



# Functional topography of a distributed neural system for spatial and nonspatial information maintenance in working memory

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## Abstract

We investigated the degree to which the distributed and overlapping patterns of activity for working memory (WM) maintenance of objects and spatial locations are functionally dissociable. Previous studies of the neural system responsible for maintenance of different types of information in WM have reported seemingly contradictory results concerning the degree to which spatial and nonspatial information maintenance leads to distinct patterns of activation in prefrontal cortex. These inconsistent results may be partly attributable to the fact that different types of objects were used for the “object WM task” across studies. In the current study, we directly compared the patterns of response during WM tasks for face identity, house identity, and spatial location using functional magnetic resonance imaging (fMRI). Furthermore, independence of the neural resources available for spatial and object WM was tested behaviorally using a dual-task paradigm. Together, these results suggest that the mechanisms for the maintenance of house identity information are distributed and overlapping with those that maintain spatial location information, while the mechanisms for maintenance of face identity information are relatively more independent. There is, however, a consistent functional topography that results in superior prefrontal cortex producing the greatest response during spatial WM tasks, and middle and inferior prefrontal cortices producing their greatest responses during object WM tasks, independent of the object type. These results argue for a dorsal–ventral functional organization for spatial and nonspatial information. However, objects may contain both spatial and nonspatial information and, thus, have a distributed but not equipotent representation across both dorsal and ventral prefrontal cortex.

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## 1. Introduction

Working memory (WM) is the means by which a limited amount of information is actively maintained and processed for a short period of time. Single cell recordings of monkey prefrontal cortex during delayed match to sample and delayed response tasks have shown that cells exhibit stimulus specific sustained activity over delay periods, presumably reflecting information maintenance (e.g. [20,22,23,43], for reviews see [24,25]). Functional magnetic resonance imaging (fMRI) studies of human subjects also show sustained activity over delay periods of WM tasks in prefrontal cortex (e.g. [9,11,78]).

The role of regions within the prefrontal cortex in maintaining different types of information in WM is under debate, however. While there appear to be dissociations

between prefrontal regions based on the type of processing required, independent of the type of information involved [11,14,49,56,70], the question remains whether those prefrontal areas involved in simple maintenance of information also have a functional organization according to the type of information maintained. It has been proposed that the visual system is divided into two (interconnected) processing streams. The ventral pathway, including occipitotemporal cortex, is thought to represent perceptual properties that are important for object identification, such as color, texture, and shape. The dorsal pathway, including parietal cortex, on the other hand, processes information regarding the spatial locations of objects, the spatial relationships among objects, and the guidance of motor movements toward objects [26,33,73,74]. One model proposes that this ventral/dorsal, object/spatial dissociation extends to the prefrontal cortex, resulting in separate functionally specialized areas for object and spatial WM maintenance (for review see [38]). Single neurons in the monkey dorsolateral prefrontal cortex,

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near the posterior end of the principal sulcus, have been shown to exhibit spatially selective delay-related activity during visuospatial delayed response tasks (e.g. [20,23,37]). In contrast, neurons in the inferior convexity in the ventrolateral prefrontal cortex that do not respond during spatial delayed response tasks, do often respond selectively to textures, shapes, and faces, and respond best to stimuli presented foveally. Neurons of this sort are very seldom found in the principal sulcus. These neurons often have sustained stimulus-selective activity in object–response association tasks and even in tasks that do not have a required memory or response component ([47,77], review in [38]).

Behavioral deficits resulting from lesions in both humans and monkeys also suggest a different neuroanatomical organization for spatial and nonspatial WM. In monkeys, lesions of cortex within the posterior portion of the principal sulcus impair spatial WM but not object WM [21,41,52,53]. Results from lesions of ventral prefrontal cortex (the inferior convexity) can impair performance on both spatial and object WM tasks, although the nature and duration of the deficits is unclear [38,42,66]. In humans, a recent report described a patient with a lesion of the right superior prefrontal cortex that showed a selective deficit for spatial WM. This patient had no impairment of verbal or object WM and no visual perceptual or attention deficit [7]. A different individual patient with a lesion restricted to inferior lateral prefrontal cortex who had a selective deficit for nonspatial WM has also been reported [5]. Transient “lesions” induced by repetitive transcranial magnetic stimulation in humans demonstrated a double dissociation, with dorsal medial stimulation (near the superior frontal sulcus (SFS)) producing selective impairment of a spatial WM task and ventral lateral stimulation producing selective impairment of a face WM task [45].

Accordingly, many imaging studies in humans have shown that the ventral prefrontal cortex, such as the inferior and middle frontal gyri (IFG/MFG), is most consistently activated during WM for faces [11], objects other than faces [6,39,67], and verbal information [3,17,35,54,61,63,68]. More dorsal prefrontal cortex, specifically an area of the superior frontal sulcus, has been most consistently activated during spatial WM tasks [4,8,10,34,40,46,50,55,68,78]. Significant double dissociations in the amount of activation in dorsal and ventral prefrontal cortex for spatial and nonspatial information have been shown with both visual [10,12] and auditory [2] stimuli.

It should be noted, however, that both dorsal and ventral prefrontal regions are frequently activated for both spatial and object WM tasks relative to low-level control tasks and several imaging studies in humans have found no significant differences in the patterns of activation for these two types of tasks [4,6,39,46,50,59,67]. Single cell recording data also suggest that many cells across both dorsal and ventral prefrontal cortex maintain both spatial and object information and it has been suggested that object and spatial information are integrated, rather than segregated into specialized areas, in prefrontal cortex. Individual cells have been found in the

prefrontal cortex that show sample-specific activity over the delay period for either object, location, or the combination of object and location information with no obvious topological organization regarding the anatomical distribution of these cell populations [44,62,64].

The reason for these apparently conflicting results regarding the functional segregation or the integration of WM maintenance in the prefrontal cortex is unclear. Human neuroimaging studies that did not find significant differences in the activation between object and spatial WM tasks within the prefrontal cortex used either geometric shapes or patterns as stimuli in the object task [46,51,58,59]. A study by Courtney et al. [12] which demonstrated a clear dorsal–ventral double dissociation for spatial and object identity information used faces as stimuli. In the monkey frontal cortex, the representation of faces in particular appears to be restricted to the ventral inferior convexity [47,48]. If the representation of faces is restricted to the ventral prefrontal cortex while the other object representations are not, then the dorsal–ventral double dissociation between face and spatial WM observed in the Courtney et al. [12] study could be specific to faces and not a general principle extending to all objects [60].

Some categories of objects may require a greater representation of spatial information than other categories of objects. If the objects to be remembered varied between sample and test in terms of spatial aspects (e.g. spatial relationships among parts), rather than in terms of nonspatial aspects (e.g. color or texture), this could lead to a different pattern of brain activation and different behavioral performance on tasks involving these different categories of objects. For example, greater activation of parietal cortex for houses than for faces has been observed previously in studies of object perception [28,29,31,32]. This activation of parietal areas by house perception could reflect a distributed representation of houses across both ventral (nonspatial) and dorsal (spatial) visual areas. Alternatively, it could reflect an activation that is due to some spatial aspect of house stimuli (e.g. spatial navigation associations, spatial scale, or spatial variation between exemplars) that would not be necessary to the task of identifying the house. The distributed representation account would imply shared neural resources for a spatial location task and a house identity task while the incidental activation account would imply independent neural resources.

In the current study, we investigated the pattern of activation during WM tasks for face identity, house identity, and spatial location of faces and houses using fMRI (Experiments 1–3). We also performed a behavioral experiment utilizing a dual task paradigm to determine the extent to which spatial location information can be maintained concurrently with separate face or house identity information (Experiment 4). If faces and houses place differential demands on the neural substrates necessary for location WM, then there should be different behavioral effects when attempting to maintain location information while simultaneously maintaining face or house information. The fMRI and behavioral results

together suggest that the mechanisms for the maintenance of house identity information (and perhaps other objects) are distributed and overlapping with those that maintain spatial location information, while the mechanisms for maintenance of face identity information are relatively more independent. There is, however, a consistent functional topography that results in superior prefrontal cortex producing the greatest response during spatial WM tasks, and middle and inferior prefrontal cortices producing their greatest responses during object WM tasks, independent of the object type.

## 2. Materials and methods

### 2.1. Subjects

Subjects for the preliminary behavioral testing of the tasks used in the fMRI experiments (Experiment 1 and 2,  $N = 11$ ; Experiment 3,  $N = 7$ ), and for the behavioral dual-task experiment ( $N = 10$ ), consisted of Johns Hopkins University students. Participants were recruited from a pool of students volunteering to do psychology experimentation in return for extra credit in undergraduate psychology classes.

Subjects for the fMRI portions of this study were non-smokers in good health that had no history of head injury, neurological or mental disorders, drug or alcohol abuse, and no current use of medications that affect the central nervous system or the cardiovascular function, and were separate from those that participated in the behavioral portions. The experimental protocol was approved by the Review Board on the Use of Human Subjects of the Johns Hopkins University and by the Joint Committee on Clinical Investigations of the Johns Hopkins University School of Medicine. Participants in the fMRI portion of the study were compensated with US\$ 50. All the subjects gave written informed consent. No significant differences existed between the three fMRI experiments regarding age or educational background of the subjects (Experiment 1:  $N = 6$ ; Experiment 2:  $N = 5$ ; Experiment 3:  $N = 4$ ). Across all fMRI experiments, the mean age of subjects was 25, with a range of 18–45 years old. Mean educational background was 17 years.

### 2.2. Stimuli

Stimuli consisted of gray-scale photographs of 24 faces and 24 houses. The faces consisted of one set of 12 male faces and one set of 12 female faces. All the faces were chosen from a high school yearbook, cropped to remove hair and clothing, and no face had obvious features (i.e. glasses, facial hair, etc.). All face stimuli were oriented in a similar position (roughly 3/4 profile, facing left) and were displaying a similar emotional expression. The house stimuli consisted of 12 photographs that were exemplars of “brick tudors” in and around Bethesda, MD and 12 exemplars of “beach houses” along the shoreline of North Carolina. Each

subset maintained a similar architectural design and all the photographs were taken from roughly the same angle of view (approximately 3/4 profile, front of house facing left).

Faces and houses were initially unfamiliar. Subjects saw each of the faces and/or houses twice in a training session before scanning, 10 times during scanning in Experiment 1, 16 times in Experiment 2, and 8 times in Experiment 3. Control stimuli consisted of the same images Fourier transformed, phase scrambled, and then inverse Fourier transformed. The resulting images retained overall contrast, luminance and frequency information.

The face stimuli were  $6.2^\circ \times 6.8^\circ$  of visual angle in Experiments 1 and 2, and  $6.2^\circ \times 6.2^\circ$  of visual angle in Experiments 3 and 4. The house stimuli were  $8^\circ \times 5.5^\circ$  of visual angle in Experiments 1 and 2, and  $6.2^\circ \times 6.2^\circ$  of visual angle in Experiments 3 and 4. The field of view for all the experiments measured  $33^\circ \times 26^\circ$  of visual angle.

For Experiments 1 and 2, each stimulus could appear in any 1 of the 24 locations on the screen. The 24 locations for face and house stimuli differed so that there were 24 possible locations for faces and 24 different possible locations for houses. Spatial positioning on the screen and overlap of stimulus presentation locations was manipulated to equate the difficulty between the object and spatial tasks during behavioral testing of the tasks. All stimuli were presented in the center of the screen during Experiment 3. In Experiment 4, the house and face stimuli for the object task were presented at fixation, and location task stimuli could appear in any of 12 fixed locations around 2 concentric circles centered about fixation. Stimuli were presented and behavioral data for Experiments 1–3 were collected on a Power Macintosh G3 desktop computer using Superlab software. An LCD projector located outside the scanning room, back projected the stimuli onto a screen located inside the bore of the scanner. Subjects viewed the stimuli via a mirror mounted to the top of the head coil. Responses were made with left or right thumb presses of hand held button boxes that were connected via a fiber optic cable to a Cedrus RB-6x0 Response Box. Experiment 4 was run and data was collected on a Dell Inspiron desktop computer using Visual Basic Software.

### 2.3. Tasks

fMRI data was collected in three experiments, each done with a separate group of subjects. Across the three fMRI experiments, there were four WM tasks (an object delayed recognition task for either faces or houses, and a spatial delayed recognition task using either faces or houses) and a sensorimotor control task. Experiment 1 used all the four WM tasks, Experiment 2 used only the house identity and house location WM tasks; and Experiment 3 used only the face identity and house identity WM tasks.

Each trial in all conditions consisted of: (1) an instruction cue presented for 3000 ms; (2) an instruction delay of 3000 ms consisting of a blank screen with a fixation cross in the center; (3) the presentation of three sample stimuli,

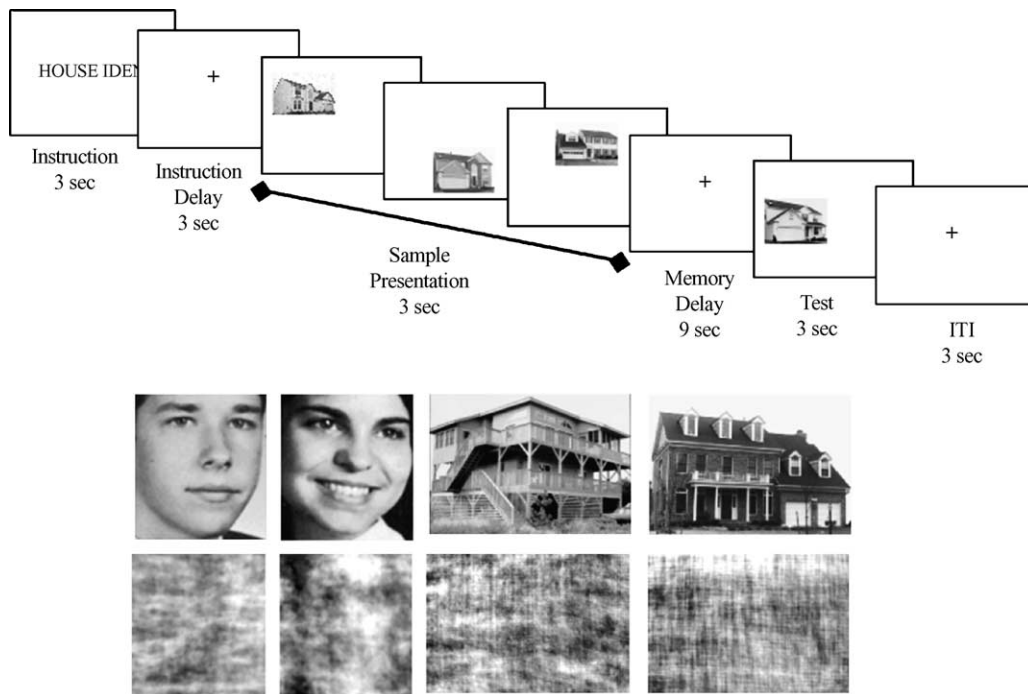


Fig. 1. A sample trial of the fMRI paradigm (Experiments 1–3). Shown here is a house identity trial, however sequence and timing of events were constant for house identity, face identity, house location, and face location tasks. For Experiment 3, all the stimuli were presented in center of screen. Below are examples of the stimuli used in the experiments.

one at a time for 1000 ms each and each in a different 1 of the possible 24 locations on the display; (4) a WM delay of 9000 ms consisting of a blank screen with a fixation cross at the center; (5) the presentation of a test stimulus for 3000 ms in 1 of the 24 locations possible; (6) an intertrial interval (ITI) of 3000 ms consisting of a blank screen with a fixation cross at the center (see Fig. 1). The instruction cue informed the subject as to what information in the sample presentation needed to be remembered during the delay period (face identity, house identity, location, or nothing).

Within each face trial, the three sample faces were either all males or all females with a corresponding test face of the same gender. Within each house trial, the three sample houses were of a common architectural style with a corresponding test house of the same architectural style. Within each object trial, no location on the screen was repeated (sample or test). Within each spatial trial, no object was repeated (sample or test).

Phase scrambled stimuli were used during the sensorimotor control trials. In control trials, the scrambled stimuli were held constant to one type of object category for each trial, such that in the control trials preceding or following a face trial, only scrambled images of faces were used. Similarly, in the control trials preceding or following house trials, only scrambled images of houses were used. Neither the object identity nor the spatial location was repeated within a control trial.

Subjects were instructed to look directly at each of the images while it was present on the screen, and to fixate

on the cross in the center of the screen any time it was present (during ITIs and memory delays). Subjects were instructed to respond using a left or right button press when the test image appeared. A “match” response for “identity” meant that the test image matched the identity of one of the sample images. A “match” response for location meant that the test image was presented in the same location on the screen as one of the sample images. Subjects were told that object identity was “irrelevant” during location trials and that spatial location was “irrelevant” during identity trials. For control trials, subjects were instructed that they need not remember anything and to respond by pressing both buttons during the presentation of the test stimulus.

All WM conditions used in an experiment were presented in each run. Conditions were blocked into groups of four trials, with four blocks in each run, counterbalanced across runs. In Experiment 1, each subject participated in 8 runs, for a total of 32 trials per condition. In Experiments 2 and 3, each subject participated in six runs, for a total of 48 trials per condition. Condition order was counterbalanced within subjects. Run order was counterbalanced across subjects. Prior to any testing, subjects were provided with training that included feedback so that s/he could become comfortable with the level of discrimination necessary for the task.

A dual-task behavioral paradigm was implemented by embedding a spatial WM task within the delay of an object WM task. The experimental paradigm is shown in Fig. 2. There were two types of objects (face or house) and two levels of spatial load (two or four spatial locations) and, therefore,

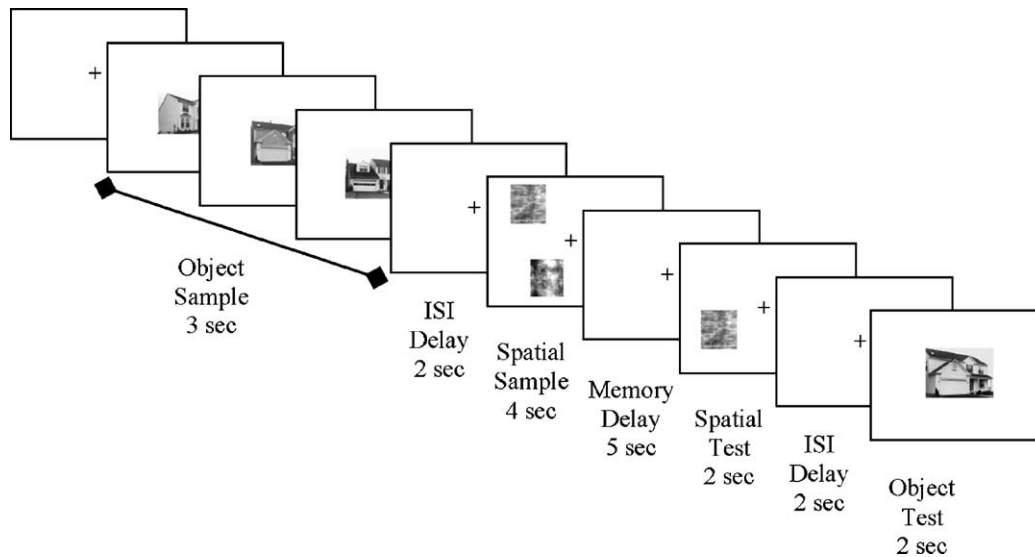


Fig. 2. A sample trial from the dual-task paradigm (Experiment 4). Shown here is a house/load-two trial, however sequence and timing of events were constant for all conditions.

four experimental conditions that resulted from the combination of each object type with each spatial load. A trial consisted of: (1) sequential presentation of three faces or three houses for 1000 ms each in the center of the screen; (2) blank screen with fixation for 2000 ms; (3) simultaneous presentation of two or four phase scrambled images in non-overlapping spatial locations for 4000 ms; (4) blank screen with fixation for 5000 ms; (5) presentation of a spatial test for 2000 ms; (6) blank screen with fixation for 2000 ms; (7) presentation of house or face test for 2000 ms in the center of the screen. Subjects were instructed to fixate on the center of the screen throughout the trial (fixation mark was on screen throughout all delays and spatial presentations). Subjects were instructed to indicate whether the spatial test matched one of the sample locations with a button press (1: yes, 2: no) while the spatial test item was on the screen. Subjects were instructed to indicate whether the face or house test matched one of the sample faces or houses with a button press (1: yes, 2: no) while the object test item was on the screen.

Each subject participated in two practice blocks before undergoing eight experimental blocks. Each block contained four trials of each experimental condition, for a total of 16 trials per block. Therefore, there were 32 experimental trials per condition. Conditions were randomized on a trial-wise basis within a block.

#### 2.4. Imaging protocol

For all the subjects, a high-resolution T1 weighted structural image (70 axial slices, 2.5 mm thickness, TR = 40 ms, TE = 4.6 ms, flip angle = 0°, matrix: 256 × 256, FOV 230 mm) was obtained before acquiring functional data, to allow for anatomical localization. During the performance

of the cognitive tasks, a T2\* weighted, interleaved gradient echo, echo planar imaging (EPI) scan was obtained (21 axial slices, 4.5 mm thickness, 0.5 mm gap, TR = 3000 ms, TE = 40 ms, flip angle = 90°, matrix 64 × 64, FOV 230 mm). All scans were performed at the F.M. Kirby Research Center for Functional Brain Imaging on a 1.5 T Philips Gyroscan ACS NT Powertrak 6000.

#### 2.5. Multiple regression analysis of time series data

Functional EPI data were phase-shifted using Fourier transformation to correct for slice acquisition time, and motion-corrected using three-dimensional volume registration [13]. Multiple regression analysis was performed on the time series data at each voxel using Analysis of Functional Neuroimages (AFNI) software [13,18,30,76]. The WM and control tasks were broken down into four cognitive components: instruction, sample stimuli, delay period, test stimulus. The regressors were vectors representing the time series of each of the four components, for each task (face identity, face location, house identity, house location, and control) separately, convolved with a gamma function model of the hemodynamic response.

General linear contrasts were performed on the regression coefficients. For each WM task type, the WM task components were each contrasted with the corresponding sensorimotor control task components. In addition, direct comparisons between WM tasks were done. The contrasts of interest were for Experiment 1: object identity delays versus spatial location delays (collapsed across stimulus type, i.e. the main effect of task), face delays versus house delays (collapsed across the object and spatial tasks, i.e. the main effect of stimulus), house identity delays versus house location delays, face identity delays versus house identity

Table 1

Performance data from behavioral testing of Experiments 1–3, training from Experiment 1 and fMRI for Experiments 2 and 3.

	Face identity		House identity		Face location		House location	
	Correct (%)	RT (ms)	Correct (%)	RT (ms)	Correct (%)	RT (ms)	Correct (%)	RT (ms)
Behavioral testing								
Experiments 1 and 2	80.3	1312	79.8	1428	82.3	1110	82.8	1173
Experiment 3	82.8	1355	83.1	1468				
fMRI								
Experiment 1: training	78.3	1398	77.9	1487	81.4	1163	82.8	1214
Experiment 2			83.3	1422			85.2	1187
Experiment 3	84.9	1339	84.4	1415				

delays, and the difference between face identity and face location delays versus the difference between house identity and house location delays (i.e. the interaction between stimulus and task). The contrast of interest in Experiment 2 was object identity delays versus spatial location delays, and for Experiment 3: face identity delays versus house identity delays.

Reported here are the “typical” activation patterns, similar to the approach described by Friston et al. [19]. The results from analyses performed within each of the individual subjects are reported in order to assess whether the results are consistent across subjects. Fixed-effects group activation maps were consistent with the individual subject analyses and are also reported.

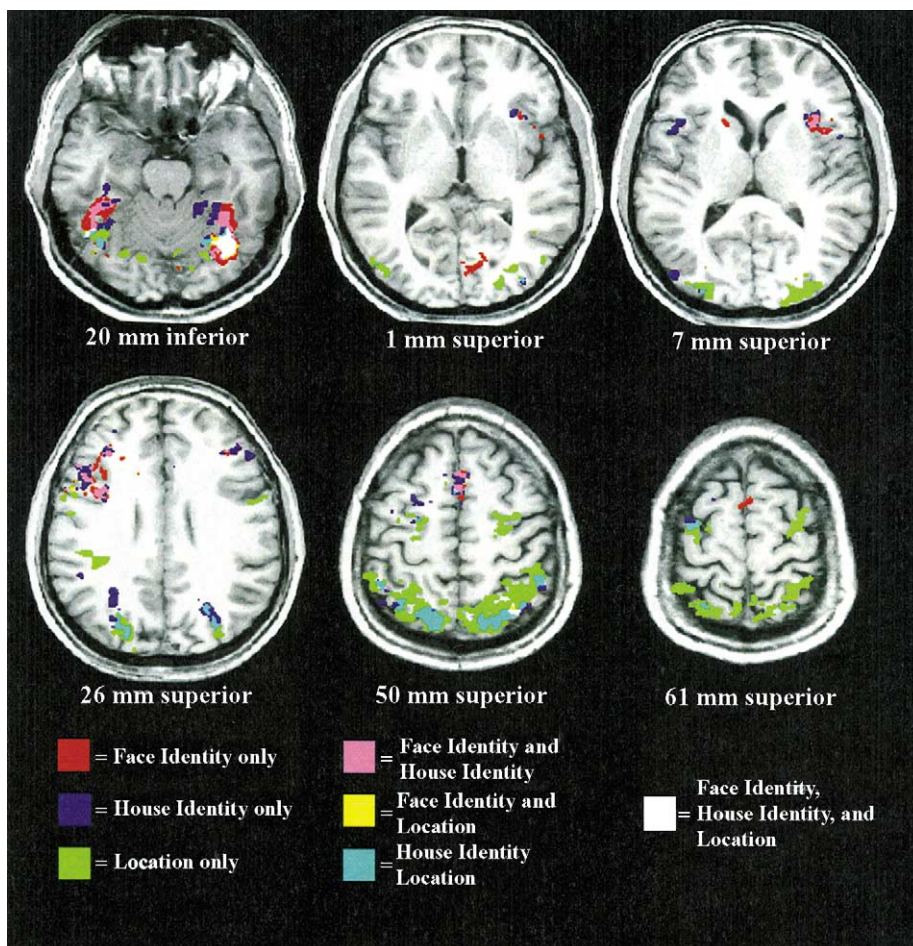


Fig. 3. Threshold statistical maps of significant activity for each task delay greater than the sensorimotor control delay and their overlap. Areas showing face identity delay activity only are shown in red; house identity delay activity only in blue; location activity only in green; overlap between face identity and house identity delay activity in purple; overlap between face identity and location delay activity in yellow; overlap between house identity and location in cyan; and overlap among all the conditions in white.

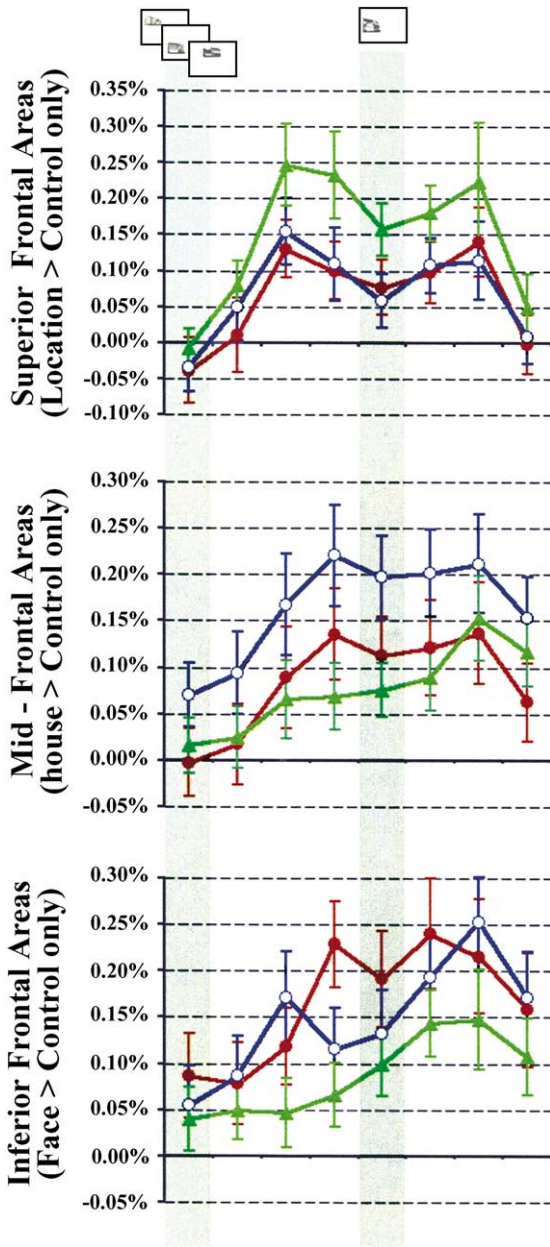


Fig. 4. Time courses averaged across trials, subject, and voxels within regions of interest for Experiment 1 beginning with the presentation of the sample image and including eight TRs. Gray bars indicate times of sample and test presentation. Signal is plotted as percent change from TRs three to five of the control task (representative of control delay period activity according to the modeled hemodynamic response). Red solid circles indicate the timecourse for face WM trials; blue open circles indicate the timecourse for house WM trials; and green triangles represent the timecourse for spatial WM trials. Frontal cortex was divided into three broad regions of interest for these averages: inferior, middle and superior. All the regions were defined in Talairach space on an average anatomical image of all subjects in Experiment 1. The posterior boundary for all the regions was approximately 6 mm anterior to the precentral sulcus or to the most ventral or dorsal ends of the precentral sulcus. The inferior frontal region extended from 13 mm below to 13 mm above the bicommissural line, and included both frontal cortex and an anterior portion of the insula. The middle frontal region extended from 14 to 42 mm above the bicommissural line. The superior region extended from 43 to 63 mm above the bicommissural line and included cortex within

Single subject analyses were performed on unsmoothed data. Statistical Z-maps were created for each of the contrasts of interest. Individual subject Z-maps were transformed into the Talairach coordinate system [72], resampled to 1 mm<sup>3</sup>, spatially smoothed with a Gaussian kernel (2 mm FWHM), and cross-subject average Z-maps were computed by dividing the sum of Z-values by the square root of the sample size. Activations were anatomically localized in the averaged data on the Talairach transformed T1-weighted images and in individual maps using both EPI and T1-weighted images.

All tests of voxel-wise significance were held to a Z threshold of 2.34, corresponding to a  $P < 0.01$ , and corrected for multiple comparisons ( $P < 0.05$ ) using a measure of probability based on the individual voxel Z-score threshold, the spatial smoothness of the data, and the number of contiguous significant voxels. Based upon a Monte Carlo simulation with 1000 iterations run via AFNI [75] on the union of all subject's brain volumes (as classified using the EPI signal intensity threshold), it was estimated that a 386  $\mu$ l contiguous volume (six voxels, each measuring 3.59 mm  $\times$  3.59 mm  $\times$  5.0 mm) would meet the  $P < 0.05$  threshold. For the direct comparison between WM tasks, the analysis was restricted to only those voxels showing significantly greater activity for any of the WM tasks versus control. Within this restricted number of voxels, a 193  $\mu$ l contiguous volume (three voxels) satisfied a 0.05 experiment-wise probability. Analyses of group and single subject data used the same thresholds for statistical significance.

### 3. Results

#### 3.1. Performance data for fMRI tasks

Prior to collecting fMRI data, all tasks were tested behaviorally on separate groups of subjects from those participating in the fMRI portion of the study. Technical difficulties during Experiment 1 prohibited the collection of behavioral data during scanning. Mean percent correct and reaction time for each of the tasks (including training performance for subjects in Experiment (1) is given in Table 1. There were no significant differences in the accuracy for stimulus type (faces versus houses), task (spatial versus object), or their interaction (all  $P > 0.1$ ) either in the preliminary behavioral

6 mm of either side of the SFS. Timecourses shown from the inferior frontal region are from the voxels within this anatomical region showing significant WM delay period activity greater than control delay period activity only for the face identity task. Similarly, timecourses shown from the middle frontal area are from the voxels within this anatomical region showing significant WM delay period activity greater than control delay period activity only for the house identity task. Finally, timecourses shown from the superior frontal area are from the voxels of the areas within this anatomical region showing significant WM delay period activity greater than control delay period activity only for the location tasks.

testing or during scanning. Reaction times (RTs) did show main effects of stimulus ( $P < 0.01$ ) and task ( $P < 0.05$ ), such that RTs for faces (1267 ms) were faster than for houses (1366 ms) and RTs for spatial location tasks (1141 ms) were faster than for object identity tasks (1386 ms), but there was no stimulus by task interaction ( $P > 0.1$ ).

### 3.2. Imaging data

The delay periods of each of the WM tasks relative to the sensorimotor control delay period demonstrated activation in widely distributed areas of anterior and posterior regions in all experiments. Areas in which activation was significantly greater for each of the WM tasks than for control, are depicted in statistically thresholded maps in Fig. 3. There were very few voxels showing significant activation for all the three WM tasks relative to control. There were some areas in middle and inferior frontal cortex that showed overlap between the house and face identity tasks and some areas in superior frontal cortex that showed overlap be-

tween the house identity and location tasks. Some regions in prefrontal cortex appear, in these thresholded maps, to be exclusively activated by only one of the WM tasks. However, analysis of the average time courses of MRI activity for each of the tasks (Fig. 4) demonstrates that areas “exclusively activated” by one type of task relative to control (i.e. those regions in Fig. 3 demonstrating no overlap) may be contributing measurable and possibly meaningful (albeit sub-threshold) signal during the other tasks. Fig. 4 suggests that there are regional gradations in the relative magnitudes of activation for each of the three WM tasks, independent of the comparison to the control task. As has been discussed previously in the literature, “rest” and other supposedly “low-level” sensorimotor control tasks can have quite variable and unexpected “activation” patterns [27,69]. What may be more reliable and meaningful is the direct comparison between cognitive tasks that are tightly matched.

A topographical representation of the regional gradations in magnitude of activation between tasks (a “functional topography”) averaged across subjects is shown in Fig. 5.

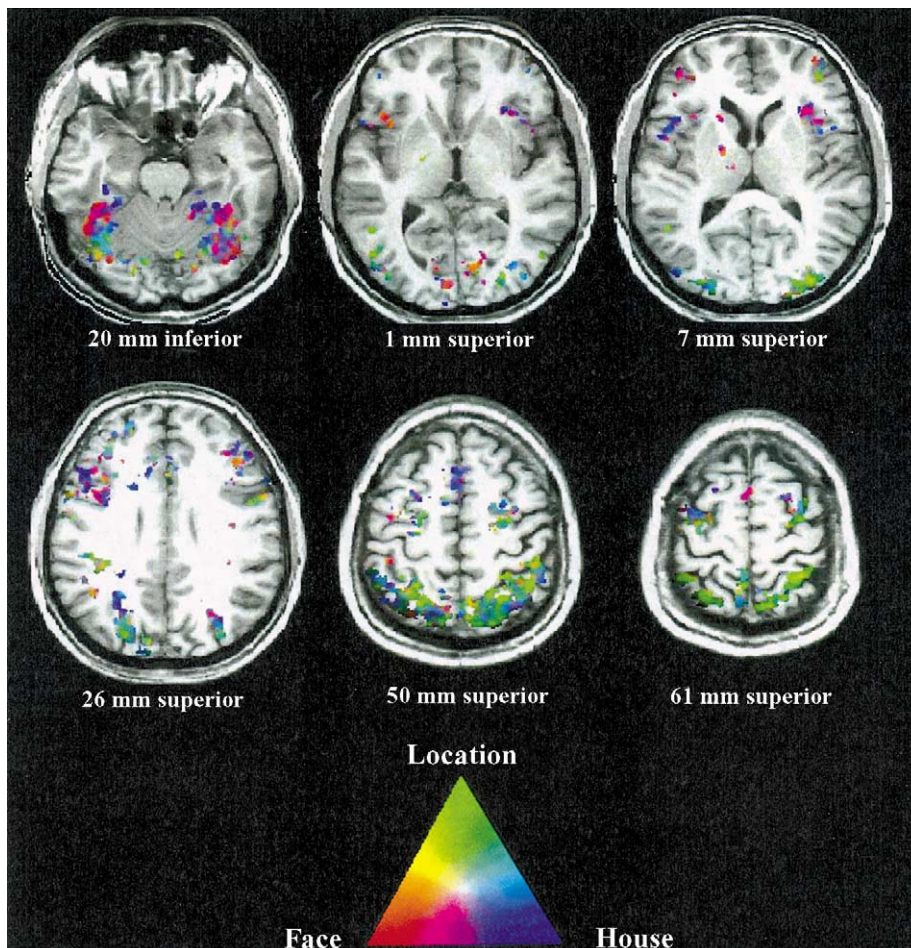


Fig. 5. Topographical map of areas showing statistically greater response during any WM delay than during control delays. The color of an area indicates the magnitude of response to each type of WM delay relative to that of the other WM task delays. Colors were assigned separately for the red–green–blue channels based on normalized  $\beta$  coefficient magnitudes for the three delay types (face: red, location: green, house: blue). This allows for visual inspection of the “response profile” of a voxel or an area, indicated by the blend in color.



In Fig. 5, the areas showing greater activity during any WM delay than during control delays appear in color overlaid onto a single subject's high-resolution structural image. This allows for visualization of the variations in the distributed patterns of activation without statistical thresholding. However, in order to evaluate the reliability of these apparent

differences in response magnitude across tasks and stimulus types, voxel-wise direct statistical comparisons of the magnitudes of activation during the delay periods of each of the different WM tasks were performed within the regions showing significant delay activity for any of the WM tasks relative to control delays.

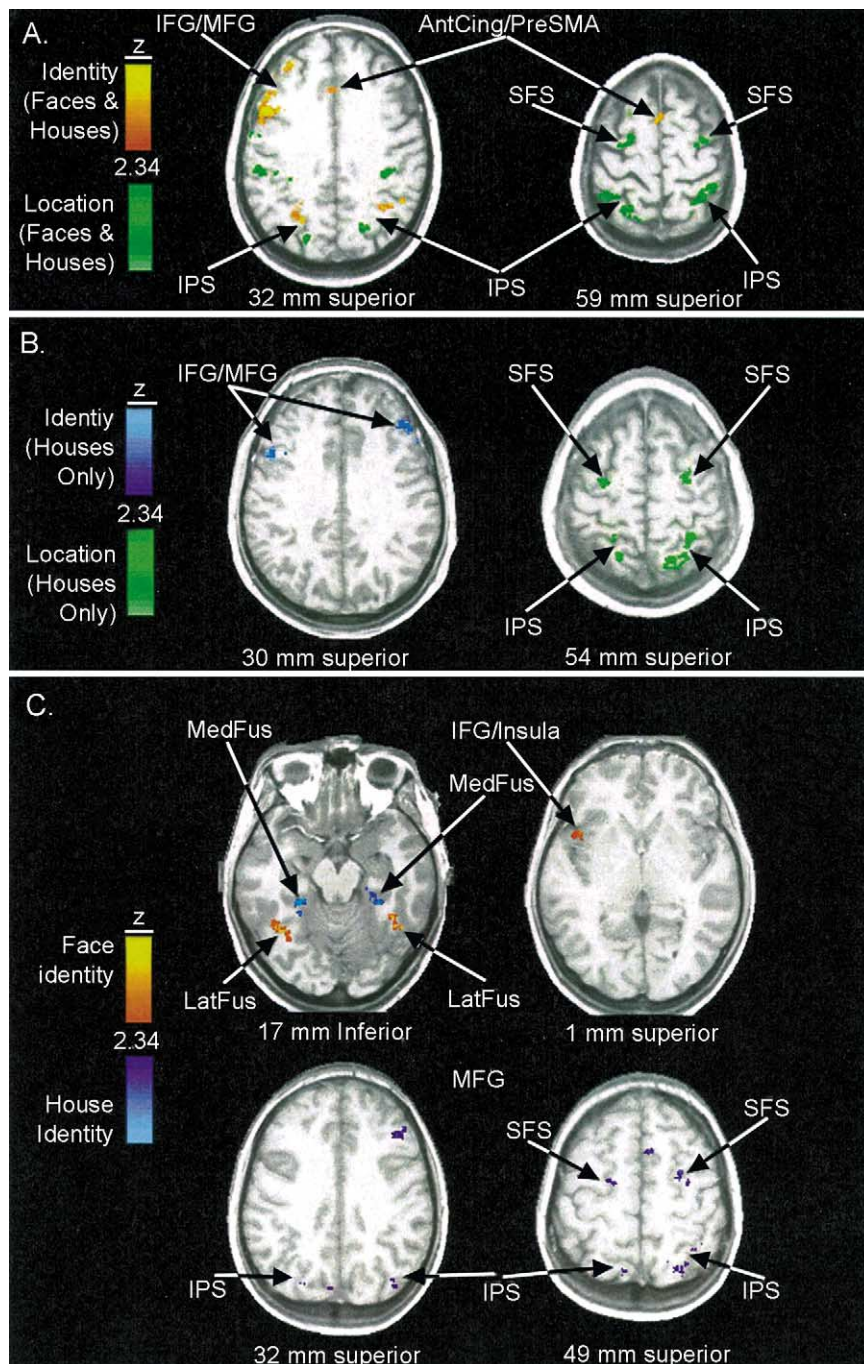


Fig. 6. Cross-subject average statistical maps of direct comparisons overlaid on a Talairach normalized anatomical image. (A) Experiment 1: object vs. spatial WM for faces and houses. Areas shaded red to yellow represent greater activity during object delays than during spatial delays. Areas shaded dark to light green represent greater activity during spatial delays than during object delays. (B) Experiment 2: object vs. spatial WM for houses only. Areas shaded dark to light blue represent greater activity during object delays than during spatial delays. Areas shaded dark to light green represent greater activity during spatial delays than during object delays. (C) Experiment 3: object WM for faces vs. houses. Areas shaded red to yellow represent greater activity during face delays than during house delays. Areas shaded dark to light blue represent greater activity during house delays than during face delays.

Modulation of delay period activity was evident during Experiment 1 between the object and spatial WM task delay periods (collapsed across stimulus type). Averaged statistical maps (see Fig. 6) indicated that activation in an area of ventral prefrontal cortex, including parts of the inferior (IFG) and middle (MFG) frontal gyri, and the anterior insula, was consistently greater during object delays than during spatial delays, across subjects. Additionally, delay activity was greater for object delays than spatial delays in bilateral lateral and medial fusiform, the left lateral occipital gyrus, an inferior part of bilateral intraparietal sulcus (IPS), and the anterior cingulate/pre-supplementary motor area. Activation in bilateral SFS was greater during spatial delays than during object delays. In addition, activation in the left middle temporal gyrus, bilateral superior IPS, bilateral intraoccipital sulcus, bilateral postcentral sulcus, and left precentral sulcus was greater during spatial than object delay periods (Table 2).

In order to evaluate the consistency of these results in single subjects and to get better spatial resolution, we also examined the statistical maps in individual subjects, unsmoothed and not spatially normalized. The results showed that all the six subjects had significantly greater activity for the maintenance of object information than for spatial information in right IFG/MFG. Five of the six subjects also showed greater object than spatial activity in left IFG/MFG.

All the six subjects showed greater activity for the maintenance of spatial information than for the object information in SFS, four bilaterally, one on the left, and one on the right.

Voxel-wise contrasts of face delays versus house delays (collapsed across task), house identity delays versus house location delays, face identity delays versus house identity delays, and the interaction of stimulus and task did not yield any significant differences. However, Experiment 1 had a limited amount of data in each condition within each subject and, therefore, in order to avoid misinterpreting a null result, we ran two additional experiments and performed a region-wise re-analysis of the data from Experiment 1. Experiment 2 was performed in order to examine whether the dorsal-ventral functional topography for spatial and object information could be replicated using only house stimuli, or whether it may have been driven solely by the face task in Experiment 1. Experiment 3 was performed in order to examine whether there were any differences between the face and house identity tasks that were not detected in Experiment 1. The region-wise analysis of Experiment 1 tested for the interaction between stimulus and task within the SFS and within the inferior and middle frontal cortex.

Experiment 2 was identical to Experiment 1, but contained only the house identity, house location, and sensorimotor control tasks. Averaged statistical maps (see Fig. 6) indicate that areas of ventral prefrontal cortex, including the IFG and

Table 2

Talairach coordinates of center of mass, volume of activation (in mm<sup>3</sup>) and mean Z-score of brain areas showing a significant difference in the magnitude of activity during object WM delays compared to spatial WM delays for Experiments 1 and 2

Anatomical area	Experiment 1 (face and house)					Experiment 2 (houses only)				
	x	y	z	Volume	Mean Z	x	y	z	Volume	Mean Z
Object delay > spatial delay										
IFG/insula/MFG	-43	14	29	2325	3.27	-49	13	34	389	2.95
	-41	36	18	596	3.49	-44	16	24	256	2.88
	-29	43	30	197	3.29	42	35	27	587	3.35
	31	21	5	398	3.47	48	23	36	211	3.00
Cingulate/preSMA	1	18	44	1730	3.21	1	13	43	389	3.15
Fusiform gyrus	-39	-42	-19	700	3.14	-36	-52	-14	1576	3.17
	-37	-47	-9	286	2.90					
	33	-65	-19	195	2.70					
	32	-43	-20	620	3.15					
Lateral occipital gyrus	-25	-86	-5	372	3.46					
	33	-79	-10	456	2.95					
Inferior IPS	-27	-58	34	792	3.05					
	41	-53	36	350	3.04					
Spatial delay > object delay										
Superior frontal sulcus	-24	-9	62	548	3.04	-30	-8	55	209	2.75
	28	-9	61	239	3.24	29	-4	51	488	3.01
Middle temporal gyrus	-47	-51	7	231	3.20					
Precentral sulcus	-54	-4	35	241	2.91					
Postcentral sulcus	-51	-30	34	439	3.18					
	37	-32	35	444	3.04					
Superior IPS	-19	-68	46	2602	3.38	-22	-54	55	1070	3.27
	-23	-57	51	5305	3.23	21	-60	51	1972	3.48
	34	-43	51	1898	3.18	41	-40	50	195	3.50
Intraoccipital sulcus	32	-82	13	1858	3.28					
	-23	-80	18	1167	3.04					

MFG, were more active during object delays than during spatial delays. Additionally, delay activity was greater for object delays than spatial delays in left medial fusiform and the anterior cingulate/pre-supplementary motor area. Activation in bilateral SFS was greater during spatial delays than during object delays. In addition, activation bilaterally in IPS was greater during spatial than object delay periods (Table 2).

Again, single subject analysis was done on non-Talairach-transformed, unsmoothed data. The results showed that four of the five subjects had activity in bilateral IFG/MFG that was significantly greater during object delays than during spatial delays. All five subjects showed greater activity during spatial delays than during object delays in bilateral SFS. Therefore, the dorsal–ventral functional topography for spatial location and object identity was significant, and replicated in two different groups of subjects, one using houses only.

In Experiment 3, a third group of subjects performed only the house and face identity tasks in order to obtain a greater amount of data per condition in each subject. Direct comparisons of the two WM conditions show that the left IFG/anterior insula showed greater activation during face delays than during house delays. Additional areas showing greater activity for face than for house delays were bilateral lateral fusiform gyrus, and the right lateral occipital gyrus. Prefrontal areas showing greater activation for house delays than during face delays consisted of right MFG, bilateral SFS, and the anterior cingulate/preSMA. In addition, greater house delay activity than face delay activity was observed in bilateral medial fusiform, the precuneus/superior parietal lobule, bilateral intraoccipital sulcus, bilateral superior IPS, and right postcentral sulcus (see Fig. 6 and Table 3).

These results were also consistent across individual subjects, single subject analysis of data demonstrated that activity in the SFS was greater during house delays than face delays in three of the four subjects (one bilaterally and two on the right). Activity in the MFG was greater for houses than for faces bilaterally in two subjects and on the right in a third. Three of the subjects showed left IFG/anterior insula activity that was greater for face delays than for house delays.

To test whether there was a greater dissociation within dorsal and ventral prefrontal cortex between face identity and location than between house identity and location, we did an additional analysis of the data from Experiment 1 (see Fig. 7). The difference in magnitude of activation between the house identity and house location tasks and between the face identity and face location tasks was determined within the SFS and within the IFG/MFG. These signal differences were calculated by averaging across all voxels within each region of activation identified by the comparison of identity and location tasks (collapsed across stimulus type, Fig. 6 top panel, Table 2) in each subject. A paired *t*-test was then run within each region. The magnitude of the difference between the object identity and the location task

Table 3

Talairach coordinates of center of mass, volume of activation ( $\text{mm}^3$ ), and mean Z-score of brain areas showing a significant difference in the magnitude of activity during face identity WM delays compared to house identity WM delays for Experiment 3

Anatomical area	Experiment 3 (face and house)				
	x	y	z	Volume	Mean Z
Face identity > house identity					
IFG/insula	-42	13	2	202	3.86
Lateral fusiform	-38	-55	-16	541	3.86
	43	-55	-13	725	4.28
Lateral occipital gyrus	41	-80	-12	200	3.48
House identity > face identity					
MFG	40	27	28	341	3.84
Superior frontal sulcus	-19	-8	51	213	3.74
	29	-5	53	482	3.95
Anterior cingulate/preSMA	6	13	51	216	4.38
Medial fusiform	-25	-38	-15	294	5.31
	28	-32	-14	558	4.89
Intraoccipital sulcus	-23	-75	26	452	4.87
	36	-73	28	309	3.99
Superior IPS	-14	-68	43	360	4.22
	24	-68	45	1082	3.98
Post central sulcus	41	-50	44	208	3.73
Precuneus/SPL	-5	-78	39	298	4.12

activations in SFS was significantly greater for faces than for houses (face location – face identity: mean = 0.07%; house location – house identity: mean = 0.04%; *P* (two tailed) = 0.02). Within the IFG/MFG, however, there was no significant difference between faces and houses in the magnitude of the difference between identity and location tasks (face location – face identity: mean = -0.022%; house location – house identity: mean = -0.020%; *P* (two tailed) = 0.83).

### 3.3. Behavioral dual-task experiment results

The imaging results indicate that there is more overlap in the activation pattern of spatial location WM with that of

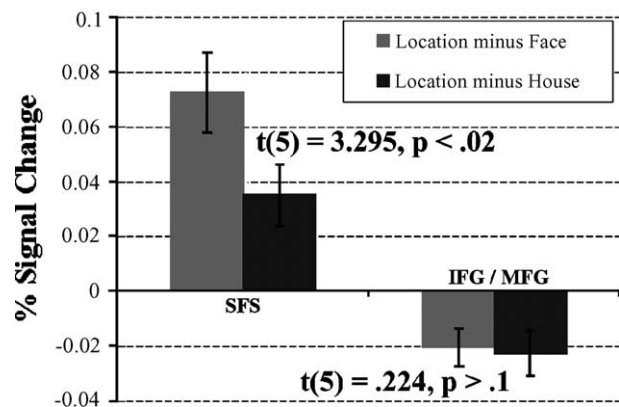


Fig. 7. Differences between delay activity during face location and face identity (gray bars) and house location and house identity (black bars) in the SFS regions showing greater location delay activity than object delay activity and regions of the inferior and middle frontal gyrus showing greater object delay activity than location delay activity in Experiment 1.

house identity WM than there is with face identity WM. To test whether this co-activation indicated a necessary sharing of neural resources, a behavioral dual-task interference experiment was run using two levels of spatial WM load (see Section 2 and Fig. 2). The factorial combination of object type and spatial load resulted in four conditions: (1) face WM – spatial WM [load two]; (2) face WM – spatial WM [load four]; (3) house WM – spatial WM [load two]; and (4) house WM – spatial WM [load four]. Responses were collected for both object and spatial WM tasks. A repeated measures ANOVA was run on the accuracy data from the house and face identity tasks (means for face WM with spatial WM [load two] = 76.563, spatial WM [load four] = 73.281; house WM with spatial WM [load two] = 72.969, spatial WM [load four] = 75.469). In the object WM task, no significant effects of object type, spatial load, or their interaction were found ( $F(1, 9) = 0.041, 0.030, 1.656$ , respectively, all  $P > 0.1$ ). A separate repeated measures ANOVA analysis of the performance on the spatial WM tasks (means for spatial WM load two with faces = 81.719, with houses = 84.531; load four with faces = 80.469, with houses = 73.125) also showed no main effect for object type ( $F(1, 9) = 2.901, P > 0.1$ ) or spatial load ( $F(1, 9) = 3.634, P > 0.08$ ). There was however an interaction between the two ( $F(1, 9) = 10.263, P < 0.05$ ), such that performance on the spatial WM task was more sensitive to load when simultaneously engaging in house WM than when simultaneously engaging in face WM (see Fig. 8).

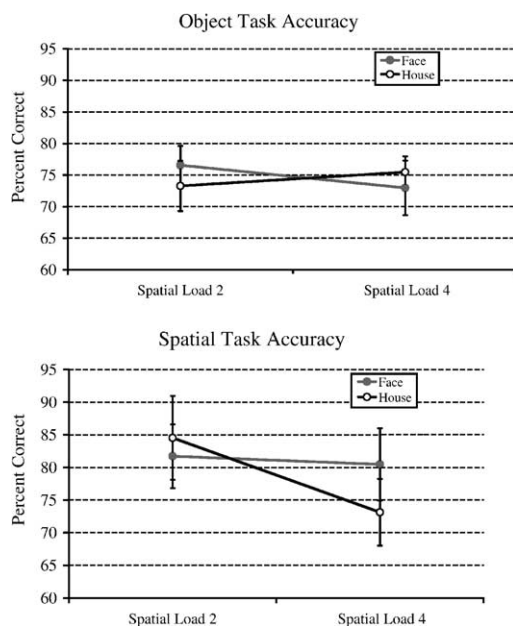


Fig. 8. Behavioral dual-task performance accuracy results. No significant effects of object type, spatial load or their interaction were found in the object identity tasks ( $F(1, 9) = 0.041, 0.030, 1.656$  respectively, all  $P > 0.1$ ). The spatial WM tasks also showed no main effect for object type ( $F(1, 9) = 2.901, P > 0.1$ ) or spatial load ( $F(1, 9) = 3.634, P > 0.08$ ). There was, however, an interaction between the two ( $F(1, 9) = 10.263, P < 0.05$ ).

Analysis of the reaction time data showed no evidence of a speed accuracy trade-off. A repeated measures ANOVA of the reaction times for each of the spatial WM tasks (means for spatial WM load two with faces = 1113.826, with houses = 1114.238; load four with faces = 1197.833, with houses = 1183.695) revealed that while sensitive to the main effect of load ( $F(1, 9) = 18.046, P < 0.01$ ), measures of reaction time showed no evidence for a main effect of object type ( $F(1, 9) = 0.103, P > 0.1$ ) or an interaction between the object type and spatial load ( $F(1, 9) = 0.725, P > 0.1$ ).

#### 4. Discussion

It is evident from all the three fMRI experiments that a large-scale, distributed cortical network underlies the active maintenance (storage and rehearsal) of visual information in WM, as reported in previous studies. Areas in temporal, parietal, and both ventral and dorsal prefrontal cortices showed greater activity for either the spatial or object WM tasks relative to the sensorimotor control task. However, there exists a differential pattern of response associated with the maintenance of different types of information over delay periods that reflects what appears to be a consistent functional topography across the regions within temporal, parietal, and prefrontal cortices. The existence of such a functional topography for areas of the prefrontal cortex that are involved in simple maintenance within working memory does not preclude other organizational schemes. Indeed, other parts of prefrontal cortex seem to be involved differentially according to the type of executive processes involved in the task, independent of the type of information [14,49,56,70]. The current study demonstrates that the information domain-based aspect of prefrontal functional topography appears to be based on general spatial versus nonspatial information maintenance demands.

In both Experiments 1 and 2, object delays elicited greater activity than spatial delays in the lateral occipital gyrus, an inferior portion of the IPS, and the fusiform gyrus. Within ventral temporal cortex, Experiment 3 demonstrated the same pattern of activity for faces versus houses that has previously been observed, namely medial fusiform cortex showing greater activity for houses and lateral fusiform cortex showing greater activity for faces [1,15,16,28,29,32,36]. Spatial delays elicited greater activity than object delays (for both faces and houses) in intraoccipital sulcus and superior portions of the IPS.

The SFS exhibited greater activity during delays when subjects needed to maintain only spatial information than when they were required to maintain only the identity of the objects. Middle and inferior prefrontal cortices, however, show the opposite pattern in that they were significantly more active during object delays than spatial delays, independent of whether the object used was a house or a face.

House identity WM did, however, produce a different pattern of response than did face identity WM. Superior and right middle prefrontal cortices showed greater delay activity for houses than for faces, while left inferior prefrontal cortex showed the opposite pattern with more activity for faces than for houses (direct tests of hemispheric laterality were not significant, however). The intraoccipital sulcus and superior IPS also showed greater activity for houses than faces. Therefore, regions of occipital, parietal and prefrontal cortex that in Experiments 1 and 2 had a greater relative response in spatial WM than object WM were engaged more by the maintenance of house identity than face identity. This result is consistent with the finding in the region-based analysis of Experiment 1 that, within the SFS, the difference between the object identity and the location activations was greater for faces than for houses.

In any WM task involving a stimulus presentation followed by a memory delay, there will inevitably be some difficulty in distinguishing hemodynamic activation that is due strictly to maintenance processes during the delay from activation that is related to the presentation of the stimulus itself. To test whether the delay period activity was sustained throughout the 9 s, we re-analyzed the data from Experiment 1 with three separate regressors for the beginning, middle and end of the delay period. There were no significant differences between the beginning and middle of the delay versus the end of the delay regarding the magnitude of activation relative to the control task for any of the four WM tasks in any area, except for the house location task within the SFS. For the house location task within the SFS, the magnitude of activation was significantly less at the end of the delay than at the beginning. This decreasing delay activity, however, does not change the main result. Considering only the regressor for the end of the delay, the difference between the face location and face identity was again significantly greater than the difference between the house location and house identity within SFS, as was observed using the regressor covering the entire delay period (see Fig. 7). From the reaction times for the three different tasks (location, house identity and face identity) there were apparently differences in the amount of time spent processing the different stimulus types. These differences in reaction times, however, do not explain the patterns of activation. The location task had the shortest reaction time, followed by face identity, and then house identity. The activation patterns, however, were more similar for house identity and location than for face identity and location.

Given that face, house, and location WM tasks all show overlapping activation patterns, the question arises as to what degree performance on spatial and object WM tasks depend on the same set of neural resources. The activation patterns suggest that the neural system for house identity WM overlaps to a greater extent with the neural system for spatial WM than does that for face WM. The results of the behavioral dual task experiment support this conclusion. Performance on the spatial WM task was more sensitive to load

when simultaneously engaging in house WM than in face WM, suggesting that house WM consumes a greater part of the limited capacity of the neural system for spatial WM, than does face WM.

These results suggest a different perspective on the traditional “what” versus “where” definitions of the dorsal and ventral visual pathways [74] and their projections to prefrontal cortex. The dorsal pathway, including the parietal and superior prefrontal areas, may be involved in analyzing spatial aspects of object vision in addition to perception and WM for spatial locations of objects and for reaching movements toward objects (e.g. [12,25,26,74]). The ventral pathway, on the other hand, may represent the aspects of the visual appearance of objects such as color, texture and shape. However, the representation of objects themselves in WM may be distributed across dorsal and ventral regions of visual and prefrontal cortex.

One possible “spatial” aspect of house stimuli is that they may be perceived as landmarks that play a role in navigation. Houses strongly activate the medial fusiform gyrus, an area that is also activated by other scenes depicting three-dimensional spaces and that has been called the “parahippocampal place area” [16]. Further studies of the “parahippocampal place area,” however, suggest that the crucial factor in activating this area while viewing places is the perception of the spatial layout of the scene [15], rather than navigation through the scene.

Patients with bilateral parietal damage (Balint syndrome) cannot perceive more than one object in the visual field and have difficulty on a wide variety of spatial tasks. Studies suggest that these patients also have difficulty perceiving the spatial organization of features within an object, suggesting that parietal cortex plays a role in spatial aspects of object vision as well as object localization [65]. Some categories of objects may require a greater representation of spatial information than would other categories of objects. Research suggests that the visual processing of faces and houses differ in that faces are processed holistically while houses are subject to decomposition into parts [71]. The organization and layout of features composing house stimuli necessary for the perception of houses may be represented by the coding of spatial relationships among parts by the dorsal visual stream.

Greater activation of parietal cortex for houses than for faces has been observed previously in studies of object perception [28,29,31,32]. The preferential involvement of the dorsal visual stream for the perception of houses relative to faces suggests that prefrontal areas engaged most by the maintenance of spatial information would also be more involved in the maintenance of house identity than that of face identity, as they were in both Experiments 1 and 3.

This interpretation could help explain the apparently contradictory results in the literature regarding the degree of segregation of object and location information in prefrontal cortex. Geometrical shapes, as have been used in previous studies (e.g. [58]), may contain relatively greater amounts of

spatial information and relatively less information regarding ventral pathway attributes such as color and texture. This would lead to a greater involvement of superior prefrontal and less involvement of inferior prefrontal for the maintenance of these objects, thus lessening differences in activation between the “object” and “spatial” tasks. Pollman and Yves von Cramon [57] came to a similar conclusion concerning delay activity of the SFS in an object WM task using “three-dimensional paper-clip” objects. In their study, the subjects had to maintain representations of “distorted paper-clips” that differed as to the angular disparity between the projections of the object. Delay period activity in the SFS was attributed to the maintenance of this spatial component of the objects. It appears that the regions of prefrontal cortex that contribute to the active maintenance over delay periods do show a functional topography according to the type of information being maintained. However, this is manifested as a graded response pattern indicative of the general spatial or nonspatial information maintenance demands rather than an absolute division between “object” and “location” WM tasks.

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### References

- [1] Aguirre GK, Zarahn E, D’Esposito M. An area within human ventral cortex sensitive to “building” stimuli. *Neuron* 1998;21:373–83.
- [2] Alain C, Arnott S, Hevenor S, Graham S, Grady C. “What” and “where” in the human auditory system. *Proceedings of the National Academy of Sciences of the United States of America* 2001;98:12301–6.
- [3] Awh E, Jonides J, Smith EE, Schumacher EH, Koeppel RA, Katz S. Dissociation of storage and rehearsal in verbal working memory: evidence from positron emission tomography. *Psychological Science* 1996;7:25–31.
- [4] Baker SC, Frith CD, Frackowiak RS, Dolan RJ. Active representation of shape and spatial location in man. *Cerebral Cortex* 1996;6:612–9.
- [5] Bechara A, Damasio H, Tranel D, Anderson S. Dissociation of working memory from decision making within the human prefrontal cortex. *Journal of Neuroscience* 1998;18:428–37.
- [6] Belger A, Puce A, Krystal JH, Gore JC, Goldman-Rakic PS, McCarthy G. Dissociation of mnemonic and perceptual processes during spatial and nonspatial working memory using fMRI. *Human Brain Mapping* 1998;6:14–32.
- [7] Carlesimo G, Perri R, Turriziani P, Tomaiuolo F, Caltagirone C. Remembering what but not where: independence of spatial and visual working memory in the human brain. *Cortex* 2001;36:519–34.
- [8] Carlson S, Martinkauppi S, Rämä P, Salli E, Korvenoja A, Aronen HJ. Distribution of cortical activation during visuospatial *n*-back tasks as revealed by functional magnetic resonance imaging. *Cortex* 1998;8:743–52.
- [9] Cohen JD, Perlstein WM, Braver TS, Nystrom LE. Temporal dynamics of brain activation during a working memory task. *Nature* 1997;386:604–48.
- [10] Courtney SM, Ungerleider LM, Keil K, Haxby JV. Object and spatial visual working memory activate separate neural systems in human cortex. *Cerebral Cortex* 1996;6:39–49.
- [11] Courtney SM, Ungerleider LG, Keil K, Haxby JV. Transient and Sustained activity in a distributed neural system for human working memory. *Nature* 1997;386:608–11.
- [12] Courtney SM, Petit L, Maisog JM, Ungerleider LG, Haxby JV. An area specialized for spatial working memory in human frontal cortex. *Science* 1998;279:1347–51.
- [13] Cox RW. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical Research* 1996;29:162–73.
- [14] D’Esposito M, Postle BR, Ballard D, Lease J. Maintenance versus manipulation of information held in working memory: an event-related fMRI study. *Brain and Cognition* 1999;41:66–86.
- [15] Epstein R, Harris A, Stanley D, Kanwisher N. The parahippocampal place area: recognition, navigation, or encoding? *Neuron* 1999;23:115–25.
- [16] Epstein R, Kanwisher N. A cortical representation of the local visual environment. *Nature* 1998;392:598–601.
- [17] Fiez JA, Raife EA, Balota DA, Schwarz JP, Raichle ME, Petersen SE. A positron emission tomography study of the short-term maintenance of verbal information. *Journal of Neuroscience* 1996;16:808–22.
- [18] Friston KJ, Holmes AP, Poline JB, Grasby PJ, Williams CR, Frackowiak RS. Analysis of fMRI time-series revisited. *NeuroImage* 1995;2:45–53.
- [19] Friston KJ, Holmes AP, Worsley KJ. How many subjects constitute a study? *NeuroImage* 1999;10:1–5.
- [20] Funahashi S, Bruce CJ, Goldman-Rakic PS. Mnemonic coding of visual space in the monkey’s dorsolateral prefrontal cortex. *Journal of Neurophysiology* 1989;61:331–49.
- [21] Funahashi S, Bruce CJ, Goldman-Rakic PS. Dorsolateral prefrontal lesions and oculomotor delayed-response performance: evidence for mnemonic “scotomas”. *Journal of Neuroscience* 1993;13:1479–97.
- [22] Fuster JM, Alexander GE. Neuron activity related to short-term memory. *Science* 1971;173:652–4.
- [23] Fuster JM. Unit activity in prefrontal cortex during delayed-response performance: neuronal correlates of transient memory. *Journal of Neurophysiology* 1973;36:61–78.
- [24] Fuster JM. *The prefrontal cortex: anatomy, physiology, and neuropsychology of the frontal lobe*. 3rd ed. Philadelphia (PA): Lippincott-Raven; 1997.
- [25] Goldman-Rakic PS. Cellular basis of working memory. *Neuron* 1995;14:477–85.
- [26] Goodale MA, Milner AD. Separate visual pathways for perception and action. *Trends in Neuroscience* 1992;15:20–5.
- [27] Gusnard DA, Raichle ME. Searching for a baseline: functional imaging and the resting human brain. *Nature Reviews Neuroscience* 2001;2:685–94.
- [28] Haxby JV, Gobbini MI, Furey ML, Ishai A, Schouten JL, Pietrini P. Distributed and overlapping representations of faces and objects in ventral temporal cortex. *Science* 2001;293:2425–30.
- [29] Haxby JV, Ungerleider LG, Clark VP, Schouten JL, Hoffman EA, Martin A. The effect of face inversion on activity in human neural systems for face and object perception. *Neuron* 1999;22:189–99.
- [30] Haxby JV, Maisog JM, Courtney SM. Multiple regression analysis of effects of interest in fMRI time series. In: Fox P, Lancaster J,

- Friston K, editors. Mapping and modeling the human brain. New York: Wiley, in press.
- [31] Ishai A, Ungerleider LG, Martin A, Haxby JV. The representation of objects in the human occipital and temporal cortex. *Journal of Cognitive Neuroscience* 2000;12(Suppl 2):35–51.
- [32] Ishai A, Ungerleider LM, Martin A, Schouten JL, Haxby JV. Distributed representation of objects in the human ventral visual pathway. *Proceedings of the National Academy of Sciences of the United States of America* 1999;96:9379–84.
- [33] Jeannerod M, Rossetti Y. Visuomotor coordination as a dissociable visual function: experimental and clinical evidence. *Baillieres Clinical Neurology* 1993;2:439–60.
- [34] Jonides J, Smith EE, Koeppel RA, Awh E, Minoshima S, Mintun MA. Spatial working memory in humans as revealed by PET. *Nature* 1993;363:623–5.
- [35] Jonides J, Schumacher EH, Smith EE, Lauber EJ, Awh E, Minoshima S, et al. Verbal working memory load affects regional brain activation as measured by PET. *Journal of Cognitive Neuroscience* 1997;9:462–75.
- [36] Kanwisher N, McDermott J, Chun MM. The fusiform face area: a module in human extrastriate cortex specialized for face perception. *Journal of Neuroscience* 1997;17:4302–11.
- [37] Kubota K, Niki H. Prefrontal cortical unit activity and delayed cortical unit activity and delayed alternation performance in monkeys. *Journal of Neurophysiology* 1971;34:337–47.
- [38] Levy R, Goldman-Rakic PS. Segregation of working memory functions within the dorsolateral prefrontal cortex. *Experimental Brain Research* 2000;133:23–32.
- [39] McCarthy G, Puce A, Constable RT, Krystal JH, Gore JC, Goldman-Rakic PS. Activation of human prefrontal cortex during spatial and nonspatial working memory tasks measured by functional MRI. *Cerebral Cortex* 1996;6:600–11.
- [40] Mellet E, Tzourio N, Crivello F, Joliot M, Denis M, Mazoyer B. Functional anatomy of spatial mental imagery generated from verbal instructions. *Journal of Neuroscience* 1996;16:6504–12.
- [41] Mishkin M, Manning FJ. Non-spatial memory after selective prefrontal lesions in monkeys. *Brain Research* 1978;143:313–23.
- [42] Mishkin M, Vest B, Waxler M, Rosvold HE. A re-examination of the effects of frontal lesion on object alternation. *Neuropsychologia* 1969;7:357–63.
- [43] Miller EK, Erickson CA, Desimone R. Neural mechanisms of visual working memory in prefrontal cortex of the macaque. *Journal of Neuroscience* 1996;16:5154–67.
- [44] Miller EK. The prefrontal cortex: complex neural properties for complex behavior. *Neuron* 1999;22:15–7.
- [45] Mottaghy FM, Gangitano M, Sparing R, Krause BJ, Pascual-Leone A. Segregation of areas related to visual working memory in the prefrontal cortex revealed by rTMS. *Cerebral Cortex* 2002;12:369–75.
- [46] Nystrom LE, Braver TS, Sabb FW, Delgado MR, Noll DC, Cohen JD. Working memory for letters, shapes, and locations: fMRI evidence against stimulus-based regional organization in human prefrontal cortex. *NeuroImage* 2000;11:424–46.
- [47] O'Scalaidhe SP, Wilson FA, Goldman-Rakic PS. Areal segregation of face-processing neurons in prefrontal cortex. *Science* 1997;278:1135–8.
- [48] O'Scalaidhe SP, Wilson FA, Goldman-Rakic PS. Face-selective neurons during passive viewing and working memory performance of rhesus monkeys: evidence for intrinsic specialization of neuronal coding. *Cerebral Cortex* 1999;9:459–75.
- [49] Owen AM, Evans AC, Petrides M. Evidence for a two-stage model of spatial working memory processing within the lateral frontal cortex: a positron emission tomography study. *Cerebral Cortex* 1996;6:31–8.
- [50] Owen AM, Milner B, Petrides M, Evans AC. Memory for object features versus memory for object location: a positron-emission tomography study of encoding and retrieval processes. *Proceedings of the National Academy of Sciences of the United States of America* 1996;93:9212–7.
- [51] Owen AM, Stern CE, Look RB, Tracey I, Rosen BR, Petrides M. Functional organization of spatial and nonspatial working memory processing within the human lateral frontal cortex. *Proceedings of the National Academy of Sciences of the United States of America* 1998;95:7721–6.
- [52] Passingham RE. Delayed matching after selective prefrontal cortex lesions in monkeys (*Macaca mulatta*). *Brain Research* 1975;92:89–102.
- [53] Passingham RE. Memory of monkeys (*Macaca mulatta*) with lesions in prefrontal cortex. *Behavioral Neuroscience* 1985;99:3–21.
- [54] Paulesu E, Frith CD, Frackowiak RS. The neural correlates of the verbal component of working memory. *Nature* 1993;362:342–3.
- [55] Petit L, Orssaud C, Tzourio N, Crivello F, Berthoz A, Mazoyer B. Functional anatomy of a prelearned sequence of horizontal saccades in humans. *Journal of Neuroscience* 1996;16:3714–26.
- [56] Petrides M. The role of the mid-dorsolateral prefrontal cortex in working memory. *Experimental Brain Research* 2000;133:44–54.
- [57] Pollman S, Yves von Cramon D. Object working memory and visuospatial processing: functional neuroanatomy analyzed by event-related fMRI. *Experimental Brain Research* 2000;133:12–22.
- [58] Postle BR, D'Esposito M. “What”–then–“where” in visual working memory: an event-related fMRI study. *Journal of Cognitive Neuroscience* 1999;11:585–97.
- [59] Postle BR, Stern CE, Rosen BR, Corkin S. An fMRI investigation of cortical contributions to spatial and nonspatial visual working memory. *NeuroImage* 2000;11:409–23.
- [60] Postle BR, D'Esposito M. Evaluating models of the topographical organization of working memory function in frontal cortex with event-related fMRI. *Psychobiology* 2000;28:132–45.
- [61] Prabhakaran V, Narayanan K, Zhao Z, Gabrieli JDE. Integration of diverse information in working memory within the frontal lobe. *Nature Neuroscience* 2000;3:85–90.
- [62] Rainer G, Asaad WF, Miller EK. Memory fields of neurons in the primate prefrontal cortex. *Proceedings of the National Academy of Sciences of the United States of America* 1998;95:15008–13.
- [63] Rämä P, Sala JB, Gillen JS, Pekar JJ, Courtney SM. Dissociation of the neural systems for working memory maintenance of verbal and nonspatial visual information. *Cognitive, Affective, and Behavioral Neuroscience* 2001;1:161–71.
- [64] Rao SC, Rainer G, Miller EK. Integration of what and where in the primate prefrontal cortex. *Science* 1997;276:821–4.
- [65] Robertson L, Treisman A, Friedman-Hill S, Grabowecky M. The interaction of spatial and object pathways: evidence from Balint's syndrome. *Journal of Cognitive Neuroscience* 1997;9:295–317.
- [66] Rushworth M, Nixon P, Eacott M, Passingham R. Ventral prefrontal cortex is not essential for working memory. *Journal of Neuroscience* 1997;17:4829–38.
- [67] Smith EE, Jonides J, Koeppel RA, Awh E, Schumacher EH, Minoshima S. Spatial versus object working memory: PET investigations. *Journal of Cognitive Neuroscience* 1995;7:337–56.
- [68] Smith EE, Jonides J, Koeppel RA. Dissociating verbal and spatial working memory using PET. *Cerebral Cortex* 1996;6:11–20.
- [69] Stark CEL, Squire LR. When zero is not zero: the problem of ambiguous baseline conditions in fMRI. *Proceedings of the National Academy of Sciences of the United States of America* 2001;98:12760–6.
- [70] Stern CE, Owen AM, Tracey I, Look RB, Rosen BR, Petrides M. Activity in ventrolateral and mid-dorsolateral prefrontal cortex during nonspatial visual working memory processing: evidence from functional magnetic resonance imaging. *NeuroImage* 2000;11:392–9.
- [71] Tanaka JW, Farah MJ. Parts and wholes in face recognition. *Quarterly Journal of Experimental Psychology* 1993;46A:225–45.
- [72] Talairach J, Tournoux P. Co-planar stereotaxic atlas of the human brain. New York: Thieme; 1988.
- [73] Ungerleider LG, Haxby JV. ‘What’ and ‘where’ in the human brain. *Current Opinion in Neurobiology* 1994;4:157–65.

- [74] Ungerleider LM, Mishkin M. Two cortical visual systems. In: Ingle DJ, Goodale MA, Mansfield RJW, editors. *Analysis of visual behavior*. Cambridge: MIT Press; 1982.
- [75] Ward BD. Simultaneous inference for fMRI data [on-line 2000]. Available: <http://afni.nimh.nih.gov/afni/docpdf/AlphaSim.pdf>.
- [76] Ward BD. Deconvolution analysis of FMRI time series data [on-line 2001]. Available: <http://afni.nimh.nih.gov/afni/docpdf/3dDeconvolve.pdf>.
- [77] Wilson FA, O'Scalaidhe SP, Goldman-Rakic PS. Dissociation of object and spatial processing domains in primate prefrontal cortex. *Science* 1993;260:1955–8.
- [78] Zarahn E, Aguirre GK, D'Esposito M. Temporal isolation of the neural correlates of spatial mnemonic processing with fMRI. *Cognitive Brain Research* 1999;7:255–68.