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Distraction-spanning sustained activity during delayed recognition of locations

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This study investigated the neural systems that may make necessary contributions to the retention in working memory of location information. Particularly controversial in this regard have been the roles of various regions of frontal cortex. The task featured a multi-delay ABCA procedure designed to isolate target-related delay-period activity that would be sustained across intervening, distracting stimuli. This property is necessary for fMRI signal from a brain area to be considered necessary for successful retention of target-related information. Across single-subject analyses and two different group analyses, the Frontal Eye Fields (FEF), Supplementary Eye Fields, and Intraparietal Sulcus were most reliably found to support multi-delay sustained activity, and effects tended to be more robust in left than right hemisphere. Such activity was not found reliably, however, in the Superior Frontal Sulcus anterior to the FEF nor in dorsolateral prefrontal cortex. These results are interpreted as inconsistent with memory systems accounts holding that certain frontal regions are specialized for spatial working memory functions. They are consistent, however, with the view that spatial working memory functions are the product of the operation of spatial selective attention and motor preparatory processes.

Introduction

It is well established that spatial working memory tasks recruit activity in a widely distributed network of cortical and subcortical regions (e.g., Corbetta et al., 2002; Jonides et al., 1993; LaBar et al., 1999). What is less clear, however, is which of the many regions identified in functional neuroimaging studies might make necessary contributions to this behavior. Particularly controversial have been the roles of various regions of frontal cortex. Some early neuroimaging studies implicated human dorsolateral prefrontal cortex (PFC) as an important site for the domain-specific retention of location information (Belger et al., 1998; Courtney et al., 1996; McCarthy et al., 1996), results that echoed an influential model of the organization of working memory function in the monkey PFC (Goldman-Rakic, 1987; Wilson et al., 1993). These were followed by several studies that failed to find evidence for domain segregation of lateral PFC working memory activity (e.g., D'Esposito et al., 1998; Nystrom et al., 2000; Owen et al., 1998; Postle et al., 2000b). The implications of this debate were, and continue to be, broader than the narrow brain-mapping question of where different working memory functions are performed, because underlying it are two very different conceptions of working memory. The *memory systems* view holds that domain-segregated PFC working memory-related activity corresponds to the storage buffers of the multiple-component model of working memory (Baddeley and Hitch, 1974; Baddeley and Logie, 1999). By this account, working memory is supported by specialized systems of the mind and brain, just as visual perception is supported by a visual system (e.g., Courtney, 2004). The *emergent processes* view, in contrast, sees working memory as a function that arises from the activation, via attention, of systems that have evolved to accomplish perceptual-, representational-, and action-related functions (Postle, in press(b)). By this latter account, spatial working memory can be produced by spatial selective attention (Awh et al., 1998, 2000) and/or by motor preparation (Postle and D'Esposito, 2003; Postle et al., in press; Theeuwes et al., 2005). Further, it holds that delay-period activity of the PFC typically does not reflect the operation of storage processes, but rather, the operation of general purpose control processes (see, e.g., Johnson and Hirst, 1993; Lebedev et al., 2004; Postle, in press(a); Rose and Colombo, 2005).

The neuroimaging studies reviewed up to this point were ill-suited to resolve the debate over the functional organization of visual working memory because they relied on blocked designs that do not permit isolation of specific cognitive components of interest (Friston et al., 1996; Postle and D'Esposito, 2000; Zarahn et al., 1997). They were followed by a second generation of functional magnetic resonance imaging (fMRI) studies employing event-related designs that are capable, in principle, of isolating delay-period activity, a signal that is a candidate neural correlate of storage in short-term and working memory. Early among reports of these event-related fMRI studies was one that argued that the frontal area "specialized" for spatial working memory storage is

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not in dorsolateral PFC (dlPFC) but, instead, is in the portion of the Superior Frontal Sulcus (SFS) immediately rostral to the Frontal Eye Fields (FEF, Courtney et al., 1998). A study from a different group produced evidence that, consistent with some earlier studies, implicated the dlPFC (Leung et al., 2002). Several subsequent studies have produced data both consistent with (e.g., Leung et al., 2004; Munk et al., 2002; Rama et al., 2004; Sala et al., 2003; Slotnick, 2005) and inconsistent with (e.g., Passingham and Rowe, 2002; Postle, 2005; Postle and D'Esposito, 1999; Postle et al., 2000a) these updated memory systems accounts of spatial working memory.

And so the literature on the cognitive and neural bases of spatial working memory is inconclusive. One reason for this is that understanding of the nature of the information that is being represented by delay-period activity in any given task is a complex undertaking. Possibilities arising from eletrophysiological studies of nonhuman primates include spatial information itself (the interpretation compatible with memory systems views, e.g., Constantinides and Procyk, 2004; Constantinides et al., 2001; Funahashi et al., 1993), motor preparation (Fukushima et al., 2004; Takeda and Funahashi, 2002, 2004), and covert spatial attention (Lebedev et al., 2004). These possibilities have each also been invoked in interpretation of delay-period activity in the human (e.g., Curtis and D'Esposito, 2003; Curtis et al., 2004; Leung et al., 2004; Passingham and Sakai, 2004). A second reason is that, despite the improvement that event-related designs represented over the earlier blocked-design studies, the inferential scope of event-related fMRI studies, too, is limited by the inherently correlational nature of cognitive neuroimaging.

The study reported here employed an experimental procedure intended to permit stronger inference with fMRI data than has been afforded by the neuroimaging studies reviewed up to this point. It applied the logic that sustained activity that is necessary for spatial working memory must persist across intervening distractors, whereas activity that is not necessary may be "filtered out" by these distractors. More specifically, it used an ABCA design, in which a trial could require evaluation of one (an "AB" trial), two (an "ABA" trial), or three memory probes against the target stimulus. Retention of activity across the three delay periods of this task would be a necessary (although not sufficient) condition that a region must meet if it were to be considered necessary for successful working memory performance. The present study can be seen as a companion to a previous study requiring working memory for faces. This previous study found that only posterior fusiform cortex supported delay-period activity that was reliably sustained across three delay periods (Postle et al., 2003).

In the present study, we predicted that we would find distractor-spanning sustained delay-period activity in several cortical regions, including the FEF, Intraparietal Sulcus (IPS), and Superior Parietal Lobule (SPL), and perhaps also in caudate nucleus. Importantly, we also predicted that we would not find evidence for distractor-spanning delay-period activity in dlPFC or in posterior SFS. We made these predictions for two reasons. One derives from the fact that spatial working memory and spatial selective attention share largely overlapping networks (e.g., Corbetta et al., 2002; LaBar et al., 1999), and the spatial attentional networks that overlap with working memory are generally not found anterior to the FEF (e.g., Corbetta et al., 1998, 2002; Kim et al., 1999; Yantis and Serences, 2003). Additionally, evidence for the "attention-based rehearsal" of spatial information has been found in posterior, but not frontal, cortical regions (Awh et al., 2000; Postle et al., 2004). The second reason for our predictions is that our previous direct tests have been unable to dissociate spatial delay-period activity from object delay-period activity (Postle and D'Esposito, 1999) or from oculomotor control-related activity (Postle et al., 2000a) (see also Postle, 2005; Slotnick, 2005), leading us to hypothesize that the delay-period activity of neither dlPFC nor posterior SFS is necessary for spatial working memory.

Methods

Subjects

Our methods were approved by the Health Sciences Institutional Review Board of the University of Wisconsin–Madison. Sixteen healthy young adults who reported no history of neurological or psychiatric disorders, and no recent use of psychoactive drugs, participated after giving informed consent. The fMRI data from 3 subjects were discarded due to excessive movement in the scanner.

Behavioral task

Materials and apparatus

Stimuli were presented, and responses collected, on a PC running Eprime software. Stimuli were white circles of approximately 2° of visual angle in diameter, displayed on a black background. Because all stimuli had identical features, stimulus identity was determined solely by position on the screen. A description of how stimulus positions were determined follows the introduction of constraining aspects of the task and experimental procedure, in the next few subsections. Subjects viewed stimuli through eyepieces that displayed a rectangular screen subtending approximately 24.5 horizontal × 17 vertical degrees of visual angle (Avotec Silent Vision).[1] They responded to each probe stimulus via a fiber optic button box connected to the PC. Center of gaze was monitored with an infrared-based system (SMI iView X) integrated with the eyepieces.

Task

Each trial began with the 1-s presentation of a target stimulus, followed by a blank 7-s delay period (Delay 1), followed by a 1-s memory probe (Probe 1). On 1-delay trials, Probe 1 was followed by a blank 3-s period, followed by the word "End" (1 s), which signaled the end of the trial. On 2-delay trials, Probe 1 was followed by a blank 7-s delay period (Delay 2), followed by Probe

[1] Due to the optics of this system, and the fact that we did not control the distance from each subject's eyes to the display screens in the eyepieces, our conversions from screen pixels (the metric by which Eprime controlled stimulus position, and in which eye position was measured) to degrees of visual angle could yield only approximate values. All quantitative analyses of stimulus position and gaze position, therefore, were performed in screen pixels. Where practical, however, these values are converted to degrees of visual angle for ease of communication in narrative sections of this report.

2 (1 s) and, 3 s later, the end cue. Three-delay trials also presented Delay 3 and Probe 3 in the same manner. Each trial type, regardless of length, was followed by an intertrial interval (ITI) of 10 s (Fig. 1). Subjects were instructed to evaluate each memory probe as a match or a nonmatch of the target. Instructions included the explicit explanation that matching probes would appear in precisely the same location as had the Target, and that no portion of any of nonmatching probe stimulus would overlap any of the screen area that had been covered by the target from that trial. Additionally, subjects were instructed to keep their gaze focused on the center of the display area (despite the absence of a fixation spot), including the explicit instruction to return their gaze to the center should they make a saccade to a stimulus.

Design, procedure, and stimulus positioning

Each experimental session comprised 32 delayed recognition trials of each length, evenly divided into match and nonmatch trials, and evenly distributed across 8 blocks of 12 trials each (one EPI scan per block). The task was programmed with 96 hard-coded trials, with trial order for each subject determined by pseudorandom selection without replacement, constrained by the rules balancing trial type across blocks, and the rule that no more that three trials of one length could occur in succession. Target positions were determined pseudorandomly with two constraints: (1) across an experimental session, 24 targets appeared in each quadrant of the screen: and (2) no two targets were centered on precisely the same coordinates. Within each trial, intermediate probe positions (e.g., Probe 1 on a 2- or 3-delay trial) were determined pseudorandomly, with the constraint that they did not overlap the location of any other stimuli from the trial (hence, an "ABCA," rather than an "ABBA", procedure). The unpredictability of trial length meant that subjects always had to retain information about the target stimulus during each of the three delay periods. Nonmatching trial-final probes (e.g., Probe 2 on a 2-delay trial) appeared an average of 4.4° of visual angle (SD = 1°; min = 2°; max = 10.7°) distant from the target position. That is, the average distance between the closest edges of a target and a nonmatching trial-final probe was equivalent to the diameter of these stimuli.

Table 1
Behavioral results

	Trial length (number of delay periods)		
	1	2	3
Accuracy (mean % correct [SE])	89.2 [3.3]	82.9 [3.5]	78.2 [3.2]
RT (ms [SE])	870.3 [47.5]	890.0 [46.6]	852.6 [41.3]

Scoring

Despite the fact that responses to Probe 1 were required on 2-delay trials, and to Probe 1 and Probe 2 on 3-delay trials, accuracy and RT to only the trial-final probe from each trial were scored and are reported here. In addition to button presses, eye position from the middle 4 s of each delay period were analyzed offline (with ILAB software, Gitelman, 2002), and we planned to use these data in two ways. Firstly, fixation was scored as *maintained* or *broken* depending on whether the center of gaze traveled further than 1° of visual angle from its position at the beginning of the 4-s epoch, regardless of the location of this starting position (i.e., stable fixation of the upper right-hand corner of the display would be scored as "maintained"). It is this 4-s epoch to which delay-period covariates of the fMRI analyses were most sensitive (see Methods, fMRI methods, Analyses). Sorting delay periods by fixation status would permit comparison of delay-period activity in the presence vs. the absence of concurrent eye movements. Secondly, we also planned to exclude from further analyses trials during which subjects used a strategy of maintaining fixation on the location of the target stimulus, a strategy that was explicitly discouraged during training.

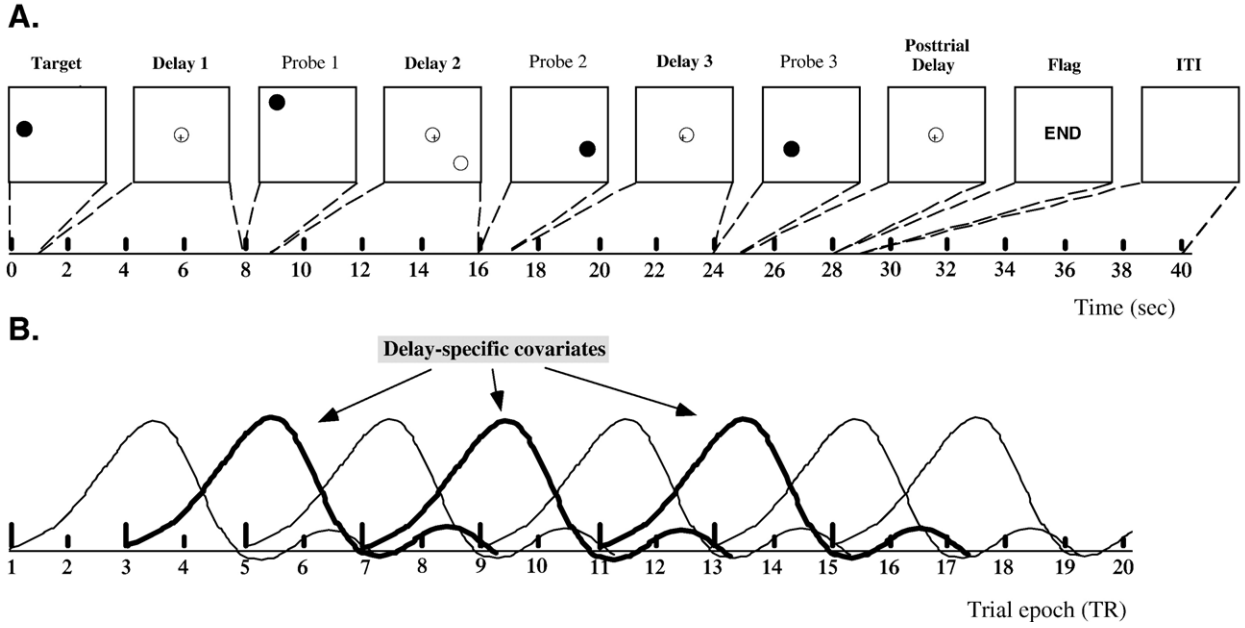

Fig. 1. (A) Schematic diagram of a 3-delay trial. On 1- and 2-delay trials, the "End" message appeared at times 12 s and 20 s, respectively. (B) Schematic representation of the analysis model corresponding to this trial. Short bars represent unmodeled epochs of the task; tall bars represent impulse (or "stick function") covariates that were convolved with the HRF to yield the final covariate set. An HRF was derived empirically for each subject, and this figure illustrates a representative HRF; HRFs depicted in thicker lines correspond to delay-specific covariates for Delay 1, Delay 2, and Delay 3.

Table 2
Tabulation of number of subjects with ROIs displaying delay-period activity, from single subject data

ROI	Delay 1			Delay 2			Delay 3		
	Left hemisphere	Midline-spanning	Right hemisphere	Left hemisphere	Midline-spanning	Right hemisphere	Left hemisphere	Midline-spanning	Right hemisphere
dlPFC	6		2	3		1	2		0
SFC	5		3	2		0	2		0
Posterior SFS	1		4	1		2	1		0
ACC[a]		3			3			3	
FEF	8		6	7		5	6		5
SEF		7			7			7	
LatPMC	5		5	5		3	1		1
PreCG	3		4	2		4	2		2
PostCG	3		4	1		2	0		1
Precuneus[a]		1			1			1	
SPL[a]		9			5			3	
IPS	8		4	5		3	4		2
Extrastriate	8		5	4		5	2		0
Caudate nucleus	3		2	1		0	0		0

Values in the Delay 2 and Delay 3 columns are limited to cases in which the activity was sustained from the previous delay period (see Methods).
[a] Midline-spanning ROIs were not divided by hemisphere.

fMRI methods

Data acquisition and preprocessing

Whole-brain images were acquired with a 3T scanner (GE Signa VH/I). High resolution T1-weighted images (30 axial slices, 0.9375 mm × 0.9375 mm × 4 mm) were obtained in all participants, and a gradient echo, echoplanar sequence (TR = 2000 ms, TE = 50 ms) was used to acquire data sensitive to the blood oxygen level-dependent (BOLD) signal (Kwong et al., 1992; Ogawa et al., 1992) within a 64 × 64 matrix (30 axial slices coplanar with the T1

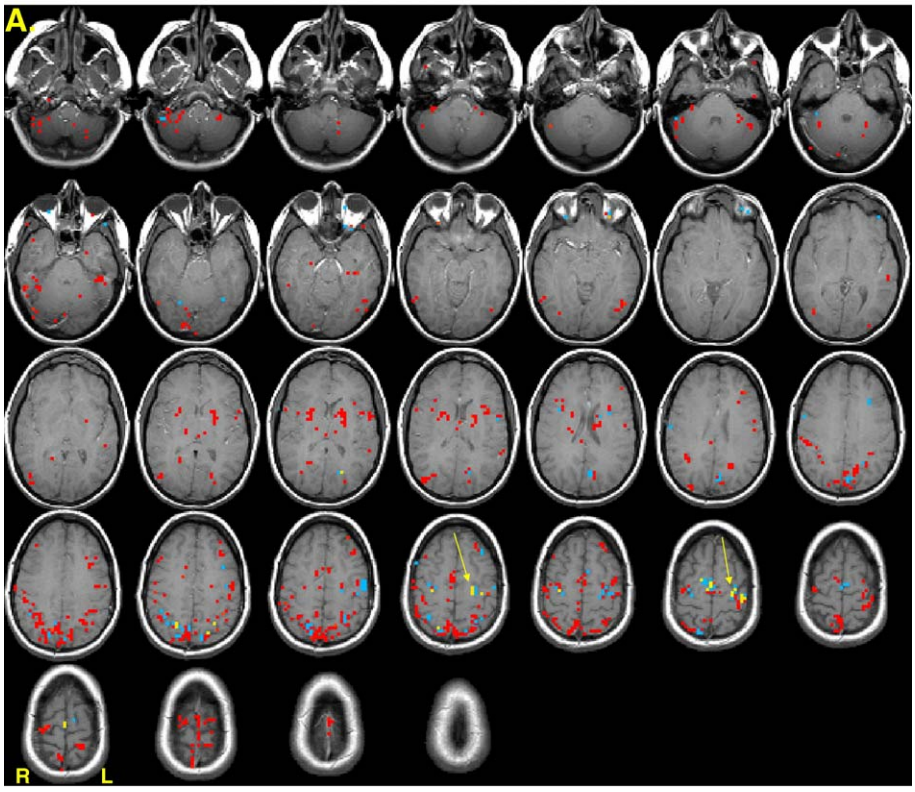

Fig. 2. (A) Results from the single-subject analysis of data from subject #9. Voxels in red demonstrated suprathreshold activity for Delay 1 only. The subset of voxels with delay-period activity sustained across Delay 1 and Delay 2 are rendered in blue. The still smaller subset of voxels with delay-period activity sustained across all three delay periods are rendered in yellow. Arrows highlight the voxels from left FEF, whose activity is shown in panels B, C, and D. (B) Activity from left FEF 3-delay voxels (see panel A) averaged across 1-delay trials. "Delay 1 effect" corresponds to the Delay 1 covariate, scaled by its parameter estimate. Grey bar along the horizontal axis indicates the duration of the delay period. (C) Activity from left FEF 3-delay voxels averaged across 2-delay trials. Graphical conventions are the same as in panel B. (D) Activity from left FEF 3-delay voxels averaged across 3-delay trials. Graphical conventions are the same as in panel B.

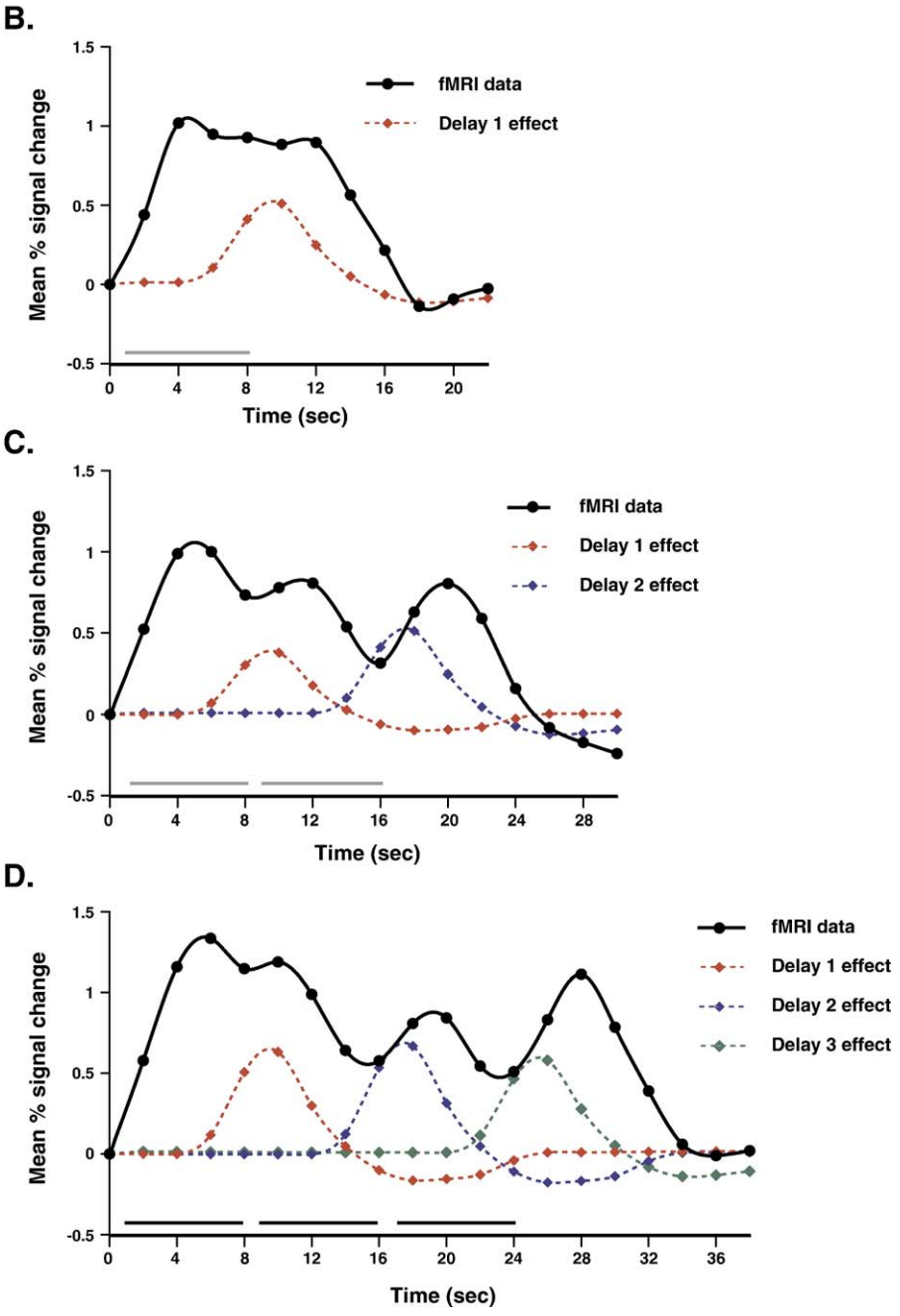

Fig. 2 (*continued*).

acquisition, 3.75 mm × 3.75 mm × 4 mm). Scans of the delayed recognition task were preceded by a scan in which we derived an estimate of the hemodynamic response function (HRF) for each participant. During this scan, each participant performed a simple reaction-time task that required a bimanual button press once every 20 s in response to a brief change in shape of the fixation stimulus. A partial *F* test associated with a Fourier basis covariate set (Josephs et al., 1997) was used to evaluate the significance of task correlated activity in each voxel of primary somatosensory and motor cortical regions of interest (ROIs). An HRF estimate was extracted from the suprathreshold voxels of these ROIs by pooling their time series, filtering the resultant averaged fMRI time series to remove high (>0.244 Hz) and low (<0.05 Hz) frequencies, adjusting it to remove the effects of nuisance covariates (Friston et al., 1995), and trial averaging. The HRF characterizes the fMRI response resulting from a brief impulse of neural activity (Boynton et al., 1996) and can vary markedly across participants (Aguirre et al., 1998; Handwerker et al., 2004). The subject-specific HRFs were used to convolve independent variables entered into the modified general linear model (GLM, Worsley and Friston, 1995) that we used to analyze the data from the scans of the working memory task. The eight scans of the working memory task each lasted 6 min 44 s (6:24 of task preceded by 20 s of dummy pulses to achieve a steady state of tissue magnetization).

Analyses

Three types of analyses were performed, single-subject analyses and two group analyses. Underlying each was the fMRI time series analysis that modeled the signal changes evoked by each stimulus presentation epoch with covariates comprised of BOLD HRFs shifted along the timeline of the task to represent various trial epochs (Postle et al., 2000c; Zarahn et al., 1997). The least-squares solution of the GLM of the fMRI time series data yielded parameter estimates that were associated with each covariate of interest. The smoothness of the fMRI response to neural activity allows fMRI evoked responses that arise from temporally dependent events to be resolved on the order of 4 s (Zarahn et al., 1997). Fig. 1 illustrates the positioning of covariates that yielded uncontaminated estimates of delay-period activity. Differences in epoch-evoked signal vs. baseline were tested by computing *t* statistics from contrasts between parameter estimates associated with the covariates in question.

The procedure for the *single-subject analyses* was to first generate a statistical map of Delay 1 activity (collapsed across all three trial types), thresholded to a Bonferroni-corrected whole brain-wise α of 0.05. Next, a mask was made by replacing all suprathreshold voxels from the statistical map with a value of 1 and all subthreshold voxels with a value of 0. Next, a statistical map of Delay 2 activity was generated (collapsing across 2-delay and 3-delay trials), and this map was masked with the Delay 1 mask, then thresholded to a Bonferroni-corrected Delay 1 mask-wise α of 0.05. This had the effect of identifying voxels that sustained the Delay 1 signal during Delay 2. (Note that the critical *t* value for the masked Delay 2 map was considerably lower than was the critical *t* for the Delay 1 map because the masked Delay 2 map contained many fewer voxels.) Next, a binary mask was created from the masked Delay 2 map, and this was used to mask (and threshold) the Delay 3 statistical map. The final result was a statistical map identifying the voxels that sustained the Delay 1 signal across all three delay periods. Note that this yielded a conservative map, in that it's effective α was (0.05*0.05*0.05=)0.000125.

Two types of group analysis were also performed. *Region of interest (ROI)-based group analyses* were performed within regions identified by the single-subject analyses, plus in regions about which we had a priori hypotheses, but that may not have been identified in the single-subject analyses. These were done by identifying, within each subject, voxels with Delay 1 activity in each anatomically defined region, and then extracting from these voxels the delay-evoked effect from each of the three delay periods. Note that this analysis was limited to voxels with task-related activity and did not collapse across entire anatomically defined ROIs. One motivation for the ROI-based group analysis was to compensate for the stringency of thresholding in the single-subject analyses, and the possibility that some critical voxels may have been excluded by the single-subject approach. This was accomplished by implementing a procedure that identified all voxels that met a liberal threshold for delay-period activity. The threshold used to identify voxels for the ROI-based group analyses was $t = 3.5$, a value corresponding to the Bonferroni-corrected threshold for a region of 200 voxels that yielded an $\propto$ of 0.05 (single subject GLMs in this study had around 1100 effective *df*). Despite this lowered threshold, there remained, for each ROI, at least one subject in whose data that ROI contained no Delay 1-active voxels. In these instances, voxels exceeding the region-wise threshold for target-evoked activity were selected. The reliability of group trends was evaluated across subjects, by region and by delay period.

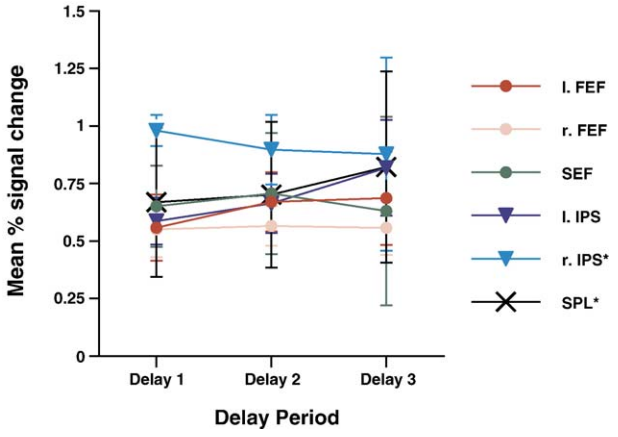

Fig. 3. Mean delay effect sizes, from voxels identified in the single-subject analyses as showing 3-delay sustained activity. The number of observations (i.e., subjects) per ROI corresponds to the Delay 3 values provided in Table 2. Error bars represent 95% confidence intervals.

Table 3
Data used for ROI-based group analysis

ROI	Number of subjects	Mean number of voxels/subject [SD]
Left dlPFC	10	16.3 [19.8]
Right dlPFC	10	6.1 [6.6]
Left posterior SFS	7	3.6 [3.8]
Right posterior SFS	5	3.2 [2.9]
ACC	10	3.7 [3.3]
Left FEF	13	14.2 [16.2]
Right FEF	12	10.9 [13.4]
SEF	12	21.6 [28.5]
Left latPMC	9	12.8 [10.8]
Right latPMC	10	4.3 [4.7]
SPL	11	52.4 [84.7]
Left IPS	12	20.5 [16.8]
Right IPS	10	21.5 [37.2]

Tabulated here, by ROI, is the number of subjects, and the mean number of voxels per subject, with Delay 1 activity at the ROI-wise threshold of $t \geq 3.5$. Note that, for each ROI with fewer than the full complement of 13 subjects, voxels with target-evoked activity were substituted from the data of the subjects that lacked Delay 1 activity for the ROI in question. These data contributed to the results displayed in Fig. 4.

The second type of group analysis was a *spatial normalization-based group analysis*. It was performed by first warping unthresholded statistical volumes from each subject to a template in MNI space, smoothing them to 8 mm FWHM, then evaluating the reliability of these statistical maps across subjects. As with the ROI-based group analysis, the intent with this group analysis was to employ liberal thresholds because the most theoretically important hypotheses in this study were the predictions that we would not find effects in certain frontal regions. A null result would be most convincing if it were demonstrated despite permissive thresholding. Thus, the Delay 1 group map (with 12 *df*) would be thresholded at a highly permissive $P \leq 0.01$ (uncorrected), and the statistical map converted to a binary map in order to implement the same sequential masking procedure described for the single-subject analyses. To emulate the manner in which, for the single-subject analyses, the thresholding *t* value decreased for each of the nested contrasts, the α for the masked Delay 2 map was set at 0.03 (uncorrected), and for the masked Delay 3 map at 0.05 (uncorrected).

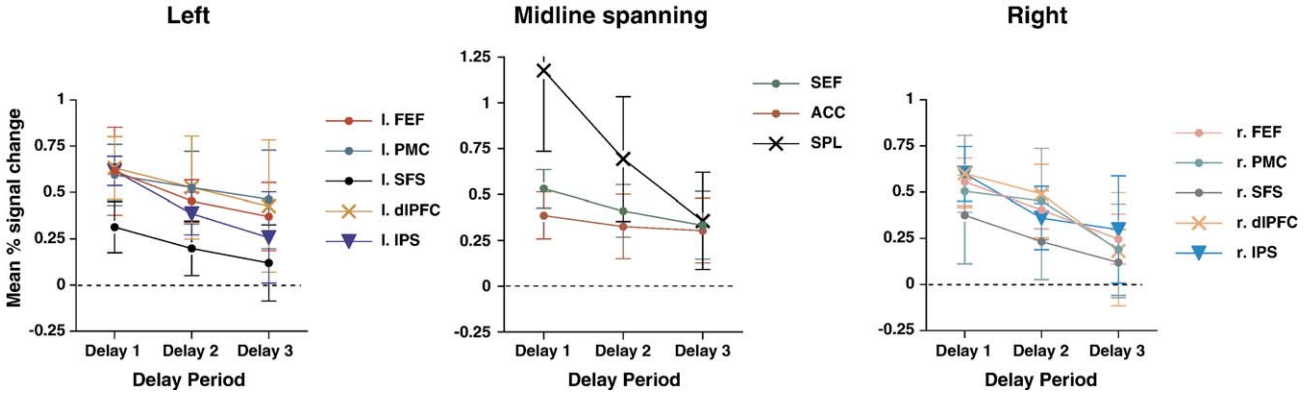

Fig. 4. Results from ROI-based group analyses, by left hemisphere, midline-spanning, and right hemisphere ROIs. Data for each ROI were derived from 12 or 13 observations. The proportion of observations from Delay 1-evoked vs. Target-evoked voxels can be inferred from the "Number of subjects" column of Table 3. Error bars represent 95% confidence intervals.

ROIs

The anatomical determination of ROIs was as follows: dlPFC, corresponding to the portions of the Middle and Inferior Frontal Gyri comprising Brodmann Areas (BA) 9 and 46 (as detailed in Damasio, 1995; Duvernoi, 1999; Rajkowska and Goldman-Rakic, 1995; Talairach and Tournoux, 1988);[2] superior frontal cortex (SFC), corresponding to the portions of BA 8 in Superior Frontal Gyrus and anterior SFS; dorsocaudal anterior cingulate cortex (ACC), corresponding to BA 24; posterior SFS (SFS), corresponding to the portion of the SFS lying immediately anterior to the FEF; FEF, corresponding to the 6 mm of the SFS immediately anterior to the intersection of the SFS and the precentral sulcus (PCS), and the 6 mm of the rostral bank of the PCS immediately lateral to this intersection; Supplementary Eye Field (SEF), in the medial wall in the upper part of the paracentral sulcus; lateral Premotor Cortex (latPMC), the cortex in both banks of the Precentral Sulcus and of the convexity immediately anterior to it, bounded superiorly by the FEF;[3] Precentral Gyrus (preCG); Postcentral Gyrus (postCG); Precuneus; SPL (BA 7); IPS; dorsal extrastriate cortex, corresponding to dorsal portions BAs 18 and 19 of the occipital lobe. ROIs that spanned the midline were not divided by hemisphere.

Results

Behavioral

Accuracy declined as a function of the number of delay periods ($F(2,30) = 15.9$; $P < 0.0001$). Reaction time (RT), on the other hand, did not vary with trial type ($F(2,30) = 1.5$; n.s.) (Table 1). To validate the assumption that subjects used spatial information to perform the task (as opposed to, for example, an internally generated verbal code), we evaluated performance on nonmatching trials as a function of the distance between the target stimulus and the trial-final probe stimulus. This analysis confirmed this assumption, indicating that accuracy was inversely related to this distance (mean distance on incorrect trials = 112.6 pixels (SD = 6.4) or approximately 4.1° of visual angle; mean distance on correct trials = 120.2 pixels (SD = 1.1) or approximately 4.4° of visual angle; $t(15) = 4.7$; $P < 0.0005$). The eye position data indicated that subjects complied with the instruction to maintain delay-period gaze at the center of the display screen (i.e., they did not simply fixate the target location throughout the trial). However, they only maintained steady delay-period fixation during 21.6% of Delay 1 delay periods, 22.0% of Delay 2 delay periods, and 20.7% of Delay 3 delay periods. These low levels of compliance were most typically produced by excessive drift in eye position, perhaps due to the absence of a fixation stimulus. Because of this, meaningful comparison of signal from delay periods with maintained vs. broken fixation was not possible.

fMRI

Single-subject analyses

Results are summarized in Table 2 and illustrated in Figs. 2 and 3. The regions most likely to demonstrate delay-period activity sustained across the three delay periods were FEF, SEF, left IPS, and SPL, with one to three subjects also showing sustained three-delay-period activity in left dlPFC, left SFC, left posterior SFS, ACC, latPMC, preCG, right postCG, Precuneus, and left extrastriate cortex. Three-delay sustained activity was not seen in any subject in the caudate nucleus.

ROI-based group analyses

The results, summarized in Table 3 and Fig. 4, indicated that, of the regions investigated, delay-period activity declined to levels not different from 0 in left and right posterior SFS and in right dlPFC and right PMC. Fig. 5 illustrates activity from two frontal ROIs.

Spatial normalization-based analysis

Delay 1 activity was observed in several regions in this analysis (summarized in Table 4). And as was the case with the single-subject

[2] The sources cited here differ as to whether the ventral-most portion of BA 46 spans the Inferior Frontal Sulcus and extends into a portion of anterior IFG. Because the ROI-based group analyses were limited within each anatomically defined region to the voxels with Delay 1 activity, we resolved this ambiguity in the following way: Delay 1 activity in anterior IFG that was contiguous with MFG activity was included in the dlPFC ROI; anterior IFG voxels with Delay 1 activity that were not contiguous with MFG voxels with Delay 1 activity were not included in the dlPFC ROI. This limited IFG contribution to dlPFC ROIs to those cases in which MFG activity "spilled over" into IFG.

[3] Any Delay 1 active voxels in this region that were contiguous with activity that met criteria for the FEF were also included in the FEF ROI. Thus, voxels classified as latPMC were always topographically discontinuous from voxels classified as FEF.

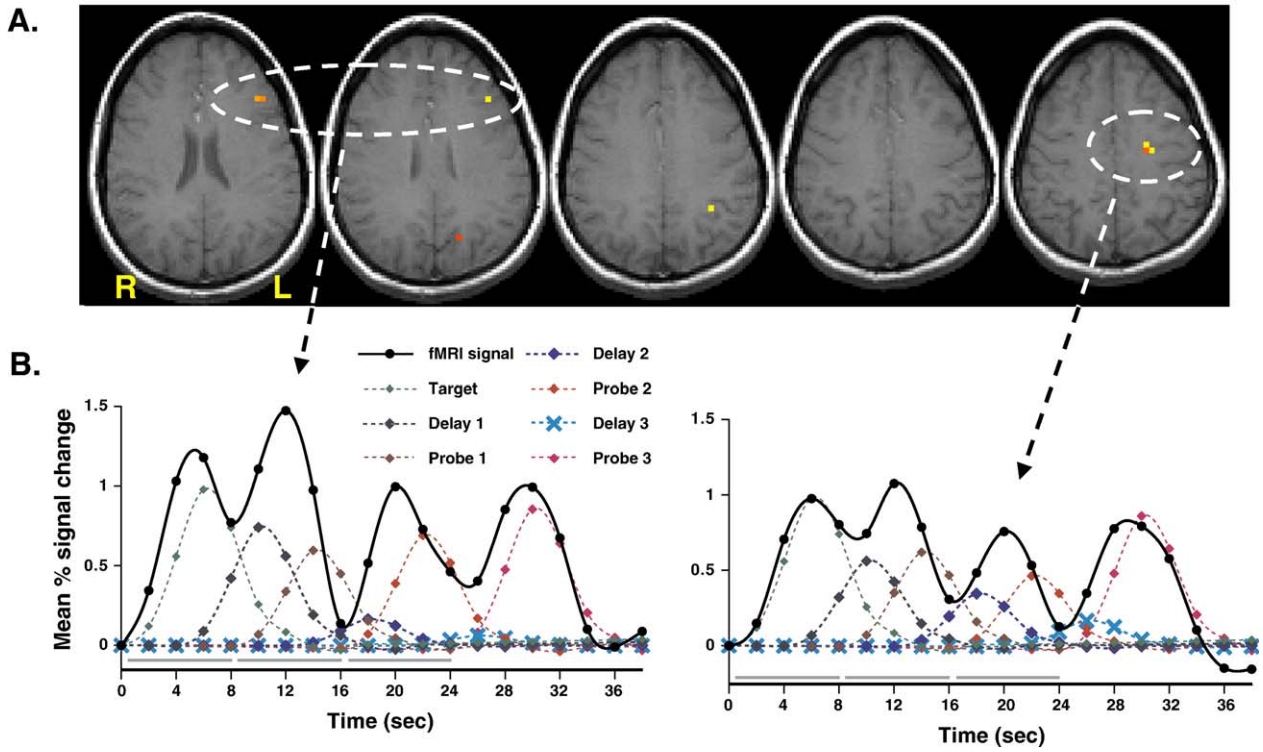

Fig. 5. Example of activity from two frontal ROIs in the data of subject #11. Panel A shows Delay 1 activity (thresholded at the ROI-wise level) from five contiguous axial slices. Circled are voxels in left middle frontal gyrus (MFG; two left-most slices of the image) and in left FEF. Panel B shows fMRI time series data, averaged across 3-delay trials, as well as the quantitative fits of each of the covariates of interest from this trial. For the data shown here, Delay 3 activity in the left MFG did not achieve significance ($t(1083) = 0.41$; n.s.), whereas the Delay 3 activity in left FEF approached significance ($t(1083) = 1.51$; $P = 0.065$).

analyses, only a small subset of Delay 1 voxels retained their signal across Delay 2, and even fewer still retained it across Delay 3. The areas showing sustained 3-delay delay-period activity were left Inferior Frontal Gyrus (Brodmann's area (BA) 47); left frontal pole (BA 10); left extrastriate cortex (two sites, both BA 18); posterior cingulate gyrus (BA 23); left lateral premotor cortex (BA 6); left and right IPS (BA 7/40); left FEF (BA 6); SEF (BA 6); and right SPL (BA 7; Fig. 6).

Discussion

Consistent with our predictions, and with many previous studies, we found location delay-related activity in a broadly distributed network of cortical regions, including frontal and parietal regions associated with attention and oculomotor control. Across three types of analyses, these regions were seen to support sustained, distraction-spanning signals that may correspond to the mnemonic retention of the location of the target stimulus. Also consistent with our predictions was the absence of reliable sustained delay-period activity in posterior SFS and dlPFC regions. Of these, only left dlPFC demonstrated evidence for reliable 3-delay sustained activity in only one of the three analyses—the ROI-based group analysis that identified Delay 1 voxels with a permissive ROI-wise threshold. On the balance, therefore, these results do not support the view that frontal areas anterior to the FEF make a necessary contribution to the short-term retention of location information. More broadly, these results are difficult to reconcile with the view that spatial working memory depends on the operation of one or more specialized memory systems. They are easily accommodated, however, by the view that spatial working memory is a cognitive phenomenon that emerges from the operation of spatial attention- and motor preparation-related processes.

What mental processes may have been indexed by the sustained delay-period activity that was isolated in this study? Two candidates that have previously been proposed as possible mechanisms for the short-term retention of location are attention-based rehearsal and prospective motor coding. The former refers to the covert allocation of spatial selective attention to the to-be-remembered location during the delay period. Although many of the regions identified by this study could represent the source, and in some cases the site, of such attentional signals, the experimental procedures of this task do not permit a direct test for the operation of this mechanism (see, for example, Awh et al., 1999, 2000; Postle et al., 2004). A second candidate mechanism is prospective motor coding, the transformation of visual coordinates into motor coordinates (as would be required, for example, for a saccade or a grasp), and the retention of these motor coordinates as a means of spanning the delay period. One might object that a role for this mechanism to the present study is questionable because subjects did not maintain steady fixation during the majority of the delay periods. This might be problematic because previous work has demonstrated that delay-period eye movements can disrupt spatial memory performance (Baddeley, 1986; Hale et al., 1996; Lawrence et al., 2004; Pearson and Sahraie, 2003; Postle et al., in press), presumably by interfering with the target-related motor plan. This does not necessarily rule out a contribution from a prospective motor coding mechanism, however,

Table 4
Delay period activity from spatial-normalization group analysis

Region of activation (Brodmann area)	MNI coordinates			Effect size (mean %signal change)		
	x	*y*	*z*	Delay 1	Delay 2	Delay 3
Cerebellum	−7.5	−71.25	−32	0.62	–	
Cerebellum	0	−71.25	−24	0.20	–	
L. Inf. frontal gyrus (47)	−45	22.5	−12	0.99	1.42	1.52
R. Inf. temporal gyrus (19)	45	−63.75	−4	0.28	–	
R. middle temporal gyrus (37)	45	−52.5	−4	0.33	–	
L. white matter	−22.5	−86.25	0	0.37	–	
L. frontal pole (10)	−7.5	63.75	4	1.19	1.39	0.87
R. Ant. occipital sulcus (19/39)	41.25	−78.75	8	0.51	–	
L. insula	−30	−3.75	12	0.33	–	
R. insula	41.25	3.75	12	0.22	–	
R. insula	33.75	−30	12	0.29	–	
R. Mid. temporal gyrus (39)	45	−60	12	0.26	–	
L. extrastriate (18)	−18.75	−101.25	16	0.93	0.59	0.40
White matter	−22.5	−52.5	20	0.23	–	
Post. cingulate (23)	−11.25	−60	20	0.65	0.50	0.37
L. extrastriate (18/19)	−26.25	−82.5	20	0.36	–	
R. precentral gyrus (4/6)	63.75	−11.25	20	1.01	–	
R. Sup. temporal gyrus (22)	63.75	−45	20	0.36	–	
L. extrastriate (19)	−26.25	−71.25	24	0.22	–	
R. central sulcus	45	−18.75	24	0.35	0.27	–
R. Sup. temporal sulcus (39)	45	−60	24	0.26	–	
R. precentral gyrus (4)	60	−15	24	0.58	–	
L. lateral premotor cortex (6)	−52.5	−11.25	28	0.80	–	
L. angular gyrus (39)	−48.75	−7.5	28	0.44	–	
L. Sup. temporal sulcus (39)	−48.75	−63.75	28	0.29	–	
L. extrastriate (18)	−11.25	−67.5	28	0.33	0.39	0.17
R. angular gyrus (39)	33.75	−60	32	0.24	–	
R. lateral premotor cortex (6)	37.5	−18.75	32	0.30	–	
R. supramarginal gyrus (40)	56.25	−60	32	0.46	–	
L. dlPFC (9)	−22.5	37.5	40	0.58	–	
L. anterior cingulate (24)	−18.75	−15	40	0.22	–	
L. posterior cingulate (31)	−3.75	−30	40	0.27	–	
L. Inf. parietal lobule (BA 40)	−30	−52.5	40	0.36	–	
L. extrastriate (19)	−15	−93.75	40	1.04	–	
L. lateral premotor cortex (6)	−48.75	−18.75	44	0.95	0.53	0.29
L. white matter	−26.25	−33.75	44	0.28	–	
L. extrastriate (19)	−30	−60	44	0.66	–	
R. white matter	26.25	−33.75	44	0.23	0.26	0.13
R. Inf. parietal lobule (40)	56.25	−41.25	44	0.62	–	
L. Inf. parietal lobule (40)	−41.25	−48.75	48	0.58	–	
L. IPS (7/40)	−26.25	−67.5	48	0.61	0.54	0.20
R. IPS/Inf. parietal lobule (40)	33.75	−67.5	48	0.43	0.24	0.23
R. Inf. parietal lobule (40)	41.25	−41.25	48	0.60	–	
R. postcentral gyrus (3)	63.75	−22.5	48	0.44	–	
L. central sulcus (4/3)	−26.25	−37.5	52	0.62	–	
L. IPS (7/40)	−18.75	−75	52	0.77	–	
L. SPL (7)	−11.25	−90	52	0.59	0.32	–
R. central sulcus (4/3)	15	−30	52	0.40	–	
R. FEF (6)	22.5	−22.5	52	0.21	–	
R. FEF (6)	30	−18.75	52	0.69	–	
R. SPL (7)	37.5	−86.25	52	0.55	–	
R. IPL (40)	48.75	−52.5	52	0.42	–	
L. Sup. temporal sulcus (37)	−37.5	−37.5	56	0.72	–	
L. central sulcus (4/3)	−30	−45	56	0.38	–	
L. FEF (6)	−15	−22.5	56	0.55	0.47	0.27
L. IPS (7/40)	−22.5	−63.75	56	0.39	–	
SEF (6)	−3.75	−18.75	56	0.82	0.51	0.27
L. SPL (7)	−7.5	−75	56	0.59	0.34	
R. SPL (7)	11.25	−82.5	56	0.53	–	
R. SLP (7)	41.25	−63.75	56	0.74	–	
R. postcentral gyrus (3)	48.75	−45	60	0.70	0.51	–

Table 4 (*continued*)

Region of activation (Brodmann area)	MNI coordinates			Effect size (mean %signal change)		
	x	*y*	*z*	Delay 1	Delay 2	Delay 3
R. precentral gyrus (4)	45	−30	64	0.74	–	
R. postcentral gyrus (5)	37.5	−41.25	64	0.71	–	
R. postcentral gyrus (5)	41.25	−56.25	68	0.56		
R. SPL (7)	18.75	−48.75	68	0.50	0.44	0.30

because the disruptive effects of eye movements are attributable to their control, but not to the movement per se (Postle et al., in press), and much of the delay-period eye movement in the present study would be best characterized as "drift" that may have required minimal, if any, control. Further problematic for the invocation of prospective motor coding in the present study, however, may be the absence of sustained activity in the caudate nucleus. This structure has been implicated in a previous direct test of this mechanism (Postle and D'Esposito, 2003). But, as was the case with attention-based rehearsal, the design of the present study precludes a direct test of evidence for this mechanism.

Finally, it is important to consider what factors might underlie the "distractor-spanning" nature of the activity isolated in the present study. Several recent studies of resistance to distraction and/or interference have pointed to a critical role for PFC-based control mechanisms, yet our results failed to produce strong evidence for sustained delay-period activity in the PFC. This discrepancy may be explained by critical differences in experimental procedures and analysis methods, which, in turn, reflect differences in theoretical motivation. One set of studies has implicated the PFC in a sensory gating (or "attentional filtering") process that protects the contents of working memory by dampening the sensory response to task-irrelevant delay-period distractors (Chao and Knight, 1995, 1998; Postle, in press(a)). In the present study, however, potentially distracting stimuli were not known to be irrelevant (indeed, they required a response), and a sensory filtering strategy would not, therefore, have been appropriate. In another recent study, Sakai et al. (2002) found that PFC activity during an unfilled delay period predicted task accuracy on trials when this unfilled period was followed by a distractor task. They attributed this to a PFC-controlled "active maintenance" process that strengthened mnemonic representations via the strengthening of the coupling of activity between SFC (Brodmann's area (BA) 8) and IPS. This control process, which is reminiscent of the "active maintenance" proposed by Miller and Cohen (2001), may, indeed, explain a portion of the extensive Delay 1 activity observed in dlPFC in the present study. Inspection of the data from the Sakai et al. (2002) report suggests that this PFC "active maintenance" activity was not sustained throughout the distractor task that followed the unfilled delay. Similarly, the

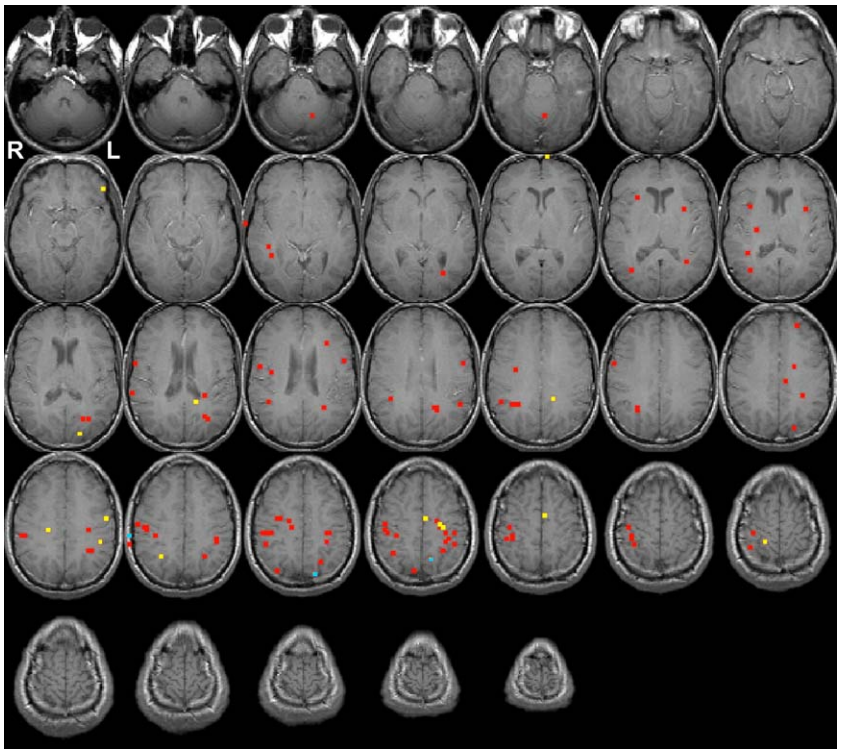

Fig. 6. Results from the spatial normalization-based group analysis, displayed on an individual anatomical template in MNI space. Graphical conventions are as in Fig. 2A. Voxels in red demonstrated suprathreshold activity for Delay 1 only; those in blue sustained their activity across Delay 1 and Delay 2; those in yellow sustained their activity across all three delay periods. This map contains 117 Delay 1 voxels, 17 Delay 2 voxels, and 14 Delay 3 voxels. Brain regions and MNI coordinates are identified in Table 4.

present study did not find strong evidence for multi-delay sustained activity in dlPFC or in SFS ROIs. Finally, Gray et al. (2003) found that PFC activity correlated with performance on trials of an n-back working memory task that featured a high level of proactive interference, but only in subjects who had been independently determined to be of high general fluid intelligence. In that task, the distraction was fundamentally different in that it required attention to be switched away from, and then back to, each memory representation. (e.g., in a 2-back task, attention is switched away from the 1-back item while the item on the screen is compared against the 2-back item.) In the present study, in contrast, attention was never drawn away from the representation of the target location because each "distracting" probe had to be compared against the target location. And so it may be that the task relevance of the distractors in this study actually facilitated the sustained retention of the target location.

In the present study, there was considerable variability at the single-subject level, with no single ROI showing distraction-spanning sustained activity in even one-half of the subjects in our sample. This may reflect true intersubject variability of behavioral strategies and/or of brain systems engaged by task performance (e.g., Feredoes and Postle, 2005; Miller et al., 2002). Alternatively, it may reflect the inherently conservative nature of the sequential masking procedure that we employed in the single-subject analyses. Evaluating these alternatives might be most effectively done by combining fMRI measures with a neurodisruptive method, such as repetitive transcranial magnetic stimulation. And because the results of this study were somewhat equivocal with respect to left dlPFC, a neurodisruptive approach will also be necessary in order to evaluate conclusively the contributions of this region to spatial working memory.

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