Selection, Integration, and Conflict Monitoring: Assessing the Nature and Generality of Prefrontal Cognitive Control Mechanisms

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Summary

Prefrontal cortex (PFC) supports flexible behavior by mediating cognitive control, though the elemental forms of control supported by PFC remain a central debate. Dorsolateral PFC (DLPFC) is thought to guide response selection under conditions of response conflict or, alternatively, may refresh recently active representations within working memory. Lateral frontopolar cortex (FPC) may also adjudicate response conflict, though others propose that FPC supports higher order control processes such as subgoaling and integration. Anterior cingulate cortex (ACC) is hypothesized to upregulate response selection by detecting response conflict; it remains unclear whether ACC functions generalize beyond monitoring response conflict. The present fMRI experiment directly tested these competing theories regarding the functional roles of DLPFC, FPC, and ACC. Results reveal dissociable control processes in PFC, with mid-DLPFC selectively mediating resolution of response conflict and FPC further mediating subgoaling/integration. ACC demonstrated a broad sensitivity to control demands, suggesting a generalized role in modulating cognitive control.

Introduction

Flexible behavior requires a system for relating responses to the current context and one's goals. Cognitive control processes enable this flexibility by selecting contextually relevant perceptual, mnemonic, and response representations or processing pathways, and organizing and integrating these representations to meet higher level goals. The loss of cognitive control results in an overdependence on external stimuli to guide responses (e.g., utilization behavior) and hence a loss of adaptive, goal-directed behavior (Shallice and Burgess, 1991; Stuss and Benson, 1987). Neuropsychological evidence of executive dysfunction following prefrontal damage has led to a predominant theoretical focus on prefrontal cortex (PFC) (Gehring and Knight, 2002; Shimamura, 1995). Extensive neurophysiological data from nonhumans and neuroimaging evidence from humans have provided complementary insights into the role of PFC in guiding controlled behavior (Duncan, 2001; Duncan and Owen, 2000; Miller and Cohen, 2001; Petrides, 2000; Smith and Jonides, 1999; Wagner, 1999).

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Though PFC is engaged by a wide range of tasks demanding cognitive control, uncertainty remains regarding (1) the specific character and locus of PFC-mediated control processes and (2) the specificity of modulatory mechanisms that signal a need for increased control.

Dorsolateral prefrontal cortex (DLPFC) is a key neural substrate of cognitive control, although debate remains regarding the putative functions subserved by this region. From one perspective, DLPFC control processes are conceptualized in terms of the bias-competition framework of attention-mediated dynamic filtering (Cohen and Servan-Schreiber, 1992; Dehaene and Changeux, 1995; Desimone and Duncan, 1995; Miller and Cohen, 2001; Shimamura, 1995, 2002). From this perspective, DLPFC computations serve to represent the task context and provide a top-down bias signal that favors task-relevant response pathways over competitors. Consider, for example, the critical conflict condition of the Stroop task (MacDonald et al., 2000; Stroop, 1935), wherein a color name is presented in an incongruent ink color (e.g., the word "green" printed in red). When one is engaged in naming the ink color, the presence of the incongruent but prepotent response to the word cue results in conflict, evident as an increase in response time relative to neutral trials. Within the bias-competition framework, when the context demands a response based on the color-naming pathway, a control process is required that can bias processing in favor of—and thus select—the color-naming pathway over the prepotent word reading pathway (Cohen et al., 1990; Cohen and Servan-Schreiber, 1992). Neuroimaging, neuropsychological, and electrophysiological data implicate neurons in DLPFC as central to implementing such context-dependent biasing or dynamic filtering, and in so doing, DLPFC is thought to support "response selection" (Banich et al., 2001; Bench et al., 1993; Carter et al., 1995; MacDonald et al., 2000; Milham et al., 2001, 2002; Miller and Cohen, 2001; Pardo et al., 1991; Taylor et al., 1997).

An alternative, or perhaps complementary, view of DLPFC control processing posits that DLPFC mechanisms serve to reactivate representations that, though recently active, have not been maintained over a delay (Johnson et al., 2002, 2003; Raye et al., 2002). That is, DLPFC mechanisms are thought to bring back to mind representations that were recently active but that have subsequently begun to decay—a process termed "refreshing." Experimental support for the refresh hypothesis comes from observations that when subjects are cued to bring back to mind a recently encountered word, greater DLPFC activation is observed relative to when subjects are asked to read a presented word (Raye et al., 2002). Given these distinct perspectives on DLPFC function, an unanswered and important question arises as to whether DLPFC computations mediate this posited refresh mechanism, response selection, or both. Accordingly, one objective of the present fMRI experiment was to examine DLPFC contributions to conditions differing in the demands placed on putative response selection and refresh mechanisms.

The role of PFC in cognitive control is clearly not

restricted to functions supported by DLPFC. Rather, in addition to DLPFC, numerous studies have implicated lateral frontopolar cortex (FPC) in supporting flexible behavior through cognitive control. For example, several imaging investigations of response selection have shown that FPC is sensitive to response conflict, as FPC and very anterior DLPFC activation has been observed in a variety of response conflict paradigms, including Stroop (Bench et al., 1993; Carter et al., 1995; Milham et al., 2001; Taylor et al., 1997), Eriksen flanker (Van Veen et al., 2001), and go/no-go tasks (Paus et al., 1993). Such observations raise the possibility that FPC, in conjunction with DLPFC, supports mechanisms that resolve conflict by biasing or selecting task-relevant response pathways.

Other imaging data, however, have implicated lateral FPC in processes that appear to extend beyond simply resolving conflict between competing responses. Notably, FPC activation has been observed during the performance of tasks that involve minimal response conflict but require the generation of subgoals and the integration of representations deriving from different subgoal stages (Braver and Bongiolatti, 2002; Koechlin et al., 1999). For example, Braver and Bongliolatti (2002) required subjects to monitor for a target during a sequence of words. To identify the target, subjects had to first perform a subgoal, semantically categorizing a current word as either abstract or concrete. Subsequent to executing this subgoal, subjects had to relate the resulting categorization of the present word to the semantic status of the previous word in the sequence (i.e., they had to integrate two sources of information). Relative to a condition that lacked these subgoal and/or integration demands, FPC activation was observed. Such findings have led to the hypothesis that FPC mediates second-order control processes, such as subgoaling and/or integration mechanisms, that are necessary to satisfy more complex goals. Thus, as with DLPFC, multiple perspectives have been advanced to account for FPC function. A second objective of the present study was to assess the degree to which FPC mechanisms are sensitive to conditions that demand resolution of response conflict and those that require establishment of subgoals and integration across representations.

Critically, cognitive control processes are only effective to the extent that monitoring processes detect conditions that require increased control, modulating the level of cognitive control accordingly. For example, to engage response selection mechanisms, an additional process is required that signals PFC to the presence of response conflict and the need for increased control to resolve this conflict (Botvinick et al., 2001). Neuroimaging evidence has implicated anterior cingulate cortex (ACC) in monitoring and detecting response conflict (Banich et al., 2001; Barch et al., 2001; Botvinick et al., 1999; Braver et al., 2001; Carter et al., 1998; MacDonald et al., 2000; Milham et al., 2001; Van Veen and Carter, 2002). Furthermore, computational models of ACC function have suggested that this region receives inputs from the response layer of the processing pathway (Botvinick et al., 2001). Accordingly, these findings, together with recent neuroimaging data (Milham et al., 2001, 2002; Van Veen et al., 2001), have led some theorists to hypoth-esize that ACC may be exclusively sensitive to the presence of conflict between competing responses.

The corollary to a strict response conflict view of ACC function is that ACC does not monitor and signal the need for other forms of cognitive control (Jonides et al., 2002; Milham et al., 2001, 2002; Van Veen et al., 2001). Although some evidence suggests that ACC may specifically monitor for response conflict (Milham et al., 2001, 2002; Van Veen et al., 2001), questions remain as to whether ACC processes are also engaged during conditions requiring refreshing, subgoaling, and/or representational integration. Accordingly, a third objective of the present study was to determine the extent to which ACC monitoring mechanisms are restricted to detecting response conflict or whether these mechanisms generalize to signal the need for control beyond the response domain. We further sought to test the hypothesis that ACC signals serve to upregulate lateral PFC control mechanisms by examining whether ACC demonstrates a functional coupling with DLPFC and FPC.

To summarize, there were three objectives of the present fMRI experiment. First, we sought to assess the nature and generality of DLPFC processes, directly contrasting DLPFC sensitivity to response conflict and to the need to refresh recently active representations. Second, we sought to distinguish and specify FPC cognitive control processes under contexts of differential response conflict and subgoaling/integration demands. Finally, we sought to determine the degree to which ACC monitoring processes are exclusively sensitive to response-based conflict or are more generally sensitive to the need for cognitive control, modulating engagement of multiple lateral PFC control mechanisms. To address these issues, an experimental design was developed that directly crossed (1) the relationship between an expected and a cued response with (2) whether or not refreshing recently active representations was required.

Subjects performed a verbal working memory task that required establishment of an expectation about which of a set of items held in working memory was most likely to be relevant to a subsequent response. At the outset of each trial, three words were serially presented (Figure 1A), and subjects were instructed to remember the words so as to be able to respond at the end of the trial. Immediately following presentation of the memory set, a bias cue (i.e., a number) signaled subjects as to which of the three words was most likely to be relevant to their subsequent response. Subjects were informed that in most cases the cue would signal the task-relevant response, and thus they should use the cue to anticipate this response. In this manner, the bias cue elicited preparation of an expected (and thus prepotent) response.

On each trial, a 3 s delay followed presentation of the bias cue, and then a final response cue was presented to signal the target response to be immediately executed (Figure 1A). The response cue signaled either the expected or an unexpected response—a manipulation of response selection demands. Moreover, the cue stimulus either directly mapped onto a response or required access to recently active representations within working memory—a manipulation of refresh and subgoal/inte-
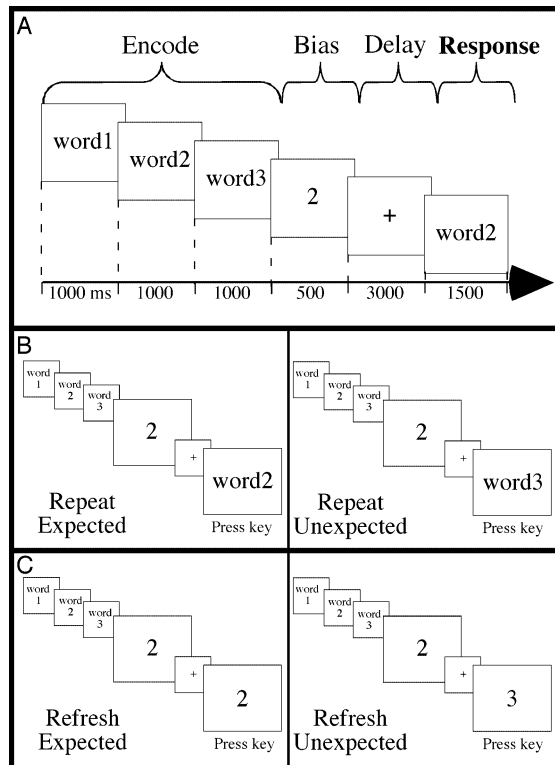
Figure 1. Task Schematic Depicting the Order and Timing of Events during Each Trial and Illustrating the Four Conditions at Response

(A) All trials began with the serial presentation of three words followed by a bias cue. Subjects used this cue to select or prepare the expected response. Following a 3000 ms delay, a response cue was presented in red. The subject was given 1500 ms to respond. There were two types of Response cues, with each cueing either an Expected or Unexpected response, resulting in four conditions at response.

(B) When a word (Repeat) cue was presented at response, subjects covertly repeated the word and pressed a button. On 75% of Repeat trials, the word cued the Expected response; on the remaining 25% of trials, the response was Unexpected.

(C) When a number (Refresh) cue was presented, subjects covertly repeated the word from the memory set that corresponded to that number in ordinal position (e.g., "2" cued the second word). Again, on 75% of the trials the number cued the Expected response, and on 25% of the trials the response was Unexpected.

gration demands. These conditions and their implications for control processing are further detailed below.

The sensitivity of PFC to "response selection" demands was tested by arranging a mismatch on conflict trials between the expected response, based on the bias cue, and the cued response (Figure 1B). On half of the trials, the response cue was a word (Repeat cue), and subjects were instructed to covertly repeat the word and press a button once having done so. The word was always one of the three words from that trial's memory set. Furthermore, 75% of the time the Repeat cue, and thus the response, was the same as the word that had been expected based on the bias cue presented prior to the delay and so was consistent with the Expected response (i.e., no response conflict). For the remaining 25% of Repeat trials, the response cue corresponded to one of the other words in the memory set, thus requiring an Unexpected response. Accordingly, during Unex-

pected trials, the prepared or prepotent response was incongruent with the response signaled by the response cue. Hence, analogous to the Stroop task, Repeat-Unexpected trials required selection of a response pathway based on bottom-up visual input in the face of a task-irrelevant, prepotent response (although, in contrast to Stroop, here the prepotent response was established by a top-down bias or selection process engaged upon presentation of the bias cue rather than a learned preexperimental association). Thus, for Repeat trials any sensitivity of PFC to expectation would reflect response conflict and response selection demands.

To test the sensitivity of PFC to refresh and subgoaling/integration demands, we devised two additional conditions in which response conflict was present or absent in the face of a need to execute a subgoal entailing the integration of two cues, and to subsequently refresh a recently active representation (Raye et al., 2002). Specifically, in the Refresh condition, the response cue entailed a symbolic stimulus that required retrieval of a representation from within working memory, with some trials requiring an expected response and others requiring an unexpected response (Figure 1C). During the half of all events that were Refresh trials, the response cue was a number (Refresh cue), rather than a word. As with the bias cue, the Refresh cue referred to the ordinal position of one of the words. In response to the Refresh cue, subjects were to covertly repeat the corresponding word that was cued by the number (Raye et al., 2002) and to press a button once having done so. Hence, differential sensitivity to this condition over the Repeat condition might reflect processes engaged to refresh a recently active representation within working memory. Importantly, Refresh trials further required subgoaling/integration because the symbolic response cue had to be specified prior to response selection. That is, Refresh trials necessitated that the response cue be compared/integrated with the bias cue to determine if the prepared response was or was not the target response. This integration stage entailed execution of a subgoal en route to satisfying the global goal of executing a response independent of whether the response was expected or not, a distinction that differentiates this integration process from the hypothesized refresh process. Hence, to the extent that a region of PFC is engaged in refreshing, it should principally reveal a difference between Refresh-Unexpected and Repeat-Unexpected. Whereas, if a region of PFC is critical for subgoaling/integration, it should be sensitive to the need to Refresh regardless of whether the response is expected or unexpected, because both conditions require subgoaling and integration.

In addition to the main effects of refreshing and subgoaling/integration, response conflict was also manipulated within the Refresh condition. As in the Repeat condition, for 75% of Refresh trials the number cued the same word as had been indicated by the bias cue, and so the response was Expected even though the representation cueing the response (a symbolic cue) differed from the prepared representation (the response word). For the remaining 25% of Refresh trials, the number cued one of the other two words, and so the response was Unexpected. Thus, as with the Repeat-Unexpected condition, the Refresh-Unexpected condition required
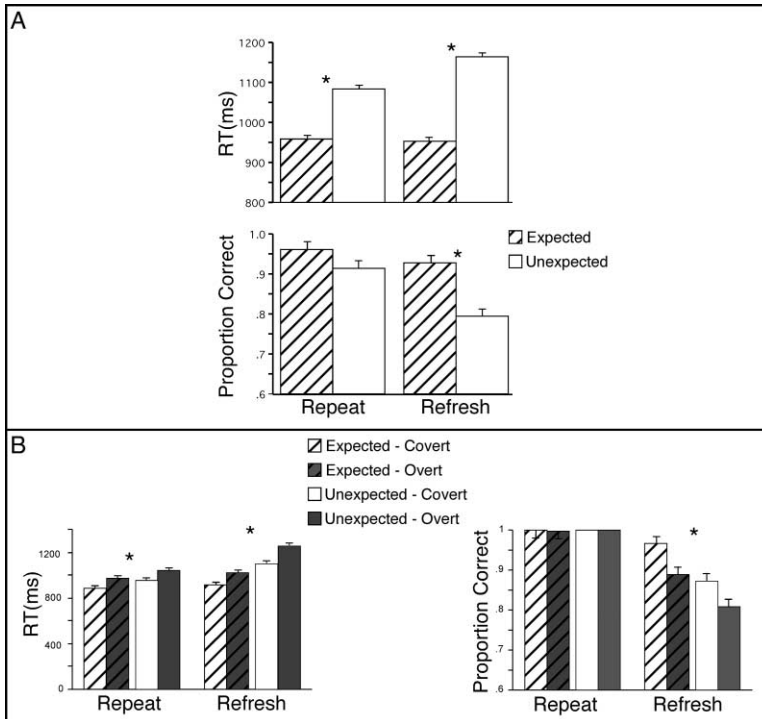
Figure 2. Behavioral Results from fMRI and Pilot Experiments

Response times (RTs) and the proportion of correct responses are depicted across conditions from (A) the fMRI experiment and (B) the pilot behavioral study.

a response in the presence of conflict from the prepared but irrelevant response.

Results

Behavioral Performance

Behavioral measures of reaction time (RT) and accuracy were collected during fMRI scanning via a button-press response that followed each covert verbal response (Figure 2A; see Experimental Procedures). Consideration of RT on correct trials validated that subjects used the bias cue to select a representation from within working memory and to prepare the expected response. Subjects were slowed by response conflict when the target response differed from the prepared response as revealed by longer RTs on Unexpected (1094 ms) than on Expected trials [925 ms; F(1,15) = 63.0, p < 0.0001] (Figure 2A). Expectation affected RT regardless of whether the response cue was a word [Repeat: Unexpected-Expected = 117 ms; F(1,15) = 52.8, p < 0.0001] or a symbolic cue [Refresh: Unexpected-Expected = 222 ms; F(1,15) = 189.8, p < 0.0001]. A larger RT cost for expectancy violation during Refresh trials was evident in a significant Response (Repeat/Refresh) × Expectation (Expected/Unexpected) interaction [F(1,15) = 21.2, p < 0.0005]. This interaction suggests that when the target response is unexpected and cannot be based directly on the response cue (because the stimulus does not correspond to a response option), increased cognitive control may be required because subjects must select a response based on an alternate encoded representation.

The collection of manual responses as markers of the subjects' covert verbal responses during fMRI enabled recording of RT measures (as just described), while min-

imizing potential motion artifact. While a number of published reports have implemented designs using overt verbal responses (Barch et al., 1999, 2000), the experimental paradigms in which verbal responses have been collected (e.g., verb generation) have tended to consider accuracy, rather than RT, perhaps because simultaneous collection of verbal responses and RT in the scanner further complicates the experimental procedures. Complex experimental tasks, such as the present for which RT is a critical dependent measure, have typically used covert responses accompanied by a proxy manual response.

To determine whether covert verbal responses followed by manual responses results in a faithful pattern of RT and accuracy across conditions, we conducted a behavioral pilot study (n = 15) during which subjects performed the tasks outside of the scanner and were instructed to either covertly or overtly respond and then to press a button (i.e., the covert condition was identical to the fMRI condition). This pilot study revealed two important outcomes (Figure 2B). First, the effects of the experimental factors on RT were comparable across the Output modes (covert and overt), as Output mode did not interact with the experimental factors [Fs(1,14) < 1.6, ps > 0.22]. Second, subjects' reports of whether they successfully retrieved the target word were largely reflective of their actual performance (using overt accuracy levels as the benchmark). That is, within each Response condition, there was no reliable interaction between Output mode and Expectation [Repeat: F(1,15) = 0.3, p = 0.63; Refresh: F(1,15) = 2.2, p = 0.16]. Hence, though the self-report procedure adopted during fMRI has the potential of misclassifying a few error trials as "correct," the behavioral pilot study suggests that the absolute number of such misclassified error trials was
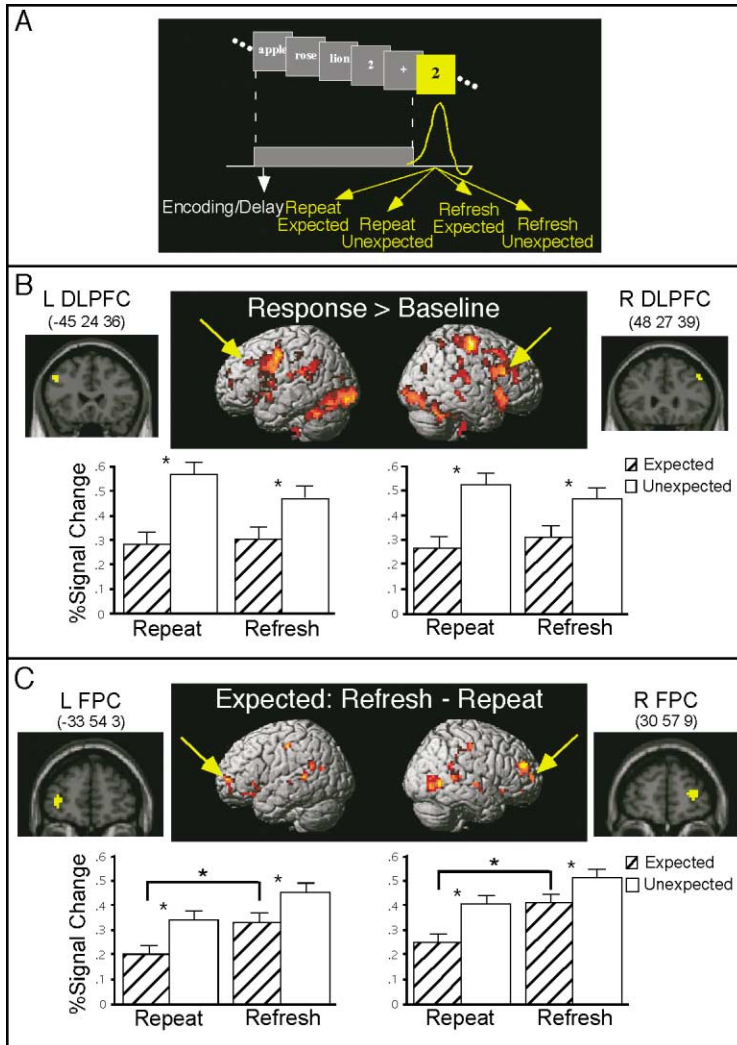
Figure 3. Statistical Maps and Response Period Data from Lateral Prefrontal ROIs

(A) Data analyses contrasted neural signals during correctly performed trials from each of the four response conditions.

(B) The percent signal change in left and right mid-DLPFC regions is depicted for ROIs defined from the voxel-wise contrast of all Response trials versus Fixation. Both mid-DLPFC regions showed greater activation during Unexpected than Expected trials. This was the case both in the Repeat and the Refresh conditions. The interaction was not reliable.

(C) The percent signal change in left and right FPC regions is depicted for ROIs defined from the voxel-wise contrast of Refresh-Expected versus Repeat-Expected. Bilateral FPC regions showed increased response to both Unexpected relative to Expected trials and Refresh relative to Repeat trials. The two factors contributed additively to changes in FPC response.

small (e.g., only 1.6 trials for the critical Refresh-Unexpected condition). This outcome lends support for analyzing the accuracy data collected during fMRI.

Analyses of button press indices of accuracy during fMRI indicated that subjects performed well in all conditions (Figure 2A). When subjects made an error, the vast majority of errors (66%) reflected a failure to respond during the response window. Reliable performance differences tracked those observed for RT, as the proportion correct was lower when Refreshing (0.86) than when Repeating [0.94; F(1,15) = 9.0, p < 0.01], and when the response was Unexpected (0.85) than when it was Expected [0.95; F(1,15) = 16.0, p < 0.005]. The interaction approached significance, revealing a greater cost of expectation violation during Refresh trials [F(1,15) = 4.5, p = 0.051].

fMRI Activation during the Response Period
Functional analyses, which were restricted to correct trials, focused on the response portion of the experimental trials, corresponding to the onset of the response cue and response execution (Figure 3A). Voxel-wise comparison of all response conditions—collapsed across

Expectation and Response factors—to the fixation baseline revealed activation in ACC, bilateral DLPFC and ventrolateral PFC (VLPFC), and left lateral FPC (Table 1; Figure 3B). Beyond the frontal lobe, this global response phase analysis revealed activation in posterior parietal and superior and middle temporal cortices.

As the central theoretical questions concern the functional roles of DLPFC, lateral FPC, and ACC in cognitive control, directed voxel-wise contrasts and region-of-interest (ROI) analyses sought to more fully assess the sensitivity of these regions to response conflict, refresh, and subgoaling/integration demands.

DLPFC Sensitivity to Response Conflict
During Repeat trials, subjects were required to respond by covertly repeating the response cue (i.e., the externally presented word). In cases in which the target response was Unexpected, selection of the appropriate response had to be performed in the face of competition from a prepared but irrelevant response. Voxel-based comparison of Repeat-Unexpected to Repeat-Expected trials revealed bilateral activation in DLPFC, FPC, and VLPFC, with these regions overlapping with those ob-

Table 1. Prefrontal Regions Engaged during the Response Period—Contrasting All Response Conditions to Fixation

Region	MNI Coordinates			~Brodmann Areas	Peak Z Score
	x	y	z		
Medial frontal/ACC	−6	6	51	6/32	5.30
Medial frontal	6	3	54	6	4.47
ACC/Medial frontal	0	27	36	32/8	4.41
ACC	9	18	39	32	3.94
ACC	−6	21	24	24/32	3.88
ACC	3	27	21	24	3.42
ACC	6	12	27	24	3.29
R middle frontal	42	18	48	8	4.01
R middle frontal	48	12	51	8/6	3.76
R inferior/middle frontal	36	36	9	45	3.99
R inferior frontal	39	21	21	45	3.93
R middle/inferiorfrontal	57	21	27	9/45	3.85
R inferior frontal	51	12	24	44	3.72
R inferior frontal	39	15	30	44/9	3.67
R middle frontal	45	39	18	46	3.62
R inferior frontal	57	21	−3	47/45	3.91
R middle frontal (DLPFC)	48	27	39	9/46	3.79
R middle frontal	36	42	12	46	3.41
R middle frontal	54	33	24	46/9	3.39
R middle frontal	39	42	30	9/46	3.28
L precentral	−48	3	36	6	4.52
L inferior frontal	−57	15	27	44/9	3.64
L inferior frontal	−60	12	6	44	3.53
L inferior frontal	−45	18	18	44/45	3.23
L inferior frontal	−36	30	−6	47	3.21
L middle frontal (DLPFC)	−24	33	18	46	3.70
L middle frontal	−33	30	36	9/46	3.50
L middle frontal	−45	24	36	9	3.49
L middle/inferior frontal	−51	15	39	9/44	3.89
L inferior/middle frontal	−54	12	33	44/9/8	3.58
L frontopolar	−39	54	9	10	3.45
L frontopolar	−30	57	21	10	3.30
L frontopolar	−30	54	27	10/9	3.23

ACC, anterior cingulate cortex; DLPFC, dorsolateral PFC; L, left; R, right; SMA, supplementary motor area. Coordinates from regions outside PFC are available upon request.

served in the global analysis of response phase activation (a complete set of coordinates is available upon request). Consistent with this observation, ROIs in bilateral mid-DLPFC (BA 9/46), defined from the global response phase analysis, demonstrated reliably greater activation during Repeat-Unexpected relative to Repeat-Expected trials [Left: $F(1,15) = 25.9$, $p < 0.0001$; Right: $F(1,15) = 17.5$, $p < 0.001$; Figure 3B]. These findings indicate that subregions in bilateral DLPFC are sensitive to response conflict.

As with Repeat-Unexpected trials, during Refresh-Unexpected trials, the target response was incongruent with the prepared response. Thus, to the extent that these mid-DLPFC regions are engaged during response selection in the face of response conflict, they also should show greater activation during Refresh-Unexpected relative to Refresh-Expected trials. Notably, however, in both the Expected and Unexpected trials of the Refresh task, additional cognitive control processes (refreshing and/or subgoaling and integration) were required relative to the Repeat trials. Regions that selectively mediate response selection should be insensitive to these additional demands, and thus should not show a main effect of Refresh versus Repeat, nor a Response (Refresh, Repeat) × Expectation (Unexpected, Expected) interaction.

Direct voxel-based comparison of Refresh-Unex-

pected to Refresh-Expected trials failed to reveal suprathreshold activation in DLPFC at the standard statistical threshold ($p < 0.001$). Rather, above threshold activation was observed in right parietal cortices, bilateral VLPFC, and frontal opercula. This apparent absence of differential DLPFC activation appears to reflect a thresholding effect, as a slight lowering of the threshold ($p < 0.005$) revealed bilateral mid-DLPFC responses in regions close to those observed in the Repeat-Unexpected minus Repeat-Expected contrast.

Consistent with these voxel-wise outcomes in a priori predicted DLPFC regions, ROI analyses of the mid-DLPFC regions observed in the global response analysis revealed greater activation during Refresh-Unexpected than during Refresh-Expected trials in left [$F(1,15) = 9.4$, $p < 0.01$] and right DLPFC [$F(1,15) = 6.5$, $p < 0.05$] (Figure 3B). Critically, neither region showed a main effect of Response (Fs < 1.2), and the interactions between Expectation and Response were not reliable (Fs < 2.1, ps > 0.15; Figure 3B). Thus, bilateral mid-DLPFC was selectively sensitive to the need to select task-relevant response pathways in the presence of response conflict.

DLPFC Sensitivity to Refresh Demands
To more broadly examine the effects of Response, a voxel-wise comparison of Refresh and Repeat trials,

averaged across Expected and Unexpected conditions, was conducted. Importantly, for present purposes, this contrast failed to reveal suprathreshold activation in DLPFC, and this was the case at both canonical and more lenient (p < 0.005) thresholds. Rather, activation was observed bilaterally in inferior frontal gyrus (pars orbitalis), in ACC, and in bilateral FPC at the reduced threshold (p < 0.005).

Although this voxel-wise analysis, along with the ROI analyses discussed in the preceding section, suggests that DLPFC is relatively insensitive to the additional control demands associated with the Refresh task, one might argue that this apparent insensitivity arises due to inclusion of the Expected trials in the main effect contrast between Refresh and Repeat. The refresh hypothesis of DLPFC function posits that this putative process operates on recently accessed but subsequently unattended information. Because the target representation is likely to have been maintained during the delay period on Refresh-Expected trials, since this representation maps to the anticipated response, refresh demands might be minimal during this condition. Accordingly and critically, comparison of Refresh-Unexpected to Repeat-Unexpected trials may most closely match the conditions in which putative refresh responses have been detected in prior studies (Raye et al., 2002). Importantly, as depicted in Figure 3B, ROI analyses indicated that activation in bilateral mid-DLPFC demonstrated a pattern that was quantitatively (though not reliably) the opposite to the refresh prediction, ruling out the possibility that this null result reflects a thresholding effect.

It is worth noting that the preceding mid-DLPFC ROIs were derived on the basis of averaging across all four response conditions, and thus other regions that are sensitive to only one of the four conditions potentially could be overlooked if analyses were restricted solely to consideration of these ROIs. To avoid this potential bias, we conducted a voxel-wise comparison of Refresh-Unexpected to Repeat-Unexpected. Critically, this voxel-based comparison failed to reveal differences in DLPFC activation at either canonical (p < 0.001) or very lenient (p < 0.01) thresholds. Accordingly, voxel-wise analyses (conducted using lenient thresholds) and the preceding ROI analyses of mid-DLPFC function converge to suggest that the control mechanisms mediated by mid-DLPFC subserve response conflict resolution rather than a refresh process.

Lateral FPC Sensitivity to Subgoaling/Integration
During Refresh-Expected trials, though the expected response is congruent with the cued response, the response cue itself does not directly transmit this information (e.g., by naming the response). Rather, to meet task goals, the response cue must be interpreted in relation to the bias cue to verify that the response it cues is consistent with the expected, prepared response. This process of cue verification could be achieved by attempting to match the current cue to the bias cue, or by determining if the item in working memory that maps to the response cue corresponds to the cued/expected response. Either way, during Refresh-Expected trials, an intermediate step of cue verification is critical for determining whether the prepared response is sufficient

to meet task goals. Hence, regions sensitive to subgoaling and integration should be detected when comparing Refresh-Expected to Repeat-Expected trials, and importantly, any such effects are unlikely to reflect response conflict, given that in both conditions the prepotent response was the target response.

Voxel-based comparison of the Expected trials across the Refresh and Repeat conditions revealed robust activation (Refresh-Expected > Repeat-Expected) in prefrontal regions, including bilateral FPC, right anterior DLPFC, and ACC (Figure 3C). The right FPC region was continuous with the right anterior DLPFC region, both of which fell well anterior to the mid-DLPFC regions identified as selectively sensitive to response conflict (Figure 3B).

Assessment of ROIs defined from the right and left FPC revealed that bilateral FPC regions were sensitive to the need to verify the response cue, even when the cued response was congruent with the expected response. This was evident in main effects of Refresh versus Repeat [Fs(1,15) > 12.4, ps < 0.005]. Moreover, these bilateral FPC regions were sensitive not only to the need to verify the cue but also to specify the response. That is, ROI analyses revealed that activation in FPC was greater under conditions of greater response conflict, evident in a reliable main effect of Unexpected versus Expected [Fs(1,15) > 5.2, ps < 0.05]. Finally, subgoaling/integration and response selection had independent effects on FPC processing (Expectation × Response: Fs < 1; Figure 3C). That is, the pattern of activation on Refresh-Unexpected trials was consistent with an additive contribution of the Expectation and Response factors relative to Repeat-Expected trials.

To further directly examine whether the subgoaling/integration effect represents a distinct processing demand from the response selection demand captured by the Expectation manipulation, the main effect of Refresh > Repeat was again computed, though this time excluding voxels that showed even a trend (p < 0.1) for an Unexpected > Expected effect. The only region in lateral PFC to show greater activation during Refresh versus Repeat trials (thresholded at p < 0.005) was in a right FPC region that was slightly more anterior and notably more dorsal (33, 60, 21) compared to the bilateral FPC regions that showed an effect of both Response and Expectation. Thus, all identified FPC voxels were sensitive to subgoaling/integration demands, with a subset being further sensitive to response selection demands.

Functional Dissociations between Mid-DLPFC and Lateral FPC
Across-region assessment of the patterns of mid-DLPFC and FPC sensitivity to response conflict and subgoaling/integration demands revealed dissociations in the functional response properties of these prefrontal subregions. Specifically, ROI analyses demonstrated a reliable Region [FPC, DLPFC] × Response interaction [F(1,15) = 11.0, p < 0.005] and a Region × Expectation interaction [F(1,15) = 5.3, p < 0.05)]. The interaction with Response stemmed from the fact that, with respect to Expected trials, during which response conflict was minimized, only FPC demonstrated a difference between Refresh and Repeat trials. The interaction with Expectation stemmed from the fact that, though both FPC and mid-DLPFC demonstrated sensitivity to response con-

A

ACC
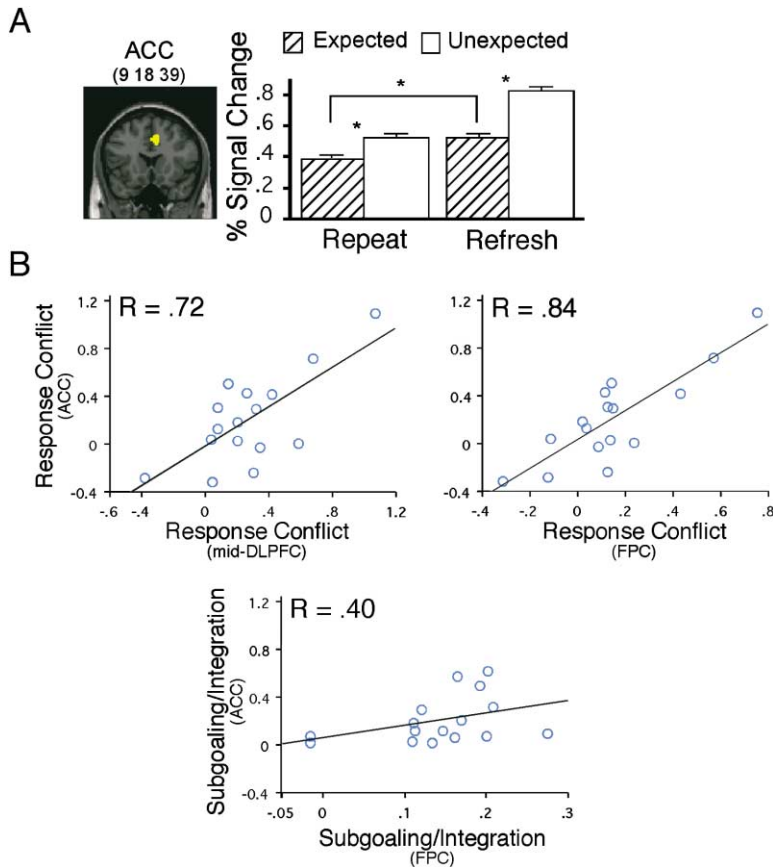(9 18 39)

B

R = .72

R = .84

R = .40

Figure 4. ACC Demonstrated a Sensitivity to Multiple Cognitive Control Demands and Functional Connectivity with Mid-DLPFC and Lateral FPC

(A) ROI analysis of ACC revealed sensitivity to response conflict (Unexpected > Expected) and subgoaling/integration demands (Refresh > Repeat), and a strong trend for an overadditive interaction.

(B) Regression plots show the relation between ACC sensitivity to response conflict (top graphs) and subgoaling/integration (bottom graph) and the corresponding effects in mid-DLPFC and lateral FPC.

flict, this effect was more pronounced in the mid-DLPFC regions.

As noted above, activation was also observed in right anterior DLPFC, in a region situated slightly dorsal and posterior to bilateral FPC (Figure 3C; xyz = 42, 48, 24). ROI analysis in this anterior DLPFC region revealed a pattern of sensitivity that did not differ reliably from that observed in FPC (Fs < 1), with the region demonstrating main effects of Refresh versus Repeat [F(1,15) = 10.0, p < 0.01] and Unexpected versus Expected [F(1,15) = 10.4, p < 0.01] and no interaction [F(1,15) = 1.9, p = 0.29]. As with FPC, the pattern of sensitivity in anterior DLPFC to the Response factor was distinct from that observed in mid-DLPFC [Region × Response: F(1,15) = 27.7, p < 0.0001].

ACC Sensitivity to Conflict
The preceding analyses demonstrated a functional distinction between mid-DLPFC and FPC, with the former being selectively sensitive to response conflict and the latter demonstrating an additional sensitivity to subgoaling/integration demands. Given this pattern, one might ask whether ACC conflict monitoring processes are selectively sensitive to response conflict or are more generally sensitive to increased cognitive control demands, irrespective of whether they arise from response conflict or from demands to engage in subgoaling/integration.

Robust voxel-wise activation was observed in ACC when comparing all response trials to baseline (Table 1; Figure 4A). Subsequent ROI analyses demonstrated a main effect of response conflict [Unexpected versus

Expected: F(1,15) = 14.3, p < 0.005], with ACC activation being greater during Unexpected versus Expected trials in both the Repeat [F(1,15) = 12.0, p < 0.005] and the Refresh conditions [F(1,15) = 41.1, p < 0.0001]. Importantly, in addition to its sensitivity to response conflict, ACC exhibited a main effect of Response, being more active during Refresh than during Repeat trials [F(1,15) = 28.8, p < 0.0001]. Moreover, even when response conflict was likely to be absent (i.e., on Expected trials), ACC activation was greater during the Refresh relative to the Repeat condition [F(1,15) = 12.0, p < 0.005]. Finally, a strong trend for a Response × Expectation interaction [F(1,15) = 4.3, p = 0.055] revealed that ACC showed a greater Expectation effect on Refresh trials than on Repeat trials (Figure 4A). Collectively these analyses indicate that differential ACC activation generalized beyond the detection of response conflict, with the effects of Response and Expectation being over-additive.

ROI analyses further revealed that the pattern of ACC activation differed from that observed in the mid-DLPFC subregions that showed a selective sensitivity to response conflict, as evidenced by a Region × Response × Expectation interaction [F(1,15) = 17.3, p < 0.001]. Likewise, the over-additive pattern in ACC differed from the additive pattern observed in lateral FPC [Region × Response × Expectation: F(1,15) = 8.4, p < 0.05].

Functional Connectivity between ACC and Lateral PFC
To the extent that ACC activation reflects the detection of conditions requiring increased control and subse-

quently serves to increase engagement of lateral prefrontal control processes, across-subject variance in ACC response conflict and subgoaling/integration activation might be accounted for by variance in lateral prefrontal activation to the corresponding conditions. Such correlations would suggest that ACC and lateral PFC are functionally coupled in the face of increasing control demands. Consistent with this perspective, ROI analyses revealed strong positive correlations between indices of ACC and lateral PFC sensitivity to response conflict (Figure 4B). Specifically, the pure effect of response conflict (Repeat-Unexpected versus Repeat-Expected) on ACC activation correlated with the average of this effect across the mid-DLPFC regions (R = 0.72, p < 0.005). Likewise, there was a corresponding correlation of response conflict effects between ACC and bilateral FPC (R = 0.84, p < 0.0001). These effects held even when the main effects of Expectation (i.e., Unexpected versus Expected) were substituted for the pure effects (i.e., Repeat-Unexpected versus Repeat-Expected) as the explanatory variables for mid-DLPFC (R = 0.60, p < 0.05) and FPC (R = 0.68, p < 0.005). Thus, ACC and lateral PFC were functionally coupled in the face of elevated response conflict.

Importantly, the ACC-lateral PFC correlations were not due to a general difference in between-subject BOLD responsiveness, nor did they generalize beyond the response selection network. First, regression analyses were conducted to assess whether across-subject variance in the increased responsiveness of ACC in the face of increasing conflict (i.e., Repeat-Unexpected versus Repeat-Expected) could be accounted for either by variance in the responsiveness of ACC to the low conflict condition relative to baseline (Repeat-Expected versus Baseline) or by variance in the responsiveness of ACC to the high conflict condition relative to baseline (Repeat-Unexpected versus Baseline). These regression analyses indicated that variance in BOLD responsiveness to either the low or the high conflict condition did not account for significant variance in the change in ACC BOLD signal in the face of increasing conflict (ps ≥ 0.12). Thus, the observed coupling between ACC and lateral PFC appears to emerge as a functional response to increased response conflict, rather than to individual differences in general BOLD responsiveness. Second, consistent with the preceding conclusion, a split-half analysis—sorting subjects according to whether they showed a large or small ACC signal increase in the face of increasing conflict—revealed that the magnitude of the ACC BOLD response during the high conflict trials (Repeat-Unexpected) did not reliably differ between the two groups (p > 0.28). Hence, both groups showed comparable above-baseline ACC responses in the face of high conflict; what differed was the magnitude of change in the ACC response due to increasing conflict. Importantly, the correlation indicates that the corresponding change in lateral PFC coupled with this change in ACC. Finally, ACC functional coupling in the face of enhanced response conflict was not present with regions thought to be uninvolved in the response selection pathway, such as extrastriate visual cortex (xyz = 36, −84, −12; R = 0.17, p = 0.53). Thus, the ACC-lateral PFC correlation was not due to nonspecific differences across subjects, but rather was restricted to coupling within the response selection circuit.

Beyond these demonstrations of functional connectivity between ACC and multiple lateral prefrontal regions in the face of response conflict, there was a positive but nonsignificant correlation between the pure effect of subgoaling/integration (Refresh-Expected versus Repeat-Expected) on ACC and FPC activation (R = 0.40, p = 0.12; Figure 4B).

Discussion

The present results provide compelling new evidence that further specifies the organization and operation of PFC-mediated cognitive control processes. In particular, four central findings were evident. (1) Bilateral mid-DLPFC regions were selectively engaged when a response had to be selected in the presence of a competing, prepotent response. (2) Bilateral FPC regions were engaged, not only for response selection, but also for managing subgoals and integrating representations during the course of ongoing processing. (3) Rather than exclusively detecting response conflict, ACC demonstrated a more general sensitivity to control demands, showing engagement under conditions of minimal response conflict but heightened subgoaling/integration demands. (4) ACC was observed to functionally couple with multiple lateral prefrontal regions, as revealed by strong positive correlations between their activation patterns across subjects.

Response Selection in Mid-DLPFC
Mid-DLPFC regions were robustly engaged when subjects were required to make a response incongruent with a prepotent response. In the present experiment, the prepotent response emerged by eliciting volitional preparation of an expected, but ultimately task-irrelevant, response. In this manner, our results complement and extend imaging studies of the Stroop task, as well as of other paradigms that elicit competition between response alternatives, demonstrating that neural computations in mid-DLPFC contribute to biasing a context-relevant response pathway when it is not otherwise automatically available (Bunge et al., 2002; Carter et al., 1995, 1998; MacDonald et al., 2000; Pardo et al., 1991; Wagner et al., 2001).

The observed pattern of mid-DLPFC activation advances our understanding of the sources of response conflict that may be resolved by DLPFC selection mechanisms. Prior studies have revealed DLPFC response conflict effects in the incongruent condition of the Stroop paradigm, in which conflict emerges from representations that are activated by a bottom-up process. That is, strong stimulus-response mappings result in automatic/bottom-up activation of the task-irrelevant, prepotent response pathway (word reading), which competes with the task-relevant, but nondominant, pathway (color naming). By contrast, in the present Repeat and Refresh tasks, the task-irrelevant response pathway is not prepotent because of prior training or automatic association with the response cue, but rather because the subject has been attending to the expected response and hence rendering it more active through top-down processes. Thus, in the Repeat condition, conflict emerges between the internally maintained representation and the representation elicited by the bottom-up

response cue. Moreover, in the Refresh condition, conflict emerges between the internally maintained representation and a target representation that must also be selected via top-down processing. The fact that the latter two sources of conflict result in comparable effects in mid-DLPFC, in regions similar to those observed in studies of the Stroop paradigm, suggests that these distinctions between how competing representations become active are irrelevant with respect to engaging the response selection circuitry. What appears to elicit upregulation of response selection processes is that there is competition between an active irrelevant pathway/representation and a relevant pathway/representation, irrespective of the means through which this competition has emerged. Given that conflict emerges due to top-down control in the present paradigm, this leads to an intriguing and counterintuitive prediction about the impact of cognitive control on subsequent control processing. Namely, the more effective a subject is at biasing/selecting the task-relevant response during the encode/bias/delay phase, the more control they will need to exert at the response phase when the initially selected response is ultimately task irrelevant. Accordingly, special populations that suffer from control deficits, such as older adults or individuals undergoing transient disruption of mid-DLPFC function during the bias/delay period via transcranial magnetic stimulation, might demonstrate an attenuated conflict response on Unexpected trials. This counterintuitive result would contrast with other tasks in which conflict emerges from preexperimental prepotency (e.g., Stroop), wherein diminished control is associated with amplified interference effects.

The present results also indicate that the control process mediated by the identified mid-DLPFC regions operates at the level of response representations rather than stimulus identification/specification (Kornblum, 1994). Evidence to this effect stems from the fact that when the response cue differed from the prepared response (i.e., the symbolic cue on Refresh trials differed from the target word response), this stimulus difference had no impact on mid-DLPFC activation (i.e., there was no main effect of Refresh versus Repeat). Accordingly, the computations supported by these mid-DLPFC regions appear to be relatively selective, operating at the level of the response representation (Van Veen et al., 2001).

The response selectivity of mid-DLPFC in the present study would appear to differ from a report of more generalized conflict sensitivity in DLPFC within the context of the Stroop task (Milham et al., 2001). Milham et al. (2001) observed two spatially distinct foci in DLPFC—one showing selective sensitivity to response-level interference and one to non-response-level interference. Interestingly, the response-sensitive DLPFC subregion in their study ($xyz = 53, 19, 42$; converted from Talairach to MNI) fell closer to the mid-DLPFC regions reported here than did their non-response-sensitive subregion ($xyz = -40, 4, 27$). Indeed, this latter region fell well posterior to the presently reported mid-DLPFC regions and may well correspond to a posterior VLPFC/premotor region previously associated with phonological computations (Poldrack et al., 1999). Accordingly, the present observation, together with that of Milham et al. (2001),

provides strong evidence that subregions within bilateral mid-DLPFC are selectively sensitive to response conflict—and thus are upregulated in the face of increasing response selection demands.

The convergence between the present and past studies of response conflict strongly suggests that mid-DLPFC mediates response selection, although an alternative interpretation of mid-DLPFC activation during Unexpected trials—that it reflects a novelty or surprise response due to the "oddball" nature of the Unexpected events—warrants consideration. Specifically, so as to encourage subjects to exploit the bias cue to prepare the expected response during the encode/bias/delay period, Unexpected trials occurred only 25% of the time and thus corresponded to lower frequency events. Although imaging studies of "oddball" effects have typically used designs in which the low frequency events occur between 5%–15% of the time, and we know of no oddball imaging study that implemented an oddball frequency as high as 25%, nevertheless oddball-elicited activation has been observed in several regions of lateral PFC, including VLPFC and DLPFC (Ardekani et al., 2002; Berns et al., 1997; Horn et al., 2003; Huettel et al., 2002; Kiehl and Liddle, 2003; Kirino et al., 2000; McCarthy et al., 1997). Importantly, however, recent evidence indicates that the simple presence of oddball or novel stimuli is insufficient to elicit activation in DLPFC (i.e., stimulus novelty or surprise per se does not appear to account for the DLPFC effects). Rather, lower frequency stimuli must be response relevant to engage DLPFC (Kirino et al., 2000; Michelon et al., 2003), a characteristic that is consistent with the present suggestion that mid-DLPFC selects and represents relevant response rules. In oddball paradigms, it seems plausible that DLPFC responses may reflect enhanced response selection demands due to the need to select nondominant response configurations in the face of prepotent, but irrelevant, configurations. Accordingly, in the present paradigm, it would appear that it is the need to generate an unexpected response in the face of a competing response that differentially elicits mid-DLPFC activation during Unexpected trials.

Refreshing and Mid-DLPFC

Although consistent with the response selection perspective, the present data failed to provide evidence that mid-DLPFC regions mediate a refresh mechanism (Raye et al., 2002). Refreshing has been hypothesized to be required when a task-relevant representation is allowed to decay from working memory and subsequently must be reaccessed. The purest case of such a condition in the present experiment corresponds to the difference between Refresh and Repeat trials when the required response was Unexpected and hence went largely unrehearsed. Comparison of these conditions revealed no difference in mid-DLPFC activation even at a very lenient threshold; quantitatively, the data showed a reverse effect (Figure 3B).

There are at least two possible accounts for the present failure to identify a neural marker of refresh processing in mid-DLPFC. First, the DLPFC regions previously associated with refreshing (Johnson et al., 2003, 2002; Raye et al., 2002) are spatially distinct from those

reported here, falling well anterior to the mid-DLPFC regions associated with response selection. This spatial divergence lends further support for the perspective that mid-DLPFC regions differentially subserve response selection. Second, one might hypothesize that the putative refresh process may be akin to a response selection mechanism in that it requires the top-down allocation of attention to a representation that was recently active in working memory. From this perspective, when representations are "refreshed," this may entail the selection or biasing of a particular response based on recently active working memory representations. To some extent, such an account would be consistent with other reports of DLPFC involvement in selection from within working memory (Passingham and Rowe, 2002; Rowe et al., 2000; Wagner et al., 2001). Such an account, however, would seem to predict a main effect of Refresh versus Repeat, a pattern that was not observed in mid-DLPFC but was observed in bilateral FPC and right anterior DLPFC. We return to this observation below.

Subgoaling/Integration Processing in FPC

In contrast to mid-DLPFC, bilateral FPC was sensitive not only to a mismatch between prepared and executed responses, but also to the need to execute the subgoal of integrating the results of intermediate processes to ultimately satisfy a superordinate goal. In the present experiment, subgoaling/integration was required because a symbolic response cue had to be integrated with either a symbolic bias cue or with the selected representation from within working memory (Refresh trials). Critically, this subprocess was required on all Refresh trials, even when the prepared response was consistent with the cued response. Activation in bilateral FPC, and right anterior DLPFC, revealed a main effect of these subgoal/integration demands.

Our FPC findings build on a growing literature surrounding FPC function in human cognition. Several recent imaging experiments (Braver and Bongiolatti, 2002; Christoff et al., 2001; Koechlin et al., 1999) and at least one review (Christoff and Gabrieli, 2000) have suggested that FPC is critical for either maintaining/generating subgoals or integrating the results of subgoal processing with an on-going task. FPC activation also has been consistently observed during studies of episodic retrieval (Buckner et al., 1995; Rugg et al., 1996; Squire et al., 1992; Tulving et al., 1994; Wagner et al., 1998), and some have suggested that such effects reflect subprocesses during retrieval wherein the mnemonic products elicited by current retrieval cues are integrated with decision criteria (Dobbins et al., 2002; Rugg and Wilding, 2000). In the present experiment, Refresh trials may have necessitated an initial attempt to verify that the response cue matched the bias cue presented moments earlier, in essence requiring reflection back to an earlier experience and integrating that information with the current goal/judgment criterion.

Although we interpret the main effect of Refresh versus Repeat on FPC and right anterior DLPFC activation as marking engagement of subgoal/integration processes, one might be tempted to alternatively suggest that this effect reflects engagement of putative refresh mechanisms. However, consideration of the pattern of results in these anterior prefrontal foci suggests that the response properties of these structures are not entirely consistent with a refresh process, per se. Of particular note is the fact that FPC and right anterior DLPFC showed a main effect of Refreshing, not only when the response information had decayed from working memory (Refresh-Unexpected trials), but also when the response was entirely expected and hence would have been well rehearsed (Refresh-Expected trials). This logic rests on the assumption that subjects indeed actively rehearsed the eventual response to a greater extent on Refresh-Expected than on Refresh-Unexpected trials. Though future research may be required to provide further convergent evidence to this effect, the currently observed behavioral effects suggest that subjects were indeed differentially maintaining the biased response over the unbiased responses in working memory, as indicated by RT slowing on Unexpected trials (Figure 2A).

Other aspects of the present findings also would appear inconsistent with a strong refresh account of FPC activation. Specifically, these regions were differentially engaged during Repeat trials when the response was Unexpected, relative to when Expected, whereas a central feature of reports of prefrontal activation associated with refresh demands is the relative insensitivity of PFC refresh regions to reading of unrehearsed words (Raye et al., 2002). Furthermore, our FPC foci, as well as the right anterior DLPFC focus, fell anterior and ventral to the DLPFC regions previously associated with refreshing. Accordingly, a subgoaling/integration interpretation would appear to best handle the present outcomes and their relation to the extant literature, though we cannot definitely rule out the possibility that (1) refreshing was present in both the Expected and Unexpected Refresh contexts, and (2) that the neural correlates of refreshing are sufficiently variable that such effects can be selectively observed in FPC, as revealed by the currently reported masked analysis, but also selectively in DLPFC regions, as revealed by prior reports (Johnson et al., 2003; Raye et al., 2002).

In addition to suggesting that mechanisms in bilateral FPC are upregulated in the face of subgoal/integration demands, the present data provide novel evidence that a subset of FPC foci are also sensitive to response conflict. That is, in addition to demonstrating a main effect of Refresh versus Repeat, activation in bilateral FPC foci further revealed a main effect of Unexpected versus Expected response. Given the sensitivity of these foci to both subgoaling/integration and response selection demands, an important question is whether these effects reflect the operation of a single process or multiple processes within FPC. Though the present study cannot definitively distinguish between these alternative accounts of FPC function, our data suggest that the observed effects may arise from distinct neural processes. In particular, the two effects did not interact, such that each appears to contribute an additive increment in FPC response. Notably, this additive response pattern differed reliably from that observed in ACC, which tended toward an over-additive pattern when both processing demands were present. Moreover, the pattern of FPC and right anterior DLPFC activation was functionally distinct from that in bilateral mid-DLPFC. Thus, the additive FPC pattern suggests that, unlike

mid-DLPFC, FPC may prove to be a more functionally heterogeneous region, supporting multiple forms of cognitive control. Future investigations using fMR adaptation (Grill-Spector and Malach, 2001) or dual-task interference paradigms may serve to further address whether the same or distinct subpopulations of neurons within FPC support subgoaling/integration and response selection mechanisms. Moreover, to the extent that FPC subgoaling/integration and response selection mechanisms are independent, engagement of these distinct mechanisms may be temporally segregated depending on the task demands. High temporal resolution imaging (e.g., magnetoencephalography) could provide the necessary test of whether these independent FPC mechanisms have distinct temporal onsets.

Generalized Sensitivity to Control
Demands in ACC

ACC showed greater engagement when an unexpected response had to be generated and, hence, demonstrated sensitivity to the presence of interference from a volitionally prepared, but ultimately irrelevant, response. This observation lends additional empirical support to the theoretical perspective that ACC monitors for and detects the presence of response conflict (Botvinick et al., 2001). Importantly, variants of this theoretical account of ACC function make two critical predictions: (1) there should be a functional relationship between ACC indices of response conflict and the observed upregulation of lateral prefrontal activation required to support response selection in the face of response conflict, and (2) changes in ACC activation should only track changes in levels of response conflict (Jonides et al., 2002; Milham et al., 2001, 2002; Van Veen et al., 2001).

The currently observed across-region correlations, while not providing direct indices of temporal interactions between brain regions, provide support for a functional coupling of ACC conflict monitoring responses with lateral prefrontal control mechanisms, consistent with the view that ACC monitoring signals serve to upregulate processes in lateral PFC. In particular, correlational analyses revealed a strong positive relation between individual differences in the effect of response conflict on ACC activity and the same effect on activity in mid-DLPFC and in FPC (Figure 4B). Consideration of the effects of individual differences in BOLD responsiveness during either the high or low response conflict conditions indicated that this correlation does not reflect between-subject variance in overall BOLD responsiveness, but rather correlated changes in ACC-PFC responses in the face of heightened response conflict. A conceptually related coupling between ACC and left VLPFC was recently reported within the context of a letter decision task (Stephan et al., 2003), and ACC also appears to couple with right DLPFC during certain forms of declarative memory retrieval (Bunge et al., 2004).

The present data provide important new evidence demonstrating that the same ACC region correlates with multiple lateral prefrontal structures. However, this functional coupling of ACC with PFC was a selective, rather than general, phenomenon, as ACC activity did not functionally couple with activity in regions beyond the response selection circuit (e.g., extrastriate visual cortex).

Accordingly, although the important issue of functional directionality remains to be determined—an outcome that is required for any causal interpretations—these observations suggest that ACC functionally interacts with multiple PFC subregions to resolve response conflict and to instantiate cognitive control. A focus for further research should be to determine whether, in addition to the currently observed ACC-PFC coupling across individuals, these regions demonstrate correlated moment-to-moment fluctuations within individuals depending on conflict demands (e.g., Botvinick et al., 2001).

The present data also indicate that, in contrast to prior suggestions (Milham et al., 2001; Van Veen et al., 2001), ACC function generalizes to other contexts requiring increased cognitive control (see also Van Veen and Carter, 2002). In particular, in the present study, the level of response conflict was posited to be similar across the Refresh-Expected and Repeat-Expected conditions, because both required execution of a prepotent, expected response. However, these conditions unambiguously differed in subgoaling/integration demands, which do not entail an obvious response conflict component, and consistent with this perspective, the mid-DLPFC regions sensitive to response conflict demonstrated comparable activation during Refresh-Expected and Repeat-Expected trials. Critically, in contrast to mid-DLPFC, ACC was more active during Refresh-Expected than Repeat-Expected trials (Figure 4A), and when both response selection and subgoaling/integration demands were present, in contrast to FPC, the response in ACC was greater than the simple addition of the two individual effects. These findings indicate that a singular process in ACC is sensitive to the presence of both response conflict and subgoaling/integration demands, suggesting that this ACC process serves as a more generalized detection mechanism that modulates engagement of multiple cognitive control processes.

Although we consider it unlikely, it remains conceivable that response conflict may be greater during Refresh than Repeat trials, and thus, in line with a selective response-conflict account, the observed differential activation in FPC and ACC in this contrast could reflect differences in response conflict. For example, during the Refresh condition, the elaborated processing required by subgoaling may produce interference in working memory, and this in turn may yield greater competition among the three alternative responses. From this perspective, on both Expected and Unexpected trials, the Refresh condition would potentially entail greater response conflict.

Our conclusion that ACC function generalizes beyond the detection of response-level conflict stems not simply from a task analysis of the Refresh versus Repeat conditions, but also (1) from the broader pattern of observed activation in ACC, together with that in mid-DLPFC, and FPC, and (2) from the assumption that there is a single form of response conflict. That is, if there were a singular form of response-level conflict and this form of conflict is evident in the Unexpected versus Expected and the Refresh versus Repeat main effects, it would be difficult to account for the observed dissociation between mid-DLPFC and FPC. Of course, one could speculate (1) that there is an additional form of response conflict that is

present in the Refresh conditions, (2) that this form of response conflict is not adjudicated by mid-DLPFC but rather is adjudicated by FPC, and (3) that ACC is sensitive to both forms of response conflict. However, it is difficult to determine what the characteristics of this second form of response-level conflict would be that distinguish it from the type brought about by the expectation violation manipulation. Alternatively, one might suggest that FPC and ACC, but not mid-DLPFC, are sensitive to response conflict, but this alternative perspective is faced with the difficulty of (1) accounting for the robust and selective effect of Expectation in mid-DLPFC without recourse to response conflict, and (2) resolving this account with the vast literature on DLPFC and response selection. Moreover, given the evidence implicating FPC in subgoaling/integration and the unambiguous presence of such processes in the Refresh conditions, we propose that it is more plausible and parsimonious that ACC monitoring mechanisms generalize to the detection of conditions requiring multiple forms of cognitive control.

It remains an open question as to what aspect of subgoaling/integration serves to signal or trigger engagement of ACC mechanisms. One possibility is that the present subgoaling/integration demands also entailed conflict between an expected and presented stimulus configuration (rather than response conflict). Further investigation is required to more definitively specify the boundary conditions of ACC sensitivity. Nevertheless, the present study provides some of the strongest evidence that the ability to engage in context-relevant behavior depends on recruiting multiple cognitive control mechanisms in mid-DLPFC and lateral FPC, mechanisms that are upregulated through functional interactions with ACC.

Experimental Procedures

Participants

Sixteen right-handed, native English speakers (eight female; ages 18–27) were remunerated $50 for participation. Data from five additional subjects were excluded due to poor behavioral performance, having an overall accuracy rate ≤0.75; this low accuracy rate reflected a difficulty in meeting the 1500 ms response deadline (when excluded subjects responded in time, their performance was qualitatively similar to that of subjects included in the analysis). Informed consent was obtained in a manner approved by the Human Subjects Committee of Massachusetts General Hospital and the Committee on the Use of Humans as Experimental Subjects at MIT.

Design

All trials, regardless of response condition, were identical in structure, from the encoding phase of the trial through the delay period (Figure 1A). Subjects were unaware of the experimental condition for a given trial until the response cue was presented. The experimental conditions were defined based on the nature of the response cue and its relation to the bias cue. The four conditions (Repeat-Expected, Repeat-Unexpected, Refresh-Expected, and Refresh-Unexpected; Figures 1B and 1C) were intermixed in an event-related fashion. Based on the response cue, subjects covertly generated a response by either subvocally repeating the visually presented response word (Repeat trials) or repeating one of the words held in working memory (Refresh trials). For both Refresh and Repeat conditions, 75% of the time the Expected response signaled by the bias cue was the target response; 25% of the time an Unexpected response was required (i.e., the bias cue and the response cue diverged with respect to the target response). Subjects pressed a button to indi-

cate when they had completed subvocally saying the target response; during Refresh trials, subjects pressed a second key if they were unable to remember the word that had been cued at response. Trials were considered correct if the subject reported, during the response window, that they had successfully repeated the target word to themselves; RT data were collected in the scanner on the basis of the button press.

Across eight fMRI scan runs, subjects were presented with 216 trials: 108 Repeat trials and 108 Refresh trials. Within each of the response conditions (Repeat/Refresh), 75% of the events (81 trials) were Expected and 25% (27 trials) were Unexpected. Each of the eight scans began with a 16 s baseline period during which the subject fixated on a central cross. Subsequently, 8 s experimental trials were presented, with trials being jittered in time using variable-duration (0–12 s) fixation null events. The order of experimental and null events was determined by optimizing the efficiency of the design matrix (Dale et al., 1999).

Word stimuli consisted of three-syllable abstract words equated across conditions for mean word frequency and word length. Each trial consisted of a unique set of three words; across subjects, the word sets were counterbalanced across conditions. Three-syllable words were chosen to keep the number of to-be-maintained lexical representations fairly low, but to make the task demanding enough that exploiting the bias cue to prepare an expected response would be an advantageous strategy for the subject. Stimuli were presented and responses were recorded on a Macintosh G3 laptop computer running MATLAB.

fMRI Procedures

Whole-brain imaging was performed on a 3T Siemens Allegra MRI system. Functional data were acquired using a gradient-echo echo-planar pulse sequence (TR = 2 s, TE = 30 ms, 21 axial slices, 3.125 × 3.125 × 5 mm, 1 mm interslice gap, 170 volume acquisitions per run). High-resolution T1-weighted (MP-RAGE) anatomical images were collected for anatomical visualization. Head motion was restricted using firm padding that surrounded the head. Visual stimuli were projected onto a screen and were viewed through a mirror attached to the standard head coil.

Data were preprocessed using SPM99 (Wellcome Dept. of Cognitive Neurology, London). Functional images were corrected for differences in slice acquisition timing, followed by motion correction (using sinc interpolation). Structural and functional data were spatially normalized to a template based on the MNI305 stereotactic space (Cocosco et al., 1997)—an approximation of canonical space (Talairach and Tournoux, 1988)—using a 12-parameter affine transformation along with a nonlinear transformation using cosine basis functions. Images were resampled into 3 mm cubic voxels and spatially smoothed with an 8 mm FWHM isotropic Gaussian kernel.

Statistical models were constructed using SPM99 under the assumptions of the general linear model. Analysis focused on two portions of each trial and modeled each differently (Figure 3A). The initial portion of each trial—from the encoding of the three words into working memory, to selection from within working memory due to presentation of the bias cue, to maintenance across the delay—was identical irrespective of the response condition. Accordingly, the encode/bias/delay period was modeled as a single 6.5 s epoch regardless of response condition, with correct trials being modeled separately from incorrect trials. Consideration of the neural correlates active during this initial period provided leverage on regions that encode and maintain phonological representations in working memory and regions that mediate the selection of one of the maintained representations based on the bias cue. In addition to modeling this initial portion of the trials, the response portion of each trial was modeled as an event, assuming a canonical HRF (Friston et al., 1998). There were four response conditions (i.e., Refresh/Repeat × Expected/Unexpected; Figure 1B); correct and incorrect trials were modeled separately. Hence, though the encode/bias/delay period always preceded the response period, the regressors for each period were sufficiently uncorrelated to allow assessment of the unique contribution of each to the overall variance in fMRI signal.

Effects were estimated using a subject-specific fixed-effects model, with session-specific effects and low-frequency signal components treated as confounds. Linear contrasts were used to obtain

subject-specific estimates for each effect. These estimates were entered into a second-level analysis treating subjects as a random effect, using a one-sample t test against a contrast value of zero at each voxel. Regions were considered reliable to the extent that they consisted of at least 5 contiguous voxels that exceeded an uncorrected threshold of $p < 0.001$.

The group-level voxel-based contrasts were supplemented with region-of-interest (ROI) analyses that further characterized the effects of Expectation (Expected/Unexpected) and Response type (Refresh/Repeat) in functionally defined regions. These ROI analyses also provided quantitative characterization of the effects observed in the group-level voxel-based analyses. ROIs were identified by including all significant voxels within a 6 mm radius of the chosen maximum identified, unless otherwise noted, from the group contrast of all response trials to the fixation baseline. Selective averaging with respect to peristimulus time allowed assessment of the signal change associated with each condition, thus permitting ROI analyses based on the data rather than on the parameter estimates. ROI data are expressed in peak percent signal change, and the resultant data were subjected to repeated-measures analyses of variance (ANOVA).

Acknowledgments

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