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An fMRI Investigation of Cortical Contributions to Spatial and Nonspatial Visual Working Memory

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The experiments presented in this report were designed to test the hypothesis that visual working memory for spatial stimuli and for object stimuli recruits separate neuronal networks in prefrontal cortex. We acquired BOLD fMRI data from subjects while they compared each serially presented stimulus to the one that had appeared two or three stimuli previously. Three experiments failed to reject the null hypothesis that prefrontal cortical activity associated with spatial working memory performance cannot be dissociated from prefrontal cortical activity associated with nonspatial working memory performance. Polymodal regions of parietal cortex (inferior and superior parietal lobules), as well as cortex surrounding the superior frontal sulcus (and encompassing the frontal eye fields), also demonstrated equivalent levels of activation in the spatial and object conditions. Posterior cortical regions associated with the ventral visual processing stream (portions of lingual, fusiform, and inferior temporal gyri), however, demonstrated greater object than spatial working memory-related activity, particularly when stimuli varied only along spatial or featural dimensions. These experiments, representing fMRI studies of spatial and object working memory in which the testing procedure and the stimuli were identical in the two conditions, suggest that domain-specific visual working memory processing may be mediated by posterior regions associated with domain-specific sensory processing.

INTRODUCTION

An important role for dorsolateral prefrontal cortex (PFC) in the mediation of spatial working memory has been established through lesion (e.g., Funahashi *et al.*, 1993; Goldman and Rosvold, 1970; Mishkin, 1957) and electrophysiological (Funahashi *et al.*, 1990; Fuster and Alexander, 1971) investigations in monkeys. Goldman-Rakic has proposed that PFC may be organized into discrete, domain-specific modules, each supporting working memory function, but each preferentially devoted to a specific kind of sensory information (Goldman-Rakic, 1987). Particularly influential for students of memory has been the proposal that working memory for visuospatial information and working memory for visuofeatural information are supported by discrete PFC networks (Goldman-Rakic, 1987; Wilson *et al.*, 1993). The computational validity of a what/where dissociation in human working memory has been supported by behavioral (Hecker and Mapperson, 1997; Owen *et al.*, 1997; Postle *et al.*, 1997a,b; Smith *et al.*, 1995; Tresch *et al.*, 1993) and electrophysiological (Mecklinger and Muller, 1996) studies. To date, however, neuroimaging studies designed to identify the anatomical substrates of spatial and object visual working memory in humans have produced equivocal results: Some groups have reported impressive dissociations between anatomical regions supporting spatial and object working memory (Belger *et al.*, 1998; Courtney *et al.*, 1996, 1998; McCarthy *et al.*, 1996; Smith *et al.*, 1995), whereas others have failed to find domain-specific differences in activation studies (D'Esposito *et al.*, 1998; Owen, 1997; Owen *et al.*, 1998; Postle and D'Esposito, 1999).

The experiments presented in this report were designed to test the hypothesis that visual working memory for spatial stimuli and for object stimuli recruits discrete neuronal networks in PFC. We used several variants of the *n*-back task to ensure that our conclusions about the neural substrates of spatial and object memory were not complicated by the presence of confounding variables. Experiment 1 employed 2-back tests with stimuli that contained exclusively spatial or exclusively object information; Experiment 2 employed 2-back tests with stimuli that contained spatial and object information in both conditions, with only the subject's behavioral set determining whether he per-

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formed a spatial memory or an object memory task; and Experiment 3 employed *n*-back tests that were matched for difficulty: spatial 3-back vs object 2-back. Previous fMRI experiments in our laboratory using a 2-back task with letter vs false-font stimuli revealed bilateral increases in working memory-related signal intensity in prefrontal cortex (area 46) bilaterally, lateral and medial premotor cortex (areas 6 and 8), and parietal cortex (areas 40 and 7) (Stern *et al.*, 1995). Thus, we were confident that our task would elicit strong signal intensity changes throughout the cortex. In addition to probing the anatomical substrates of spatial and object working memory in PFC, our experiment permitted the exploration of the extent to which the posterior sensory and polymodal areas that demonstrate clear what/where dissociation in the sensory processing of visual information (Belger *et al.*, 1998; Ungerleider and Haxby, 1994) also demonstrate domain-specific mnemonic properties.

GENERAL METHODS

Subjects

Our subjects were between the ages of 18 and 35 and were recruited from the MIT community. None had a history of neurological or psychiatric problems.

Functional Imaging

We conducted conventional MR imaging and echo-planar MR imaging combined with asymmetric spin-echo imaging sequences (TR = 2500 ms) using a high-speed 1.5-T scanner (Baker *et al.*, 1992, 1993; Belliveau *et al.*, 1992; Dixon, 1984) at the MGH–NMR Center. High-resolution T1-weighted images were used to localize functional activity. In each study, we obtained 20 contiguous coronal slices (7 mm thick), beginning at the frontal pole and extending posteriorly to approximately the level of the parietooccipital sulcus. Each slice contained a 64 × 64 matrix of 3.125 × 3.125 × 7-mm voxels.

Behavioral Tasks

We used several variations of the *n*-back working memory task, in which subjects viewed a sequence of stimuli presented one at a time and pressed a key whenever they saw a stimulus that repeated after $n - 1$ intervening stimuli (Cohen *et al.*, 1994; Gevins and Cutillo, 1993; Kirchner, 1958). We consider this a working memory task because it entails temporary storage and manipulation of information to guide behavior (Baddeley, 1992; Goldman-Rakic, 1987). Specifically, this task requires (a) encoding a stimulus into a memory store; (b) maintaining the representation of this stimulus in memory despite the subsequent presentation of additional interfering, attentionally salient stimuli; (c) shifting attention back to this mnemonic representation when necessitated by task contingencies; (d) making a discrimination between this mnemonic representation and the stimulus on the screen and guiding behavior with the outcome of this discrimination; and (e) actively discarding this mnemonic representation so that it won't interfere with subsequent operations to be performed with other mnemonic representations. Each *n*-back task was paired with a control task that featured the same sensory and motor components, but minimized working memory demands.

Each scan corresponded to a 4-min testing session of a particular condition (spatial or object) of the behavioral task that comprised alternating 1-min blocks of *n-back/control/n-back/control*. Each 1-min block began with an instruction message (5 s) followed by 18 stimuli (2-s exposure duration, 1-s ISI; a 2-s ISI followed the final stimulus of each block). In the spatial 2-back task the stimuli appeared serially, pseudorandomly, in any of nine different spatial locations on the screen. Spatial stimuli in Experiment 1 were identical black circles and in Experiments 2 and 3 were drawn from a set of nine abstract "Attneave" shapes that each look distinctive (Attneave and Arnoult, 1956) and are difficult to verbalize (Vanderplas and Garvin, 1959). The nine locations corresponded to the cells of a 3 × 3 grid, measuring 6 by 6 in. vertically and centered on the computer screen. (All stimuli were scaled to the largest size that would fit into a 1.5 in. wide by 2 in. high box. No grid lines or boxes outlining the boundaries of the nine locations were ever presented.) For the 2-back task, a match occurred when two stimuli appeared in the same location on the screen, with one intervening stimulus appearing in a different location (Fig. 1). The spatial control task was a simple detection task in which subjects viewed a succession of stimuli appearing at different locations on the screen and indicated each time a stimulus appeared in a prespecified position—the upper leftmost position. This control task required subjects to retain one position in mind throughout a control block and thus did not require the constant encoding, updating, and discarding of information that was required by the *n*-back task. Subjects responded with a "yes" or "no" button press on every trial of each task.

Stimuli in the object 2-back condition in each of the three experiments were Attneave shapes. In Experiment 1 they appeared at the center of the screen in a pseudorandom serial order; in Experiments 2 and 3 they appeared in the nine different locations described previously, in a pseudorandom order. A match occurred when a shape was repeated, with one different intervening stimulus (Fig. 1). In the object control condition, subjects viewed a series of Attneave shapes and indicated each time a prelearned target stimulus appeared. The features of this target stimulus were designed to

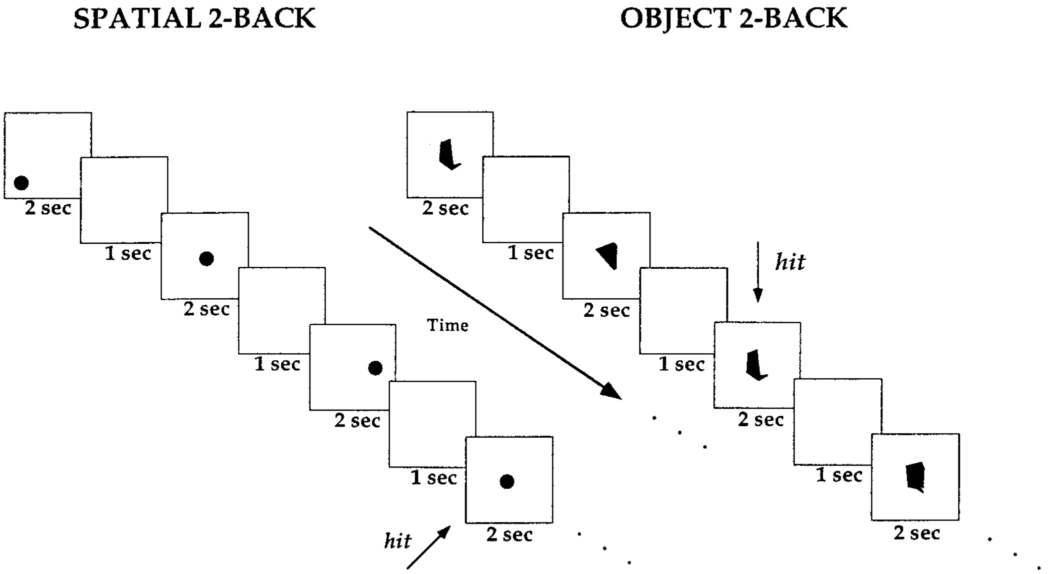

FIG. 1. Experiment 1. Schematic illustration of the spatial 2-back and the object 2-back tasks.

be markedly different from the nine Attneave shapes, but also to be abstract and difficult to verbalize. Subjects were trained to recognize this shape prior to scanning.

Stimulus Presentation

Computer-generated visual stimuli were projected into the scanner using a Sharp XG-2000f liquid crystal rear-projection projector. The stimuli were displayed on a translucent screen placed above the subject's chest. Subjects viewed the stimuli through an overhead mirror.

Data Analysis

All data analyses were performed by the first author in the laboratory of M. D'Esposito at the University of Pennsylvania. Offline data processing was performed on SUN Ultra workstations using programs written in Interactive Data Language (Research Systems, Boulder, CO). After image reconstruction the data were motion corrected with the six-parameter (three translational and three rotational), rigid-body, least-squares realignment routine from the SPM96b package. The effect of this realignment procedure has been demonstrated (Friston *et al.*, 1995) to be very similar to that of another frequently employed registration technique, the Automated Image Registration routine (Jiang *et al.*, 1995; Woods *et al.*, 1992). Next, we applied a slice-wise motion compensation routine that removed spatially coherent signal changes via the application of a partial correlation method to each slice in time (Zarahn *et al.*, 1997a). Prior to statistical analyses the functional data were smoothed spatially with a three-dimensional 9.375-mm (FWHM) isotropic smoothing kernel—a kernel equivalent to three times the in-plane resolution at which the data were acquired.

Because fMRI data are autocorrelated temporally under the null hypothesis (Aguirre *et al.*, 1997; Zarahn *et al.*, 1997a), the data analysis was conducted within the framework of the modified general linear model for serially correlated error terms proposed by Worsley and Friston (1995). Within the K matrix (Worsley and Friston, 1995), we placed a time-domain representation of the expected $1/f$ power structure (Zarahn *et al.*, 1997a) and a filter that removed frequencies at and around the Nyquist frequency (0.4 Hz). Scan-effect covariates were included in the model to account for mean signal change across scans. Variance in the fMRI time series data was assessed statistically with contrasts derived from the parameter estimates that corresponded to the "boxcar" reference function modeling each component of the task (i.e., spatial working memory, spatial control, object working memory, object control). The boxcar independent variables were smoothed with an empirically derived average impulse response function (Aguirre *et al.*, 1998) so that they would match more closely the expected shape of components of the fMRI time series data that were correlated with our task (Aguirre *et al.*, 1997; Zarahn *et al.*, 1997a).

Individual Subject Analyses

The analyses of each experiment proceeded in two steps. First, we assessed patterns of activation associated with spatial and object working memory at the individual subject level; then we performed group analyses (no group analyses were performed for Experiment 3). For the analysis of data from individual subjects, the corrected false-positive rate was controlled at

$P \leq 0.05$ per map or per region of interest (ROI) (i.e., correction for multiple comparisons) using Gaussian field theory (Aguirre *et al.*, 1997; Worsley, 1994). These analyses were qualitative comparisons of the regions activated by the two working memory conditions. Our design had insufficient power to permit quantitative comparison of spatial vs object working memory within single subjects.

Group Analyses

After completing our analyses of individual subject data, we performed group analyses of the data from Experiments 1 and 2 with random-effects models. The random-effect approach permits generalization of results obtained from a sample to the population represented by that sample, an inferential step that cannot be made with the fixed-effects group analyses that have, until recently, been employed by the majority of fMRI experimentalists (Friston *et al.*, 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. The group analyses provided a quantitative measure with which we could compare the qualitative results of the single-subject analyses.

Prior to performing the group analyses we drew ROIs corresponding to seven cortical regions that have been implicated in previous studies of spatial and nonspatial working memory. We drew the ROIs 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. These regions were: (a) fusiform and lingual gyri (F/LG), including portions of areas 18, 19, and 37, extending posteriorly to $y = -70$ and anteriorly to $y = -40$; (b) inferior temporal gyrus (ITG), including portions of areas 37 and 20, extending posteriorly to $y = -70$ and anteriorly to $y = -34$; (c) superior parietal lobule (SPL), incorporating much of area 7, extending posteriorly to $y = -70$ and anteriorly to $y = -34$; (d) inferior parietal lobule (IPL), corresponding to areas 39 and 40, extending posteriorly to $y = -58$ and anteriorly to $y = -22$; (e) dorsolateral prefrontal cortex (DLPFC), corresponding to areas 9 and 46; (f) ventrolateral prefrontal cortex (VLPFC), corresponding to areas 44, 45, and 47; and (g) superior frontal sulcus (SFS), incorporating 6 mm of cortex surrounding the sulcus in area 8, extending posteriorly to the intersection of the SFS with the precentral sulcus (Fig. 4). We chose the anteriormost extents of the F/LG and ITG ROIs based on the published results of previous studies reporting sensory and mnemonic activity in these regions associated with the presentation of nonspatial stimuli (Belger *et al.*, 1998; Courtney *et al.*, 1996). The SFS ROI was included because of a recent proposal that this region might play a privileged role in spatial working memory processing (Courtney *et al.*, 1998). Next, we transformed into Talairach space the T1 anatomical images and the EPI images for each subject, using the nine-parameter affine transformation (rigid body and zooms) routine in SPM96b. By defining our anatomical ROIs objectively, on a normalized brain, we intended to restrict our hypothesis testing to volumes defined in a standard anatomical space, thereby reducing bias for an anatomical dissociation. Because some individual anatomical variability is preserved in the normalization process, we adjusted the ROIs to better correspond to the normalized anatomical images of some subjects so that they would mask perfectly the intended brain regions.

To perform the random-effects analysis, we first identified for each subject a set of voxels within a particular ROI that demonstrated an effect of memory. This was accomplished by generating a statistical map of the contrast (spatial *n*-back + object *n*-back) − (spatial control + object control) at a threshold that highlighted between 50 and 150 voxels.[2] Next, we extracted a spatially averaged time series for these memory-related voxels and compared spatial vs object working memory effects in this time series with the two-tailed contrast (spatial *n*-back + object control) − (spatial control + object *n*-back), a contrast that is orthogonal to the contrast used to identify memory-related voxels. This contrast yielded a *t* value that provided a normalized index of the working memory-related effect in a region.[3] A positive *t* value generated by this contrast would indicate that the spatial working memory effect was greater than the object working memory effect; a negative *t* value would indicate the converse. For a given ROI, the random-effects analysis was realized with a paired *t* test that used these *t* values as the dependent data, one contributed by each subject (Tables 1 and 2). Thus, the group analyses assessed the reliability of effect sizes within a priori defined regions, not extents of activation (as might be assessed by the number of activated voxels). It is important to keep in mind that the *t* values listed in Tables 1–3 reflect the direct statistical contrast of spatial vs object working memory and not the magnitude of the working memory effect that was observed in a particular condition. For example, a small *t* value in a particular ROI means

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[2] Although the threshold used to identify voxels varied across regions within subjects, as well as within regions across subjects, care was taken that the number of voxels per subject, per region, was comparable.

[3] The *t* value provides a suitable dependent measure for a group analysis because it provides an index of the signal-to-noise ratio for a given contrast and minimizes unexplained intersubject variance that would introduce noise into random effects analyses, thereby decreasing their power. Note that, when employed as dependent measures as described here, *t* values are indices of *effects*, rather than of signal intensity per se (Postle *et al.*, 2000b).

that the magnitudes of the spatial working memory effect and the object working memory effect in this region were comparable, but cannot be interpreted as a reflection of the "amount of activation" in that subject.

EXPERIMENT 1

Methods

Subjects

We tested 10 right-handed subjects (mean age = 22.7, *SD* 4.5; 8 male) in this experiment.

Procedure

Each subject was tested on two scans each of the spatial and object tasks in an alternating fashion, with spatial testing always preceding object testing. Spatial stimuli were identical black circles that appeared in each of the nine locations on the screen, object stimuli were Attneave shapes that each appeared centrally. Eight of the subjects were also tested, during the same scanning session, on a version of these tasks that is reported as Experiment 2. These additional scans followed the Experiment 1 scans for six subjects and occurred after the first two Experiment 1 scans for two others.

Results

Behavioral Results

Analysis of the behavioral performance indicated that the spatial 2-back task was considerably easier for subjects (spatial 2-back mean % correct = 94.6, *SD* 7; spatial control mean % correct = 95.4; *SD* 9.9) than was the object 2-back task (object 2-back mean % correct = 77.7, *SD* 8.5; object control mean % correct = 97.9; *SD* 3.1). It is also likely that object working memory performance was partly mediated by verbal coding of stimuli. Research in our laboratory indicates that a verbal strategy is engaged automatically by object *n*-back performance, regardless of the difficulty of the task. Spatial *n*-back performance, however, can be independent of a verbal strategy at the level of difficulty presented by Experiment 1 (Kim *et al.*, 1997; Postle *et al.*, 2000a).

Individual Subject Analyses

Inspection of *n*-back vs control task fMRI data revealed considerable variability of patterns of PFC activation across subjects, although middle frontal gyrus (MFG) was activated in eight subjects in the spatial condition and in eight subjects in the object condition at an ROI-wise *t* threshold. Only one subject showed no MFG activation in either condition. Within-subject comparisons indicated that the same regions of PFC were activated in both conditions (Fig. 2): For any particular subject, specific loci of working memory-related PFC activation that appeared in one condition were also found in the other condition. And although extent of activation in a given region was often larger in one of the two conditions for an individual subject, neither condition was associated with systematically larger foci of PFC activations across subjects.

Our analyses also revealed robust activation of premotor and supplementary motor cortex (areas 6 and 8), bilaterally, and of left inferior parietal lobule (40) in both conditions in each of the 10 subjects (Fig. 3). Inspection of individual fMRI data suggested that consistent condition-specific patterns of activation might be located in SPL and in posterior ventral stream regions (lingual, fusiform, and inferior temporal gyri). The former seemed to be associated to a greater extent with spatial working memory performance, whereas the latter were clearly associated with greater object working memory performance. We did not observe any consistent subcortical activations.

Group Analyses

The results of our group analyses (Table 1) confirmed our assessment of the individual subject data that there was no evidence of systematic, reliable differences in patterns of activation in either PFC ROI (Fig. 4). Indeed, exactly one-half of the subjects showed greater spatial than object working memory effects in DLPFC, and three of these subjects showed greater spatial than object working memory effects in VLPFC. Similarly, exactly one-half of the subjects showed greater spatial than object working memory effects in the SFS ROI; three of these were subjects who showed greater spatial than object working memory effects in DLPFC.

In posterior regions, the group analysis indicated that activation in the posterior parietal ROIs was not associated reliably with greater effects in either of the working memory conditions. Both ventral stream ROIs, however, demonstrated significantly greater object than spatial working memory effects (Table 1).

Discussion

The results of Experiment 1 suggested that the pattern of PFC activation is not a good predictor of visual working memory test condition. The (2-back − control) contrasts indicated that individual subjects demonstrated robust activation of PFC areas in both working memory conditions and that, for any individual subject, the same regions of PFC tended to be activated by the two conditions. Further, the results suggested that domain-specific visual working memory computations may be supported by posterior cortex. Specifically, the group analysis indicated that activity in the F/LG and ITG ROIs was preferentially associated with object

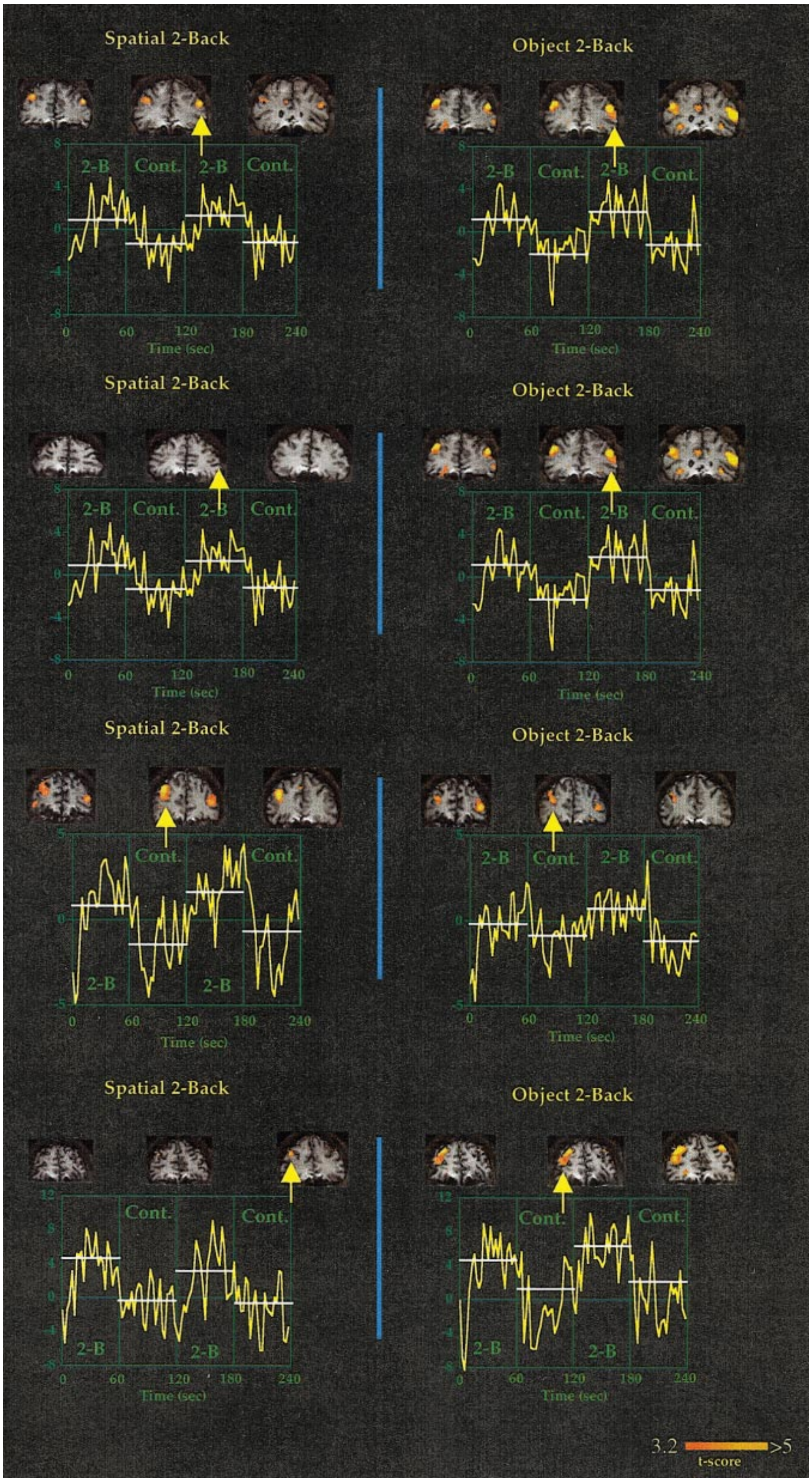

FIG. 2. Experiment 1. PFC activation associated with spatial working memory and object working memory in four subjects; each brain slice is presented in radiological conventions with respect to left and right. Mean-centered time series data for each subject were extracted from the same cluster of voxels (highlighted by yellow arrows) for both conditions. Horizontal lines in each behavioral block of the time series plots represent mean fMRI signal intensity. The time series plots are unsmoothed and unaveraged temporally.

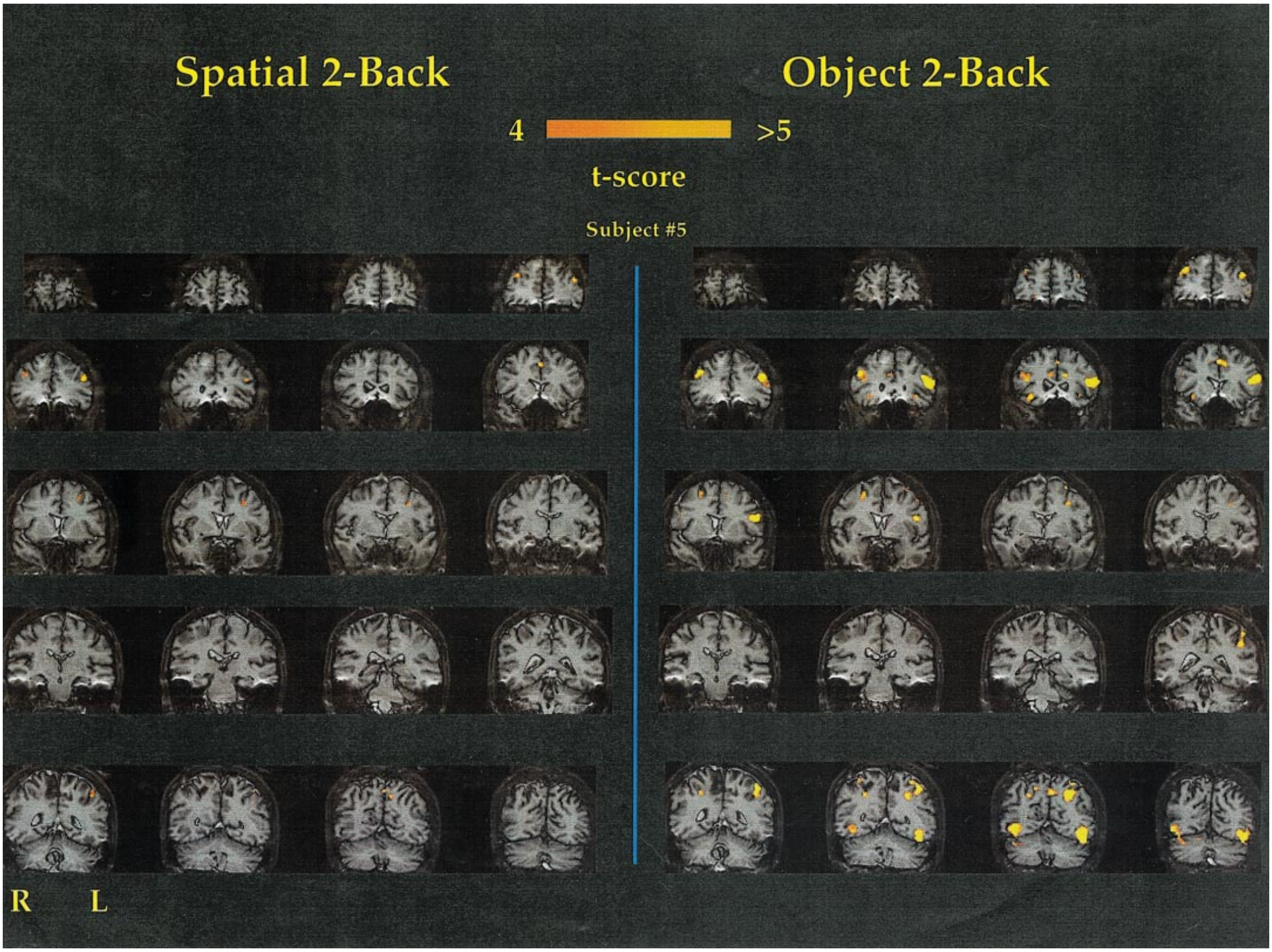

FIG. 3. Experiment 1. Whole-brain activation associated with spatial working memory and object working memory in a representative subject. Anteriormost slice appears in the upper left corners.

working memory performance. Within the SPL and IPL ROIs, as with the PFC ROIs, we found no evidence for preferential domain-specific mnemonic activity. These results are similar to those reported in a PET study that compared spatial delayed response and object delayed matching across two groups of subjects (Baker *et al.*, 1996). It should be noted that the SPL ROI extended posteriorly only to the level of the parietooccipital sulcus. We, therefore, could not detect spatial working memory-specific activity that may have been present in dorsal stream areas of the occipital cortex, as would be predicted from the results of other studies (Belger *et al.*, 1998; Courtney *et al.*, 1996; Postle and D'Esposito, 2000; Smith *et al.*, 1995).

The data presented in the preceding section must be interpreted with the knowledge that Experiment 1 confounded two important factors with stimulus material: sensory stimulation and difficulty. Because each condition in Experiment 1 featured stimuli that changed along only one stimulus dimension, the sensory components of the working memory and control tasks in the two conditions were necessarily different—identical black circles presented in nine different locations in the spatial condition and nine different Attneave shapes presented in a single position in the object condition. Although the assumptions of the cognitive subtraction approach to neuroimaging experimental design posit that matching the sensory components of the experimental and the control task in a memory experiment should remove any contribution of sensory portions of the task to the subtracted image (Posner *et al.*, 1988), the validity of these assumptions have been challenged on theoretical grounds (Friston *et al.*, 1996), and they have been shown to fail in an event-related fMRI study of spatial delayed response (Zarahn *et al.*, 1997b). Thus a decisive test of spatial vs object working memory should include an experiment in which the sensory components of these two conditions are

TABLE 1

Group Analyses from Experiment 1

Subject	Fusiform and lingual gyri	Inferior temporal gyrus	Superior parietal lobule	Inferior parietal lobule	Dorsolateral PFC	Ventrolateral PFC	Superior frontal sulcus
1	−2.09	−2.65	−1.86	0.2	−0.06	−1.2	−0.65
2	−0.66	−3.59	0.4	0.17	1.1	0.03	0.53
3	0.82	0.9	0.39	1.95	0.95	−0.09	2.4
4	0.8	0.38	0.95	1.67	0.76	2.61	1.5
5	−3.12	−2.54	−0.16	−0.74	0.21	−1.04	−1.13
6	−1.49	−1.33	−0.68	−0.18	−0.52	−0.31	−0.75
7	0.52	0.86	1.26	1.38	0.66	0.57	−0.03
8	−1.65	−0.85	−0.99	−1.4	−2.23	−1.65	0.85
9	−0.91	−0.85	0.84	−0.11	−1	−0.56	0.85
10	−1.66	−2.23	−0.89	−0.36	−1.53	−0.16	−1.07
$t(df)$	−2.26 (9)	−2.32 (9)	−0.23 (9)	0.57 (9)	−0.46 (9)	−0.48 (9)	0.06 (9)
P	0.05	<0.05	>0.8	>0.4	>0.6	>0.6	>0.9

Note. The t values associated with the [(spatial 2-back − spatial control) − (object 2-back − object control)] contrast in voxels within each ROI showing working memory-related activity, and results of the paired t test for each ROI are shown. Positive sign for t values indicates spatial working memory > object working memory; negative sign indicates object working memory > spatial working memory.

matched (Smith *et al.*, 1995). It should be noted, however, that matching the sensory components of spatial and object conditions of a working memory experiment would tend to *decrease* the likelihood of finding differences between the two conditions. The confounding of independent variables is much more problematic for interpretation of a study that purports to find a difference between two conditions than it is for interpretation of a study that fails to find such a difference.

The confound of difficulty also complicated the interpretation of the results of Experiment 1. Some regions that seemed to be activated equally by the two conditions may in fact have been associated preferentially with spatial working memory function, a property that could have been obscured by the greater processing demands of the more difficult object 2-back task. Experiment 2 used a modification of the 2-back task that was intended to address the confounds present in Experiment 1.

EXPERIMENT 2

The sensory and difficulty confounds present in Experiment 1 had been anticipated when we designed our study. Thus, many of the subjects participating in Experiment 1 were also tested, during the same session, with modified versions of the spatial and object working memory tasks in which the sensory characteristics of stimuli in the two conditions were identical (see General Methods).

Methods

Subjects

Data from each of the eight right-handed subjects participating in this experiment (mean age = 22.0, *SD* 3.9, six males) were collected from the same scanning sessions presented in Experiment 1.

Procedure

Each subject was tested on one block each of the modified spatial and object 2-back tasks, with spatial testing always preceding object testing. Our instructions to the subject indicated the stimulus dimension to which to attend and stated explicitly that variation along the other stimulus dimension was to be ignored. The scans corresponding to Experiment 2 followed two Experiment 1 scans in the case of two subjects and followed four Experiment 1 scans in the case of six subjects.

Results

Behavioral Results

The change in testing format from Experiment 1 to Experiment 2 made little difference in the difficulty of the two tasks: Spatial 2-back performance (spatial 2-back mean % correct = 96.1, *SD* 7.4; spatial control mean % correct = 95.3; *SD* 6.5) was superior to object 2-back performance (object 2-back mean % correct = 79.7, *SD* 12.8; object control mean % correct = 99.0; *SD* 3.0). Experiment 2, therefore, was not successful at removing the difficulty confound that had been present in Experiment 1. Because the implementation of the modified procedure removed the sensory confound that had been present in Experiment 1, however, this experiment permitted direct assessment of the effect of manipulating the similarity of sensory characteristics of the stimuli.

Individual Subject Analyses

Inspection of 2-back vs control task fMRI data revealed patterns of PFC activation that were markedly reduced from those seen in Experiment 1. Foci of activation were generally smaller, fewer, and of lower intensity. Only three subjects exhibited suprathreshold PFC activation at an ROI-wise *t* threshold in both conditions. For these three subjects, the results were qualitatively similar to what was seen in Experiment 1: the loci of PFC activations in one condition were predictive of the loci of PFC activations in the other condition. Overall, MFG was activated in just four of eight subjects in the spatial condition and in five of eight subjects in the object condition. Two subjects showed no suprathreshold PFC activation in either condition. Posterior regions also exhibited less activation than was seen in Experiment 1. IPL, for example, a region that showed activation in both conditions in every subject in Experiment 1, was activated at a suprathreshold level in only two subjects in the spatial condition and in only three subjects in the object condition. In addition to the change in testing procedure, an important factor in this general reduction of task-related activation (in comparison with Experiment 1) was likely the reduced power of Experiment 2, because subjects were scanned during only one run per condition.

Group Analyses

Reduced statistical power arising from fewer observations did not affect the group analysis of Experiment 2, however, because this analysis was sensitive to relative differences between the spatial and the object conditions, rather than to the magnitude of the memory effects. These group analyses therefore represent a direct assessment of the modified testing procedure employed in Experiment 2, uncomplicated by questions of statistical power. Table 2 presents the results of the group analysis from Experiment 2 and reveals two important differences from the results of Experiment 1. First, the two posterior ventral stream ROIs no longer exhibited significantly greater object than spatial working memory effects. Second, the three frontal ROIs each demonstrated greater object than spatial working memory effects at levels approaching significance.

Discussion

Interpretation of the results from Experiment 2, a test of spatial and object visual working memory in which the stimulus displays looked identical in the two conditions, was complicated by two unattended effects. First, the introduction of the modified testing procedure was not effective in equating the spatial and object conditions for difficulty. Second, the fact that Experiment 2 featured only one scan per subject in each condition contributed to levels of activation that were markedly reduced in comparison to Experiment 1. The change to stimuli that varied along both spatial *and* object characteristics in both conditions was undoubtedly partly responsible for the general decrease in activation that we observed across these two experiments. A similar manipulation in an earlier study of spatial and object working memory also resulted in a marked decrease in working memory-related activation (Smith *et al.*, 1995).

Precisely because the levels of difficulty were maintained across these two experiments, however, Experiment 2 presented an opportunity to compare directly the effects of the manipulation of sensory presentation of stimuli on the relative strengths of activation of spatial and object working memory in different cortical ROIs. In posterior cortex, we observed a lessening in the relative superiority of object working memory, such that the F/LG and ITG ROIs no longer demonstrated significantly greater object than spatial working memory activation. The results in posterior cortex can be interpreted as an indication that changing stimuli along more than one stimulus dimension during an *n*-back task, despite instructions to ignore irrelevant changes, results in an attenuation of the domain-specific dissociation in working memory-related activity in certain areas. The introduction of stimuli that changed identity from trial to trial in a spatial working memory task may, for example, have led to a broader recruitment of areas supporting performance on the task, such that cortical areas of the ventral visual processing stream were recruited to a greater extent by the spatial condition of Experiment 2 than of Experiment 1. This would lead to a reduction in the disparity in working memory-related effects in the F/LG and ITG ROIs across spatial and object conditions. This hypothesis cannot be tested directly, however, because of the disparity in power between Experiments 1 and 2.

In frontal cortex, in contrast, the relative effect of object working memory became much more pronounced. These results indicated that testing subjects with identical stimulus displays in the two conditions resulted in relatively greater object working memory-related activity in each of the three frontal ROIs. Compared to the results of Experiment 1, this might be interpreted as suggesting that changing the featural identity of stimuli in a spatial working memory task has a greater influence on frontal cortical regions than does changing the position of stimuli in a nonspatial working memory task. This result was not anticipated, and we do not have a good explanation for it. The implication of this result for the principal hypothesis of this experiment, however, is clear. The effect of changing procedure between Experiment 1 and Experiment 2 was comparable for each of these ROIs, consistent with the conclusion from Experiment 1 that these fron-

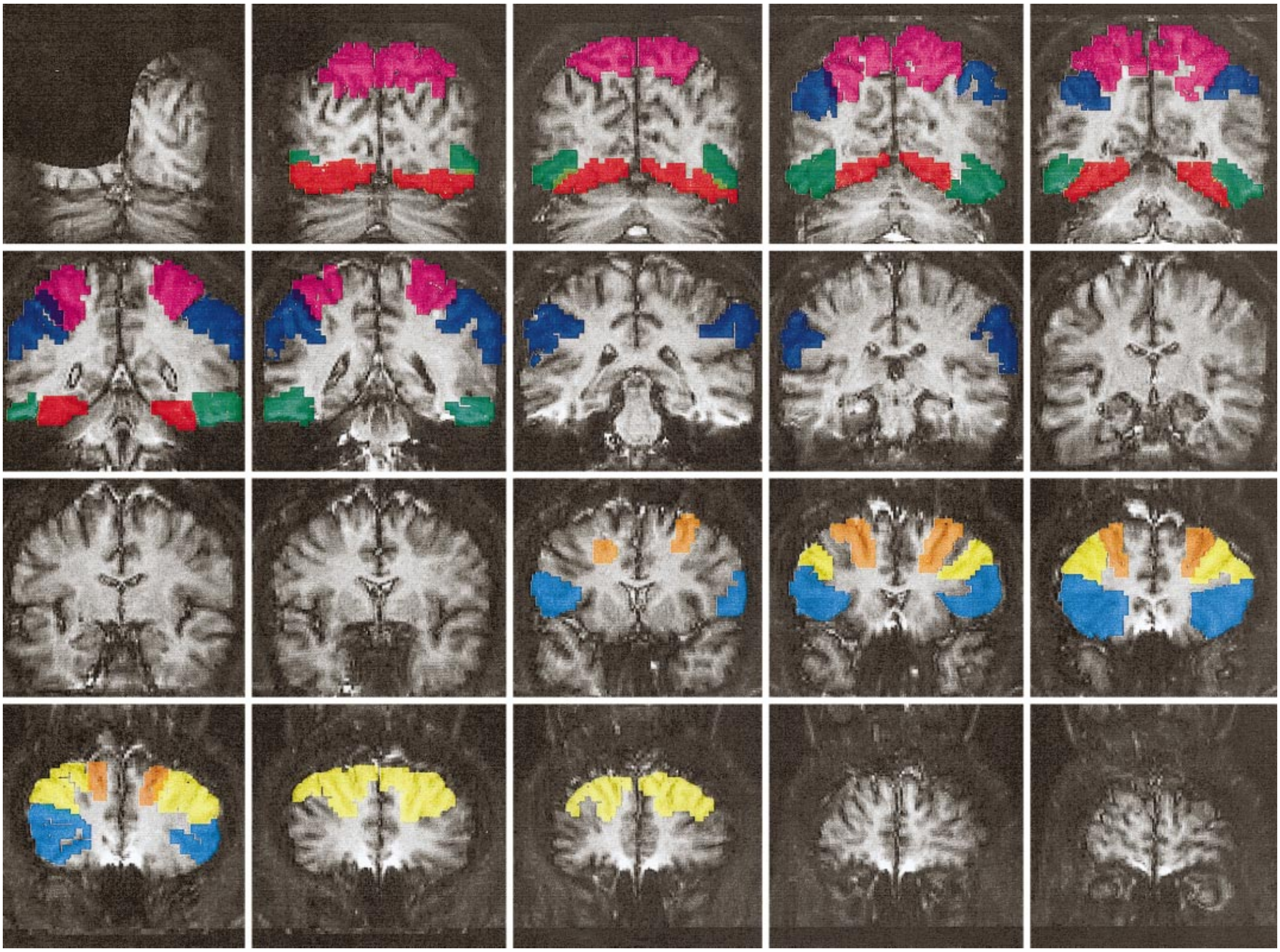

FIG. 4. Illustration of the seven ROIs used for group analyses in each of the three experiments, displayed on the normalized T1 anatomical images of a single subject. Purple, SPL; dark blue, IPL; green, ITG; red, F/LG; orange, SFS; yellow, DLPFC; light blue, VLPFC. See text for abbreviations.

tal regions are not differently sensitive to spatial vs object working memory task performance.

EXPERIMENT 3

Because Experiment 2 was not successful in removing the difficulty confounds from the 2-back studies, we modified the spatial working memory task to become a 3-back task. This change increased the memory load of the spatial task, as well as the demands on nonmnemonic processes that support *n*-back performance, such as attentional shifting among items in working memory and selecting among the remembered items for each discrimination with a stimulus on the screen. We anticipated that this change would increase the difficulty of the spatial task, thereby facilitating the direct comparison of spatial and object working memory. Previous studies that manipulated parametrically the memory load in an *n*-back task using letters as stimuli have reported load-dependent behavior in PFC ROIs, but not the recruitment of additional PFC regions with increasing memory load (Braver *et al.,* 1997; Cohen *et al.,* 1997). Thus, we did not anticipate that changing the spatial working memory task to a 3-back task would result in the emergence of previously undetected regions of spatial-specific working memory processing. We were interested to see, however, whether increasing the difficulty of the spatial working memory task would differentially affect the frontal ROIs, perhaps leading to relatively greater spatial working memory-related activation in one or more of them.

Methods

Subjects

We scanned four right-handed subjects (mean age = 21.0, *SD* 2.4, two males) who had not participated in the previous experiments.

TABLE 2

Group Analyses from Experiment 2

Subject[a]	Fusiform and lingual gyri	Inferior temporal gyrus	Superior parietal lobule	Inferior parietal lobule	Dorsolateral PFC	Ventrolateral PFC	Superior frontal sulcus
2	−0.02	−0.41	2.01	1.05	−0.27	−0.42	−0.87
3	0.68	0.99	0.0	0.67	0.39	−0.7	−0.13
4	−0.95	3.25	0.99	1.07	0.11	0.55	−1.09
6	0.58	0.55	0.19	0.82	0.17	0.26	0.28
7	−1.49	−1.54	−1.15	−0.61	−0.48	−1.19	0.23
8	−1.66	−2.23	−0.89	−0.36	−1.53	−0.16	−1.07
9	−2.17	−1.95	−1.65	−1.89	−1.61	−1.87	−0.11
10	−0.19	−1.37	−0.49	−0.86	−2.18	−3.03	−1.77
$t(df)$	−1.68 (7)	−0.37 (7)	−0.38 (7)	−0.34 (7)	−2.0 (7)	−2.29 (7)	−2.29 (7)
P	>0.1	>0.7	>0.7	>0.7	0.09	0.06	0.06

Note. The t values associated with the [(spatial 2-back − spatial control) − (object 2-back − object control)] contrast in voxels within each ROI showing working memory-related effects, and results of the paired t test for each ROI are shown. Positive sign for t values indicates spatial working memory > object working memory; negative sign indicates object working memory > spatial working memory.

[a] Subject identification numbers correspond to those presented in Table 1.

Procedure

Each subject was tested on three blocks each of spatial 3-back and object 2-back tasks in an alternating fashion, with spatial testing always preceding object testing. In the spatial 3-back task, subjects judged, for each serially presented stimulus, whether that stimulus occupied the same position that had been occupied three stimulus presentations previously. Other than the change to spatial 3-back, all other aspects of the experiment were the same as in Experiment 2.

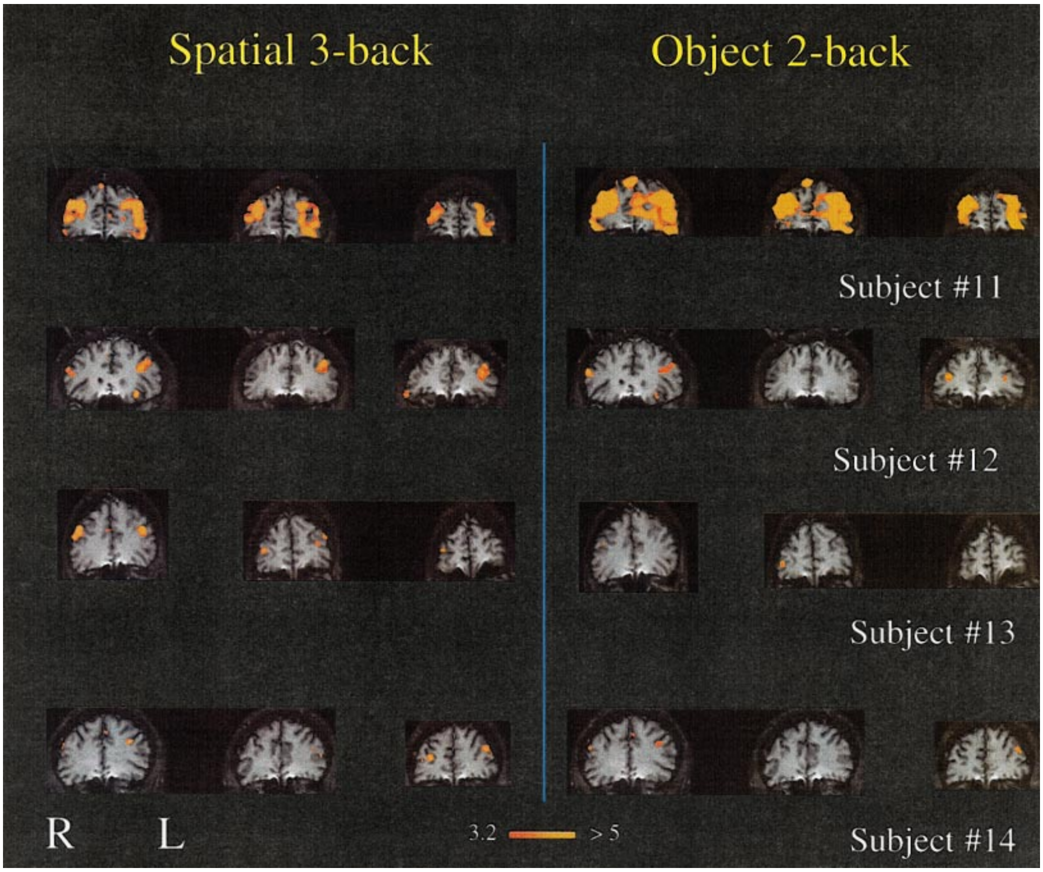

FIG. 5. Experiment 3. PFC activation associated with spatial working memory and object working memory in each subject.

TABLE 3

Group Data from Experiment 3

Subject	Fusiform and lingual gyri	Inferior temporal gyrus	Superior parietal lobule	Inferior parietal lobule	Dorsolateral PFC	Ventrolateral PFC	Superior frontal sulcus
11	−0.19	−1.37	−0.49	−0.86	−2.18	−3.03	−1.77
12	−0.02	−0.41	2.01	1.05	−0.27	−0.42	−0.87
13	−0.95	3.25	0.99	1.07	0.11	0.55	−1.09
14	0.58	0.55	0.19	0.82	0.17	0.26	0.28

Note. The t values associated with the [(spatial 3-back − spatial control) − (object 2-back − object control)] contrast in voxels within each ROI showing working memory-related activity are shown. Positive sign for t values indicates spatial working memory > object working memory; negative sign indicates object working memory > spatial working memory.

Group Data

Although the small number of subjects participating in Experiment 3 precluded a quantitative group analysis of these data, ROI-wise t values were nonetheless extracted from each subject in the same manner as they had been for the group analyses from Experiments 1 and 2.

Results

Behavioral Results

The modification of the spatial working memory task had the desired effect of making it more difficult: Spatial 3-back performance (spatial 3-back mean % correct = 71.7, *SD* 13.1; spatial control mean % correct = 94.6; *SD* 9.9) was inferior to object 2-back performance (object 2-back mean % correct = 83.3, *SD* 8.6; object control mean % correct = 97.9; *SD* 4.2).

Individual Subject Analyses

Similar to the results from the previous two experiments, we observed considerable variability in the locus and extent of PFC activation across subjects, but remarkably similar patterns of activation across conditions within subjects (Fig. 5). Whole-brain maps from the spatial 3-back scans were reminiscent of those generated from the spatial 2-back scans from Experiment 1, with activation in PFC, premotor cortex, and inferior and superior parietal lobules. Two of the four subjects also showed sparse posterior ventral stream activation. Whole-brain maps from the object 2-back scans were similar to those described in Experiment 2.

Group Data

Inspection of Table 3 reveals no evidence of a trend toward a domain-specific dissociation among frontal ROIs.

Discussion

These results are consistent with the conclusions from the previous experiments, providing no indication of a trend toward differential representation of spatial and object working memory in frontal cortex. These results serve as an important complement to Experiments 1 and 2 because their interpretation is not complicated by sensory or difficulty confounds.

GENERAL DISCUSSION

Across three fMRI experiments, we were unable to find evidence consistent with the hypothesis that spatial and object visual working memory are supported by discrete modules within frontal cortex. The results of our study, therefore, are not consistent with models postulating segregation of working memory function into domain-specific modules in frontal cortex (Goldman-Rakic, 1987; Ungerleider *et al.*, 1998). Other recent studies have also failed to confirm this hypothesis (Cullen *et al.*, 1998; D'Esposito *et al.*, 1998; Nystrom *et al.*, 2000; Oster *et al.*, 1997; Owen *et al.*, 1998; Postle and D'Esposito, 2000; Rao *et al.*, 1997). In addition to the results in frontal cortex, we found evidence that object working memory computations may be preferentially supported by the posterior cortical regions associated with sensory processing of featural information. The strong superiority of object working memory-related activity in fusiform, lingual, and inferior temporal gyri that we observed in an experiment employing stimuli that varied only along either the spatial or the featural dimension was somewhat attenuated in experiments featuring stimuli that changed along both spatial and featural dimensions. We found no evidence for analogous spatial-specific working memory-related activity in polysensory posterior parietal areas 7, 39, and 40. A similar result has been described in a PET study (Baker *et al.*, 1996). Other studies have localized activation specific to spatial working memory to the occipital lobe (Belger *et al.*, 1998; Courtney *et al.*, 1996; Postle and D'Esposito, 2000; Smith *et al.*, 1995), from which we did not gather data in this experiment.

The experiments presented in this report highlight the issue of difficulty in working memory research. Surely, decisive tests of hypotheses about differential representation of working memory for different kinds of information need to feature conditions that are matched for difficulty. Difficulty, however, is typically indexed by performance, a measure that is sensitive to many different kinds of task manipulations. A working memory task, for example, can be made more difficult by increasing perceptual difficulty at encoding, by increasing memory load, by increasing computational demands, or by increasing the difficulty of target/foil discrimination by increasing the similarity between the two. The former manipulation can be assumed to have its effects on memory encoding processes, the middle two affect processing of information after encoding takes place, and the final manipulation affects decision and response processes. It is possible, therefore, to match two tasks for performance by increasing the difficulty of different components of each task and thus by emphasizing different information processing stages in the two tasks.

The choice of how to control difficulty in an experimental design can impact the results of a brain-mapping experiment. The results of studies that manipulate load and computational demands within subjects suggest that such manipulations affect signal intensity within the PFC regions activated by the task, but do not influence the number of regions recruited by the task (Braver *et al.*, 1997; Cohen *et al.*, 1997; D'Esposito *et al.*, 1995). Within-subject manipulation of sensory difficulty, in contrast, can influence the number of PFC regions activated by a task (Barch *et al.*, 1997). It follows from these findings that regions not detected in a perceptually "easy" version of a memory task may emerge in a modification of the same task that presents stimuli in a way that challenges the perceptual system. In the present study, we manipulated difficulty by increasing the number of items that had to be shuffled through working memory. The jump from 2-back to 3-back increased the memory load and the computational demands of the task, but did not affect its sensory demands. Indeed, stimulus exposure durations were held constant at an unchallenging 2 s in every study reported here. The discrepancy between our results and those of some previous studies that have reported spatial/object working memory differences in frontal cortex may reflect, in part, the fact that these other studies featured computationally simple memory tasks (delayed response) that relied on perceptual difficulty (rapid exposure durations (Belger *et al.*, 1998; Smith *et al.*, 1995) or difficult-to-discriminate stimuli (Courtney *et al.*, 1996)) to bring subject performance below ceiling. That is, a delayed-response task presenting one or two stimuli per trial as memoranda is a simple task for a college undergraduate to perform. Making such a task more difficult by degrading the stimuli perceptually or by making target/foil judgments more challenging may result in the recruitment of regions that are sensitive, in a domain-specific way, to perceptual difficulty. If so, such working memory task designs may be more likely to elicit domain-specific patterns of activation in frontal cortex.

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