The role of frontopolar prefrontal cortex in subgoal processing during working memory

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Abstract

Neuroimaging studies have implicated the anterior-most or frontopolar regions of prefrontal cortex (FP-PFC, e.g., Brodmann’s Area 10) as playing a central role in higher cognitive functions such as planning, problem solving, reasoning, and episodic memory retrieval. The current functional magnetic resonance imaging (fMRI) study tested the hypothesis that FP-PFC subserves processes related to the monitoring and management of subgoals while maintaining information in working memory (WM). Subjects were scanned while performing two variants of a simple delayed response WM task. In the control WM condition, subjects monitored for the presence of a specific concrete probe word (LIME) occurring following a specific abstract cue word (FATE). In the subgoal WM condition, subjects monitored for the presence of any concrete probe word immediately following any abstract cue word. Thus, the task required semantic classification of the probe word (the subgoal task) while the cue was simultaneously maintained in WM, so that both pieces of information could be integrated into a target determination. In a second control condition (control subgoal), subjects performed abstract/concrete semantic classification without WM demands. A region within right FP-PFC was identified which showed significant activation during the subgoal WM condition, but no activity in either of the two control conditions. However, this FP-PFC region was not modulated by direct manipulation of active maintenance demands. In contrast, left dorsolateral PFC was affected by active maintenance demands, but the effect did not interact with the presence of a subgoal task. Finally, left ventral PFC regions showed activation in response to semantic classification, but were not affected by WM demands. These results suggest a triple dissociation of function within PFC regions, and further indicate that FP-PFC is selectively engaged by the requirement to monitor and integrate subgoals during WM tasks.
Introduction

The prefrontal cortex (PFC) has long been thought to play a central role in higher cognition (Fuster, 1989; Goldman-Rakic, 1987; Stuss & Benson, 1986). With the advent of high spatial resolution functional neuroimaging it has become possible to study the functional properties of specific PFC subregions. Consequently, there has been an explosion of research examining more fine-grained relationships between different PFC subregions and specific cognitive processes. For example, much attention has been focused on the role of the dorsal and ventral PFC in active maintenance and manipulation processes within working memory (WM) (Cabeza & Nyberg, 2000; D'Esposito et al., 1998; Smith & Jonides, 1999). More recently, there have also been studies focused on the most anterior lateral regions of PFC, also termed frontopolar PFC (FP-PFC). In particular, it has been found that the FP-PFC is consistently engaged during episodic retrieval from long term memory (Buckner & Koutsala, 1998; Tulving, Kapur, Craik, Moscovitch, & Houle, 1994). Subsequent research has been directed towards understanding the specific nature of this involvement (Konishi, Wheeler, Donaldson, & Buckner, 2000; Lepage, Ghaffar, Nyberg, & Tulving, 2000; McDermott, Jones, Petersen, Lageman, & Roediger, 2000; Rugg & Wilding, 2000). FP-PFC activity also appears to be reliably elicited during planning, problem solving and reasoning tasks. For example, Baker et al. (1996) observed FP-PFC activity in the Tower of London paradigm selectively under conditions that involved extensive planning. A recent review by Christoff and Gabrieli (2000) catalogued a number of similar studies using different task paradigms (such as the Wisconsin Card Sort Task and Raven’s Progressive Matrices) that also have resulted in FP-PFC activity.

These findings suggest that FP-PFC regions are reliably activated across a number of different domains within higher cognition. However, the specific nature of this activation is still not well understood. Nevertheless, there have been some recent suggestions regarding the nature of FP-PFC function. Based on their review of the literature, Christoff and Gabrieli (2000) suggest that FP-PFC, specifically Brodmann's Area (BA) 10, may subserve the monitoring of internally
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(versus externally) generated information. They propose a hierarchical system in which dorsolateral PFC (DL-PFC) is involved when externally generated information is evaluated, and FP-PFC is additionally recruited when internally generated information must be evaluated, such as in reasoning tasks or in tasks requiring episodic memory. A related view regarding the functions of FP-PFC has been put forth by Koechlin et al. (1999), who proposed the term "cognitive branching" to describe the involvement of FP-PFC in situations requiring the maintenance of primary task goals while simultaneously allocating attention to subgoals. A subgoal is defined as a task that must be completed first before a higher-order goal is satisfied. Koechlin et al. observed selective FP-PFC activity during a fairly complex task that required integrating WM with attentional reallocation.

The goal of the current study was to try to extend this previous work, by attempting to provide a clearer specification of the conditions needed to elicit activity in FP-PFC. In particular, we put forward a hypothesis similar to that espoused by Koechlin et al. (1999), but aimed to more specifically define the conditions under which FP-PFC activity is elicited. We suggest that a necessary minimal condition for FP-PFC activity is the requirement to perform a subgoal task while simultaneously maintaining primary goal-related information in WM. Our main goal was to test this hypothesis using a simple, and highly interpretable task design, in which each of the individual task components (i.e., active maintenance and subgoal task) are both clearly understood and well-validated from previous research. The experimental logic was to test whether each of these task subcomponents alone (WM or subgoal task) were sufficient to elicit FP-PFC activity or whether FP-PFC activity would only be present when these two components were combined. A secondary goal of the study was to further specify the nature of FP-PFC activity by testing two alternative hypotheses regarding the exact role of this region in subgoal processing during WM.

The first hypothesis is that FP-PFC activation may reflect a specialized representational code that is used to actively maintain information in tasks that require subgoal processing. Previous research indicates that DL-PFC appears to be generally involved in tasks requiring active maintenance of goal-related or context information. However, during tasks that involve active
maintenance and subgoal processing, FP-PFC may be additionally recruited to provide storage of this information in a form that is more protected from interference (due to the intervening subgoal task). A second hypothesis is that FP-PFC may be critically involved in the actual integration of the results of subgoal processing with the information that had been actively maintained prior to the subgoal task. Thus, under this second hypothesis, it is the need to integrate the two sources of information (primary task and subgoal task results) that elicits FP-PFC activity.

In order to test these hypotheses, we designed a simple paradigm based upon a WM task that we have studied extensively in previous neuroimaging and behavioral research. This task, known as the AX-CPT, is a variant of the delayed response paradigm, and requires maintenance of a cue over a delay period in order to determine the appropriate response to a subsequent probe (Barch et al., 1997; Barch et al., 2001; Braver et al., in press; Braver & Cohen, in press; Cohen, Barch, Carter, & Servan-Schreiber, 1999; Servan-Schreiber, Cohen, & Steingard, 1996). The current study added a subgoal component to the basic task paradigm by making stimulus categorization dependent upon elaborative semantic processing. We then compared this condition to two other closely matched conditions, one which required active maintenance in WM but had no subgoal component, and another which required performing the subgoal task (elaborative semantic processing) but had no WM component. Based on prior neuroimaging studies with the AX-CPT paradigm, we expected that without a subgoal component the WM demands of the AX-CPT would elicit activity in DL-PFC but not in FP-PFC. Likewise, tasks that require elaborative semantic processing in the absence of an explicit WM load, appear to engage left ventrolateral PFC (VL-PFC) regions, but not DL-PFC or FP-PFC (Demb et al., 1995; Poldrack et al., 1999). Thus, we expected that only the subgoal WM condition would result in the presence of FP-PFC activity.

The task design also included a manipulation of the delay between cue and probe, while holding the total trial duration constant. Such a manipulation should increase the demands on active maintenance processes (since the cue information must be maintained for a longer period), and lead to increased activity in brain regions that support active maintenance. In our previous research, we have found increased activity in DL-PFC regions resulting from such manipulations.
(BA 46/9) (Barch et al., 1997; Barch et al., 2001; Braver & Cohen, in press). Moreover, the delay manipulation is a selective one because all other components of the task remain the same. In the current study, the delay manipulation was used to test whether FP-PFC was also specifically involved in active maintenance (under subgoal conditions). If so, we would expect to observe a significant effect of delay in this region during the subgoal WM task. In contrast, the absence of a delay effect would be more consistent with the hypothesis that FP-PFC is specifically involved in serving an integration function under these conditions.

Methods

Subjects. 21 right-handed subjects with no evidence of neurological compromise participated in this study. Subjects were 11 males and 10 females with a mean age of 23 years (age range 18-31 years). Subjects gave informed consent per guidelines set by the Washington University Medical Center Human Studies Committee and were paid $25 for each hour of participation.

Behavioral Tasks. Subjects performed two delayed-response WM tasks and a semantic classification task. The WM tasks were two variants of the AX version of the Continuous Performance Task (AX-CPT). The original AX-CPT requires subjects to make a positive target response to the probe letter "X", but only when it follows the cue letter "A", and to make a nontarget response to all other conditions (Servan-Schreiber et al., 1996). Accurate responses to the probe letter require maintenance of information about the cue letter. The two tasks designed for the current study, which we termed the Word AX-CPT and the Semantic AX-CPT, retained the basic format of the original task but used words instead of letters. In the Word AX-CPT task, the target was the word "LIME" when it occurred following the word "FATE." The target for the Semantic AX-CPT was any concrete word immediately following any abstract word. Thus, the Word AX-CPT is directly analogous to the original AX-CPT in that it requires subjects to actively maintain context information. The Semantic AX-CPT, however, additionally requires subjects to
semantically classify each word, which produces a subgoal processing requirement. Consequently, to perform the task appropriately, subjects must classify the probe word while simultaneously maintaining the context provided by the previous cue (the subgoal task), so that the information from both cue and probe can be integrated into a target determination. Subjects also performed a third task condition, Semantic Classification, which required subjects to make abstract-concrete judgments for words. This condition allowed us to isolate the subgoal component of the Semantic AX-CPT task.

For both AX-CPT tasks, words were presented in cue-probe pairs, one word at a time. All probes were underlined to differentiate them from the cue. Target and nontarget trials appeared intermixed in a pseudorandom sequence. Target trials (FATE-LIME or ABSTRACT-CONCRETE) occurred with 70% frequency, and nontarget trials occurred with 30% frequency. The frequency of non-target trials was evenly distributed as follows: 10% "BX" trials in which an invalid cue preceded the target; 10% "AY" trials in which a valid probe was followed by a non-target probe; and 10% "BY" trials, in which an invalid cue was followed by a non-target probe. The frequencies of the various trial types replicates those used in many previous studies with the AX-CPT paradigm (Braver et al., in press; Cohen et al., 1999).

The words for all three tasks were presented centrally on a visual display, in 36-point Helvetica font. Words were taken from standardized lists of abstract and concrete nouns. All words were 3-7 letters in length and consisted of one or two syllables. Each word was presented for 750 ms. Responses to stimuli were made by pressing different buttons on a hand-held response box. In the AX-CPT tasks, subjects responded with their index finger for targets and their middle finger for nontargets. In the Semantic Classification task, subjects responded with their index finger if the word was abstract, and with their middle finger if the word was concrete.

A second factor, delay, was also manipulated in this study. Specifically, in the AX-CPT tasks, we hypothesized that regions involved with active maintenance of context should be influenced by the duration over which context should be maintained (i.e., the cue-probe delay period). Thus, we had subjects perform the AX-CPT under conditions of both short and long cue-
probe delays. The short delay was 1 second in duration. In 12 of the subjects, the long delay was 5 seconds; in the remaining 9 subjects it was 7.5 seconds. Total trial duration was equated by counterbalancing the intertrial interval (ITI) with the cue-probe delay (e.g. for the short delay version, the delay was 1 second and ITI was 5 or 7.5 seconds). In the Semantic Classification condition, the timing of the words was also varied to control for the delay manipulation in the AX-CPT tasks. Thus, trials were arbitrarily presented as two-word pairs (but with neither word of the pair underlined), and the delay between the first and second words of the pair was either short (1 second) or long (5 or 7.5 seconds).

**Functional Imaging.** Images were acquired on a Siemens 1.5 Tesla Vision System (Erlangen, Germany) with a standard circularly-polarized head coil. A pillow and tape were used to minimize head movement. Headphones dampened scanner noise and enabled communication with participants. Both structural and functional images were acquired at each scan. High-resolution (1.25 x 1 x 1) structural images were acquired using a sagittal MP-RAGE 3D T1-weighted sequence (TR=9.7 mm, TE=4, flip=12°, TI=300 ms) (Mugler & Brookeman, 1990). Functional images were acquired using an asymmetric spin-echo echo-planar sequence (TR=2500, TE=50 ms, flip = 90°). Each image consisted of 16 contiguous, 8 mm thick axial slices acquired parallel to the anterior-posterior commissure plane (3.75x3.75 mm in-plane), allowing complete brain coverage at a high signal-to-noise ratio (Conturo et al., 1996). Subjects performed two repetitions of each of the 6 task conditions (Word AX-CPT, Semantic AX-CPT and Semantic Classification at each of Short and Long delays) in separate scanning runs (12 runs total). Each run consisted of alternating cycles of task and fixation blocks. Task blocks were 10 trials in duration. Fixation blocks (denoted by a centrally presented crosshair) were either 25 or 37.5 seconds in duration. Finally, the first four images in each scanning run were used to allow the scanner to reach steady-state, and hence were discarded. Each run lasted approximately 5 minutes, and a 2 minute delay occurred between runs, during which time subjects rested.

Visual stimuli were presented using PsyScope software (Cohen, MacWhinney, Flatt, & Provost, 1993) running on an Apple PowerMac G4. Stimuli were projected to subjects with an
AmPro LCD projector (model 150) onto a screen positioned at the head end of the bore. Subjects viewed the screen through a mirror attached to the head coil. A fiber-optic, light-sensitive key press interfaced with the PsyScope Button Box was used to record subjects’ behavioral performance.

**Data Analysis.** Behavioral performance data were analyzed for differential difficulty across the three task conditions by conducting ANOVAs on accuracy and RT measures. Analyses were only conducted on probe trials because these were the only trials requiring response selection in the two AX-CPT conditions. In the Classification condition, probe trials were defined arbitrarily as the second of a two-stimulus pair. Functional imaging data were analyzed according to the following procedures. All functional images were first corrected for movement using a rigid-body rotation and translation correction (Friston, Williams, Howard, Frackowiak, & Turner, 1996; Snyder, 1996), and then registered to the subject’s anatomical images (in order to correct for movement between the anatomical and function scans). The data were then scaled to achieve a whole-brain mode value (used in place of mean because of its reduced sensitivity to variation in brain margin definition) of 1000 for each scanning run (to reduce the effect of scanner drift or instability), and spatially smoothed with an 8mm FWHM Gaussian kernel. Subjects' structural images were transformed into standardized atlas space (Talairach & Tournoux, 1988), using a 12-dimensional affine transformation (Woods, Cherry, & Mazziotta, 1992; Woods, Grafton, Holmes, Cherry, & Mazziotta, 1998). The functional images were then registered to the reference brain using the alignment parameters derived for the structural scans.

Group analyses were conducted using a voxelwise random-effects model with subject serving as the random effect. In order to control for linear drift during and between scanning runs, mean difference images were first computed for each run by subtracting activity during fixation blocks from activity during task blocks. All analyses were then conducted on these mean difference images. To protect against false positive activations, in all analyses an identified region was only considered to be significant if it both passed the statistical criteria set with an image-wise significance threshold at $p < .05$, and occurred within a cluster of 8 or more contiguous voxels. Finally, to increase interpretability, only positive activations were considered in these analyses.
Three primary analyses were conducted to test for semantic selectivity, active maintenance selectivity, and selectivity to subgoal processing (i.e., semantic processing during active maintenance). Following the primary analyses, region-of-interest (ROI) analyses were then conducted to quantitatively estimate the effect of experimental factors on the identified regions. We were particularly interested in the effect of delay in the subgoal-selective regions. For these analyses, data were expressed in terms of percent-change relative to fixation.

Because of technical difficulties, behavioral data from one subject was unusable, and the scanning session had to be ended early, with only half of the scans performed (one run in each condition). We thus excluded this subject from all behavioral analyses, and imaging analyses were performed both including and excluding the subject's data. None of the reported imaging results differed as a function of inclusion or exclusion.

Results

Behavioral Data. Accuracy and reaction time data were examined to determine whether the Semantic AX-CPT was significantly more difficult than the other two conditions. The results are summarized in Table 1. An analysis of error rates indicated a significant main effect of task (F(2,38) = 11.52, p<.001). Pair-wise comparisons indicated that performance on the Word AX-CPT task was significantly less error-prone than in either Semantic AX-CPT or Semantic Classification (Word vs. Semantic AX-CPT: t(19) = 3.78, p<.001; Word vs. Classification: t(19) = 4.13, p<.001). However, the Semantic AX-CPT and Classification conditions were not significantly different in error rates (t(19)=1.64, p>.1). A similar analysis was performed on the reaction time data. Again, a highly significant main effect of task was observed (F(2,38) = 208.36, p<.001). As with error rates, the Word AX-CPT was found to have significantly shorter RTs than Semantic AX-CPT or Classification (Word vs. Semantic AX-CPT: t(19) = 9.87, p<.001; Word vs. Classification: t(19) = 26.98, p<.001). Additionally, it was found that Semantic AX-CPT RTs were significantly shorter than in Classification (t(19)=8.66, p<.001). These findings indicate that the Semantic AX-CPT was not associated with greater task difficulty, at least when compared to Classification.
Instead, they suggest that if anything the Classification task was slightly more difficult than the Semantic AX-CPT.

**Imaging Data.** Three different analyses of the imaging data were conducted, one testing for semantic effects, one testing for active maintenance effects, and the other testing for subgoal processing effects. Although we collected whole-brain imaging data, our focus was on activated regions within PFC, and only those are reported. Task-related activity was also observed in non-frontal regions (e.g., parietal activity related to active maintenance, and temporal activity related to semantic processing). Data regarding these non-frontal regions are available upon request from the author. The results of these analyses are summarized in Table 2, and described in detail below.

**Semantic Processing.** Semantic-selective PFC regions were identified based on the following tests: 1) significant activation during runs involving semantic processing (i.e., both Classification and Semantic AX-CPT); and 2) significantly greater activity for either semantic processing condition when compared against the non-semantic condition (i.e., Word AX-CPT). Voxels were masked out of semantic-selective regions if they showed a significant activation response during Word AX-CPT runs. This analysis identified regions in VL-PFC that were primarily left-lateralized. Activity was observed in several large foci distributed across BA 44, 45 and 47 (see Figure 1). ROI analyses of these regions indicated a high level of activity during both conditions involving semantic processing (i.e. Classification and Semantic AX-CPT), but no activation in the condition that did not require semantic processing (i.e., Word AX-CPT). Moreover, in none of these regions did activity differentiate between the two semantic processing conditions, suggesting that VL-PFC regions are not sensitive to the additional processing requirements associated with the Semantic AX-CPT.
There were also no effects of delay in any of these PFC regions, consistent with a selective role in semantic processing rather than active maintenance.

**Active Maintenance.** Maintenance-selective PFC regions were identified based on the following tests: 1) a significant activation response during runs involving active maintenance (i.e., both AX-CPT tasks); and 2) significantly greater activity for the long delay condition relative to the short delay. Voxels were masked out of maintenance-selective regions if they showed a significant delay effect during the Classification condition (since in this condition the delay factor was not meaningful). This analysis revealed activation in left DL-PFC, BA 46/9 (in addition to activation in bilateral supplementary motor areas). The location of this activity replicates the results of our previous studies (Barch et al., 1997; Barch et al., 2001; Braver & Cohen, in press). As Figure 2 shows, the effect of delay was present in both AX-CPT conditions (although slightly stronger in the Word AX-CPT). Additionally, activity was stronger overall in the Semantic AX-CPT condition, suggesting an additive effect of task that did not interact with delay. Interestingly, ROI analysis indicated that the left DL-PFC region was also activated during performance of the Classification condition, although the response was not effected by delay (as defined by the analysis procedure).

**Subgoal Processing.** Our primary analysis of interest was to identify regions activated during the Semantic AX-CPT condition, but not the other two tasks. Such a pattern of activity would suggest that the region was selectively engaged by conditions requiring the conjunction of active maintenance and subgoal processing, rather than by individual components associated with either task. Subgoal-selective PFC regions were identified based on the following tests: 1) a significant activation response during runs involving subgoal processing (i.e., the Semantic AX-CPT); and 2) significantly greater activity during the Semantic AX-CPT when compared against either of the two
control conditions (i.e., Word AX-CPT, Classification). Voxels were masked out of subgoal-selective regions if they showed a significant activation response during either the Word AX-CPT or Classification runs. This analysis procedure identified two regions in PFC showing subgoal-selective activity. Both regions were in the right hemisphere, one in DL-PFC (BA 46/9) and most importantly, the other in FP-PFC (BA10; see Figure 3). After identifying this FP-PFC ROI, we determined whether the region showed an additional effect of delay during the Semantic AX-CPT. Examination of the delay effect allowed us to further test whether and how activation in the region is influenced by active maintenance demands. This ROI analysis revealed no effect of delay on the anterior PFC activity during the Semantic AX-CPT (F<1). Interestingly, there was a trend for a delay effect in the Word AX-CPT condition, although this trend did not reach significance.

Discussion

The goal of the current study was to look at potential functional dissociations between different subregions of PFC. In particular, we were interested in determining the task conditions that elicit activity in FP-PFC as compared to the conditions that engage DL-PFC and VL-PFC regions. To examine this question, we utilized cognitive tasks that when performed in isolation reliably activate either VL-PFC regions (semantic classification) or DL-PFC regions (working memory), but do not engage FP-PFC. We then employed an experimental design in which these tasks were combined in a particular fashion that we hypothesized would lead to frontopolar activity. Specifically, the critical experimental condition required performing semantic classification as a subgoal task while concurrently maintaining information in WM, and then using the results of both sources of information (WM contents and classification judgment) to determine the appropriate response. The results confirmed our hypotheses while being consistent with prior research. Replicating prior findings, semantic classification judgments engaged primarily left-lateralized VL-PFC regions (Demb et al., 1995; Poldrack et al., 1999), while the active maintenance of information
in WM engaged left DLPFC (Barch et al., 1997; Barch et al., 2001; Braver & Cohen, in press). Moreover, when these tasks were performed in isolation, there was no activity in FP-PFC. However, in the critical experimental condition, FP-PFC was significantly activated. These results suggest a specialized role for FP-PFC in enabling the processing of subgoal tasks during WM.

Our findings confirm and extend the recent work of Koechlin and colleagues (1999), who also observed FP-PFC activity related to subgoal processing in WM. The interpretation of Koechlin et al. was that FP-PFC is engaged under conditions that involve “cognitive branching.” However, the particular functions subserved by FP-PFC during cognitive branching were not clearly specified in the Koechlin et al. study. For example, the task design utilized by Koechlin et al. was both novel and complex; consequently, it was not clear whether the phenomenon of branching would generalize across different task domains. Moreover, from the results presented by Koechlin et al. it was not clear whether FP-PFC is engaged by the unique maintenance requirements associated with cognitive branching, or by the demands associated with resuming a primary task after completing a subgoal task. In the current study, we observed FP-PFC activity during performance of a simple WM task that was directly related to the presence of a subgoal processing requirement. This finding demonstrates that the subgoal processing effect, or “cognitive branching” in the terminology of Koechlin et al., is a phenomenon that generalizes across task domains. More importantly, our results also further specify the nature of FP-PFC involvement in subgoal processing. Specifically, we observed that FP-PFC activity was not increased in relationship to increased maintenance demands occurring under subgoal conditions (i.e., the null delay effect). This finding suggests that in our task, FP-PFC was not selectively responsible for maintaining cue information over the delay period.

The lack of delay effect in FP-PFC favors alternative hypotheses of FP-PFC function that relate activity in this region specifically to the integration of WM and subgoal task processing. One such hypothesis is that FP-PFC is engaged to resolve potential interference occurring specifically during the period in which the subgoal task is being completed. In our task, this would correspond to the period immediately following probe presentation, when the probe word must by semantically...
classified, while at the same time, active maintenance of the cue information must continue. Under this hypothesis, it is the simultaneous demands on WM and subgoal processing that elicits FP-PFC activity, especially under conditions when these two demands involve the same neural substrates for processing. Moreover, under these conditions, it is the duration of subgoal processing rather than the duration of active maintenance in WM that influences FP-PFC activity. A source of support for this hypothesis is the finding in the current study that the left DL-PFC appears to be activated both by semantic processing requirements and by active maintenance of the cue. When these two tasks were combined in the Semantic AX-CPT condition, FP-PFC may have been additionally engaged to help reduce the interference that would otherwise occur in the DL-PFC. A second hypothesis is that FP-PFC is primarily engaged under conditions in which the results of subgoal processing need to be integrated with the information stored in WM, in order to determine appropriate responding. This hypothesis suggests that the primary factor that influences FP-PFC is not subgoal processing during WM, but rather the requirement to integrate these two sources of information. Thus, a task that requires the integration of subgoal processing with WM contents would be predicted to elicit greater activation than an equivalent task in which the two sources of information (i.e. WM contents and subgoal results) remain unintegrated and unrelated. Both of these hypotheses are consistent with the current results, and accordingly, warrant more direct investigation in future studies.

One conclusion to be drawn from the current results is that FP-PFC may play a very specific computational role in cognition that nevertheless appears across a wide variety of behavioral domains. The coordination and management of subgoal tasks is a computation that is present in many behaviors, such as planning, problem solving, reasoning, and other complex cognitive activities. For example, the classic Tower of Hanoi problem is one that requires subjects to decompose a higher-order goal (moving the disks to a specific peg) into a hierarchical sequence of subgoals (e.g., to move the second disk, first move the top disk to a spare peg). Each of these subgoals must be appropriately chained together, while at the same time keeping them integrated with the higher-order goal. Our findings begin to suggest the specific computations that require
the engagement of FP-PFC during performance of these types of behaviors. Interestingly, another domain that may require the management of subgoals is intentional retrieval of information from episodic memory. For example, episodic retrieval involves carrying out the subgoal task of searching LTM based upon a retrieval cue while actively maintaining the overall task goal (the episodic context to be recovered), and then comparing the outputs from LTM with that task goal to determine whether the information actually satisfies the goal. This conceptualization of episodic retrieval in terms of monitoring subgoal processes in WM has important implications for studies of FP-PFC function (Christoff & Gabrieli, 2000; Koechlin et al., 1999). Specifically, hypotheses regarding FP-PFC function might be better characterized in terms of general computational operations related to subgoal processing, rather than those specifically associated with the cognitive domain of episodic memory. An important test of this reconceptualization will be to directly examine whether the FP-PFC regions engaged under conditions of episodic retrieval are also engaged under situations that more clearly involve subgoal processing in WM, but which do not seem to involve episodic retrieval. With regard to this hypothesis, it is worth noting that the region of FP-PFC activated in our study, though falling within BA 10, is somewhat posterior to the region typically identified in episodic retrieval studies (e.g., Lepage et al., 2000). Thus, it will be important to conduct within-subjects comparisons to determine whether or not the areas are truly anatomically dissociable.

Despite our reconceptualization, the current emphasis in the neuroimaging literature on the role of FP-PFC in episodic retrieval and the generally reliable finding of FP-PFC activity under retrieval conditions (Cabeza & Nyberg, 2000; Lepage et al., 2000), suggest that it might provide a viable alternative interpretation of the current results. In particular, a retrieval interpretation suggests that subjects are using episodic retrieval to perform the Semantic AX-CPT more reliably than in the control conditions. One problem with this interpretation of the results is that the Semantic AX-CPT seems very different from most episodic memory tasks. Specifically, subjects need to store only one piece of information (the cue) and hold it over a short period of time (less than 10 seconds). Moreover, subjects were not instructed to use episodic retrieval to complete the task. Finally, the
question remains as to why subjects may have adopted this strategy more in the Semantic AX-CPT condition than in the Word AX-CPT condition, given that they are both similar in task demands. It is possible that subjects may have spontaneously adopted a strategy of rapidly storing each cue in LTM and then retrieving it following completion of the subgoal task. Such a retrieval strategy may have been adopted preferentially in the Semantic AX-CPT because of the high load imposed by the addition of the subgoal task. Specifically, the subgoal task may have made it difficult for subjects to have used WM to maintain cue information. Although this is a plausible hypothesis, it is also one that seems difficult to falsify. Independent of the presence of FP-PFC activity, it is not clear how one could ascertain whether a task involves the use of covert episodic retrieval strategies on the part of subjects.

In addition to the retrieval hypothesis, there are also other possible alternative interpretations of the current results. One such interpretation is that the selectively increased activity in the Semantic AX-CPT condition reflects the increased task difficulty of this condition, rather than more specific computations associated with subgoal processing during WM. This interpretation is unlikely to be correct in that the behavioral data indicated that the Semantic AX-CPT was not significantly more difficult than the control tasks. On the contrary, we observed significantly slower RTs (and equal accuracy) during performance of the Classification task than during the Semantic AX-CPT. Thus, if anything, the Classification task appeared to be more difficult than the Semantic AX-CPT. One might question this result (i.e., slower RTs in Classification vs. Semantic AX-CPT) as anomalous, but in fact, it is entirely consistent with the AX-CPT experimental design. Specifically, the manipulation of trial type frequencies that occurs in the Semantic AX-CPT (e.g., 70% target trials), leads to the ability to partially predict the semantic category of the probe word based on the category of the cue. For example, following an abstract cue, subjects can predict that the probe word will likely be concrete (given that this will occur 87.5 percent of the time). This increased predictability can serve to prime the appropriate response prior to probe onset, thus leading to a significant facilitation in RT. In the Classification condition, no equivalent facilitation occurred because there was no predictive relationship between the first and second items in a pair.
Another possible interpretation of the current results is that the Semantic AX-CPT condition may represent a dual-task situation, whereas the Classification condition and Word AX-CPT involve only single-task processing. Specifically, the Semantic AX-CPT requires the processes associated with both the Word AX-CPT and Classification conditions to be completed concurrently. Under the dual-task hypothesis, it is this requirement to complete two concurrent tasks that elicits activity in FP-PFC during the Semantic AX-CPT. Although it is true that the Semantic AX-CPT does contain a dual-task component, it does not seem likely that this component, per se, is the cause of FP-PFC activity. Previous neuroimaging studies investigating processes associated with dual-task performance have not identified FP-PFC as a brain region that is critically involved in these situations (Bunge, Klingberg, Jacobsen, & Gabrieli, 2000; D'Esposito et al., 1995; Klingberg, 1998). In contrast, DL-PFC regions are most likely to be engaged under standard dual-task conditions. More importantly, Koechlin et al (1999) directly compared dual-task with subgoal processing conditions and found significantly greater FP-PFC activity in the latter condition. Thus, it appears that subgoal processing in WM appears to be an important special case of a dual-task condition that preferentially engages functions subserved by FP-PFC regions. Nevertheless, it would be important to more completely test this hypothesis in future work.

Thus, to summarize, the results of this study are consistent with the hypothesis that FP-PFC subserves cognitive functions related to the coordination, monitoring, and integration of subgoal processes within WM. Using a simple and highly decomposable experimental paradigm, we observed that neither the subgoal task itself nor the WM demand were sufficient to engage FP-PFC, but when the subgoal task was required in conjunction with WM, FP-PFC was reliably activated. However, manipulation of the duration of WM maintenance had no effect on FP-PFC activity, suggesting that this region was not specifically subserving maintenance functions within the task. In contrast, DL-PFC regions were affected by manipulations of active maintenance requirements, but showed no interaction with the presence of a subgoal task. Finally, we observed that VL-PFC regions were sensitive to the subgoal task of semantic classification, but were not further modulated by the addition of WM demands. Taken together, these findings represent a
triple dissociation of function within ventrolateral, dorsolateral and frontopolar PFC regions. We suggest that the hypothesized function of FP-PFC in subgoal processing during WM represents an important fundamental cognitive computation, that may be present across a number of domains, including episodic memory. Such a reconceptualization of FP-PFC function may help to drive further research within cognitive neuroscience regarding the central mechanisms underlying higher cognition.
Table 1

<table>
<thead>
<tr>
<th></th>
<th>Classification</th>
<th>Word AX-CPT</th>
<th>Semantic AX-CPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent Errors</td>
<td>.090 (.025)</td>
<td>.018 (.016)</td>
<td>.124 (.053)</td>
</tr>
<tr>
<td>Reaction Time (msec)</td>
<td>827.0 (39.2)</td>
<td>527.3 (34.4)</td>
<td>658.7 (46.8)</td>
</tr>
</tbody>
</table>

Data are expressed as mean values across subjects with 95% confidence intervals in parentheses.
<table>
<thead>
<tr>
<th>Brain Region</th>
<th>Brodmann Area</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Size (mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Semantic Processing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left Inferior Frontal Cortex</td>
<td>45</td>
<td>-46</td>
<td>26</td>
<td>14</td>
<td>1188</td>
</tr>
<tr>
<td>Left Inferior Frontal Cortex</td>
<td>47</td>
<td>-42</td>
<td>19</td>
<td>-8</td>
<td>513</td>
</tr>
<tr>
<td>Right Inferior Frontal Cortex</td>
<td>45</td>
<td>40</td>
<td>28</td>
<td>17</td>
<td>270</td>
</tr>
<tr>
<td>Right Frontal Operculum</td>
<td>47/Insula</td>
<td>27</td>
<td>20</td>
<td>-1</td>
<td>351</td>
</tr>
<tr>
<td><strong>Active Maintenance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left Dorsolateral PFC</td>
<td>46/9</td>
<td>-43</td>
<td>19</td>
<td>29</td>
<td>2673</td>
</tr>
<tr>
<td>Left Supplementary Motor Area</td>
<td>6</td>
<td>-22</td>
<td>6</td>
<td>52</td>
<td>540</td>
</tr>
<tr>
<td>Right Premotor / Supplementary</td>
<td>6</td>
<td>29</td>
<td>3</td>
<td>42</td>
<td>8127</td>
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<tr>
<td>Motor Area</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Right Frontal Operculum / Insula</td>
<td>Insula</td>
<td>33</td>
<td>11</td>
<td>8</td>
<td>270</td>
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<tr>
<td><strong>Subgoal Processing</strong></td>
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<td>-2</td>
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<tr>
<td>Right Dorsolateral PFC</td>
<td>46/9</td>
<td>44</td>
<td>28</td>
<td>28</td>
<td>1026</td>
</tr>
</tbody>
</table>

Regions are listed according to location of activation centroid. Coordinates are determined from the Talairach & Tournoux (1988) atlas.
FIGURE CAPTIONS

Figure 1. Left inferior frontal cortex activation during semantic classification. A. Activation superimposed on an axial anatomic image. Images are in the Talairach and Tournoux (1988) atlas space at various z-coordinate locations, with activation overlaid on the corresponding anatomy image. Left of the image refers to the left side of the brain. B. Plots showing effects of task and delay. Error bars represent 95% confidence interval of the mean.

Figure 2. Left dorsolateral PFC activation associated with active maintenance. A. Activation superimposed on an axial anatomic image. B. Plots showing effects of task and delay

Figure 3. Right frontopolar PFC activation associated with subgoal processing during WM. A. Activation superimposed on an axial anatomic image. B. Plots showing effects of task and delay.
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Figure 1

A

+9 mm

Task Effect

Delay Effect

Classification | Word AX-CPT | Semantic AX-CPT

% Signal (Task - Fixation)

% Signal (Long - Short Delay)
Figure 2

A

B

Task Effect

Delay Effect

% Signal (Task - Fixation)

Classification

Word AX-CPT

Semantic AX-CPT

% Signal (Long - Short Delay)

Classification

Word AX-CPT

Semantic AX-CPT

+30 mm
**Figure 3**

A

![Brain image with a marker at -3 mm](image)

B

**Task Effect**

![Bar chart showing % Signal (Task - Fixation) for Classification, Word AX-CPT, and Semantic AX-CPT](image)

**Delay Effect**

![Bar chart showing % Signal (Task - Fixation) for Classification, Word AX-CPT, and Semantic AX-CPT](image)