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A Direct Comparison of Anterior Prefrontal Cortex Involvement in Episodic Retrieval and Integration

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Retrieval of information from episodic memory reliably engages regions within the anterior prefrontal cortex (aPFC). This observation has led researchers to suggest that these regions may subserve processes intimately tied to episodic retrieval. However, the aPFC is also recruited by other complex tasks not requiring episodic retrieval. One hypothesis concerning these results is that episodic retrieval recruits a general cognitive process that is subserved by the aPFC. The current study tested a specific version of this hypothesis — namely, that the integration of internally represented information is this process. Event-related fMRI was employed in a 2 (memory task: encoding versus retrieval) × 2 (level of integration: low versus high) factorial within-subjects design. A functional dissociation was observed, with one aPFC subregion uniquely sensitive to level of integration and another jointly sensitive to level of integration and memory task. Analysis of event-related activation latencies indicated that level of integration and memory task effects occurred with significantly different timing. The results provide the first direct evidence regarding the functional specialization within lateral aPFC and the nature of its recruitment during complex cognitive tasks. Moreover, the study highlights the benefits of activation latency analysis for understanding functional contributions and dissociations between closely linked brain regions.

Keywords: episodic retrieval, fronto-polar cortex, integration, prefrontal cortex, subgoal

Introduction

The prefrontal cortex (PFC) has long been considered critical for the control of behavior (Goldman-Rakic, 1987; Fuster, 1989). Recently, technological advances have allowed researchers to investigate the functional properties of specific PFC subdivisions via the use of neuroimaging techniques. Consequently, much attention has been focused on examining the relationship between these particular subdivisions of the PFC and specific cognitive processes. In particular, the functional properties of the anterior PFC (aPFC) have generated a great deal of recent interest.

The aPFC, loosely defined as lateral Brodmann's area (BA) 10, was first targeted for investigation due to its involvement in episodic memory (Tulving *et al.*, 1994). Subsequent studies have confirmed and elaborated on the role of the aPFC in retrieval processes, and regions of the aPFC have been hypothesized to underlie retrieval-specific operations and phenomena, such as retrieval attempt (Schacter *et al.*, 1996), retrieval success (McDermott *et al.*, 2000), retrieval mode (Nyberg *et al.*, 1995; Duzel *et al.*, 1999; Lepage *et al.*, 2000) and post-retrieval monitoring (Rugg *et al.*, 1996). More recently, several studies have identified regions of the aPFC in tasks not requiring episodic retrieval (MacLeod *et al.*, 1998; Koechlin *et al.*, 1999; Burgess *et al.*, 2001; Braver *et al.*, 2003). These findings have led to the generation of an alternative set of hypotheses regarding the functional role of the aPFC in cognition, such as the integration of diverse information content (Prabhakaran *et al.*, 1997, 2000; Christoff and Gabrieli, 2000; Christoff *et al.*, 2003) or the management of multiple task-relevant goals (Koechlin *et al.*, 1999; Braver and Bongiolatti, 2002; Braver *et al.*, 2003).

One hypothesis concerning the apparent discrepancy in previous results is that there are multiple subdivisions of the aPFC, some of which are recruited selectively during episodic retrieval and some of which are recruited by a more general cognitive process. To investigate this possibility, the current study used an experimental design in which two cognitive functions previously associated with aPFC recruitment (episodic retrieval and level of integration) were manipulated orthogonally. The factorial manipulation allowed for inferences regarding whether the identified regions were performing the same cognitive process in both conditions. If different regions of the aPFC were responsive to the two manipulations, it would suggest that each manipulation taps a different process, and further, that functionally distinct regions of the aPFC subserve these processes. However, if the same region of the aPFC were responsive to the two manipulations, then the pattern of recruitment within this region provides insight into the underlying cognitive processes. According to additive-factors logic, the presence of an interactive effect suggests that the two factors recruit the same underlying process at the same time (Sternberg, 1969). We predicted that (i) regions of the aPFC would be recruited in retrieval relative to encoding; (ii) regions of the aPFC would be recruited in high relative to low integration demand; (iii) regions of the aPFC would be sensitive to both effects; and (iv) these regions would be sensitive to both factors in an interactive fashion.

Materials and Methods

Participants

Twenty-one right-handed participants with no evidence of neurological compromise participated in this study. Participants were nine males and 12 females, with a mean age of 22.5 years (age range 18–28 years). Participants provided 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

While being scanned, participants performed multiple blocks of a semantic encoding task (deciding whether words referred to abstract or concrete concepts) and an episodic retrieval task (an old/new recognition memory test) under both low and high integration conditions. In all conditions, two words were presented simultaneously

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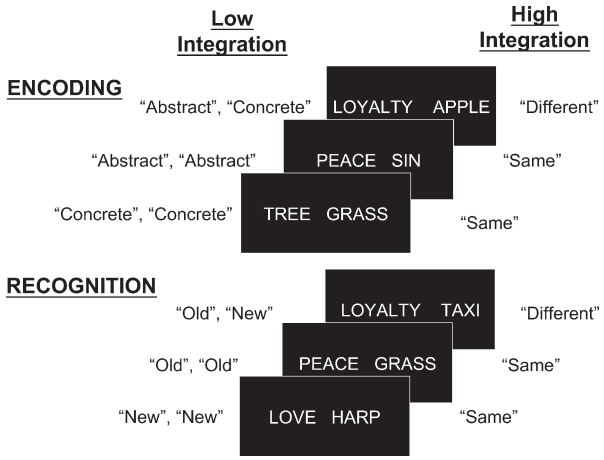

Figure 1. Task design. Three possible stimuli presented during an encoding run (top row) or during an episodic retrieval run (bottom row). The left column corresponds to the correct responses during a low integration run, whereas the right column corresponds to the correct responses during a high integration run.

on a computer screen. In the low integration condition, participants evaluated and responded to each word separately, resulting in two responses per trial. In the high integration condition, participants evaluated each word separately (as in the low integration condition) but also had to perform an additional processing step: they were asked to compare the results of the two separate judgements and make a single response based on whether the judgements were the same (e.g. abstract/abstract, new/new) or different (e.g. abstract/concrete, old/new). It is important to note that both the semantic (abstract/concrete) and episodic retrieval (old/new) judgements could not be based on perceptual properties of the stimuli; therefore, participants were required to use internal representations as a basis for the integration judgement. This internal representation is important, because the recruitment of the aPFC appears to be sensitive to the processing of internally represented information but not to the processing of externally presented information (Christoff and Gabrieli, 2000; Christoff *et al.*, 2003).

There were four conditions (low integration encoding, high integration encoding, low integration retrieval and high integration retrieval), yielding a 2 × 2 factorial design (see Fig. 1). The words studied during each encoding block were then tested during an immediately subsequent retrieval block. This design led to a fixed ABAB order of encoding, retrieval, encoding, retrieval, etc. However, within this fixed ordering of encoding and retrieval, the order of low and high integration demand conditions was counterbalanced both within and across subjects. The word lists were counter-balanced across the low and high integration demand conditions. For the recognition judgements, participants were informed that all words would be either novel (presented for the first time in the experiment) or studied in the immediately preceding encoding block.

The words were presented at the center of a visual display, side-by-side, in 24-point Times New Roman font. Words were taken from standardized lists of nouns. Participants responded to stimuli by pressing buttons on a hand-held response box with either the index or middle finger of the right hand. Within each trial the timing and sequence of events was as follows. Both words appeared on the screen simultaneously. In the low integration condition, participants were instructed first to evaluate the word on the left and make an appropriate response and then to evaluate the word on the right and make an appropriate response. In the high integration condition, participants were instructed first to evaluate the word on the left, then evaluate the word on the right, then internally compare the result of the two judgements and execute a single response based on this comparison. Participants were instructed to make a decision as quickly and accurately as possible. The trials were quasi-self-paced, such that the stimuli stayed on the screen until a response was made. The response for the current trial initiated the start of the next trial. The 'quasi' nature of the self-pacing resulted from the variable nature of the inter-trial interval (ITI), which varied between 500 and 5500 ms in steps of 2500 ms. The variability in ITI allowed for estimation of the event-related hemodynamic response (Friston *et al.*, 1995). The self-paced aspect of the design was useful, because it caused the trials to begin at a variable point relative to the start of a whole-brain acquisition (T_R), thus removing any possible aliasing effects occurring due to the relatively low temporal resolution of fMRI (Josephs *et al.*, 1997; Maccotta *et al.*, 2001; Miezin *et al.*, 2000). Each scanning run consisted of 40 trials.

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 × 1 × 1) structural images were acquired using a sagittal MP-RAGE 3D T1-weighted sequence (T_R = 9.7 ms, T_E = 4 ms, flip = 12°, T_I = 300 ms) (Mugler and Brookeman, 1990). Functional images were acquired using an asymmetric spin-echo echo-planar sequence (T_R = 2500 ms, T_E = 50 ms, flip = 90°). Each image consisted of 18 contiguous, 7 mm thick axial slices acquired parallel to the anterior–posterior commissure plane (3.75 × 3.75 mm in-plane), allowing complete brain coverage at a high signal-to-noise ratio (Conturo *et al.*, 1996).

Prior to the scanning session, participants were given instructions regarding all tasks to be performed, and then a block of practice trials to perform. During practice trials, the experimenter answered any further questions, validated that instructions were understood, and ensured that the tasks were performed appropriately and with a reasonably high level of accuracy.

During the scanning session, participants performed eight BOLD runs, with two BOLD runs occurring in each of the four conditions. For eight of the 21 participants, blocks of fixation (15 frames) were included at the beginning, middle and end of the scanning session. The first three images in each scanning run were used to allow the scanner to reach a steady state, and hence were discarded. Each run lasted ~6.5 min, with a 2 min delay occurred between runs, during which time participants rested.

Visual stimuli were presented using PsyScope software (Cohen *et al.*, 1993) running on an Apple PowerMac G4 (Cupertino, CA). Stimuli were projected to participants with an AmPro LCD projector (model 150) onto a screen positioned at the head end of the bore. Participants 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 participants' behavioral performance.

Data Analysis

Behavioral data were analyzed by conducting repeated-measures analyses of variance (ANOVAs) on accuracy and response time (RT). In order to control for differences between conditions in the number of responses required per trial (i.e. two in low integration, one in high integration), cumulative RT and accuracy measures were derived for the low integration conditions. Specifically, in these conditions, a trial was counted as correct only if both responses were correct. RT was measured for these trials by measuring the time between stimulus onset and the execution of the participant's second response. These measures (cumulative error rates and RT for each task) were then subjected to 2 (integration: low versus high) × 2 (memory task: encoding versus retrieval) repeated-measures ANOVAs.

Functional imaging data were pre-processed prior to statistical analysis according to the following procedures. All functional images were first corrected for movement using a rigid-body rotation and translation correction (Friston *et al.*, 1996; Snyder, 1996), and then registered to the participant's anatomical images (in order to correct for movement between the anatomical and functional scans). The data were then temporally realigned using cubic-spline interpolation, and temporally interpolated to a rate of one whole brain image/1250 ms (i.e. acquisition time = TR/2). 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),

resampled into 3 mm isotropic voxels, and spatially smoothed with a 9 mm full-width half-maximum Gaussian kernel. Participants' structural images were transformed into standardized atlas space (Talairach and Tournoux, 1988), using a 12-dimensional affine transformation (Woods *et al.*, 1992, 1998). The functional images were then registered to the reference brain using the alignment parameters derived for the structural scans. A general-linear model approach (Friston *et al.*, 1995) was used to estimate event-related responses for each voxel using in house software (Ollinger *et al.*, 2001). Event-related responses were estimated by modeling each time point within the hemodynamic response epoch with a delta function. The response epoch began at trial onset and covered a 22.5 s window (18 interpolated scan frames). Using delta functions as the basis functions in the model avoids assumptions about the shape of the blood oxygen level-deficient (BOLD) response (Josephs *et al.*, 1997). This was important in the current study, as estimated time courses in the aPFC tend to show features that do not fit well with the assumptions of standard hemodynamic models, including a late onset and a variable early dip in activity (Schacter *et al.*, 1997; Buckner *et al.*, 1998a). Each condition in the current experiment was modeled using a different set of delta functions, resulting in an estimated time course for each condition.

Regions of interest (ROIs) were identified by conducting a 2 (integration level: low versus high) × 2 (memory task: encoding versus retrieval) × 18 (frame) repeated-measures ANOVA on the estimated time courses. The current study investigated the extent to which the integration and memory task manipulations modulated the event-related responses in regions of BA 10, and therefore the primary effects of interest are reflected in the interactions between the manipulated variables (i.e. integration level and memory task) and frame. ROIs were identified by searching within an a priori, anatomically defined mask of BA 10. This mask was restricted further by including only voxels showing a positive event-related response in one of the conditions hypothesized to recruit the aPFC (any of the high integration or retrieval conditions), as defined by both a main effect of frame and a positive cross-correlation with a canonical hemodynamic response function (HRF). This additional step was used in order to ensure that the subsequently identified ROIs were responsive during the conditions of interest, and that therefore the effects could not be due solely to deactivations in the less demanding conditions. This set of responsive voxels was then searched for responses that demonstrated one of four patterns: (i) sensitivity to integration (i.e.. an integration level × frame interaction); (ii) sensitivity to memory task (i.e. a memory task × frame interaction); (iii) sensitivity to both demands in an interactive fashion (i.e. an integration level × memory task × frame interaction); or (iv) sensitivity to both demands in an additive fashion (i.e. both an integration level × frame and a memory task × frame interaction).

Due to the confined search space, a voxelwise alpha rate of 0.01 was used in order to identify voxels for each of these contrasts. ROIs were then constructed by identifying peaks of activity and assigning each sensitive voxel to a cluster associated with the nearest peak. Each voxel was retained only if it was part of a cluster of eight or more contiguous voxels. The cluster-size requirement provided further assurance that the false-positive rate was well controlled (Forman *et al.*, 1995; McAvoy *et al.*, 2001). All effects tested in the voxel-wise analyses were then validated as statistically significant ($P < 0.05$) at the level of the ROI. All ROIs described below met this criterion.

Investigation of the estimated time courses indicated that the manipulations of interest influenced the hemodynamic response during different periods in the hemodynamic epoch. In order to investigate this question empirically, a bootstrap procedure (Effron and Tibshirani, 1998) was used to estimate the variability in the time point of the peak difference between conditions. This procedure consisted of randomly sampling (with replacement) from the 21 individual difference time courses (e.g. the estimated time course for retrieval, averaged across both high and low integration minus the estimated time course for encoding, averaged across both high and low integration) in order to form a new bootstrapped sample of 21 difference time courses. These 21 difference time courses were averaged to form a mean difference time course, and the time point of the peak difference was then identified. For each significant effect in each ROI, this procedure was replicated for 10 000 different bootstrapped samples, and the 10 000 replicates were used to estimate the sampling distribution of the peak time point.

The sampling distributions were then used to test whether the different ROIs had different latency parameters. The first test was used to determine whether the time-to-peak estimate for each effect was statistically different than the time-to-peak estimate taken from a validation ROI identified in motor cortex. The time-to-peak estimate from the motor ROI was assumed to approximate the time-to-peak value expected from an ROI responding at the time of overt motor responding. Thus, if one assumes that there is a consistent coupling between neural activity and the resultant hemodynamic response across brain regions, then a time-to-peak estimate that is significantly earlier than the reference value should indicate an ROI whose event-related response occurred prior to the motor response. In contrast, a comparison ROI with a time-to-peak parameter significantly later than the reference value should indicate an ROI whose event-related response occurred after the motor response. The distribution of the differences in peak time was estimated by taking the difference between the time-to-peak values for each ROI and subtracting the time-to-peak value for the motor ROI for each bootstrapped sample. A *Z*-score was then formed from this bootstrapped distribution of differences in peak time by dividing the mean of the distribution by its standard deviation.

A final analysis tested for functional dissociations among the identified ROIs within the aPFC. This additional analysis was performed in order to determine whether the different regions identified by the ROI-identification procedure represented distinct subregions of the aPFC, or whether multiple identified ROIs reflect the same region of the aPFC, but were separated by the use of a hard threshold in the ROI-identification process. One way of investigating this question is via the use of an ANOVA statistical test that includes ROI as a factor in the analysis. An interaction between the factor coding for ROI and other factors of interest would suggest that the regions are functionally dissociable. The six ROIs identified were analyzed in a 6 (ROI) × 2 (integration) × 2 (memory task) × 18 (frame) repeated-measures ANOVA. This analysis was followed up with specific paired contrasts between ROIs in order to determine which ROIs were functionally dissociable from the others.

Validation of Analysis Procedure

Prior to any investigations of the primary questions of interest regarding the aPFC, a validation procedure was used to verify that the analysis procedure could sensitively estimate changes in the hemodynamic response. This validation procedure was seen as necessary because the experimental design involved estimation of event-related responses in the midst of a self-paced timing component, and such a design is relatively novel in the literature and involved a degree of temporal interpolation. An ROI within the left somato-motor cortex was expected to be sensitive to the changes in motor responding across the high and low integration conditions (one and two manual responses, respectively). Specifically, the low integration condition, which required two responses, was predicted to show a greater hemodynamic response than the high integration condition. Moreover, because the hemodynamics in the motor cortex are well defined, the estimated time courses were expected to show a canonical shape relative to fixation (i.e. similar to a gamma function). Thus, the integration contrast provided a validation test as to whether the responses in a somato-motor cortex could be accurately estimated and identified using our set of ROI identification procedures.

Results

Behavioral Data

After controlling for the number of responses in each condition, there was no difference in accuracy between the low and high integration conditions [$F(1,20) = 1.73$, $P > 0.2$]. However, participants were more accurate in the encoding tasks relative to the retrieval tasks [$F(1,20) = 122.8$, $P < 0.001$; see Table 1]. These effects were not interactive ($F < 1$). Participants were faster in the low integration conditions relative to the high

integration conditions [$F(1,20) = 4.8$, $P < 0.05$], and they were faster in the encoding conditions relative to the retrieval conditions [$F(1,20) = 6.1$, $P < 0.05$]. These two effects displayed a significant interaction [$F(1,20) = 9.2$, $P < 0.01$], such that the effect of the integration manipulation was significant in the encoding conditions [$t(20) = 4.8$, $P < 0.001$] but not in the retrieval condition [$t(20) = 0.2$, $P > 0.8$], and likewise, the effect of the memory task manipulation was significant in the low integration conditions [$t(20) = 5.0$, $P < 0.001$] but not in the high integration conditions [$t(20) = 0.03$, $P > 0.9$].

The low rate of accuracy in the retrieval conditions could prompt a concern that participants were randomly guessing on the task. This interpretation is unlikely in that chance performance corresponds to 25% rather than 50% accuracy, since correct responses were dependent upon the product of two correct retrieval judgements (averaging across both hits and correct rejections, a correct response for both judgements would be 0.5 × 0.5). The average retrieval accuracy of 56% was well above this level. Nevertheless, strictly speaking, it is possible that in the high integration retrieval condition chance accuracy could still represent 50% rather than 25% if participants treated the task as a single guess rather than as a true integration of two separate retrieval judgements. However, participants were explicitly told not to use such strategies in performing the task. Moreover, the performance profile in this condition suggests this did not occur, since accuracy and response times were equivalent to that seen in the low integration condition, when such strategies were not possible. Finally, even if one takes chance accuracy as 50% in the high integration condition, performance was still significantly above that level [$t(20) = 3.4$, $P < 0.005$].

One additional concern is that the data suggested a potential speed–accuracy trade-off as a function of integration demand, since the high integration demand conditions resulted in numerically greater accuracy but slower RTs relative to the low integration demand conditions. This question was investigated in two ways. First, we examined whether RT interacted with task accuracy by performing a median split on RT and examining whether speed interacted with the other two task factors via a 2 (integration) × 2 (memory task) × 2 (speed of responding: fast versus slow) repeated-measures ANOVA on error rates. If there were a speed–accuracy trade-off, then one would expect to see higher error rates on the fast trials in some conditions, and one would expect speed of responding to interact with one of the manipulations. This was not the case. There was a significant main effect of speed on the error rates, such that errors were associated with slower RTs in all conditions [$F(1,20) = 16.9$, $P < 0.001$]. There was a marginal speed × memory task interaction that suggested there was a stronger link between RTs and error rates in the encoding task [$F(1,20) = 3.4$, $P < 0.1$], but all conditions had greater error rates in the trials with the slowest RT. Speed had no other significant contributions to error rates (all other $P > 0.25$). The second test for a speed–accuracy trade-off was to correlate response time and error rates across participants. If a speed–accuracy trade-off were present across participants, then there should be significant negative correlation between response time and error rate (i.e. faster participants should make more errors). In all conditions, this correlation was non-significant (all $P > 0.4$). In order to ensure that there was not a speed–accuracy relationship as a function of the integration manipulation, the same between-subjects analysis was performed on the differences in accuracy and RT across the integration manipulation (high integration– low integration). This correlation was positive and not significant [$r(19) = 0.13$, $P > 0.5$]. Thus, there was no evidence for speed–accuracy trade-offs affecting performance in any condition or across participants.

Table 1
Behavioral performance

	Memory task			
	Encoding		Retrieval	
	Low integration	High integration	Low integration	High integration
Cumulative accuracy	0.80 (± 0.04)	0.82 (± 0.04)	0.55 (± 0.04)	0.57 (± 0.04)
Cumulative response time (ms)	2515 (± 227)	2993 (± 342)	2973 (± 296)	2997 (± 234)

Data refer to group means, with 95% confidence intervals in parentheses.

Imaging Data

Validation Analysis

The comparison between high and low integration conditions identified a large ROI within the somato-motor cortex (see Fig. 2). As predicted, an integration × frame interaction [$F(17,340) = 9.0$, $P < 0.001$] indicated that the low integration condition (in which two motor responses were required per trial) was associated with a greater hemodynamic response than the high integration condition (in which only one motor response occurred per trial). Visual inspection of the time courses revealed an event-related response pattern that closely approximated the canonical HRF frequently observed in the literature (Boynton *et al.*, 1996; Friston *et al.*, 1998). The results indicate that neither the self-paced nature of the experimental design nor the temporal interpolation done during pre-processing heavily influenced the shape of estimated event-related responses.

aPFC Regions

A total of six regions within the aPFC were identified as showing sensitivity to integration demand, memory task, or both factors. Two regions (B and C; see Table 2 and Figs 3 and 4), one in each hemisphere, were identified as showing sensitivity to the memory task [min $F(17,340) = 2.3$, $P < 0.005$], but not to integration [max $F(17,340) = 1.1$, $P > 0.3$]. These regions

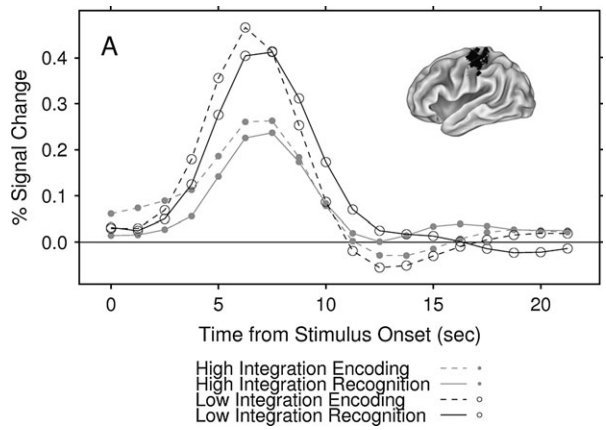

Figure 2. Hemodynamic responses in region A. The panel presents the averaged estimated time courses relative to fixation for each of the four conditions within region A.

correspond closely to the coordinates of regions previously identified as being sensitive to episodic retrieval (Buckner *et al.*, 1995; McDermott *et al.*, 1999a, 2000) and, consistent with that observation, they demonstrated greater responses during retrieval than encoding.

Three ROIs within the aPFC, two in the right hemisphere and one in the left, displayed sensitivity to integration [min $F(17,340) = 3.4$, $P < 0.001$; D, E and F; see Table 2 and Figs 3 and 5], but not to memory task (all $F < 1$). The center of mass of region F is close to that seen in other integration processing studies, and it overlapped with a more exploratory ROI reported by Braver and Bongiolatti (2002; previous centroid: 34, 45, 6). Although a salient aspect of the estimated event-related responses was an early dip in activity in the low integration conditions (Fig. 5), the predicted pattern of differences across conditions was maintained, such that high integration conditions showed a greater response relative to low integration conditions.

Table 2
Regions of interest

Region of interest	*x*	*y*	*z*	Volume (mm^3)
Validation region				
A — left primary motor/somatosensory	−38	−27	57	11799
Sensitive to memory task				
B — left BA 10	−34	51	18	351
C — right anterior BA 10	26	57	6	540
Sensitive to Integration				
D — left BA 10	−22	60	12	648
E — right anterior BA 10	38	54	12	1485
F — right posterior BA 10	46	45	3	378
Sensitive to both				
G — right anterior BA 10	32	57	9	378

Coordinates supplied are in Talairach atlas space (Talairach and Tournoux, 1988).

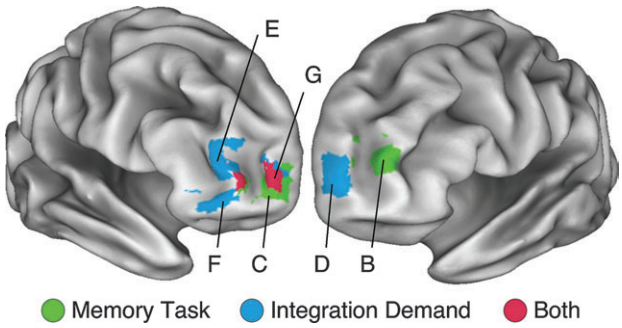

Figure 3. Regions of interest projected onto inflated representations of both hemispheres (Van Essen *et al.*, 1998, 2001). Regions B and C were sensitive to episodic retrieval, whereas regions D–F were sensitive to integration. Region G was sensitive to both demands.

One ROI within the right aPFC (region G) was identified as being sensitive to both integration demand [$F(17,340) = 2.4$, $P < 0.005$] and memory task [$F(17,340) = 2.0$, $P < 0.05$] in an additive fashion (three-way interaction: $F < 1$). This ROI demonstrated a greater response to the high integration condition relative to the low integration condition, and a greater response in the retrieval condition relative to the encoding condition (Table 2 and Fig. 6).

Contrary to the initial predictions, no ROIs were identified as showing interactive responses to the integration and memory task manipulations. Additionally, none of the ROIs identified as demonstrating sensitivity to either integration or memory task exhibited this interaction (all $F < 1$).

One potential concern is that the different hemodynamic responses across conditions are due to the different error rates and RTs in each of the conditions. The issue of error rates is particularly relevant for the ROIs sensitive to memory task, as the conditions showing increased responses also show substantially higher error rates. In order to investigate whether errors differentially contributed to the differences across conditions, new generalized linear models were computed for each individual in which time courses were estimated separately for both errors and correct trials for each condition. The averaged time courses for each identified ROI were then interrogated with a 2 (integration) × 2 (memory task) × 2 (error status) × 18 (frame) repeated-measures ANOVA. To the extent that errors contributed differentially to the identified ROIs, one should expect the error status variable to interact with the effects that the ROI demonstrated. However, this was not the case: error status did not moderate sensitivity to the memory task in any of the ROIs sensitive to memory task

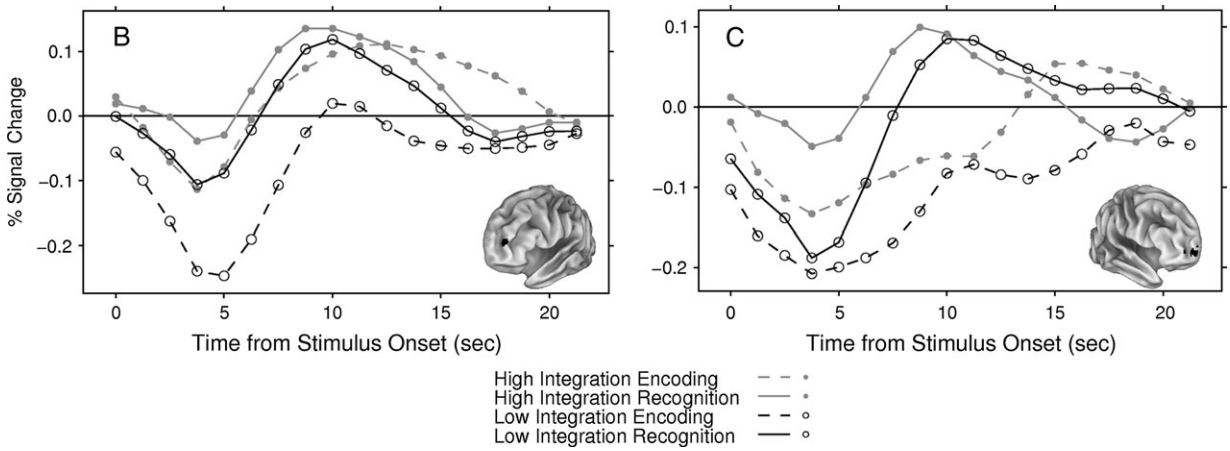

Figure 4. Hemodynamic responses in regions B and C. These ROIs were identified as sensitive to memory task. The left panel reflects the estimated time courses in the left hemisphere ROI sensitive to memory task (region B) and the right panel reflects the estimated time courses in the right hemisphere ROI (region C). The difference between solid and dashed lines reflects the effect of memory task. For region B, the peak of the difference between conditions occurs between 2.5 and 7.5 s after stimulus onset. For region C, the peak of the difference occurs between 7.5 and 10 s after stimulus offset (see also Fig. 7).

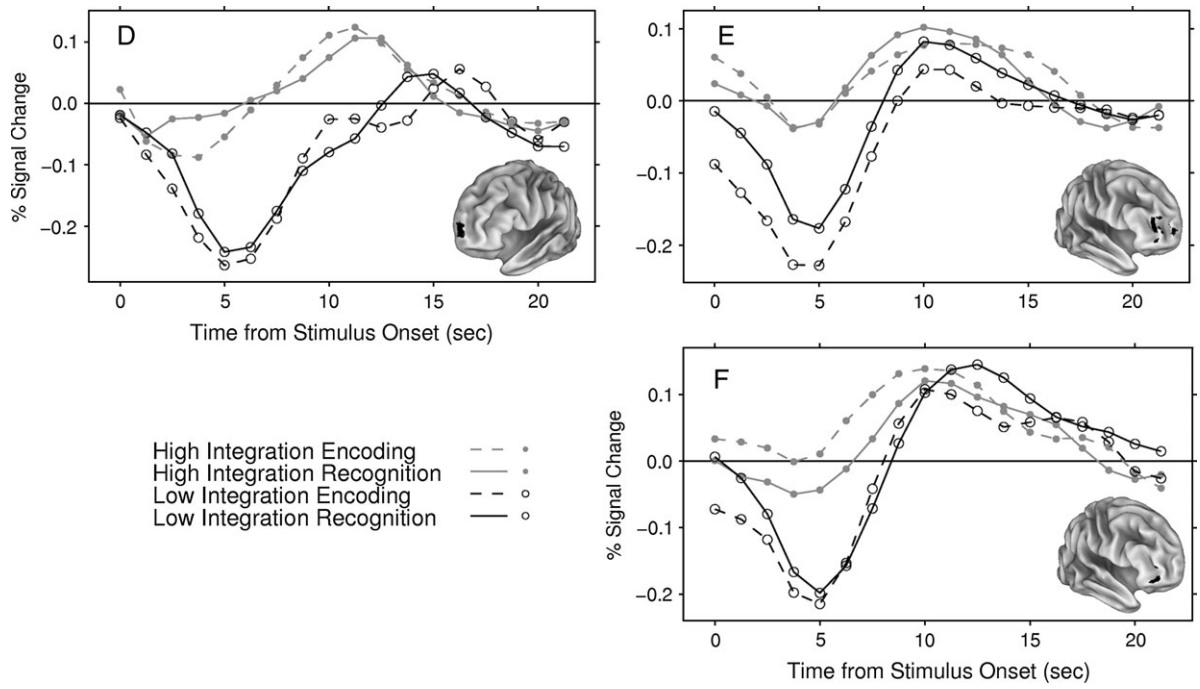

Figure 5. Hemodynamic responses in regions D, E and F. These ROIs were identified as sensitive to integration. The top left panel reflects the estimated time courses in the left hemisphere ROI sensitive to integration (region D) and the right panels reflect the estimated time courses in the right hemisphere ROIs (top: region E; bottom: region F). The difference between gray and black lines reflects the effect of integration. For region D, the peak of the difference between conditions occurs ~5 s after stimulus onset, but continues until ~13.75 s after stimulus onset. For regions E and F, the peak of the difference occurs between 3.75 and 5 s after stimulus onset and disappears between 8.75 and 10 s after stimulus onset (see also Fig. 7).

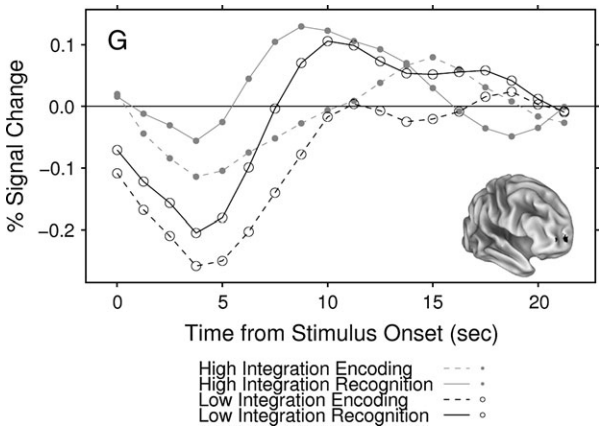

Figure 6. Hemodynamic responses in region G. This ROI was identified as sensitive to both memory task and integration. The difference between solid and dashed lines reflects the effect of memory task, and the difference between gray and black lines reflects the effect of integration. The peak of the memory effect is similar to that seen in region C (see Figs 4 and 7) and occurs between 7.5 and 10 s after stimulus onset; the peak of the integration effect occurs between 3.75 and 6.25 s after stimulus onset (see also Fig. 7).

[including the ROI sensitive to both: max $F(17,340) = 1.1$, $P > 0.3$], and error status did not moderate sensitivity to the integration manipulation in any of the ROIs sensitive to it (including the ROI sensitive to both: all $F < 1$). Therefore, errors did not appear to differentially contribute to the responses in the identified ROIs.

In order to investigate the contribution of RT to the different estimated time courses, specific contrasts were used to compare individual conditions that were matched in terms of RT. Behavioral measures indicated that three of the four conditions in the current experiment were very closely matched in terms of response time (all within 24 ms of each other; see Table 1). If the differences across conditions remain when interrogating only those conditions in which RTs are matched, then the differences between conditions cannot be attributable to differences in RT. One of the two ROIs sensitive to memory task met this criterion: region C demonstrated a significant memory task × frame interaction when only considering the conditions matched on response time [high integration encoding and high integration retrieval; $F(17,340) = 3.0$, $P < 0.001$]. However, region B did not meet this criterion, as it did not demonstrate a significant memory task × frame interaction when considering the conditions matched on RT ($P > 0.15$). All ROIs sensitive to the integration manipulation demonstrated sensitivity to the manipulation when comparing only the conditions matched in RT [the low and high integration retrieval conditions; min $F(17,340) = 1.7$, $P < 0.05$]. Finally, the ROI sensitive to both integration and memory task met both criteria, as it demonstrated a significant integration × frame interaction when analyzing the low and high integration retrieval conditions [$F(17,340) = 1.7$, $P < 0.05$] and a significant memory task × frame interaction when analyzing the high integration encoding and retrieval conditions [$F(17,340) = 2.3$, $P < 0.005$]. Therefore, differences in four of the five identified ROIs cannot be attributable to differences in response time across conditions.

Latency Analyses

The finding that effects of integration and retrieval were additive, rather than interactive, suggests that maybe the two effects occurred at distinct latencies during task processing. This is consistent with visual inspection, as the retrieval effect

appeared to be later than the integration effect in the ROI sensitive to both effects (region G). We quantified these observations by first determining the peak latency parameter for each aPFC ROI and then comparing that to the latency of the somato-motor ROI, which could be taken as a rough index of motor execution latency (see Fig. 7). Within the ROIs sensitive to memory task, the right hemisphere region (region C) had a latency parameter that was statistically greater than the latency of the somato-motor ROI (difference in time-to-peak = 2.5 s, $Z = 2.5$), consistent with previous data suggesting that regions of the aPFC tend to have a particularly late onset during retrieval (Schacter *et al.*, 1997; Buckner *et al.*, 1998a). The latency parameter for the left hemisphere region (region B) did not differ from that of the somato-motor ROI (difference in time-to-peak = 0.0 s, $Z = 0.0$).

None of the ROIs sensitive to integration demonstrated peak latency parameters that were different from that in the validation ROI cortex (max $Z = -1.35$). However, the direction of the latency effect was opposite to that of the ROIs sensitive to memory task, suggesting that, if anything, the effects of integration were occurring prior to the effects associated with memory task.

To directly investigate this question, the peak latency of the integration effect in the ROI sensitive to both effects (region G) was directly contrasted with the peak latency of the memory task effect in the same ROI. The time point of the peak of the retrieval effect was found to occur significantly later than the time point of the of integration effect (mean difference: 3.75 s, $Z = 2.0$).

Functional Dissociations

The full ANOVA (with all 6 ROIs included) indicated that there was a significant ROI × integration × frame interaction [$F(85,1700) = 2.1$, $P < 0.001$] and a significant ROI × memory task × frame interaction [$F(85,1700) = 2.1$, $P < 0.001$], suggesting that some ROIs could be dissociated from one another.

The sources of dissociations based on retrieval demand were twofold. First, the ROIs demonstrating late responses to the retrieval task (regions C and G) were dissociated from the other ROIs [region C dissociated from all ROIs but region G: min $F(17,340) = 2.1$, $P < 0.01$; region G dissociated from all ROIs but regions B and C: min $F(17,340) = 2.2$, $P < 0.005$]. Second, the response in region F (the posterior aPFC ROI sensitive to integration demand) was dissociable from all ROIs other than region D [min $F(17,340) = 1.9$, $P < 0.05$]. This effect was driven by the fact that region F was the only ROI to demonstrate numerically greater responses in the encoding conditions relative to the retrieval conditions for the time period between 2.5 and 8.75 s after stimulus onset: all other ROIs demonstrated at least a numerical increase in retrieval trials relative to encoding trials over this same period.

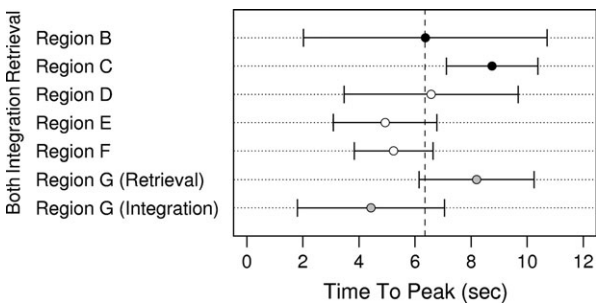

Figure 7. Latencies (time-to-peak) for significant effects. The vertical dashed line corresponds to the time-to-peak for the integration effect in region A (the motor validation ROI). Black dots and confidence intervals reflect the latencies of the memory effects found in the ROIs sensitive to memory task (B and C). Open circles and confidence intervals reflect the latencies of the integration effects found in the ROIs sensitive to integration (D, E and F). Gray circles and confidence intervals correspond to the estimates found in region G (the region sensitive to both manipulations). 95% confidence intervals were determined through the bootstrap procedure.

The primary dissociations related to integration demand were from the left hemisphere ROIs. Region B, the left hemisphere ROI sensitive to the memory task, was dissociated from all of the ROIs sensitive to integration [min $F(17,340) = 2.4$, $P < 0.005$], and region D, the left hemisphere ROI sensitive to integration, was dissociable from all other aPFC ROIs [min $F(17, 340) = 1.7$, $P < 0.05$]. Both left hemisphere ROIs demonstrated increased duration of their responses to integration relative to the other ROIs. Region G (sensitive to both manipulations) showed a differential sensitivity to integration relative to the ROIs sensitive to memory task [region B: $F(17,340) = 1.6$, $P < 0.055$; region C: $F(17,340) = 1.9$, $P < 0.05$].

To summarize the functional dissociations, the left hemisphere ROIs were dissociable from the other ROIs on the basis of their longer lasting response to the integration manipulation, and the two ROIs demonstrating a late response to the memory task were dissociated from other ROIs on the basis of the latency of this response. Additionally, the more posterior ROI sensitive to integration demand was dissociated from other ROIs based on the fact that it showed increased responses in the encoding conditions relative to the retrieval conditions, whereas all other ROIs displayed the opposite pattern.

One potential concern regarding time courses in region G is that its sensitivity to both manipulations reflects an averaged response of the two ROIs that it is adjacent to, and therefore simply reflects the smoothing that was performed in the pre-processing stages. Consistent with that argument, the memory task response in region G was not dissociable from the memory task response in region C [$F(17,340) = 1.1$, $P > 0.3$] and the integration response in region G was not dissociable from the integration response in region E ($F < 1$). In order to address whether the smoothing process contributed to the presence of the jointly sensitive ROI, an unsmoothed analysis was performed at the ROI level. The results from the initial, smoothed analysis were confirmed; importantly, in the unsmoothed analysis, the jointly sensitive ROI still displayed similar effects of both retrieval and integration (both $P < 0.01$). As such, it is difficult to argue that these results are due to smoothing performed in our pre-processing stages.

Discussion

The current study advances understanding of the cognitive processes subserved by regions of the aPFC by directly comparing the effects of integration and episodic retrieval within the same participants. The results replicate those of the previous studies by identifying functional regions within the aPFC that are sensitive to either integration (Koechlin *et al.*, 1999; Prabhakaran *et al.*, 2000, 2001; Christoff *et al.*, 2001, 2003; Braver and Bongiolatti, 2002) or episodic retrieval (Buckner *et al.*, 1995, 1998a,b; Schacter *et al.*, 1997; Nolde *et al.*, 1998; Wagner *et al.*, 1998; McDermott *et al.*, 1999a,b, 2000). More importantly, the results of this study offer several extensions of this previous work.

aPFC Involvement in Episodic Retrieval and Integration

Anatomically distinct regions within the aPFC were differentially sensitive to the different manipulations. These ROIs are consistent with those regions found in the previous literature, both with respect to the pattern of event-related responses and the anatomical localization of the regions. Specifically, the memory task response of a posterior region of the aPFC sensitive to integration (region F) was functionally dissociable from all of the aPFC ROIs that were sensitive to retrieval. Whereas previous researchers have dissociated regions of the aPFC that are involved in integration from regions of left inferior prefrontal cortex that are involved in semantic retrieval (Bunge *et al.*, 2005), the current study is the first to dissociate integration-related activity in the aPFC from that related to episodic retrieval. Additionally, other researchers have identified functional dissociations between lateral and medial surfaces of the aPFC (Koechlin *et al.*, 2000), but the current study is the first to identify multiple functionally dissociable regions on the lateral surface of the aPFC.

The presence of a jointly sensitive ROI suggests that a subregion within the aPFC might be engaged by the cognitive computations required for both episodic retrieval and integration processing. It has been speculated previously that aPFC involvement in episodic retrieval may be driven by a demand to integrate multiple pieces of internally generated information (Christoff and Gabrieli, 2000; Nyberg *et al.*, 2003). Episodic retrieval likely has multiple component processes associated with it, and successful performance of retrieval tasks could depend on the ability to integrate the results of more ancillary processes with the results of the more central retrieval processes. Previous investigators have proposed similar processing steps and, in fact, a distinct cognitive system has been proposed to perform them: an episodic buffer (Baddeley, 2000). The current study is the first to demonstrate that, within the same participants, a single ROI of the aPFC is sensitive to both integration processing and episodic retrieval, and this provides initial direct evidence suggesting that such a hypothesis may be true.

Nevertheless, detailed inspection of the jointly sensitive ROI revealed that while it was sensitive to both effects, the responses to each effect occurred at different times within the hemodynamic epoch, such that the retrieval effect occurred much later than the integration effect. Although previous investigators have demonstrated additive effects within the aPFC (Badre and Wagner, 2004), to the authors' knowledge, this is the first study establish the presence of functional region exhibiting an additive relationship between two cognitive factors due to different latencies of response to each factor.

Latency of Hemodynamic Response with the aPFC

The different latencies of the hemodynamic responses seen in the current study are informative with regard to the general hemodynamic properties of the aPFC. Previous reports have frequently identified a delayed hemodynamic response in regions of the aPFC (Buckner *et al.*, 1998a; Schacter *et al.*, 1997). However, the interpretation of this delayed response has been difficult, as it is possible that anatomical considerations, such as the presence of large draining veins, could cause the latency of the hemodynamic response to shift relative to the underlying neural activity. If this de-coupling between the neural and hemodynamic responses were driving the latency of the BOLD response seen in this region, then the relative timing of the delayed hemodynamic response would not be interesting, as the underlying neural processing could potentially still be occurring early in the trial. The current study provides strong evidence that this type of purely physiological consideration cannot be solely responsible for the delayed responses, because both early and late latency hemodynamic responses were found within the same aPFC ROI. Because this aPFC ROI displayed an event-related response that could be shifted earlier in time as a result of a within-subjects experimental manipulation, it is clear that the late response in at least this particular region could not have been purely due to underlying physiological properties. Thus, this result indicates that within this aPFC region, the delayed hemodynamic response observed under retrieval conditions was likely reflecting a neural response that was also delayed in time. These data are consistent with ERP data suggesting that there are robust late differences between old and new items that begin 800 ms after trial onset in conditions in which RTs were between 800 and 1150 ms (Rugg and Allan, 2000; Rugg *et al.*, 2000), suggesting that the late hemodynamic responses do reflect late neural responses as well. Our ability to quantify the latency of responses relative to activity in a region related to motor processing suggested that the late response is near to, or more likely after, the time at which the behavioral response had been made. If such delayed hemodynamic activity actually reflects post-response neural activity, it must be seen as a strong constraint on theories regarding the functional contribution of this region to cognitive processes associated with episodic retrieval. Further investigations in conjunction with methods of higher temporal resolution (such as response-locked event-related potentials) will be necessary to more precisely and accurately test whether responses in the aPFC are actually occurring in a post-response manner.

One tentative hypothesis concerning late responses in the aPFC is that during episodic retrieval conditions this activity reflects inter-item processing that may serve as a prediction regarding upcoming events. Inter-item processing may be particularly relevant in blocks of episodic retrieval, because in such blocks, previous stimuli can be used as context to determine whether the current stimulus is old (i.e. both came from the same prior episode). However, the cognitive system has to wait for the information about the current stimulus to become stable (e.g. a judgement has to be made) before this information can be used to contextualize subsequent stimuli. As such, the response would have to be late. This late response is not seen in the high integration conditions relative to the low integration conditions, because this specific type of inter-item processing is not useful for the integration processing in the current study: previous stimuli do not provide any information about the current stimulus. However, integrating two judgements is a specific type of inter-item processing that is required within each trial. Because this type of processing does not span multiple trials, regions supporting inter-item processing must be recruited before a response is made in these conditions. Consequently, the integration processing conditions recruit this region of the aPFC earlier than do the retrieval conditions. Although *post hoc*, this is one potential explanation for why a single process involved in inter-item processing would be recruited at different stages of processing by different tasks.

Alternative Explanations

One potential concern about the current experiment is that the integration effects may be due to differences in working

memory load across the high and low integration conditions. In the low integration condition, participants can respond to the first stimulus of each word-pair, forget it and then move on to the next stimulus. In the high integration conditions, participants must evaluate the first stimulus, maintain it while performing the second judgement, and then integrate the two judgements. The authors believe that the maintenance of the first judgement, in and of itself, is not driving aPFC activity in the high integration condition, because previous experiments have found that manipulations of working memory maintenance do not influence aPFC responses (Braver and Bongiolatti, 2002; Christoff *et al.*, 2003). Although pure active maintenance is probably not driving the responses of the aPFC, it is possible that the differences in aPFC activity between the low and high integration conditions reflect differences in the demand for subgoal processing (or the management of multiple task-goals). In fact, the encoding conditions of the current experiment are a conceptual replication of a previous study designed to investigate the role of the aPFC in sub-goal processing (Braver and Bongiolatti, 2002). The current experiment does not address the issue of whether subgoal or integration processing better describes aPFC function; the 'integration' label used for the current study was merely a term of convenience, and was not intended to favor one of these two hypotheses over the other. Nevertheless, the relationship and potential overlap between subgoal and integration accounts of aPFC function remains an important question, and thus worthy of further study.

Further Questions

As well as addressing several empirical questions, the current study also raises many additional questions for future research. Although the general effects of both the retrieval and integration factors were highly consistent with our predictions, the shapes of the estimated event-related response time courses relative to fixation were surprising. Specifically, the low integration conditions showed significant event-related deactivation relative to fixation in several of the ROIs. One hypothesis that may account for this finding is that the aPFC may subserve processes that are active during passive viewing of fixation trials (Christoff *et al.*, 2004). This hypothesis is consistent with the idea that the aPFC is involved in the processing of internally generated information (Christoff and Gabrieli, 2000); fixation trials correspond to events in which the thought processes of participants are not constrained, and therefore participants are likely to spontaneously generate and process stimulus independent thoughts.

It is also possible that the aPFC is responsive in a more sustained fashion (Duzel *et al.*, 1999; Braver *et al.*, 2003; Velanova *et al.*, 2003) in addition to the transient (i.e. event-related) responses reported here. Because the current design was not designed to extract sustained responses, the transient responses that were observed could reflect deviations from undetected state related activity. Further work needs to be done to determine the nature of the temporal dynamics within this region.

Conclusions

The current experiment provides several novel contributions regarding the cognitive functions performed in the aPFC. An area within the lateral aPFC was found to be selectively responsive to integrating information. However, a functionally and anatomically distinct region was found to be jointly sensitive to both integration and memory task demands. This finding suggests that the commonly observed activity within the aPFC during episodic retrieval conditions may not actually reflect a retrieval-specific cognitive operation, but rather the engagement of a more general computation or function. Regions of the aPFC were found to be recruited with distinct latencies, depending on the task demands. These results indicate that the typically late hemodynamic responses found in the aPFC may not be an artifact of the physiological characteristics of this area, but may instead reflect meaningful differences in the timing of underlying neural processing.

Notes

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