

# Verbal Working Memory Load Affects Regional Brain Activation as Measured by PET

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## Abstract

■ We report an experiment that assesses the effect of variations in memory load on brain activations that mediate verbal working memory. The paradigm that forms the basis of this experiment is the "n-back" task in which subjects must decide for each letter in a series whether it matches the one presented *n* items back in the series. This task is of interest because it recruits processes involved in both the storage and manipulation of information in working memory. Variations in task difficulty were accomplished by varying the value of *n*. As *n* increased, subjects showed poorer behavioral performance as well as monotonically increasing magnitudes of brain activa-

tion in a large number of sites that together have been identified with verbal working-memory processes. By contrast, there was no reliable increase in activation in sites that are unrelated to working memory. These results validate the use of parametric manipulation of task variables in neuroimaging research, and they converge with the subtraction paradigm used most often in neuroimaging. In addition, the data support a model of working memory that includes both storage and executive processes that recruit a network of brain areas, all of which are involved in task performance. ■

## INTRODUCTION

In recent years there has been a dramatic increase in the study of cognitive processes by measuring changes in regional cerebral blood flow using neuroimaging techniques. One reason for this increase has been the adoption of a subtraction paradigm for conducting experimental studies, first introduced by Fox, Mintun, Reiman, and Raichle (1988), Petersen, Fox, Posner, Mintun, and Raichle (1988) and Posner, Petersen, Fox, and Raichle (1988). This paradigm is based on the rationale that one can isolate the brain mechanisms corresponding to a set of target cognitive processes by:

1. Constructing a pair of tasks for subjects to perform, one of which includes these target processes and the other of which does not
2. Measuring regional cerebral blood flow using positron emission tomography (PET) or measuring oxygen usage using functional magnetic resonance imaging (fMRI)
3. Examining the difference in the patterns between the two tasks

If task 1 includes the target processes of interest and

task 2 includes all of the processes of task 1 *except* the processes of interest, subtracting the flow measure in task 2 from that in task 1 should yield brain activation (as measured by changes in flow), reflecting the target processes of interest. This rationale has been used to isolate brain regions that participate in many cognitive processes, including verbal long-term memory (Grasby, Firth, Friston, Frackowiak, & Dolan, 1993a; Tulving, Kapur, Craik, Moscovitch, & Houle, 1994), semantic processing of single words (Petersen et al., 1988), working memory storage (Jonides et al., 1993; Paulesu, Frith, & Frackowiak, 1993), motor skill acquisition (Karni et al., 1995), and others. In short, the subtraction paradigm dominates the investigation of cognition in neuroimaging studies.

The subtraction paradigm used in neuroimaging studies has its roots in the *subtraction method* introduced by Donders (1868) for the study of reaction time (RT). Donders reasoned that RT was composed of the cumulative times taken by all the stages of processing involved in a task. If one could construct two tasks that differed by only a single target-stage of processing, the subtraction of RT for one of these tasks from RT for the other should leave the time required for this target-stage. As Sternberg (1969) has noted, this line of reasoning de-

pends on the validity of the assumption of "pure insertion." That is, two tasks can differ by one and only one stage and that stage does not affect the operation of other stages. This assumption has been called into question on various grounds. For example, Kulpe (1895) was among the first to argue that the alleged addition of a single stage of processing could well affect the operation of other stages, thereby violating the assumption of pure insertion. Thus, any difference in RT between two tasks might not purely reflect simply the operation of a putatively inserted stage.

This same argument can be applied to the subtraction paradigm in neuroimaging research. Unless there is compelling independent reason to justify the assumption of pure insertion, subtraction images may be ambiguous about the processes they are assumed to illuminate. For example, the insertion of a memory requirement into an otherwise perceptual task may alter some aspects of the perceptual processing. One way to avoid this problem is to replace the subtraction method with a method of parametric variation. According to this method, one parametrically varies an experimental factor that presumably affects the operation of a single target-stage and determines if the factor affects regional cerebral activation in a systematic way.

Grasby et al. (1993a; 1993b; 1994) introduced this technique for the study of memory and applied it to verbal memory for varying-length lists of items (see also Price et al., 1992, and Binder et al., 1994, for the use of parametric variation in the study of auditory perception). Of the several results of these studies, one stands out as a marker of the usefulness of parametric variation. There was a strong correlation between the magnitude of bilateral hippocampal activation and measures of long-term memory engagement. Because the hippocampus has been widely associated with long-term memory processes in humans and other animals (Scoville & Milner, 1957; Squire & Zola-Morgan, 1991; Squire, 1992), the results of Grasby et al. indicate that neuroimaging data resulting from parametric variation can be a useful index of memory processes. Courtney, Ungerleider, Keil, and Haxby (1995) extended this result to the short-term storage of information about faces and spatial locations. They discovered anterior areas whose activation systematically varied with the length of a retention interval when faces had to be stored, and both anterior and posterior areas whose activation increased with the length of a retention interval for spatial information. In a different domain, Just, Carpenter, Keller, Eddy, and Thulborn (1996) have applied the principle of parametric variation to the study of language comprehension, showing that an increase in the complexity of sentences predicts an increase in brain activation (as measured by functional magnetic resonance imaging) in superior temporal cortex.

In this paper, we report a study that includes parametric variation of memory load to study processing in

verbal working memory. Working memory is a critical construct in understanding complex cognitive processes because it appears to participate widely in processes of language comprehension, problem solving, and reasoning (see Jonides, 1995, for discussion). As such, understanding the mechanisms underlying working memory should contribute significantly to understanding many aspects of cognition. The study of verbal working memory has benefited from several previous neuroimaging experiments using the subtraction technique (Awh, Jonides, Smith, Schumacher, & Koeppe, 1996; Cohen et al., 1994; Fiez et al., 1996; Paulesu et al., 1993; Petrides, Alivisatos, Meyer, & Evans, 1993; Schumacher et al., 1996; Smith, Jonides, & Koeppe, 1996). The tasks in these experiments differed from one another, but there is a good deal of agreement about the involvement in verbal working memory of bilateral structures in dorsolateral prefrontal cortex, premotor cortex, parietal cortex, and cerebellum as well as inferior prefrontal cortex in the left hemisphere.

Here, we focus on one task that has been used in some of these studies as a paradigmatic case of working memory. In this *n*-back task, subjects are shown a sequence of letters, and for each one they have to decide whether it matches in identity the letter that preceded it by *n* places in the series. For example, when subjects are engaged in the two-back version of this task, they should respond positively if a letter matches the letter that appeared two items previously in the series. A major virtue of this task is that it recruits two sorts of processes. First, it requires that subjects store one or more letters in working memory, the number depending on the value of *n* in the task. Second, it requires that subjects update the contents of their working memory with the presentation of each new letter—dropping the oldest item, adding the newest, and keeping track of the order of presentation of each. The *n*-back task thus engages processes involved in the manipulation of information as well as processes required for the storage of that information. In this way, the task fits the modal definition of working memory developed by Baddeley (1986, 1992), among others, and it goes beyond the study of simple short-term storage.

Neuroimaging studies of the *n*-back task using subtraction methodology have revealed activation in several brain areas that are consistent with other studies of working memory using different tasks (Awh et al., 1996; Cohen et al., 1994; Schumacher et al., 1996). Thus, the task seems to be a representative case of working memory, including both storage and manipulation processes. We present here a PET study that uses a parametric variation of the *n*-back task. We use the results to test the validity of parametric variation in working-memory studies, to test the assumption of pure insertion, and to identify the brain regions involved in the verbal-working-memory circuit.

We conducted an experiment in which subjects en-

gaged in the  $n$ -back task at four levels of difficulty, shown in Figure 1. In the most difficult version, they had to match each letter to the one that had appeared three items back in the series. In easier versions, they had to engage in two-back and one-back matching. And in the least demanding version, they had to match each letter in a series against a constant target that was specified prior to the beginning of the series (we call this "zero-back"). In addition to these four memory conditions, we included a control condition in which subjects simply viewed a series of letters and pressed a response key when each was presented. This control condition was used as a baseline whose activation was subtracted from those of each of the memory conditions to remove any baseline effects that might differentiate subjects. With these conditions, the experiment provides a strong way of parametrically manipulating the difficulty of the working-memory tasks that subjects faced.

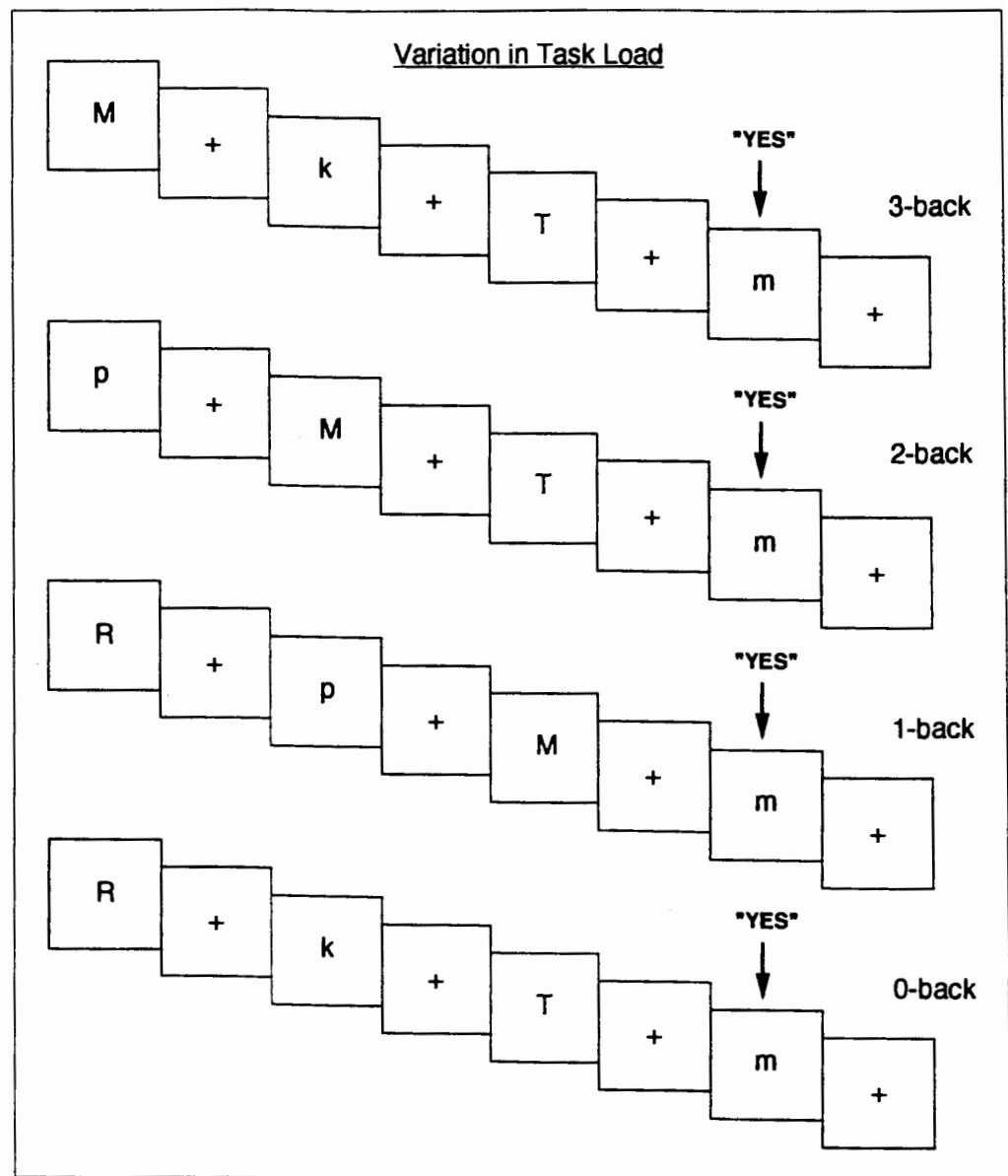
Subjects practiced all the tasks in one session, and then they engaged in all the tasks again in a later session in which PET measurements were taken. During the PET session, subjects were tested on each of the five conditions (four memory plus one control) twice each, for a total of ten scans. Behavioral data (in the form of accuracy and response times) were collected from each session for the 18 subjects who participated.

## RESULTS

### Behavioral Data

We analyzed the accuracies and response times from the practice and PET sessions separately; these are shown in Figure 2. The data in the figure show that, as anticipated, increases in processing load made the task more difficult, as reflected in both the response times and the accura-

**Figure 1.** Schematic diagrams illustrating the four experimental conditions of the experiment. The tasks differ in working-memory load, varying from zero- to three-back. In addition to these conditions, the experiment also included a Control condition in which letters were presented in sequence and subjects simply had to respond with a keypress upon presentation of each letter.



cies (Practice session:  $RT-F(3, 48) = 50.8$ , Accuracy— $F(3, 48) = 12.5$ ; PET session:  $RT-F(3, 51) = 22.6$ ; Accuracy— $F(3, 51) = 38.8$ ). For all analyses,  $p < 0.05$ .

Of interest is the shape of these effects of task load: The decrease in task performance as task load increases is positively accelerated. This was confirmed by analyses that showed significant quadratic as well as linear trends for the reaction time and accuracy functions of the practice and PET sessions ( $p < 0.05$  in all cases). The shape of these functions indicates that an increase in the number of items that must be monitored in the series produces more than a linear change in performance. This stands in contrast to other tests of working memory that often show either linear or negatively accelerated worsening of task performance with memory load (e.g., Sternberg, 1969). The fact that the functions are overadditive suggests that increased load may cause a need to recruit additional mechanisms to accomplish the task, beyond just incrementing the work of a fixed set of mechanisms by some constant amount with each increment to the task's difficulty. This, in turn, suggests that increased processing load may be reflected in not just additional activation in a fixed set of brain areas, but in the recruitment of new areas as the task becomes more difficult. We turn to the neuroimaging data to test this prediction and to examine the pattern of brain activations elicited by each level of task difficulty.

### Neuroimaging Data

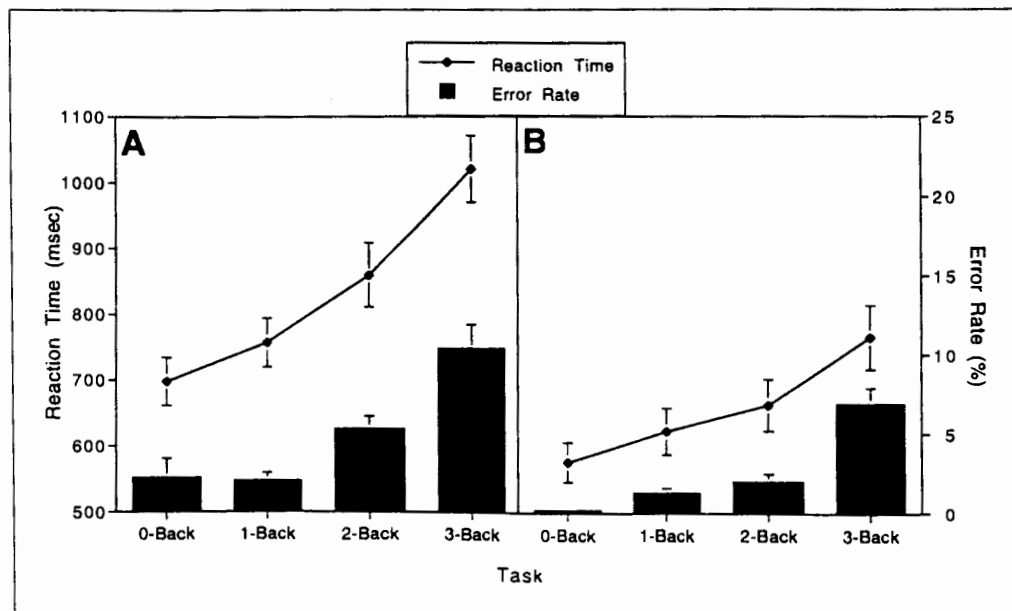
Tables 1, 2, 3, and 4 list the coordinates of the peak activation voxels for all the memory-minus-control subtractions that passed our criterion for statistical significance ( $p < 0.05$ , after correction for multiple comparisons; adopting current convention, we show left-hemisphere activations and deactivations as positive

$x$ -values and right as negative), and Figure 3 shows surface-rendered lateral and superior images for each of the activation-subtractions shown in Tables 1 through 4. The most striking feature of the data in the tables and figure is that there are many more areas of reliable activation in the two-back and three-back subtractions (22 significant activation foci in each) than in the zero- and one-back subtractions (two and three significant foci, respectively). This difference among the tasks is also true of the number of negative activations (which we call "deactivations"). This leads to the claim, for which statistical support is given below, that brain activation and deactivation increase as the working-memory task becomes more demanding. The tables suggest that these increases come about at least in part because increasing memory load causes more brain areas to be recruited to the task. There is evidence (presented below) that the increase in statistically significant areas may actually *not* be a function of the recruitment of new regions. Rather, regions that are active, but below a statistically significant threshold, pass that threshold with increasing task load. Before examining this point in detail, we discuss the extent to which the present data replicate those of previous experiments using similar tasks.

### Replicability of the Three- and Two-Back Tasks

There is excellent agreement between the areas that were activated and deactivated in the present three-back task and areas reported in another study using this task (Schumacher et al., 1996). This was determined via a region-of-interest (ROI) analysis (using spherical regions of 5.4-mm radius in these and other analyses below) in which the memory-minus-control activations of that study were placed on the current data. Likewise, we placed similar ROIs from the present experiment on the

**Figure 2.** Behavioral performance in the practice session preceding the session of PET recording (A) as well as in the PET session itself (B). Each graph includes a line-function showing reaction time and a bar graph showing accuracy, both as a function of task load.



**Table 1.** Significant Activation and Deactivation Foci in the Three-Back Minus Control Subtraction

Stereotaxic Coordinates				Z Score	Brain Area <sup>a</sup>
x	y	z			
Left hemisphere:					
-26	-4	50	6.86	SMA (Area 6)	
-48	1	36	5.65	Premotor (Area 6)	
-21	-67	36	9.02	Superior Parietal (Area 7)	
-35	-49	36	9.66	Posterior Parietal (Area 40)	
-44	8	27	5.67	Broca's Area (Area 44)	
-39	44	18	5.70	Dorsolateral Frontal (Area 46)	
-64	-1	14	5.67	Premotor (Area 6)	
-57	14	25	5.04	Broca's Area (Area 44)	
-26	12	4	5.39	Insula	
-37	-42	-34	7.27	Cerebellum	
-33	-55	-15	7.80	Cerebellum	
-30	21	-15	-5.99	<i>Superior Frontal (Area 8)</i>	
-46	-69	25	-8.12	<i>Posterior Parietal (Area 39)</i>	
-33	28	-9	-5.26	<i>Inferior Frontal (Area 47)</i>	
-51	-13	-20	-11.14	<i>Mid-Temporal (Area 20)</i>	
-44	5	-22	-8.80	<i>Anterior Temporal (Area 21)</i>	
-30	8	-27	-8.82	<i>Anterior Temporal (Area 38)</i>	
Right hemisphere:					
26	-1	52	9.15	SMA (Area 6)	
30	-58	40	8.99	Posterior Parietal (Area 40)	
42	32	29	8.72	Anterior Frontal (Area 9)	
42	3	27	4.15 <sup>b</sup>	Premotor/Broca's (Area 6/44)	
37	48	18	6.06	Dorsolateral Frontal (Area 46/10)	
26	19	-	4.48 <sup>b</sup>	Insula	
24	48	-11	5.61	Orbital Frontal (Area 11)	
35	-55	-22	8.61	Cerebellum	
26	-58	-15	7.82	Cerebellum	
55	-64	14	-4.24 <sup>b</sup>	<i>Posterior Parietal (Area 39)</i>	
42	-6	4	-5.60	<i>Insula</i>	
53	-13	-14	-6.56	<i>Mid-Temporal (Area 21)</i>	
26	-1	-22	-6.41	<i>Medial Temporal (Area 28)</i>	
48	-8	-25	-6.94	<i>Mid-Temporal (Area 21)</i>	
28	8	-29	-7.03	<i>Anterior Temporal (Area 38)</i>	
21	-82	-29	-4.25 <sup>b</sup>	<i>Cerebellum</i>	
Midline:					
-3	8	40	8.26	Anterior Cingulate (Area 32)	
8	-13	4	6.59	Thalamus	
1	-19	-4	5.99	Red Nucleus	
3	-69	-18	8.15	Cerebellum	
-6	39	47	-9.95	<i>Superior Frontal (Area 8)</i>	
-8	48	36	-10.39	<i>Anterior Frontal (Area 9/8)</i>	
-3	-55	20	-11.09	<i>Posterior Cingulate (Area 23/30)</i>	
-3	55	14	-11.79	<i>Anterior Frontal (Area 10)</i>	
1	32	-9	-12.37	<i>Anterior Cingulate (Area 32)</i>	

<sup>a</sup> Brodmann areas shown in parentheses. Deactivations shown in italics.

<sup>b</sup> Not significant but  $z > 4.0$  (used in ROI analysis).

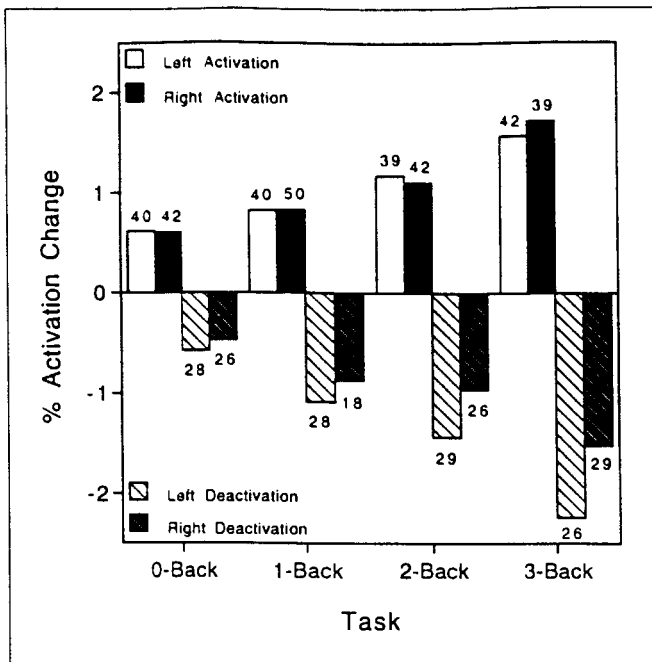
**Table 2.** Significant Activation and Deactivation Foci in the Two-Back Minus Control Subtraction

Stereotaxic Coordinates				Z Score	Brain Area <sup>a</sup>
x	y	z			
Left hemisphere:					
-26	-6	50	4.69	SMA (Area 6)	
-35	-51	38	7.16	Posterior Parietal (Area 40)	
-21	-64	36	6.52	Superior Parietal (Area 7)	
-51	-8	34	5.09	Premotor (Area 6)	
-37	1	27	6.02	Broca's Area (Area 44)	
-39	-71	-14	5.95	Cerebellum	
-39	-55	-18	4.63	Cerebellum	
-37	-49	-45	4.79	Cerebellum	
-28	21	45	-6.66	<i>Superior Frontal (Area 8)</i>	
-48	-67	25	-6.99	<i>Posterior Parietal (Area 39)</i>	
-35	30	-9	-4.64	<i>Inferior Frontal (Area 47)</i>	
-51	-13	-22	-7.18	<i>Mid-Temporal (Area 20)</i>	
-35	8	-29	-7.27	<i>Anterior Temporal (Area 38)</i>	
Right hemisphere:					
28	1	54	5.30	SMA (Area 6)	
35	-49	40	6.76	Posterior Parietal (Area 40)	
30	-60	38	6.65	Posterior Parietal (Area 40)	
44	30	29	5.00	Anterior Frontal (Area 9)	
42	50	22	4.73	Anterior Frontal (Area 10)	
12	-15	7	4.91	Thalamus	
35	-55	-22	4.78	Cerebellum	
21	-62	-22	4.64	Cerebellum	
33	-51	-32	4.78	Cerebellum	
21	-58	-43	5.20	Cerebellum	
48	-4	-25	-5.16	<i>Mid-Temporal (Area 21)</i>	
28	8	-32	-5.48	<i>Anterior Temporal (Area 38)</i>	
Midline:					
-3	8	40	6.57	Anterior Cingulate (Area 32)	
-6	-17	4	4.68	Thalamus	
3	-51	-20	6.79	Cerebellum	
-1	-69	-34	5.13	Cerebellum	
-6	35	47	-8.62	<i>Superior Frontal (Area 8)</i>	
-3	-55	18	-7.27	<i>Posterior Cingulate (Area 23)</i>	
-3	57	14	-8.48	<i>Anterior Frontal (Area 10)</i>	
-6	35	-7	-8.50	<i>Anterior Cingulate (Area 32)</i>	

<sup>a</sup> Brodmann areas shown in parentheses. Deactivations shown in italics.

data of Schumacher et al. Using a relaxed criterion of  $p < 0.10$ , all 16 ROIs from Schumacher et al. were activated in the present experiment (after multiple-comparison adjustment), and 21 of 24 ROIs from the present experiment were activated in the data of Schumacher et al. Similarly, all 13 deactivations found by Schumacher et al. were reliable in the present study, and 16 of 18 ROIs from the present study were deactivated in the data of Schumacher et al.

A similar set of analyses revealed excellent agreement between the data of the present two-back task and those



**Figure 7.** Percentage change in activation or deactivation as a function of task load shown separately for left and right hemispheres. The bars show the mean activation in each of 68 spherical regions (20.25-mm diameter) in each hemisphere; the values above each bar indicate the number of these spherical regions that were either activated (averaged over all voxels in that sphere) or deactivated for the left and right hemispheres.

in those areas that had positive activation (note, of course, that this level increases with task load, a fact we have discussed above). Analysis of these activation levels reveals no significant difference between left and right hemispheres for any of the four levels of task load ( $p > 0.20$  for all analyses).

We also calculated the same statistics for areas that were deactivated in each condition, and these are reported in Figure 7 also. Once again, there is no reliable trend for there to be more deactivated regions in the left or right hemisphere. Furthermore, although there is a weak trend for deactivation to be greater in the left than the right hemisphere, this trend is not significant for any of the levels of task load ( $p > 0.10$  in all cases except that for three-back deactivations, for which  $.05 < p < 0.10$ ).

We conclude from these analyses that there is no reliable tendency for activation or deactivation to favor the left or right hemisphere in the present experiment. Furthermore, there does not appear to be any systematic change in the laterality of the activations or deactivations with increasing task load. We recognize that this pattern is at odds with several previous studies of verbal working memory, and so we urge caution in its interpretation. Nevertheless, we observe that lateralization of activations in verbal working memory may not be an inevitable result.

## DISCUSSION

Our primary mission was to test whether there are systematic changes in brain activation in a working-memory task as a function of parametric variations of task load. The present experiment clearly demonstrated that a large number of areas, mainly cortical, show systematic changes in their levels of activation as the working-memory task is made more demanding. This result confirms and goes beyond that of Braver et al. (1995), who used comparable tasks to those employed here. Taking their measurements with functional MRI, Braver et al. showed monotonic changes in activation in Broca's area and in dorsolateral prefrontal cortex. In that study, there was no opportunity to discover how widespread the systematic changes of activation with task load were because the brain was imaged in eight coronal slices anterior to the anterior commissure. The present study shows that the monotonic relationship of brain activation with task load is quite pervasive. It is manifested in anterior and posterior brain structures in both cerebral hemispheres as well as in cerebellum and some subcortical structures.

There are two implications of these results. One is purely methodological. As discussed above, the paradigm most commonly used in neuroimaging research relies on the examination of subtraction images, comparing one condition with another. This has certainly been true for the study of working memory, for example. Our present results show that parametric variation offers an enhancement to strictly subtractive methodology, one that makes the collection of imaging data more nearly comparable to the collection of behavioral data such as response time and accuracy. This way of examining neuroimaging data is similar to the examination of dose-response curves in psychopharmacology. That is, the technique allows a finer-grained assessment of the response of the brain to changes in task requirements than does subtractive methodology. As such, parametric variation in task variables may permit a better assessment of the functional tie between activation in some area of the brain and task performance.

Note that the substantial overlap in significant regions between this study and other studies of working memory that *did* use the subtraction method (Awh et al., 1996; Schumacher et al., 1996) supports the validity of using subtraction—at least for the study of working memory. As such, there is a pleasing convergence between the use of the subtraction method and the parametric variation of memory load in revealing the circuitry underlying verbal working memory.

The second implication of our results has to do with the substance of working memory. Why do so many brain areas show task-load sensitivity? One answer is that all of these areas are simply responding to the increased effort required by higher task loads. This claim, however, is not analytic about the particular brain mechanisms that are engaged by the  $n$ -back task and that change in

back)

5. Temporal ordering processes to keep the ordinal position of each stored letter tagged so that the present letter can be matched to the one  $n$ -back

6. Inhibition processes needed to dampen the trace of the oldest letter in memory so it can be replaced by the newest letter in the series

7. Response processes required to execute the response

In our analyses, we found that activation in regions having to do with perception and response did not show any systematic variation as a function of task load. These regions presumably reflect processes listed above in stages 1 and 7. The remaining five stages of processing provide a theoretical framework to organize the majority of the brain activations that were sensitive to task load.

Several previous investigators have argued that activations in posterior parietal cortex, in Brodmann's region 40, are symptomatic of storage of information in working memory (e.g., Paulesu et al., 1993; Smith et al., 1996). In addition, there is by now strong evidence that the circuit mediating rehearsal of verbal information involves structures in the supplementary motor area, premotor cortex, Broca's area, parts of insula cortex, and right cerebellum (see Awh et al., 1996). The temporal coding and inhibition processes that are needed in the  $n$ -back task may be mediated by dorsolateral prefrontal activity, as suggested by Moscovitch and Winocur (1992) and by the work of Diamond and Goldman-Rakic (1989) among others. Finally, there is growing evidence that attentional structures in superior parietal and anterior cingulate areas, among others (see Awh & Jonides, in press). Taken together, these hypotheses account for the majority of cognitive processes involved in the  $n$ -back task (although not all: It is not clear from previous research what structures may be involved in matching a current

for zero-, one-, two-, and three-back, respectively. The major effect of load is at the higher values (i.e., not at zero- and one-back). This is consistent with the hypothesis that the dorsolateral prefrontal cortex is involved in temporal coding. Furthermore, this pattern of activation-change with load is reliably different than that for a region claimed to be involved in storage of material directly—posterior parietal cortex—as revealed by an interaction of load with these two areas ( $p < 0.05$ ).

We applied this same argument about the effect of load to Broca's area, which is presumably involved in rehearsal. If the zero- and one-back tasks are accomplished with little need for rehearsal, this area also might show little change in activation for these two tasks, but larger changes for two- and three-back tasks. Again, the pattern of activations confirms this suggestion: The activations for the zero- through three-back tasks are 0.97%, 1.07%, 4.40%, and 5.00%, respectively. Once again, the big change in activation is between one- and two-back tasks. This pattern of change is again different from that shown in the posterior parietal area ( $p < 0.05$ ). We offer these additional analyses both as examples of how activation data may be used analytically about the underlying processes of interest and as suggestive points for further study of the underlying mechanisms involved in working-memory tasks.

In summary, we propose that a network of structures is recruited by the  $n$ -back task whose function is to implement the cognitive processes outlined here. Furthermore, we find that this network increases its overall rather than recruiting new areas to the task. This suggests that each region must recruit more neuronal activity as greater burden is placed on each process by an increase in task load. From the point of view of task analysis, this is a sensible claim because increasing  $n$  in the  $n$ -back task places greater demand on storage, rehearsal, tempo-

present letter matched the one that had been presented two-back in the sequence (there were 14 such matches as in three-back). Second, three one-back and three three-back matches were included in the sequence of 45 trials in each block to ensure that subjects accurately responded on the basis of a two-back match rather than just the general familiarity of that same letter.

### *One-Back*

This task was also identical to the three-back task except that subjects had to decide for each letter whether it matched the one that had been presented immediately previously in the sequence. In a fashion similar to the other tasks, three letters were included that matched the letter presented two-back in the sequence, and three letters were included that matched the letter presented three-back.

### *Zero-Back*

This condition also required a match or mismatch decision on each trial but had a minimal memory requirement and did not include keeping track of previously presented letters. In this zero-back task, subjects were presented with a sequence of 45 letters, and they had to decide for each whether it matched in identity a single target that was specified before the sequence began (e.g., the letter G; the letter used as the target in this condition varied with each block of the task). In each block of trials, there were again 14 matches.

### *Control*

A final condition was included to control for any subject-specific activations that might have been present in the data. In each block of this Control condition, subjects saw a sequence of 45 letters at the same pace as in the other conditions. The task was simply to press the response button when each letter was presented. For one block of trials that subjects received in the PET session, they responded with a single keypress, and for the other block, they responded with a double keypress, so that over both blocks, subjects emitted responses similar to those emitted in the memory conditions. Thus, this condition should have resulted in patterns of activation specific to individual subjects with task-related activations only for perceptual and response processes. These processes are, of course, not central to an examination of the effects of memory load, as we show above.

### **Subjects**

Thirty-six female volunteers were recruited as potential subjects for the experiment. These volunteers were paid to participate in a prescreening session in which they were given two blocks of trials each on the two- and

three-back tasks, with the order of tasks counterbalanced across subjects. Of these subjects, 19 passed a prescreening criterion of at least 64% accuracy on both matches and mismatches. These subjects were then paid for participation in the experiment proper, including a session of practice and a session of PET testing. The data from one of these subjects was excluded from analysis because extraneous environmental noise at the time of the PET testing interfered with her concentration on the task.

### **Design**

The experiment proper consisted of a session of practice and a session of PET testing the day following the practice session. The practice session provided subjects with experience with each of the memory conditions described above. Subjects received one block of practice on the zero- and one-back tasks, this being sufficient to familiarize them with these tasks. In addition, subjects received practice on the two- and three-back tasks, the amount of practice varying with their need for experience with these tasks to perform at the same criterion of accuracy comparing one with the other. Fifteen of the subjects received two blocks of practice on each of two- and three-back tasks; two subjects received two blocks of practice on the two-back task and three on the three-back task; the final subject received one block of practice on each of the two- and three-back tasks. The order of the tasks was counterbalanced across subjects with the restriction that subjects complete practice on each task before moving on to the next.

During the PET session, subjects began by receiving one block of practice on each of the one-, two-, and three-back tasks to refamiliarize them with the procedures. The order of these practice blocks was counterbalanced across subjects.

The PET session proper consisted of 10 scans, 2 for each of the memory conditions (zero-, one-, two-, and three-back) and 2 for the Control condition. The order in which subjects received these conditions was counterbalanced across subjects in the following manner. Each subject was cycled through all five tasks in the first five scans before cycling through them again in the same order. The tasks were counterbalanced such that the zero-back and Control scans occurred either in second or fourth position, and one-, two-, and three-back occurred either in position 1, 3, or 5. Before each scan in the session, subjects received a short block of practice that was specific to the upcoming task.

### **PET Details**

#### *Imaging Procedure*

A Siemens ECAT EXACT-47 PET scanner was used. It produced 47 contiguous slices that were 3.375 mm (center to center) apart. The reconstructed in-plane reso-



First, intrasubject registration by an automated algorithm corrected motion between scans within a subject's PET session (Minoshima et al., 1993a). PET image sets for each subject were then transformed to a standard bicommissural stereotactic system (Talairach and Tournoux, 1988). The transformation procedure consisted of three steps: (1) detection of the midsagittal plane of the brain (Minoshima, Berger, Lee, & Mintun, 1992), (2) detection of the bicommissural (AC-PC) line of the midsagittal plane (Minoshima et al., 1993b), and (3) linear scaling followed by nonlinear warping of the brain to remove anatomic differences among subjects (Minoshima, Koeppe, Frey, & Kuhl, 1994). Next, a subtraction image set was created for each subject between the averaged images for each *n*-back task minus the Control condition.<sup>1</sup> The subtraction image sets were then averaged across subjects, producing a group-average subtraction-image set consisting of mean and standard deviation of CBF changes for each brain voxel. Standard deviations for the voxels were averaged within the brain to create a pooled estimate of variance, and *t*-statistical values were calculated for each voxel using a pooled variance estimate and correcting for multiple nonindependent comparisons (Friston et al. 1991; Worsley et al., 1992). Significant CBF changes were localized using stereotactic coordinates and are displayed in the figures on a standard nonlinearly warped MRI for visual interpretation.

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