"What"—Then—"Where" in Visual Working Memory: An Event-Related fMRI Study

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Abstract

■ Behavioral studies indicate that spatial and object working memory are computed by dissociable subsystems. We investigated the neural bases of this dissociation with a whole-brain fMRI design and analysis technique that permitted direct assessment of delay-period activity, uncontaminated by other components of the trial. The task employed a "what"-then-"where" design, with an object and a spatial delay period incorporated in each trial; within-trial order of delay conditions was balanced across each scan. Our experiment failed to find evidence, at the single-subject level and at the group level, for anatomical segregation of spatial and object working memory function in the frontal cortex. Delay-period activity in the caudate nucleus revealed a sensitivity to position in the trial in the spatial, but not the object, condition. In posterior regions, spatial delay-period activity was associated with preferential recruitment of extrastriate areas falling within Brodmann's area 19 and, less reliably, the superior parietal lobule. Object-specific delay-period activity was found predominantly in ventral regions of the posterior cortex and demonstrated more topographic variability across subjects than did spatial working memory activity. ■

INTRODUCTION

The concept of working memory was first introduced to the behavioral sciences by Pribram, who saw in artificial intelligence work on problem solving (Newell, Shaw, & Simon, 1958) an apt analogy for a system supporting high-level behaviors that were disrupted by prefrontal cortical (PFC) lesions in monkeys (Miller, Galanter, & Pribram, 1960; Pribram, Ahumada, Hartog, & Roos, 1964). Subsequent studies of PFC electrophysiology have confirmed that subpopulations of neurons in the vicinity of the principal and arcuate sulci demonstrate activity during delayed-response performance consistent with short-term storage of task-relevant information (Funahashi, Bruce, & Goldman-Rakic, 1990; Fuster, 1997; Fuster & Alexander, 1971) and thus may represent a neural substrate of working memory. One model proposes that visual working memory is organized into two systems within the PFC, with spatial working memory supported by the dorsolateral PFC in the vicinity of the principal sulcus, and object working memory supported by the ventrolateral PFC of the lateral convexity (Goldman-Rakic, 1987; Wilson, O'Scalaidhe, & Goldman-Rakic, 1993). Behavioral and electrophysiological studies in humans have confirmed the psychological validity of the what/where organization of human visual working memory (Hecker & Mapperson, 1997; Mecklinger & Muller, 1996; Postle, Jonides, Smith, Corkin, & Growdon, 1997; Smith et al., 1995; Tresch, Sinnamon, & Seamon, 1993). Inconsistent with a segregation model, however, are results from electrophysiological studies of monkey PFC demonstrating evidence of integration of delay- period representation of spatial and nonspatial information within individual neurons (Watanabe, 1981) and of intermixing of spatially and nonspatially tuned delay units throughout much of the PFC (Fuster, Bauer, & Jervey, 1982). Simulations with an artificial neural network model have demonstrated that dorsal/ventral segregation of working memory function in the PFC, such as that described by Wilson and colleagues (1993), might arise as a by-product of blocked training with just one type of stimulus material at a time, as monkeys are typically trained (Braver & Cohen, 1995). The physiological plausibility of this simulation was supported by evidence that overtraining on a visual search task in which stimuli are defined by color induces color selectivity in neurons of the frontal eye fields, or FEF (Bichot, Schall, & Thompson, 1996). Rao and colleagues tested segregation versus integration models by training monkeys to perform object and spatial delayed response within the same trial and found that the majority of delay-specific PFC neurons from which they recorded did not discriminate spatial from object delay periods (Rao, Rainer, & Miller, 1997). Rainer, Asaad, and Miller (1998) also found a high degree of integration of "what" and "where" in the principal sulcus of monkeys performing a delayed matching task that required memory for an object in a specific location. Additionally, object working memory performance has been shown to be independent of ventrolateral PFC integrity (Rushworth, Nixon, Eacott, & Passingham, 1997).

Our experiment was designed to investigate the neural basis of spatial and nonspatial working memory in the human PFC, and throughout the brain, with event-related functional magnetic resonance imaging (fMRI). Our what-then-where delayed-response task (Figure 1; based on Rao et al., 1997) featured two discrete delay periods during each trial, and our technique permitted assessment of delay-period activity that was uncontaminated by other portions of the trial (Zarahn, Aguirre, & D'Esposito, 1997b). This event-related analysis is similar in principle to techniques employed by single- and multiunit and transcranial electrophysiologists: inferential statistical comparison of signal associated with an experimental treatment with baseline signal. Our experiment featured sufficient sensitivity to permit analysis of unsmoothed data from single subjects and differed from previous neuroimaging studies of human working memory in three important ways: (1) Its spatial resolution was superior to that permitted by techniques that smooth and average data across subjects. (2) Its statistical power permitted inspection of effects within individual subjects, and thus assessment of individual variability (e.g., subject-by-task interactions), whereas group averaging approaches are constrained to detection of activation patterns that are consistent across subjects in a standard space. (3) The group analyses used a random-effects model, permitting stronger inference than fixed-effects models employed in most published working memory studies to date.

RESULTS

Behavioral performance on the two trial types was comparable: what-then-where = 84.9% correct (*SD* = 4.4); where-then-what = 82.3% correct (*SD* = 6.8).

Single-Subject Analyses

The results of single-subject analyses are presented by region: the frontal cortex, parietal cortex, temporooccipital cortex, and caudate nucleus. Analyses in each region proceeded in three stages: (1) assessment of delay-related signal intensity change in each of the two conditions (i.e., spatial delay versus baseline and object delay versus baseline), (2) direct contrasts of delay-related activity elicited in the two conditions (i.e., spatial versus object), and (3) tests for interactions of delay position (delay 1, delay 2) with stimulus condition (spatial, object).

Prefrontal Cortex

Five of the six subjects showed delay-specific activity in areas 9 and 46 of the dorsolateral PFC in both conditions, and (the same) five of six subjects exhibited delay-specific activity in areas 44, 45, and 47 of the ventrolateral PFC. Inspection of delay-period *t* maps from each of these five subjects revealed that loci of suprathreshold voxels corresponding to spatial and object mnemonic activity overlapped to a remarkable extent (Figure 2). Variability in location of suprathreshold voxels within the PFC varied to a much greater extent across subjects and within condition than within subject and across condition. PFC activation was bilateral in four of the five subjects in the spatial condition and in three of the five in the object condition. Direct spatial versus object delay contrasts performed within the two PFC regions of interest (ROI) revealed voxels with significantly greater spatial delay-period activity in the dorsolateral PFC in one subject and voxels with significantly greater object delay-period activity in the dorsolateral PFC in one (different) subject. No suprathreshold voxels were detected in the ventrolateral PFC. Finally, contrasts investigating trial-position differences of delay activity in the two stimulus conditions yielded null results.

Each of the six subjects showed delay-specific activity in both conditions in the cortex bounding the superior frontal sulcus (SFS) and the anterior bank of the precentral sulcus (an ROI intended to encompass the frontal eye fields; Courtney, Petit, Maisog, Ungerleider, & Haxby, 1998), and, as in PFC, material-specific delay-period maps looked virtually identical in the two conditions (Figure 3). Direct contrasts of spatial versus object delay-period activity revealed no suprathreshold voxels in any subject, nor did contrasts investigating trial-position effects.

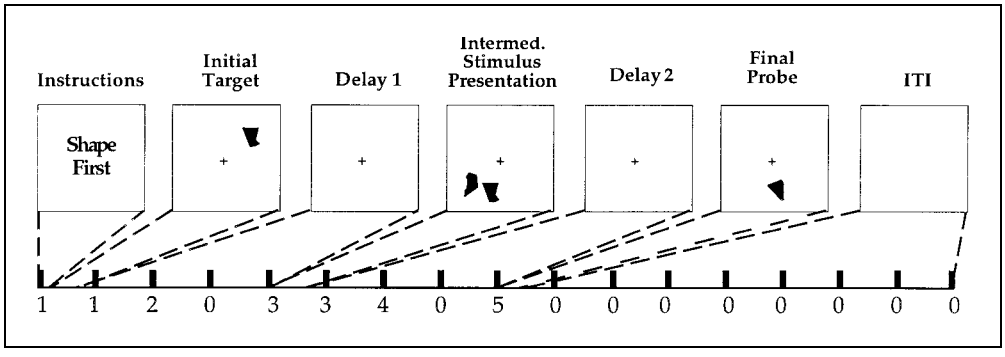

Figure 1. Schematic diagram and time line of a what-then-where trial. Each box represents a stimulus display event, and the dotted lines connecting each box to the time line represent the sequence and duration of each of these events. The numbers along the time line represent the positioning of the five independent variables in our statistical model (see Methods, fMRI Data Processing).

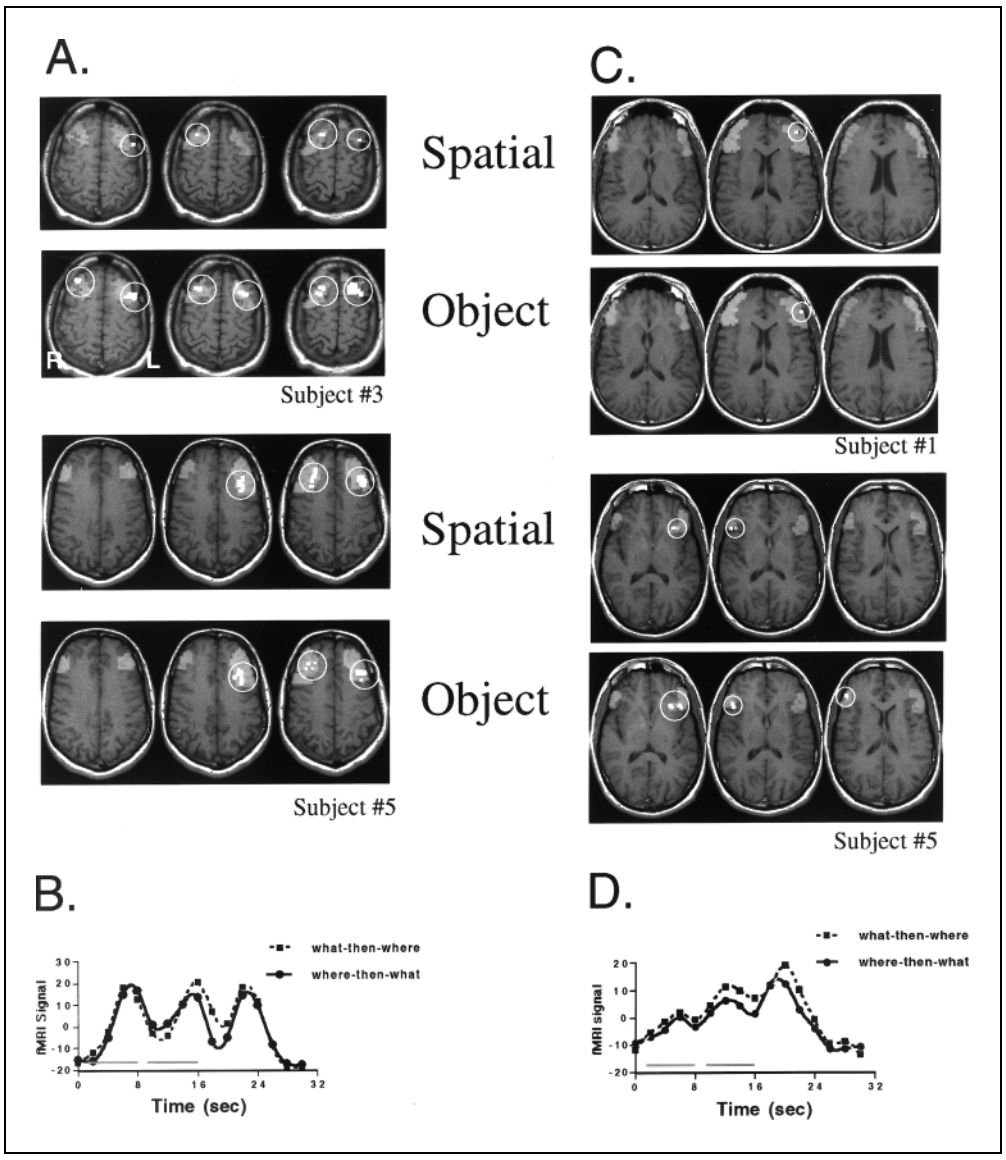

Figure 2. (a) Activation maps displaying suprathreshold activity (circled) in spatial and object delay periods in dorsolateral PFC in two subjects. ROIs are rendered in translucent white overlays. This figure illustrates the marked degree of overlap in dorsolateral PFC activity in the two conditions. (b) Trial-averaged time series extracted from dorsolateral PFC voxels with object delay-period activity in subject #3 [displayed in (a)]. Note the similarity of fMRI signal intensity changes in spatial and object delay periods. (c) Activation maps displaying suprathreshold activity in spatial and object delay periods in the ventrolateral PFC in two subjects. ROIs are rendered in translucent white overlays. This figure illustrates the marked degree of overlap in the ventrolateral PFC activity in the two conditions. (d) Trial-averaged time series extracted from ventrolateral PFC voxels with spatial delay-period activity in subject #5 [displayed in (c)]. Note the similarity of fMRI signal intensity changes in spatial and object delay periods.

Parietal Cortex

In the superior parietal lobule (SPL), all subjects showed delay-specific activity in both conditions. Unlike PFC, the topographical distribution of area 7 voxels with suprathreshold *spatial* delay-period activity was consistent across subjects, with most activity concentrated in the lateral cortex near the midline, bilaterally, and in the precuneus. This cluster of perimidline activation spanned the parietooccipital sulcus in all subjects and thus included portions of the superior and middle occipital gyri (dorsal area 19). Also at variance with the results in PFC, within-subject comparisons of delay-period maps revealed marked quantitative and qualitative differences: There were more spatial than object suprathreshold voxels in most subjects, and activation patterns showed considerable topographic variability across conditions. Direct contrasts revealed voxels demonstrating significantly greater spatial than object delay-period activity in three subjects and voxels demonstrating the converse in one subject (Figure 4). No trial position effects were detected.

In the inferior parietal lobule (IPL) ROI there was also delay-related activity in every subject in both conditions. Inspection of delay-period maps revealed a greater degree of topographic variability across subjects than was evident in area 7, with no common area activated consistently across subjects. Direct contrasts revealed voxels with significantly greater object than spatial delay-period activity in two subjects, one of whom also exhibited voxels with greater spatial than object delay-related activity. No trial position effects were detected.

Temporal and Occipital Cortex

All six subjects showed delay-specific activity in posterior ventral stream regions—areas 18, ventral 19, 37, and 20—in both conditions. Spatial and object delay maps

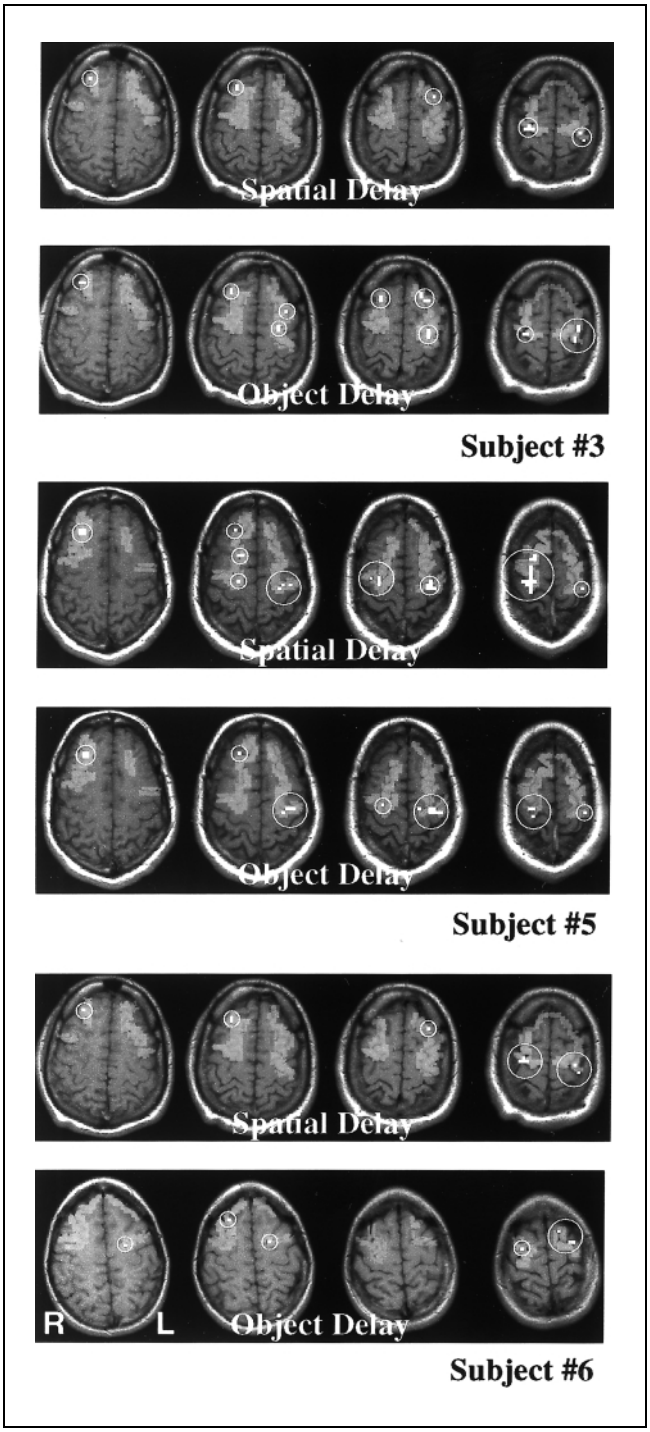

Figure 3. Activation maps displaying suprathreshold activity (circled) in spatial and object delay periods in the SFS in three subjects. ROIs are rendered in translucent white overlays. This figure illustrates the marked degree of overlap in SFS and precentral sulcal activity in the two conditions.

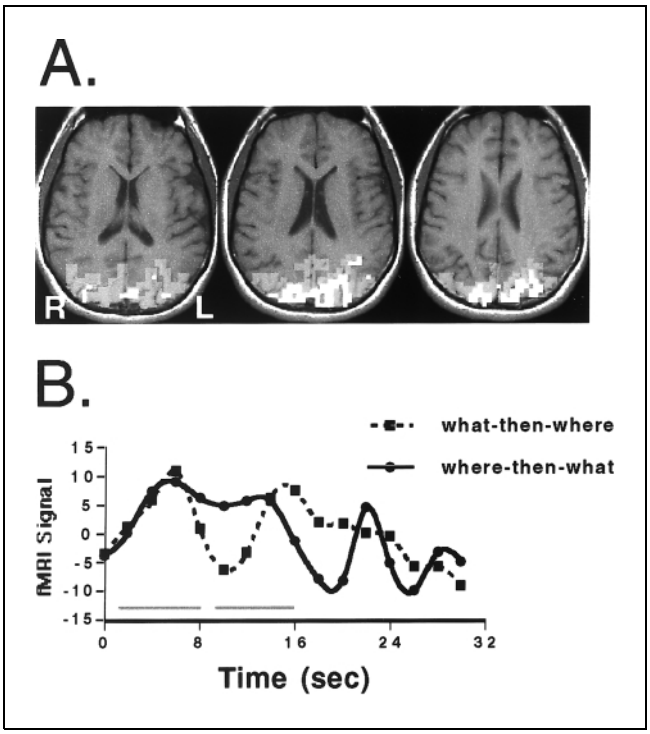

Figure 4. (a) Activation map from SPL in a representative subject displaying voxels demonstrating a main effect of delay-period activity collapsed across spatial and object conditions. ROI is rendered in translucent white overlays. (b) Trial-averaged time series from voxels identified in (a), illustrating greater spatial than object delay-period activity in both trial types.

were quite similar within subjects and extremely variable across subjects, as they were for the PFC. Direct contrasts of delay-period activity revealed voxels with greater object than spatial activity in three subjects: in the inferior temporal and fusiform gyri (areas 20 and 37), bilaterally, in one subject; in the fusiform gyrus (area 37), bilaterally, in a second subject; and in the left fusiform gyrus (ventral area 19) in a third subject (Figure 5). These contrasts also revealed greater spatial than object activity bilaterally in the posterior fusiform gyrus (ventral area 19) in two other subjects. No trial position effects were detected in any ventral stream ROI.

Caudate Nucleus

In the caudate nucleus, spatial delay-period activity was observed in four subjects (bilateral in three, left in one), and object delay-period activity was observed in five subjects (bilateral in two, left in three). Direct spatial/object contrasts revealed no suprathreshold voxels in any subject. Contrasts investigating trial position differences, at variance with the results of comparable analyses in each of the cortical ROIs, achieved significance in the caudate nucleus for four subjects in the spatial condition (delay 2 > delay 1) and for one subject in the nonspatial condition (delay 2 > delay 1). In light of this

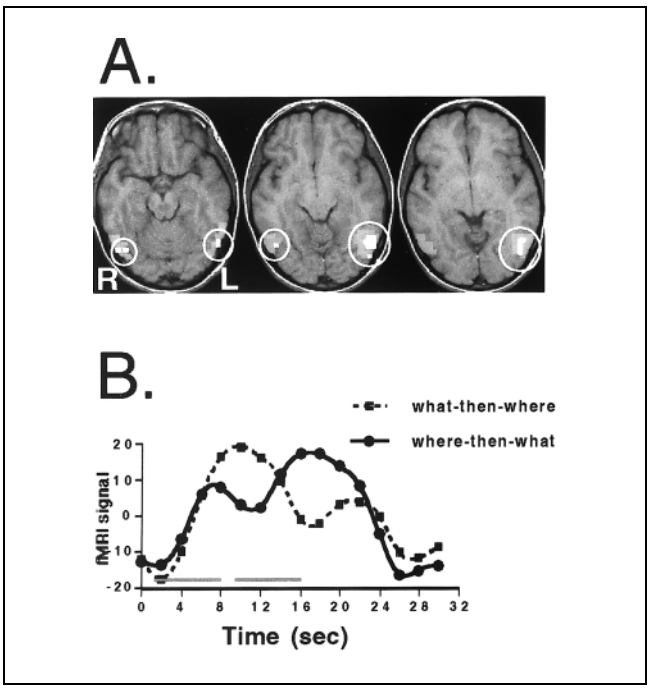

Figure 5. (a) Activation map from Brodmann's area 37 in a representative subject displaying voxels demonstrating a main effect of delay-period activity collapsed across spatial and object conditions. ROI is rendered in translucent white overlays. (b) Trial-averaged time series from voxels identified in (a), illustrating greater object than spatial delay-period activity in both trial types.

result, we performed post hoc contrasts of final-probe-related activity in the caudate nucleus and in M1. These contrasts permitted assessment of the functional nature of these interactions in delay-period activity because differences in final-probe activity that paralleled increases in delay 2 activity would be consistent with a motor preparatory role for the delay 2 activity. Final-probe-related activity, however, did not differ by condition in caudate nucleus or in M1 in any subject.

Group Analyses

Spatial delay-period activity was significantly greater than object delay-period activity at the group level in dorsal area 19, and this difference approached significance in the ventral area 19 (Table 1). Object delay-period activity, in contrast, was not significantly greater than spatial delay-period activity at the group level in any ROI.

DISCUSSION

Our experiment failed to find evidence, at the single-subject level and at the group level, for anatomical segregation of spatial and object working memory function in the PFC. Additionally, no subject in our study showed evidence of segregation of spatial and object working memory function in more superior and posterior regions of the frontal cortex, including in the vicinity of the frontal eye fields, which has been proposed as a site specialized for spatial working memory (Courtney et al., 1998). Although several early reports of neuroimaging studies of visual working memory have described anatomical segregation for working memory for "what" and "where" in the frontal cortex, there is very little consistency among them: One study reported spatial activity in the right inferior PFC versus no object activity in the PFC (Smith et al., 1995), and a second reported spatial activity in the right dorsolateral PFC versus object activity in dorsolateral PFC bilaterally (McCarthy et al., 1996). A third study found greater spatial activity in the dorsolateral and ventrolateral PFC bilaterally versus greater object activity in the left ventrolateral PFC (Baker, Frith, Frackowiak, & Dolan, 1996), a fourth reported greater spatial activity in the superior frontal sulcus in the premotor cortex versus greater object (face stimuli) working memory activity in the right inferior and orbital frontal cortex (Courtney, Ungerleider, Keil, & Haxby, 1996), and a fifth reported greater spatial activity in the medial superior frontal gyrus versus greater object activity in the middle and inferior frontal gyri bilaterally (Belger et al., 1998). Note that the foci of the spatially related superior frontal cortex activation reported by the fourth (Courtney et al., 1996) and fifth (Belger et al., 1998) studies did not overlap because the former did not find spatial activation in the PFC, and the latter did not acquire data from the premotor cortex.

The results of the present experiment are consistent with other results that have emerged more recently and that support a model positing no material-specific differences in the functional anatomical organization of visual

Table 1. Results of paired *t* tests performed as random-effects group comparisons of spatial versus object delay-period activity in each ROI. Positive *t* values indicate greater spatial effects; and negative *t* values indicate greater object effects; significant results are printed in bold typeface. See text for abbreviations.

ROI										
BA 18	*BA 37*	*BA 20*	*Ventral BA 19*	*Dorsal BA 19*	*SPL*	*IPL*	*Dorsolateral PFC*	*Ventrolateral PFC*	*SFS*	*Caudate Nucleus*
0.50	−0.70	−0.33	2.38[a]	**3.48**	0.84	−0.92	−0.13	0.65	0.13	−1.43

[a] *P* value associated with this *t* is 0.06.

working memory in the frontal cortex (D'Esposito, Aguirre, Zarahn, & Ballard, 1998; Owen et al., 1998; Postle, Stern, Rosen, & Corkin, submitted; Rao et al., 1997). This aspect of our data is illustrated by the trial-averaged time series extracted from the dorsolateral PFC voxels demonstrating delay-period activity—the response of PFC voxels is virtually identical during both delay periods of what-then-where and where-then-what trials (Figure 2). Our null results in the PFC cannot be attributed to a lack of statistical power because we did find statistically significant spatial/object delay-period differences in many regions of the posterior cortex.

Because the statistical power of our technique permitted single-subject analyses of spatially unsmoothed datasets, our results also offer a more detailed view of the topographical organization of spatial and nonspatial working memory in posterior cortical regions than has been available in previous fMRI studies, most of which feature spatially smoothed, group-averaged data. Our results reveal the remarkable extent to which delay-period activity, associated with memory for locations and memory for objects, is distributed across the dorsal and the ventral streams of the visual system. It is worth reiterating, in conjunction with this observation, that our assessment of delay-period activity is immune from contamination by activity linked to sensory stimulation. Our results can thus be interpreted in one of two ways: as evidence that subjects remember actively both the positional and featural characteristics of stimuli despite task contingencies that require attention to only one of these perceptual dimensions; or that working memory for stimulus location and working memory for stimulus features each recruits ensembles of neurons in areas traditionally thought of as specialized for visual perception of one or the other kind of attribute. These two interpretations are not mutually exclusive. The second interpretation is consistent with suggestions that both the dorsal and the ventral visual processing streams are equipped to process spatial and featural characteristics of stimuli under perceptually nonchallenging conditions (Schiller, 1993).

Consistent across subjects was the preferential recruitment of extrastriate areas falling within Brodmann's area 19 during spatial delay periods. Visual processing modules associated with the dorsal visual stream, including areas MT and MST, have been localized to this region in humans. Our finding of more consistent spatial-specific delay-period activity in the occipital than in the posterior parietal cortex is consistent with the failure of Postle and colleagues to find reliable spatial-specific working memory-related activity in the SPL in an fMRI study of spatial and nonspatial two-back performance (Postle, Stern, et al., submitted). Evidence for spatial-specific delay-period activity in the posterior parietal cortex (PPC) in the individual data of several of the subjects in our experiment, however, indicates that neurons in the PPC did subserve spatial working memory functions in a preferential way, at least in three of our subjects. The failure of this trend to achieve significance at the group level in our study may reflect a dilution of contributions to the blood oxygen level dependent (BOLD) signal by the material-specific delay-period activity in certain subgroups of PPC neurons by nonmnemonic, polymodal activity subserved by proximal ensembles of cells in this region of the "association" cortex (Hyvarinen, 1981). The strong evidence for specialized delay-specific processing of spatial stimuli in areas 19 and 7 revealed in this experiment argues for a model of visual working memory function in which material-specific mnemonic representations are maintained in the same neuronal networks that subserve sensory analysis of these stimuli, or by ensembles of cells that are anatomically proximal to these sensory networks (Corbetta, Miezin, Dobmeyer, Shulman, & Petersen, 1990; Crowder, 1993).

Evidence for object-specific delay-period activity was more variable than were the spatial results and thus failed to achieve significance in any single ROI in the group analyses. The most consistently observed locus of object delay-period activity in the cortex associated with the ventral visual processing stream was in the lateral fusiform gyrus in the posterior temporal lobe, encompassed by Brodmann's area 37, with other subjects demonstrating object-specific delay-period activity in loci anterior to or posterior to this region. We also observed a trend in four of the six subjects of relatively greater object than spatial delay-period activity in areas 39 and 40 of the IPL. A role for this area in object sensory processing, analogous to the spatial sensory processing that can be attributed to areas 19 and 7, would be difficult to reconcile with the large body of evidence for specialized object processing centers in the fusiform and lingual gyri (Aguirre, Zarahn, & D'Esposito, 1998; Kanwisher, McDermott, & Chun, 1997). We suspect, rather, that this trend in the data may reflect the greater role of verbal encoding in the object than spatial conditions of our experiment. Although our experiment was not designed to test this possibility directly, we know from previous behavioral studies that working memory for the abstract shapes used in the present experiment engages obligatorily a strategy of verbal mediation. The same is not true for spatial working memory (Postle, Kim, D'Esposito, & Corkin, submitted). A post hoc random effects group analysis testing for laterality effects in object delay-period activity in area 40, that is, (left hemisphere spatial delay − left hemisphere object delay) < (right hemisphere spatial delay − right hemisphere object delay), revealed no trend in lateralization.

Our analyses of delay-period activity in the caudate nucleus revealed evidence of sensitivity to position in the trial in several subjects in the spatial, but not the object, condition. Thus, the caudate nucleus appears to be sensitive to the response contingencies of different portions of the trial when memoranda are defined spa-

tially. Specifically, spatial delay-period activity in the caudate nucleus is greater when a motor response will follow the delay period than when no overt response follows the delay period. We have interpreted this result (Postle & D'Esposito, 1999) as evidence for a role of the caudate nucleus in egocentric localization, the integration of egocentric spatial sensory information into a motor plan (Kesner, Bolland, & Dakis, 1993; Potegal, 1971). The process that we detected in our experiment operates at an abstract level of motor control, because the specific vectors of the motor response at the end of the trial were unpredictable during delay 2. Interestingly, despite the strong anatomical connection between the caudate nucleus and PFC (via the thalamus; Alexander, DeLong, & Strick, 1986), the PFC did not show the same sensitivity to the coincidence of spatial delay and position in the trial. This suggests that the selective spatial working memory deficit in early Parkinson's disease (Owen, Iddon, Hodges, Summers, & Robbins, 1997; Postle, Jonides, et al., 1997; Postle, Locascio, Corkin, & Growdon, 1997) reflects dysfunction in the caudate nucleus itself rather than disordered spatial mnemonic processing in the PFC resulting from abnormal striatal outflow.

Although results of our experiment are inconsistent with models positing anatomical segregation of visuospatial working memory-related activity for different classes of stimulus material in the frontal cortex (Ungerleider, Courtney, & Haxby, 1998; Wilson et al., 1993), they do not suggest an alternative organizational scheme. Consideration of data from other experiments, however, does provide clues for an alternative principle along which working memory-related function in the frontal cortex may be organized. Meta-analysis of the neuropsychological literature indicates that short-term memory for digits and for spatial locations, as assessed on span tests, is independent of PFC integrity but that a dependent relationship begins to emerge if distracting tasks or interference are introduced to a working memory task (D'Esposito & Postle, 1999). (And empirical data indicate that it is also independent of striatal integrity; D'Esposito & Postle, in press.) Thus, although we and many other groups observe delay-period activity in the PFC during performance on simple delayed-response tasks, this PFC activity may not reflect the operation of processes that are *necessary* for supporting task performance.

Neuroanatomically dissociable PFC-dependent processes may become necessarily recruited, however, as the demands of a working memory task become more complex. For example, although delay-period activity can often be observed in the left frontal operculum during simple delayed-response performance, experiments that manipulate the degree of overlap in stimulus items across trials in a delayed-response test (and, therefore, manipulate the degree of proactive interference associated with each trial) reveal a positive association of significant increases in activity in the left opercular cortex with proactive-interference trials (D'Esposito, Postle, Jonides, & Smith, 1999; Jonides, Smith, Marshuetz, Koeppe, & Reuter-Lorenz, 1998). Another example is provided by delayed-response tasks requiring manipulation of memoranda during the delay period (e.g., reordering randomly ordered letters into alphabetical order). Delayed-response trials featuring no manipulation demands activate bilateral regions of the dorso- and ventrolateral PFC, but only the dorsolateral PFC voxels show a significant increase in activity when alphabetization demands are added to the working memory task (D'Esposito, Postle, Ballard, & Lease, in press; Postle, Berger, & D'Esposito, in press). We propose, therefore, that the functional anatomical organization of the PFC contributions to working memory function might be better characterized in terms of the nonmnemonic control processes that can contribute to working memory performance, depending on task demands. Thus, the dorsolateral PFC may subserve manipulation operations performed on items held in working memory (D'Esposito et al., in press; Postle et al., in press) that are required by certain tasks, whereas the left inferior PFC may govern inhibitory operations that can also (independently) be required by working memory tasks (D'Esposito et al., 1998; Jonides et al., 1998). Other candidate non-mnemonic processes that can be recruited by working memory tasks, and that may be supported by neuroanatomically dissociable regions of the PFC, include selection of items from semantic memory (Thompson-Schill, D'Esposito, Aguirre, & Farah, 1998), shifting attention among memoranda (Garavan, 1998; McElree, 1998), "updating" the ordinal tags associated with each item held in working memory (Belleville, Rouleau, & Caza, 1998; Kiss, Pisio, Francois, & Schopflocher, 1998; Morris & Jones, 1990), and monitoring the affective valence and/or the behavioral salience of memoranda (Pribram, 1973).

METHODS

Subjects

We studied six right-handed subjects (five males; mean age = 23 years). All were recruited from the undergraduate and medical campuses of the University of Pennsylvania, and all gave informed consent.

Materials

Target stimuli for all object trials were 16 abstract polygon stimuli drawn from Attneave & Arnoult (1956) and determined in normative testing to be difficult to associate with real-world objects (Vanderplas & Garvin, 1959). Four nonmatching probe stimuli were developed for each target stimulus by modifying a single prominent feature of the probe (e.g., removing or changing the orientation of a point or widening or narrowing a portion of the polygon). All stimuli were presented in 1 of 16 locations, each spaced equidistantly along an imagi-

nary circle centered on the fixation point with a radius of 0.5° of visual angle. Nonmatching object probes were selected randomly from among the four variants corresponding to the target stimulus, and nonmatching spatial probes appeared with equal probability in either position adjacent to the target position.

Behavioral Procedure

Placing both spatial and nonspatial delay periods in the same trials and randomizing trial order (what-then-where and where-then-what) obviated the development of extramnemonic context-dependent effects that can develop across a block of trials drawn from the same experimental condition (e.g. Donaldson & Rugg, 1998). Additionally, randomization obviated order effects, such as temporal association of only one delay type with the end-of-the-trial response. The behavioral task began with an instructional cue (500 msec), followed by an initial target stimulus presentation (1 sec), followed by a delay period (delay 1; 6.5 sec), followed by the presentation of the initial target (match) stimulus and a foil stimulus (intermediate stimulus presentation; 1.5 sec), followed by a second delay period (delay 2; 6.5 sec), followed by a probe stimulus (final probe; 1 sec; Figure 1). An intertrial interval (ITI) of 15 sec separated each trial; the time from trial onset to trial onset was 32 sec. A fixation cross appeared with the onset of the initial target and remained on the screen until the offset of the final probe. The instructional cue read "shape first" or "location first" in a pseudorandomly determined order. In shape first, or what-then-where, trials, subjects were trained to encode the featural details of the initial target, ignoring its location on the screen, and to retain this featural information during delay 1. The two intermediate stimuli both appeared in a location different from that occupied by the initial target, and their onset prompted a discrimination as to which of the two was an identical featural match with the initial target. Immediately upon making this discrimination, subjects encoded the location of the match stimulus and retained this location information during delay 2. (In this way, the match probe for the "what" portion of the trial became the target for the "where" portion of the trial.) Upon presentation of the final probe, subjects judged whether or not it occupied the same location as the location target stimulus (i.e., as the match stimulus from the intermediate stimulus presentation) and indicated their decision with a yes or no button press (Figure 1). In location first, or where-then-what, trials, one of the two intermediate stimuli, the match stimulus, occupied the same location as the initial target, the nonmatching probe occupied an adjacent location, and the final probe always appeared in a location different from the locations occupied by the intermediate stimuli. Subjects were trained to perform spatial delayed response during the first half of the trial, to encode featural information about the location-match stimulus from the intermediate stimulus presentation, and to perform object delayed response during the second half of the trial. Each block of trials, corresponding to one fMRI scan, contained six what-then-where and six where-then-what trials, presented in random order, and each featuring an equal number of yes and no trials. Each experiment consisted of eight scanned blocks of testing, or 96 trials (and, therefore, 96 spatial delay periods and 96 object delay periods). (One subject, identified as #6, was tested on five scanned blocks, or 60 trials.)

fMRI Procedure

Imaging was carried out on a 1.5T SIGNA scanner (GE Medical Systems) equipped with a prototype fast gradient system for echoplanar imaging. A standard radio-frequency (RF) head coil was used with foam padding to restrict comfortably head motion. High-resolution sagittal and axial T1-weighted images were obtained in every subject. A gradient echo, echoplanar sequence (TR = 2000 msec, TE = 50 msec) was used to acquire data sensitive to the BOLD signal. Scans of the behavioral task were preceded by a scan in which we derived the impulse response function (IRF) for each subject. The IRF, which characterizes the fMRI response resulting from a brief impulse of neural activity (Boynton, Engel, Glover, & Heeger, 1996), was used to convolve independent variables entered into the general linear model (GLM) for autocorrelated observations that we used to analyze the results of the scans of our behavioral task (Worsley & Friston, 1995). The derive-IRF scan lasted 5 min 40 sec (160 images/slice). Each fMRI scan of the behavioral task lasted 6 min 44 sec (180 images/slice). fMRI data collection during all scans was preceded by 20 sec of dummy gradient and RF pulses to achieve a steady state of tissue magnetization.

fMRI Data Processing

The principle of the fMRI time series analysis was to model the fMRI signal changes occurring during particular temporal periods of the behavioral trials with covariates comprised of shifted, BOLD IRFs (Zarahn et al., 1997b). The fMRI time series were tested with covariates that modeled the expected BOLD signal response in the event of an increase in neural activity (relative to the ITI) occurring during each behaviorally significant portion of each trial (Figure 6). There were 10 covariates of interest in our model, 5 associated with each of the two trial types: initial target stimulus; delay 1; intermediate stimulus presentation; delay 2; final probe. This method yielded measures of delay-period activity that were not contaminated by variance in the fMRI time series attributable to stimulus presentation or response activity. This is because smoothness of the fMRI response to neural activity allows neural events spaced by about 4 sec to be resolved (Zarahn et al., 1997b). Contrasts between a com-

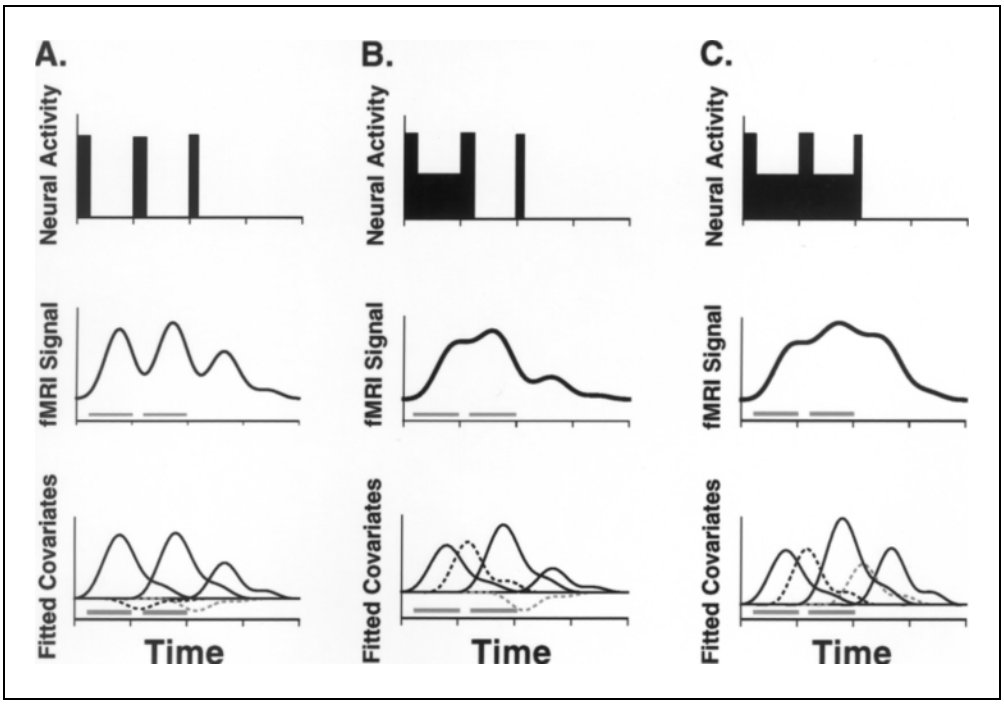

Figure 6. Event-related fMRI data analysis implemented for a what-then-where experimental design. Column (A) represents a voxel exhibiting brief periods of simulated neural activity (top row) associated with initial stimulus presentation, intermediate stimulus presentation, and the response periods of a trial, with no increase above baseline of neural activity during the delay period. Such neural activity change would lead to a particular profile of fMRI signal change (second row), which we simulated by convolving the simulated neural activity depicted in the top row with an empirically derived mean IRF (Zarahn et al., 1997b). The model covariates (which have the same shape as the IRF), scaled by their resulting least-squares coefficients, are shown in the third row. The covariates modeling the first and second delay periods (black and grey dashed lines, respectively) would make a negligible contribution to variance explanation in (A). In contrast to (A), columns (B) and (C) depict situations in which there is some neural activity increase, relative to baseline, during the delay period(s). The covariate(s) modeling the delay period(s) would explain a larger amount of variance in the fMRI signal in (B) and (C) than in (A). Gray bars in graphs in second and third rows represent the two delay periods.

ponent of the trial (e.g., delay) in the two conditions (i.e., spatial versus object) or between different components of the trial within the same condition (e.g., initial target stimulus$_{spatial}$ versus delay 1$_{spatial}$) were realized as the difference between the coefficients associated with the two covariates in question. False positive rates were controlled at $\alpha = 0.05$ by Bonferroni correction for the number of voxels per map or per ROI (Zarahn, Aguirre, & D'Esposito, 1997a). Suprathreshold voxels identified by a particular contrast were therefore voxels for which the *t* values associated with that contrast exceeded the threshold for significance, as determined from the number of effective degrees of freedom of the contrast and the number of multiple comparisons.

Our method for deriving the IRF is described in detail elsewhere (D'Esposito et al., in press). Briefly, we derived the IRF from the primary sensorimotor cortex in each subject by scanning while the subject performed a simple button-press reaction-time task. The fMRI data from this scan were analyzed by creating an impulse basis set for the mean evoked response versus the ITI (baseline). A *t* map was generated for each subject for the reaction-time task using the summed effect of the second and third independent variables (corresponding to 4 and 6 sec following the onset of the target stimulus). IRF estimates were extracted from the suprathreshold voxels by averaging their time series, filtering the resultant spatially averaged fMRI time series to remove high (>0.244 Hz) frequencies, adjusting it to remove the effects of nuisance covariates (Friston, Holmes, Poline, Heather, & Frackowiak, 1995), and trial averaging it.

Many of our analyses were performed with ROIs. We created ROIs for each cortical region in which we would test hypotheses by drawing them onto the "canonical" representation of a brain in Talairach space that is provided in SPM96b, using the atlas of Talairach and Tournoux (1988) to confirm our identification of anatomical landmarks. Next, we transformed these ROIs from Talairach space into the native space in which each subject's data had been acquired by applying the 12-parameter affine transformation (Friston et al., 1995) with nonlinear deformations (Ashburner & Friston, 1996) routine in SPM96b (effectively, a "reverse normalization"). These ROIs corresponded to: dorsolateral PFC (areas 9 and 46); ventrolateral PFC (areas 44, 45, and 47); SFS, incorporating 6 mm of cortex surrounding the sulcus in area 8, extending posteriorly to the intersection of the SFS with the precentral sulcus and incorporating the anterior bank of the precentral sulcus (this ROI was intended to encompass the frontal eye fields, Courtney et al., 1998); SPL (area 7); IPL (portions of areas 40 and 39); superior extrastriate occipital cortex (dorsal area 19; portions of the middle and superior occipital gyri equal and superior to a Talairach coordinate of $z = +16$ mm); inferior extrastriate occipital cortex (ventral area 19; incorporating the portions of the middle occipital, inferior temporal,

fusiform, and lingual gyri corresponding to area 19 that are inferior to a Talairach coordinate of $z = +16$); peristriate area 18; area 37; and area 20. ROIs for primary motor cortex (M1) and for the caudate nucleus were drawn for each subject on that subject's T1 anatomical images, using a method described elsewhere (Postle & D'Esposito, 1999).

Single-Subject Analyses

Our analyses were performed in two steps: single-subject analyses and group analyses. Single-subject analyses permitted us to maintain the high spatial resolution afforded by fMRI and to detect any evidence of intersubject variability. Such information is lost in analysis approaches that combine data from all subjects at an early stage of analysis and are thus restricted to testing for activation patterns that are consistent enough across subjects in a standard space to be detected after group averaging. Our single-subject analyses, in contrast, treated each subject as a case study and permitted us to assess replication of (as well as variation in) effects across individual cases. Single-subject analyses with methods comparable to those used in the present study (and, importantly, with a large number of observations per subject, as in the present study) feature ample sensitivity to detect delay-specific signal intensity changes (D'Esposito et al., in press; Zarahn et al., 1997b; Zarahn, Aguirre, & D'Esposito, 1999).

All analyses were performed on unsmoothed data, permitting assessment of our data at the resolution of $3.75 \times 3.75 \times 5$ mm at which they were acquired. Analyses representing direct tests of our hypotheses proceeded in three stages: (1) assessment of delay-related signal intensity change in each of the two conditions (i.e., spatial delay versus baseline and object delay versus baseline), (2) direct contrasts of delay-related activity elicited in the two conditions (i.e., spatial versus object), and (3) tests for interactions of delay position (delay 1, delay 2) with stimulus condition (spatial, object). The first stage of analysis featured generation and inspection of whole-brain t maps and of trial-averaged time series. Although relying on the output of the GLM to identify voxels showing activation significantly different from baseline, this stage of analysis can be characterized as "descriptive" in its approach, because it permits assessment of brain activity as it actually occurred during our experiments, but it does not effect direct inferential statistical tests of the spatial/object hypothesis. In stage 2 of our single-subject analyses we used activation information acquired from stage 1, as well as a priori knowledge of specific brain regions implicated in working memory function, to test spatial versus object hypotheses. The principal hypothesis tests, consisting of two-tailed (what-then-where delay 2 + where-then-what delay 1) − (where-then-what delay 2 + what-then-where delay 1) contrasts, were performed on the restricted sets of voxels comprising each ROI and thus were assessed for significance at lower critical t values than were the whole-brain maps generated in stage 1. This approach provided greater sensitivity for spatial/object contrasts and would permit identification of brain regions supporting material-specific mnemonic activity in each subject participating in our study. In stage 3 of our analyses we tested for the presence of delay-position effects, which would manifest themselves as a main effect of delay position (what-then-where delay 1 + where-then-what delay 1) − (what-then-where delay 2 + where-then-what delay 2) and/or an interaction of stimulus material and position in delay-period activity (what-then-where delay 1 − where-then-what delay 2) for the object condition, and (where-then-what delay 1 − what-then-where delay 2) for the spatial condition. The latter analysis would test whether delay-period activity with a particular type of stimulus material was sensitive to position within the trial.

Group Analyses

Assessment of the reliability of trends in activation across subjects was effected in the context of random-effects models, an approach that permits generalization of results obtained from a sample to the population represented by that sample. This inferential step cannot be made with the fixed-effects group analyses that have been employed in the majority of published neuroimaging studies to date (Friston, Holmes, & Worsley, 1999; Woods, 1996). Importantly, random-effects analyses are invulnerable to spurious results that can arise if a disproportionately large effect size in a single subject "drives" the mean effect size for the group, as can happen with fixed-effects analyses. All our group analyses used t values as dependent measures, because they represent an index of the signal-to-noise ratio for a given contrast. T values are proportional to the magnitude of the hypothesized effect, and they are normalized measures because they are scaled by the error in each subject (Postle, Zarahn, & D'Esposito, in press). Although ROI-wise analyses on unsmoothed datasets endowed our single-subject analyses with high spatial resolution, the variability across subjects in number and location of suprathreshold voxels within each ROI made this approach unsuitable for a random-effects group analysis. Instead, we employed a method that would yield a single measure indexing the relative level of spatial versus object delay-period activity in each ROI, in each subject. Importantly, this measure was a quantitative measure that could be compared across subjects. We first identified for each subject the voxels within the ROI in question that showed a main effect of memory (what-then-where delay 2 + where-then-what delay 1 + where-then-what delay 2 + what-then-where delay 1). From these voxels we extracted a spatially averaged time series and calculated the orthogonal contrast of (what-then-where delay

2 + where-then-what delay 1) – (where-then-what delay 2 + what-then-where delay 1). The resultant *t* value represented, for each subject, the extent to which delay-period activity was greater for the spatial or the object condition: A positive *t* value would indicate that spatial delay-period activity was greater than object delay-period activity, and a negative *t* value would indicate the converse (Table 1). A paired *t* test on these *t* values, one contributed by each subject, assessed the significance of any trends in the data across subjects, for this ROI.

To summarize, the single-subject analyses featured higher spatial resolution, by permitting inference at the single-voxel level, whereas the group analyses featured greater statistical sensitivity, by pooling signals from many voxels and thereby reducing multiple statistical comparisons to a single comparison that was generalized to an entire ROI. Additionally, the measure produced for the group analyses would index the relative contributions of the spatial versus object condition to delay-period activity regardless of the magnitude of the difference between these two conditions. For example, voxel-wise spatial versus object contrasts performed for a subject in the single-subject analysis might fail to yield any suprathreshold voxels within a particular ROI. The group analysis approach to this ROI in this subject, however, would nevertheless produce a *t* value that would index the *relative* strength of spatial versus object delay-period activity within this ROI.

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REFERENCES

Aguirre, G. K., Zarahn, E., & D'Esposito, M. (1998). An area within human ventral cortex sensitive to "building" stimuli: Evidence and implications. *Neuron, 21,* 373–383.

Alexander, G. E., DeLong, M. R., & Strick, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annual Review of Neuroscience, 9,* 357–381.

Ashburner, J., & Friston, K. (1996). Fully three-dimensional nonlinear spatial normalization: A new approach. *Neuroimage, 3,* S111.

Attneave, F., & Arnoult, M. D. (1956). Methodological considerations in the quantitative study of shape and pattern perception. *Psychological Bulletin, 53,* 221–227.

Baker, S. C., Frith, C. D., Frackowiak, R. S. J., & Dolan, R. J. (1996). Active representation of shape and spatial location in man. *Cerebral Cortex, 6,* 612–619.

Belger, A., Puce, A., Krystal, J. H., Gore, J. C., Goldman-Rakic, P., & McCarthy, G. (1998). Dissociation of mnemonic and perceptual processes during spatial and nonspatial working memory using fMRI. *Human Brain Mapping, 6,* 14–32.

Belleville, S., Rouleau, N., & Caza, N. (1998). Effect of normal aging on the manipulation of information in working memory. *Memory and Cognition, 26,* 572–583.

Bichot, N. P., Schall, J. D., & Thompson, K. G. (1996). Visual feature selectivity in frontal eye fields induced by experience in mature macaques. *Nature, 381,* 697–699.

Boynton, G. M., Engel, S. A., Glover, G. H., & Heeger, D. J. (1996). Linear systems analysis of functional magnetic resonance imaging in human V1. *Journal of Neuroscience, 16,* 4207–4221.

Braver, T. S., & Cohen, J. D. (1995). A model of the development of object and spatial working memory representations in prefrontal cortex. *Second Annual Meeting of the Cognitive Neuroscience Society,* 95.

Corbetta, M., Miezin, F. M., Dobmeyer, S., Shulman, G. L., & Petersen, S. E. (1990). Attentional modulation of neural processing of shape, color, and velocity in humans. *Science, 248,* 1556–1559.

Courtney, S. M., Petit, L., Maisog, J. M., Ungerleider, L. G., & Haxby, J. V. (1998). An area specialized for spatial working memory in human frontal cortex. *Science, 279,* 1347–1351.

Courtney, S. M., Ungerleider, L. G., Keil, K., & Haxby, J. (1996). Object and spatial visual working memory activate separate neural systems in human cortex. *Cerebral Cortex, 6,* 39–49.

Crowder, R. G. (1993). Systems and principles in memory theory: Another critique of pure memory. In A. Collins, S. Gathercole, M. Conway, & P. Morris (Eds.), *Theories of memory* (pp. 139–161). Hove, U.K.: Erlbaum.

D'Esposito, M., Aguirre, G. K., Zarahn, E., & Ballard, D. (1998). Functional MRI studies of spatial and non-spatial working memory. *Cognitive Brain Research, 7,* 1–13.

D'Esposito, M., & Postle, B. R. (1999). The dependence of span and delayed-response performance on prefrontal cortex. *Neuropsychologia., 37,* 89–101.

D'Esposito, M., & Postle, B. R. (in press). Neural correlates of component processes of working memory: Evidence from neuropsychological and pharmacological studies. In S. Monsell & J. Driver (Eds.), *Attention and performance XVIII* Cambridge, MA: MIT Press.

D'Esposito, M., Postle, B. R., Ballard, D., & Lease, J. (in press). Maintenance versus manipulation of information held in working memory: An event-related fMRI study. *Brain & Cognition.*

D'Esposito, M., Postle, B. R., Jonides, J., & Smith, E. E. (1999). The neural substrate and temporal dynamics of interference effects in working memory as revealed by event-related fMRI. *Proceedings of the National Academy of Sciences USA, 96,* 7514–7519.

Donaldson, D. I., & Rugg, M. D. (1998). Context dependent changes in the ERP correlates of associative recall and associative recognition. *Cognitive Neuroscience Society 1998 Annual Meeting Abstract Program,* 117.

Friston, K. J., Ashburner, J., Frith, C. D., Poline, J.-B., Heather, J. D., & Frackowiak, R. S. J. (1995). Spatial registration and normalization of images. *Human Brain Mapping, 2,* 165–189.

Friston, K. J., Holmes, A. P., Poline, J.-B., Heather, J. D., & Frackowiak, R. S. J. (1995). Analysis of fMRI time-series revisited. *Neuroimage, 2,* 45–53.

Friston, K. J., Holmes, A. P., & Worsley, K. J. (1999). How many subjects constitute a study? *Neuroimage, 10,* 1–5.

Funahashi, S., Bruce, C. J., & Goldman-Rakic, P. S. (1990). Visuospatial coding in primate prefrontal neurons revealed by oculomotor paradigms. *Journal of Neurophysiology, 63,* 814–831.

Fuster, J. M. (1997). *The prefrontal cortex: Anatomy, physiology, and neuropsychology of the frontal lobe.* Philadelphia, PA: Lippencott-Raven.

Fuster, J. M., & Alexander, G. E. (1971). Neuron activity related to short-term memory. *Science, 173,* 652–654.

Fuster, J. M., Bauer, R. H., & Jervey, J. P. (1982). Cellular discharge in dorsolateral prefrontal cortex of the monkey in cognitive tasks. *Experimental Neurology, 77,* 679–694.

Garavan, H. (1998). Serial attention within working memory. *Memory and Cognition, 26,* 263–276.

Goldman-Rakic, P. S. (1987). Circuitry of the prefrontal cortex and the regulation of behavior by representational memory. In V. B. Mountcastle, F. Plum, & S. R. Geiger (Eds.), *Handbook of neurobiology* (pp. 373–417). Bethesda, MD: American Physiological Society.

Hecker, R., & Mapperson, B. (1997). Dissociation of visual and spatial processing in working memory. *Neuropsychologia, 35,* 599–603.

Hyvarinen, J. (1981). Regional distribution of functions in parietal association area 7 of the monkey. *Brain Research, 206,* 287–303.

Jonides, J., Smith, E. E., Marshuetz, C., Koeppe, R. A., & Reuter-Lorenz, P. A. (1998). Inhibition of verbal working memory revealed by brain activation. *Proceedings of the National Academy of Sciences, 95,* 8410–8413.

Kanwisher, N., McDermott, J., & Chun, M. M. (1997). The fusiform face area: A module in human extrastriate cortex specialized for face perception. *Journal of Neuroscience, 17,* 4302–4311.

Kesner, R. P., Bolland, B. L., & Dakis, M. (1993). Memory for spatial locations, motor responses, and objects: Triple dissociation among the hippocampus, caudate nucleus, and extrastriate visual cortex. *Experimental Brain Research, 93,* 462–470.

Kiss, I., Pisio, C., Francois, A., & Schopflocher, D. (1998). Central executive function in working memory: Event-related brain potential studies. *Cognitive Brain Research, 6,* 235–247.

McCarthy, G., Puce, A., Constable, R. T., Krystal, J. H., Gore, J. C., & Goldman-Rakic, P. S. (1996). Activation of human prefrontal cortex during spatial and nonspatial working memory tasks measured by functional MRI. *Cerebral Cortex, 6,* 600–611.

McElree, B. (1998). Attended and non-attended states in working memory: Accessing categorized structures. *Journal of Memory & Language, 38,* 225–252.

Mecklinger, A., & Muller, N. (1996). Dissociations in the processing of "what" and "where" information in working memory: An event-related potential analysis. *Journal of Cognitive Neuroscience, 8,* 453–473.

Miller, G. A., Galanter, E., & Pribram, K. H. (1960). *Plans and the structure of behavior.* New York: Holt.

Morris, N., & Jones, D. M. (1990). Memory updating in working memory: The role of the central executive. *British Journal of Psychology, 81,* 111–121.

Newell, A., Shaw, J. C., & Simon, H. A. (1958). Elements of a theory of human problem solving. *Psychological Review, 65,* 151–166.

Owen, A. M., Iddon, J. L., Hodges, J. R., Summers, B. A., & Robbins, T. W. (1997). Spatial and non-spatial working memory at different stages of Parkinson's disease. *Neuropsychologia, 35,* 519–532.

Owen, A. M., Stern, C. E., Look, R. B., Tracey, I., Rosen, B. R., & Petrides, M. (1998). Functional organization of spatial and nonspatial working memory processing within the human lateral frontal cortex. *Proceedings of the National Academy of Sciences, USA, 95,* 7721–7726.

Postle, B. R., Berger, J. & D'Esposito, M. (in press). Functional neuroanatomical double dissociation of mnemonic and executive control processes contributing to working memory. *Proceedings of the National Academy of Sciences, USA.*

Postle, B. R., & D'Esposito, M. (1999). Dissociation of caudate nucleus activity in spatial and nonspatial working memory. *Cognitive Brain Research, 8,* 107–115.

Postle, B. R., Jonides, J., Smith, E., Corkin, S., & Growdon, J. H. (1997). Spatial, but not object, delayed response is impaired in early Parkinson's disease. *Neuropsychology, 11,* 1–9.

Postle, B. R., Kim, L. H., D'Esposito, M., & Corkin, S. (submitted). Effects of verbal and nonverbal interference on spatial and object visual working memory.

Postle, B. R., Locascio, J. J., Corkin, S., & Growdon, J. H. (1997). The time course of spatial and object visual learning in early Parkinson's disease. *Neuropsychologia, 35,* 1413–1422.

Postle, B. R., Stern, C. E., Rosen, B. R., & Corkin, S. (submitted). An fMRI investigation of cortical contributions to spatial and nonspatial visual working memory.

Postle, B. R., Zarahn, E., & D'Esposito, M. (in press). Using event-related fMRI to assess delay-period activity during performance of spatial and non-spatial working memory tasks. *Brain Research Protocols.*

Potegal, M. (1971). A note on spatial-motor deficits in patients with Huntington's disease: A test of a hypothesis. *Neuropsychologia, 9,* 233–235.

Pribram, K. H. (1973). The primate frontal cortex—executive of the brain. In K. H. Pribram & A. R. Luria (Eds.), *Psychophysiology of the frontal lobes* (pp. 293–314). New York: Academic Press.

Pribram, K. H., Ahumada, A., Hartog, J., & Roos, L. (1964). A progress report on the neurological processes disturbed by frontal lesions in primates. In J. M. Warren & K. Akert (Eds.), *The frontal granular cortex and behavior* (pp. 28–55). New York: McGraw-Hill.

Rainer, G., Asaad, W. F., & Miller, E. K. (1998). Memory fields of neurons in the primate prefrontal cortex. *Proceedings of the National Academy of Sciences, USA, 95,* 15008–15013.

Rao, S. C., Rainer, G., & Miller, E. K. (1997). Integration of what and where in the primate prefrontal cortex. *Science, 276,* 821–824.

Rushworth, M. F. S., Nixon, P. D., Eacott, M. J., & Passingham, R. E. (1997). Ventral prefrontal cortex is not essential for working memory. *Journal of Neuroscience, 17,* 4829–4838.

Schiller, P. H. (1993). The effects of V4 and middle temporal (MT) area lesions on visual performance in the rhesus monkey. *Visual Neuroscience, 10,* 717–746.

Smith, E. E., Jonides, J., Koeppe, R. A., Awh, E., Schumacher, E. H., & Minoshima, S. (1995). Spatial versus object working memory: PET investigations. *Journal of Cognitive Neuroscience, 7,* 337–356.

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

Thompson-Schill, S., D'Esposito, M., Aguirre, G. K., & Farah, M. J. (1998). Role of left inferior prefrontal cortex in retrieval of semantic knowledge: A reevaluation. *Proceedings of the National Academy of Sciences, USA, 94,* 14792–14797.

Tresch, M. C., Sinnamon, H. M., & Seamon, J. G. (1993). Dou-

ble dissociation of spatial and object visual memory: Evidence from selective interference in intact human subjects. *Neuropsychologia, 31,* 211–219.

Ungerleider, L. G., Courtney, S. M., & Haxby, J. V. (1998). A neural system for visual working memory. *Proceedings of the National Academy of Sciences, USA, 95,* 883–890.

Vanderplas, J. M., & Garvin, E. A. (1959). The association value of random shapes. *Journal of Experimental Psychology, 57,* 147–163.

Watanabe, M. (1981). Prefrontal unit activity during delayed conditional discriminations in the monkey. *Brain Research, 225,* 51–65.

Wilson, F. A. W., O'Scalaidhe, S. P., & Goldman-Rakic, P. S. (1993). Dissociation of object and spatial processing domains in primate prefrontal cortex. *Science, 260,* 1955–1958.

Woods, R. P. (1996). Modeling for intergroup comparisons of imaging data. *Neuroimage, 4,* S84-S94.

Worsley, K. J., & Friston, K. J. (1995). Analysis of fMRI time-series revisited—again. *Neuroimage, 2,* 173-182.

Zarahn, E., Aguirre, G. K., & D'Esposito, M. (1997a). Empirical analyses of BOLD fMRI statistics. I. Spatially unsmoothed data collected under null-hypothesis conditions. *Neuroimage, 5,* 179–197.

Zarahn, E., Aguirre, G. K., & D'Esposito, M. (1997b). A trial-based experimental design for fMRI. *Neuroimage, 6,* 122–138.

Zarahn, E., Aguirre, G. K., & D'Esposito, M. (1999). Temporal isolation of the neural correlates of spatial mnemonic processing with functional MRI. *Cognitive Brain Research, 7,* 255–268.