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Research report

The where and how of attention-based rehearsal in spatial working memory

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Abstract

Rehearsal in human spatial working memory is accomplished, in part, via covert shifts of spatial selective attention to memorized locations (''attention-based rehearsal''). We addressed two outstanding questions about attention-based rehearsal: the topography of the attention-based rehearsal effect, and the mechanism by which it operates. Using event-related fMRI and a procedure that randomized the presentation of trials with delay epochs that were either filled with a flickering checkerboard or unfilled, we localized the effect to extrastriate areas 18 and 19, and confirmed its absence in striate cortex. Delay-epoch activity in these extrastriate regions, as well as in superior parietal lobule and intraparietal sulcus, was also lateralized on unfilled trials, suggesting that attention-based rehearsal produces a baseline shift in areas representing the to-be-remembered location in space. No frontal regions (including frontal eye fields) demonstrated lateralized activity consistent with a role in attention-based rehearsal.

Theme: Neural basis of behavior
Topic: Cognition

Keywords: Attention-based rehearsal; Spatial working memory; fMRI

Awh et al. [2,3] have hypothesized that the rehearsal of stored spatial representations is necessary for successful performance on tests of spatial short-term and working memory, and that spatial rehearsal is accomplished by means of covert shifts of spatial selective attention to memorized locations (''attention-based rehearsal''). Empirical evidence for this mechanism has drawn on the fact that the allocation of attention to a region of space can result in the enhancement of neural signals representing the attended location and/or a decrement of neural signals representing unattended locations (e.g., Refs. [29,38,40]). (These neurophysiological effects are consistent with the well-known fact that orienting spatial selective attention to a particular location leads to a relative improvement of visual processing at the attended over unattended locations [48].) Thus, it has been demonstrated that fMRI [4] and ERP [27] responses to a task-irrelevant flickering checkerboard are enhanced in a hemisphere-specific manner when the checkerboard is presented while participants are remembering the location of stimuli presented in the corresponding visual field. These effects have been observed in posterior visual areas of the brain, perhaps excluding V1 [4]. Two ERP studies have confirmed that these attention-like modulations that are observed in spatial working memory tasks are comparable to those observed in analogous spatial attention tasks that lack any overt mnemonic demands [5,27].

Several additional neuroimaging reports have provided data consistent with the idea that spatial attention and spatial working memory are linked in important ways, by demonstrating considerable overlap between brain areas active during directed attention tasks and those active during spatial working memory tasks (e.g., Refs. [9,13,33,55]). These studies have implicated, in particular, a network of

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posterior parietal and superior frontal areas, including the frontal eye fields (FEF) in Brodmann's area 6 of the premotor cortex (PMC). It remains unresolved, however, whether the parietal and frontal areas implicated by these studies also implement attention-based rehearsal. One alternative to this possibility is that, whereas spatial attention and spatial working memory recruit partially overlapping networks in these parietal and frontal regions, they are supported by the operation of distinct mechanisms. (Such a situation would simply be another case of multiple cognitive functions being supported by the same brain areas [15–17].) A second alternative is that the anterior regions identified in studies of spatial attention and spatial working memory contribute to a working memory-related process that is different from attention-based rehearsal. By this scenario, whereas attention-based rehearsal would be implemented in parietal and extrastriate areas, a distinct spatial memory-supporting process (e.g., prospective motor coding [50]) would be implemented in frontal areas.

The present study was designed to address two categories of outstanding questions about the attention-based rehearsal model of spatial working memory: the topography of the attention-based rehearsal effect, and the mechanism by which it operates. To accomplish this, we sought to replicate the results of the previous fMRI study by Awh et al. [4] using a method and design that would permit us to surpass the inferential limits of this earlier study in important ways. First, it would assess delay-period activity with a method that would not be contaminated by variance in the fMRI signal attributable to stimulus presentation- or response-related portions of the trial (see Methods, fMRI data processing). (The blocked nature of the earlier study meant that a portion of the laterality effects that were observed were likely stimulus driven, and thus not related to the putative role of attention in rehearsal of spatial working memory.) Second, the whole-brain scanning used in the present study (see Methods, fMRI data acquisition) would permit localization of effects of interest to anatomically defined regions of the brain (see Methods, Regions of interest). (The earlier study had used a surface coil and an analysis method that did not permit precise neuroanatomical localization of effects of interest.) Third, our whole-brain scanning method would also permit assessment of whether the spatial attention mechanism may also operate in regions anterior to the posterior portion of the brain to which the earlier study was limited. Finally, the nature of the stimuli and the procedure differed between the present experiment and those employed by Awh et al. [4], and a replication would thereby also indicate that the attention-based rehearsal effect generalizes across different materials and methods. (Note that we did not need to incorporate a procedurally similar, but nonmnemonic, spatial attention condition that would permit testing the fundamental claim of the attention-based rehearsal model, because this had been done in previous studies [5,27].) The second and third points highlight how we would investigate the topography of attention-based rehearsal. An aspect of the fourth point—the inclusion of trials with unfilled delay epochs—would permit us to address a question about the mechanism underlying attention-based rehearsal and its control: Does attention-based rehearsal, like spatial selective attention, produce a "baseline shift" in activity in visual areas representing the attended location in space [30,35]? If so, we would expect to see elevated levels of activity in cortical areas representing the remembered location even on unfilled trials. (That is, the extrastriate areas that show enhanced responses to task-irrelevant visual stimuli presented in a memory field [4,5] would also show increased levels of activity (relative to nonmemorized locations) on trials requiring memory for the same location, but during which no task-irrelevant visual stimulation was presented.)

1. Methods

1.1. Participants

Nine neurologically healthy participants between the ages of 18 and 25 years were recruited from the University of Pennsylvania community. Each provided informed consent prior to participating.

1.2. Design and procedure

1.2.1. Visual stimulation scan

Prior to the memory task, participants watched passively as a bilateral flickering checkerboard was presented in a 16-s ON/16-s OFF blocked fashion during a 5-min 20-s scan. The checkerboard stimulus filled the area from $-45°$ below to $+45°$ above the horizontal meridian in both visual fields, except for a small circle centered on the fixation cross. The purpose of this scan was to identify visually responsive areas in a scan that was independent of the memory task.

1.2.2. Delayed-recognition task

Our 2×2 experimental design featured two factors, each with two levels: delay (filled, unfilled) and visual field (left, right). Each trial lasted 11.5 s, presenting sequentially fixation (2 s), target presentation (500 ms), delay epoch (7.5 s), and probe (1.5 s). An ITI of 14.5 s separated each trial. The initial fixation epoch was designed to ensure that participants were fixating centrally prior to the presentation of the target. The target stimulus was a bar ($0.5°$ of visual angle) that appeared either to the left or the right of fixation, centered on, orthogonal to, and at one of three distances along an invisible radius passing through the fixation cross and oriented at $0°$, $+30°$, or $-30°$ from horizontal. The delay epoch featured either the fixation cross alone (unfilled) or a flickering checkerboard stimulus identical to that used in the visual stimulation scan (filled). The probe, a vernier stimulus consisting of two perfectly aligned bars, each $0.5°$ in length, and separated by a gap the length of the

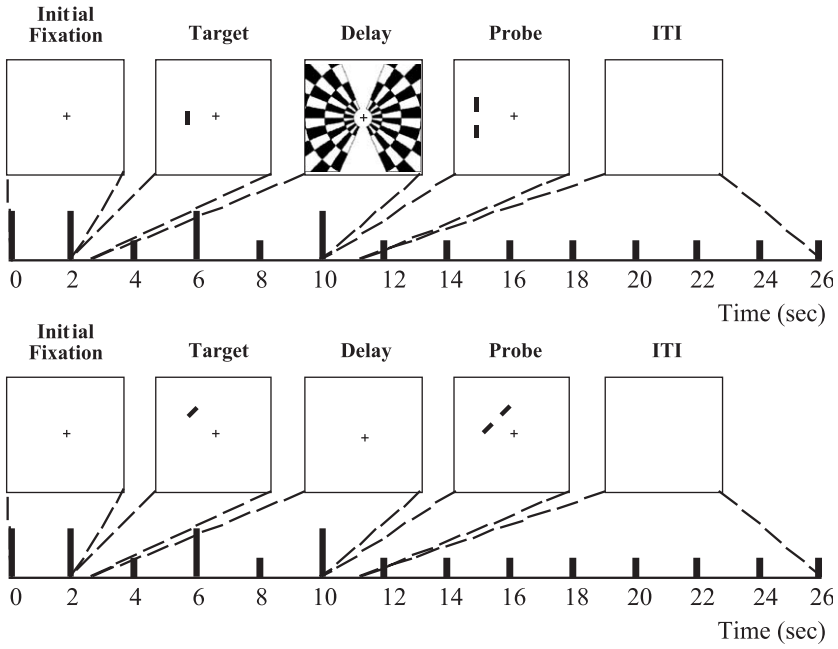


Fig. 1. Schematic illustration of filled (top) and unfilled (bottom) trials from the working memory task. For each condition, each square represents the initial fixation, target presentation, delay, and probe epochs of the task, respectively. Tall bars along the Time axes represent the positioning of the preconvolved covariates associated with each of these epochs.

target, was always centered on and oriented orthogonal to the same imaginary radius that anchored the target on that trial, and was closer to ($p = 0.5$) or further from ($p = 0.5$) fixation than had been the target (Fig. 1). Subjects indicated the relative eccentricity from fixation of the probe with respect to the target with a bimanual button press (''nearer'' = inner buttons; ''farther'' = outer buttons). (Note that the task employed by Awh et al. [4] was a match/nonmatch judgment.) Subjects were trained to fixate centrally through the entire length of each trial, and to relax their eyes during the ITI. Trials were administered in 8 blocks of 12 trials each, yielding a total of 96 trials, 24 of each type. Each block (corresponding to a scan) featured 3 trials drawn from each of the 4 cells of our design matrix, presented in random order.

1.3. fMRI data acquisition

Whole-brain images were acquired with a 1.5-T scanner equipped with a prototype fast gradient system for echo-planar imaging. High-resolution T1-weighted images (21 axial slices, $.9375 \times 0.9375 \times 5$ mm) were obtained in every participant, 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 [32,42] within a 64×64 matrix (21 axial slices, $3.75 \times 3.75 \times 5$ mm). Scans of the working memory task were preceded by two others: passive viewing of the flickering checkerboard stimulus (blocked presentation of 20-s ON/20-s OFF for 5 min 20 s), in order to identify visually responsive voxels for each subject; and 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 16 s in response to a brief change in shape of the fixation stimulus. A partial *F*-test associated with a Fourier basis covariate set [28] was used to evaluate the significance of task correlated activity in each voxel of primary somatosensory and motor cortical regions of interest [1]. An HRF estimate was extracted from the suprathreshold voxels of these ROIs by spatially averaging 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 [19], and trial averaging. The HRF characterizes the fMRI response resulting from a brief impulse of neural activity [7], and can vary markedly across participants [1]. The participant-specific HRFs were used to convolve independent variables entered into the modified general linear model (GLM [60]) that we used to analyze the data from the scans of the working memory task.[1] The eight scans of the working memory task each lasted 5 min 12 s.

[1] The HRF also varies in shape across brain regions within an individual participant [35,48]. However, recent work indicates that the magnitude of variability in the shape of the HRF is greater across individuals within a region than it is across regions within an individual [26]. Additionally, it indicates that employing a participant-specific HRF can improve the sensitivity and magnitude estimates of the least-squares solution of the GLM over comparable analyses that employ a generic HRF model (with or without its first derivative) in analyses of the data from all participants [26].

1.4. fMRI data processing

The fMRI time series data were filtered and adjusted as described previously [52]. The principle of the fMRI time series analysis was to model the fMRI signal changes evoked by each stimulus presentation epoch with covariates comprised of BOLD impulse response functions shifted along the timeline of the task to represent various trial epochs [52,64]. The least-squares solution of the GLM of the fMRI time series data yielded parameter estimates that were associated with each covariate of interest (Fig. 2). 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 [64]. Fig. 1 illustrates the positioning of epoch-representing covariates in our task, prior to convolution with the HRF. Note that the preconvolved "delay-epoch" covariate did not span the entire delay period, as would a 7.5 s-long boxcar covariate. Rather, it was a "stick" that sampled activity from the middle of the delay period. Although this approach made this delay-epoch covariate inherently conservative (in that it was not sensitive to activity from the entire delay period), it also produced a crucial feature of our design and analysis method (illustrated in Fig. 2): estimates of delay-period activity could not be contaminated by variance in the fMRI signal attributable to neural activity that occurred during the Target or Probe epochs.[2] Differences in fMRI signal (either between conditions or vs. baseline) were tested by computing *t*-statistics associated with linear combinations of parameter estimates associated with the covariates in question.

1.5. Regions of interest

Structurally defined regions of interest (ROI) corresponded to neuroanatomically defined regions of the brain as defined by Brodmann [8] and Talairach and Tournoux [57], with the exception of FEF. They were created for each subject by transforming ROIs that had been created on a representation of a brain corresponding to a standardized coordinate frame into coordinates corresponding to that subject's fMRI scan (effectively, a reverse normalization, this method is detailed in Ref. [51]). Structurally defined ROIs, restricted to the right or left hemisphere, corresponded to Brodmann areas (BA) 17, 18, 19, and 37, and to the portion of the inferior parietal lobule (IPL) corresponding to BA 40, the superior parietal lobule (SPL, corresponding to BA 7), the intraparietal sulcus (IPS),

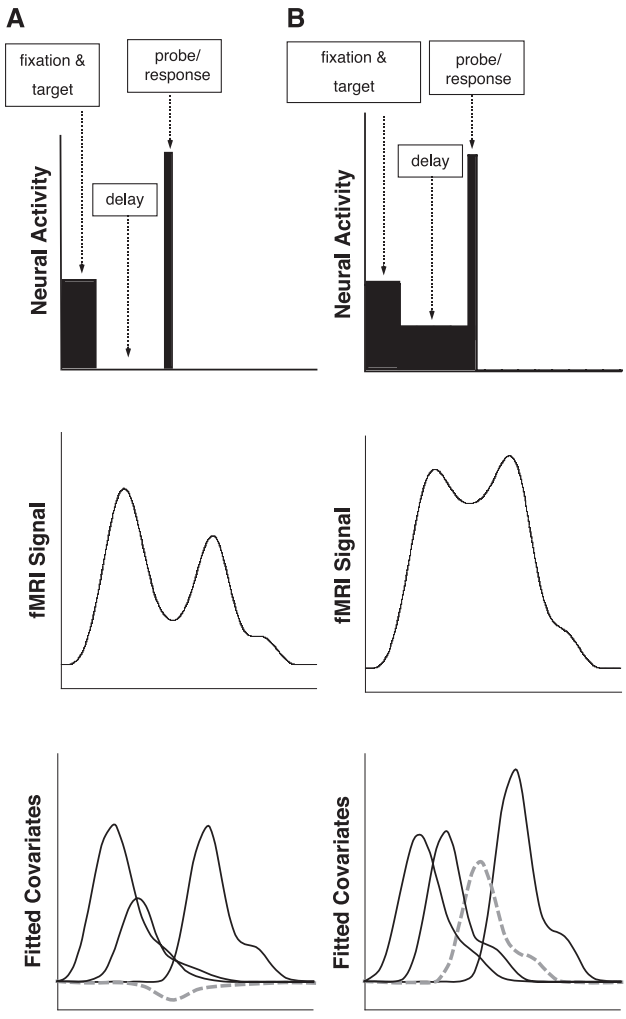


Fig. 2. Event-related fMRI data analysis implemented for the working memory task. Column (A) depicts a voxel exhibiting brief periods of simulated neural activity (top row) during the initial fixation, target presentation, and probe epochs of a trial, but with no increase above baseline of neural activity during the delay epoch. Such neural activity change would lead to a particular profile of fMRI signal change (second row), which we simulated by convolving the simulated neural activity depicted in the top row with an empirically derived mean HRF [63]. The model covariates (which have the same shape as the HRF), scaled by their resulting least-squares coefficients, are shown in the third row. The covariate modeling the delay epoch (dashed line) would make a negligible contribution to variance explanation in (A). (This demonstrates that, with this method, estimates of delay-epoch activity are not contaminated by variance in the fMRI signal that is attributable to trial epochs immediately preceding or following the delay epoch.) In contrast to (A), column (B) depicts a voxel in which there is an increase, relative to baseline, in simulated neural activity during the delay epoch. The covariate modeling the delay epoch would explain a larger amount of variance in the fMRI signal in (B) than in (A).

[2] Note that a delay period-spanning covariate with the preconvolved shape of a 7.5-s-long boxcar would not have this property, and thus it might, for example, be sensitive to variance in the fMRI signal attributable to neural activity that preceded the delay period, or was only present at the very beginning of the delay period but not sustained throughout. And what if, for example, participants in our study did not maintain spatial attention on the to-be-remembered location throughout the delay period, but rather were slow by several hundred milliseconds in moving their attention away from that location after the offset of the target (e.g., although the offset of the target is at time 2.5 s, attention actually lingered at this location until, say, 3 s, before shifting to another location)? It would be unlikely, in this scenario, that such sluggishness of the shift of attention away from the critical location would bias the estimates of the delay-epoch covariates. Rather, variance attributable to such "early delay period activity" would be explained by the target-epoch covariate (which is positioned at 2 s, much closer to this "early delay period" than the delay-epoch covariate, which is positioned at 6 s).

lateral PMC (a portion of BA 6), superior frontal cortex (SFC, corresponding to BA 8), dorsolateral PFC (DLPFC, corresponding to BAs 9 and 46), and ventrolateral PFC (VLPFC, corresponding to BAs 44, 45, and 47). FEF ROIs were drawn de novo on the structural scans of each participant. Details about the anatomical definition of each of the ROIs are presented in Table 1.

These structurally defined ROIs were used to localize voxels demonstrating either visual or mnemonic function. Thus, functionally defined ROIs were created by identifying the intersection of voxels within a structurally defined ROI with those demonstrating a particular function. ''Visual-evoked ROIs'' comprised voxels demonstrating a significant response to the blocked presentation of a bilateral flickering checkerboard. ''Delay-evoked ROIs'' comprised voxels demonstrating a significant level of activity during the delay epoch of unfilled trials. These voxels were identified with the contrast [$\text{Delay}_{\text{unfilled, RVF}} + \text{Delay}_{\text{unfilled, LVF}}$], thresholded at $\alpha = 0.05$, corrected at the bilateral structural ROI-wise level [52].

1.6. Hypothesis testing

We tested three hypotheses. Hypothesis tests were performed with two types of group analyses, ROI-based and normalized group average-based. The former represented the primary hypothesis-testing method, and it will be the focus of most of this section. In summary, ROI-based analyses consisted of first computing a laterality index from each functionally defined ROI of each participant's data, and then assessing the reliability of these results with paired t-tests, one for each functionally defined ROI. We used this approach because it would be sensitive to functionally significant activity within ROIs regardless of whether the foci of activity within a particular ROI overlapped topographically across participants, a constraint imposed by normalized group average-based analyses. (On the other hand, normalized group average-based analyses can be more sensitive to subtle subthreshold effects that would not be detected in the data of individual participants, but that is nonetheless reliable across a sample.) *The first hypothesis test* would be a replication of the previous fMRI study by Awh et al. [4]: On filled trials, we hypothesized that delay epoch checkerboard-evoked activity would be greater in the hemisphere contralateral to the visual field in which the target stimulus had been presented on that trial. We tested this hypothesis in visual-evoked ROIs with data from filled trials. To each of these functionally defined ROIs, we applied the contrast [$\text{Delay}_{\text{filled, RVF}} - \text{Delay}_{\text{filled, LVF}}$] to determine the differential effects of ipsi- vs. contralateral target stimulus presentation, and then generated a laterality index for each ROI by subtracting the result of the [$\text{Delay}_{\text{filled, RVF}} - \text{De-Delay}_{\text{filled, LVF}}$] contrast from the right hemisphere of that ROI from the result of the [$\text{Delay}_{\text{filled, RVF}} - \text{Delay}_{\text{filled, LVF}}$] contrast from the corresponding left hemisphere of that ROI. The attention-based rehearsal model predicted a numerically greater result of the [$\text{Delay}_{\text{filled, RVF}} - \text{Delay}_{\text{filled, LVF}}$] contrast from left hemisphere ROIs than from right hemisphere ROIs, and thus, a positive value of the laterality index in any given BA. Laterality index values of 0, in contrast, would indicate an absence of lateralized modulation of checkerboard-evoked activity by visual field of target presentation. Note that this procedure could only be applied to ROIs for which visual evoked activity occurred bilaterally.

The second hypothesis, that attention-based rehearsal produces a baseline shift in extrastriate regions representing the memory field, was tested by measuring activity during unfilled trials in visual evoked ROIs. In each ROI, we applied the contrast [$\text{Delay}_{\text{unfilled, RVF}} - \text{Delay}_{\text{unfilled, LVF}}$] to determine the differential effects of ipsi- vs. contralateral target stimulus presentation, and then generated a laterality index for each ROI by subtracting the result of the [$\text{Delay}_{\text{unfilled, RVF}} - \text{Delay}_{\text{unfilled, LVF}}$] contrast from the right hemisphere of that ROI from the result of the [$\text{Delay}_{\text{unfilled, RVF}} - \text{Delay}_{\text{unfilled, LVF}}$] contrast from the corresponding left hemisphere of that ROI. Lateralization of this delay-evoked activity would represent a baseline shift.

The third hypothesis test would assess evidence for lateralized delay-epoch activity in regions anterior to the visually responsive striate and extrastriate areas involved

Table 1
Anatomical definition of structural ROIs

ROI	Anatomical landmarks
BA 17	Calcarine sulcus
BA 18	Cuneus and lateral occipital cortex adjacent to BA 17
BA 19	Cuneus and lateral occipital cortex adjacent to the parietooccipital sulcus
BA 37	Posterior Middle Temporal Gyrus
IPL (BA 40)	Portion of IPL corresponding to the supramarginal gyrus (bounded inferiorly by the Superior Temporal Gyrus, posteriorly by the IPS, and anteriorly by the Inferior Postcentral Sulcus
FEF	The 6 mm of the SFS immediately anterior to the intersection of the SFS and the PCS, and the 6 mm of the rostral bank of the PCS immediately lateral to this intersection [31,36,44–46,56]
Lateral PMC (BA 6)	Cortex in both banks of the Precentral Sulcus and of the convexity immediately anterior to it, bounded superiorly by the FEF
SFC (BA 8)	Superior Frontal Gyrus and Superior Frontal Sulcus, bounded posteriorly by FEF
DLPFC (BAs 9 and 46)	Middle Frontal Gyrus
VLPFC (BAs 44, 45, and 47)	Inferior Frontal Gyrus

The following atlases were used to assist in developing these definitions and in identifying landmarks [14,18,37].

in the first hypothesis test: On unfilled trials, delay-epoch activity would also be greater in the hemisphere contralateral to the visual field in which the target stimulus had been presented on that trial. The rationale behind the third hypothesis test was that not all brain regions that have been implicated in spatial working memory function (e.g., the parietal and frontal ROIs) are likely to respond reliably to a flickering checkerboard stimulus. Thus, our third hypothesis test was applied to voxels demonstrating delay-evoked activity during unfilled trials with the contrast [$\text{Delay}_{\text{unfilled, RVF}} + \text{Delay}_{\text{unfilled, LVF}}$]. Such delay-epoch activity is assumed to incorporate activity associated with the retention (i.e., the storage) of representations of memoranda in working memory tasks such as our delayed-recognition task (e.g., Refs. [24,25,64]). This third hypothesis was tested in delay-evoked ROIs whose BAs did not contain visual-evoked ROIs, and it was tested on activity from unfilled trials. Other than these differences, the hypothesis test was implemented with the same procedure as that for visual-evoked ROIs. The third hypothesis was also tested with a normalized group average-based analysis, in which *t*-maps produced by the contrast [$\text{Delay}_{\text{unfilled, RVF}} - \text{Delay}_{\text{unfilled, LVF}}$] were generated from individual participant data, then smoothed (to 7 mm in each dimension), normalized to the MNI template, and entered into a second-level analysis model that treated participant as a random effect. Loci of maxima were identified by first converting their coordinates from MNI to Talairach, using the "mni2tal" Matlab routine of Matthew Brett (http://www.mrc-cbu.cam.ac.uk/Imaging/Common/mnispace.shtml), then entering these values into the Talairach Daemon. We confirmed the results of this procedure against the atlas of Talairach and Tournoux [57].

Note that this third hypothesis was not a direct test of the attention-based rehearsal model, because such tests require evidence of the modulation of visual processing by attention, and no visual stimulation was present during the delay epoch of unfilled trials. Thus, whereas evidence of lateralized differences of delay-evoked activity would be consistent with the attention-based rehearsal model (particularly if we also found evidence for a baseline shift in extrastriate regions), one could not rule out the possibility that these effects were not due to attention, but rather to enhancement of some other spatial memory mechanism.

This third hypothesis test would also address another important question about spatial working memory, one independent of that of attention-based rehearsal: Is spatial working memory-related activity in the human frontal cortex lateralized by visual field of the memorandum? Some evidence from the monkey [21,22] predicts that it is. To our knowledge, this question has not been addressed directly in human neuroimaging research, although some have proposed that regions of frontal cortex, including PFC, SFC, and possibly PMC are critical for the storage of spatial information during working memory tasks (e.g., Refs. [34,58]), whereas others suggest that working memory storage functions are supported in a domain-specific manner in posterior cortex, and that frontal cortical areas support the operation of stimulus domain-independent control functions (e.g., Refs. [43,47,49,53]). Evidence of lateralized modulation of delay-epoch activity in frontal cortex would be consistent with the view that domain-specific storage of spatial information is supported by frontal cortex.

2. Results

2.1. Behavior

Performance on the two trial types was nearly identical (mean percentage correct [S.E.]): filled, 82.5 [2.4]; unfilled, 82.2 [2.0].

2.2. Visual-evoked ROIs

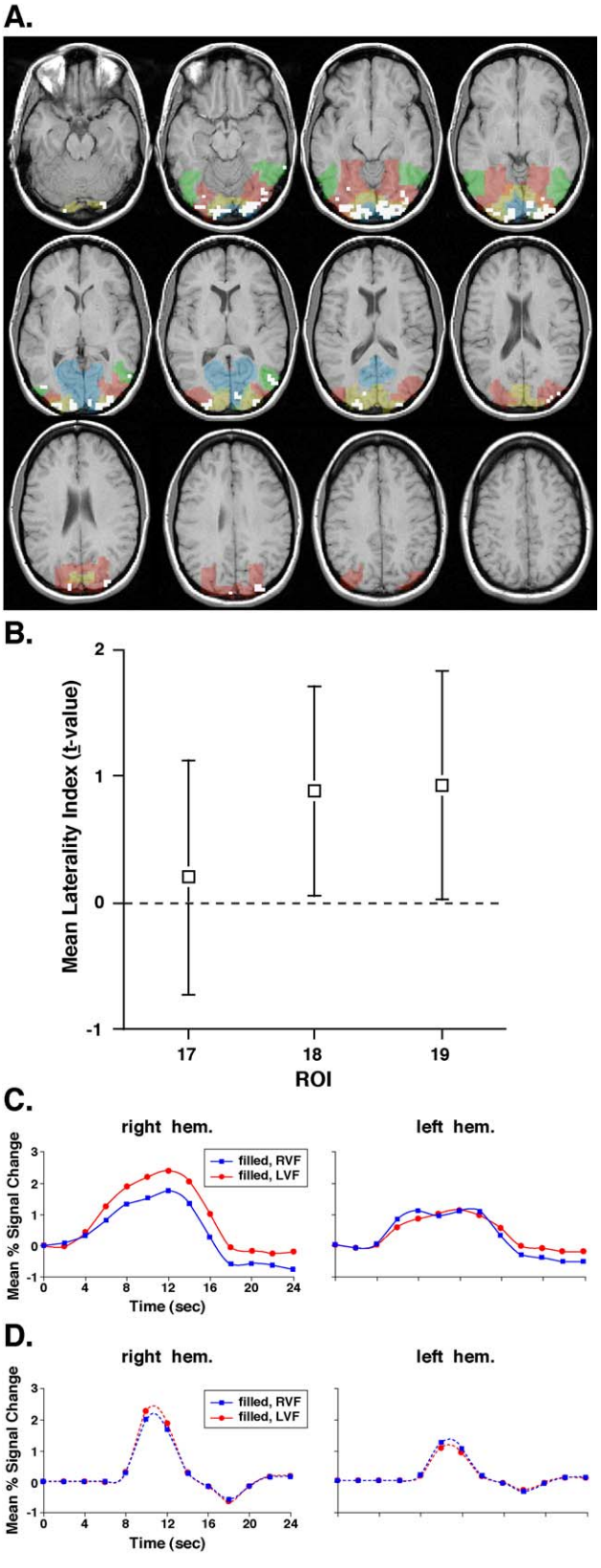
2.2.1. First hypothesis

Visual-evoked activity was observed bilaterally in eight participants in area 17 and in all nine participants in areas 18 and 19. It was observed in four participants or fewer in all remaining structural ROIs. Thus, we tested the attention-based rehearsal hypothesis in BAs 17, 18, and 19. Delay-epoch activity in filled trials was not reliably lateralized in BA 17 ($t(7) = 0.5$; n.s.), but it was in BAs 18 ($t(8) = 2.5$; $p < 0.05$) and 19 ($t(8) = 2.4$; $p < 0.05$) (Fig. 3).

2.2.2. Second hypothesis

Because we found an attention-based memory effect in BAs 18 and 19, we tested our second hypothesis—that attention-based rehearsal is supported by a baseline-shift mechanism—in the visual-evoked ROIs in these regions. Results indicated that delay-epoch activity in unfilled trials was reliably lateralized in both of these regions: BA 18 ($t(8) = 2.9$; $p < 0.05$) and BA 19 ($t(8) = 3.9$; $p < 0.005$) (Fig. 4). Indeed, the lateralization indices in both BAs were quantitatively larger in unfilled than in filled trials, an effect that was not reliable in BA 18 ($t(8) = 1.2$; n.s.), but that was in BA 19 ($t(8) = 2.9$; $p < 0.05$). One explanation for this difference could be that the dynamic range over which attention could have its effect was larger in unfilled than in filled trials, because neuronal activity might have been closer to saturation levels in filled than in unfilled trials. We assessed this possibility by measuring delay-evoked activity in the hemisphere ipsilateral to the visual field in which the target was presented, a measure that would index the magnitude of delay-evoked activity that was relatively unaffected by selective attention. Consistent with the disparity-of-dynamic-range interpretation, delay-evoked activity was significantly greater in filled than in unfilled trials in both hemispheres of

BA 18 (right: $t(8)=10.5$, $p<0.0001$; left: $t(8)=10.5$, $p<0.0001$) and BA 19 (right: $t(8)=8.9$, $p<0.0001$; left: $t(8)=9.9$, $p<0.0001$).



2.3. Delay-evoked activity

2.3.1. Normalized group-average data

To confirm the validity of our procedure and data, and to facilitate comparison of our results with those of other studies, we generated a group-average map of delay period activity, whose results are summarized in Fig. 5 and Table 2.

2.3.2. Third hypothesis

Because visual-evoked activity only occurred reliably in the three ROIs described in the previous section, we sought to test the laterality of delay-evoked activity on unfilled trials in ROIs corresponding to brain regions that have previously been implicated in spatial working memory performance: IPL, IPS, SPL, FEF, PMC, SFC, DLPFC, and VLPFC. Bilateral activity (identified with the contrast [$\text{Delay}_{\text{unfilled, RVF}} + \text{Delay}_{\text{unfilled, LVF}}$]) was identified in four participants in IPL, in nine in SPL, in seven in IPS and PMC, in eight in DLPFC, and in six in FEF, SFC and VLPFC. Thus, we tested the laterality hypothesis with ROI-based analyses in IPS, SPL, FEF, PMC, SFC, DLPFC, and VLPFC. Delay-epoch activity in unfilled trials was reliably lateralized in SPL ($t(8)=3.1$; $p<0.05$) and in IPS ($t(6)=3.9$; $p<0.01$), but not FEF ($t(5)=1.9$; n.s.), PMC ($t(6)=1.7$; n.s.), SFC ($t(5)=0.9$; n.s.), DLPFC $t(7)=-0.8$; n.s.), or VLPFC ($t(5)=1.7$; n.s.) (Fig. 4).

We also assessed the third hypothesis with a normalized group average-based analysis. This second group analysis served a confirmatory function in that it was not limited to our a priori selected ROIs, nor would it exclude the data from any participants, as did the ROI-based analyses for each ROI except SPL. The results of this random-effects analysis, thresholded at $p<0.001$ (uncorrected), did not detect any reliable effects in the a priori ROIs that had not also been detected in the ROI-based analyses. It also identified additional areas about which we had made no predictions. The results of this analysis are summarized in Table 3.

3. Discussion

3.1. Visual-evoked ROIs

Across our sample, voxels in three BAs—17, 18, and 19—responded reliably to the blocked presentation of a

Fig. 3. Results from visual-evoked ROIs. (A) illustrates the visual-evoked ROIs in a representative participant, displayed in the radiological convention. Structural ROIs are identified by translucent colors—BA 17 (blue), BA 18 (yellow), BA 19 (red), and BA 37 (green)—and are overlaid by visually responsive voxels, which appear white. (B) illustrates the group results (mean and 95% confidence interval) of the first hypothesis test (in visual-evoked ROIs), indicating that the laterality index was significantly different from 0 in BAs 18 and 19, but not in BA 17. (C) illustrates trial-averaged fMRI data from filled trials for the two hemispheres of the BA 19 visual-evoked ROI of the participant illustrated in (A). (D) illustrates quantitatively the delay effects (delay-epoch covariates scaled by their parameter estimates) estimated by the GLM from the data illustrated in (C).

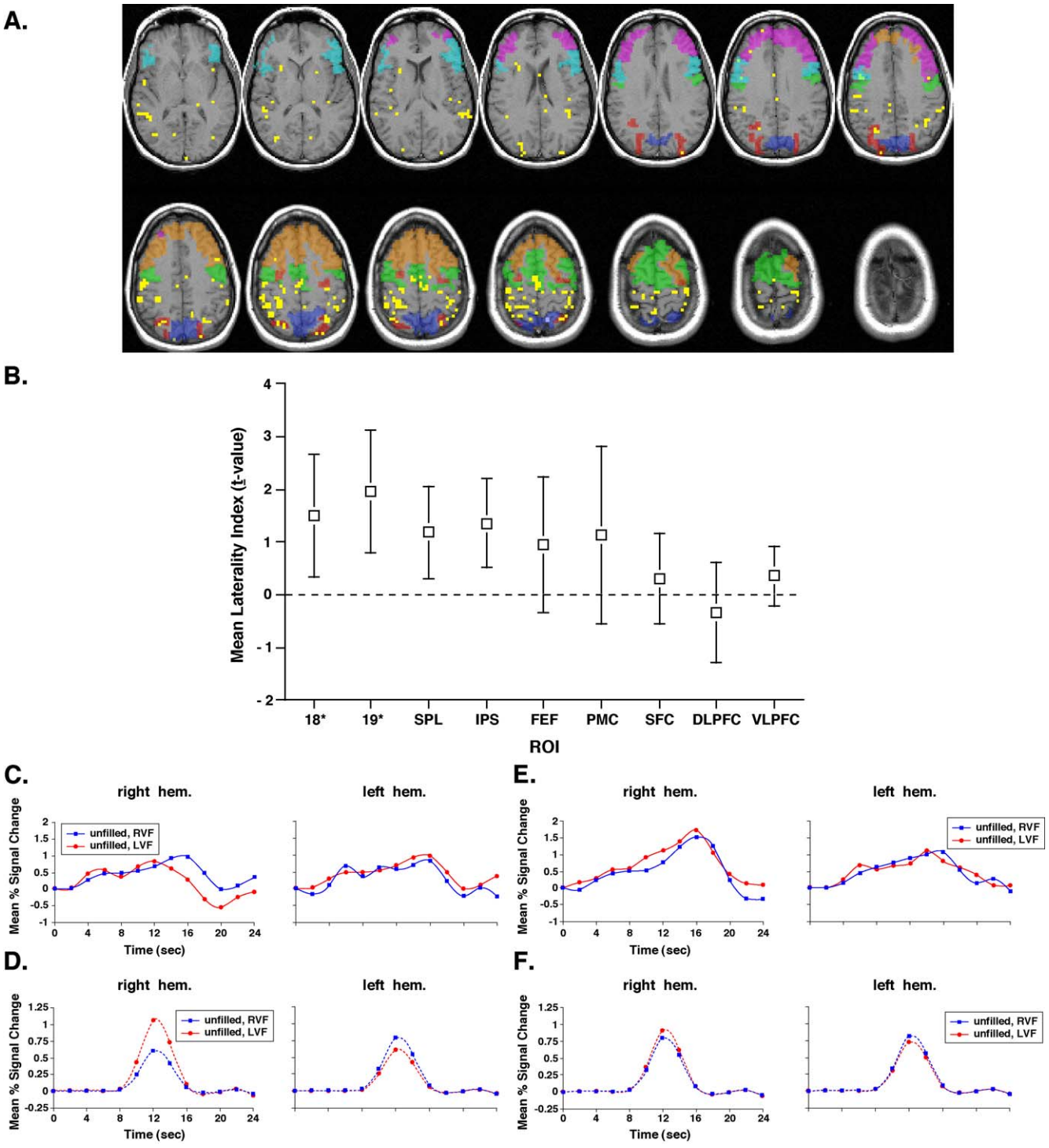


Fig. 4. Results from delay-evoked ROIs. (A) illustrates the delay-evoked ROIs in a representative participant, displayed in the radiological convention. Structural ROIs are identified by translucent colors—SPL (dark blue), IPS (red), PMC (green), FEF (red), SFC (orange), DLPFC (fuchsia), VLPFC (light blue)—are overlaid by delay responsive voxels, which appear yellow and orange. (B) illustrates the group results (mean and 95% confidence interval) of the third hypothesis test (in delay-evoked ROIs), indicating that the laterality index was significantly different from 0 in IPS and SPL, but not in any of the frontal cortical ROIs. Also plotted are the laterality indices for unfilled trial activity within the visual-evoked ROIs of BAs 18 and 19. That these laterality indices are significantly different from 0 is consistent with the baseline shift model of the attention-based rehearsal effect. (C) illustrates trial-averaged fMRI data from unfilled trials for the two hemispheres of the SPL delay-evoked ROI of the participant illustrated in (A). (D) illustrates quantitatively the delay effects (delay-epoch covariates scaled by their parameter estimates) estimated by the GLM from the data illustrated in (C). (E) illustrates trial-averaged fMRI data from unfilled trials for the two hemispheres of the IPS delay-evoked ROI of this same participant. (F) illustrates quantitatively the delay effects (delay-epoch covariates scaled by their parameter estimates) estimated by the GLM from the data illustrated in (E).

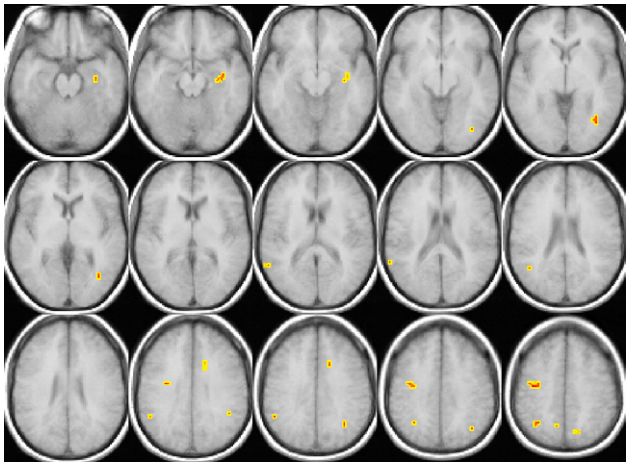


Fig. 5. Results from the normalized group-average contrast of [$Delay_{unfilled,\ RVF} + Delay_{unfilled,\ LVF}$], thresholded at $p < 0.001$ (uncorrected), displayed in the radiological convention. Locations of maxima are reported in Table 2.

flickering checkerboard stimulus. Within visually responsive voxels in these BAs, we found an attention-based rehearsal effect—significantly lateralized modulation of the checkerboard-evoked response on filled trials—in BAs 18 and 19. The effect in BA 17 was numerically small, and not statistically reliable. The present results are closely concordant with the fMRI results of Awh et al. [4]. For example, the 35-mm rostrocaudal extent of visual activity identified in the earlier study corresponds to the three BAs in which we identified visual-evoked ROIs. Further, Awh et al. [4] found that the lateralized spatial modulation effect increased across their coronal slices in a caudal-to-rostral manner, and they speculated that BA 17 does not participate in this type of spatial rehearsal. Our results confirm this speculation, and specify that the attention-based rehearsal effect is localizable to BAs 18 and 19.

That we did not observe an attention-based rehearsal effect in BA 17 is generally consistent with the fact that, in studies of spatial selective attention, modulations of visual evoked activity are more readily observed in BAs 18 and 19 than in BA 17 [10,11,30,39], perhaps scaling with the increasing size of receptive fields of neurons in progressively downstream regions of extrastriate cortex [30]. It may be that such effects only manifest themselves in BA 17 in tasks that involve difficult visual discriminations, such as in a crowded visual environment [39,41,54]. This was not the case in our study, nor in the previous studies of Awh et al. [4,5]. Thus, whether attention-based rehearsal effects in spatial working memory can be seen in striate cortex under the right conditions is a question that requires further study.

An additional question that was not resolved by our results in visual-evoked ROIs is whether the attention-based rehearsal effect can be observed downstream from the extrastriate regions identified by our visual-evoked ROI analysis, and by Awh and Jonides [4]. A limitation of our experimental method was that we could not address this question directly, because we were limited to testing this hypothesis in regions that responded to the flickering checkerboard. As we shall see in our discussion of the results from delay-evoked ROIs, below, however, our results do permit us to speculate about the source of control of attention-based rehearsal.

3.2. Delay-evoked ROIs

Delay-epoch activity was identified in many of the regions that are often implicated in studies of spatial working memory function, but that could not be included in the visually evoked ROI analysis: IPS, SPL, FEF, PMC, SFC, DLPFC, and VLPFC. In the delay-evoked ROIs corresponding to these regions, we found evidence for lateralized delay-epoch activity (on unfilled trials) only in IPS and SPL. One interpretation of these results is that PPC, like BAs 18 and 19, may also be a site whose activity is influenced by attention-based rehearsal, but that frontal areas are not. By this view, the source of the attention-based rehearsal effect would likely be in frontal cortex, perhaps FEF and/or DLPFC. A second

Table 2
Summary of activity identified in normalized group-average map of delay-period activity from unfilled trials (i.e., with the contrast [$Delay_{unfilled,\ RVF} + Delay_{unfilled,\ LVF}$])

Talairach coordinates (x, y, z)	BA	Brain region	Effect size (mean % signal change [SE]
−33.4 −15.3 −15	—	Hippocampus and medial temporal lobe	.62 [.11]
−37.1 −76.6 −2.5	18	Inferior occipital gyrus	.77 [.16]
−37.1 −61.7 3.1	37	Temporooccipital suclus	.50 [.13]
−44.6 −42.6 22.9	39	Inferior Parietal Lobule	1.35 [.27]
−18.8 15.8 26.8	24	Cingulate gyrus	.36 [.12]
−33.4 −53.2 26.8	39	Superior Temporal Gyrus	1.17 [.38]
−40.8 −60.3 30.7	39	Inferior Parietal Lobule	1.57 [.38]
−14.8 −63.8 34.3	7	Precuneus	.79 [.11]
63.1 −54.1 9.6	21	Middle Temporal Gyrus	.67 [.17]
40.8 −53.8 16.5	39	Superior Temporal Gyrus	.53 [.13]
48.2 −42.6 22.9	40	Inferior Parietal Lobule	.70 [.20]
40.8 −9.2 31.5	6	Precentral sulcus	1.13 [.27]
33.4 −56.6 33.9	39	Intraparietal Sulcus	1.30 [.24]
11.1 −60.0 37.5	7	Precuneus	.78 [.16]

These data correspond to Figure 5.

Table 3
Summary of activity identified in normalized group-average map of lateralized delay-period activity from unfilled trials (i.e., with the contrast [$Delay_{unfilled,\ RVF} - Delay_{unfilled,\ LVF}$])

$Delay_{unfilled,\ RVF} > Delay_{unfilled,\ LVF}$ Talairach coordinates (x, y, z)	BA	Brain region	Effect size (mean % signal change [SE])
−33.8 −47.8 −10.2	—	Cerebellum	.28 [.04]
7.5 −56.3 −7.5	—	Cerebellum	.41 [.08]
−37.1 −40 −1.1	27	Parahippocampal gyrus	.23 [.03]
−52 −40.1 −1.1	19	Middle Temporal Gyrus	.21 [.02]
3.7 −51.0 −.6	—	Cerebellum	.11 [.02]
−3.7 −10.7 3.5	—	Thalamus	.37 [.07]
−14.9 −46.7 12.7	30	Parahippocampal gyrus	.27 [.05]
7.4 −24.2 25.6	23	Posterior Cingulate gyrus	.48 [.16]
$Delay_{unfilled,\ LVF} > Delay_{unfilled,\ RVF}$			
3.7 −37.1 −13.9	—	Brainstem	−.22 [.03]
11.1 −7.7 −9.0	—	Brainstem	−.13 [.06]
18.5 −94.8 −1.6	17	Cuneus	−.45 [.08]
−11.1 −29.1 1.5	—	Thalamus	−.38 [0.07]
37.1 −35.8 12.2	41	Heschl's Gyrus	−.39 [.08]
29.7 −67.8 27.6	19	Middle Occipital Gyrus	−.26 [.05]
25.9 −42.2 29.7	39	Inferior Parietal Lobule	−.42 [.07]

interpretation is that the lateralized delay-period activity in PPC may not reflect an effect at the site of attention-based rehearsal, but rather its source. That is, this activity may have corresponded to the control of the sustained allocation of spatial attention to a memory field. A variant of this interpretation that is equally consistent with our data is that whereas the sustained, lateralized delay period activity that we observed in IPS may represent a source of sustained control of attention (e.g., Refs. [13,61]), the comparable activity in SPL may represent a site of the effects of this control. Of course, a comprehensive account of the functional organization of attention-based rehearsal-related activity in PPC almost certainly needs to be more complex than what we can infer directly from the delay-epoch activity in our study. For example, the results from previous studies of attention-related activity in PPC suggest the possibility that subregions of PPC may participate differentially in attention-based rehearsal. Taking these into account suggests that different areas of PPC may differentially support dissociable aspects of attentional control: lateralized shifts of attention, central control of shifts of attention, and sustained maintenance of attention.

These results from delay-evoked ROIs also suggest a dissociation between the involvement of PPC and frontal regions in attention-based rehearsal. In contrast to IPS and SPL, no frontal ROIs demonstrated lateralization of delay-period activity. Thus, our study failed to find evidence that any frontal areas are involved in lateralized components of attention-based rehearsal. The implications of these findings for models of the neural bases of working memory are considered in Section 3.4.

3.3. Relation to studies of spatial attention

Our results in delay-evoked ROIs reveal both commonalities and differences with previous studies of spatial attention. One commonality is sustained activity in IPS. Many studies of spatial attention have reported sustained activity in IPS on tasks that require sustained maintenance of attention (e.g., Refs. [6,12,13,59,62]), and in some cases this activity is lateralized [13]. An important difference, however, is that these studies typically also observe sustained activity in FEF that is undifferentiable from that in IPS. In our study, however, delay-period activity in IPS was lateralized according to the visual field to which attention was allocated, whereas in FEF it was not. Another difference between our study and studies of spatial attention is that the latter rarely find evidence for sustained activity in SPL. Our results, in contrast, revealed robust sustained activity in SPL during the delay period, consistent with the results from the vast majority of previous neuroimaging studies of spatial working memory. And as with IPS, the sustained delay-period activity in SPL was lateralized with respect to the memory field. These discrepancies may be due to methodological differences between our study and many studies of spatial attention. They may also mean, however, that attention-based rehearsal and spatial selective attention that is engaged in the absence of mnemonic demands may differ in some ways. Addressing this question will require a study that compares attention-based rehearsal and spatial selective attention directly, with comparable behavioral paradigms, within subject.

3.4. Relation to studies in the monkey

An additional feature of our results is their seeming inconsistency with previous findings in the monkey. For example, Funahashi et al. [22] found that a small unilateral lesion of DLPFC produced impaired performance on a test of spatial working memory for the location of targets presented in circumscribed regions of the contralateral

visual field, and that single units in this region demonstrated delay-period activity that was tuned for small memory fields in the contralateral visual field [21]. Our results, in contrast, provided no evidence of reliably lateralized delay-period activity anywhere in FC. In particular, delay period activity in DLPFC was slightly (although not reliably) biased in an ipsilateral manner. One way to reconcile this inconsistency, suggested by inspection of Fig. 4B, is to speculate that the extent of lateralization of representation of spatial memoranda decreases in a continuous manner as one moves rostrally from extrastriate cortex to PFC. By this view, the difference between PMC and SPL, for example, is one of degree, rather than an indication that qualitatively different working memory-related processes are mediated by these two regions. The difference between the present results and those from the monkey can then be reconciled with the idea that evolution has "pushed" caudally in humans many functions supported by PFC in the monkey [58]. An alternative approach is to consider whether the discrepant results might be attributable to methodological differences. For example, the studies of Funahashi et al. [20–23] employed variants of the spatial delayed-response task, which, in principle, can be solved by two different delay-epoch strategies: maintaining a (retrospective) sensory representation of the target stimulus; or maintaining a (prospective) motor representation of the response required to acquire the target stimulus. One cannot know, therefore, whether the impairments of performance associated with DLPFC damage [22] resulted from disruption of retrospective sensory memory or of prospective motor memory. (Note that the results of the eye-movement control tasks employed in this study do not discount the prospective motor memory alternative, because memory-guided delayed response may require different mechanisms than stimulus-guided response. Indeed, there is empirical evidence that this is so in humans [64].) The delayed-recognition task employed in the present study, in contrast, was most almost certainly performed by our participants with a sensory memory strategy. The discrepancy between the present results and those reported in the monkey, therefore, may be explained by this fundamental difference between the behavioral strategies afforded by the delayed-recognition vs. the delayed-response tasks.

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