

# Load-Dependent Roles of Frontal Brain Regions in the Maintenance of Working Memory

Bart Rypma,\* Vivek Prabhakaran,† John E. Desmond,\* Gary H. Glover,‡ and John D. E. Gabrieli\*†

\*Department of Psychology, †Department of Radiology, and ‡Program in Neuroscience, Stanford University

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**Brain imaging studies have suggested a critical role for prefrontal cortex in working memory (WM) tasks that require both maintenance and manipulation of information over time in delayed-response WM tasks. In the present study, functional magnetic resonance imaging (fMRI) was used to examine whether prefrontal areas are activated when only maintenance is required in a delayed-response WM task, without the overt requirement to manipulate the stored information. In two scans, six subjects performed WM tasks in which, on each trial, they (1) encoded 1, 3, or 6 to-be-remembered letters, (2) maintained these letters across a 5-second unfilled delay, and (3) determined whether a single probe letter was or was not part of the memory set. Activation of left caudal inferior frontal gyrus was observed, relative to the 1-letter task, when subjects were required to maintain 3 letters in WM. When subjects were required to maintain 6 letters in WM, additional prefrontal areas, most notably middle and superior frontal gyri, were activated bilaterally. Thus, increasing the amount of to-be-maintained information, without any overt manipulation requirement, resulted in the recruitment of wide-spread frontal-lobe regions. Inferior frontal gyrus activation was left-hemisphere dominant in both the 3- and 6-letter conditions, suggesting that such activation reflected material-specific verbal processes. Activation in middle and superior frontal gyri appeared only in the 6-letter condition and was right-hemisphere dominant, suggesting that such activation reflected material-independent executive processes.** © 1999 Academic Press

Working memory (WM) refers to cognitive functions that allow individuals to temporarily maintain and manipulate information in the service of higher order tasks such as reading, planning, and problem-solving. Baddeley (e.g., 1986) proposed that WM could be divided into separate components, including “slave system” buffers for the temporary retention of visuospatial and phonological information, and a supervisory attentional system (Norman and Shallice, 1980), or “central executive,” that controls allocation of attention and coordinates information held in the slave system buffers.

Studies with infrahuman primates and humans have attempted to localize the neural mediators of these WM components. Anatomical tracing and metabolic imaging studies with infrahuman primates show that prefrontal cortex mediates WM (e.g., Kubota and Niki, 1971; Fuster and Alexander, 1971; Goldman-Rakic and Friedman, 1991; Funahashi *et al.*, 1989). Single cell recording of infrahuman primate brains have shown persistent activity in both dorsolateral prefrontal cortex cells and posterior parietal cortex cells during the delay period of a delayed-match-to-sample task (Goldman-Rakic and Friedman, 1991). This persistent activity provides a plausible cellular mechanism for maintenance of information in WM.

Neuroimaging studies with humans have also provided important clues about which brain regions mediate components of WM. Studies of slave-system WM components have mainly relied on tasks that compare maintenance of information with or without a delay while holding memory load constant. Studies of WM executive components, in contrast, have relied on more complex tasks that require manipulation of retained information and varying memory loads. This leaves unanswered the basic question of whether or not executive processes are invoked when maintenance processes alone, without manipulation, are taxed by increasing memory load.

A number of PET studies have identified the slave-system components of WM with caudal inferior frontal regions. Brief retention of phonological information resulted in activation associated with subvocal rehearsal in caudal portions of left inferior frontal cortex identified as Brodmann’s Area (BA) 44 (Paulesu *et al.*, 1993). Activation in right hemisphere regions of parietal and prefrontal cortex has been demonstrated in spatial WM tasks (e.g., Jonides *et al.*, 1993). Thus, the selective activation of right or left hemisphere regions depending on the verbal or spatial nature of the task appears to reflect lateralized slave-systems for the retention of phonological and spatial information.

Imaging studies that employ more difficult WM tasks have found results that differ from those of simple retention studies in two important ways. First, prefrontal

tal activations often occur bilaterally, independent of the type of material used in the task. Second, the activations often occur in regions dorsal to those found in studies of simple retention (e.g., BAs 9 and 46). Petrides *et al.* (1993a, b) compared cortical activation while subjects performed self-ordered or externally ordered tasks to that while they carried out control tasks. The requirement to order performance, rather than follow external cues, resulted in bilateral dorsolateral prefrontal cortex (BAs 9 and 46) activation.

Another study compared activation that occurs when performing a single task to that obtained when performing those two tasks concurrently (D'Esposito *et al.*, 1995). Activation occurred bilaterally in prefrontal cortex (BAs 9 and 46) when the two tasks were performed concurrently, but not during performance of either task individually. Based on these data, D'Esposito *et al.* argued that dorsolateral prefrontal cortex (BAs 9 and 46) mediates WM central executive functions, the allocation of attentional resources to different task components, and coordination of slave-system processes.

Prefrontal cortical activation occurs not only when two tasks must be performed at once, but also when WM demands increase within a single task. In one study, for instance, subjects performed a "sequential letter memory task" (the *n*-back task), in which they viewed single letters that appeared one-by-one on a computer screen (Cohen *et al.*, 1997). Memory load was parametrically varied by requiring subjects to press a button (1) when the letter X appeared (0-Back condition) or (2) when a letter appeared that was the same as one that appeared a prespecified number of trials earlier (1-, 2-, or 3-Back conditions). Two different patterns of activation occurred in different regions. Transient, load-dependent signal changes occurred in inferior frontal regions, associated with rehearsal processes (e.g., Broca's Area, BA 44) in earlier studies (e.g., Awh *et al.*, 1996; Paulesu *et al.*, 1993). Sustained load-dependent signal change occurred in right-hemisphere regions that have been associated with central executive functions, such as right frontal regions (BAs 9, 46). Cohen *et al.* interpreted these results as suggesting that updating and temporal tagging operations occurred in posterior frontal regions while anterior frontal regions mediated maintenance of information.

The results of the Cohen *et al.* (1997) study suggest that the specific roles of different frontal areas mediating executive and maintenance processes may be more complex than previously thought. Like the D'Esposito *et al.* dual-task study and Petrides *et al.*'s self-ordered tasks, however, the *n*-back task requires a number of distinct operations to be performed simultaneously (e.g., maintaining the contents of WM, updating the contents, temporal tagging of contents). Thus, manipulation demands increase concurrently with maintenance demands. It is unknown, therefore, how frontal

regions would be activated in a task that requires temporary maintenance of differing amounts of information without overt demands for multiple WM operations.

In this study, we asked how an increase in memory load alone (without dual-task or manipulation requirements) would activate prefrontal cortex during a delayed-response WM task. Across different studies, it appears that less demanding tasks (e.g., Awh *et al.*, 1996; Paulesu *et al.*, 1993; Jonides *et al.*, 1993) tend to invoke more ventral frontal regions and the laterality of activation in these tasks appears to be largely determined by the nature of the material (i.e., verbal material is left-lateralized and spatial material is right-lateralized). More demanding tasks, on the other hand, tend to invoke more dorsal and bilateral activation that is material-independent in nature (e.g., D'Esposito *et al.*, 1995; Cohen *et al.*, 1997; Petrides *et al.*, 1993a, b). These observations are speculative, however, because they involve comparisons of different studies, different tasks, and/or different groups of subjects.

In the present study, we systematically increased memory maintenance requirements within one task, within the same subjects, and without the additional overt operations that are required in dual-task and *n*-back studies. We had subjects perform a verbal short-term memory task during fMRI scanning. Subjects were required to maintain 1, 3, or 6 letters in WM for 5 s. The question of interest was whether an increase in WM load would activate the prefrontal regions typically associated with tasks that require manipulation of information held in WM.

## METHOD

### *Subjects*

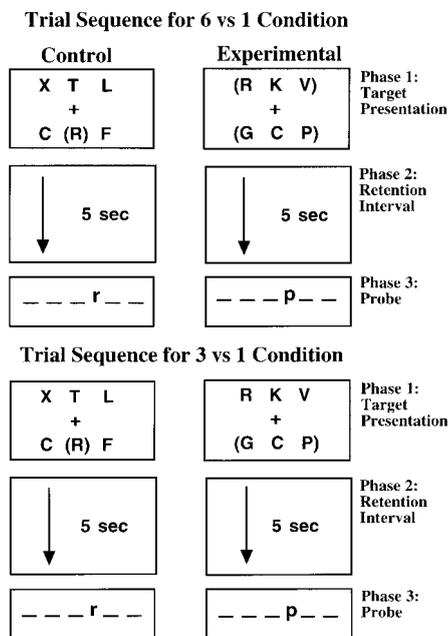
Six right-handed subjects (4 females, 2 males; mean age = 25.3) were recruited from the Stanford University Psychology Department. All subjects were pretrained to assure familiarity with the task prior to scanning.

### *Cognitive Task*

Each trial of the Sternberg task was composed of three phases (See Fig. 1). Phase 1 (1500 ms) was a Target presentation phase in which subjects viewed 6 upper-case consonant letters on the computer screen. Letters to be remembered (1, 3, or 6) were enclosed in parentheses. Phase 2 (5000 ms) was an unfilled retention interval in which the subjects viewed a blank screen. Phase 3 (2000 ms) was a probe phase in which a single lower case letter appeared among a series of dashes. In the scanner, subjects pressed a response button that triggered an optical switch if the probe letter matched one of the to-be-remembered letters.

### *MRI Scanning Procedure*

Imaging was performed with a 1.5T whole-body MRI scanner (General Electric Medical Systems Signa, Rev.



**FIG. 1.** Trial sequence and examples of stimuli in the 3 vs 1 and 6 vs 1 conditions.

5.6). For functional imaging, a prototype whole-head coil was used for signal amplification. Head movement was minimized using a bite-bar formed with each subject's dental impression. A T2\*-sensitive gradient-echo spiral pulse sequence (Meyer *et al.*, 1992), which is relatively insensitive to cardiac pulsatility motion artifacts (Noll *et al.*, 1995), was used for functional imaging with parameters of TR = 720 ms, TE = 40 ms, and flip angle = 65°. Four interleaves were obtained for each image, with a total acquisition time (sampling interval) of 2.88 s per image and an inplane resolution of 2.35 mm × 2.35 mm. T1-weighted, flow-compensated, spin-warp anatomy images (TR = 500 ms, minimum TE) were acquired for all sections that received functional scanning. Pixels found to be significantly activated during the functional scan were overlaid on these structural images. Eight 6-mm-thick slices were acquired in the horizontal plane of the Talairach and Tournoux (1988) atlas starting from 7.5 mm below the anterior commissure (AC)–posterior commissure (PC) plane, with a 1-mm interslice interval. Stimuli were generated from a computer and back-projected onto a screen located above the subject's neck via a magnet-compatible projector. Visual images were viewed from a mirror mounted above the subject's head. The sequence of the presentations of the stimuli were synchronized with the imaging sequence of the scanner.

#### Data Analysis

Image analysis was performed off-line by transferring the raw data to a Sun SparcStation. A gridding algorithm was employed to resample the raw data into

a cartesian matrix prior to processing with 2d FFT. Once individual images were reconstructed, the time series of each pixel was obtained and correlation methods that take advantage of periodically oscillating paradigms were used to analyze functional activation (Friston *et al.*, 1994). As described by Friston *et al.* (1994), the reference function was computed by convolving a square-wave at the task frequency with a data-derived estimate of the hemodynamic response function. The frequency of the square-wave was computed from the number of task cycles divided by the total time of the experiment. For the experiments, one task cycle consisted of a control block and an experimental block each of equal duration. There were six cycles presented over a 465-s scan-time period (frequency = 0.0129 Hz).

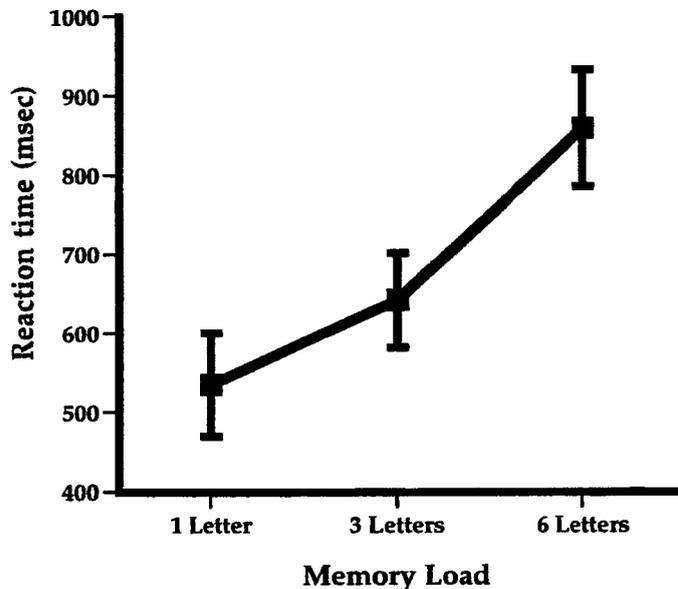
To construct functional activation maps, the data were analyzed using a cross-correlation method. Pixels that satisfied the criterion of  $z \geq 1.96$  (representing a significance of  $P < 0.025$ , one-tailed) were selected. Raw functional images were motion-corrected and then spatially filtered using a Gaussian filter of 8-mm full-width at half-maximum. This map was then processed with a median filter with a spatial extent of 2 pixels to emphasize spatially coherent patterns of activation. The filter was used on the assumption that pixels with spuriously high  $z$ -values (i.e., false positives due to type I errors) were less likely to occur in clusters than pixels with genuinely high  $z$  values, and thus clusters of pixels with high  $z$  values were more likely to reflect an active region. The resulting map was overlaid on a T1-weighted structural image.

To obtain composite maps of activation over all subjects, average functional activation maps were created by transforming each section from each subject to a corresponding standardized horizontal section (Talairach and Tournoux, 1988) at the same distance above and below the AC/PC plane (Desmond *et al.*, 1995). This transformation was done individually for all horizontal sections. Following transformation, the average  $z$ -value for each pixel in a section was computed across subjects and pixels that reached a statistical threshold corresponding to  $P < 0.005$  or lower were displayed on each map. Difference maps between the 3 vs 1 and 6 vs 1 conditions were created by computing the difference between  $z$  values for each pixel in corresponding slices for each subject. The average  $z$ -difference was computed across subjects and pixels whose  $z$ -difference exceeded a  $z$ -criterion corresponding to  $P < 0.005$  or lower were displayed on each map.

## RESULTS

#### Behavioral Results

Subjects responded more slowly with increasing WM loads:  $F(2, 10) = 19.1$ ,  $P < .001$ ,  $MSe = 8557.5$  (see Fig.



**FIG. 2.** Behavioral results of the 1-, 3-, and 6-letter memory load conditions.

2). Bonferroni-corrected *t* tests (Holm, 1979) indicated that response times in the 6-letter load condition were significantly slower than response times in the 3-letter and 1-letter load conditions,  $t(5) = 3.4$ ,  $P < 0.03$ , and  $t(5) = 6.7$ ,  $P < 0.02$ , respectively, but that response times in the 3-letter and 1-letter load conditions were not significantly different,  $t(5) = 2.3$ ,  $P < 0.07$ . Subjects were uniformly accurate in the 1- and 3-letter load conditions ( $M = 100\%$  in both conditions). Accuracy was only slightly worse in the 6-letter load condition (89.7%), but the differences across the 3 conditions were not significant,  $F(2, 10) = 2.7$ ,  $MSe = 1.0$ ,  $P > 0.1$ .

### fMRI Results

The 3-letter vs 1-letter scan (referred to as the 3-1 condition from now on) yielded a number of activations which were greater for the 3-letter than the 1-letter task (Fig. 3, middle; Table 1). The major focus of activity was in left inferior frontal/precentral gyrus (BAs 44/6). Minor foci of activity were also observed in the area of the left middle temporal gyrus (BA 21) and right posterior cingulate gyrus (BA 23) and right post-central (BA 1, 2, 3) and parietal gyri (BA 40).

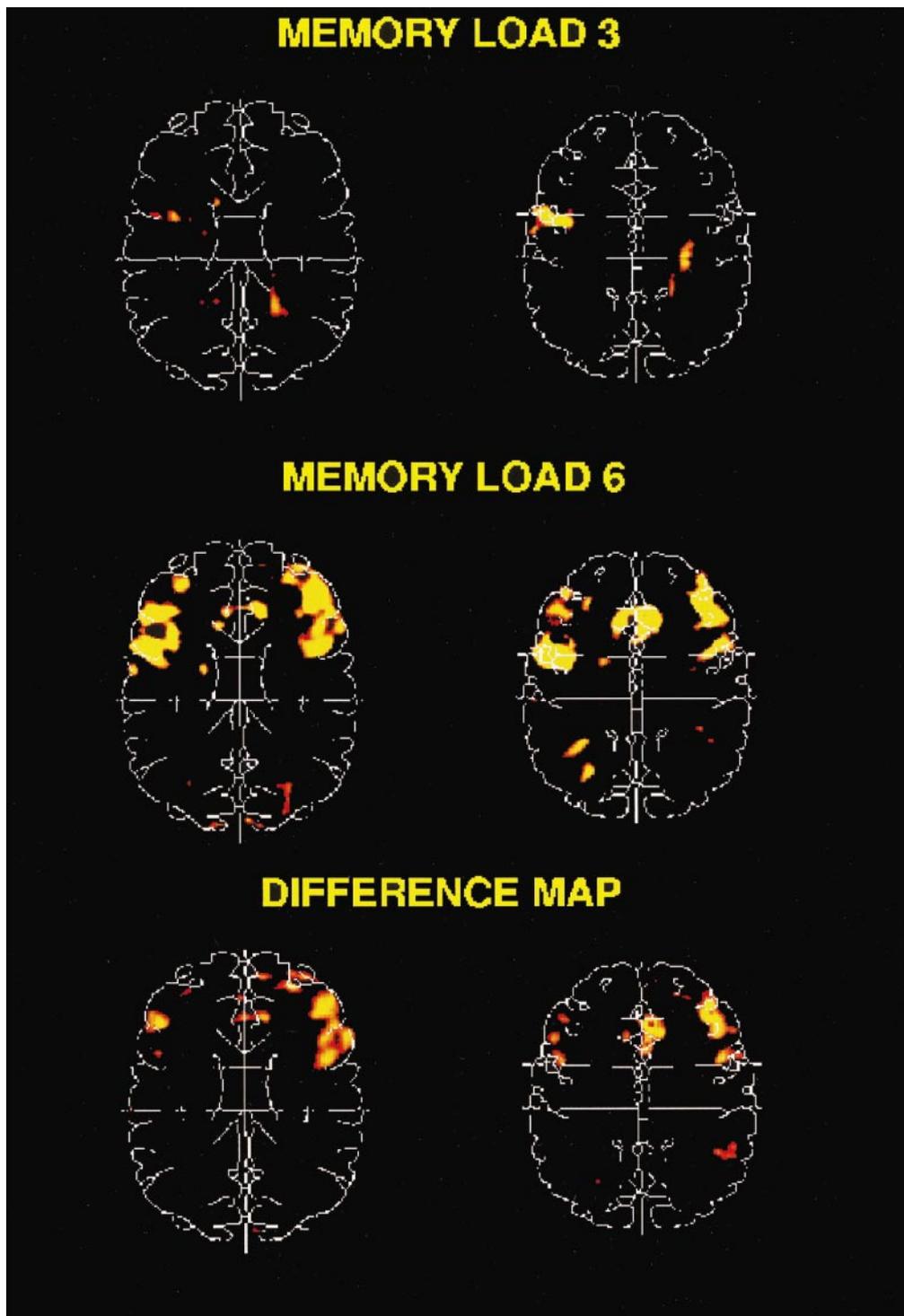
The 6-letter vs 1-letter scan (referred to as the 6-1 condition from now on) yielded a number of activations greater for the 6-letter than the 1-letter task (Fig. 3, top; Table 1). Major foci of activity occurred bilaterally in inferior frontal gyrus (BAs 44, 45) and precentral gyrus (BA 6), more in spatial extent on the left than on the right. Middle frontal gyrus activity was also observed bilaterally (BAs 8, 9, and 46) but was greater (that is, *z*-values were greater), and extended more superiorly, on the right than on the left. Activation also occurred in

bilateral superior frontal regions (BA 10) and was greater in dorsal-ventral extent on the right than on the left. Other regions of major activity in this scan were anterior cingulate (BA 32) and medial frontal gyrus (BA 24). Minor foci of activity occurred bilaterally in middle temporal lobes (BA 21), left superior occipital gyrus (BA 19), and bilaterally in inferior parietal lobes (BA 40).

A *t* test comparison of the difference between the 6-1 and 3-1 conditions revealed a number of activations that were greater for the 6-1 than 3-1 condition (Fig. 3, bottom). Significantly greater activations occurred bilaterally in superior, middle, and inferior frontal regions as well as caudate nucleus. Differences for middle and superior frontal regions were more pronounced in the right than in the left hemisphere. Activation differences between the 6-1 and 3-1 conditions were minimal in inferior frontal regions in the left hemisphere but were large and pronounced in the right hemisphere. Other regions where significant increases in activation occurred between the 6-1 and 3-1 conditions were right temporal lobe and right and left parietal lobes.

Only in the 6-1 condition did significant activation occur in middle frontal and superior frontal gyri. This finding suggests that those regions were activated only by a 6-letter memory load. An alternative explanation is that those regions were active for the 3-letter memory load condition but at levels below the threshold of  $z \geq 1.96$ . To explore whether these regions were recruited exclusively in the 6-1 condition, we drew regions-of-interest around these gyri based on their definition in a standard anatomical atlas (Duvernoy, 1991). We then computed for each subject a ratio of regional activity (defined as the average *z*-value increase) to whole-scan-slice activity for these regions. This analysis allowed examination of regional activation independent of any *z*-threshold. Comparison of the activity in that region to that in the entire slice allowed formation of a "relative ratio" of activity. A ratio greater than one would indicate that subthreshold activation was present in the region of interest above and beyond the increased activation that occurs in any random brain region with the elimination of a threshold. In contrast, a ratio of one or less would indicate the absence of subthreshold activation because the activation in the region of interest is no more than that which occurs in any random brain region with the elimination of a threshold.

The results of this analysis (Table 2) indicated that, in a number of regions, activation occurred in the 6-1, but not the 3-1, condition, within the measurement sensitivity of fMRI. Two patterns of results can be observed. The first pattern involved one region, left inferior frontal gyrus, which showed a ratio greater than one in both the 3-1 and 6-1 conditions. Activation was greater on the left than on the right in both conditions for this region. Thus, subthreshold activa-



**FIG. 3.** FMRI results of the 3-1 (top panel), 6-1 (middle panel) conditions, and matched  $t$  test comparison of the 3-1 and 6-1 conditions (bottom panel).

tion appeared to occur in the inferior frontal gyrus for both memory loads. A second pattern of results was observed in superior frontal gyrus and middle frontal gyrus. This analysis indicated no discernible subthreshold activation in the 3-1 condition for these regions

while both of these areas showed subthreshold activation in the 6-1 condition.

An examination of the percentage of active pixels (computed for each region by dividing the number of active pixels in the region by the total number of pixels

**TABLE 1**

Regions of Significant Activation in 3-1 and 6-1 Conditions

Lobe	Region of activation	Hemisphere/ Brodmann's	Talarach			Z score	Voxels	
			x	y	z			
3-1 Condition								
Frontal	Inferior/premotor	L44/6	-45	-1	24	3.11	305	
			-52	1	32	3.28	1256	
Cingulate	Premotor	L6	-54	-9	45	3.01	162	
	Paracentral lobule	L24	-16	-19	45	2.96	57	
	Posterior	R23	18	-39	32	4.38	1283	
Temporal	Superior	L23	-13	-47	24	2.72	55	
		L22	-64	-35	8	3.36	135	
	Middle	R22	31	-56	20	3.16	76	
		R21	52	-38	-4	3.50	96	
Occipital	Cuneus	L21	-48	-39	1	2.99	26	
		R18	2	-91	20	3.31	39	
	Precuneus	L7	-1	-8	45	2.84	43	
Subcortex	Caudate/putamen/GP	R7	19	-33	45	2.94	126	
		L	-27	-16	-4	3.72	91	
	Caudate	R	22	-25	20	3.14	58	
	Clastrum	R	23	25	8	3.04	65	
6-1 Condition								
Frontal	Superior/middle	L10	-27	53	1	4.07	398	
		L46/10	-37	29	20	3.72	2001	
		R10	28	35	12	3.72	1730	
	Middle	R9	29	31	32	3.72	2162	
		R6, 8	41	1	45	3.72	2390	
	Middle/inferior	L46	-48	43	8	3.04	86	
		R10	25	53	1	4.07	1795	
		R44, 45, 46, 10	33	12	8	3.72	4064	
		R45/46	32	23	20	3.53	1733	
		R45, 46, 10	35	28	24	3.72	5006	
	Inferior frontal	L45	-49	26	1	3.94	239	
		L46	-39	35	12	3.31	335	
		L44	-52	5	20	3.72	549	
		R44	41	5	32	3.72	2162	
		L44/6	-52	2	32	3.72	5648	
	Inferior/premotor	L45	-38	22	12	3.72	1348	
		L6	-59	4	12	3.53	389	
	Cingulate	Medial frontal	B8	0	24	45	3.18	292
		Anterior	B24/32	1	20	32	3.72	4413
	Parietal	Inferior parietal	L40	-49	-34	45	3.16	560
Supramarginal/angular		L39	-30	-53	32	3.55	753	
Superior parietal		L7	-25	-63	45	3.33	444	
Temporal	Superior	L22/42	-66	-34	8	3.72	388	
		L21	-53	-30	1	3.97	891	
	Middle inferior	L21/37	-57	-53	8	3.72	603	
		R21	43	-50	1	3.14	101	
		L37/21	-49	-56	-4	3.60	309	
Occipital	Lingual	R37/21	56	-45	-4	3.60	290	
		L18/19	-18	-73	1	3.48	604	
	Cuneus	R19	12	-59	1	3.40	139	
		R18	5	-9	24	2.94	452	
Subcortex	Precuneus	R31	20	-69	20	2.74	129	
		L7	0	-73	45	3.38	471	
	Caudate/putamen/GP	R	16	10	8	3.43	1000	
		R	14	-5	20	3.67	1028	
	GP	L	-18	6	20	3.26	469	
		L	-13	2	-4	3.23	87	
	Putamen	L	-20	11	12	3.01	251	
		R	24	22	1	3.82	616	
		R	24	22	1	3.82	616	
	Thalamus	B	-6	-22	12	3.72	2923	

that comprised the region) is shown in Fig. 4. A region (4)  $\times$  memory load (2)  $\times$  hemisphere (2) repeated-measures ANOVA indicated that all regions showed greater activation in the 6-1 than 3-1 conditions; there was a significant main effect of memory load,  $F(1, 5) = 8.91$ ,  $P < 0.03$ ,  $MSe = 50.1$ . Further, regions differed significantly in the percentage of pixels active in the 3-1 and 6-1 conditions as indicated by a significant memory load  $\times$  region interaction  $F(3, 15) = 3.3$ ,  $P < 0.05$ ,  $MSe = 33.0$ , and a significant memory load  $\times$  hemisphere  $\times$  region interaction,  $F(3, 15) = 4.0$ ,  $P < 0.03$ ,  $MSe = 16.0$ . The percentage of pixels active in inferior frontal gyrus was greater than other regions, and activation was greater on the left than on the right in both memory load conditions for this region. For other regions, however, the percentage of active pixels in each hemisphere depended on memory load condition. Middle frontal gyrus, superior frontal gyrus, and caudate all showed equivalent activation in both hemispheres in the 3-1 condition. Activation was (in contrast to the inferior frontal gyrus) significantly greater on the right than on the left in the 6-1 condition for all of these regions.

## DISCUSSION

When subjects were required to maintain three letters, relative to one letter, in WM across a delay period the activation in frontal regions was limited to caudal left inferior frontal gyrus (BA 44). When subjects were required to maintain six letters, relative to one letter, across a delay period there was enhanced activation in the left inferior frontal gyrus. Importantly, activation of additional dorsal prefrontal cortical areas (middle and superior frontal gyri) as well as caudate nucleus also occurred. In these regions, activation was bilateral, but it was greater in the right hemisphere than in the left hemisphere, despite the verbal nature of the material.

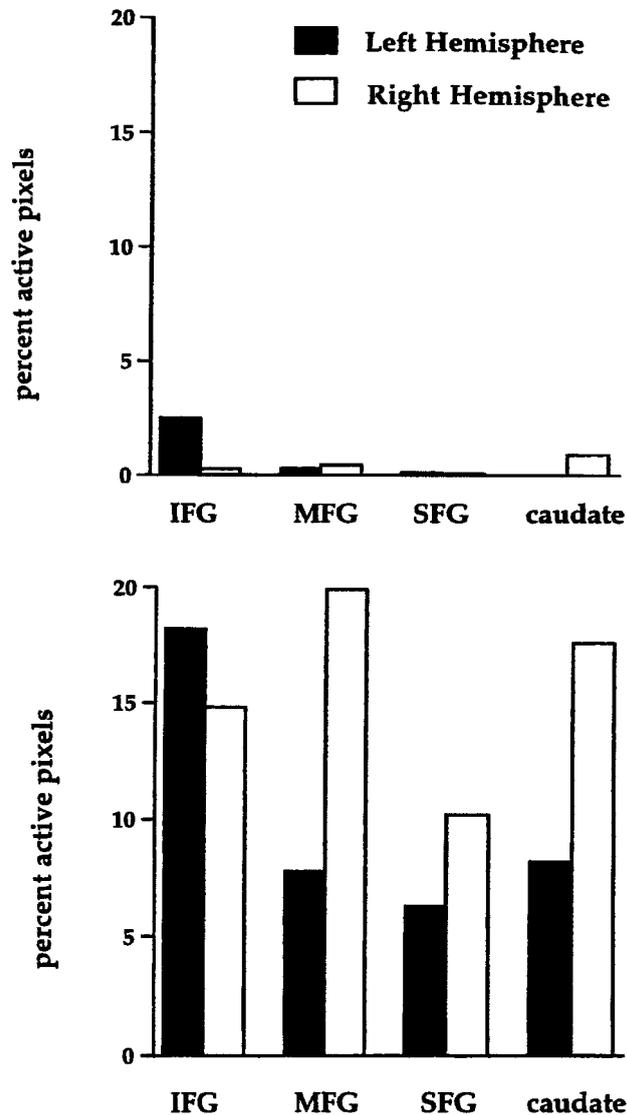
The unilateral inferior frontal activation we observed in the 3-1 condition may reflect phonological slave-system processes in WM. Our results are consistent with the notion that maintenance of verbal information

**TABLE 2**

Ratios of Regional Activity in the 3-1 and 6-1 Conditions

Frontal region	Memory load condition			
	3-1		6-1	
	Left	Right	Left	Right
Superior	1.00	0.87	1.30	1.50
Middle	0.97	0.87	1.11	1.72
Inferior	1.30	0.89	1.72	1.60

*Note.* A value above 1.00 suggests the presence of regional sub-threshold activation.



**FIG. 4.** Percentages of active pixels in frontal regions and caudate in the 3-1 and 6-1 conditions.

is mediated by unilateral ventral regions, specifically, caudal left inferior frontal cortex (Broca's Area; BA 44). Broca's Area and adjacent speech-related regions (SMA) may mediate maintenance of stored information through a process of verbal rehearsal (Awh *et al.*, 1996; Paulesu *et al.*, 1993; Vallar and Baddeley, 1984).

Some apparent differences between our results and those of other studies likely reflect the selection of baseline tasks. In another study of WM maintenance, Paulesu *et al.* (1993) required subjects to remember 6 items (similar to our 6-1 condition). Given our results, one might wonder why prefrontal activation outside of BA 44 did not occur in Paulesu *et al.*'s study. The answer may involve differences in the baseline comparison tasks. Our study used a baseline task (remembering a single letter) that minimized storage require-

ments. Paulesu *et al.*, on the other hand, used a baseline task that matched their experimental task in storage requirements, but required subjects to remember meaningless objects instead of the letters required in the experimental task. Thus, the results of the Paulesu *et al.* study mainly emphasize differences in information *content*, verbal or object. It is possible, then, that activation of prefrontal cortex superior to BA 44 may have occurred in the Paulesu *et al.* study but went undetected because it occurred in both the verbal and object tasks. Such differences in baseline task may also account for the minimal activation of parietal cortex (along with Broca's area) in the 3-1 condition of our study. Minimal differences in the storage requirements between 3-letter and 1-letter memory loads may have yielded similar levels of activation in parietal cortex.

Another important distinction among WM maintenance tasks is between those that stress WM capacity with *time* (with memory load held constant, e.g., Awh, *et al.*, 1996) and those that stress WM capacity with *memory load* (with retention interval held constant, e.g., the present study). Awh *et al.* (1996) did not observe temporal-lobe activation in their WM maintenance task, whereas activation of this region was observed in our study and that of Paulesu *et al.*'s. This variance in results may have occurred if the memory load in Awh *et al.*'s control condition produced enough activation (despite the brief retention interval) to cancel that in the longer retention interval of their experimental condition. The additional activations that we observed in middle and superior prefrontal cortex during the 6-1 condition may reflect domain-independent central-executive processes.

#### *Central Executive Involvement in WM Maintenance: Converging Evidence*

The results of our study demonstrate that middle and superior prefrontal cortex is activated not only by tasks that overtly demand manipulation in WM, but also when the demands of maintenance exceed the capacity of slave systems. Estimates of the capacity of short-term storage (the temporary maintenance of information in WM) vary, but most estimates indicate a fairly narrow capacity of 2–3 items (Waugh and Norman, 1965; Glanzer and Razel, 1974). When this short-term storage capacity is exceeded, strategic processes may need to be employed to maintain items in WM. Indeed, results from behavioral studies support the notion of central executive involvement in WM storage tasks with above-capacity memory loads. Baddeley and Hitch (1974), for instance, required subjects to comprehend prose passages while simultaneously holding 0, 3, or 6 letters in WM. When they compared comprehension in the 0- and 3-letter memory-load conditions, performance did not change (73 and 70% accuracy). This

result suggests that when subjects must carry out a complex task while retaining a subcapacity memory load, resources can be devoted entirely to the more demanding task. Significant decrements in prose comprehension were observed, however, when subjects were required to hold six items in WM (60% accuracy). This result suggests, as does our study, that memory loads that approach the capacity of short-term storage may require the resources of the central executive. As the Baddeley and Hitch result also suggests, there are consequences to this resource trade-off in cognitive performance. In their study, direction of executive resources to WM maintenance operations led to comprehension performance reductions. The demonstration of comprehension deficits with high WM load indicates that maintenance and text-comprehension must compete for central executive resources when the requirements of both are sufficiently demanding.

Studies of high-level reasoning suggest that it, like comprehension and maintenance, requires central-executive involvement. Prabhakaran *et al.* (1997a) observed right dorsolateral prefrontal activation when they compared fMRI activation while subjects solved Raven Progressive Matrices problems to that while subjects carried out a pattern matching task. Raven problems require induction of abstract relations in addition to strategy shifting and goal management functions. A broad literature now supports the conclusion that reasoning involves many of the same basic cognitive processes and neural substrates that mediate the executive component of WM (Prabhakaran *et al.*, 1997b; Baker *et al.*, 1997; Gabrieli, 1996; Salthouse, 1996; Fry and Hale, 1996; Kyllonen and Christal, 1990). Indeed, patients with frontal-lobe lesions demonstrate specific deficits in reasoning tasks such as the Tower of London (Shallice, 1982), Wisconsin Card Sort (Milner, 1963, 1964), and Cattell's Culture Fair Test (Duncan *et al.*, 1994).

#### *The Role of Central Executive in WM Maintenance*

What might be the function of the central executive in WM maintenance tasks? One possibility is that, when maintenance demands are met by limited-capacity domain-specific buffers (or slave-systems), as in the 3-1 condition of this study, then central executive processes are not invoked. When maintenance demands exceed capacity, as in the 6-1 condition of this study, successful maintenance of the information may require involvement of processes beyond those of the domain-specific buffers. Once capacity is exceeded, then processes associated with manipulation may be required.

Indeed, the locations of the prefrontal activations observed in the 6-1 condition of the present study are similar to those found in WM studies using more complex tasks (D'Esposito *et al.*, 1995; Cohen *et al.*,

1994, 1997; Corbetta *et al.*, 1991; Petrides *et al.*, 1993a, b; Prabhakaran *et al.*, 1997a, b). It may be that suprathreshold maintenance of information requires cognitive operations similar to those required in these more complex tasks. These operations include monitoring the contents of working memory (such as would be required in self-ordered tasks), updating of the contents of working memory (such as would be required in *n*-back tasks), coordination of slave-system processes (such as would be required in dual-tasks), allocation of attention among multiple stimulus domains (such as would be required in divided attention tasks), and organization and planning of behavior (such as would be required in high-level reasoning tasks). These operations are among those that WM central executive has been posited to perform.

Suprathreshold information maintenance may also require more varied and demanding mnemonic strategies. Strategy shifting is one cognitive operation ascribed to the central executive component of WM (Deiber *et al.*, 1991; Jenkins *et al.*, 1994). For example, while subjects may rely solely on simple rehearsal in the control task they may employ a number of internally generated mnemonic strategies in the experimental task such as relying on the temporal order of the stimuli (Petrides *et al.*, 1993) and generating associative properties among items in the memory set in addition to simple rehearsal.

#### *Functional Segregation of Frontal Cortex*

Results from neuroimaging studies investigating the functional segregation of prefrontal cortex have suggested a number of possible organization frameworks. Some researchers posit that prefrontal cortex is functionally segregated according to the type of information that must be processed. One form of these *domain-specific* theories, formulated from results in human and infrahuman primate studies, postulates that nonspatial processing is subserved by ventrolateral frontal regions, while spatial processing is subserved by dorsolateral frontal regions (e.g., Goldman-Rakic, 1995; Courtney *et al.*, 1997). Another form of domain-specific frontal organization, based on results from studies with humans, posits that spatial information is processed in the right hemisphere while nonspatial information is processed in the left hemisphere (Smith *et al.*, 1996; Jonides *et al.*, 1993).

Other researchers propose that prefrontal cortex is functionally divided according to the type of cognitive process that must be performed on information held in WM. These *process-specific* theories posit that prefrontal cortex is functionally segregated according to the type of process that must be performed. In one form of this theory, information maintenance is subserved by ventrolateral prefrontal cortex while information manipulation is subserved by dorsolateral frontal regions

(e.g., Owen *et al.*, 1996; Petrides, 1996; D'Esposito *et al.*, 1998).<sup>1</sup>

The results of the current study suggest that the occurrence of domain- or process-specific activation may depend on the nature of the demand placed on WM processes. In the subcapacity load condition of our study, where executive processes may not be required, activation appears mainly in left inferior frontal regions, consistent with *domain-specific* theories of frontal function. When memory load approaches capacity and executive processes may be invoked we observed bilateral, but more right-hemisphere, activation in dorsolateral regions of prefrontal cortex, a result that is consistent with *process-specific* theories of frontal function (e.g., Petrides, 1996; D'Esposito *et al.*, 1998). Thus, domain-specificity of frontal regions may apply when tasks place minimal demands on memory processes. Domain-independent processing may be added to domain-specific processing when memory demands are high and the degree of executive involvement increases (cf. Owen, 1997). These results are not inconsistent with studies showing increased activity in the principal sulcus region of dorsolateral prefrontal cortex while monkeys briefly remembered the spatial location of a single target stimulus (Goldman-Rakic, 1987), but inferior convexity activity while monkeys briefly remembered a single nonspatial object. Our results suggest that, under higher memory demand conditions (i.e., multiple locations or multiple objects), additional domain-independent prefrontal areas would be active for both kinds of tasks.

#### *Laterality of Function in Prefrontal Cortex*

In the current set of results, activation of prefrontal regions was limited to the left hemisphere, specifically, left inferior frontal gyrus in the 3-1 condition. In the 6-1 condition, inferior frontal gyrus showed a greater extent of activation in the left hemisphere than the right hemisphere consistent with other WM maintenance studies (e.g., Awh *et al.*, 1996; Paulesu *et al.*, 1993). In middle and superior frontal regions, however, activation was bilateral, but greater in extent in the right hemisphere than in the left hemisphere.

Greater activation of middle and superior frontal gyri in the right hemisphere than in left hemisphere suggests that the right hemisphere may play the principal role in the executive components of WM. Previous studies using *n*-back, dual tasks, and self-ordering tasks have shown evidence of right-hemisphere involve-

<sup>1</sup>Process-specific theories may posit domain-specific segregation within the dorsal and ventral systems. Thus, domain-specific *manipulation* processes may be mediated by different regions of dorsal prefrontal cortex and domain-specific *maintenance* processes may be mediated by different regions of ventral prefrontal cortex (e.g., Petrides, 1996).

ment in frontal regions (e.g., D'Esposito *et al.*, 1995; Petrides *et al.*, 1993a, b; Awh *et al.*, 1996; Schumacher *et al.*, 1996; Smith *et al.*, 1996; Jonides *et al.*, 1997). The results of these studies have not been consistent in the extent to which activation of these regions is unilateral or bilateral. For instance, when D'Esposito *et al.* compared dual-task (dot-location and semantic categorization) activation to a single semantic task baseline, they observed bilateral middle-frontal activation. When the dual-task was compared to a single dot-location task, however, the middle frontal activation appeared more on the right than on the left. Jonides *et al.* (1997) found little evidence for differential hemispheric activation of frontal regions in a study using a parametric version of the *n*-back task with letters (with 0-back, 1-back, 2-back, 3-back conditions). It may be important that when manipulation of information was minimal (in the 1-back condition) activity was greater on the right than on the left in Jonides *et al.*'s study (contrary to the results of other WM maintenance studies). Further research is clearly required to determine the conditions under which differential or equivalent hemispheric involvement is observed in WM tasks.

#### *The Role of the Caudate Nucleus in WM*

In our study, we observed increases in the head of caudate that corresponded to increases in prefrontal activity under high memory load conditions. Clinical, anatomical and electrophysiological studies all suggest evidence for the role of a frontostriatthalamic loop in WM (e.g., Houk and Wise, 1993). One possible role of caudate nucleus in WM could be to mediate the sustained activity shown to occur in dorsolateral prefrontal cortex during the delay period of trials in WM tasks (Goldman-Rakic, 1995; Cohen *et al.*, 1997). Houk and Wise (1993) have suggested that output from the striatum, whose cells code stimulus features relevant for WM, to the pallidum causes phasic inhibition of that structure and its inhibitory connection to the thalamus. As a result, resonating activity between the thalamus and dorsolateral prefrontal cortex could be expected to occur, given known bidirectional connections between these structures. Such a mechanism could mediate the availability of resources available for WM maintenance and manipulation and cause sustained activity in ipsilateral caudate and prefrontal cortical regions during delay periods of WM tasks observed in our study and other studies (e.g., Braver *et al.*, 1997).

#### *Conclusion*

The current study is not without limitations. The block design employed in this study does not permit inferences about the role of specific regions during the various components of trials (encoding, retention and response). "Trial-based" paradigms (e.g., Cohen *et al.*,

1997; Courtney *et al.*, 1997; Zarahn *et al.*, 1996) will allow more accurate inferences to be drawn about the role of cortical regions in components of cognitive tasks (Rypma and D'Esposito, 1998). Nonetheless, our study provides informative evidence about the network of cortical regions that mediate WM maintenance tasks. Verbal tasks which involve minimal WM demands are supported by left inferior prefrontal, parietal, and temporal areas. When a WM maintenance task becomes more demanding as a result of greater memory load, central executive functions may be necessary, hence the involvement of bilateral inferior and superior frontal regions in this working memory task.

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