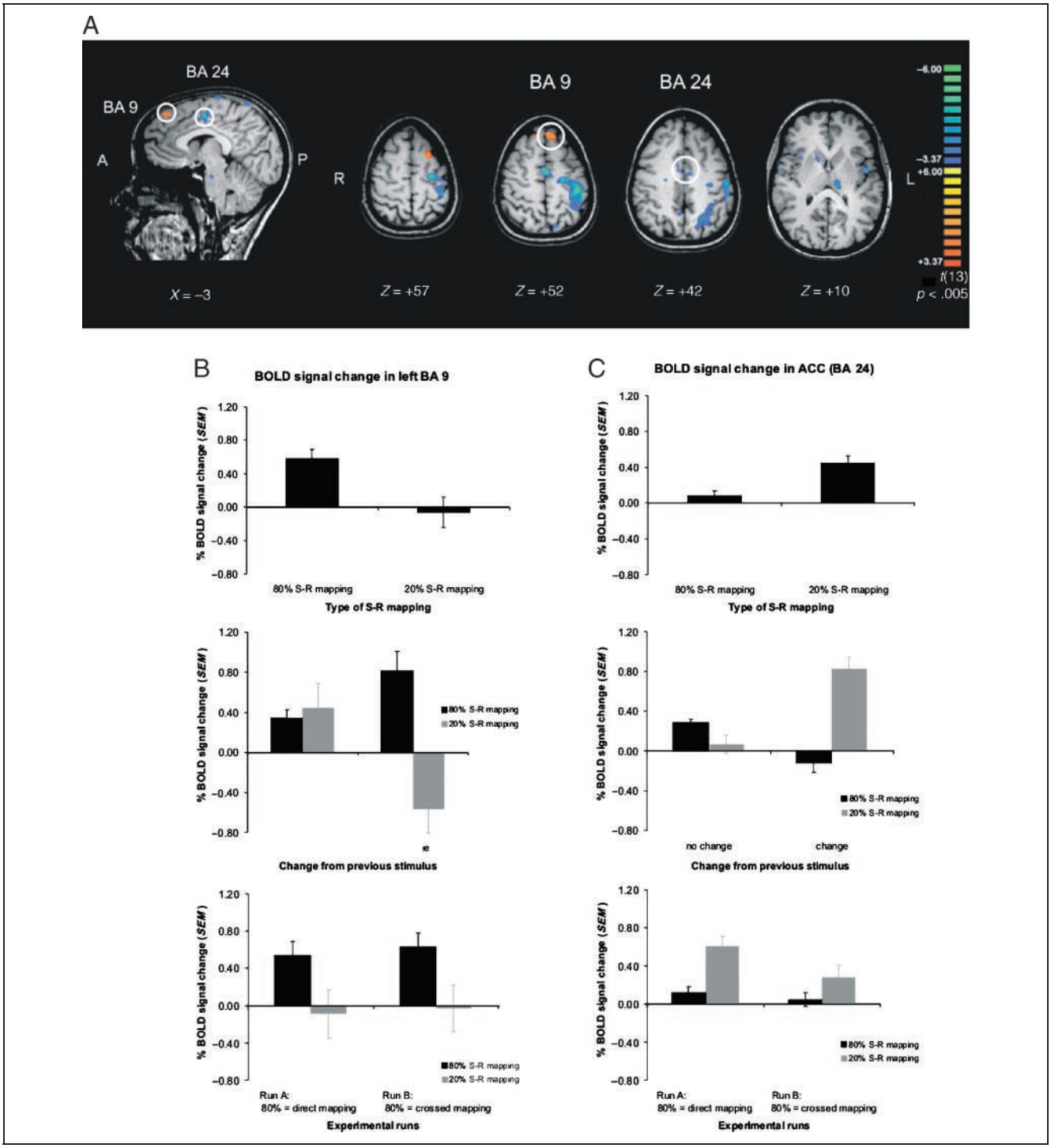

Figure 3. (A) Areas activated by the contrast *more frequent S-R mapping > less frequent S-R mapping* in probability blocks. Orange-yellow areas showed an increase in activity for the more frequent S-R mapping compared to the less frequent. Blue-green areas showed the opposite pattern. (B) The change in BOLD signal in the left superior frontal gyrus (BA 9) for more frequent and less frequent stimuli in both experimental runs combined (top), in each experimental run (bottom), and as a function of the type of preceding stimulus (middle). (C) The change in BOLD signal in the medial caudal ACC (BA 24) for more frequent and less frequent stimuli in both experimental runs combined (top), in each experimental run (bottom), and as a function of the type of preceding stimulus (middle).

random block. By contrast, the SMA, ventral putamen, and inferior temporal gyrus appeared to be sensitive to decreases in stimulus frequency. Given that the PFC and the ACC were functionally dissociated (or at least acting in a complementary way) in the probability blocks, we may attribute the role of control ''trigger'' to regions that were sensitive to increases in frequency, especially the pre-SMA, which would seem to fit well with the role

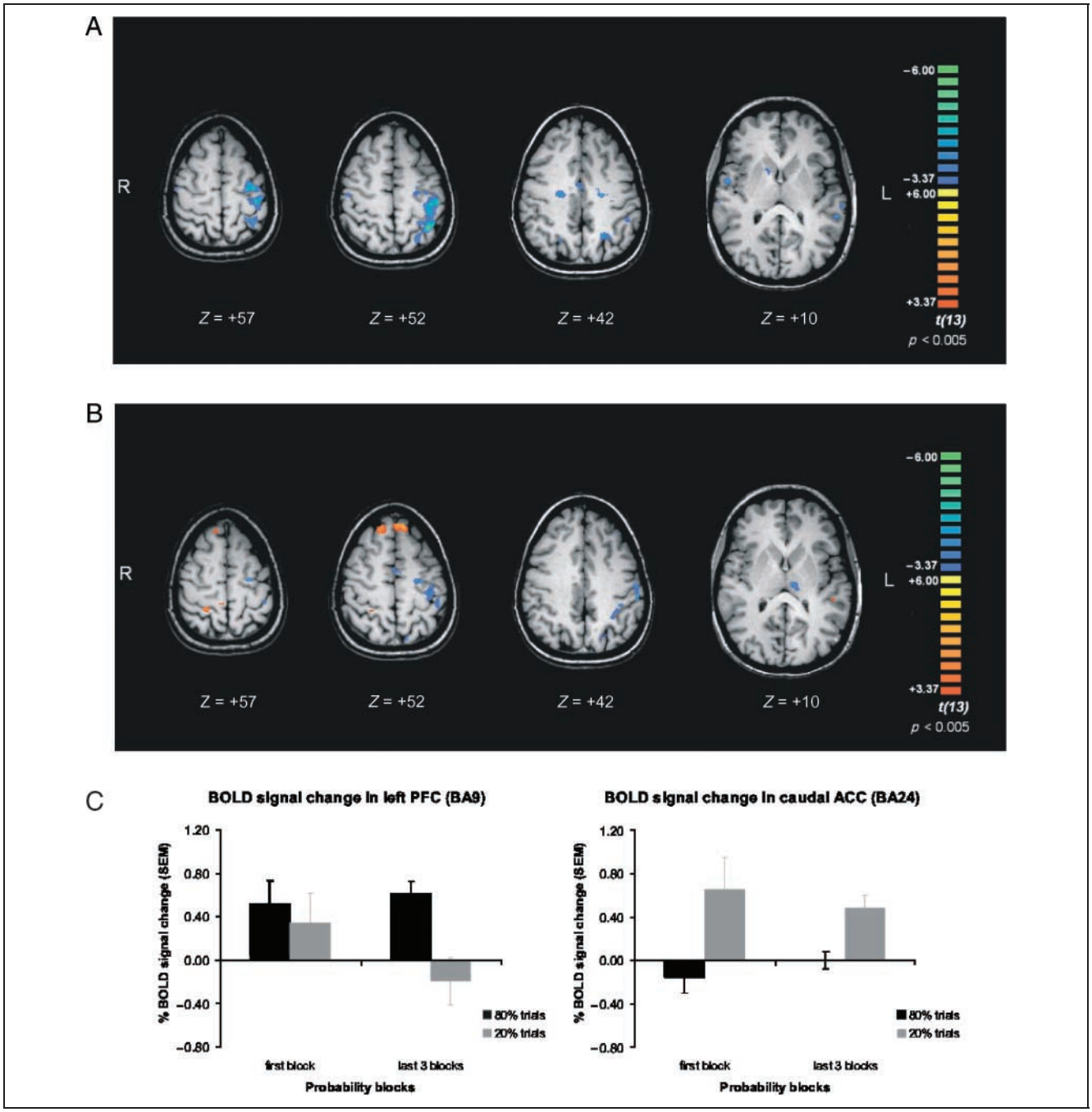

Figure 4. Areas activated by the contrast *more frequent S-R mapping > less frequent S-R mapping* in the first probability block (A) and in the last three probability blocks (B). Orange-yellow areas showed an increase in activity for the more frequent S-R mapping compared to the less frequent S-R mapping. Blue-green areas showed the opposite pattern. (C) The change in BOLD signal during the first and the last three probability blocks for compatible and incompatible trials in the medial PFC (left) and caudal ACC (right).

of this structure in planning (Amador & Fried, 2004; Hoshi & Tanji, 2004).

DISCUSSION

Our data show that subjects may use different cognitive control mechanisms depending on the behavioral context, each associated with a distinct neural substrate. The task we used was a variant of the SRC task similar to that used in the mixed condition of Experiment 1 by Vu and Proctor (2004). In each trial, subjects had to make a two-step decision, one relating to the rule (same/opposite) and the other involving the hand (right/left) to use, in order to select the correct response. In the random blocks, in which subjects could not form expectations about the upcoming stimuli, they used a transient form of cognitive control that was based on local task features

Table 4. Regions Activated by Contrasting the Activity in the First Probability Block with That in the First Random Block

	Talairach Coordinates			
Region (BA)	*x*	*y*	*z*	*Voxels*
80% Stimuli in probability block > 80% type stimuli in random block				
Right superior frontal gyrus (6)	10	14	60	150
Right medial frontal gyrus (9)	9	35	52	188
Left superior/medial frontal gyrus (9)	−10	24	55	884
20% Stimuli in probability block > 20% type stimuli in random block				
Left superior frontal gyrus (6)	−69	0	63	435
Left ventral putamen	−22	19	−6	101
Left fusiform gyrus	−48	−28	−23	129

The comparisons were between stimuli of a certain frequency in the probability block with those trials of the same stimulus type in the random block. The statistical threshold for all voxels in these regions was $t(13) \geq 3.3725$, $p < .005$.

(e.g., SRC) and comprised all the essential features described by the response conflict hypothesis (MacDonald et al., 2000; Botvinick et al., 1999; Carter et al., 1998) or other forms of control that are primarily response based (Brown & Braver, 2005; Garavan et al., 2002). However, in the probability blocks, when information about stimulus frequency was available in the environment, subjects used this information to exert cognitive control, regardless of the SRC. Both the response time changes and the pattern of errors were driven by the frequency of the stimuli. This suggests that expectancy about the type of stimulus likely to come up next, and not response conflict per se, was the signal that modulates control in the probability blocks. Given that the only additional information available to subjects in probability blocks was the frequency of a particular color (or rule), subjects must have prepared this in advance to account for the response time savings we documented. Of course, they were not able to make a response until they knew the location of the stimulus. However, knowing the rule with a high probability of success (80%) in advance facilitated their ability to respond quickly. Thus, the control mechanism was based on global task features (frequency), ignoring the local ones (compatibility). In contrast, subjects could not develop such expectancies in the random blocks because the two types of stimuli were equal in frequency. Based on our task design and on previous findings in the SRC literature (de Jong, 1995), the control mechanism should rely on response conflict (e.g., overcoming a prepotent response) in random blocks and be based on anticipating the next stimulus in probability blocks (Marble & Proctor, 2000). The neural basis of what we propose to be separate cognitive control mechanisms focuses on the ACC, the PFC, and their interaction.

Monitoring and the ACC

Any system that regulates or assigns control must have a monitoring component that informs the organism when control is needed and, after it has been implemented, whether it has been successful. It is generally agreed, though some have suggested other structures (Rushworth, Walton, Kennerley, & Bannerman, 2004; Garavan, Ross, Kaufman, & Stein, 2003; Stuphorn et al., 2000), that the ACC performs such a monitoring role for the responses to particular stimuli when subjects cannot predict upcoming events. There has been much debate as to what aspect of the response triggers control, be it conflict (MacDonald et al., 2000; Botvinick et al., 1999; Carter et al., 1998), expected reward (Shima & Tanji, 1998), goal selection (Matsumoto et al., 2003), performance monitoring (Magno, Foxe, Molholm, Robertson, & Garavan, 2006; Ullsperger & von Cramon, 2004; Walton et al., 2004; Ito, Stuphorn, Brown, & Schall, 2003), errors (Garavan et al., 2002), or the potential for error (Brown & Braver, 2005). However, the purpose of the current experiment was not to reexamine in detail the factors that might lead to activation of the ACC and an increase in control, but rather to contrast how the anterior cingulate might be engaged in two fundamentally different types of control: transient (as in response conflict) and sustained (based on global task features). The activation of the ACC in the random blocks of the current experiment had similar properties and spatial location to that described by the response conflict theory (MacDonald et al., 2000; Botvinick et al., 1999; Carter et al., 1998) and other forms of response monitoring. Accordingly, the ACC was more activated in trials with incompatible S-R mappings, especially when they followed a compatible mapping, in which case the conflict was at its highest. This is consistent with the view that when conflict is located at the response level, ACC activity will indicate the need for control when the amount of conflict is high and control is limited (Botvinick et al., 2004). Thus, the role of the ACC in the random blocks is transient and corresponds to that of a detector of response conflict, at least in the context of the current experiment. We would like to emphasize that the lack of an RT difference during the two different trial types in the random blocks does not mean that there was no evidence of conflict. In fact, the absence of an SRC effect when compatible and incompatible trials are mixed in equal frequency is to be expected based on previous findings and is generally interpreted (Vu & Proctor, 2004; de Jong, 1995) as indicative of a suppression of a prepotent mapping rule.

By contrast, in the probability blocks, the more anterior portion of the ACC, which was engaged during the

random blocks, was not activated for any of the contrasts we performed, including one for the level of SRC. Therefore, if we accept the general tenets of the neural basis of response conflict (Botvinick et al., 2004; Botvinick et al., 1999; Carter et al., 1998), none was being detected by subjects in the probability blocks. However, we did document more activation in the caudal part of the ACC (BA 24) during the less frequent compared to the more frequent stimuli, regardless of the S-R mapping. This differential activation cannot be due to conflict at the response level, as the motor responses were evenly distributed irrespective of the frequency of the different stimuli. In addition, the transitions from compatible to incompatible stimuli and vice versa were equal in frequency (17.7% of total number of trials). Therefore, the only plausible explanation for activation in the caudal ACC is that it was related to conflict at the level of the rule associated with each *type* of stimulus. Subjects formed expectations about the frequency of a particular rule and experienced conflict at the *cognitive* level when these expectations were violated, such as when the less frequent rule (stimulus) was encountered. This finding is consistent with those of Weissman et al. (2003), who found that the caudal/dorsal ACC was activated by global and local features of the task. Furthermore, previous studies have shown that activity in the caudal ACC was associated not only with attention (Lie, Specht, Marshall, & Fink, 2006) and cognitive (Davis et al., 2005) demands, but also with the violation of expectancies during explicit sequence learning (Aizenstein et al., 2004). The differential activation in the ACC we documented supports the concept that subareas within this structure are sensitive to different types of conflict (Lie et al., 2006; van Veen & Carter, 2005; Fan, Flombaum, McCandliss, Thomas, & Posner, 2003), which may indicate processing of local or global task features. The ACC has also been shown to predict error likelihood in a given context (Brown & Braver, 2005), and this is entirely consistent with its activation during the less frequent stimuli in the probability blocks.

The Role of the PFC

The right lateral PFC was activated more by incompatible than compatible trials in the random blocks and this activity remained high, regardless of the type of preceding trial. The same location within the PFC has been associated with errors (Carter et al., 1998) and with response conflict (Milham et al., 2001; van Veen, Cohen, Botvinick, Stenger, & Carter, 2001). Thus, the overall activation pattern was similar to that described for imposing control in other contexts (Kerns, Cohen, MacDonald, et al., 2004) in that it reflects the role of the lateral PFC in adaptation to response conflict and in achieving task-related goals, hence global features.

During the probability blocks, a different part of the PFC, the medial PFC (bilateral superior frontal gyrus), was more active for frequent than for the infrequent trials, regardless of SRC, as may be seen in the third portion of Figure 3B. This portion of medial PFC (BA 9) has a different histological structure and somewhat different connectivity than the principal divisions of lateral PFC (BA 9/46, BA 46) and is recognized to have different functional properties (Petrides & Pandya, 1999). The medial PFC has been found to be sensitive to preceding context in a go/no-go task (Durston et al., 2002), to be more activated in high-adjustment, postconflict, and post-error trials (Kerns, Cohen, MacDonald, et al., 2004), and to be associated with maintaining task demands over time (Yarkoni et al., 2005). In addition, several studies (Durston et al., 2002; Casey et al., 2001) examining the effect of stimulus frequency and stimulus history in a go/no-go task have found activation in various regions of the PFC. Furthermore, portions of the medial PFC in the nonhuman primate have been found to be associated with the representation of task goals (Matsumoto et al., 2003). In the context of the current task, we propose that the functional properties of medial superior frontal gyrus are consistent with a role in the representation of global task demands (Miller & Cohen, 2001), which would require continuous updating of working memory (Wager & Smith, 2003).

A Synthesis: Interaction between the ACC and the PFC

The functional relationship between the ACC and the PFC in the current experiment varied with the type of trial block. During the random blocks, the ACC and PFC cooperated in control implementation as described by the response-conflict theory to the extent that they were both activated by high conflict trials but ACC activation preceded and modulated that of the PFC (Kerns, Cohen, MacDonald, et al., 2004). It is worth noting that the ACC had higher activity during the incompatible trials that followed compatible ones, whereas the PFC maintained a high level of activation for all incompatible trials.

In the probability blocks, the activity of the ACC was in apparent opposition or at least complementary to that of the PFC. The prefrontal areas showed higher activation for the most frequent stimuli, whereas the ACC was more sensitive to less frequent stimuli. This pattern suggests a functional dissociation between these regions and a different control mechanism from that seen in response conflict, for example. The decoupling between these areas was most evident when switching from the less to the more frequent stimuli or vice versa (Figure 3B and C, middle). We propose that the control mechanism used by subjects in probability blocks is feed-forward in nature and is based on global expectations about the upcoming type of stimulus. By actively anticipating the most frequent stimuli, subjects were able to improve their performance in the task, both in terms of RT and

errors (Figure 1) on the basis of increased control due to persistent PFC activity. One consequence of this strategy is that the less frequent stimuli might be given less attention, at the cost of slower RT and increased errors. However, given their low frequency, a slow RT or a higher error rate would not significantly impair the overall performance in the task. Such a strategic control mechanism in situations in which the environment was predictable would enable an organism to be persistent in pursuit of a behavioral goal (e.g., response time savings in the current experiment) even when some aspects of the task, the low-frequency stimuli, were demanding and challenging.

Our results support a view of cognitive control whereby the ACC plays an evaluative role and the PFC plays an executive one (Carter et al., 2000; MacDonald et al., 2000). However, any coupling between the ACC and the PFC depends on the origin and focus of the control signal (local vs. global). Activity in the ACC is coupled with that of the PFC when the focus is local and immediate, where control is implemented through facilitation of the response selection; one might regard this type of control as ''bottom-up.'' However, the activity of the ACC and PFC is uncoupled, when the focus is global and mediated by experience, where control is implemented through ''top-down'' processing, as in the probability blocks. The dominance of one mechanism over the other is yet to be explored and was not the primary focus of this study. One possibility is that one mechanism is the default condition (probably one based on response properties), whereas the other mechanism is activated only when information beyond the immediate perceptual context of the stimulus is available. This would reflect the subjects' internal goals, expectations, or general task demands. We believe that having the different control mechanisms we described enables humans to be both persistent in attaining their goals when the environment is predictable, yet flexible.

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Reprint requests should be sent to James Ashe, Brain Sciences Center (11B), Veterans Affairs Medical Center, One Veterans Drive, Minneapolis, MN 55417, or via e-mail: ashe@umn.edu.

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