

# Working Memory for Letters, Shapes, and Locations: fMRI Evidence against Stimulus-Based Regional Organization in Human Prefrontal Cortex

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**Investigations of working memory (WM) systems in the frontal cortex have revealed two stimulus dimensions along which frontal cortical representations may be functionally organized. One hypothesized dimension dissociates verbal from nonverbal WM processes, dividing left from right frontal regions. The second hypothesized dimension dissociates spatial from nonspatial WM, dividing dorsal from ventral frontal regions. Here we used functional magnetic resonance imaging to probe WM processes associated with three different types of stimuli: letters (verbal and nonspatial), abstract shapes (nonverbal and nonspatial), and locations (nonverbal and spatial). In a series of three experiments using the “*n*-back” WM paradigm, direct statistical comparisons were made between activation patterns in each pairwise combination of the three stimulus types. Across the experiments, no regions that demonstrated responses to WM manipulations were discovered to be unique to any of the three stimulus types. Therefore, no evidence was found to support either a left/right verbal/nonverbal dissociation or a dorsal/ventral spatial/nonspatial dissociation. While this could reflect a limitation of the present behavioral and imaging techniques, other factors that could account for the data are considered, including subjects’ strategy selection, encoding of information into WM, and the nature of representational schemes in prefrontal cortex.** © 2000 Academic Press

## INTRODUCTION

Working memory (WM) is the limited-capacity storage system involved in maintenance and manipulation of information over short periods of time (Baddeley, 1986). Attempts to localize brain regions responsible for WM processes, involved in all forms of higher-level cognition, have consistently implicated regions within frontal cortex. Studies of human patients with frontal

cortical lesions have often found impairments of WM functions (for reviews, see Petrides, 1989; Stuss *et al.*, 1994). Neurophysiological studies of primates have found cells in prefrontal cortex that fire during the delay periods in tasks requiring the short-term internal maintenance of target information (for reviews, see Fuster, 1997; Goldman-Rakic, 1987; Miller, 2000). In addition, over the past half-decade, the explosion of human functional neuroimaging experiments has reinforced earlier human and primate neurobiological findings, supporting the conclusion that the human prefrontal cortex (PFC) plays a critical role in the storage and manipulation of information in WM (e.g., Awh *et al.*, 1996; Baker *et al.*, 1996; Barch *et al.*, 1997; Braver *et al.*, 1997; Cohen *et al.*, 1994, 1997; Courtney *et al.*, 1996, 1997, 1998; D’Esposito *et al.*, 1995, 1998; Fiez *et al.*, 1996; Goldberg *et al.*, 1996; Haxby *et al.*, 1995; Jonides *et al.*, 1993, 1997; McCarthy *et al.*, 1994, 1996; Owen *et al.*, 1996, 1998; Paulesu *et al.*, 1993; Petrides *et al.*, 1993a,b; Salmon *et al.*, 1996; Schumacher *et al.*, 1996; Smith *et al.*, 1995, 1996; Swartz *et al.*, 1995; Sweeney *et al.*, 1996).

The theme of a growing body of recent neuroimaging experiments has been the attempt to partition prefrontal cortex into smaller regions that may subservise different components of WM. Baddeley (1986) has proposed that WM is not served by a unitary system, but rather by several distinct functional units: a central executive that supplies attentional control plus separate subordinate systems that are used to hold particular types of information in a form available for retrieval and/or manipulation by the central executive. According to Baddeley, one of these subordinate “slave” systems holds verbal (phonological/articulatory) information, while another deals with visuospatial information. In light of the putative dominance of the left hemisphere for verbal processes and the right hemisphere for nonverbal functions (Sperry, 1974), it has

been proposed that WM processes subdivide along the same dimensions within frontal cortex, with verbal WM implemented in the left frontal cortex and visual WM in the right. Some neuroimaging studies have specifically addressed this possibility, offering tentative evidence for a relative, although not absolute, left-right specialization of verbal versus nonverbal WM functions (Smith and Jonides, 1997).

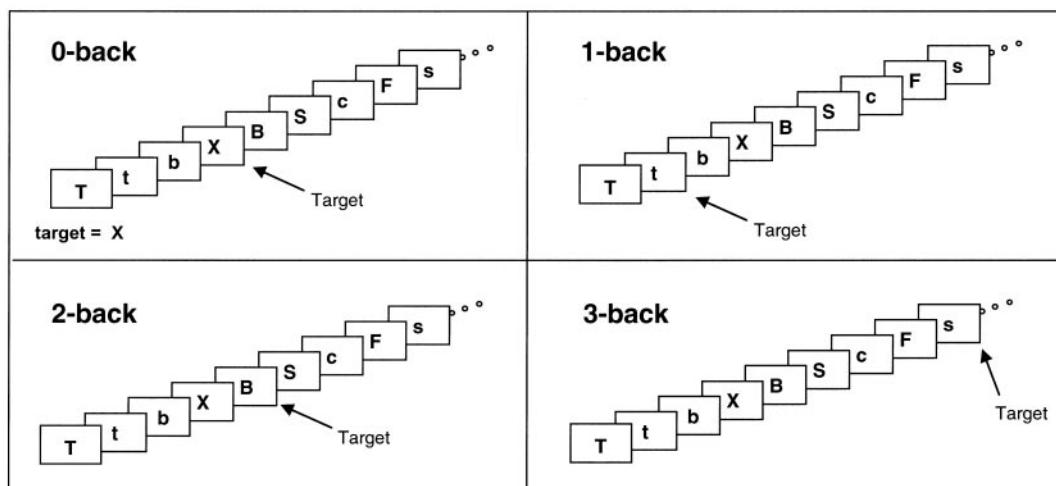
In addition to this verbal/nonverbal dimension, a second contrasting dimension has arisen from studies of primate neuroanatomy and neurophysiology. This second dichotomy contrasts WM of spatial versus nonspatial (or object) information, motivated by the division of posterior cortical regions into a dorsal pathway representing spatial ("where") and a ventral pathway representing visual form ("what") information (Ungerleider and Haxby, 1984). Some anatomical evidence suggests connectivity of differing degrees between frontal areas and these two posterior cortical streams. For instance, ventrolateral frontal areas receive input from inferotemporal cortex (Webster *et al.*, 1994), whereas middorsolateral frontal regions receive input from posterior parietal cortex (Cavada and Goldman-Rakic, 1989; but see also Petrides, 1994). Lesions or cooling of ventrolateral frontal cortex can impair non-human primates' performance on object-recognition WM tasks, while lesions to dorsolateral frontal cortex can impair performance on object-location WM tasks (for reviews, see Petrides, 1994; Fuster, 1997). Furthermore, Goldman-Rakic and colleagues have reported individual cells within dorsolateral cortex that appear to specialize in coding for the spatial location of objects during a delay period (Funahashi *et al.*, 1989, 1990) and a separate set of neurons within ventrolateral cortex coding for the visual object identities (Wilson *et al.*, 1993). These findings have led to the claim that primate prefrontal cortex is divided between a dorsal partition supporting spatial WM and a ventral partition supporting object WM (Goldman-Rakic, 1988, 1995). Motivated by this claim, neuroimaging studies of human frontal cortex have attempted to find regional variation in frontal activation during spatial versus object WM tasks, sometimes using tasks modeled directly on the nonhuman primate WM paradigms (e.g., Baker *et al.*, 1996; Courtney *et al.*, 1996, 1998; McCarthy *et al.*, 1996; Owen *et al.*, 1998; Smith *et al.*, 1995).

Collectively, the findings from neuroimaging investigations of both verbal/nonverbal and spatial/object dissociations have been inconclusive. Two recent comprehensive literature reviews and meta-analyses have concluded that the existing body of neuroimaging studies fails to support a dorsal/ventral dissociation between spatial and nonspatial WM functions (Owen, 1997; D'Esposito *et al.*, 1998). In addition to some supportive evidence, they report an abundance of findings contradicting the dissociation, including object-related

dorsal activation and spatial-related ventral activation. With regard to a left/right dissociation, D'Esposito *et al.* (1998) found some suggestions of a relative specialization for right-hemisphere processing of spatial information and left-hemisphere processing of nonspatial information, but only within ventral and not within dorsal PFC regions. This finding was not intended to specifically address the question of verbal versus nonverbal hemispheric specialization, however, as tasks were collapsed across both verbal and nonverbal stimuli. Nevertheless, there does seem to be an indication of a relative preference for processing of verbal materials in the left ventrolateral frontal region. A third review (Fiez *et al.*, 1996) found a dissociation much like the one found by D'Esposito *et al.* (1998): a left lateralization of activation within ventral frontal cortex for verbal WM processes. This left-hemisphere specialization is not surprising, given that the left ventral region implicated in these two reviews is typically identified as Broca's area, known for over a century to be specialized for speech-related processes. Thus, meta-analyses provide some evidence for the specialization of left ventral frontal cortex—perhaps merely Broca's area—for verbal processing, but little additional support for either of the two hypothesized dissociative dimensions.

Meta-analyses, however, are limited in that they compare results from different types of WM tasks, performed by different subjects in different labs. Accordingly, while they can map the central tendencies of focal activations in different stimulus conditions across studies, they cannot directly compare the degree to which these areas activate in the different stimulus conditions. To produce solid evidence for dissociations, within-subject experimental manipulations of the stimulus dimensions are necessary. To date, there have been several within-subject experiments directly testing for dissociations between object and spatial WM (Baker *et al.*, 1996; Belger *et al.*, 1998; Courtney *et al.*, 1996, 1998; McCarthy *et al.*, 1996; Owen *et al.*, 1998; Petit *et al.*, 1998; Smith *et al.*, 1995), but fewer directly contrasting verbal and spatial WM (D'Esposito *et al.*, 1998; Smith *et al.*, 1996) or verbal and object WM (Paulesu *et al.*, 1993; Salmon *et al.*, 1996).

In addition to within-subject experimental manipulations, an ideal test for dissociations would involve direct statistical comparisons between all conditions to avoid false-positive findings. Indirect comparisons, such as visual inspections of contrasting statistical maps or tabulations of Talairach coordinates, are less than sufficient. For example, suppose that the same single brain area participates equally in two WM tasks involving two different stimulus types, yet the area differs in its response to the two corresponding matched control tasks. Without direct statistical comparisons between all four conditions, a false inference of WM-related dissociation could be drawn, as the WM-



**FIG. 1.** Trial schematic of  $n$ -back task conditions (e.g., Braver *et al.*, 1997). Note that the sequence of stimuli may be identical between conditions, while the target changes by condition.

minus-control subtractions within each stimulus type may not be distinguishable from a situation in which the area responded equally to the control tasks but differently between WM tasks. Problems with indirect comparisons of subtraction images can be further compounded by the statistical thresholding used in most neuroimaging analyses. Activation patterns are ignored below arbitrary significance thresholds; consequently, if the experiment has limited power and activation is detectable only at levels of significance close to threshold, noisy distributions of activation will appear in statistical maps. Inferences of dissociation are sometimes drawn from the apparent absence of activation in a brain region based on statistical thresholds left to the discretion of investigators, when in fact activation may be present, unexamined, just below the arbitrary threshold. Instead of using indirect comparisons, direct statistical evidence for dissociations can be accomplished using fully factorial ANOVA or GLM models, with one factor for stimulus type and a second factor for WM load. A main effect of stimulus type will identify stimulus-specific brain regions, though not necessarily WM related; the interaction between the two factors can identify regions specific to WM processing of one or the another stimulus type.

The present series of experiments provided controlled comparisons between WM for three different types of stimuli. All three experiments used consistent methodologies and analyses in a widely used WM paradigm. Experiment 1 tested WM for letters and abstract shapes, holding spatial locations constant, and thereby provided a test of verbal versus nonverbal WM. Experiment 2 involved WM for spatial locations and letters to test spatial versus (verbal) nonspatial WM. Experiment 3 contrasted WM for shapes versus locations, diminishing the verbal component through articulatory suppression, to directly test spatial versus

(nonverbal, nonspatial) object WM. Although a direct three-way comparison between WM for letters, shapes, and locations would have been desirable within subjects, it was not feasible due to the conflicting demands of having to collect sufficient numbers of trials of each type while having to restrict the duration of the time each subject spent in the scanner. Furthermore, as noted later under General Discussion, the possibility of discovering dissociations may be diminished in any paradigm that interleaves task demands to maintain different types of information. This danger would have been magnified if all three types of task had been combined within an hour-long session.

All three experiments used the “ $n$ -back” task, in which subjects view a continuous sequence of stimuli, deciding for each stimulus whether it matches the stimulus shown  $N$  stimuli earlier in the sequence (Awh *et al.*, 1996; Braver *et al.*, 1997; Cohen *et al.*, 1994, 1997; Gevins and Cutillo, 1993; Smith *et al.*, 1996). For example, in a 3-back condition of the letter  $n$ -back task, subjects should respond positively whenever the letter they see is the same as the one viewed three letters earlier (see Fig. 1). In a 0-back condition, subjects respond positively to any appearance of a prespecified letter. At all levels of WM load, both the series of stimuli and the responses can be identical; only the task instructions distinguish between conditions. An additional attraction of the  $n$ -back paradigm is that it can be used equally well with different types of stimuli, including letters, shapes, and spatial locations. For example, stimuli can be letters (verbal) or shapes (nonverbal) that appear at varying locations, and subjects can be asked to respond to repeats of either stimulus identity (nonspatial) or location (spatial). Thus, by varying WM load and crossing this with stimulus type, it was possible to identify areas of brain activity related to WM function and to evaluate their specificity

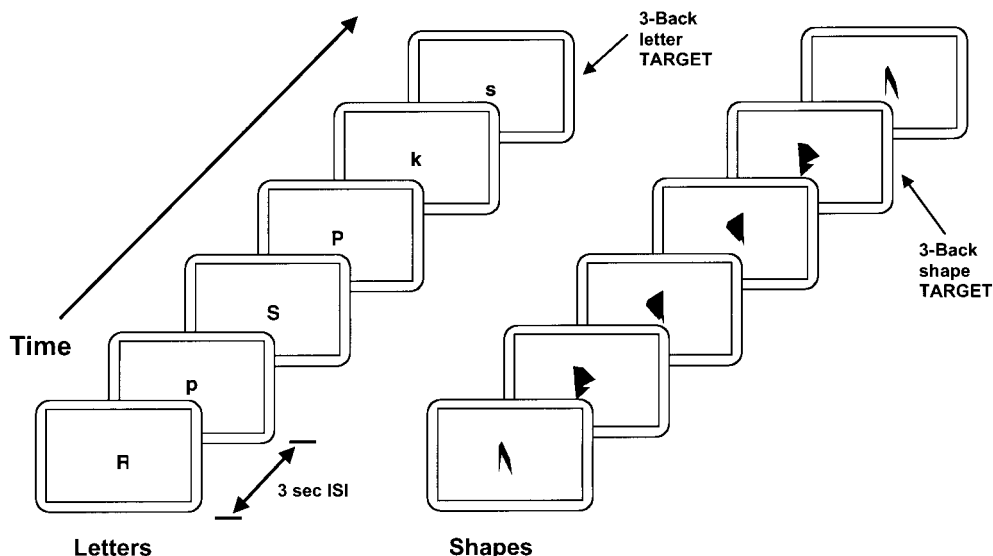


FIG. 2. Task conditions specific to the  $n$ -back variant used in Experiment 1.

to information type in a series of within-subject experiments.

### EXPERIMENT 1: LETTERS VERSUS SHAPES

The first experiment contrasted WM for letters versus abstract visual shapes. This comparison addresses the hypothesis that human PFC has regional specializations for verbal versus nonverbal information. Although a direct comparison between letter and shape memory requires the use of somewhat different stimuli across the two types, this contrast avoids conflation with the hypothesized contrast between spatial and nonspatial WM, because both letters and shapes can be presented centrally, holding spatial location constant.

The letters condition was an extension of prior functional magnetic resonance imaging (fMRI) experiments using the  $n$ -back letter task (Braver *et al.*, 1997, in which a subset of this experiment's data was originally reported). In our earlier studies, we observed bilateral activation of both dorsolateral (BA 46/9) and ventrolateral (BA 44) PFC, as well as bilateral activation of premotor (BA 6) and parietal (BA 7/40) cortex, all regions commonly coactivated in WM tasks. Interestingly, although activation was bilateral, there was a tendency for right prefrontal regions to have a larger spatial extent of activation than regions in the left hemisphere, which is inconsistent with the hypothesis that left frontal cortex is relatively specialized for verbal WM. Parenthetically, it is worth noting that activation of both dorso- and ventrolateral regions in this nonspatial task also argued against a ventral specialization for nonspatial information.

The shapes condition in Experiment 1 was developed as a direct analogue to the letters condition, with the

only difference being the presentation of abstract, unfamiliar shapes in place of letters (see Fig. 2). The shape stimuli were drawn from the standard set of Attneave and Arnoult (1956), normed for verbalizability. Stimuli with the lowest verbalizability scores were chosen, following use of such stimuli in a previous PET study of WM (Smith *et al.*, 1995, Experiment 2). These stimuli provide the opportunity to contrast Baddeley's two proposed slave WM stores (Baddeley, 1986): the verbal articulatory loop, presumably used to remember letters, and the nonverbal visuospatial sketchpad, used to remember visual shapes.

Two prior experiments have directly compared verbal with nonverbal nonspatial WM processes, using verbal tasks with consonants and visual tasks with Korean letters for which subjects had no verbal representation (Paulesu *et al.*, 1993; Salmon *et al.*, 1996). In both experiments, relatively greater activation was found with the verbal tasks in left premotor and left posterior inferior frontal (Broca's) areas, as well as left superior temporal, bilateral insula, left inferior parietal, and bilateral sensorimotor activation. Paulesu and colleagues also obtained activation bilaterally in the supplementary motor areas (SMA) and cerebellum, along with right-lateralized homologues of each of their left-hemisphere activations (albeit with lower statistical significance). In Salmon *et al.* (1996), activation in the visual WM task was found primarily in the left parieto-occipital sulcus plus bilateral activation in several occipital areas, with some tentative reports of left inferior temporal and left middle and medial frontal activation; Paulesu *et al.* (1993) did not report visual task activation. Thus, existing studies have reported no evidence of a right-hemisphere dominance for nonverbal WM processes, while supporting a relative, but



not absolute, left-hemisphere dominance for verbal WM processes.

## Materials and Methods

### Subjects

Informed consent was obtained from eight neurologically normal right-handed subjects (two female, six male). Their ages ranged from 18 to 25 years ( $M = 21.8$ ). All subjects were given practice with the task and were scanned only after reaching a criterion level of performance (75% accuracy or greater) in each condition.

### Cognitive Task

Subjects performed a variant of the  $n$ -back task using letters and abstract shapes as memoranda (see Fig. 2). Four levels of memory load (0-, 1-, 2-, and 3-back) were presented in a factorial design fully crossed with the two levels of stimulus type (letters and shapes), yielding a total of eight task conditions. Trials were blocked by condition, with 19 trials per block and 56 blocks presented in a pseudorandom order which ensured that each of the eight conditions was presented once within every set of 8 blocks.

A block of a single condition lasted 63 s, consisting of a 3-s presentation of task instructions (e.g., "Target = 2-back letter repeats"), followed by a 3-s pause and then 19 3-s test trials. Each test trial began with a 0.5-s presentation of a stimulus (letter or shape), followed by a 2.5-s blank-screen interstimulus interval. The use of a 3-s trial duration replicated the trial durations in our earlier letter  $n$ -back experiments (Braver *et al.*, 1997, Experiment 1). At the end of each set of trials, subjects saw the word PAUSE for approximately 20 s before the next block of trials began, providing a rest period while fMRI data were written to disk. Seven sets of eight blocks were run within a period of approximately 70 min.

On each trial, subjects observed stimuli presented in the center of a visual display, projected into the MR scanner from a Macintosh computer running PsyScope software (Cohen *et al.*, 1993). Letters were presented in a 24-point Helvetica font, in randomly chosen upper- or lowercase. The letter stimuli were chosen from a set of 18 letters (all consonants except L, W, and Y) selected to minimize the lexicality and pronounceability of strings of sequential letters. Shape stimuli were chosen from a set of 40 Attneave shapes: 6-sided random abstract polygons (Attneave and Arnoult, 1956). Subjects responded to each stimulus presentation by pressing one of two buttons on a response box held in their right hand, with a fiber-optic connection to the Macintosh computer. To respond to a stimulus as a target, subjects pressed the button under their index finger; to

respond to a stimulus as a nontarget, they pressed the button under their middle finger.

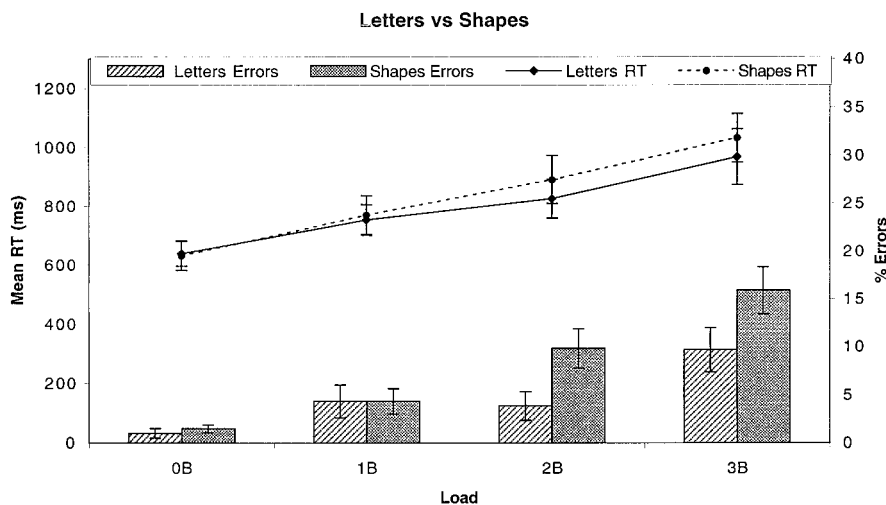
In the 0-back condition, a single stimulus was specified as the target in the instructions at the beginning of a block (e.g., "Target = X" or "Target = this shape: <>"). In the 1-back condition, the target was any stimulus identical to the immediately preceding stimulus. In the 2-back and 3-back conditions, the target was any stimulus identical to the stimulus presented two or three trials prior, respectively (see Figs. 1 and 2). Subjects were told not to distinguish between upper- and lowercase presentations of the same letter. This mixing of cases was intended to encourage subjects to encode and rehearse letter stimuli as verbal phonemes, instead of as visual letter forms. Stimuli were targets on 33% of trials; of the remaining 66% nontargets, 6% of the stimuli were chosen from each of the other three  $n$ -back conditions, while 48% used stimuli that had not appeared in any of the previous three trials. Thus, the frequency and distribution of repeated items was the same across all levels of load.

### MRI Scanning Procedures

Images were acquired using a conventional 1.5-T GE Signa whole-body scanner and standard RF head coil at the MR Research Center at the University of Pittsburgh Medical Center. Twenty-seven contiguous slices (3.75-mm<sup>3</sup> isotropic voxels) were obtained parallel to the AC-PC line. Double-oblique slice locations were prescribed following a procedure designed to maximize reliability of localization across subjects (Noll *et al.*, 1997). Structural images were acquired in the same locations as the functional images, using a standard T1-weighted pulse sequence. Functional images were acquired using a 4-interleave spiral pulse sequence (TR = 750 ms, TE = 35 ms, FOV 24 cm, flip 40°; Noll *et al.*, 1995). This T2\*-weighted pulse sequence allowed 9 slices to be acquired every 3 s, completing a set of 27 slices every 9 s. The same set of 9 slices was scanned for three consecutive trials at a time, following which a different set of 9 slices was scanned. Slice set order was counterbalanced across blocks to control for asynchronous acquisitions across regions. Scanning occurred during only 12 of the 19 trials in each block. No scans were acquired during the first 4 trials to allow the loading of subjects' working memories and the settling of the fMRI signal to a steady state. The other 3 unscanned trials occurred while switching between sets of 9 slices. Thus, 4 complete 27-slice volumes were acquired in each block of 19 trials; with 56 blocks run, a total of 224 functional volumes were collected.

### Behavioral Data Analysis

Behavioral data were analyzed to confirm subject compliance with task performance and the effectiveness of the manipulation of WM load and to evaluate



**FIG. 3.** Behavioral data from Experiment 1. Bar graphs denote error rate with the scale on the right. Line graphs denote reaction time, with the scale on the left. Error bars represent standard errors.

relative performance across stimulus type. Subjects' performance was evaluated with 4 (load)  $\times$  2 (stimulus type) ANOVAs, using both response time (RT) and accuracy measures.

#### Imaging Data Analysis

Functional images from each subject were corrected for head movement using 6-parameter rigid-body transformations determined by an automated algorithm (Woods *et al.*, 1992). Structural images from each of the eight subjects were coregistered to a common reference brain using a 12-parameter affine transformation (Woods *et al.*, 1993). The transform of the structural images was applied to the functional images from each subject, then the transformed functional images were smoothed using a three-dimensional Gaussian filter (8-mm FWHM) to accommodate between-subject anatomic differences. The functional images were also globally mean-normalized to equate overall image intensities over time and between subjects.

A repeated-measures two-way mixed-model ANOVA was performed independently on each voxel in the entire set of coregistered data, treating subjects as a random factor and WM load and stimulus type as within-subjects factors. Voxels were identified that exhibited either a significant main effect of stimulus type ( $F(1,7) = 12.25$ ,  $P < 0.01$ ) or a load-by-stimulus type interaction ( $F(3,21) = 4.87$ ,  $P < 0.01$ ). These two ANOVA terms identify only those voxels that significantly differ in their response to the two stimulus types. The main effect of load was not formally examined, because it does not distinguish between stimulus types and therefore cannot identify dissociations. Furthermore, areas of dissociation, responsive to one and not the other stimulus type, would not necessarily ap-

pear in a map of main effect of load, given the dilution of the mean load effect from the "nonpreferred" stimuli.

Regions comprising eight or more contiguous suprathreshold voxels were then identified, as a precaution against type 1 errors (Forman *et al.*, 1995), ensuring an effective image-wide false-positive rate of 0.01. Only those regions that exhibited increased activation with higher memory loads in at least one of the stimulus conditions were included for further analysis. The regions meeting these criteria were overlaid onto the structural MR scan corresponding to the reference brain and then transformed to the standard Talairach stereotaxic space (Talairach and Tournoux, 1988) using AFNI software (Cox, 1996).

## Results

#### Behavioral Data

As shown in Fig. 3, response latencies increased significantly with increased load ( $F(3,21) = 23.13$ ;  $P < 0.0001$ ), as did error rates ( $F(3,21) = 25.17$ ;  $P < 0.0001$ ). Response times did not significantly differ between stimulus types ( $F(1,7) = 1.87$ ;  $P > 0.1$ ), and there was no interaction between load and stimulus-type effects on RT ( $F(3,21) = 2.10$ ;  $P > 0.1$ ). However, subjects made more errors overall with shapes than with letters ( $F(1,7) = 10.72$ ;  $P < 0.05$ ). This main effect was moderated by a significant interaction ( $F(3,21) = 4.90$ ;  $P < 0.01$ ); at the two lower loads, accuracy did not differ between stimulus types, whereas at higher loads, accuracy was worse with shapes than with letters.

#### Imaging Data

The ANOVA on the fMRI data yielded several regions meeting the criteria of voxel-wise significance ( $P < 0.01$ ), extent (eight or more contiguous voxels),

and load-related signal increases. Six regions exhibited a significant main effect of stimulus type (see Fig. 4a and Table 1). In four of the six regions, the mean MR signal was higher in the Shapes conditions: right superior parietal lobe (BA 7), left inferior parietal lobe (BA 40), right middle frontal gyrus (BA 46), and a region covering part of the anterior cingulate (BA 32) and a portion of the medial frontal gyrus (BA 8). The two regions with higher mean signal during the Letters conditions included a region straddling the inferior portion of the left precentral gyrus (BA 6) and the left superior temporal gyrus (BA 22) and one covering another portion of the anterior cingulate (BA 32), superior and posterior to the previously noted anterior cingulate region, and a portion of the medial frontal gyrus (BA 6).

In addition to areas exhibiting a main effect of stimulus type, there were two areas associated with a significant interaction between load and stimulus type ( $P < 0.01$ ; see Fig. 4b and Table 1). One of these was within the anterior cingulate (BA 32), corresponding to a subset of the voxels in the more rostral of the two regions observed in the stimulus type main effect. In this region, higher memory loads increased the MR signal to a greater extent in the Shapes conditions than it did in the Letters conditions. The second region was observed in the left precentral gyrus (BA 6), just superior to BA 44. In this region, the MR signal increased more in the Letters than in the Shapes conditions at higher levels of load.

## Discussion

Experiment 1 provided only limited evidence for a left/right asymmetry in verbal/nonverbal WM processes. The asymmetry manifested as regions exhibiting a greater sensitivity to letters than to shapes in left premotor and temporal regions. In addition, the asymmetry also appeared in a medial region in the anterior cingulate (AC) and SMA (or more precisely, "pre-SMA"; cf. Petit *et al.*, 1998; Picard and Strick, 1996). No letter-specific areas were found lateralized to the right hemisphere. Conversely, the right dorsolateral prefrontal cortex (DLPFC) contained one region, showing relatively greater activation with shapes WM. Additional regions responding more to shapes were observed in the AC and in two posterior cortical regions, the right superior parietal lobe and the left supramarginal gyrus. In the left frontal areas, no regions responded more in the Shape conditions. Thus, on the surface,

these results extend those of Paulesu *et al.* (1993) and Salmon *et al.* (1996), in appearing to support a full double dissociation between left and right frontal regions for verbal versus nonverbal processes. However, such a conclusion must be tempered by important qualifications.

For instance, an examination of the pattern of activity within the right DLPFC shape-sensitive region reveals that it was also sensitive to letter WM. It exhibited a more linear response to increasing WM load with letter than with shape stimuli, and the 3-back level of load there was no difference in MR signal response between stimulus types. The same right DLPFC region has appeared in earlier letter *n*-back studies (Braver *et al.*, 1997; Cohen *et al.*, 1997). Furthermore, this same general region was found to be sensitive to spatial WM and *not* object WM in an earlier PET study (Smith *et al.*, 1995, Experiment 2). Thus, it would be problematic to consider this right DLPFC region dedicated to WM processing of object shape alone.

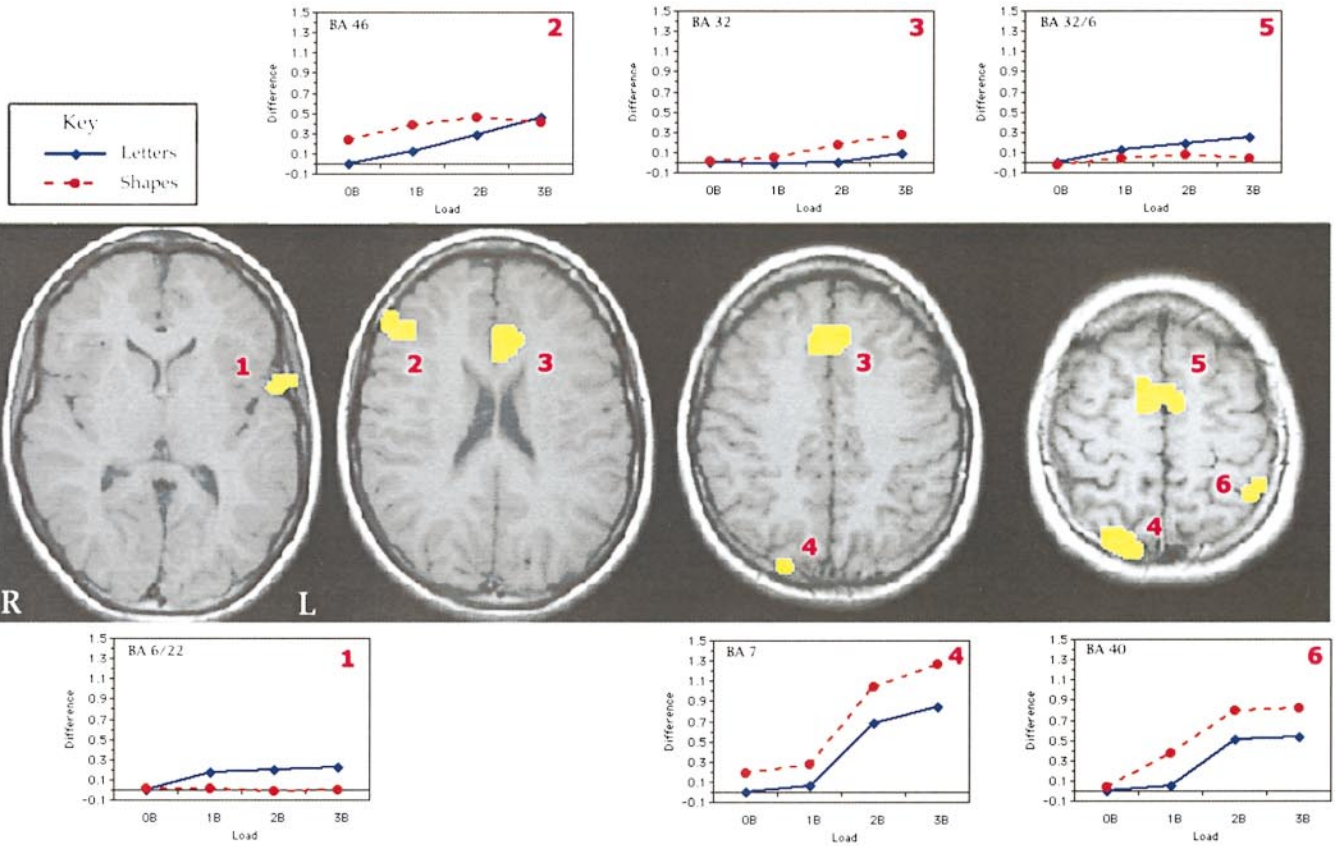
Moreover, the left-lateralized regions, more sensitive to manipulations of letter WM, were not in the DLPFC at all, but rather in more posterior premotor and superior temporal (auditory association) areas. Surprisingly, there was no Broca's area (left area 44/45) region found to be differentially sensitive to letter WM, even though this area is considered central to verbal WM rehearsal; the aforementioned letter-specific regions were located just posterior and inferior to Broca's area. In the premotor region, exhibiting a true statistical interaction between memory load and stimulus type, the interaction was not the result of activation occurring only with letters at higher loads, which would indicate a clean dissociation, but rather a more complex relationship wherein both activations increased to increasing load with stimulus types.

Furthermore, the left supramarginal gyrus, a parietal region commonly believed to be part of the verbal WM articulatory loop along with Broca's area (Paulesu *et al.*, 1993), showed greater activation for shapes. This, along with the failure to differentially activate Broca's area, raises a suspicion that subjects may have used verbal strategies for naming and subvocally rehearsing shapes, despite our efforts to use objects designed to be difficult to name. Indeed, posttest interviews with subjects revealed that most attempted to verbally label at least some subset of the shape stimuli. None reported success in attempting to label all of the shapes, however, so it appears that they relied on a

**FIG. 4.** Regions of activity in Experiment 1 associated with (a) significant main effects of stimulus type (Letters vs Shapes) and (b) significant interactions between load (0-back through 3-back) and stimulus type. Graphs plot percentage signal change in each condition relative to signal in the 0-back Letters condition. Four representative axial slices are shown from a reference brain registered to Talairach space (Talairach and Tournoux, 1988). Slices are shown at heights  $z = +8, +24, +40,$  and  $+56$  mm. The same four slices are depicted in all subsequent figures. Images are displayed according to the radiologic convention (left hemisphere is shown on the right) in this and all subsequent figures.



**a**



**b**

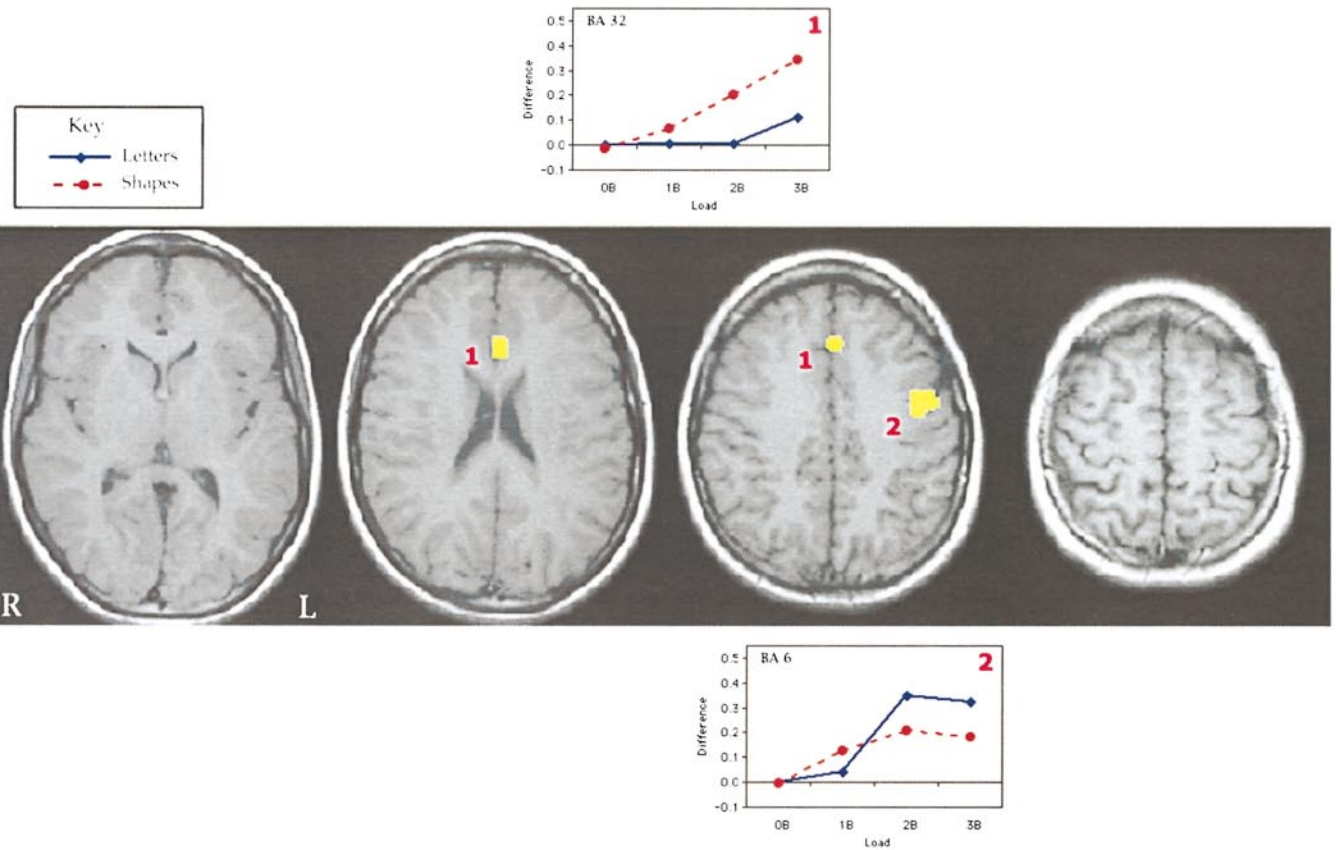




TABLE 1

Location of Regions of Activation Obtained in Each Experiment by Brodmann's Area (BA) and Talairach Coordinates, with Mean and Peak Significance Level Indicated as a Standardized Z Statistic

Experiment	Gyrus/region	Talairach coordinates				Mean Z	Peak Z
		BA	x	y	z		
<b>1. Letters vs Shapes</b>							
Main effects							
Shapes > Letters	Ant cingulate	32	2	27	35	3.06	4.22
	L inf parietal	40	-41	-47	56	3.01	3.47
	R sup parietal	7	21	-75	48	2.81	3.53
	R mid frontal	46	47	33	18	2.65	3.08
Letters > Shapes	Ant cingulate + medial frontal	32/6	6	11	45	2.79	3.47
	L premotor + L sup temporal	6/22	-57	4	4	2.63	2.96
Interactions							
	L premotor	6	-43	-1	36	2.94	3.78
	Ant cingulate	32	-1	26	28	2.72	3.47
<b>2. Letters vs Locations</b>							
Main effects							
Locations > Letters	L mid frontal + sup frontal	6/8	-24	5	50	2.80	3.37
	L fusiform	19	-34	-47	-10	2.60	2.79
	R mid frontal + sup frontal	6/8	25	7	48	2.61	2.92
	R sup/inf parietal + L/R precuneus	7/40	21	-62	44	2.81	4.11
	R inf frontal	44	49	14	15	3.17	3.75
Interactions							
	R inf parietal	40	35	-37	37	2.91	3.42
	R inf frontal	45/47	35	25	2	2.69	3.42
	Ant cingulate	32	-6	15	39	2.51	2.87
<b>3. Shapes vs Locations</b>							
Main effects							
Locations > Shapes	R sup/inf parietal + L/R precuneus	7/40	11	-73	46	2.95	4.12
	R mid frontal	6/8	25	0	51	2.40	2.58
Shapes > Locations	L inf frontal	44/45	-37	18	18	2.50	2.83
Interactions							
	R ant cingulate	32	12	23	31	2.84	3.84
	R mid frontal	9/8	47	12	32	2.72	3.64
	R premotor	6	30	4	43	2.67	3.10
	L mid frontal + L inf frontal	9/8/44	-37	11	28	2.57	2.93

combination of verbal and visual maintenance strategies. This concern limits the conclusions that can be drawn from this experiment about regional specializations for nonverbal WM. Experiment 3, below, addresses this issue of verbal strategy confounds through the use of vocal suppression of verbal WM processes in an experiment involving the same shape stimuli.

An additional caveat about the current experimental data arises from the fact that despite our efforts to equate the difficulty of the *n*-back task between the two stimulus types, the behavioral data indicated that the Shapes conditions were somewhat more difficult at higher levels of WM load. This inequality might account for the anterior cingulate region demonstrating shape WM sensitivity, as the AC is commonly found to be sensitive to increases of task difficulty and degradation of performance (Barch *et al.*, 1997; Dehaene *et al.*, 1994; Gehring *et al.*, 1993; Paus *et al.*, 1993). Of course, this fails to explain the other AC region showing letter WM sensitivity. Note, however, that this letter-related medial region was localized not only to the AC, but also contained adjoining portions of the pre-SMA, from the same Brodmann's area as the let-

ter-related region in the premotor cortex. Both areas, pre-SMA and premotor, are believed to be used in verbal planning (Fiez *et al.*, 1996; Paulesu *et al.*, 1993). Considerations of task difficulty may also cloud interpretation of the response of the parietal regions, activated in both Letters and Shapes conditions, but to a greater degree in Shapes conditions perhaps due simply to the increased difficulty.

Finally, while the WM task was identical in both Shapes and Letters conditions, the visual stimuli themselves differed. This raises the possibility that the different patterns of activation may have been due, at least in part, to different activation from letters due to differences in low-level visual complexity. Some investigations of spatial WM have avoided the problem by presenting a particular type of stimulus (letter, face, or shape) in different locations, contrasting spatial and nonspatial WM with identical stimulus arrays (e.g., Courtney *et al.*, 1996; Smith *et al.*, 1995). Experiments 2 and 3, below, employed this same strategy in combination with manipulations designed to avoid possible verbal encoding of nonverbal stimuli.

## EXPERIMENT 2: LETTERS VERSUS SPATIAL LOCATIONS

This experiment contrasted WM processes with letters versus spatial locations. It was designed, in part, to minimize the likelihood that subjects would be driven to maintain nonverbal stimuli using a verbal coding strategy. Posttest questioning of pilot subjects revealed that in a spatial variant of the *n*-back task, subjects reported using a geometric nonverbal strategy to remember and sequentially order spatial locations, perhaps akin to covert eye-movement planning or visual imagery. This nonverbal strategy is just the type of process that Baddeley (1986) proposed should occur in the visuospatial “scratchpad” slave system. Furthermore, by presenting letters in varying locations with sequential *n*-back trials, the same set of stimuli could be used in all conditions, differentiating between letter WM and location WM simply through task instructions. This would ensure that subjects receive identical visual displays in both conditions and eliminate a potential confound between WM and differential low-level visual experience. Finally, this task provided another opportunity to equate performance between stimulus types, to minimize the chance that one type would activate some regions more strongly due to increased effort.

Note that a contrast between letters and spatial locations tests both of the two hypothesized dissociations: the verbal/nonverbal dichotomy tested in Experiment 1 and also the spatial/nonspatial contrast advocated by Goldman-Rakic (1995). According to the latter contrast, one would expect to find more dorsal activation with spatial WM task and more ventral activation with the letter (nonspatial) task. Evidence inconsistent with this hypothesis has already been reported in Experiment 1, in which both types of stimulus (centrally presented letters and shapes) presumably recruited only nonspatial WM. Whereas the dorsal/ventral hypothesis predicts that both types of nonspatial stimuli should activate only ventral frontal regions, we in fact observed activation in right dorsal PFC for shapes WM.

Two prior experiments have also compared letter and location WM activation, yet they arrived at two different conclusions. The first, a PET experiment by Smith *et al.* (1996, Experiment 2), compared letter with location WM using 3-back and 0-back tasks. They found activation in the letter conditions in Broca’s area, and bilaterally in the DLPFC, and parietal cortex, although activation in the right hemisphere was less significant than in the left. In the location conditions, activation was also found bilaterally in parietal areas, DLPFC, and SMA, although the magnitude of activation was greater on the right. Their analysis was limited by the fact that they compared only the results of the 3-back minus 0-back subtractions with each

stimulus type, without directly comparing the two types. Smith *et al.* (1996) concluded that, despite the bilateral appearance of regions, these results supported the hypothesis of a left/right asymmetry between verbal and nonverbal WM processes. It is worth noting that these results did not support a dorsal/ventral dissociation, however. In contrast, in an fMRI experiment by D’Esposito *et al.* (1998), no differences at all were found between activation in letter and location WM conditions. This second experiment therefore found no evidence for either a left/right or a dorsal/ventral dissociation. On the other hand, one might be cautious in drawing negative conclusions from this second experiment because it involved different stimulus arrays in the letter and location conditions and because, like the Smith *et al.* (1996) experiments, it lacked a direct statistical comparison between activation in the two types of stimulus conditions.

## Materials and Methods

### Subjects

Informed consent was obtained from seven neurologically normal right-handed subjects (three female, four male). Their ages ranged from 18 to 27 years ( $M = 20.6$ ). All subjects were given practice with the task and were scanned only after reaching a criterion level of performance, at least 75% accuracy in all conditions.

### Cognitive Task

Subjects performed a variant of the *n*-back task using both spatial locations and letters as memoranda (see Fig. 5). Two levels of memory load (0- and 3-back) were presented in a factorial design fully crossed with the two levels of stimulus type (Locations and Letters), yielding four task conditions. The 1-back and 2-back conditions from Experiment 1 were eliminated in order to increase statistical power in the two extreme levels of WM load by doubling the relative number of trials in these two conditions. Trials were blocked by condition, with 19 trials per block and 32 blocks presented in pseudorandom order, which ensured that each of the four conditions was presented once within every set of 4 blocks.

A block of a single condition lasted 1.4 min, consisting of a 4-s presentation of task instructions (e.g., “Target = 3-back LOCATION repeats”, “Target = 1-back LETTER repeats”), followed, after a 4-s pause, by 19 4-s test trials. The duration of each trial was extended by 1 s relative to those in Experiment 1 to accommodate a newer fMRI pulse sequence that allowed for the simultaneous collection of images in an increased number of slice planes. Each test trial consisted of the presentation of a letter in a noncentral location, 500 ms in duration, followed by 3.5 s of blank screen. Following every block of 19 trials, subjects saw the word PAUSE

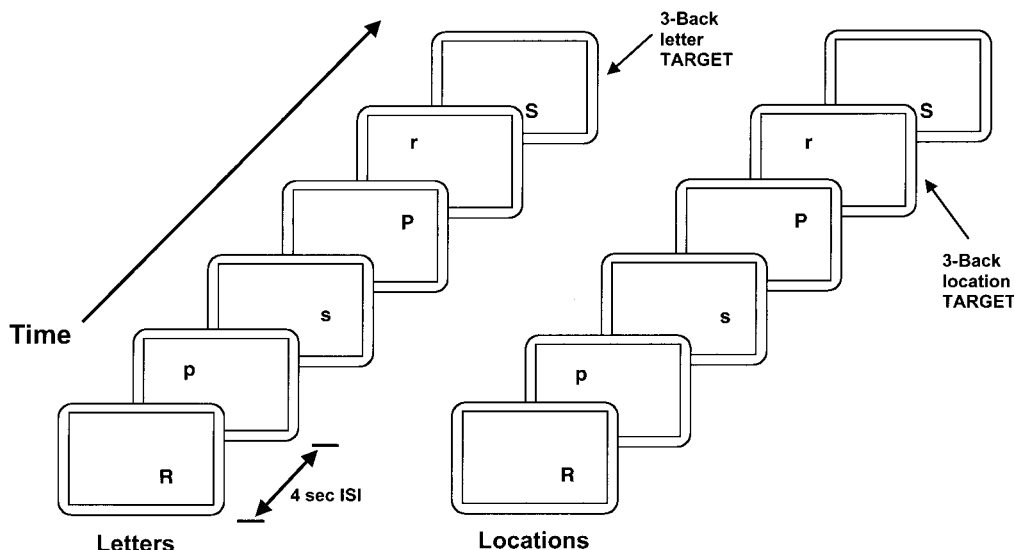


FIG. 5. Task conditions specific to the  $n$ -back variant used in Experiment 2.

for approximately 30 s before the next block of trials began. Thirty-two blocks of trials were run within a period of approximately 1 h.

Letters were chosen from the same set of 18 consonants used in Experiment 1. The locations of letter presentation were chosen from a set of 18 positions evenly spaced around the circumference of an approximately 3-in. diameter circle centered in the display. Eighteen positions were used to discourage a verbal coding for locations by decreasing the configural familiarity and ease of naming each of the locations, as might occur with a more familiar configuration like 8 locations (akin to a compass) or 12 locations (like the face of a clock). Subjects responded to each letter presentation in the same manner as in Experiment 1.

The 0-back conditions were modified to help equate performance between stimulus types. In pilot testing, it was found that if subjects were given only a single spatial location as their fixed 0-back Locations target, they could simply move their gaze to that spot and monitor for the appearance of letters, ignoring all other stimuli and qualitatively altering the nature of the task. Therefore, in the 0-back Locations condition, subjects were shown three different spots on the screen, marked with dots, and told that a letter appearing in any of the three locations should be considered a target. To equate performance between stimulus types, the 0-back Letters condition was then modified to present three different letters as the fixed target set rather than just one.

As before, 33% of trials contained targets; of the remaining 66% nontargets, 6% of the stimuli were chosen from each of the three other  $n$ -back conditions (including 1- and 2-back distractors), while 48% used new stimuli that had not appeared in any of the previous three trials.

### MRI Scanning Procedures

Images were acquired using the same 1.5-T scanner used in Experiment 1. Twenty-six contiguous slices ( $3.75\text{-mm}^3$  isotropic voxels) were obtained parallel to the AC-PC line. Structural images were acquired in the same locations as the functional images, using a standard T1-weighted pulse sequence. Functional images were acquired using a 2-interleave spiral pulse sequence (TR = 2000 ms, TE = 35 ms, FOV 24 cm, flip  $80^\circ$ ). This T2\*-weighted pulse sequence allowed 26 slices to be acquired every 4 s. Fifteen functional volumes were collected within each 19-trial block, with scans synchronized to trial onsets. No scans were collected during the first 4 trials of each block, to allow the loading of subjects' working memories and the settling of the fMRI signal to steady state. With 32 blocks, a total of 480 functional volumes were collected.

### Imaging Data Analysis

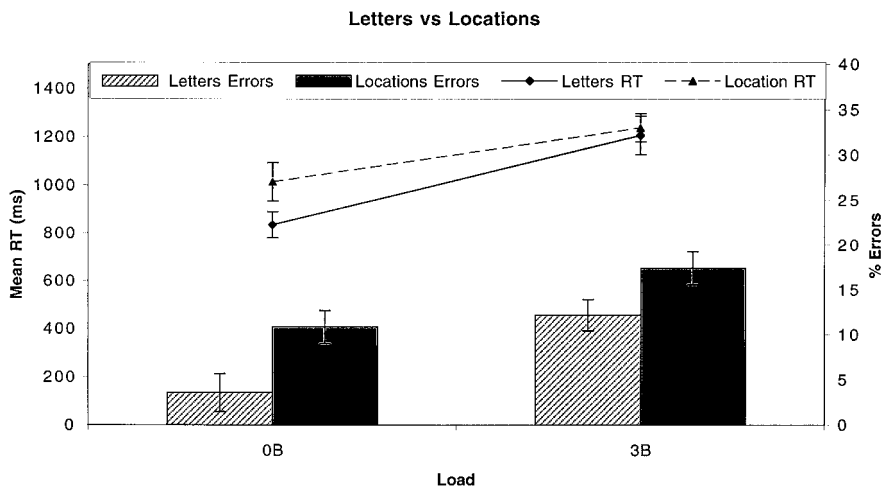
Functional images were prepared for analysis as in Experiment 1. A repeated-measures ANOVA was used to identify voxels exhibiting signal increases with higher memory load along with either: (1) a significant main effect of stimulus type or (2) a load-by-stimulus type interaction (for each,  $F(1,6) = 13.75$ ,  $P < 0.01$ ). Again, the additional constraint that regions contain eight or more contiguous voxels ensured an effective image-wide  $\alpha$  of  $P < 0.01$  (Forman *et al.*, 1995).

## Results

### Behavioral Data

Subjects' performance was evaluated using 2 (load)  $\times$  2 (stimulus type) ANOVAs, using both RT and





**FIG. 6.** Behavioral data from Experiment 2. Bar graphs denote error rate with the scale on the right. Line graphs denote reaction time, with the scale on the left. Error bars represent standard errors.

accuracy measures (see Fig. 6). As in Experiment 1, RTs increased significantly with increased load ( $F(1,6) = 39.52$ ;  $P < 0.001$ ), as did error rates ( $F(1,6) = 11.97$ ;  $P < 0.05$ ). Response times did not differ significantly between stimulus types ( $F(1,6) = 3.50$ ;  $P > 0.1$ ). However, error rates were higher with locations than with letters ( $F(1,6) = 7.38$ ;  $P < 0.05$ ). There was no significant interaction between load and stimulus type effects for RT ( $F(1,6) = 2.91$ ;  $P > 0.1$ ) or accuracy ( $F(1,6) = 0.46$ ;  $P > 0.1$ ).

### Imaging Data

Five regions were observed that exhibited a main effect of stimulus type in the ANOVA on the MR signal, along with increased activation during higher WM load (see Fig. 7a and Table 1). In all five regions, the mean MR signal was higher in the Location conditions than in the Letter conditions. The regions were located bilaterally in both the right and the left middle frontal gyri (BA 6/8), in a large region spanning the right inferior parietal lobe (BA 40), the right superior parietal lobe (BA 7), and the bilateral precuneus (BA 7) and in the right inferior frontal gyrus (BA 44) and in the left fusiform gyrus (BA 19).

In addition, three regions were obtained from the interaction between stimulus type and load (see Fig. 7b and Table 1). In all three, the slope of the increase in signal between 0-back and 3-back loads was higher for letters than for locations. In one of the regions, within the right inferior parietal lobe (BA 40), the mean signal was higher in the Location conditions at both levels of WM load. In the other two regions, the Letter conditions yielded higher signals with 3-back loads: in the anterior cingulate (BA 32) and to a lesser extent in the right inferior frontal gyrus (BA 45/47).

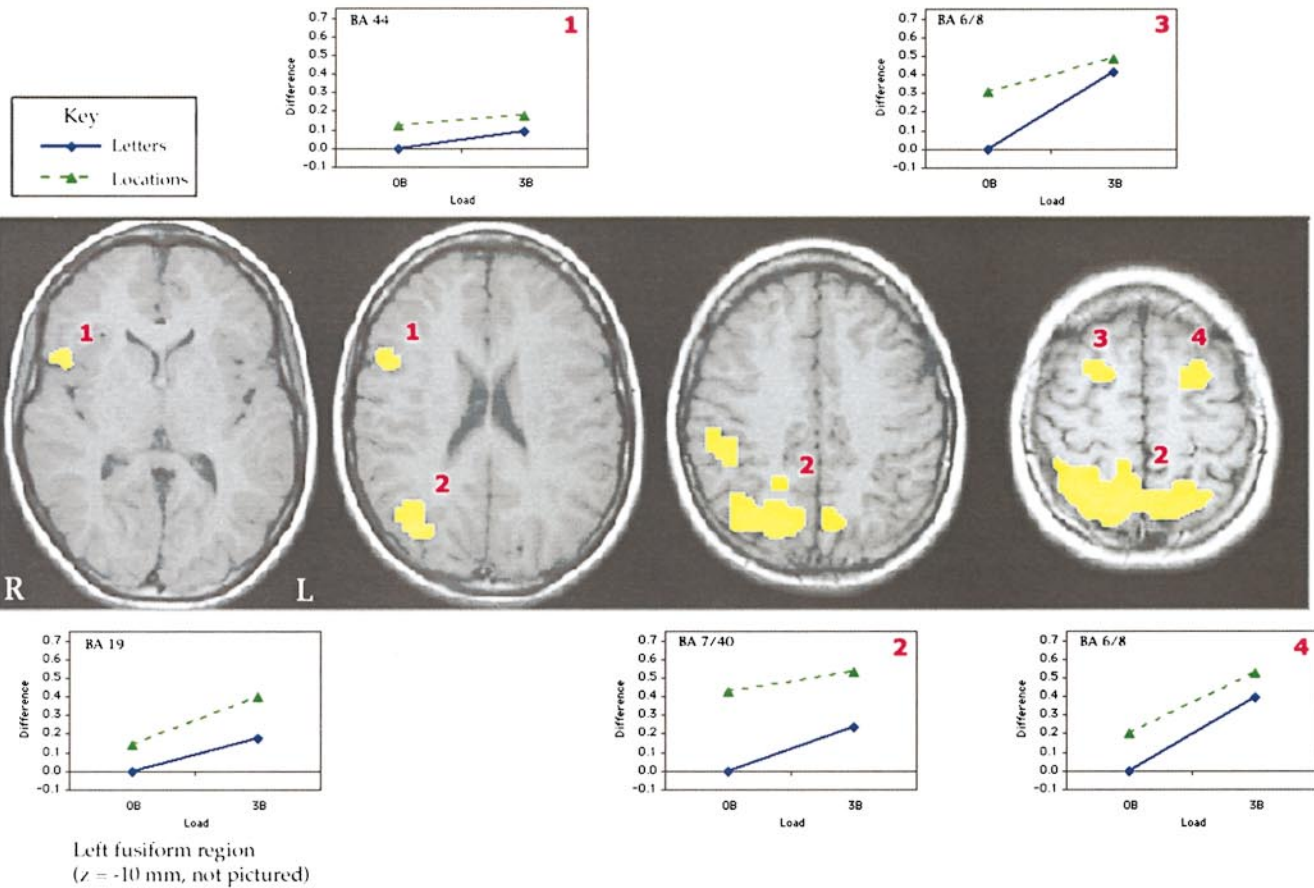
### Discussion

This experiment failed to confirm either of the two hypothesized stimulus-type WM dissociations. First, with regard to the verbal versus nonverbal WM dichotomy, this experiment obtained no clearly verbal-specific regions in the left hemisphere. This fails to support the hypothesis that verbal WM processes are left lateralized and nonverbal WM processes right lateralized. The only exclusively left-lateralized frontal region was an area in left premotor cortex anterior to the frontal eye fields, and it was more active in the spatial Location conditions. The region found in the left anterior cingulate activated more with letters than with locations at the higher level of WM load; however, at the lower load, the opposite was true. All of the other regions, including a left precuneus region, showed greater activation in the nonverbal, spatial Location conditions, although these were also the more difficult conditions.

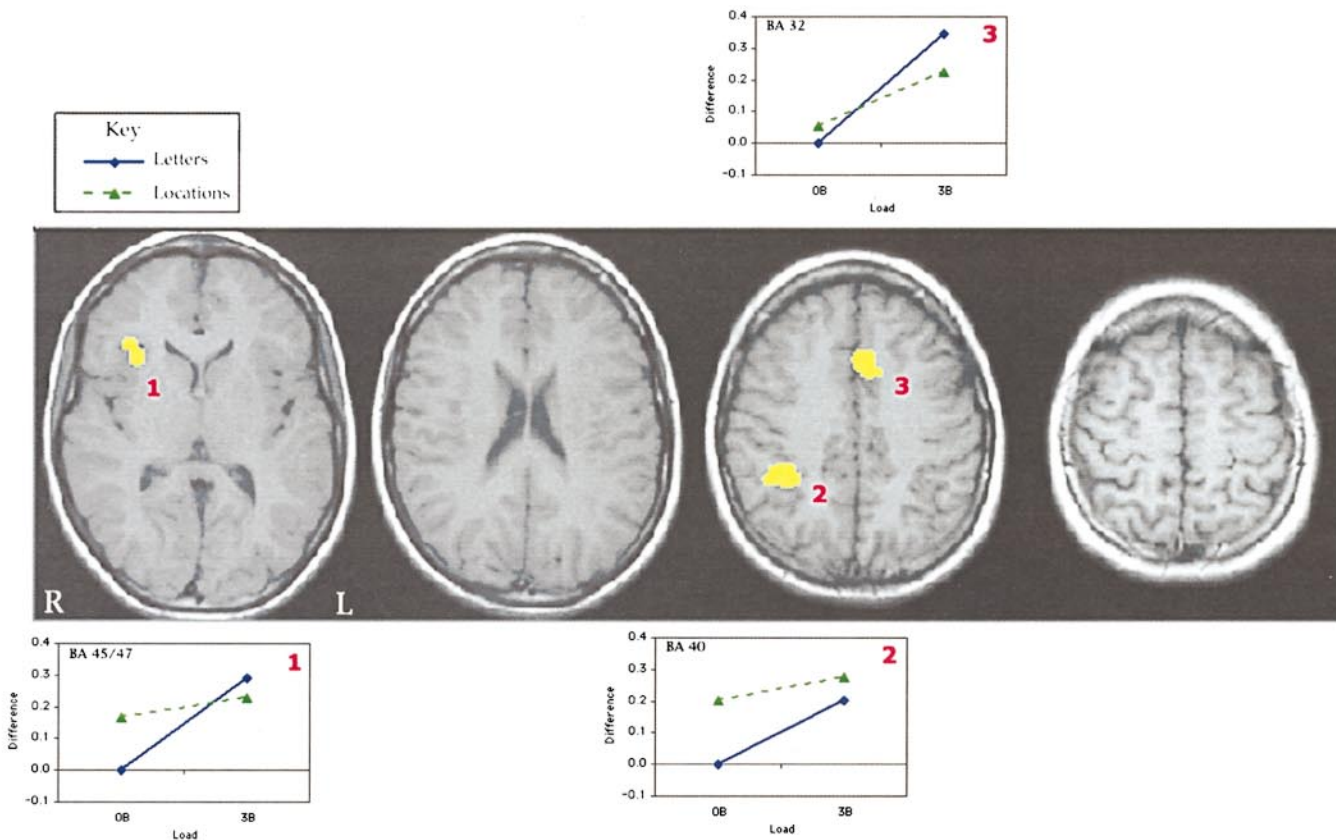
Second, with regard to the spatial/nonspatial WM dichotomy, there were no ventral regions responding to a greater extent in nonspatial (Letter) conditions. The two ventral regions, identified in different parts of the right inferior frontal gyrus, were both more active in the spatial condition.

It might be noted that several of the regions showing a greater sensitivity to spatial locations, in bilateral superior frontal sulcus between Brodmann's areas 6 and 8 and in right-lateralized parietal regions, generally coincide with existing models of the spatial attention and eye-movement systems (e.g., Posner and Petersen, 1990). These particular regions also replicate the findings of other prior experiments attempting to localize spatial WM processes (e.g., Courtney *et al.*, 1996, 1998; Petit *et al.*, 1998; Sweeney *et al.*, 1996; but see also Owen *et al.*, 1998).

**a**



**b**



It was surprising that differential letter versus location activation was not obtained in a traditionally observed verbal WM region like Broca's area. As in Experiment 1, this raises the concern that subjects might have used verbal coding strategies in the nonverbal tasks. In contrast to the reports from subjects in Experiment 1, subjects in this experiment did not report using a verbal strategy for the location task. However, it remains possible that subjects used verbal codes for locations in a nonconsciously accessible manner.

Concerns also persist regarding the differential difficulty of the tasks. Despite pilot testing to equate difficulty between stimulus types, the behavioral data revealed that subjects performed the letter WM task more accurately than the location task. The higher overall levels of MR signal obtained in the location task may reflect greater effort expended for locations and therefore greater sensitivity to areas related to spatial WM. Interestingly, however, activity in the anterior cingulate region seems to have paralleled measures of behavioral performance irrespective of stimulus type. While the mean activation of this region failed to differ between stimulus types, the slope of the load-related increase in MR signal was greater for letters than for locations, paralleling the slope of the RT curve and the increase in error rates, which was greater with letters. This relationship between stimulus type and amount of load-related increases in activation held true for several other areas as well and was apparently an underlying cause of all three regions showing statistical interaction. None of the interactions exhibited a pattern indicative of a strong dissociation, which would predict that a region would be responsive to WM load only when tested with one or the other stimulus type.

### EXPERIMENT 3: SPATIAL LOCATIONS VERSUS SHAPES

This experiment examined the remaining contrast between locations and shapes. Because it does not involve letter stimuli, it provided the opportunity to exclude the possibility of verbal coding strategies, conscious or otherwise. We did this by using articulatory suppression methods standard in cognitive psychological research. During the interstimulus interval between presentations of stimuli (shapes appearing in varying locations), subjects were asked to read aloud words as presented in the center of the screen at a rate of one every 800 ms. This secondary word-reading task engaged the full print-to-speech verbal articulatory system and presumably interfered with any other use of verbal working memory (Baddeley, 1986). Any addi-

tional activation arising from verbal processes engaged during the word-reading task should not appear in the analyses, because they would be equated across stimulus conditions.

Several earlier experiments have examined the contrast between object and spatial WM (Baker *et al.*, 1996; Belger *et al.*, 1998; Courtney *et al.*, 1996, 1998; McCarthy *et al.*, 1996; Owen *et al.*, 1998; Petit *et al.*, 1998; Smith *et al.*, 1995). Of these, the experiments of Courtney and her colleagues (1996, 1998; Petit *et al.*, 1998; cf. Haxby, this issue) used the best-matched stimuli: displays of faces appearing in varying locations. Across experiments, they found support for a dorsal/ventral dissociation between spatial and object WM processes. In the PET experiment of Courtney *et al.* (1996), the areas activating to a greater extent with location WM tasks included bilateral frontal regions at the superior frontal sulci, along with bilateral parietal and occipital regions. Areas activating to a greater extent with face WM tasks included right orbital, inferior, and middle frontal regions, along with bilateral occipital and temporal regions. In a subsequent fMRI experiment (Courtney *et al.*, 1998), they found similar results, although the inferior and middle frontal activation, greater in the face conditions, was left lateralized instead of right lateralized.

These results differ from those of other experiments directly contrasting object and spatial WM processes. Smith *et al.* (1995, Experiment 2) found right inferior frontal activation, along with right occipital and parietal activation in a location condition and left inferior temporal and parietal activation in a shape condition (with no frontal activation). McCarthy *et al.* (1996) found bilateral middle frontal and left inferior frontal activation in a shape condition, but right-lateralized activation in middle frontal region with a location condition. Baker *et al.* (1996) obtained similar results, in which shape and location WM tasks both activated middle frontal regions, more strongly on the left for shapes and on the right for locations, plus a right inferior frontal region in the location task; parietal regions were activated by both tasks. Belger *et al.* (1998) observed activation in a right middle frontal region with a location task and bilateral middle frontal activation and left inferior frontal activation in a shape task; again, parietal activation was obtained with both stimulus types. Finally, Owen *et al.* (1998) found no differences between activation in a spatial versus a nonspatial visual WM task in frontal cortical regions, but greater parietal activation in the spatial condition and greater temporal activation in the nonspatial condition. Across all of these studies, there are many in-

**FIG. 7.** Regions of activity in Experiment 2 associated with (a) significant main effects of stimulus type (Letters vs Locations) and (b) significant interactions between load (0-back and 3-back) and stimulus type. Graphs plot percentage signal change in each condition relative to signal in the 0-back Letters condition.



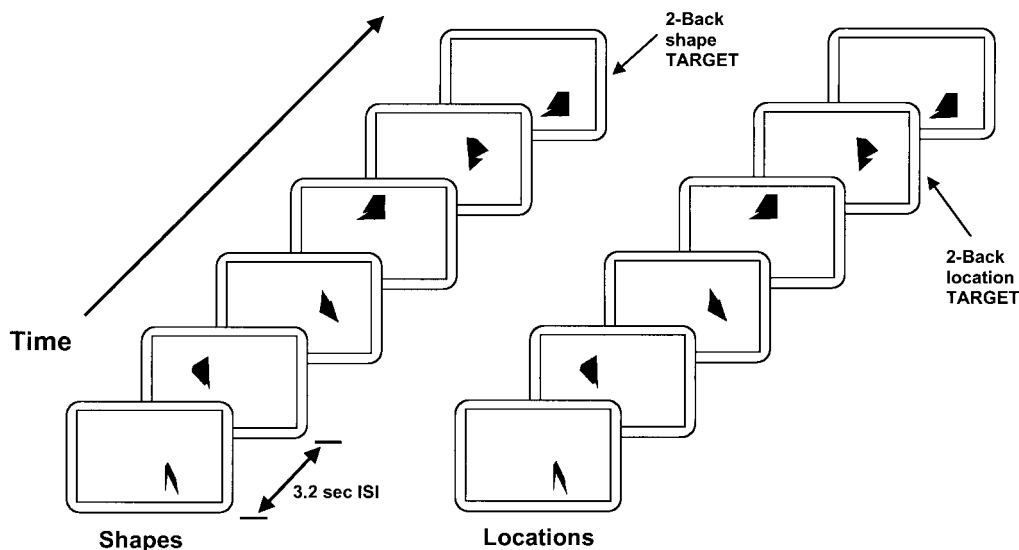


FIG. 8. Task conditions specific to the  $n$ -back variant used in Experiment 3.

consistent findings and no clear trend exhibited for a dorsal/ventral difference in spatial versus nonspatial WM processing. A different trend emerges across studies, though, yielding tentative support for a relative left/right hemispheric difference between shape and location WM, respectively. This trend parallels the hypothesized dissociation between verbal and nonverbal WM, and may in fact result from subjects processing shape identity information using verbal recording.

## Materials and Methods

### Subjects

Informed consent was obtained from 10 neurologically normal right-handed subjects (5 female, 5 male). Their ages ranged from 18 to 22 years ( $M = 20.2$ ). All subjects were given practice with the task and were scanned only after reaching a criterion level of performance (75% accuracy or greater) in all conditions.

### Cognitive Task

Subjects performed a variant of the  $n$ -back task, using both spatial locations and abstract shapes as memoranda (see Fig. 8). Because the secondary, word-reading task also made the primary WM task more difficult, due to the increased difficulty of any dual-task paradigm, the 2-back rather than the 3-back load condition was used as the high WM load condition. Two levels of memory load (0- and 2-back) were presented in a factorial design fully crossed with the two levels of stimulus type (Locations and Shapes), yielding four task conditions. Trials were blocked by condition, with 22 trials per block and 32 blocks presented in pseudorandom order, which ensured that each of the four

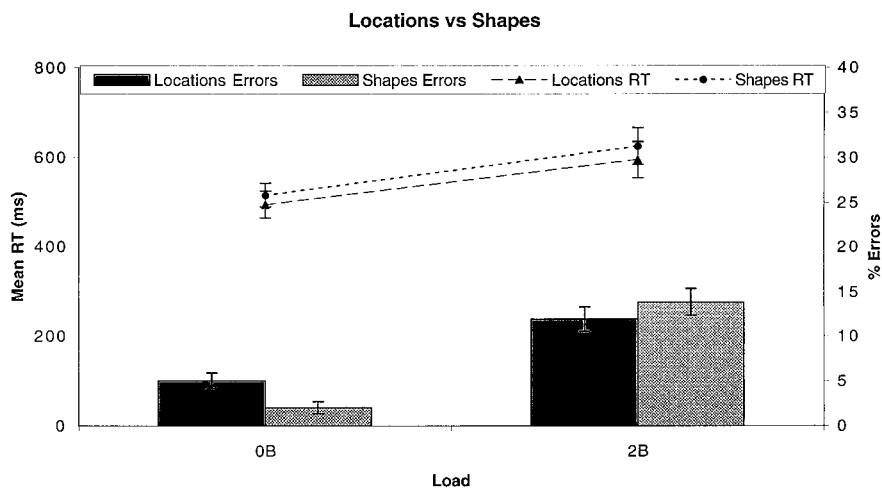
conditions was presented once within every set of 4 blocks.

In the 0-back conditions of this experiment, subjects detected a single prespecified location or shape, as in Experiment 1. We had used three 0-back positions in Experiment 2 to prevent subjects from fixing their gaze on the 0-back target position. In the current dual-task design words were presented in the center of the display, to which subjects were required to reorient their gaze between presentations of shape/location stimuli. Thus, subjects could not avail themselves of the strategy of fixing their gaze to avoid WM load.

A block of a single condition lasted 1.3 min, consisting of a 3.2-s instruction (e.g., "Target = 2-back SHAPE repeats"), followed, after a 3.2-s pause, by 22 3.2-s test trials. At the beginning of each trial, a shape was presented in a noncentral location for 500 ms. Additionally, words were presented centrally for 500 ms at three times during each trial: 800, 1600, and 2400 ms after the beginning of the trial. Following every block of 22 trials, subjects saw the word PAUSE for approximately 0.5 min before the next block of trials began, allowing them a rest period while data were loaded off the scanner. Thirty-two blocks of trials were run within a period of approximately 1 h.

Shape stimuli were chosen from the same set of 40 6-sided random polygons used in Experiment 1. The locations of shape presentation were chosen from the same set of 18 positions used in Experiment 2. Subjects responded to shape and location stimuli as in Experiments 1 and 2.

Stimuli for the secondary task were chosen from a set of 430 one-syllable words. Subjects responded to each word presentation simply by immediately reading the word aloud. Although we were unable to continu-



**FIG. 9.** Behavioral data from Experiment 3. Bar graphs denote error rate with the scale on the right. Line graphs denote reaction time with the scale on the left. Error bars represent standard errors.

ously monitor the speech of subjects above the noise produced by the scanner, subjects were periodically monitored to ensure that they were responding vocally to each word presentation.

As in Experiments 1 and 2, 33% of the trials contained targets; of the remaining 66% nontargets, 6% of the stimuli were chosen from each of the three other  $n$ -back conditions (including 1- and 3-back), while 48% used new stimuli unrelated to the previous three trials.

#### *MRI Scanning Procedures and Imaging Data Analysis*

Images were acquired using the same 1.5-T scanner used in Experiments 1 and 2. Twenty contiguous slices (3.75-mm<sup>3</sup> isotropic voxels) were obtained parallel to the AC-PC line. Structural images were acquired in the same locations as the functional images, using a standard T1-weighted pulse sequence. Functional images were acquired using a 2-interleave spiral pulse sequence (TR = 1600 ms, TE = 35 ms, FOV 24 cm, flip 60°). This T2\*-weighted pulse sequence allowed 20 slices to be acquired every 3.2 s. Twenty-two functional volumes were collected within each 22-trial block; scans were synchronized to trial onsets. With 32 blocks, a total of 704 functional volumes were collected. Functional images were prepared for analysis in the same manner as in Experiments 1 and 2; significance thresholds were again set to  $P < 0.01$  ( $F(1,9) = 10.56$ ).

## **Results**

### *Behavioral Data*

Subjects' performance was evaluated using 2 (load)  $\times$  2 (stimulus type) ANOVAs, using both RT and accuracy measures (see Fig. 9). As in Experiments 1

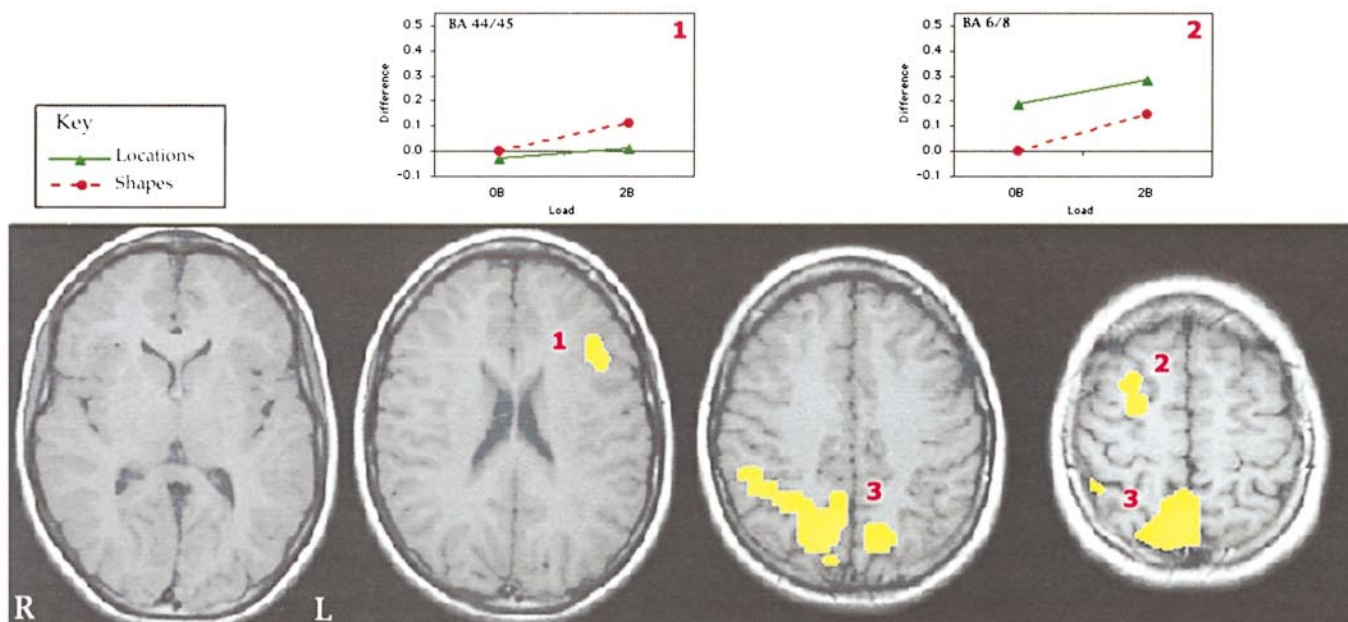
and 2, RTs increased significantly with increased load ( $F(1,9) = 19.35$ ;  $P < 0.005$ ), as did error rates ( $F(1,9) = 82.76$ ;  $P < 0.0001$ ). While RTs to shape stimuli were significantly slower ( $F(1,9) = 11.17$ ;  $P < 0.01$ ), subjects' error rates did not differ between shapes and locations ( $F(1,9) = 0.52$ ;  $P > 0.1$ ). As with Experiments 1 and 2, there was no interaction between load and stimulus-type effects on RT ( $F(1,9) = 0.57$ ;  $P > 0.1$ ). However, as in Experiment 1, the interaction was significant with respect to accuracy ( $F(1,9) = 6.49$ ;  $P < 0.05$ ). Subjects' accuracy was reduced more by increasing WM loads when the memoranda were shapes than when they were spatial locations.

### *Imaging Data*

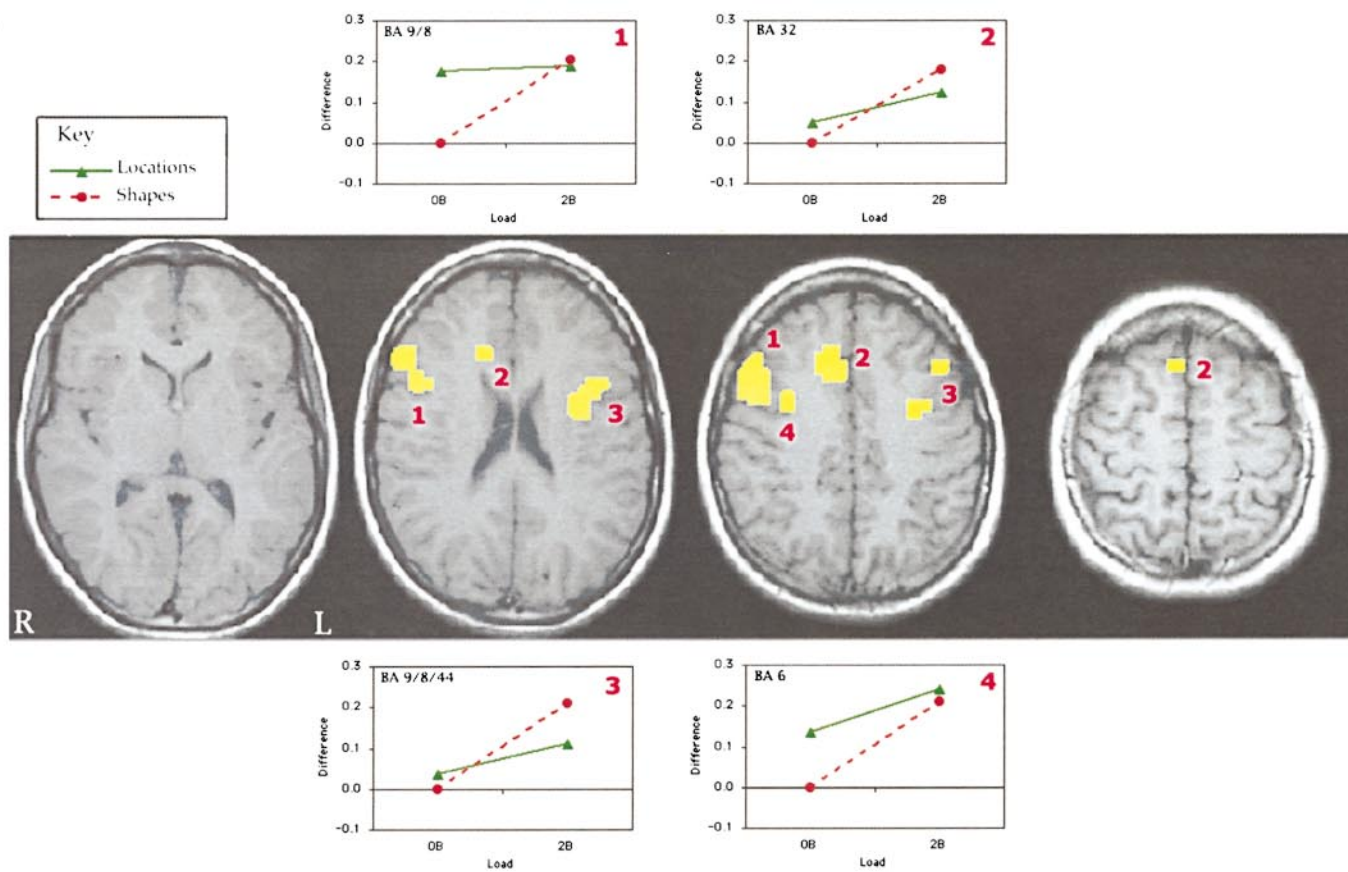
Three regions were obtained exhibiting a main effect of stimulus type in the ANOVA on the fMRI signal along with increased activation with higher WM load (see Fig. 10a and Table 1). The mean fMRI signal was higher in the Location conditions in the right middle frontal gyrus (BA 6/8) and in a large region including the right inferior parietal lobe (BA 40) as well as bilateral (predominantly right) superior parietal lobes and bilateral precuneus (BA 7). In contrast, the signal was higher in the Shapes conditions in the left inferior frontal gyrus (BA 44/45).

Four regions were obtained from the interaction between stimulus type and load (see Fig. 10b and Table 1). These areas were located in the right anterior cingulate (BA 32), the right precentral gyrus (BA 6), the right middle frontal gyrus (BA 9/8), and the left inferior and middle frontal gyri (BA 9/8/44), an area just superior to the left inferior frontal region obtained in the main effect of stimulus type. In all four regions, the slope of the signal increase between 0-back and 2-back loads was higher with Shapes than with Locations;

a



b



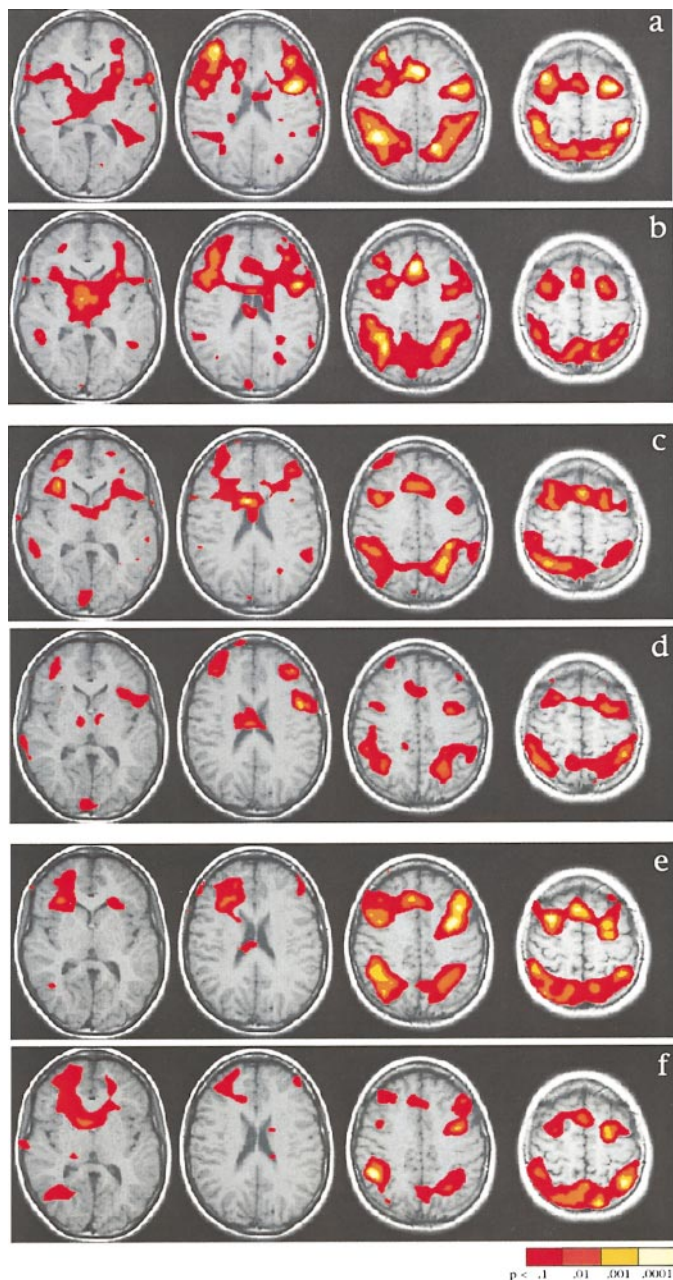


while the mean signal was higher with Locations at 0-back loads, it was equal or higher with Shapes at 2-back loads.

### Discussion

At first glance, the distribution of regions in Experiment 3 detected by the main effect of stimulus type seems to lend support to the hypothesis that WM for spatial information is localized to dorsal frontal cortex, while WM for nonspatial information is subserved by ventral frontal cortex. There were only two frontal regions observed in this main effect: (1) a more shape-sensitive region in the left inferior gyrus and (2) a more location-sensitive region in the right superior frontal sulcus. This second region is located in approximately the same place as a similarly location-sensitive region found in Experiment 2. Additional location-sensitive regions in parietal cortex, mostly in the right hemisphere, also replicated nearly identical location-sensitive parietal regions in Experiment 2. The location-sensitive areas, frontal and parietal, also replicate the areas previously identified by Courtney and colleagues (1996, 1998) in tests of spatial WM. Furthermore, the laterality of these regions is consistent with the tentative finding of a left/right asymmetry between nonspatial and spatial WM found in other earlier studies.

Nevertheless, the pattern of activation in regions exhibiting an interaction between load and stimulus-type must temper any strong conclusion about dorsal/ventral dissociations. These regions were in primarily dorsal frontal areas, yet they exhibit complex patterns of response to the various conditions that do not indicate a sensitivity particular to spatial WM manipulations. The pattern of interaction in these regions is not indicative of a dissociation, with only location stimuli causing increased activation with increasing WM load. Quite the contrary, in all four regions, the slope of the load-related increase in activation was greater for shapes than for locations. In fact, in two of them, right AC and left DLPFC/premotor cortex, the activation in Shape 2-back conditions exceeds that of Location 2-back conditions. In a third region in the right DLPFC, the activation in Location conditions is higher overall, yet remains unchanged with increasing WM load, whereas the activation in the Shape conditions increases with load. The responses of these regions may be complex, but it is clear nonetheless that one cannot safely label them as specialized for spatial WM. Note that Postle *et al.* (this issue) used designs and materials very similar to those of the present study and



**FIG. 11.** Regions of activity associated with increased WM load for each stimulus type in each experiment. Color scale indicates the significance of a one-tailed matched-sample *t* statistic contrasting MR signal increases with high WM load conditions (2-back and/or 3-back) relative to low WM load conditions (1-back and/or 0-back). The maps illustrate this contrast from: (a) Experiment 1, Letters; (b) Experiment 1, Shapes; (c) Experiment 2, Letters; (d) Experiment 2, Locations; (e) Experiment 3, Shapes; and (f) Experiment 3, Locations.

**FIG. 10.** Regions of activity in Experiment 3 associated with (a) significant main effects of stimulus type (Location vs Shape) and (b) significant interactions between load (0-back and 2-back) and stimulus type. Graphs plot percentage signal change in each condition relative to signal in the 0-back Shapes condition.

obtained no evidence for frontal dissociations between WM for shapes versus locations.

It might be possible to characterize the activation of these regions as a result of differential task performance. As discussed under Experiments 1 and 2, activation of the anterior cingulate is often found to closely follow task difficulty, as measured by behavioral performance. In this experiment as well, the activation of the AC region mirrored error rates. Error rates were higher with locations at the 0-back load, increased for both stimulus types with increased load, but became higher with shapes at the 2-back load. The activation of the AC region exhibited an identical pattern of increases with all four conditions. A similar case might be made to explain the other three regions exhibiting interactions. However, there were no preexisting hypotheses to lead us to expect that the activation of these other regions should track errors, as there was with the AC.

The use of verbal strategies with nonverbal stimuli, a potential confound in Experiments 1 and 2, should have been minimized or eliminated by the addition of the articulatory-suppression secondary task. It is surprising, therefore, that this experiment was the only one to identify a region within Broca's area. This region exhibited significantly greater activation for shapes than for locations. Because subjects in the two earlier experiments reported using verbal coding strategies in Shape, but not Location, conditions, this result may be interpreted as evidence that the vocal suppression task was not completely successful in eliminating verbal rehearsal strategies. Alternatively, the activation in Broca's area may indicate that the shapes task and the word-reading task mutually interfered to a greater extent, relative to the locations task, making Broca's area "work harder" during that dual-task combination.

## GENERAL DISCUSSION

The three experiments reported here present a complex series of results that do not lend themselves to any simple interpretation. At the very least, however, they challenge hypotheses about the functional organization of WM in the PFC according to simple distinctions such as verbal versus nonverbal or object versus spatial WM. The regions of activation did not divide cleanly along either the left/right or the dorsal/ventral dimensions that have been hypothesized for stimulus-based dissociations. While there may be some concerns remaining about particular shortcomings of each experiment, taken as a whole, this set of studies broadly supports the notion of a frontal cortex in which the regions engaged by manipulations of WM load are responsive to every type of stimulus information. One possible exception may be the regions of relative selectivity for spatial information in the (posterior) superior frontal sulcus obtained in both Experiments 2 and 3, as

well as in experiments by Courtney and colleagues (1996, 1998). Even those reliably identified regions, however, responded with increased activation to higher WM loads in both the letters and the shapes conditions, thereby failing to meet the strictest criterion for a dissociation.

Because of the lack of clean dissociations obtained in these studies, a reexamination of the data was warranted, to more specifically explore the null hypothesis that the human PFC is not reliably differentiated with regard to WM for letters, shapes, and locations. In all three experiments, the cortical regions considered thus far have been identified using statistics designed to locate dissociations between conditions: main effects of stimulus type and interactions between WM load and stimulus type.

Both for illustrative purposes and as a check that our tasks did indeed invoke WM-related areas of PFC, we performed a series of post hoc contrasts on each experiment's imaging data, separately identifying areas for each stimulus type that showed significant load-related increases in MR signal. As shown in Fig. 11, the results of these contrasts indicate that roughly the same cortical areas responded to increases in WM load across all stimulus types in all three experiments. Activation was observed bilaterally in premotor, supplementary motor, anterior cingulate, superior and inferior parietal, and superior, middle, and inferior frontal areas—all regions that are commonly implicated in WM tasks. Not a single area can be found that activated with one stimulus type without activating the other two as well. There are no dissociations apparent in these maps between left and right hemispheric activation with verbal versus nonverbal stimuli nor is there any apparent distinction between dorsal and ventral activation for spatial versus nonspatial stimuli. This demonstrates that the tasks were indeed successful in eliciting load-responsive activity and that similar areas were activated by tasks that involved WM for different materials, suggesting that there is a single common WM system operating across all three stimulus types.

Nevertheless, before accepting the null hypothesis that rejects the existence of stimulus-based dissociations of WM regions, it would be wise to first consider several alternate explanations for a failure to obtain such dissociations. For one, it is possible that stimulus-based dissociations do exist, but on a scale too small to be detected using current fMRI techniques. The spatial resolution of fMRI images in these experiments, less than 1 cm<sup>3</sup> per voxel, was certainly sufficient to detect dissociations on the gross scales—left/right hemispheric or superior/inferior—proposed by the verbal/nonverbal and spatial/nonspatial hypothesis. Moreover, prior studies providing evidence of these dissociations, especially those that used PET technol-



ogy, have had poorer spatial resolution (e.g., Courtney *et al.*, 1996; Smith *et al.*, 1995, 1996).

Another possibility is that subjects encoded, maintained, or manipulated stimuli using similar strategies and mechanisms across the various stimulus types. For example, we have already discussed concerns that subjects may have used verbal strategies for rehearsing putatively nonverbal stimuli, by naming the abstract shapes or the locations of stimuli. Similarly, it is possible that subjects processed the abstract shapes using a spatially based strategy (e.g., as configural information). For example, it is possible to encode the identity of a particular shape using a spatial coordinate system to record, relate, or traverse the various vertices of the abstract polygons, thereby rendering the shapes task more spatial in nature. It is reasonable to think that this type of configural strategy may be more compelling for processing unfamiliar and nonnaturalistic shapes like those used in the present experiments. Presumably, if one presented familiar shapes or faces instead of the abstract polygons, this strategy would be of less use to subjects (although a verbal strategy might then gain appeal.)

A third possibility is that the subjects employed similar WM processes with each stimulus type, not by processing one type of stimulus with a strategy normally associated with another type, but rather by processing all stimuli using mixtures of all strategies, either simultaneously or alternatively across trials. In fact, the design of the current experiments, requiring the switching between multiple tasks at fairly short (1-min) intervals, may have promoted an intermingling of multiple WM strategies. The fact that the stimulus presentations were identical between all conditions within Experiments 2 and 3 may have also contributed to a blending of spatial and nonspatial strategies. This intermingling would not necessarily be a controlled or conscious strategy and therefore need not have been reported in post test questioning.

A related possibility is that the relatively high cognitive demands placed on subjects by the *n*-back task may encourage recruitment of as many resources and complementary processing strategies as possible—again, with or without subjects' conscious knowledge. Evidence consistent with this hypothesis arises from recent fMRI studies of episodic memory encoding and retrieval, in which the tasks might be presumed to place less continuous demand on WM systems. In these episodic memory tasks, reliable within-subject evidence has been produced for a dissociation by stimulus domain in inferior frontal regions, with a left lateralization for words versus a right lateralization for unfamiliar faces (Kelley *et al.*, 1998) or texture patterns (Wagner *et al.*, 1998). At this time, however, it is unclear whether these positive findings of frontal dissociations differ from the negative findings of the present experiments because of the degree of WM involvement

or rather because of the involvement of episodic memory systems.

Finally, just as multiple attributes of a stimulus (such as location and identity) are automatically encoded and processed in multiple parallel streams within posterior cortical regions (Ungerleider and Haxby, 1984), perhaps multiple attributes are also automatically processed in parallel streams within anterior WM systems. Subjects could still attend to one particular stimulus attribute (e.g., letter identity) in order to make task-related decisions about stimuli, without this focus eliminating the simultaneous, obligatory or automatic maintenance of other attributes (e.g., letter location). If these parallel WM maintenance processes were modulated by executive processes to focus on task-relevant information, a stimulus-based dissociation might be obtainable only in a diminished form, if at all. It is possible that all WM-related areas activate on a more global scale with all types of stimuli due to this obligate encoding of multiple dimensions or due to highly distributed neural representations of stimulus information. In the latter case, cognitively relevant changes in brain activity may involve only subtle changes in the intensity of activity in different areas, below the level of our ability to detect (due to noise in the amplitude of the fMRI signal response).

With all of these caveats left under consideration, let us turn to alternate hypotheses that reject stimulus-based dissociations within frontal WM areas. Petrides and colleagues have proposed that the PFC is organized according to the type of WM process applied to a stimulus, irrespective of the stimulus type or modality (Petrides, 1994, 1995, 1996; Owen *et al.*, 1996, 1998; Owen, 1997; Stern *et al.*, this issue). In this theory, the prefrontal cortex is divided along a dorsal/ventral axis, but not according to the spatial/nonspatial distinction found in posterior cortical regions. Instead, it is proposed that ventrolateral prefrontal regions are used to maintain information received from more posterior association areas, while dorsolateral prefrontal regions are recruited only when executive processes are required to manipulate or monitor information within WM. Two recent reviews of WM neuroimaging experiments (Owen, 1997; D'Esposito *et al.*, 1998) generally supported the Petrides hypothesis, finding that experimental tasks that required maintenance alone tended to activate ventral PFC, while tasks that involved more complex manipulations of information in WM tended to additionally activate dorsal PFC. Note that while the mechanisms underlying "maintenance" and "manipulation" proposed within this conceptual framework remain somewhat underspecified at present, we expect that a 0- or 1-back task would be classified as a maintenance task, while a 2- or 3-back task would be seen as involving manipulation in addition to maintenance. The results of all of the present experiments would therefore be generally consistent with this theory (see

Fig. 11), as both dorsal and ventral PFC regions were activated in the 2- or 3-back tasks. However, we (and others) have also obtained dorsal PFC activation in a maintenance-only Sternberg WM task (Nystrom *et al.*, 1998; Rypma *et al.*, 1999), an apparent contradiction to the Petrides hypothesis.

It may simply be the case that WM representations of stimulus information in PFC are organized along less obvious dimensions than verbal code, shape, or location. Information in frontal cortex may be far more abstract, combinatorial, or distributed than information in other regions of the brain. This would be consistent with the fact that PFC is the cortical region most phylogenetically enlarged in primates, especially humans (Fuster, 1997). It is also the region most closely identified with abstract and associative thought processes. Representations in PFC may therefore be defined by a complex, abstract, multimodal space that does not correspond in any obvious manner with the simpler dimensions coded in posterior cortical regions (Cohen *et al.*, 1996). Thus, posterior cortically coded dimensions such as location or shape may not be the appropriate ones to use for probing frontal representations.

Recent single-cell recording studies in nonhuman primates lend support to this idea. Miller and colleagues (Rainer *et al.*, 1998a,b; Rao *et al.*, 1997) have produced striking evidence that lateral PFC neurons of monkeys may be tuned to represent either the location or the shape of objects (or both), depending on current experimental context. Rao *et al.* (1997) found some neurons specialized for object or spatial WM, but roughly half represented both types of information. Thus, even though they observed a relative bias in some neurons, at a larger scale, analogous to the scale at which neuroimaging resolves areas, there was absolute overlap in WM functions. Even if the relative bias found in subsets of neurons were spatially organized at a finer scale, Miller's data point to a much more distributed form of representation in PFC than has traditionally been considered.

Miller and colleagues have suggested that an equipotentiality of information coding in PFC neurons was evidenced specifically because the monkeys were trained in tasks requiring the simultaneous maintenance of multiple forms of information (spatial and object) instead of only one. Earlier studies reporting segregation of neurons along dorsal/ventral spatial/nonspatial dimensions (e.g., Wilson *et al.*, 1993) had trained and tested monkeys on these dimensions independently. This pattern of physiological findings is consistent with a previous computational modeling study, in which training blocked by stimulus modality was found to produce representations of actively maintained information that were modality-specific, whereas interleaved training produced multimodal, conjunctive representations (Braver and Cohen, 1995).

Therefore, we would suggest that the representations in PFC are more plastic and more highly attuned to current task demands than the representations in posterior cortex (Cohen *et al.*, 1996; Miller, 1999).

In summary, the findings from our studies present a complex pattern of results. Regarding the central question of this special issue, they do not provide convincing support for representational organization within human PFC according to simple stimulus dimensions. These findings, taken together with those reported in the other articles in this issue, suggest that organization within the PFC may adhere to a scheme that is more complex than previous research has assumed. This poses a fascinating challenge for future research—both to identify the relevant dimensions along which PFC may be organized and to understand how this may arise during development and interact with ongoing experience.

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