

A Parametric Study of Prefrontal Cortex Involvement in Human Working Memory

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Although recent neuroimaging studies suggest that prefrontal cortex (PFC) is involved in working memory (WM), the relationship between PFC activity and memory load has not yet been well-described in humans. Here we use functional magnetic resonance imaging (fMRI) to probe PFC activity during a sequential letter task in which memory load was varied in an incremental fashion. In all nine subjects studied, dorsolateral and left inferior regions of PFC were identified that exhibited a linear relationship between activity and WM load. Furthermore, these same regions were independently identified through direct correlations of the fMRI signal with a behavioral measure that indexes WM function during task performance. A second experiment, using whole-brain imaging techniques, both replicated these findings and identified additional brain regions showing a linear relationship with load, suggesting a distributed circuit that participates with PFC in subserving WM. Taken together, these results provide a “dose-response curve” describing the involvement of both PFC and related brain regions in WM function, and highlight the benefits of using graded, parametric designs in neuroimaging research. © 1997 Academic Press

Cognitive theorists have posited that higher functions such as language, planning, and problem-solving all rely on working memory (WM), which acts to temporarily maintain and manipulate task-relevant information (Baddeley, 1986; Just and Carpenter, 1992; Shallice, 1988). Neurophysiological data from nonhuman primates have suggested that prefrontal cortex (PFC) is an important component of the neural substrate for WM. In single-cell recording studies, neurons have been identified in dorsolateral PFC that remain active during delay periods in tasks that require the subject to actively maintain an internal representation of a target stimulus (Fuster, 1989; Goldman-Rakic, 1987). In humans, findings of WM impairment in patients with

damage to the frontal cortex support the involvement of this brain region in WM function (Shimamura, 1994; Stuss *et al.*, 1994). Recently, neuroimaging data have also begun to contribute to our understanding of the neurobiology of human working memory. Studies using both positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have provided strong evidence of PFC involvement in a wide variety of working memory tasks (Cohen *et al.*, 1994; Courtney *et al.*, 1996; Fiez *et al.*, 1996; Jonides *et al.*, 1993; McCarthy *et al.*, 1994; Petrides *et al.*, 1993; Swartz *et al.*, 1995). Further, activation of additional brain regions has often been observed during performance of these tasks (e.g., posterior parietal cortex, Broca's area), suggesting the possibility that WM function is subserved by multiple brain regions.

These neuroimaging studies have all identified WM-related brain activity through the use of the subtractive method. According to this method, activity generated by a “control” task is subtracted from that observed in an “activation” task. The control task is designed to engage all of the processes of the activation task except for the cognitive process of interest (Posner *et al.*, 1988). Thus, subtraction of the control images from the activation images should reveal activity that is associated with the process of interest. Although the findings from neuroimaging studies of WM have been reasonably consistent and informative there are, nevertheless, a number of well-recognized limitations to the subtractive approach (McClelland, 1979; Sternberg, 1969). The most important of these is the assumption that the “irrelevant” processes—those common to both tasks and supposed to be subtracted out—are performed in the same way in the two tasks. In neuroimaging studies, this also assumes that the irrelevant activity occurs in the same anatomic regions across both tasks. Since it is impossible to verify this assumption directly, misleading interpretations can ensue regarding the observed patterns of activation. For example, in all of

the neuroimaging studies of WM mentioned above, the increased demand on processing resources in the activation condition may cause subjects to adopt new strategies, and may even change the nature of task processes thought to be unrelated to WM, such as encoding and response execution. If these changes in task processing lead to increased activity, or to changes in the anatomic location of activated regions, they may be misinterpreted as reflecting structures involved in WM.

In behavioral studies, cognitive scientists frequently deal with the limitations of the subtractive approach by varying the process of interest in a parametric, rather than a discrete, fashion. Thus, tasks are designed to produce a specific pattern of response in the process of interest. While other processes may still vary across conditions, the likelihood is lower that they will show the same pattern of response as is predicted for the process of interest. In other words, the parametric approach places tighter constraints on the pattern of responses predicted, and thus provides greater selectivity in measuring processes of interest. Sternberg's (1969) studies of short-term memory are a classic example of a parametric experimental design. In these experiments, the number of items kept active in memory was varied incrementally. Changes observed in reaction time were then used to selectively probe and characterize the cognitive processes involved in retrieval.

Parametric designs can also be used in neuroimaging studies, to more selectively identify regions of brain activity associated with cognitive processes of interest. This approach has already begun to see application in the study of basic sensory processes (Engel *et al.*, 1994; Schneider *et al.*, 1994; Tootell *et al.*, 1995) and cognitive processes such as long-term memory (Grasby *et al.*, 1994). Here we present the results of two experiments in which we exploit the advantages of parametric designs to characterize the relationship between brain activation and WM function. In both, fMRI was used to probe brain activity during performance of a sequential letter memory task in which WM load was varied in a graded fashion. The speed and noninvasiveness of fMRI allowed us to obtain large numbers of images from multiple task conditions within a single imaging session, necessary for a parametric design. In the first experiment, we examined this relationship specifically within PFC. In the second, we used whole-brain imaging both to confirm our results and to identify additional, nonfrontal regions that may contribute to WM function.

EXPERIMENT 1

Our initial study focused on PFC, since it has been a major focus of neurophysiological studies of WM. Our analysis procedure identified PFC regions whose activ-

ity varied reliably with changes in memory load. Additionally, behavioral data were analyzed to directly validate findings concerning the relationship between PFC activity and WM function. Specifically, reaction time (RT) was used as an empirically defined measure of load, providing a convergent method for identifying regions of brain activity associated with WM function.

Methods

Subjects

Informed consent was obtained from nine neurologically normal right-handed subjects (eight males, one female; 18–31 years of age). All subjects were given a pretesting session, in which they practiced the task, and were included only after reaching a criterion level of performance (>75% accuracy on all conditions).

Cognitive Tasks

Subjects performed a variant of a sequential letter task that has been used previously in a number of neuroimaging experiments to study working memory (Awh *et al.*, 1996; Cohen *et al.*, 1994; Gevins and Cutillo, 1993; Smith *et al.*, 1996). However, these previous experiments used only two task conditions—WM and control. In the current study, four conditions were used that varied WM load incrementally from zero to three items (see Fig. 1).

Subjects observed stimuli on a visual display and responded using a hand-held response box with fiber-optic connections to a Macintosh computer in the control room running PsyScope software (Cohen *et al.*, 1993). In the 0-back condition, subjects responded to a single prespecified target letter (e.g., "X"). In the 1-back condition, the target was any letter identical to the one immediately preceding it (i.e., one trial back). In the 2-back and 3-back conditions, the target was any letter that was identical to the one presented two or three trials back, respectively. Thus, WM load increased incrementally from the 0-back to the 3-back condition. Stimuli were pseudorandom sequences of consonants (randomly varying in case), presented centrally (500-ms duration, 2500-ms interstimulus interval). Subjects responded to each stimulus with their dominant hand, pressing one button for targets (33% of trials) and another for nontargets. In each sequence, a number of stimuli were nontarget repeats that were included as foils (e.g., 2-back repeats occurring in the 3-back condition). Conditions were run in blocks of approximately 75 s (25 stimuli), during which scans were acquired. Ten repetitions of each of the four conditions were run, with condition order randomized across blocks and subjects (two subjects received only five repetitions, with no difference in results), subject to the constraint that all four conditions were sampled in every set of four blocks. A short delay between blocks (10–20 s) was

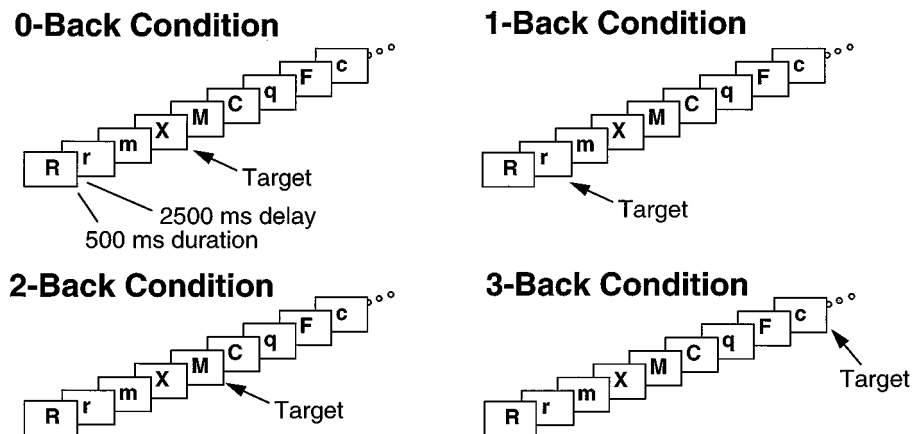


FIG. 1. A diagram of the four memory conditions of the sequential letter task.

provided as a rest break for subjects and to allow the hemodynamic response to recover from the previous block.

MRI Scanning Procedures

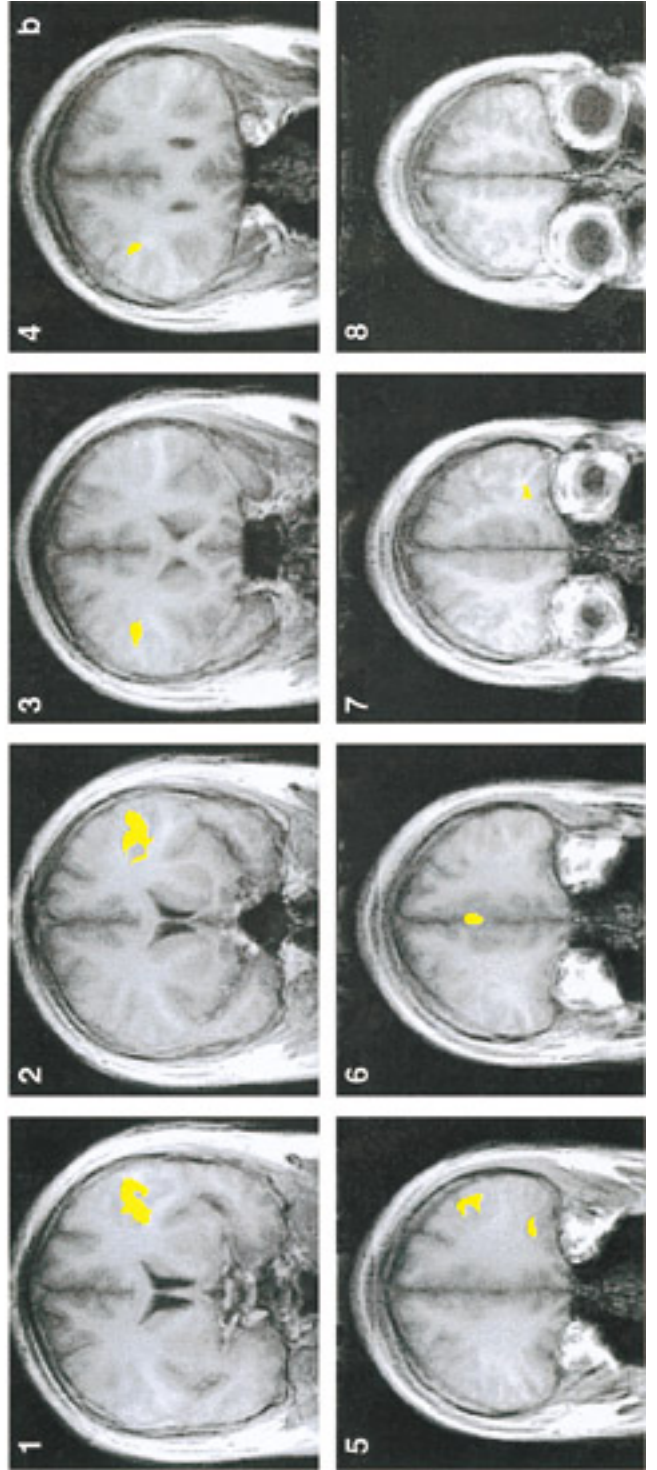
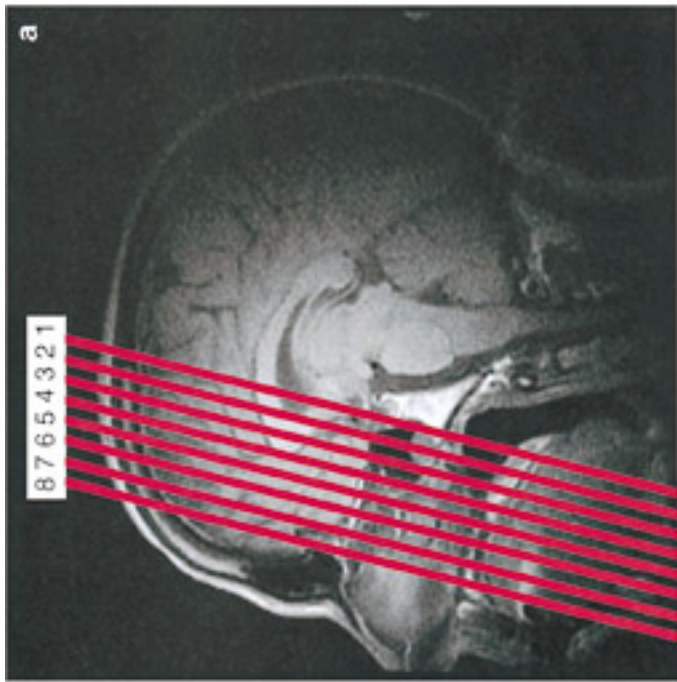
Images were acquired with a conventional 1.5-T GE Signa whole-body scanner. Two 5-in. surface coils, mounted in parallel over the frontal area, were used to maximize signal-to-noise ratio in the region of interest. Subject movement was constrained with a bite-bar consisting of an individually molded dental impression attached to a rigid plastic frame. All scans were 7 mm thick, with 1.88×1.88 -mm pixels in plane, acquired at eight contiguous locations, perpendicular to the AC-PC line, and extending rostrally from the anterior commissure (see Fig. 2a). Structural images were obtained at these locations prior to functional scanning, using a standard T1-weighted sequence. Functional images were acquired using a 10-interleave spiral scan pulse sequence (Noll *et al.*, 1995) with a TR of 640 ms, a gradient echo TE of 35 ms, a flip angle of 45° , and a field of view of 24 cm. A set of images from all eight slice locations was obtained every 6.4 s. Eleven sets were obtained during each 75-s task block.

Image Analysis Procedures

Two analyses were performed, one using memory load and the other reaction time as independent variables. Both analyses were conducted according to the following set of procedures. All functional images were first scaled to a common mean (to reduce the effect of scanner drift or instability), and then registered in-plane using an automated algorithm (Woods *et al.*, 1992). Statistical maps of activity were generated for each slice (see below for details) and then thresholded for significance using a cluster-size algorithm that takes account of the spatial extent of activation in

correcting for multiple comparisons (Forman *et al.*, 1995). A contiguity threshold of seven voxels and per-pixel false-positive rate of 0.03 were chosen, corresponding to a corrected pixel-wise α protection of 0.0006. Potential venous artifact was removed using a magnetic resonance angiography filtering procedure (Cohen *et al.*, 1995).

In the memory-load analysis, regions of memory-related activity were identified using a voxel-wise ANOVA, with memory load (4 levels) as the experimental factor and block repetition (5 or 10 levels) treated as a random factor. Treating block as a random variable allows the variance associated with spurious transients in the signal (block \times load interactions) to be separated out from the task-related effects of interest (main effect of load). Statistical maps were generated for each slice using the *F* ratio obtained for the main effect of memory load at each voxel. A cross-subject comparison was then performed, in order to identify foci of activity that were reliable across subjects. To do so, the statistical activation maps for each subject were first standardized into Talairach stereotactic coordinates (Talairach and Tournoux, 1988) by rescaling images relative to the positions of the anterior and posterior commissure and the edges of the brain (determined manually on a registered anatomical volume image) using AFNI software (Cox, 1996). The number of subjects showing significant activation at each voxel of the aligned images was computed for the data set after blurring the images with a 5-mm FWHM Gaussian filter (to accommodate between-subject anatomical variability). As a conservative criterion, only regions that showed significant activation in all nine subjects were selected for more detailed analyses. In the reaction time analysis, regions of behaviorally associated activity were identified through voxel-wise correlations of the mean activity with the subject's mean RT (correct responses only) for



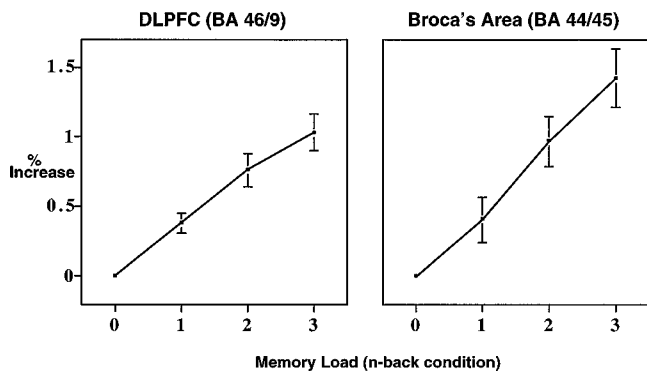


FIG. 3. Plots of the MR signal, expressed as a percentage of difference from the 0-back condition, across the four load conditions. Values are plotted for the MFG region (Talairach coordinates L38,30,22 and R35,22,27) and the IFG region (Talairach coordinates L40,6,26), the only two regions which showed a significant monotonic effect of load. The activity was averaged across the nine subjects; however, each subject showed essentially the same linear relationship to load.

each block. Statistical maps were generated for each slice using the correlation coefficient at each voxel.

Results

Memory-Load Analysis

The cross-subject comparison revealed several regions within PFC that showed significant and reliable main effects of memory load (see Fig. 2b). These were localized to the middle frontal gyrus (MFG; Brodmann's area 46/9) bilaterally, the left inferior frontal gyrus (LIFG; Brodmann's area 44/45), another left inferior site which was more anterior (Brodmann's area 47/10), and the anterior cingulate gyrus (Brodmann's area 32). However, these main effects of load could be produced by a variety of activation patterns across the four task conditions. In this study, we were particularly interested in testing whether any PFC regions showed progressively increasing activity as a function of load. For this reason, we performed a planned contrast on the above four regions that tested whether signal intensity showed a pattern of monotonic increase across the four load conditions (Braver and Sheets, 1993). This contrast revealed that of the four regions showing a main effect of load, only MFG and LIFG showed this monotonic pattern.

The PFC response to changes in WM load within the MFG and LIFG regions was examined in greater detail by plotting the fMRI signal as a function of load across the four task conditions (Fig. 3). This revealed a linear

relationship between the signal and load (for the linear trend, $P < 0.001$ for both regions; quadratic and cubic trends, NS). From this plot it was possible to determine the average change in activity per item of load in these regions. In MFG, fMRI signal intensity increased at a rate of 0.34% per item, while in LIFG the increase was 0.47%. Although effects of this magnitude may be too small to detect reliably through individual comparisons, the parametric design of the study made it possible to determine that the fMRI signal can, in fact, consistently track graded changes in cognitive load.

Reaction Time Analysis

As noted earlier, it has long been recognized that RT is sensitive to manipulations of WM load (Baddeley, 1986; Just and Carpenter, 1992; Sternberg, 1969). Thus, RT can be used as an independent and empirically defined measure of the effect of load that is uniquely derived for each subject. Significant positive correlations between the blockwise RT and fMRI signal were observed in all nine subjects (average $r = 0.49$, $P < 0.01$), but were most consistent only in the same locations within PFC (MFG and LIFG) as were previously shown to linearly track memory load (see Fig. 4). Thus, correlation with behavioral performance provided a convergent source of evidence that these areas of PFC are related to WM function. Such a correlation might have been predicted *a priori*, since RT also exhibited an expected linear relationship to load (0-back, 484 ± 24 ms; 1-back, 539 ± 35 ms; 2-back, 628 ± 45 ms; 3-back, 701 ± 45 ms; linear trend, $P < 0.001$; quadratic and cubic trends, NS). However, a linear regression with memory load only partially accounted for the variance in both RT ($R^2 = 0.36$) and fMRI signal ($R^2 = 0.24$). Thus, the two measures might have represented different, nonoverlapping components of variance and hence be uncorrelated.

Discussion

The findings from this study are consistent with previous data suggesting the involvement of PFC in WM. Memory-related activity was observed bilaterally in a middorsolateral area (MFG) that has been consistently implicated in WM tasks in both humans (Cohen *et al.*, 1994; McCarthy *et al.*, 1994; Petrides *et al.*, 1993) and nonhuman primates (Fuster, 1989; Goldman-Rakic, 1987). Additionally, we observed activity in a left inferior region (LIFG) consistent with Broca's area that is typically activated in tasks requiring verbal rehearsal (Frackowiak, 1994; Paulesu *et al.*, 1993; Pe-

FIG. 2. (a) A midsagittal T1-weighted image, indicating the location and plane of functional scans. (b) The results of the memory-load group analysis, with the regions of activation overlaid on the corresponding stereotactically normalized and averaged structural images. Colored pixels designate areas showing a main effect of memory load that was significant in all nine subjects.

tersen *et al.*, 1989). Both the anterior cingulate and the left anterior area have also been previously observed in WM tasks (Awh *et al.*, 1996; Cohen *et al.*, 1994; Courtney *et al.*, 1996; Jonides *et al.*, 1993; McCarthy *et al.*, 1994), although for the latter region activity was observed in the right rather than the left hemisphere.

Our results go beyond previous studies, however, by defining the cognitive analog of a “dose–response curve” for the relationship between WM load and the activity of circumscribed regions of PFC. The identification of this relationship to load relied on the use of a parametric design that produced a specific response pattern in both the fMRI signal and the behavioral performance. This response pattern was observed in both MFG and LIFG as a progressive, linear increase in signal with each increment of load. Furthermore, the parametric nature of the study made it possible to detect these increases in the fMRI signal in these two regions even though they were relatively small (<0.5% per item of load). In contrast, we did not observe this pattern of progressive signal increase in the anterior cingulate and the left anterior inferior region. Post hoc inspection of these areas revealed that activity actually decreased across the four load conditions. Although we do not have a clear explanation of this activity pattern, it nevertheless suggests that there are multiple brain responses to increasing load.

Finally, our ability to independently identify both the MFG and the LIFG regions through correlations with reaction time provides an important validation of the observed findings, while avoiding many of the theoretical assumptions implicit in the first analysis (i.e., by using observed behavior to index WM function rather than the predefined task manipulation). Specifically, it demonstrates that block-by-block fluctuations in PFC activity closely track fluctuations in observable behavior, suggesting that behavioral performance can be used as a psychologically relevant reference function (cf., Bandettini *et al.*, 1993; De Yoe *et al.*, 1994) by which to isolate activity related to WM. Indeed, this type of analysis may apply well to other neuroimaging studies of higher cognitive processes.

Alternative Explanations

One alternative interpretation of the findings from neuroimaging studies of WM is that the patterns of activity represent the operation of processes associated with error detection and compensation, rather than those involved in the storage and manipulation of information within WM. The fact that subjects typically make more errors in the more demanding WM conditions of these studies makes this argument a plausible one. Adding further support are recent findings from event-related potential studies suggesting changes in frontal activity immediately following error trials (Dehaene *et al.*, 1994; Gehring *et al.*, 1993). This explanation could apply to the current study as well,

because even though subjects were generally very accurate on the task (>90%), error rates increased with memory load ($F(3,24) = 12.4$, $P < 0.001$). However, a reanalysis of the imaging data using only error-free trials (by removing all scans occurring within 7 s before or after an error) yielded virtually identical results in both the areas of activity and the linear relationship to load observed. Thus, it is unlikely that the observed pattern of results was due solely to the activity of a transient frontal error-detection process. However, it must be acknowledged that our reanalysis does not rule out the possibility that tonic error-monitoring processes may be engaged in the task by the greater difficulty imposed by increasing load.

Another alternative interpretation of these findings is that they reflect the operation of more general, and diffuse, processes associated with mental effort, rather than processes specific to WM. However, the circumscribed anatomic localization of the identified regions makes this argument less plausible. Moreover, we tested the effort hypothesis directly in another recently completed experiment, in which WM and effort were independently manipulated (Braver *et al.*, 1996). Dorsolateral PFC activated in memory-demanding conditions relative to control conditions matched for difficulty and, furthermore, did not activate when difficulty was manipulated independently of WM demands (by degrading the stimuli). Thus, activation of this structure seems to reflect processes specific to WM, and not processes associated with more general forms of mental effort.

Intersubject Variability

In this study, our primary focus was on regions within PFC in which activity most reliably tracked changes in memory load. For this reason, we performed an analysis that selected only those voxels showing a significant effect of load in all of the subjects studied. Although this criterion ensures high intersubject as well as intrasubject reliability, it has the effect of detecting only the areas of maximum overlap in the PFC regions activated across subjects. Thus, it might be argued that our results present a misleading picture of the focality of the PFC regions involved in this task, by neglecting: (1) the full extent of the identified regions (i.e., MFG and LIFG) beyond their areas of highest overlap and (2) additional PFC regions that were activated in a subset, but not all of the subjects (and thus fell below our selection criterion). Indeed, the regions of MFG and LIFG identified by our analysis procedure do not fully reflect the substantial amount of intersubject variability in the location and size of the activated regions (e.g., compare Fig. 2b with Fig. 4). Furthermore, when the selection criterion was lowered from the nine-subject threshold, additional regions of activity were revealed. These included bilateral frontal operculum (insular cortex; seven subjects), bilateral

superior frontal gyrus (BA 6 and 8; seven subjects), frontopolar cortex (BA 10; six subjects), and a more posterior region of the anterior cingulate (BA 32; five subjects).

Understanding and quantifying these sources of inter-subject variability are important issues in neuroimaging and are currently areas of active research (Herholz *et al.*, 1996; O'Leary *et al.*, 1996; Wessinger and Gazzaniga, 1996). The high spatial resolution and noninvasiveness of fMRI relative to other methods have brought this issue into sharp focus. With fMRI it is possible to localize areas of activity reliably to specific anatomical structures (e.g., cortical gyri) within individual subjects. As a consequence, both intra- and intersubject variability in location and size of activated regions can be more easily observed. These technological advances are of great benefit to studies specifically focusing on individual differences or the "idiosyncrasies" of functional neural systems, as well as to studies utilizing single-subject and longitudinal designs. These types of efforts are directly analogous to ones in behavioral research, where distinct subfields and specialized methods have developed to study issues surrounding intra- and intersubject variability (e.g., psychophysics and individual differences studies). However, the goal of most behavioral and neuroimaging studies is to functionally characterize the commonalities across a group of subjects, so that inferences can reliably be drawn regarding the characteristics of a population. The current study falls into this latter category, in that our goal was to identify the PFC regions activated in common across the subject group, in order to identify those neural components that are fundamental to WM function in the normal adult population.

In neuroimaging studies with goals such as ours, the issue of intersubject variability poses a different problem, in that no standard method has emerged for reliably comparing activity across subjects. Between-subject differences in both structural anatomy and experimental effect size make it difficult to determine when a specific brain region has been reliably affected by task manipulations. Thus, a number of different approaches have been used across laboratories, and we ourselves have tried different approaches in previous work (Cohen *et al.*, 1994; Schneider *et al.*, 1993). We chose the analysis procedure used in the current study in order to select only those regions that reflected the most statistically reliable tendencies of the data. Unfortunately, with this procedure, there did not appear to be any nonarbitrary way of determining the appropriate level of Type I/Type II balance. Thus, we opted to increase our Type I protection as much as possible in order to be highly confident of the significance in any activated regions. However, our approach may have been too conservative, and may not have had sufficient power to detect subtle but real effects.

A more principled solution to this problem might be

found by comparing the situation with that found in behavioral studies, where similar issues have already been addressed. When population-wide inferences are to be drawn in a behavioral experiment, the analysis procedure treats each subject studied as a random variable. Because of this conceptualization, an investigator will not typically expect to find that every subject in the sample shows the hypothesized effect. Instead, what is sought is statistical confidence that the effect is present as a central tendency of the sample, such that statistical inferences can be drawn regarding the population of interest. Likewise, in neuroimaging studies, the expectation that every subject show an effect (as we had in the current study) is likely to be too demanding and unrealistic, especially when the effect size is small (or variability is high).

However, in behavioral studies, comparing data across subjects is much simpler than in neuroimaging, since the dependent variables of interest are usually well-defined (e.g., accuracy and RT) and easily comparable across subjects. As mentioned above, comparing activity in specific brain regions across subjects is complicated by the variability in both the size and the three-dimensional geometry of individual brains. The most common approach to this problem is to account for this variability by normalizing brains into a standardized stereotactic space and using a smoothing procedure to reduce remaining anatomical differences between subjects. Following this normalization procedure, neuroimaging data can be pooled across subjects in exactly the same fashion as in behavioral studies: treat each subject as a random factor in the design and examine each brain region individually to identify any statistically reliable effects due to experimental manipulations. This cross-subject pooling procedure is already widely used for PET studies, but has been less commonly adopted in those using fMRI. Although the procedure has its own associated problems (neither appropriate normalization techniques nor the optimal stereotactic space have been universally agreed upon; e.g., Dale and Sereno, 1993; Drury *et al.*, 1996; Friston *et al.*, 1991; Woods *et al.*, 1993), it does seem to be the best current method for formally determining the reliability and magnitude of experimental effects across a group of subjects, and for comparing effects between groups. For this reason, we adopted such an approach in Experiment 2, described below.

Spatial Distribution of WM

Our finding that activity in PFC is correlated with WM load provides a strong demonstration of the involvement of this brain region in human WM function. Moreover, these results are consistent with the neurophysiological literature, which has directly demonstrated in nonhuman primates that sustained neuronal

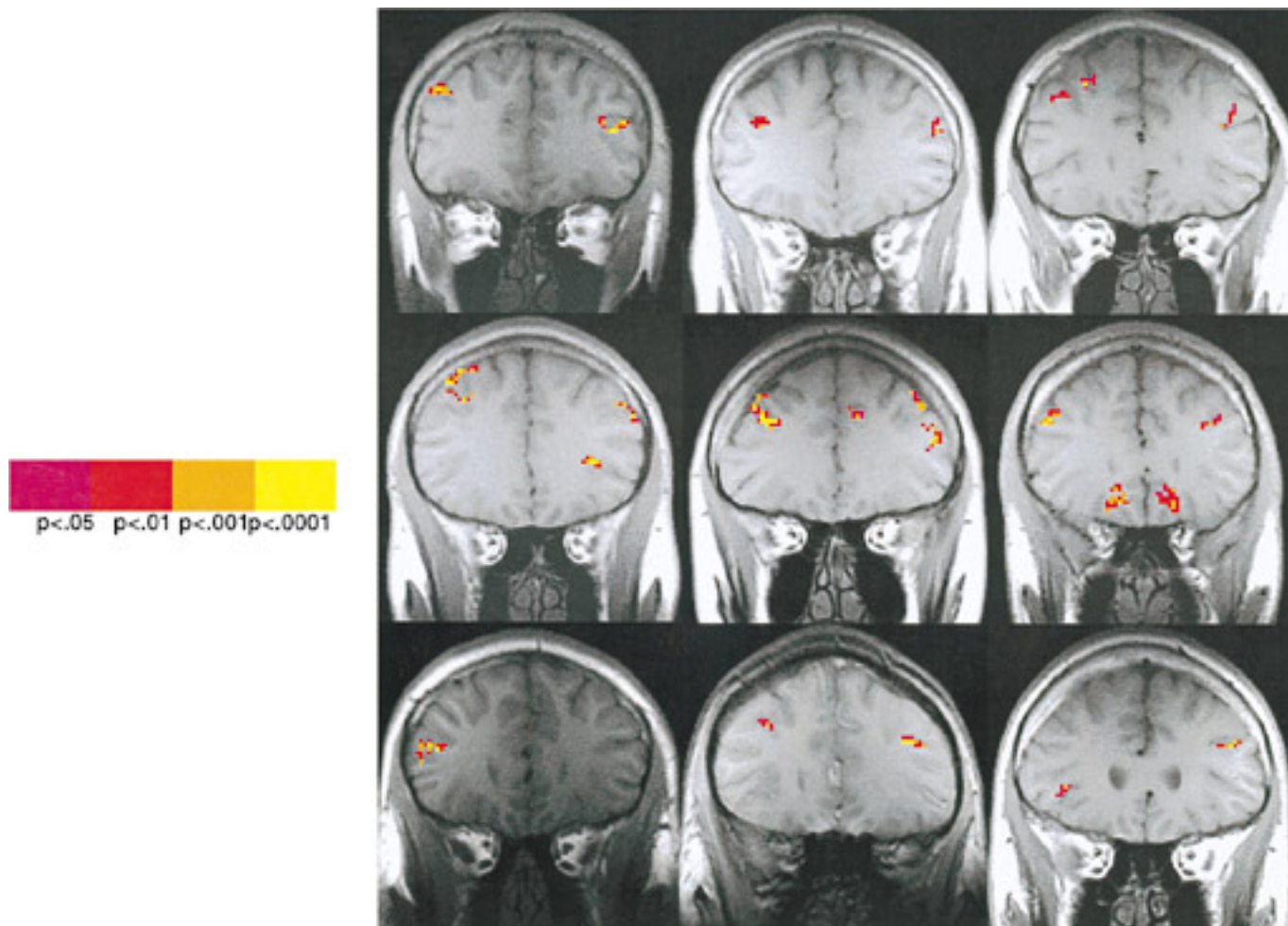


FIG. 4. A coronal slice plane (slice 4, approximately 24 mm anterior to the AC) in each of the nine subjects, showing regions in dorsolateral PFC (MFG) that were correlated with the subject's blockwise mean RT (color scale indicates degree of significance). Correlated activity was also reliably found in IFG (not shown).

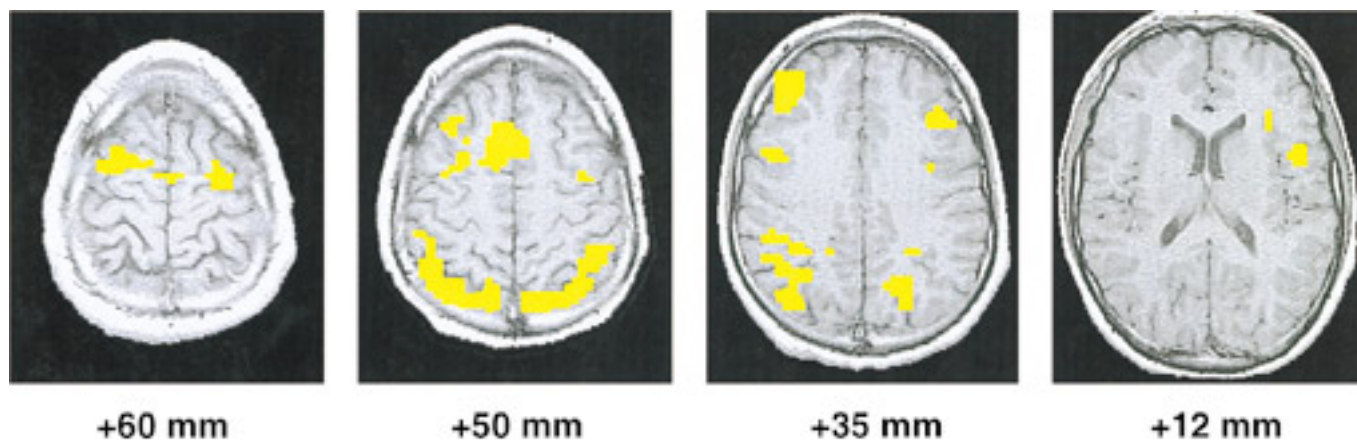


FIG. 5. Axial slices showing the results of Experiment 2, with regions showing significant load sensitivity (as determined through a focused contrast) overlaid on a stereotactically normalized reference brain. Note the replications of activity in bilateral PFC (+35 mm) and Broca's area (+16 mm), as well as the large bilateral region of activated parietal cortex (+50 mm, +35 mm). Tailarach coordinates of all significant regions of activation are given in Table 1.

activity in dorsolateral PFC is crucial for the short-term maintenance of task-relevant information (Fuster, 1989; Goldman-Rakic, 1987). However, by limiting our focus to PFC, the current study provides no information about whether other brain regions also show load sensitivity. A number of lines of evidence suggest that, in fact, this type of response might also be found in other cortical and subcortical structures. Neurophysiological studies have shown sustained neural activity in premotor, posterior parietal, and inferior temporal cortex as well as in subcortical structures, such as the basal ganglia and thalamus (Fuster and Alexander, 1973; Fuster and Jervey, 1981; Gnadt and Anderson, 1988; Schultz and Romo, 1988; Weinrich and Wise, 1982). Neuropsychological and neuroimaging data also lend support to the idea that WM is subserved by multiple neural structures. WM impairments have been observed following damage to both parietal cortex and the basal ganglia (Sagar *et al.*, 1988; Vallar and Shallice, 1990), and whole-brain neuroimaging studies typically activate a constellation of areas during performance of WM tasks (Courtney *et al.*, 1996; Smith *et al.*, 1996; Swartz *et al.*, 1995). If information is maintained in a widely distributed manner, or through the bidirectional flow of activity among these various structures, then one might expect similar patterns of load sensitivity among them.

Cognitive theories of WM provide an additional reason to predict a brain-wide distribution of activated areas during performance of the task we have studied. The dominant view of WM in cognitive psychology is of a multicomponent system involving two types of processes: executive, which are subserved by a central controller, and maintenance, which are subserved by modality-specific slave buffers (Baddeley, 1986). Accordingly, experimental tasks designed to engage WM often involve the manipulation of as well as short-term storage of information. The sequential letter task used in the current study is a good example of this. In addition to maintaining the identity of each stimulus, it is also necessary to assign the stimulus a specific temporal order (e.g., remember that B was the letter 2-back in this trial, while C was the letter 1-back), and update these assignments on each trial (e.g., C, which was the letter 1-back in the previous trial is now the letter 2-back). These functions are also likely to be load-sensitive, since the complexity and number of assignments increases with memory load. Neural structures subserving these and other executive processes engaged by the task should show activity profiles that reflect this involvement. In the following study, we examined whether additional brain regions would show a similar pattern of load sensitivity to the ones identified in the first experiment.

EXPERIMENT 2

The first goal of this experiment was to replicate the findings of Experiment 1 in a new group of subjects and following modifications to the experimental protocol. Although the same behavioral paradigm was used, a number of changes were made to specific task parameters, scanner acquisition, and analysis procedures. Most importantly, we used the pooling procedure described above to combine data across subjects. A second goal of the experiment was to use whole-brain imaging techniques to identify brain regions outside of PFC that show sensitivity to memory load and to gain a broader view of the functional circuit underlying WM function.

Methods

Subjects

Informed consent was obtained from eight neurologically normal right-handed subjects (six males, two females; 18–25 years of age). The same pretesting procedures were conducted as in Experiment 1.

Cognitive Tasks

Subjects performed the sequential letter task described above with the same four increments of WM load (zero to three items). However, two changes were made to task parameters: (1) Block duration was shortened to 57 s (19 stimuli) and (2) only seven repetitions of the four conditions were run (along with seven repetitions of another four conditions that were the focus of a different study).

MRI Scanning Procedures

Images were acquired with a conventional 1.5-T GE Signa whole-body scanner, using a multislice spiral-scanning procedure similar to the one described for Experiment 1. A number of changes were made to the scanning protocol to enable whole-brain acquisition. Functional images were acquired using a 4-interleave spiral-scan pulse sequence (Noll *et al.*, 1995) with a TR of 640 ms, a gradient echo TE of 35 ms, a flip angle of 40°, and a field of view of 24 cm. A quadrature head coil was used for homogeneous signal-to-noise ratio across the brain. Scans were composed of isotropic voxels (3.75 mm³) and acquired at 27 contiguous locations, perpendicular to the AC–PC line, thus covering over 10 cm of the superior–inferior extent of the brain. Slice locations were prescribed according to a procedure designed to maximize reproducibility across subjects (Noll *et al.*, 1996). Four scans were obtained from all 27 slice locations during each task block. Structural images were obtained at these locations prior to functional scanning, using a standard T1-weighted sequence.

Image Analysis Procedures

Prior to analysis, images for each subject were normalized to a common mean and movement-corrected using an automated registration algorithm (Woods *et al.*, 1992). Images were then coregistered and pooled across subjects using a procedure similar to one standardly used in PET studies (Wiseman *et al.*, 1996; Woods *et al.*, 1993). This was done by registering the structural images for each subject to a common reference brain using a 12-parameter version of the registration algorithm. The set of parameters derived from this procedure were used to coregister the functional scans, which were then smoothed with an 8-mm FWHM 3D Gaussian filter to accommodate between-subject differences in anatomy. A focused contrast was used to directly identify pixels showing a monotonic increase in activity as a function of load. Focused contrasts are generally considered more powerful statistical tests than simple ANOVAs when a specific theoretical hypothesis is being examined (Rosenthal and Rosnow, 1985). Statistical maps of activity were thresholded for significance using a contiguity threshold of eight voxels and per-pixel false-positive rate of 0.005, ensuring an effective pixel-wise α protection of 0.005. Anatomic localization was determined by overlaying the activation map onto the reference structural image and transforming the data into Talairach coordinates (Talairach and Tournoux, 1988) using AFNI software (Cox, 1996).

Results

Replications

Our findings replicated the results of the first study, with activation present in both bilateral MFG and LIFG (see Fig. 5 and Table 1). The replication of activity

in these areas was noteworthy, given the changes made to task parameters, image acquisition, and analysis procedures. The use of a focused contrast ensured that the areas in PFC showed the same monotonic load sensitivity as was exhibited previously. As shown in Table 1, the response function in MFG was similar in slope (0.27% increase in signal per item of load) to that found in the first experiment. In contrast, the LIFG region showed a shallower slope, increasing at a rate of 0.08% per item of load (compared to 0.47% in Experiment 1). The response profile in both regions was again fit well by a linear function (in both regions $P < 0.001$ for the linear trend; quadratic and cubic trends, NS).

Other Regions of Activation

The analysis also revealed load-sensitive activity in frontal areas not observed in the first experiment: the right homologue of the LIFG region (BA 44), the left frontal operculum (insular cortex), and a number of motor, premotor, and supplementary motor regions (BAs 4 and 6). Nonfrontal activity was also found, in bilateral posterior parietal cortex (BA 40/7) and the left caudate nucleus of the basal ganglia (see Fig. 5 and Table 1). All of these regions have been implicated in the distributed circuitry underlying WM, and most have been previously identified in PET studies using a simple subtractive version of this paradigm (Awh *et al.*, 1996; Smith *et al.*, 1996).

Discussion

The use of whole-brain imaging and cross-subject pooling in this experiment allowed us to replicate our original findings and demonstrate their robustness to acquisition protocols and analysis procedures. More-

TABLE 1

Brain Areas Showing Monotonic Increases in Activity as a Function of Memory Load

Region of interest	Brodmann area	x^a	y^a	z^a	Volume (mm ³)	1-back increase ^b (SEM)	2-back increase ^b (SEM)	3-back increase ^b (SEM)	Z score
R superior frontal gyrus	8/6	13	8	54	6,611	0.12 (0.09)	0.33 (0.04)	0.55 (0.07)	4.03
L middle frontal gyrus	46/9	-42	23	39	1,527	0.12 (0.15)	0.44 (0.05)	0.81 (0.09)	4.03
R middle frontal gyrus	46/9	37	37	33	4,273	0.18 (0.11)	0.48 (0.08)	0.81 (0.13)	5.24
L inferior frontal gyrus	44/6	-47	6	15	468	0.08 (0.05)	0.17 (0.05)	0.24 (0.04)	3.76
R inferior frontal gyrus	44	43	6	31	583	0.17 (0.03)	0.26 (0.05)	0.31 (0.06)	3.05
L frontal operculum	Insula	-32	20	8	520	0.09 (0.05)	0.15 (0.04)	0.30 (0.04)	3.43
L precentral gyrus	6	-39	-1	29	241	0.10 (0.05)	0.25 (0.03)	0.29 (0.06)	3.19
L precentral gyrus	6	-47	-2	43	350	0.05 (0.11)	0.45 (0.05)	0.50 (0.08)	3.19
L precentral gyrus	4	-30	-6	57	1,350	0.09 (0.11)	0.42 (0.03)	0.57 (0.10)	3.27
L inf/sup parietal lobule	40/7	-26	-60	45	8,737	0.17 (0.20)	0.53 (0.09)	0.75 (0.08)	4.22
R inf/sup parietal lobule	40/7	32	-56	43	12,643	0.15 (0.12)	0.52 (0.09)	0.78 (0.10)	4.29
R caudate nucleus	Basal ganglia	18	1	23	417	0.10 (0.06)	0.18 (0.05)	0.24 (0.04)	3.25

^a x , y , z are coordinates relative to standard stereotactic space.

^b Increase expressed as percentage of change in signal relative to 0-back condition.

over, these methods enabled the detection of additional regions of load-sensitive activity both within PFC and in other cortical and subcortical areas. Of these additional regions of activity, the parietal cortex was especially notable. The volume of activity in this region was the largest of any of the areas identified, and covered most of the superior and inferior lobules (BA 40/7). In magnitude of effect, both PFC and parietal cortex displayed significantly stronger load-response functions than any other regions ($P < 0.001$). In general, however, the slopes of the load-response functions in the activated areas were shallower in this experiment than in the previous one. It is likely that this decrease is due to the smoothing filter applied to the data prior to analysis. The smoothing reduces variability across the brain, but also attenuates any regional peaks in activity. Thus, the magnitude of the response decreases, but since variability is also decreased the effect is still statistically significant.

Laterality

We found no definitive evidence of lateralization in activity in this experiment. Although the total activated volume was greater in the right hemisphere than in the left (24,527 mm³ vs 13,193 mm³), it cannot be determined whether this reflects greater right hemisphere engagement or a difference which is not functional in nature (e.g., unequal anatomical variability across the hemispheres). Moreover, in a number of key regions, such as middle frontal gyrus, inferior frontal gyrus, and posterior parietal cortex, we observed bilateral activation and no evidence of hemisphere \times load interactions in activity ($P > 0.1$ for all regions). These findings are in contrast with two previous studies of verbal working memory, including one using a similar paradigm, in which subtle, but reliable left lateralization was found (Smith *et al.*, 1996).

There are a number of possible reasons for this failure to replicate a laterality effect. First, when lateralization is present, it is usually a subtle effect. Thus, the differences between the findings of the current study and that of Smith *et al.* (1996) could reflect variability in subject populations. Given that both studies only included eight subjects, this explanation is a plausible one. Second, our study differed from previous ones in the total time spent performing the task. In the 3-back task used in Smith *et al.* (1996), subjects spent a total time of approximately 8 min performing the letter conditions. In our "*n*-back" task, subjects spent a total time of approximately 28 min performing the letter conditions. Smith *et al.* (1996) suggested that right hemisphere activation during this task might reflect the functional recruitment of contralateral mechanisms to assist in task performance under highly demanding conditions. This explanation, if correct, might account for the current findings, since greater

right hemisphere activity would be expected as the time spent performing the task increases. Finally, the parametric nature of the *n*-back task used here might lead to increased sensitivity in detecting brain regions subserving the WM functions required by the task. As discussed above, parametric designs are considered to have both greater sensitivity and selectivity for detecting experimentally induced changes in a process of interest. Thus, our task design may have allowed more sensitive detection of an intrinsically bilateral neural system underlying WM.

Functional Interpretations

As mentioned above, all of the additional regions identified in this experiment have previously been implicated in WM function. Parietal activation has been observed in numerous WM studies, and has been interpreted as a buffer for modality-specific information (Paulesu, 1993). The basal ganglia form strong reciprocal connections with PFC (Alexander *et al.*, 1986), and these frontostriatal loops may be a key component of WM circuitry. The left-hemisphere motor areas (SMA, premotor, and primary motor cortex) have been identified in a 2-back version of this paradigm (Awh *et al.*, 1996). These regions, in cooperation with Broca's area, might mediate the subvocal articulatory processes that are thought to subserve verbal rehearsal. The load sensitivity observed in these areas is consistent with the increase in number of rehearsal items associated with each increase in load. Alternatively, in a subset of the motor areas, especially primary motor cortex, the activity may reflect changes in motor readiness. Since higher loads are likely to demand more processing time, this leaves less time for response preparation. The system may adapt to this by maintaining a higher level of motor readiness, producing a tonic increase in activity within primary motor areas. The left operculum was also activated in the Awh *et al.* study. Interestingly, this region has also been observed in tasks requiring retrieval of verbal information from long-term memory (Buckner and Petersen, 1996). Both situations require a comparison of internally stored representations of stimuli with externally presented ones. Thus, it is possible that the operculum may be involved in matching or recognition operations associated with these sorts of comparisons. These matching operations may become more difficult (or take longer time) as the size of the memory set increases (e.g., Sternberg, 1966).

GENERAL DISCUSSION

Active Maintenance

Our observations of load-sensitive activity in dorsolateral PFC, parietal cortex, and basal ganglia are consis-

tent with the neurophysiological literature in nonhuman primates. Single-cell recordings in these regions have observed sustained neural activity during the delay periods of short-term memory tasks, and this pattern of activity has been typically interpreted as the neural mechanism for the active maintenance of information (Goldman-Rakic, 1987). Consequently, the most obvious interpretation of our findings is that the observed regions of activity reflect the operation of maintenance processes associated with WM. The load manipulations in the task directly impact both the number of items maintained (zero to three items) and the duration of maintenance (up to 9 s for 3-back stimuli). However, this confounding of delay and load in our paradigm makes it difficult to clearly interpret whether the observed activity selectively reflects active maintenance rather than other WM-related processes. As mentioned above, there are a number of nonmaintenance processes operating in this task that are also likely to be affected by load manipulations. These include matching/comparison operations and executive processes, such as assignment of sequential order and memory updating. Thus, the question of whether the load-sensitive neural structures identified in this task are associated with maintenance vs executive or other WM-related processes cannot be answered definitively from this study alone; additional work is needed to functionally decompose the relevant task components.

A potential approach to selectively engaging brain regions subserving active maintenance is to hold WM load constant and vary only the delay over which information must be maintained. We have taken this approach in a recently completed study, and found that only dorsolateral PFC, Broca's area, and parietal cortex showed increases in activity associated with delay (Braver *et al.*, 1996). A second approach is to examine the time course of activity in the various regions during task performance. This temporal information should help to dissociate regions subserving maintenance vs executive processes, insofar as the former should exhibit sustained activity over the trial duration while the latter should be stimulus-locked and transient. fMRI can provide the temporal resolution necessary to obtain such time course information, given an adequate interstimulus interval in which to accommodate the phase lag of the hemodynamic response and to allow it to revert to baseline (Savoy *et al.*, 1995; Vazquez and Noll, 1996). We have also begun to utilize this approach and have found that we can differentiate the response profiles of the various regions activated in this task (Cohen *et al.*, 1996). In particular, we have observed that activity in PFC is sustained throughout the retention interval. This finding is particularly significant, since it has been proposed that PFC houses the executive control functions of WM, while active maintenance is carried out by other brain regions (Gathercole, 1994).

Shape of Load-Response Functions

In both of the experiments discussed here, we were able to plot the activity of specific brain regions in response to parametric changes in WM load. Although our analysis procedure was designed to select only regions showing a monotonically increasing response to load, it did not specify the particular form of the response. There are a number of different types of monotonic functions that could have been observed, including nonlinear functions such as exponentially accelerating, exponentially decelerating, or sigmoidal. Moreover, each of these types could be significant for the study of WM. For example, an exponentially decelerating function could indicate the saturation/plateauing of WM mechanisms above some level of load, while a sigmoid or step function might indicate the presence/emergence of qualitatively distinct WM mechanisms at different levels of load. In contrast, a linear function might be interpreted as indicating a single neural mechanism that additively increases by a fixed amount with each additional item of load. Likewise, the slope of such a function might specify the level of neural activation needed to process and/or maintain each item in a particular brain region. There is a precedent for these sorts of interpretations from behavioral studies, which have attributed functional significance to linear RT functions (e.g., Shepard and Metzler, 1971; Sternberg, 1966). Thus, it is of potential theoretical interest to determine the specific load-response functions found in the current data.

As we have mentioned above, a linear function seemed to best fit the PFC response and most of the other identified brain regions as well. This characterization was determined through statistical tests of linear trend as well as through visual inspection. At the same time, we believe that it would be premature to draw theoretical inferences from this finding for several reasons. First, the test of linear trend does not differentiate between linear and nonlinear monotonic functions; it is only useful for rejecting the null hypothesis that the best fitting line through the data has zero slope (Braver and Sheets, 1993). Statistical tests that could differentiate between monotonic functions would require a much larger sample and/or a wider range of load intervals to have sufficient power. Second, in other, more recent studies of this task, we have observed a number of regions showing load-response functions which appeared more step-like than linear (Cohen *et al.*, 1996; Jonides *et al.*, 1996). This suggests that the shape of these functions may be variable and/or sensitive to slight differences in experimental factors. Finally, even if the response functions could be reliably determined to be linear, it is not yet clear that theoretical inferences could be drawn without convergent data from other sources. For example, the apparent linearity of the load-response function could be an artifact of the

way neural activity is detected with fMRI methods. Since it is known that activity changes are convolved with a nonlinear hemodynamic response function (Kwong *et al.*, 1992; Vazquez and Noll, 1996), it is possible that this convolution may act to blunt or otherwise distort subtle features of the actual response. Taken together, it seems clear that neuroimaging response functions require additional study before interpretations based on their specific form are warranted.

However, even with these caveats in mind, our finding of monotonic load sensitivity in PFC and other brain areas provides important new information regarding the involvement of these regions in WM. Further, both the parametric design and the correlations with behavioral performance ameliorate many of the methodological concerns which surround simple subtractive designs. Finally, these results highlight the utility of parametric cognitive neuroimaging studies, by demonstrating that it is possible to detect slight, but reliable changes in the activity of circumscribed brain regions in response to subtle task manipulations (e.g., the 2-back vs 3-back conditions).

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