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Functional Specializations in Lateral Prefrontal Cortex Associated with the Integration and Segregation of Information in Working Memory

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Control processes are thought to play an important role in working memory (WM), by enabling the coordination, transformation, and integration of stored information. Yet little is known about the neural mechanisms that subserve such control processes. This study examined whether integration operations within WM involve the activation of distinct neural mechanisms within lateral prefrontal cortex (PFC). Event-related functional magnetic resonance imaging was used to monitor brain activity while participants performed a mental arithmetic task. In the integration (IN) condition, a WM preload item had to be mentally inserted into the last step of the math problem. This contrasted with the segregation (SG) condition, which also required maintenance of the WM preload while performing mental arithmetic but had no integration requirement. Two additional control conditions involved either ignoring the preload (math only condition) or ignoring the math problem (recall only condition). Left anterior PFC (Brodmann's Area [BA] 46/10) was selectively engaged by integration demands, with activation increasing prior to, as well as during the integration period. A homologous right anterior PFC region showed selectively increased activity in the SG condition during the period in which the math problem and preload digit were reported. Left middorsolateral PFC regions (BA 9/46) showed increased, but equivalent, activity in both the SG and IN conditions relative to both control conditions. These results provide support for the selective role of lateral PFC in cognitive control over WM and suggest more specific hypotheses regarding dissociable PFC mechanisms involved during the integration and segregation of stored WM items.

Keywords: cognitive control, episodic buffer, frontopolar cortex, mental arithmetic, subgoal

Introduction

Humans, as well as other primates, can perform multiple, novel, context-dependent, and goal-oriented behaviors. A key hypothesis within cognitive psychology is that these behaviors depend crucially upon the ability to temporarily hold and manipulate task-relevant information. This capacity, named working memory (WM) (Baddeley 2000, 2003 for recent reviews), has been a major topic of research for over thirty years, but many of its aspects are still unexplored. A vast literature from primate neuroscience research has provided clear evidence that the prefrontal cortex (PFC), in concert with posterior cortical regions, is a critical brain region for the storage of information in WM (Goldman-Rakic 1987; Fuster 1997). However, in recent years, the focus of attention has shifted toward investigating the role of PFC in control processes that act upon WM content rather than simple WM storage per se. This shift in focus has been seen not only in the primate neurophysiological literature (Miller and Cohen 2001), but is also a strong trend within the human neuroimaging literature (D'Esposito and others 1998, 2000; Smith and Jonides 1999).

A challenge for the field has been to more clearly define exactly what are the control processes that operate upon stored WM contents. There have been a number of suggestions for defining taxonomies of control processes (Miyake and Shah 1999; Smith and Jonides 1999). These typically include operations that update WM content, inhibit irrelevant information from being stored, and monitor or transform stored information in accordance with current task goals. One process that has been studied recently, and which might be central to the execution of complex WM tasks, is that of integration. Integration within WM occurs when the result of a subtask becomes combined with an already ongoing main task. As an example, imagine being presented with a math problem sequentially. First you are shown "9+," and then the stimulus is removed. Next you are shown "(3 × 7)," and then this stimulus is removed, and you are asked to compute the final answer. Such a task requires integration within WM because you must mentally retain the first portion of information ("9+"), while at the same time computing the intermediate result from the second portion of information (3 × 7 = 21), so that you can subsequently insert the first portion back into the problem (9 + 21 = 30). We operationalize the core process of integration as the requirement to combine the results of subtask processing with information that is actively maintained prior to and during the subtask execution. Thus, integration is not just insertion of WM contents into another representation, but also requires that insertion follows and depends upon subtask processing. This distinction can be seen clearly by contrasting the first example with a second one, in which you are first shown "(4 + 5)" and then shown "×3" and asked to compute the final answer. Although this latter problem is similar to the former, it does not require integration (according to our operationalization) within WM. In fact, the first portion of the task can be solved (4 + 5 = 9) without waiting for the second stimulus, and therefore, the whole task can be solved directly upon presentation of the second portion of information. In sum, in the former example, there is integration because an ongoing subtask ("3 × 7") needs to be solved before it can be combined with concurrent active information ("9+"); in the latter example, there is no integration because there is no subtask that needs to be solved before we can combine the second stimulus (×3) with the maintained result of the first subtask (9, the result of 4 + 5).

In recent theoretical treatments of WM, Baddeley has suggested that integration is a critical but previously neglected component of many WM task situations, and one that is not easily handled by the classic WM model (Baddeley 2003). As a consequence, the WM model was updated to add an additional component termed the "episodic buffer" as a specialized module within which integration operations can be conducted on WM contents. Thus, an obvious question to ask is whether there is a brain region that is specialized for carrying out integration operations upon stored WM content. Interestingly, accumulating results from the neuroimaging literature suggest that the anterior-most region of the lateral PFC near the frontal pole (Brodmann's Area [BA] 10) might serve such a specialized role within WM.

There have been very few studies directly examining integration processes per se. However, in one study of this type, Prabhakaran and others (2000) observed that integrating verbal and spatial information within WM led to anterior PFC activity, as contrasted to when those 2 types of information had to be maintained in unintegrated form. A series of less directed studies have focused on the processes of "relational integration" within the context of analogy like and other problem-solving situations, when (possibly multiple) underlying stimulus dimensions have to be compared to determine the relationships between objects (Christoff and others 2001, 2003; Kroger and others 2002; Bunge and others 2004). A consistent finding from these studies is that anterior PFC activity increases as the number of relationships that must be simultaneously considered is increased. A somewhat different set of studies have examined the processes that are involved in goal–subgoal integration, that often occurs in complex tasks such as planning (Baker and others 1996). For example, Koechlin and others (1999) proposed the term "cognitive branching," to refer to the selective activation of anterior PFC in situations when a primary task must be completed after interruption by a subtask. Braver and Bongiolatti (2002) also observed anterior PFC activity in a similar but simpler delayed response WM paradigm, under conditions that required cue information to be maintained while a subtask was performed upon a probe item. Results consistent with anterior PFC engagement in response to integration demands have also been found in a number of additional studies (Christoff and others 2001; Bunge and others 2003, 2004; Badre and Wagner 2004), including those involving other cognitive domains such as episodic retrieval (Reynolds and others 2006), affect (Gray and others 2002), and prospective memory (Burgess and others 2001, 2003).

Thus, these combined studies all point to integration demands as being relevant for the activation of anterior PFC. However, important questions remain regarding the exact role of anterior PFC in integration processes. For example, most tasks requiring integration have an obvious dual-task component to them, whereby information from the primary task has to be actively maintained in WM while the subtask is being carried out. Yet it is also clear that the core process of integration can be conceptually distinguished from other general dual-task situations and processes. In particular, many dual-task situations require maintaining information related to a primary task while a secondary task is being completed, yet the 2 tasks might be completely unrelated, and thus require segregation rather than integration of the 2 streams of information. Is the anterior PFC sensitive to this subtle distinction between segregation and integration within dual-task situations? There has not been any direct study of this question to date. Likewise, it is not clear whether anterior PFC is engaged to prepare for the expected demands of integration (i.e., in a anticipatory and sustained fashion), or only transiently, at the point when integration actually must occur. Addressing this issue requires a focused analysis of anterior PFC activity dynamics that has rarely been employed in the studies of this type (Sakai and Passingham 2003).

The goal of the current study was to ask specific questions regarding the involvement of the anterior PFC in situations requiring integration within WM. In particular, we designed our experiment so that we could more precisely contrast the process of integration from the very similar dual-task situation in which information related to each task has to be maintained in WM, but these 2 sources of information remain segregated. This is an important goal, because both segregation and integration dual-task situations involve increased WM loads and divided attention requirements. Moreover, imaging studies of dual task and divided attention conditions reliably observe activation in lateral PFC, though more typically in dorsolateral rather than anterior PFC regions (D'Esposito and others 1995; Klingberg and Roland 1997; Bunge and others 2000; Iidaka and others 2000; Kensinger and others 2003). Nevertheless, it may be the case that anterior PFC is engaged not by integration requirements per se, but instead, by the other cognitive demands that typically accompany such task situations. Consequently, a secondary goal of the study was to determine what brain regions are equivalently activated by both segregation and integration dual-task situations in contrast to otherwise matched control conditions. A final goal of the study was to examine anterior PFC activity dynamics to determine whether activation of this region occurs in a sustained fashion and in advance of integration under conditions when integration can be expected, or rather if activation only occurs in a transient fashion prompted by explicit demands to integrate information held within WM.

To examine these issues, we employed a mental arithmetic paradigm because such paradigms have been frequently used to examine WM processes (Hitch 1978; Logie and others 1994; De Stefano and LeFevre 2004). Moreover, mental arithmetic tasks frequently involve demands for integration within WM, as in the first example discussed above. Indeed, within the cognitive literature, previous studies have suggested that mental arithmetic tasks involving integration processes have unique cognitive demands associated with them (Anderson and others 1996). For example, in a recent study (Oberauer and others 2001), the demands of integrating partial arithmetic results with previously stored information were found to increase task difficulty (in terms of response time slowing), over and above the pure effects of WM load. Thus, the previous literature suggests that mental arithmetic paradigms can provide a useful test bed for examining and isolating the effects of integration demands on WM processes.

Mental arithmetic tasks are also attractive from the standpoint of neuroimaging studies, in that some of the component processes are well understood. In a review of the neuroimaging literature of mental arithmetic, Dehaene and others (2003) suggested that the left angular gyrus in parietal cortex is critically associated with verbal processing of simple numerical information. Moreover, numerical computations and storage appear to involve distinct neural systems in parietal cortex but do not seem to primarily engage PFC. In contrast, lateral PFC is sometimes engaged in sequential tasks (i.e., those having similar structure to typical mental arithmetic paradigms) when WM loads are high (Braver and others 1997). Yet, the precise conditions that elicit PFC activity in mental arithmetic are still not well understood. In some studies, PFC activity during mental arithmetic appears to reflect retrieval or active rehearsal of mathematical rules or other relevant information (Gruber and others 2001; Anderson and others 2003), where in others, it appears to reflects increased active maintenance and/or attentional control requirements (Zago and others 2000). Thus, in the current study, we contrasted simple mental arithmetic (i.e., with a low WM load) against conditions that involved a higher load. WM load was increased through the imposition of a divided attention requirement, in that in some conditions, participants were required to store additional information in WM while completing mental arithmetic problems. These high load/divided attention conditions were further distinguished by comparing 2 similar conditions, one in which the additional load had to be kept segregated from the main mathematical calculations, and a second matched condition in which the same information had to be integrated into the ongoing calculations at a specific step of the problem. In this way, we could critically distinguish brain regions that were involved in meeting the demands of high WM loads and divided attention, from those specifically involved in integration demands. Conversely, we examined whether maintaining 2 separated and segregated streams of WM content places unique demands on processing relative to integration. In particular, in such situations, when 2 tasks have a nested structure, there may be specialized processes that enable the first task to be resumed following the completion of the second (i.e., the subtask).

The specific task structure was as follows. Each trial consisted of a 4-step math problem, with every step requiring an internally stored value to be updated by applying a mathematical operation (+, −, ×) to a visually presented digit. In addition to the basic mental arithmetic task, 2 further conditions required participants to maintain additional numerical information in WM while carrying out the mental arithmetic operations. The additional WM load consisted of a single digit presented for storage prior to the start of each trial. In the integration (IN) condition, the preload digit had to be incorporated into the last step of the math problem. In the segregation (SG) condition, the preload digit was unrelated to the math problem but had to be recalled following report of the problem answer. Thus, although both conditions required performance of a nested subtask (arithmetic calculations), and while performing a main task (maintenance of a digit preload), only the first condition required that the 2 tasks be integrated. The effects of these distinct dual-task requirements were examined by comparing them with 2 matched control conditions in which 1) the preload digit was presented but not stored (math only [MO]) and 2) the math problem was presented but not performed (recall only [RO]).

Our analysis procedure was aimed at isolating brain regions selectively involved with integration processes and distinguishing these regions from those engaged by 1) the more general task demands associated with the increased WM load and divided attention imposed by dual-task conditions; 2) simple mental arithmetic processing per se; and 3) the unique demands that might be imposed by dual-task situations involving segregation rather than integration of WM content. More specifically, we hypothesized that PFC regions selectively engaged by integration should show increased activity in the IN condition relative to all 3 additional conditions. This analysis was predicted to reveal activation within anterior PFC and thus would more strongly confirm hypotheses regarding the specialized role of this brain region in integration processes. In contrast, regions engaged purely by divided attention and WM load should show increased activity in both conditions involving preload storage but with no differences in activation between the 2 conditions. Based on previous literature regarding dual-task situations, we predicted that this analysis would reveal activity in posterior and middorsolateral PFC (D'Esposito and others 1995). Likewise, brain regions involved in mental arithmetic processing per se were hypothesized to show increased and equivalent activity in all 3 conditions involving arithmetical computation (i.e., all conditions except the RO control). Based on the findings of Dehaene and others (2003), we predicted that this analysis would reveal activation of the left angular gyrus but not lateral PFC. Finally, we hypothesized that the SG condition might also make unique demands on cognitive processing, particularly at the time of preload recall. During this phase of the trial, the SG condition is unique in requiring resumption of an interrupted primary task (preload storage and recall) following the completion of a secondary task (mental arithmetic). This primary task resumption requirement in the SG condition might lead to the engagement of a number of associated neural processes, such as those associated with retrieval/reactivation of the preload information, response selection and interference control (i.e., avoiding confusion between recall of the math answer and preload), and even some form of goal–subgoal coordination related to that engaged by integration demands. In particular, primary task resumption following subtask interruption is a form of "branching," as discussed by Koechlin and others (1999) and so might also be associated with anterior PFC activity.

A final goal of the study was to examine the temporal dynamics of brain activation during task trials. Event-related functional magnetic resonance imaging (fMRI) methods were utilized to enable temporal dissociation of brain activity occurring early in the trial (e.g., prior to integration) from activity occurring late in the trial (e.g., during the recall phase).

Materials and Methods

Participants

Forty-four right-handed participants took part in this study (26 female, mean age = 20.3 years, age range = 18–25 years). Of these, a subset of 20 participants (12 females) with no evidence of neurological compromise took part in functional imaging. All participants gave informed consent, according to guidelines set by the Washington University Studies Committee. Behavioral participants received course credit, and scanned participants were paid $25/h as compensation.

Behavioral Task

Participants performed digit processing tasks in 4 different blocked conditions (see Fig. 1). In 3 of the 4 conditions, the primary task involved solving a 4-step mental arithmetic problem, presented sequentially in a frame-by-frame manner, in which each step (after the first, described later) consisted of single digits and mathematical operators (hereafter referred to as MATH-1 through MATH-4). Thus, at each frame, participants were required to compute the mathematical operation on the presented digit and then maintain an internal running total. Participants indicated when they were finished with each step of the computation with a button-press response. Following the presentation of each problem, a prompt appeared which instructed the participant to give a verbal report of the final total (hereafter referred to as REC-MATH). In addition to the mental arithmetic problem, an extra digit, appearing in a special ink color (red), was presented as the first frame of the trial (hereafter referred to as the PRELOAD). In 3 of the 4 task conditions, participants were required to encode and maintain this digit throughout the course of the trial.

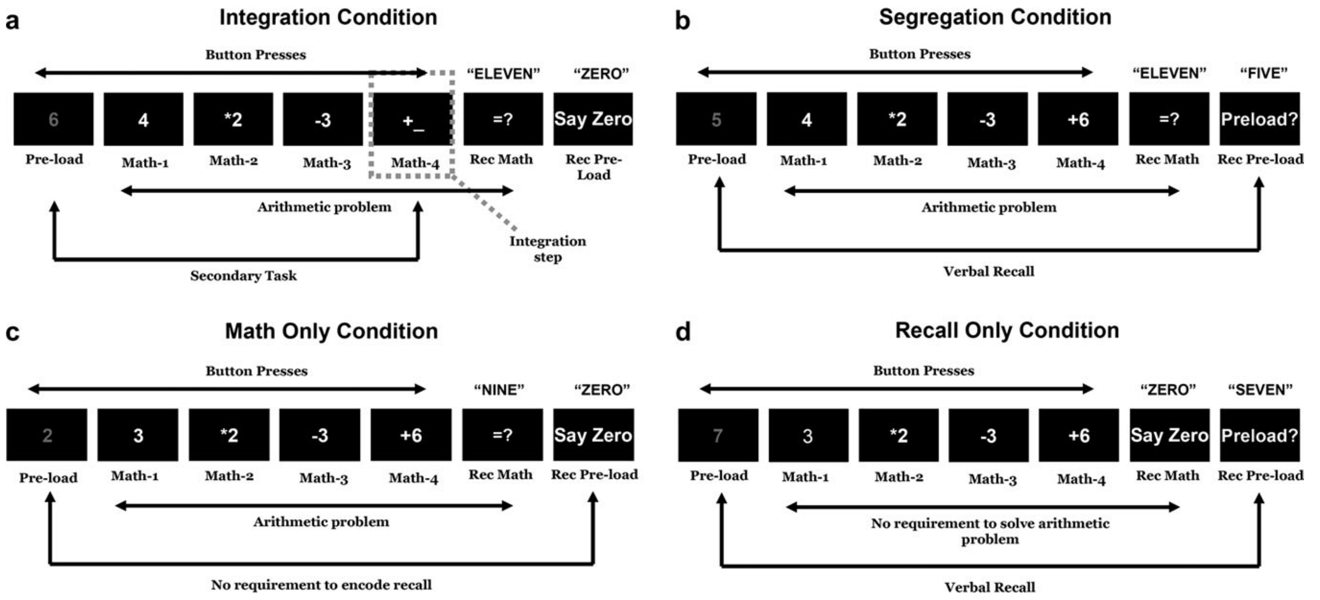

Figure 1. Task design. Participants performed digit processing tasks under 4 different block conditions. In 3 of the 4 conditions, the primary task involved solving a 4-step mental arithmetic problem, presented sequentially in a frame-by-frame manner, in which each step (after the first, described later) consisted of single digits and mathematical operators (MATH-1 to MATH-4). Participants indicated when they were finished with each step of the computation with a button-press response. Following the presentation of each problem, a prompt appeared which instructed the participant to give a verbal report of the final total (REC-MATH). In addition to the mental arithmetic problem, an extra digit was presented as the first frame of the trial (PRELOAD), presented in a different color from math problem digits. In the IN condition, the preload had to be incorporated into the math problem as part of the last arithmetic frame. There was no requirement to verbally report the preload digit, but participants always said "zero" when the last frame of the trial (REC-PRELOAD) appeared, following the report of the math problem answer (*a*). In the SG condition, the initial digit was completely unrelated to the math problem but had to be reported verbally on the REC-PRELOAD frame (*b*). In the MO condition, although participants were presented with the identical series of frames on each trial, there was no requirement to store the preload, only participants responded by saying "zero" when the REC-PRELOAD frame appeared (*c*). Finally, in the RO participants were only required to encode and store the preload digit but were not asked to perform the mental arithmetic problem (*d*).

In the critical IN condition, the PRELOAD had to be mentally inserted into the math problem as part of the last arithmetic frame. This was indicated to the participant by having the last frame present a mathematical operator along with an underline where the digit should be (see Fig. 1*a*). Thus, the IN condition required active maintenance of information in WM during ongoing processing of a subgoal task (mental arithmetic) but also critically required that the results of the subgoal task be integrated with the WM content in order to achieve the final result. The IN condition was contrasted with the very similar SG condition (see Fig. 1*b*), which also required that the PRELOAD to be encoded and maintained while performing the mental arithmetic problem. However, in the SG condition, there was no requirement to incorporate the PRELOAD into the math problem. Instead, the PRELOAD was verbally reported as the last step of the trial (hereafter referred to as REC-PRELOAD). For the IN condition, a verbal report of the preload was not required; participants merely said the fixed output word "ZERO" at this point (as indicated by the visual prompt "SAY ZERO"), to control for motor requirements. Thus, both the IN and SG conditions involved the "dual task" or "divided attention" demands of classic WM span tasks (e.g., reading span, Daneman and Carpenter 1980), in that information had to be continuously stored while completing an ongoing processing task. But only the IN condition required that the storage and processing be integrated within WM at a specific point in time. Thus, the IN condition isolates the critical components of integration that differentiate this computation from similar WM task situations. Conversely, the SG condition was also unique in that it required the resumption of a primary task (PRELOAD storage) after completion of an intervening task (mental arithmetic). This resumption effect was postulated to occur during the REC-MATH and REC-PRELOAD frames.

In addition to the IN and SG conditions, participants also performed 2 additional control conditions: MO and RO (respectively Fig. 1*c*,*d*). In both MO and RO conditions, participants were presented with the identical series of frames on each trial as the SG condition but only had to perform a single task. Specifically, there was no requirement to encode or store the PRELOAD in the MO condition, or to perform the mental arithmetic task in the RO condition. Task-dependent verbal report was only required for one of the recall frames (REC-MATH for MO and REC-PRELOAD for RO); on the other recall frame, the required response was the fixed output word "ZERO" (as in the IN condition), to again control for motor requirements. However, in both RO and MO conditions, consistent attention to task trials was ensured by still requiring button-press responses following the appearance of each digit stimulus. The order of condition presentation was counterbalanced across participants by randomly cycling through all possible order permutations.

Stimuli (both digits and prompts) in all conditions were presented centrally on a visual display, in 48-point Chicago font. Math problem digits appeared in white, whereas the preload appeared in red. Digits were selected for each frame from the set 1–9. The operators could be either +, –, or ×. Digits and operators were selected randomly for each problem and frame, subject to the constraint that the total could not go above 50 or below 0. Responses to the preload and each frame of the math problem were made by pressing a button on a hand-held response box with the index finger of the right hand. The responses to the prompts at the end of the trial were given verbally.

Each trial frame was presented for a maximum of 2000 msec or until the button-press response was made (for slow or absent responses, the task advanced to the next frame and reaction times [RTs] were not recorded). The frame stimulus-onset asynchrony (SOA) was 2500 msec, allowing for a minimum 500 msec inter-trial interval (ISI). In sum, the total trial duration was 17.5 s (2.5 s/frame × 7 frames/trial). During the preload and mental arithmetic frames, participants were instructed to complete their computation (encoding or arithmetic) as quickly and accurately as possible following target onset and indicate the completion of this process with a button press. A random variable interval of 0, 2500, 5000, or 7500 ms occurred between trials. We adopted this intertrial interval jittering to better estimate the event-related hemodynamic response on each trial, as described below (Friston and others 1995). The number of jittering events was increased for the last 7 subjects, for better estimation.

Prior to task performance (and outside of the scanner for scanned participants), instructions were provided for each condition. Participants were then given practice with each of the conditions, during which time the experimenter answered any questions, validated that instructions were understood, and ensured that the tasks were performed appropriately and with a reasonably high level of accuracy.

Functional Imaging Task

Images were acquired on a Siemens 1.5-T 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 magnetization-prepared rapid gradient echo 3-dimensional T_1-weighted sequence (time repetition [TR] = 9.7 mm, echo time [TE] = 4, flip = 12°, time to inversion [TI] = 300 ms) (Mugler and 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 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 and others 1996). One scanning run of 24 task trials was performed with each condition, for a total of 4 scanning runs per participant. Each run lasted approximately 8.5 min. There were 196 scans per run for the first 13 participants and 209 scans per run for the remaining participants (the change was due to the addition of extra intratrial interval jittering for the last participants to improve estimation; however, post hoc analysis suggested that the change was negligible). A 2-min delay occurred between runs, during which time participants rested. The first 4 images in each scanning run were used to allow the scanner to reach steady state and hence were discarded.

Visual stimuli were presented using PsyScope software (Cohen and others 1993) running on an Apple PowerMac G4. 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 performance data were analyzed for effects of task condition on computation time by measuring RTs that indicated the completion of computation during each frame of the mental arithmetic problem. The accuracy of both mental arithmetic and PRELOAD storage was assessed via off-line coding of verbal responses. However, technical difficulties prevented the coding of vocal response information for scanned subjects. Additionally, for 7 of the scanned participants, button-box failure caused loss of the computation time RTs during mental arithmetic. Thus, additional participants were recruited to perform the task outside of the scanner, to provide adequate information regarding performance in this task. Analysis of behavioral data was conducted via analyses of variance (ANOVAs) or t-tests on the accuracy and RT measures.

Functional imaging data were preprocessed prior to statistical analysis according to the following procedures. All functional images were first temporally aligned across the brain volume, corrected for movement using a rigid-body rotation and translation correction (Friston and others 1996; Snyder 1996), and then registered to the participant'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), resampled into 3-mm isotropic voxels, and spatially smoothed with a 9-mm full width at half maximum Gaussian kernel. Participants' structural images were transformed into standardized atlas space (Talairach and Tournoux 1988) using a 12-dimensional affine transformation (Woods and others 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 and others 1995) was used to estimate parameter values for the event-related responses. Each time point within the hemodynamic response epoch was estimated separately. The duration of this epoch was taken to be 37.5 sec (15 scanning frames). The event-related estimates for the time-course data were then submitted to a group analysis using voxelwise random-effects model ANOVAs. Event-related responses can be determined in this approach by using time (i.e., scan) as a factor of interest and examining significant effects of this factor (both main effects and interactions). The primary advantage of this approach is that it makes no a priori assumptions about the particular shape of the hemodynamic response (Buckner and Braver 1999). Given that the timing and shape of the hemodynamic response may vary across brain regions, incorrect assumptions regarding these parameters may lead to a significant loss of power in detecting event-related effects. Moreover, each trial in the study was assumed to be composed of multiple, sequentially related subevents. Thus, implementing a model-based analysis would necessitate making a number of possibly unwarranted assumptions about how the response to subevents summate together.

To identify brain regions showing condition-dependent event-related activation during the mental arithmetic task, we required that multiple different contrasts be satisfied, in order to ensure that the effects were selective. Each contrast was set a relatively low threshold ($P < 0.05$, uncorrected), in order to optimize the trade-off between sensitivity/power and false-positive protection (i.e., Type I vs. Type II error). Thus, for a brain region to be accepted as selective for a particular effect, all voxels within the region were required to be statistically significant in all tests for that effect (described below). The analysis was set up such that any voxel meeting criteria in all statistical tests would have alpha-protection equivalent to $P < 0.0001$ (although this value is likely to be an overestimate given nonsphericity in the error terms in the statistical contrasts). Moreover, a region was considered significant only if it contained a cluster of 8 or more contiguous voxels. The additional cluster-size requirement ensured an overall image-wise false-positive rate of $P < 0.05$ (Forman and others 1995; McAvoy and others 2001). Finally, to increase interpretability, only positive activations (relative to baseline) were considered in all of these analyses (for event-related analyses this was determined by requiring average activation to be greater than zero over a window including scans 3–8). In all analyses, the estimated activation during the intertrial interval was treated as the fixation baseline.

A set of analyses were conducted that detected regions associated with the various cognitive processes thought to be engaged during the task. These processes include those involved with basic operations associated with mental arithmetic (computation, storage), those involved with divided attention or WM load (i.e., storage in WM during ongoing subgoal processing), those involved specifically with the requirement to integrate information within WM, and those involved with the requirement to resume the task of preload recall following completion of the mental arithmetic problem. In each of these analyses, the period of mental arithmetic processing was taken to be scan frames 3–6, and the period of recall was taken to be scan frames 7–8. These assumptions accommodate the approximate 5 s lag between the timing of a neural event and the peak hemodynamic response.

Brain regions showing selective sensitivity to "integration" within WM were identified based on the following contrasts: 1) significant activation in the IN condition, relative to baseline, during the period of mental arithmetic processing (frames 3–6); 2) significantly increased activation in the IN condition during mental arithmetic processing (frames 3–6) compared with the initial period of the trial (frames 1–2); 3) significantly greater activation in the IN condition relative to each of the 3 other task conditions (SG, MO, RO) during the period of mental arithmetic processing (frames 3–6); and 4) no significant differences between task conditions during the initial period of the trial (frames 1–2).

Brain regions showing general sensitivity to "divided attention/WM load" demands were identified based on the following contrasts: 1) significant activation in both the IN and SG conditions relative to baseline, during the period of mental arithmetic processing (frames 3–6); 2) significantly greater activation in both the IN and SG conditions relative to each of the 2 single-task control conditions (MO, RO) during the period of mental arithmetic processing (frames 3–6); 3) significantly greater activation in both the IN and SG conditions (and no significant difference between the 2) during the period of mental arithmetic (frames 3–6) as compared with the initial period of the trial (frames 1–2); and 3) no significant difference between the task conditions at the initial period of the trial (frames 1–2).

Brain regions showing general sensitivity to “simple mental arithmetic processing” requirements were identified based on the following contrasts: 1) significant activation in each of the IN, SG, and MO conditions relative to baseline, during the period of mental arithmetic processing (frames 3–6); 2) significantly greater activation in each of the IN, SG, and MO conditions relative to the nonarithmetic control condition (RO) during the period of mental arithmetic processing (frames 3–6); 3) significantly greater activation in each of the IN, SG, and MO conditions (and no significant difference between the 3) during the period of mental arithmetic (frames 3–6) as compared with the initial period of the trial (frames 1–2); and 4) no significant difference between the task conditions at the initial period of the trial (frames 1–2).

Brain regions showing sensitivity to “resumption” of a primary task after the completion of a nested secondary task were identified based on the following contrasts: 1) significant activation in the SG condition, relative to baseline, during the period of PRELOAD recall (frames 7–8); 2) significantly increased activation in the SG condition during PRELOAD recall compared with the initial period of the trial (frames 1–2); 3) significantly greater activation in the SG condition compared each of the three other task conditions (IN, MO, RO) during the period of PRELOAD recall; and 4) no significant differences between task conditions during the initial period of the trial (frames 1–2).

Regions identified in each of the above voxelwise analyses were then transformed into regions-of-interest (ROIs) by averaging across all contiguous voxels within a region. Two further analyses were then conducted. The first analysis validated that all effects tested in the voxelwise conjunction analysis were statistically significant ($P < 0.05$) at the ROI level. All regions described below met these criteria. The second analysis quantitatively estimated the size of condition effects in each ROI, during both the MATH (frames 3–6) and REC (frames 7–8) periods. For these ROI analyses (and the graphs in Fig. 4 displaying the results), data were expressed in terms of mean percent change in fMRI signal relative to the fixation baseline.

Results

Behavioral Data

Overall accuracy was very high (>90%), suggesting that participants can do the task fairly easily (see Fig. 2*b*; accuracy data refer to the unscanned participants only because no verbal response was recorded from the scanned participants). There were no significant differences in math problem accuracy among MO, SG, and IN ($F_{2,46} = 1.02$, $P > 0.1$). Thus, the addition of a secondary load did not impair math computation. However, preload recall was significantly lower in SG than RO ($F_{1,23} = 16.7$, $P < 0.01$), suggesting that the interposed mental arithmetic task does cause some interference with maintenance of the preload digit.

Computation RT data (see Fig. 2*a*) were first examined through a 4 × 5–ANOVA involving condition (IN, SG, MO, RO) and task frame (PRELOAD, MATH-1 to MATH-4). A main effect of task frame and also a condition × frame interaction were observed ($P < 0.001$). These results reflect the increasing response latencies found in each step of the math problem of the task conditions in which mental arithmetic was performed (IN, SG, MO) but not in the RO condition for which the math problem was ignored. This finding suggests that mental arithmetic computation became increasingly difficult with each successive step of the problem. Additionally, secondary WM load, present in the IN and SG condition (but not in MO), caused another substantial increase in computation time (~160 ms) during mental arithmetic processing ($P < 0.001$). When directly comparing SG and IN, there was no main effect of condition, but there was a significant condition × frame interaction ($F_{4,144} = 11.2$, $P < 0.001$), due to additional slowing of response latency in the IN condition at MATH-4 ($F_{1,36} = 16.0$, $P < 0.001$), which was the point of integration. A separate analysis was conducted to determine whether any of these effects were differentially present in the scanned and unscanned participants. Although the scanned participants were as a whole about 150 ms slower than the unscanned participants, the effects of all experimental factors of interest were not significantly different in the 2 groups of participants. Thus, there is some justification for conducting analysis on the entire group.

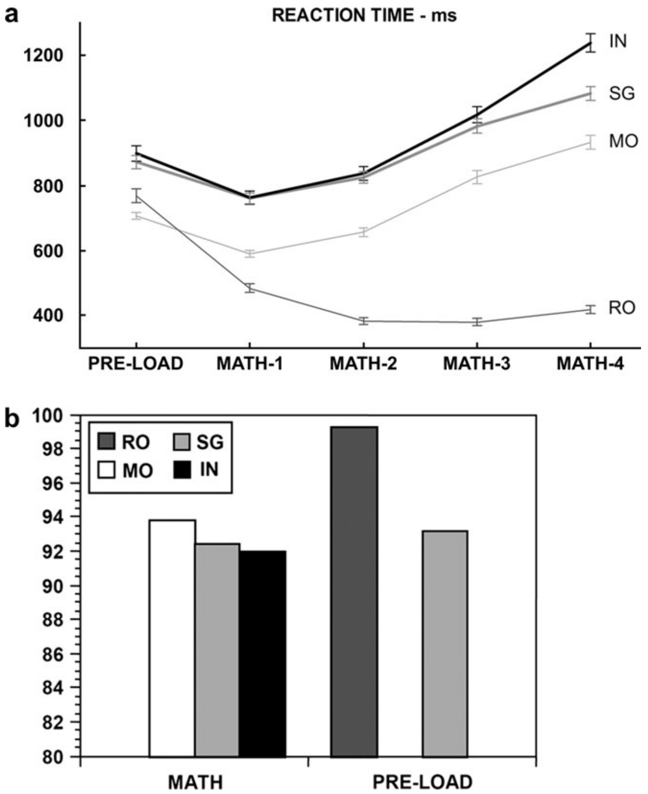

Figure 2. (*a*) RTs in the different conditions and in the frames from PRELOAD to MATH-4 both of behavioral and neuroimaging participants. (*b*) Accuracy in the different conditions for behavioral participants.

Neuroimaging Data

We conducted 4 different analyses of the whole-brain imaging data. One tested for selectivity to integration demands, one tested for sensitivity to increased WM load due to additional maintenance of the PRELOAD, a third tested for activity associated with mental arithmetic itself, and the last analysis tested for activation associated with recall of the PRELOAD following mental arithmetic processing. A summary of all identified regions in each of the task contrasts is provided in Table 1 and shown in brain surface images in Figure 3.

Integration

A number of regions were found to be sensitive to integration (orange in Fig. 3). Importantly, and consistent with predictions, one of these regions was located within left anterior PFC (BA 46/10). An additional focus of activity selective to integration was observed within right anterior cingulate cortex (ACC). The

Table 1

Brain regions identified in each of the task analyses. Coordinates are in Talairach atlas space (Talairach and Tournoux, 1988). In the integration condition, additional regions were identified when using only scan 6 (in bold font); the italicized region did not show any evidence of anticipatory activity.

Brain region	Brodmann area	*x*	*y*	*z*	Size (mm^3)
Integration					
Left middle frontal gyrus/anterior PFC	46/10	−33	42	21	486
Left precentral gyrus	6	−30	−9	42	918
Right precentral gyrus	6	27	−9	39	2241
Right ACC	32	18	15	33	837
Left precuneus	7	−18	−60	45	351
Left fusiform gyrus	20	−51	−33	−21	567
Right caudate, tail	—	24	−36	12	702
Left medial frontal gyrus	**32**	**−14**	**15**	**45**	**675**
Left inferior frontal gyrus/inferior PFC	**44**	**−46**	**7**	**20**	**567**
Right inferior frontal gyrus/inferior PFC	***44***	***44***	***14***	***15***	***405***
Right cingulate gyrus	**24**	**8**	**−3**	**39**	**351**
Left angular gyrus	**39**	**−28**	**−57**	**33**	**1377**
Right precuneus	**7**	**20**	**−60**	**36**	**405**
Increased WM load					
Left inferior frontal gyrus	44/9	−48	9	27	405
Left ACC	6	−12	3	47	486
Left middle frontal gyrus/dorsolateral PFC	9/46	−39	18	27	810
Left inferior frontal junction	44/6	−42	0	33	1404
Left precentral gyrus	6	−30	−6	51	540
Right medial frontal gyrus	6	15	−6	54	243
Right precentral gyrus	6	33	−3	51	405
Left inferior parietal lobule	40	−39	−42	42	3132
Right precuneus	7	9	−60	60	297
Mental arithmetic					
Left superior frontal gyrus	6	−6	3	63	756
Right ACC	32	18	21	24	1782
Left inferior parietal lobule	40	−30	−39	36	378
Left postcentral gyrus	43	−60	−9	18	297
Right fusiform gyrus	37	36	−60	−18	1107
Left fusiform gyrus	19	−36	−78	−15	2268
Left middle occipital gyrus	18	−24	−87	−3	270
Left angular gyrus	39/19	−30	−69	27	3132
Right lingual gyrus	18	12	−87	−9	648
Segregation					
Right middle frontal gyrus/anterior PFC	46/10	39	39	21	270
Left postcentral gyrus	43	−66	−6	12	270
Left superior parietal lobule	7	−18	−69	57	594
Right superior parietal lobule	7	12	−69	60	864
Left insula	13	−36	12	12	1998

ACC is commonly engaged in tandem with lateral PFC under conditions involving high levels of cognitive control demand. Visual inspection of the time course of trial-related activity in anterior PFC (Fig. 4*a* for the specific percentage of blood oxygen level–dependent [BOLD] signal change) suggests that the integration effect, though maximal at the time step of integration (scan 6), was also present during math processing prior to integration (scans 3–5). We tested this hypothesis explicitly via a contrast comparing the IN condition with the average of the 3 other conditions, examining each scan separately. Not only was the integration effect significant at scan 6 ($F_{1,19} = 17.0$, $P < 0.001$), but it was also significant at scan 5 ($F_{1,19} = 9.0$, $P < 0.01$) and marginally significant at scan 4 ($F_{1,19} = 3.9$, $P = 0.06$). However, this preparatory effect was not unique to the PFC region and in fact was present in all of the regions identified to be sensitive to integration.

These findings raise the possible concern that our analysis procedure was biased in favor of identifying regions showing preparation-related activity because it tested for integration effects by averaging across scans 3–6 (which included the pre-integration mental arithmetic steps, in addition to the integration step). To address this concern, we reanalyzed the data to identify integration effects using only scan 6 (the integration step). This reanalysis procedure identified, besides all of the same areas from the entire condition, a few additional areas, including right ACC, bilateral inferior PFC, and bilateral inferior parietal cortex (see bold-font regions in Table 1). Yet all of these additional areas, except for one, showed a similar sustained pattern as the originally identified regions. The exception region was located in the right inferior PFC (BA 44; italicized region in Table 1). In this region, the integration-related increase in activity was highly specific to the integration step (see Fig. 4*e*). This finding suggests an interesting temporal dissociation regarding lateral PFC involvement in integration, with anterior regions showing sustained effects and posterior–inferior regions showing transient effects.

Increased WM load

The additional WM load due to maintenance of the PRELOAD during math processing (common to the IN and SG conditions) engaged left dorsolateral (see Fig. 4*c*) and posterior PFC regions, along with inferior parietal cortex and left ACC (green in Fig. 3). Mental arithmetic alone did not activate these regions, as activity was not increased during the MO condition relative to the RO baseline. Likewise, the equivalent activity in these regions for SG and IN indicates that they are not sensitive to integration demands but only to the amount of information being maintained (or the change in attentional requirements associated with the increased load).

Mental Arithmetic

Mental arithmetic processing by itself also engaged a number of posterior brain regions. These regions exhibited increased activation in all 3 of the conditions that involved math processing (MO, SG, IN) relative to the RO baseline condition (blue regions in Fig. 3). Particularly interesting was the activation observed within left inferior parietal cortex, around the angular gyrus (Fig. 4*d*). This region is the same reported in Dehaene and others (2003), and it is associated with verbal processing of simple numerical information. ACC activity, particularly to the right, was also found to be active in this contrast, consistently with previous findings in positron emission tomography (PET) studies on subject performing simple mathematical calculations (Cowell and others 2000). It is noteworthy, however, that in this contrast isolating mental arithmetic, no regions were observed within lateral PFC. This result is consistent with the idea that the simple storage demands of mental arithmetic computations involving single digits are not sufficient to engage PFC.

Resumption of Preload Task

The SG condition makes unique demands on cognitive processing during the recall phase of each trial because only in the SG condition does the primary task (PRELOAD storage and retrieval) has to be resumed following completion of the secondary task (mental arithmetic). We observed significantly increased activity in the SG condition during the recall phase (scans 7–8) compared with the other 3 conditions in a network of regions, both within PFC and posterior cortex (red regions in Fig. 3). Intriguingly, within lateral PFC, selectively increased activity associated with preload recall was found in the right anterior PFC, in a location almost identical to the integration-related activity but on the opposite hemisphere (see Fig. 4*b*).

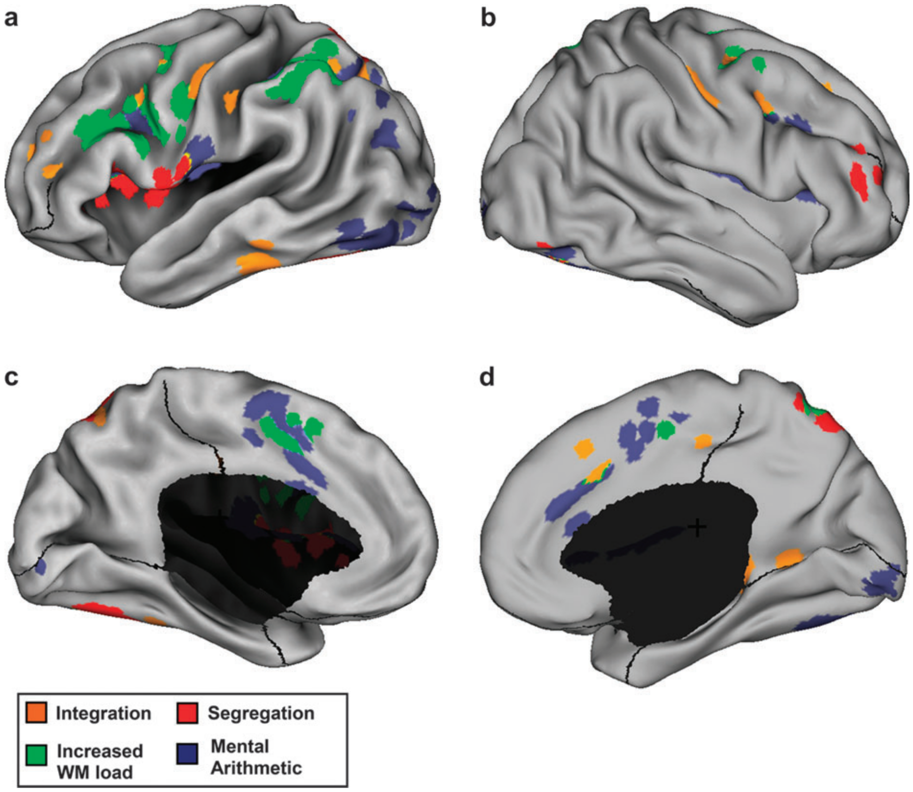

Figure 3. Lateral and medial brain views of 4 different contrasts, explained in the main text. Regions colored in orange, green, dark blue, and red are those showing significantly greater BOLD activation respectively in the integration, increased WM load, mental arithmetic, and segregation condition.

Functional Dissociations

A primary result of the study was in identifying 3 distinct networks of activity, one typified by the left anterior PFC that showed selectively increased activation in the IN condition, a second typified by the left midlateral PFC that showed equivalently increased activation in the 2 conditions involving a high WM load and divided attention (IN, SG), and a third typified by the left angular gyrus that showed equivalently increased activity in the 3 conditions involving mental arithmetic (MO, SG, IN). We sought to test whether these 3 networks were indeed reliably dissociable in function. To examine this question, we conducted a 2-factor ANOVA involving region (left anterior PFC, left dorsolateral PFC BA 9/46, left angular gyrus) and condition (MO, SG, IN) as factors. For clarity, activation was averaged across scans 3–6 and expressed as percent change relative to the RO control condition. The region × condition term was statistically significant ($F_{4,76} = 2.76$, $P < 0.05$) due to the 3 regions showing equivalent activity for the IN condition ($F < 1$) but significant differences in the expected directions for SG (angular gyrus = dorsolateral PFC > anterior PFC; $F_{2,38} = 3.38$, $P < 0.05$) and MO conditions (angular gyrus > dorsolateral PFC = anterior PFC; $F_{2,38} = 3.07$, $P < 0.06$). Thus, these 3 regions showed reliably distinct patterns of activity across the task conditions.

A second important result of the study was the identification of 2 distinct anterior PFC regions, located in nearly identical anatomic locations but on the opposite hemispheres. The left-hemisphere region selectively increased activity for the IN condition during the mental arithmetic phase of the trial, whereas the right-hemisphere region showed selectively increased activity for the SG condition later in the trial, near the recall phase. We were also interested in determining whether these 2 anterior PFC regions were truly functionally dissociable. To test this question, we conducted a 3-factor ANOVA involving anterior PFC hemisphere (left, right), condition (IN, SG), and phase of the trial (early, late) as factors. For clarity, the early phase was computed as the average activity across scans 3–6, and the late phase was the average activity in scans 7–8, expressed in terms of percent signal change in each condition of interest (IN, SG) relative to the average activity in the 2 control conditions (MO, RO). The ANOVA indicated that the full 3-way interaction was not significant ($F_{1,19} = 1.87$, $P = 0.19$). However, 2-factor ANOVAs conducted separately for each trial period (early, late) both showed significant hemisphere × condition interactions (early: $F_{1,19} = 5.34$, $P < 0.05$; late: $F_{1,19} = 5.72$, $P < 0.05$). The functional double dissociation within anterior PFC does appear to be statistically reliable, but we acknowledge that this dissociation analysis could be slightly biased because of the way the ROIs were defined, which might have led to an increased likelihood that the interaction would be significant.

Discussion

The results of this study demonstrate functional dissociations within lateral PFC when participants executed a mental arithmetic task while concurrently maintaining information in WM. A primary goal of the study was to determine if the integration of information within WM placed unique demands on cognitive processing, as distinct from very similar types of task demands, such as simple WM storage, dual-task processing/divided attention, and the segregation of distinct categories of stored information. The primary findings do support such a hypothesis. In

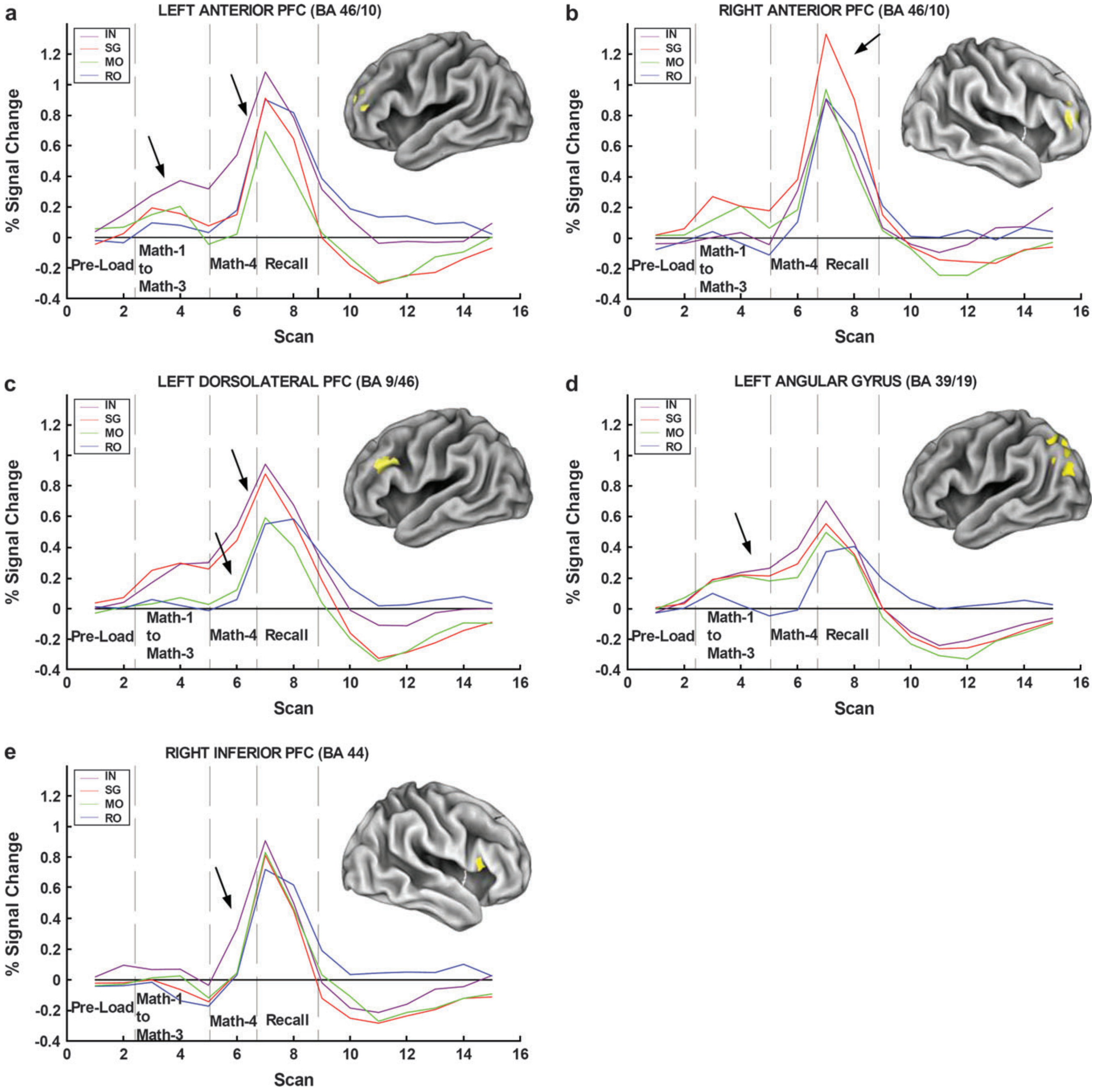

Figure 4. Hemodynamic responses in 5 key cortical regions, in particular, the left anterior PFC, sensitive to integration maximally at integration step, but also prior to it, suggesting that activation may have preparatory component (*a*); the right anterior PFC, sensitive to segregation demands, where activation specifically during recall phase suggests a role in interference prevention or WM retrieval functions (*b*); the left dorsolateral PFC, sensitive to increased WM load, but mental arithmetic alone does not activate region or integration compared with segregation (*c*); the left angular gyrus, where there is no effect of secondary load during math problem computations (*d*); the right inferior PFC, where the integration-related increased activity is transient and specific to the integration step (Math-4) (*e*).

particular, we observed that 1) simple WM storage associated with mental arithmetic processing engages ACC and parietal cortex, specifically within the left angular gyrus but not lateral PFC; 2) secondary WM load requirements (e.g., both SG and IN conditions) engage dorsolateral/posterior PFC and left ACC; 3) integration selectively engages left anterior PFC, with increased activity prior to the integration step, and right ACC; and 4) the recall phase of the SG condition selectively engages right anterior PFC.

These findings are relatively consistent with previous results. A growing literature on mental arithmetic has suggested that verbal processing and rehearsal engaged on numerical information consistently engage left parietal regions around the left angular gyrus (Cowell and others 2000; Dehaene and others 2003). The inactivity of PFC during simple math processing is also consistent with our predictions, given that single-digit processing was not particularly challenging in terms of storage and manipulation requirements. Simple WM tasks involving single items typically show only low levels of activity in lateral PFC (Rypma and others 1999). In contrast, the finding of strong posterior and dorsolateral PFC activation when WM loads were increased in the SG and IN condition is also consistent with many previous studies in WM literature (Braver and others 1997). In addition to increasing WM load, the SG and IN conditions both imposed dual task or divided attention demands on task processing because information associated with 2 different tasks or categories of content had to be simultaneously maintained and coordinated. Dual-task conditions and divided attention are also reliably associated with increased activity in midlateral PFC (D'Esposito and others 1995; Klingberg and Roland 1997; Bunge and others 2000; Iidaka and others 2000; Kensinger and others 2003). Indeed, given that the increase in WM load in the IN and SG conditions was not that great (2 items compared with 1 in the MO baseline), it is likely that the increased lateral PFC activity reflected not the increased demands on WM storage per se but rather the increased demands on time sharing, coordination, or selection between storage and rehearsal among the PRELOAD and arithmetic partial products. This interpretation is in line with the behavioral results, which indicated that the secondary task or divided attention component of the SG and IN conditions produced a dramatic slowing of computation time in mental arithmetic, without noticeably reducing computation accuracy. Such results would be expected under a time-sharing hypothesis, and have been consistently observed in similar divided attention studies, such as event-based prospective memory tasks (Smith 2003).

The key result of the study was that despite the similarities between the SG and IN conditions in terms of dual-task/divided attention requirements, there were also critical differences among the 2 conditions in terms of both behavioral performance and brain activity. Consistent with the behavioral results of Oberauer and others (2001), we found that the IN condition imposed selective costs on performance at the time point of integration, relative to otherwise matched conditions in which the WM content remains segregated. However, there were also distinctions between the 2 sets of results. In Oberauer and others (2001), there was no effect of additional WM load on mental arithmetic processing time, whereas in our results, a prominent effect was observed. This is especially surprising in that the WM load in their study was larger than in ours (3 items vs. 1 item). Additional methodological differences between the studies may complicate comparisons, however. For example, in their study even the no-load control conditions also had a dual-task component, that involved intermittently substituting letters for digits in some of the processing steps, based on reference to a displayed substitution chart.

The primary brain activation finding of selective anterior PFC activity during distinct phases of the IN and SG conditions is also consistent with previous results. For example, the left anterior PFC region associated with integration is almost identical in anatomic location to a region previously found to be parametrically sensitive to relational integration complexity but not other factors that also influenced task difficulty (Kroger and others 2002). Studies examining goal–subgoal coordination and integration have also identified similar regions of anterior PFC (Prabhakaran and others 2000; Braver and Bongiolatti 2002). It is interesting, however, that the region of anterior PFC identified in this study was somewhat posterior to regions identified in some other studies of integration (Christoff and others 2003) or subgoal processing (Koechlin and others 1999) and appears to be located in the junction of BA 46 and BA 10. It may be thus important for future studies to directly compare different kinds of integration tasks to determine if subtle differences in task content or nature of integration are associated with differences in the locus of activation within anterior PFC.

This study in some ways can be seen as similar to one performed by Anderson and others (2003), in which brain activity was also examined under mental arithmetic conditions involving mental substitution of preload digits into an algebraic problem. Anderson and others (2003) found lateral PFC activity in relationship to both the number of substitutions as well as the complexity of the mental arithmetic problem. However, this activation was in a midlateral region of PFC rather than in anterior PFC. Yet the results are not inconsistent with our own data, as the Anderson and others (2003) study did not isolate the pure effect of integration over and above the effect of WM maintenance during mental arithmetic processing, as we did in the IN versus SG contrast. Thus, the finding of midlateral PFC activity in Anderson and others is consistent with our identification of midlateral PFC activation present in both the IN and SG conditions.

The current results significantly extend what is known about the role of anterior PFC in integration, by demonstrating a dissociation between left and right anterior PFC related to the functional distinction between integration and segregation of information within WM. In particular, the left anterior PFC was selectively engaged when primary task information had to be integrated into an ongoing secondary task, whereas the right anterior PFC was engaged when the primary task had to be resumed following completion of the secondary task. This distinction between integrating subgoal information with a primary task and resuming an ongoing task following interruption by the subgoal is not the one that has been previously observed in the literature and was somewhat unexpected. Previous studies have tended to find either bilateral or right-lateralized anterior PFC activity associated with integration and goal–subgoal coordination (Koechlin and others 1999; Prabhakaran and others 2000; Braver and Bongiolatti 2002), but these studies did not use methods that enabled the type of temporal dissociation identified here. Moreover, at a conceptual level, some theorists have suggested that both integration of primary task WM content into subtask results and resumption of a primary task following subtask completion are forms of "branching," a cognitive computation uniquely proposed to be subserved by anterior PFC (Koechlin and others 1999). Thus, one possible interpretation of the results is that both computations are forms of branching but are conceptually distinct processes that are engaged by hemispherically lateralized regions within anterior PFC. However, other interpretations are possible, especially regarding the right anterior PFC activation occurring during resumption of the preload task. For example, it is possible that recall of the preload information engaged processes related to episodic retrieval. There is now a large literature accumulated which suggests that anterior PFC is reliably activated during episodic retrieval conditions and may be associated with postretrieval monitoring operations (Schacter and others 1997; Henson and others 2000). Additionally, the recall phase of the SG condition also posed unique cognitive demands due to the heightened potential for response selection interference between recall of the preload versus mental arithmetic answer. Thus, it will be necessary in further work to more clearly specify which of these alternatives represents the functional source of the hemispheric dissociation we observed in anterior PFC.

Examination of brain activation temporal dynamics during the IN condition also provided important insights regarding the functional dissociation within lateral PFC. We found that the left anterior PFC showed integration-related activity that peaked at the time point of integration, but also showed a more sustained and anticipatory time course, with significant integration-related increases occurring during mental arithmetic processing prior to the integration step. In contrast, a region within right inferior PFC was observed that showed integration-related activity that was transient rather than sustained and specifically time locked to the point of integration. These results suggest that integration processing may have multiple components, each of which require specialized neural mechanisms. Even though the task design and the several overlapping BOLD effects cumulating at the end of each trial did not allow us to clearly determine what is the function of these activities, we might speculate that the right inferior PFC might be specifically involved with the processes of representational transformation and substitution associated with the integration step. Or, alternatively, this region might be involved with inhibitory or suppressive processes that stop the normal process of WM updating that occurs on the nonintegration steps and which allow attention to be directed toward the PRELOAD digit such that it can be inserted into the problem. This latter interpretation is consistent with standard interpretations of right inferior PFC regions as being involved with inhibitory processes across a wide range of cognitive domains (Aron and others 2003).

The Functional Role of Anterior PFC

Based upon the current results, what kinds of interpretations can be drawn regarding the functional role of anterior PFC in human cognition? In particular, it is worth asking whether the region of left anterior PFC identified in this study might serve as the neural substrate of Baddeley's episodic buffer component of WM (Baddeley 2000). In some sense, the activation pattern of this region does seem to fit the functional characteristics that Baddeley has ascribed to the episodic buffer. The region was selectively engaged only when diverse streams of information needed to be integrated within WM. As such, the anterior PFC might serve as a temporary cognitive workspace that enables integration processes to occur when needed. However, in other respects, the fit of the current results to the Baddeley model is not so clear. In particular, an interesting aspect of the results is the finding that the integration-related activation of left anterior PFC appears to occur in an anticipatory and sustained fashion, with activation appearing in advance of the time when integration processes can occur. It is not clear how well such a pattern could fit within the episodic buffer framework, which would suggest that the episodic buffer only gets invoked transiently at the point when integration must occur. The only brain region which appeared to fit this functional pattern was the right inferior PFC, which showed a transient increase in activation only at the integration step. However, this latter region seems to be less plausible as a candidate for an episodic buffer based on the previous literature, which points to the right inferior PFC as more strongly involved in inhibitory rather than maintenance process. As such the results motivate other, alternative interpretations of the data.

One such interpretation of the data is that the anterior PFC does serve as a WM buffer, but with it specialized for maintaining information in the "outer loop" of a nested hierarchy, during a period in which information in an "inner loop" becomes repeatedly updated. In other words, the anterior PFC may serve to maintain the PRELOAD information in a relatively protected form while the intermediate products of the mental arithmetic processing get stored and updated with each new problem step. Under such an account, the anterior PFC might be engaged as a specialized buffer that enables WM content to be maintained for longer durations and in a relatively protected state (i.e., undisturbed by the distracting input of the mental arithmetic processing). More generally, the idea that anterior regions of PFC maintain "outer loop" information for extended periods of time and during the period of "inner loop" updating (which occurs in more posterior regions of cortex and PFC) is relatively attractive from a computational standpoint and is supported by computational analyses (Frank and others 2001). Moreover, the outer loop interpretation could account for the particular activity dynamics observed in left anterior PFC because the activation would reflect the engagement and storage of PRELOAD information that occurs at the beginning of each trial and maintains up until the point of integration, when PRELOAD maintenance is no longer needed. However, the outer loop account does not clearly distinguish between hierarchically nested WM conditions that do involve integration versus conditions in which no integration occurs because both would involve outer loop maintenance during inner loop updating. Thus, it is not clear that such an account would have predicted the key finding of this study, which is that the activation in left anterior PFC was selective to IN conditions, and not observed under nested WM conditions with no integration.

A third and related interpretation of anterior PFC function is that this region serves active maintenance, but specifically of goal-related information, such as intentions rather than of stimulus content per se. Thus, under this account, the information maintained in WM is specifically goal related, such as a representation of the form "if the integration cue (underline bar) appears, substitute with X (where X = PRELOAD)." This representation is activated at the time of the PRELOAD (and must be updated with the new PRELOAD information on each trial) and then is actively maintained to help the participant anticipate and prepare for the appearance of the integration cue. An interesting aspect of this account is that it might suggest that anterior PFC is specialized for maintenance of a relatively abstract goal or action (rather than a simple S-R mapping), which is why it might become particularly engaged under IN conditions. However, under the account, it is not integration per se that engages the anterior PFC but rather the complex demands on information maintenance that typically accompany integration task requirements. This account would fit well with previous findings demonstrating anticipatory activation in anterior PFC which seems to reflect the active maintenance of abstract task-set information (Sakai and Passingham 2003, 2006). Moreover, the selective engagement of the left anterior PFC under integration and not SG conditions might reflect the distinction between rapidly implementing a goal intention during the middle of a difficult ongoing task and instead implementing the same intention under less demanding conditions, such as when the ongoing task is completed. Under this latter situation, the intention might instead be retrieved from a less accessible store (i.e., episodic long term memory rather than WM). An attractive feature of this account is that it closely links the integration requirements of the current task with the primary components of most prospective memory tasks (e.g., cue-triggered goal intention implementation during the course of an ongoing task), which have been previously theorized to also selectively engage anterior PFC (Burgess and others 2001). Nevertheless, further direct testing is needed before this account could be said to be strongly supported.

Yet a fourth possible interpretation of anterior PFC function emphasizes the role of this region in managing conflict or interference. This idea is consistent with the general framework of the conflict-control loop theory, in which conflict is detected within the ACC and then signaled to the lateral PFC, such that control processes can be mobilized to effectively resolve or manage that interference (Botvinick and others 2001). In this mental arithmetic paradigm, conflict arises because of the 2 sources of simultaneously maintained digit information that have the potential to interfere with each other and so cause confusion regarding which information belongs to which task. Additionally, during the IN condition, an additional source of conflict might arise because of the requirement to insert the PRELOAD information into the math problem at the integration step but to resist this insertion operation during the non-integration steps. Thus a tension arises between the tendency to want to insert the PRELOAD information into the problem and to keep it segregated. The anterior PFC might serve to effectively negotiate or manage this tension, by holding the digit information segregated until just the appropriate time. Such an account could explain the anticipatory activity dynamics observed during the trial, in which the activation level progressively rises (reflected increased demands on conflict management) throughout the trial, until the time of the integration step. In the SG condition, only the primary form of conflict is present because there is no need to ever insert the PRELOAD into the problem, and so no tension between segregation and integration. This conflict account of the results can also explain why activity in right (and to a lesser extent, left) ACC during the IN condition occurs along with the left anterior PFC activation. Additionally, this account explains why both the IN and SG conditions are also associated with an additional source of activation in left ACC, along with the associated activation in midlateral PFC. The conflict account of anterior PFC in some ways is very similar to the goal intention account, in that both postulate similar roles for anterior PFC in maintaining representations that help to effectively control attention and processing during task trials. Yet one distinction is that the conflict account might postulate that the degree of anterior PFC activity during IN conditions would be linked to the potential for interference among maintained representations. Thus, the current study had a high potential for interference because both sources of maintained information were of the same category type (digits). Conversely, under conditions where the sources of information to be integrated were of different categories, then conflict demands might be lower—which could translate into lower levels of ACC and anterior PFC activity. Such predictions should be tested to examine the power of the conflict account and better differentiate it from the goal intention view.

A final possible explanation of anterior PFC activation in this study is that it does not reflect maintenance of integration-related information itself but rather represents a temporal prediction of the time when integration must occur. Under this view, the anterior PFC may serve a nonspecific preparatory function that enables the system to appropriately activate resources for the cognitively demanding task of preparation. In other words because integration may be so demanding of cognitive resources, appropriate resource allocation and preparation may be needed in order to achieve successful performance. Thus, the anticipatory-like activation dynamics observed within anterior PFC (and in other activated regions) may reflect this temporal prediction by representing how close in time is the upcoming integration step. The temporal prediction account is plausible for the current study because of a potential confound in the design, in which integration trials were blocked and the integration step always occurred at a particular point during the trial (the fourth step of the math problem). Without such predictability in the time of integration, full preparation would not be possible. The possibility of a role of anterior PFC in temporal prediction is also consistent with previous work. For example, a study of task switching found that left anterior PFC was more activated when both timing and task order where predictable, as opposed to more posterior PFC activation when the task timing was not predictable (Dreher and others 2002). Thus, in order to fully test the temporal prediction account, it will be necessary to vary the time point in which integration occurs on a trial-by-trial basis, such that integration and resource allocation demands cannot be fully anticipated.

In conclusion, the findings of this study are consistent with the hypothesis that the role of anterior PFC is to internally coordinate the integration of stored information during the execution of simultaneous WM tasks. The mental arithmetic paradigm employed in this study enabled the identification of a functional dissociation in lateral PFC, with midlateral regions becoming generally engaged under dual-task/divided attention conditions, regardless of whether information from the 2 tasks had to be maintained in segregated form or integrated at a specific point in time. In contrast, a left anterior PFC region only became activated when integration was required. This activation occurred not only at the time of integration but also in anticipation of it, suggesting a possible functional role in preparation. Finally, right anterior PFC became selectively engaged in a transient fashion under conditions when a primary task had to be resumed after completion of a secondary task. Taken together, these results shed new light on the particular nature of control processes within WM and suggest more specific hypotheses regarding the functional role of anterior PFC that can be tested in future work.

Notes

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References

Anderson JR, Reder LM, Lebiere C. 1996. Working memory: activation limitations on retrieval. Cogn Psychol 30(3):221–256.

Anderson JR, Quin Y, Sohn M, Stenger VA, Carter CS. 2003. An information-processing model of the BOLD response in symbol manipulation tasks. Psychon Bull Rev 10(2):241–261.

Aron AR, Fletcher PC, Bullmore ET, Sahakian BJ, Robbins TW. 2003. Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. Nat Neurosci 6(2):115–116.

Baddeley AD. 2000. The episodic buffer: a new component of working memory? Trends Cogn Sci 4(11):417–423.

Baddeley AD. 2003. Working memory: looking back and looking forward. Nat Rev Neurosci 4(10):829–839.

Badre D, Wagner AD. 2004. Selection, integration, and conflict monitoring; assessing the nature and generality of prefrontal cognitive control mechanisms. Neuron 41(3):473–487.

Baker SC, Rogers RD, Owen AM, Frith CD, Dolan RJ, Frackowiak RSJ, Robbins TW. 1996. Neural systems engaged by planning: a PET study of the Tower of London task. Neuropsychologia 34(6):515–526.

Botvinick MM, Braver TS, Barch DM, Carter CS, Cohen JC. 2001. Conflict monitoring and cognitive control. Psychol Rev 108:624–652.

Braver TS, Bongiolatti SR. 2002. The role of the frontopolar cortex in subgoal processing during working memory. Neuroimage 15:523–536.

Braver TS, Cohen JD, Nystrom LE, Jonides J, Smith EE, Noll DC. 1997. A parametric study of prefrontal cortex involvement in human working memory. Neuroimage 5(1):49–62.

Buckner RL, Braver TS. 1999. Event-related functional MRI. In: Bandettini P, Moonen C, editors. Functional MRI. Germany: Springer-Verlag. p 441–452.

Bunge SA, Kahn I, Wallis JD, Miller EK, Wagner AD. 2003. Neural circuits subserving the retrieval and maintenance of abstract rules. J Neurophysiol 90(5):3419–3428.

Bunge SA, Klingberg T, Jacobsen RB, Gabrieli JD. 2000. A resource model of the neural basis of executive working memory. Proc Natl Acad Sci USA 97(7):3573–3578.

Bunge SA, Wendelken C, Badre D, Wagner AD. 2004. Analogical reasoning and prefrontal cortex: evidence for separable retrieval and integration mechanisms. Cereb Cortex 15:239–249.

Burgess PW, Quayle A, Frith CD. 2001. Brain regions involved in prospective memory as determined by positron emission tomography. Neuropsychologia 39:545–555.

Burgess PW, Scott SK, Frith CD. 2003. The role of the rostral frontal cortex (area 10) in prospective memory: a lateral versus medial dissociation. Neuropsychologia 41(8):906–918.

Christoff K, Prabhakaran V, Dorfman J, Zhao Z, Kroger JK, Holyoak KJ, Gabrieli JD. 2001. Rostrolateral prefrontal cortex involvement in relational integration during reasoning. Neuroimage 14: 1136–4119.

Christoff K, Ream JM, Geddes LP, Gabrieli JD. 2003. Evaluating self-generated information: anterior prefrontal contributions to human cognition. Behav Neurosci 117(6):1161–1168.

Cohen JD, MacWhinney B, Flatt MR, Provost J. 1993. PsyScope: a new graphic interactive environment for designing psychology experiments. Behav Res Methods Instrum Comput 25(2):257–271.

Conturo TE, McKinstry RC, Akbudak E, Snyder AZ, Yang T, Raichle ME. 1996. Sensitivity optimization and experimental design in functional magnetic resonance imaging. Soc Neurosci Abstr 26:7.

Cowell SF, Egan GF, Code C, Harasty J, Watson JDG. 2000. The functional neuroanatomy of simple calculation and number repetition: a parametric PET activation study. Neuroimage 12:565–573.

D'Esposito M, Aguirre GK, Zarahn E, Ballard D, Shin RK, Lease J. 1998. Functional MRI studies of spatial and nonspatial working memory. Cogn Brain Res 7:1–13.

D'Esposito M, Ballard D, Zarahn E, Aguirre GK. 2000. The role of prefrontal cortex in sensory memory and motor preparation: an event-related fMRI study. Neuroimage 11(5 Pt 1):400–408.

D'Esposito M, Detre JA, Alsop DC, Shin RK, Atlas S, Grossman M. 1995. The neural basis of the central executive system of working memory. Nature 378:279–281.

D'Esposito M, Shin RK, Detre JA, Incledon S, Annis D, Aguirre GK, Grossman M, Alsop DC. 1995. Object and spatial working memory activates dorsolateral prefrontal cortex: a functional MRI study. Soc Neurosci Abstr 21:1498.

Daneman M, Carpenter PA. 1980. Individual differences in working memory and reading. J Verb Learn Verb Behav 19:450–466.

De Stefano D, LeFevre J. 2004. The role of working memory in mental arithmetic. Eur J Cogn Psychol 3(16):353–386.

Dehaene S, Piazza M, Pinel P, Cohen L. 2003. Three parietal circuits for number processing. Cogn Neuropsychol (20):487–506.

Dreher J-C, Koechlin E, Ali SO, Grafman J. 2002. The roles of timing and task order during task switching. Neuroimage 17:95–109.

Forman SD, Cohen JD, Fitzgerald M, Eddy WF, Mintun MA, Noll DC. 1995. Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. Magn Reson Med 33:636–647.

Frank MJ, Loughry B, O'Reilly RC. 2001. Interactions between frontal cortex and basal ganglia in working memory: a computational model. Cogn Affect Behav Neurosci 1(2):137–160.

Friston KJ, Holmes AP, Worsley KJ, Poline J-P, Frith CD, Frackowiak RSJ. 1995. Statistical parametric mapping in functional imaging: a general linear approach. Hum Brain Mapp 2:189–210.

Friston KJ, Williams S, Howard R, Frackowiak RSJ, Turner R. 1996. Movement-related effects in fMRI time-series. Magn Reson Med 35:346–355.

Fuster J. 1997. The prefrontal cortex. 3rd ed. New York: Lippincott-Raven.

Goldman-Rakic PS. 1987. Circuitry of primate prefrontal cortex and regulation of behavior by representational memory. In: Plum F, Mountcastle V, editors. Handbook of physiology—the nervous system V. Volume 5. Bethesda, MD: American Physiological Society. p 373–417.

Gray JR, Braver TS, Raichle ME. 2002. Integration of emotion and cognition in the lateral prefrontal cortex. Proc Natl Acad Sci USA 99:4115–4120.

Gruber O, Indefrey P, Steinmetz H, Kleinschmidt A. 2001. Dissociating neuralcorrelates of cognitive components in mental calculation. Cereb Cortex 11(4):350–359.

Henson RNA, Rugg MD, Shallice T. 2000. Confidence in recognition memory for words: Dissociating right prefrontal roles in episodic retrieval. J Cogni Neurosci 12:913–923.

Hitch GJ. 1978. The role of short-term working memory in mental arithmetic. Cogn Psychol 10:302–323.

Iidaka T, Anderson ND, Kapur S, Cabeza R, Craik FI. 2000. The effect of divided attention on encoding and retrieval in episodic memory revealed by positron emission tomography. J Cogn Neurosci 12(2):267–280.

Kensinger EA, Clarke RJ, Corkin S. 2003. What neural correlates underlie successful encoding and retrieval? A functional magnetic resonance imaging study using a divided attention paradigm. J Neurosci 23(6):2407–2415.

Klingberg T, Roland PE. 1997. Interference between two current tasks is associated with activation of overlapping fields in the cortex. Cogn Brain Res 6:1–8.

Koechlin E, Basso G, Pietrini P, Panzer S, Grafman J. 1999. The role of the anterior prefrontal cortex in human cognition. Nature 399:148–151.

Kroger JK, Sabb FW, Fales CL, Bookheimer SY, Cohen MS, Holyoak KJ. 2002. Recruitment of anterior dorsolateral prefrontal cortex in human reasoning: a parametric study of relational complexity. Cereb Cortex 12(5):477–485.

Logie RH, Gilhooly KJ, Wynn V. 1994. Counting on working memory in arithmetic problem solving. Memory Cogn 22(4):395–410.

McAvoy MP, Ollinger JM, Buckner RL. 2001. Cluster size thresholds for assessment of significant activation in fMRI. Neuroimage 13:S198.

Miller EK, Cohen JD. 2001. An integrative theory of prefrontal cortex function. Ann Rev Neurosci 21:167–202.

Miyake A, Shah P, editors. 1999. Models of working memory: mechanisms of active maintenance and executive control. New York: Cambridge University Press.

Mugler JPI, Brookeman JR. 1990. Three-dimensional magnetization-prepared rapid gradient-echo imaging (3D MP-RAGE). Magn Reson Med 15:152–157.

Oberauer K, Demmrich A, Mayr U, Kliegl R. 2001. Dissociating retention and access in working memory: an age-comparative study of mental arithmetic. Mem Cogn 1(29):18–33.

Prabhakaran V, Narayanan K, Zhao Z, Gabrieli JD. 2000. Integration of diverse information in working memory within the frontal lobe. Nat Neurosci 3(1):85–90.

Reynolds JR, McDermott KB, Braver TS. 2006. A direct comparison of anterior prefrontal cortex involvement in episodic retrieval and integration. Cereb Cortex 16(4):519–528.

Rypma B, Prabhakaran V, Desmond JE, Glover GH, Gabrieli JDE. 1999. Load-dependent roles of frontal brain regions in the maintenance of working memory. Neuroimage 9:216–226.

Sakai K, Passingham RE. 2003. Prefrontal interactions reflect future task operations. Nat Neurosci 6(1):75–81.

Sakai K, Passingham RE. 2006. Prefrontal set activity predicts rule-specific neural processing during subsequent cognitive performance. J Neurosci 26(4):1211–1218.

Schacter DL, Buckner RL, Koutstaal W, Dale AM, Rosen BR. 1997. Late onset of anterior prefrontal activity during true and false recognition: An event-related fMRI study. Neuroimage 6:259–269.

Smith EE, Jonides J. 1999. Storage and executive processes in the frontal lobes. Science 283:1657–1661.

Smith RE. 2003. The cost of remembering to remember in event-based prospective memory: investigating the capacity demands of delayed intention performance. J Exp Psychol Learn Mem Cogn 29:347–361.

Snyder AZ. 1996. Difference image versus ratio image error function forms in PET–PET realignment. In: Myer R, Cunnigham VJ, Bailey DL, Jone T, editors. Quantification of brain function using PET. San Diego, CA: Academic Press. p 131–137.

Talairach J, Tournoux P. 1988. Co-planar stereotaxic atlas of the human brain. New York: Thieme.

Woods RP, Cherry SR, Mazziotta JC. 1992. Rapid automated algorithm for aligning and reslicing PET images. J Comput Assisted Tomogr 16:620–633.

Woods RP, Grafton ST, Holmes CJ, Cherry SR, Mazziotta JC. 1998. Automated image registration: I. General methods and intrasubject, intramodality validation. J Comput Assisted Tomogr 22(1): 139–152.

Zago L, Pesenti M, Mellet E, Crivello F, Mazoyer B, Tzourio-Mazoyer N. 2001. Neural correlates of simple and complex mental calculation. Neuroimage 13:314–327.