

Functional connectivity during working memory maintenance

ADAM GAZZALEY, JESSE RISSMAN, and MARK D'ESPOSITO
University of California, Berkeley, California

Neurophysiological experiments with monkeys have demonstrated that working memory (WM) is associated with persistent neural activity in multiple brain regions, such as the prefrontal cortex (PFC), the parietal cortex, and posterior unimodal association areas. WM maintenance is believed to require the coordination of these brain regions, which do not function in isolation but, rather, interact to maintain visual percepts that are no longer present in the environment. However, single-unit physiology studies and traditional univariate analyses of functional brain imaging data cannot evaluate interactions between distant brain regions, and so evidence of regional integration during WM maintenance is largely indirect. In this study, we utilized a recently developed multivariate analysis method that allows us to explore functional connectivity between brain regions during the distinct stages of a delayed face recognition task. To characterize the neural network mediating the on-line maintenance of faces, the fusiform face area (FFA) was defined as a seed and was then used to generate whole-brain correlation maps. A random effects analysis of the correlation data revealed a network of brain regions exhibiting significant correlations with the FFA seed during the WM delay period. This maintenance network included the dorsolateral and ventrolateral PFC, the premotor cortex, the intraparietal sulcus, the caudate nucleus, the thalamus, the hippocampus, and occipitotemporal regions. These findings support the notion that the coordinated functional interaction between nodes of a widely distributed network underlies the active maintenance of a perceptual representation.

Working memory (WM) is a theoretical construct that encompasses the abilities to maintain and manipulate information that is no longer accessible in the environment to guide subsequent behavior; it involves the contribution of multiple subcomponent processes (Baddeley, 1986). Experimental paradigms directed at understanding the neural mechanisms of WM maintenance are most frequently delay tasks (e.g., delayed response, delayed recognition, delayed alternation, and delayed match-to-sample tasks), since they are designed to isolate WM component processes. In a typical delayed recognition trial, the subject, either an experimental animal or a human subject, is first required to remember a stimulus presented during a *cue* period and then to maintain this information for a brief *delay* interval when the stimulus is absent. Lastly, the subject responds to a *probe* stimulus to determine whether the information was successfully retained. Thus, the cognitive stages are temporally segregated and can be investigated in relative isolation by recording during distinct stages with microelectrodes

in animals and event-related functional magnetic resonance imaging (fMRI) in human subjects. Brain regions exhibiting persistent activity above resting baseline during the delay period are often interpreted as being involved in WM maintenance processes.

The first neurons discovered with persistent activity during the delay period were found in the monkey prefrontal cortex (PFC) using single-unit neuron recording techniques (Fuster & Alexander, 1971; Kubota & Niki, 1971). Since then, physiological studies in nonhuman primates have revealed active delay neurons in a large number of brain regions, including the dorsolateral and ventrolateral PFC (Funahashi, Bruce, & Goldman-Rakic, 1989; Wilson, O'Scalaidhe, & Goldman-Rakic, 1993), the intraparietal sulcus (IPS; Chafee & Goldman-Rakic, 1998), posterior perceptual areas (Fuster, 1990; Miller, Li, & Desimone, 1991), and subcortical structures, such as the caudate (Niki, Sakai, & Kubota, 1972), the hippocampus (T. Watanabe & Niki, 1985), and the thalamus (Fuster & Alexander, 1973; Kubota, Niki, & Goto, 1972). Neuroimaging studies in humans have revealed that this same collection of regions displays significantly increased blood flow during delay tasks, consistent with the interpretation that these regions are involved in cognitive processes occurring during the delay period (Courtney, Ungerleider, Keil, & Haxby, 1997; D'Esposito, Postle, & Rypma, 2000; Jha & McCarthy, 2000; Postle, Druzgal, & D'Esposito, 2003; Ranganath & D'Esposito, 2001). However, the specific roles of these regions remains a matter of continued debate, since

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most delay tasks, although effectively segregating WM processes into stages, do not take into account the multiple processes that are occurring concurrently during the delay period. These processes include information maintenance, suppression of distraction, motor response preparation, mental timing, expectancy, monitoring of internal and external states, and preservation of alertness. By varying experimental design (e.g., parametric memory load variation; Druzgal & D'Esposito, 2001a; Jha & McCarthy, 2000), attempts have been made to associate identified brain regions with different processes occurring during the delay. However, this approach has proven difficult and has yielded conflicting results, since most experimental manipulations affect multiple cognitive components.

Rather than attempting to assign a unique role to different brain regions, investigators have frequently described identified regions as being elements of a *neural network*. It is important to recognize that this is often a loose usage of the term *network*, which is more formally defined as a system of interconnected components (*Oxford English Dictionary*, 2003), and implies the presence of functional interactions between these regions that enable task performance. The use of this term is driven by the widespread belief that brain regions do not operate in isolation but, rather, are functionally interconnected nodes in widely distributed networks that subservise neural processes via their integrated influence (Fuster, 1995, 1997; Goldman-Rakic, 1995). Given the large number of anatomical studies that have characterized extensive reciprocal connections between cortical and subcortical brain regions (for a review, see Goldman-Rakic, 1988), it is often assumed that identified regions are functionally interacting. However, neither single neuron recordings nor standard univariate analyses of fMRI data, in which each brain voxel is analyzed independently of all others, reveal more than isolated activity within these regions. Thus, most assertions that regions active during the delay period are nodes of a network subserving information maintenance are based on indirect evidence. Regions identified by these techniques may, in fact, be interacting in any number of different networks supporting concurrent cognitive processes.

The formal characterization of neural networks is essential for a comprehensive understanding of WM and a more accurate assessment of the role of identified brain regions in different cognitive processes. Throughout her career, Patricia Goldman-Rakic adopted an impressive multidisciplinary approach, incorporating anatomical, physiological, and neurochemical methodologies to characterize WM. This approach afforded her a unique perspective on the neural basis of WM processes and an appreciation for neural networks, highlighted in an insightful review entitled "Topography of Cognition: Parallel Distributed Networks in Primate Association Cortex" (Goldman-Rakic, 1988, p. 152). She noted that "the picture that emerges from the new anatomy is that of a

highly integrated but distributed machinery whose resources are allocated to several basic parallel functional systems that bridge all major subdivisions of the cerebrum." She summarizes with the statement that

if subdivisions of limbic, motor, sensory, and associative cortex exist in developmentally linked and functionally unified networks, as the anatomical, physiological, and behavioral evidence reviewed here suggests, it may in the future be more useful to study the cortex in terms of information processing functions and systems rather than traditional but artificially segregated sensory, motor, or limbic components and individual neurons within only one of these components. (p. 153)

Since then, there have been several efforts to use electrophysiological techniques with nonhuman primates to investigate regional connectivity during WM tasks. In an approach pioneered by Goldman-Rakic and colleagues, simultaneous recordings from multiple closely spaced neurons, coupled with cross-correlation analysis, have been used to explore neuronal interactions within PFC circuits during the delay period (Constantinidis, Franowicz, & Goldman-Rakic, 2001a; Constantinidis & Goldman-Rakic, 2002). Unfortunately, these techniques are limited to local interactions and do not address functional connectivity between widely distributed regions. Goldman-Rakic recognized these limitations and the importance of characterizing long-range interactions in WM tasks, stating that "it is widely appreciated that the neural system providing this capacity cannot reside wholly within prefrontal cortex but extends beyond it to involve and in fact require interactions with other cortical areas" (Chafee & Goldman-Rakic, 1998, p. 2919). She contributed to this pursuit empirically by revealing strikingly similar patterns of activity within the prefrontal and the parietal cortices during a spatial WM task (Chafee & Goldman-Rakic, 1998), thus suggesting functional integration between these regions for task performance. To more explicitly explore distant interactions during delay tasks, two studies have combined single-cell recordings with experimentally induced lesions in monkeys (i.e., cortical cooling [Fuster, Bauer, & Jervey, 1985] and colossal transection [Tomita, Ohbayashi, Nakahara, Hasegawa, & Miyashita, 1999]) to reveal a mutual influence between the prefrontal cortex and the inferior temporal cortex likely mediated by cortico-cortical connections. Aside from such lesion studies and matching activity patterns, microelectrode studies in experimental animals have been limited in their ability to generate conclusions regarding distant regional interactions.

Recently, in a course parallel to the approach described above with experimental animals, investigators have begun to investigate regional interactions, employing electrophysiological techniques with human subjects. Intracranial recordings from electrodes spaced several centimeters apart in the visual association cortex (VAC) revealed synchronized oscillatory activity during the rehearsal of a stimulus over a delay period (Tallon-

Baudry, Bertrand, & Fischer, 2001). To investigate interactions between distant cortical regions, event-related potentials (ERPs) were recorded during visual discrimination (Barcelo, Suwazono, & Knight, 2000) and delay tasks (Chao & Knight, 1998) in patients with prefrontal strokes, to reveal a dependency of sensory processing in the posterior cortex on an intact PFC. This technique, although supplying critical temporal information regarding distant regional interactions, is limited in its ability to reveal detailed anatomical information.

Functional neuroimaging, however, is ideally and uniquely suited to explore networks, since it simultaneously records correlates of neural activity throughout the entire functioning brain with high spatial resolution. Despite this, almost all imaging studies have utilized univariate analysis, permitting only independent assessments of activity within each brain region, or voxel, in isolation from all others. In response to this limitation in assessing regional interactions with univariate data, multivariate approaches have been developed to analyze neuroimaging data (Friston, Frith, Liddle, & Frackowiak, 1993; McIntosh, 1998). This was originally described for positron emission tomography (PET) but has now been successfully applied to assess functional connectivity in fMRI studies of learning (Buchel, Coull, & Friston, 1999; Toni, Rowe, Stephan, & Passingham, 2002), attention (Friston & Buchel, 2000; Rowe, Friston, Frackowiak, & Passingham, 2002), and long-term memory (Maguire, Mummery, & Buchel, 2000). However, the only studies directed at characterizing regional interactions in WM have used either PET (McIntosh, Grady, Haxby, Ungerleider, & Horwitz, 1996) or block-designed fMRI with the *n*-back task (Honey et al., 2002), neither of which permits the characterization of interactions associated specifically with WM maintenance.

Unlike PET and block-designed fMRI experiments, event-related fMRI allows the selective probing of activity during the delay period of delayed recognition tasks (Zarahn, Aguirre, & D'Esposito, 1997b) and is thus an ideal technique for exploring regional interactions associated with information maintenance. However, a serious limitation in using current multivariate techniques to probe delay period connectivity with event-related fMRI designs is difficulty in generating delay period connectivity data that is uncontaminated by interactions occurring during the immediately preceding cue period or the ensuing probe period. To address this limitation, we recently developed a new multivariate method, designed specifically to characterize functional connectivity in an event-related fMRI data set and measure interregional correlations during the individual stages of a multistage cognitive task (Rissman, Gazzaley, & D'Esposito, 2004). The method, beta series correlation analysis, employs a standard general linear model (GLM) approach, as do most univariate analyses for estimating stage-specific activity (Friston et al., 1995), but adapts the model so that distinct parameter estimates are com-

puted for each trial and then used as the dependent data in a correlation analysis. Another important aspect of the technique is the use of a *seed* region to explore the network correlated with a selected region and, thus, associated with a particular cognitive process. We have recently validated this method as a suitable measure of functional connectivity (Rissman et al., 2004).

Our aim here was to characterize the network of brain regions associated with the maintenance of a representation of a visual stimulus over a short delay interval. To accomplish this, we reanalyzed two previously published event-related fMRI data sets for which similar delayed recognition paradigms were employed with different groups of subjects and a functionally defined region of the VAC was used as the exploratory seed. Since both tasks required the maintenance of face stimuli, the fusiform face area (FFA), a VAC region that is selective for viewing faces (Kanwisher, McDermott, & Chun, 1997; Puce, Allison, Gore, & McCarthy, 1995), was used as the seed. By pooling the correlation data from these two data sets into a single group-level analysis, we identified the network of brain regions that are most consistently correlated with the FFA seed during the delay period and, hence, associated with the active maintenance of the represented stimulus.

METHOD

Overview

The two data sets used in the present analysis have been previously analyzed with univariate methods, and the results of these analyses have been published elsewhere (Data Set 1, Ranganath & D'Esposito, 2001, and Ranganath, Johnson, & D'Esposito, 2003; Data Set 2, Druzgal & D'Esposito, 2001b, 2003, and Landau, Schumacher, Garavan, Druzgal, & D'Esposito, 2004). These two data sets were acquired on the same MRI scanner with the same scanning parameters and differ only in the specific nature of the face WM task employed and the individual subjects who participated. Despite differences in the cue stage, a common element across the two experiments was the requirement to maintain a representation of a face over a short delay interval and then assess whether the remembered face matched a probe face. The data collection methods and behavioral task designs will be summarized below.

To characterize the network associated with maintaining a representation of a visual stimulus in mind—specifically, the representation of a face—seven-voxel seeds in the right and left fusiform gyri of each subject (FFA) were isolated using an independent functional localizer task. These seeds were then used in a beta series correlation analysis to evaluate the network of brain regions correlating with the FFA during each stage of the delayed recognition task. Individual subject data from the two experiments were combined into a single group-level random effects analysis to identify the components of the WM maintenance network that were most consistent across the two data sets.

Subjects and Experimental Tasks

Eight right-handed subjects were scanned in Data Set 1. The subjects performed three runs of 18 delayed recognition trials, for a total of 54 trials. On each trial, the subjects were presented with a single grayscale face stimulus for a duration of 1 sec, followed by a fixation cross for 7 sec, followed by a probe face for 1 sec. The subjects were instructed to pay careful attention to the first face in

each trial and to maintain a mental image of that face throughout the delay period. When the probe face appeared, the subjects made a keypress indicating whether or not it matched the first face. Each trial was followed by a 13-sec intertrial interval.

Ten right-handed subjects were scanned in Data Set 2. The subjects performed eight runs of 12 delayed recognition trials, for a total of 96 trials. At the start of each trial, the subjects viewed four serially presented gray-scale images, which were a combination of intact and scrambled faces. Each image was displayed for 1 sec, and the subjects were instructed to remember all of the intact faces. On any given trial, from one to four of the stimuli were intact faces, and the remainder (if any) were scrambled faces. After the four stimuli had been presented, a fixation cross appeared for an 8-sec delay period. Finally, a probe face appeared for 2 sec, and the subjects made a keypress indicating whether the probe face matched any of the previously presented face stimuli. To complement the data from Data Set 1, only the data from trials in which a single intact face was viewed during the cue period were used in the subsequent analysis.

Both data sets also included a visuomotor response task in order to empirically derive a hemodynamic response function (HRF) from the sensorimotor cortex (Aguirre, Zarahn, & D'Esposito, 1998) and a *localizer* task in which the subjects passively viewed blocks of face and object stimuli to identify face-sensitive regions of the fusiform cortex (FFA) (Kanwisher et al., 1997). For one of the subjects in Data Set 2, suitable FFA seeds could not be defined, and that subject's data were excluded from all the analyses.

fMRI Acquisition and Processing

All functional images were acquired on a 1.5-T General Electric scanner with a gradient-echo EPI sequence (TR = 2,000 msec, TE = 50 msec, matrix size = 64×64 , FOV = 24 cm²). Each functional volume consisted of 21 contiguous 5-mm-thick axial slices. The fMRI data processing included sinc interpolation in time to correct for between-slice timing differences in image acquisition, motion correction using a six-parameter, rigid-body transformation algorithm (Friston et al., 1995), normalization of the time series of each voxel by its mean signal value, and spatial smoothing with an 8-mm FWHM Gaussian kernel.

Univariate Analysis

The two data sets were analyzed separately. For both data sets, BOLD responses during the cue, delay, and probe stages of the task were modeled as brief impulses of neural activity convolved with an HRF estimate obtained by averaging the empirically derived HRFs of the 13 subjects from these two data sets for whom a suitable HRF function could be obtained. To minimize collinearity between temporally adjacent covariates, the delay period was not modeled as a boxcar function beginning immediately after the offset of the cue stimulus and extending until the onset of the probe stimulus. Rather, care was taken to ensure that the onsets of temporally adjacent covariates were spaced at least 4 sec apart (Zarahn, Aguirre, & D'Esposito, 1997a). This approach minimizes the contamination of the delay period covariate by residual cue period activity and has been used to successfully model delay period activity in numerous published studies (Barde & Thompson-Schill, 2002; Curtis, Rao, & D'Esposito, 2004; Druzgal & D'Esposito, 2003; Pessoa, Gutierrez, Bandetini, & Ungerleider, 2002; Postle, Zarahn, & D'Esposito, 2000; Ranganath, Cohen, Dam, & D'Esposito, 2004). For Data Set 1, the cue, delay, and probe periods were modeled with HRFs positioned at the start of the trial, 4 sec into the trial, and 8 sec into the trial, respectively. For Data Set 2, since the cue period entailed 4 sec of visual stimulation, the cue period was modeled as the sum of two HRF functions, the first placed at the start of the trial and the second placed 2 sec into the trial. Because of the slightly longer delay period in Data Set 2, the delay period was also modeled as the sum of two HRFs, the first positioned 6 sec into the trial and the

second positioned 8 sec into the trial. The probe period was modeled with an HRF positioned 12 sec into the trial.

For each data set independently, covariates of interest were entered into the GLM for analysis with VoxBo (<http://www.voxbo.org>). The model included a separate set of covariates to model the cue, delay, and probe stages of those trials for which the subject responded incorrectly, and these data were excluded from subsequent analyses. The GLM also included covariates of no interest in order to model the effects of shifting signal levels across runs. For both data sets, a low-pass filter was used to attenuate frequencies above 0.25 Hz. A high-pass filter removed frequencies below 0.01 Hz in Data Set 1 and 0.02 Hz in Data Set 2 (these filters correspond to those employed by Ranganath & D'Esposito, 2001, and Druzgal & D'Esposito, 2003, in their respective analyses of these data sets). The GLM also incorporated an empirically derived estimate of the intrinsic temporal autocorrelation (Zarahn et al., 1997b).

All individual subject activation maps were spatially normalized into standard MNI atlas space, using routines from SPM2. Group-level random effects analyses were conducted on the data from all 17 subjects, pooled across the two data sets. We performed *t* tests separately for the cue, delay, and probe stages of the task to test whether the mean of the individual subjects' parameter estimates at each voxel was reliably greater than zero. Voxels were deemed significant if they surpassed a corrected threshold of $p < .05$. Correction for multiple comparisons was implemented using Gaussian random field theory (Friston, Worsley, Frackowiak, Mazziotta, & Evans, 1994) by applying a conservative voxel-level threshold of $p < .000001$, combined with a minimally restrictive cluster extent threshold of two contiguous voxels.

Beta Series Correlation Analysis

The seven contiguous voxels in each subject's right and left fusiform gyrus that exhibited the strongest response preference to faces versus objects in the localizer task (as assessed by a *t* test with no threshold requirement) were defined as that subject's right FFA and left FFA, respectively (Kanwisher et al., 1997) and were used as seeds in the subsequent correlation analyses. Our analyses focused primarily on the correlation data obtained using the right FFA seeds (Figure 1). Stage-specific seed correlation maps were derived

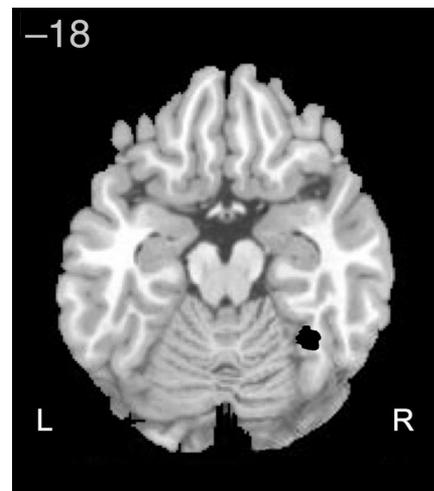


Figure 1. Location of the right FFA seed. Area in black designates the overlap of the 7-voxel right FFA seed from a minimum of 10 subjects when spatially normalized to the MNI template (slice $z = -18$).

separately for the right and the left FFA seeds, using the procedure described by Rissman et al. (2004).

For each data set independently, a new GLM design matrix was constructed in which the temporal arrangement of the covariates was identical to that used in the univariate analysis outlined above. The principal difference in this GLM was that the cue, delay, and probe stages of each individual trial were coded with a unique covariate. This resulted in a total of 162 covariates of interest being entered into the GLM for Data Set 1 and 288 covariates of interest for Data Set 2. The same covariates of no interest and band-pass filters as those used in the univariate analysis were applied here. The resulting parameter estimates, or *beta values*, were sorted according to the stage from which they were derived to form a *beta series* for each stage, reflecting the estimated activity of each voxel in each of the experimental trials that the subject performed correctly. Stage-specific whole-brain correlation maps were obtained by calculating the correlation of the FFA seed's beta series (averaged across the seven seed voxels) with that of all the brain voxels. This was done separately for each of the task stages. For Data Set 2, separate beta series and, hence, separate correlation maps were derived for each of the four WM loads, in addition to being subdivided by stage.

To allow statistical conclusions to be made on the basis of the correlation magnitudes, we applied an arc-hyperbolic tangent transform (Fisher, 1921) to the correlation coefficients of all the brain voxels. Since the correlation coefficient is inherently restricted to

range from -1 to $+1$, this transformation serves to make its null hypothesis sampling distribution approach that of the normal distribution. The transformed correlation coefficients were then divided by their known standard deviation ($1/\sqrt{N-3}$, where N is the number of data points used to compute the correlation coefficient) to yield z scores.

To construct group correlation maps, the z -transformed correlation maps of the individual subjects were spatially normalized into standard MNI atlas space, using routines from SPM2. The data from all 17 subjects were pooled, and group-level random effects t tests were then conducted separately for the cue, delay, and probe stages of the task to identify voxels for which the mean of the individual subjects' transformed correlation coefficients was reliably greater than zero. Since WM load was varied in Data Set 2, but not in Data Set 1, only the data from those trials in which a single intact face appeared were included in the pooled group analysis. In this way, the differences in the stimulation parameters and memory demands between the two data sets were minimized. Voxels were deemed significant if they surpassed a corrected threshold of $p < .05$. Correction for multiple comparisons was implemented in the same fashion as that described above for the univariate group analyses.

For the purposes of a control correlation analysis using a non-cortical seed, we also defined a 7-voxel seed in the white matter of each subject (chosen in a consistent left-hemisphere location in the first axial slice superior to the ventricles). Group-level white mat-

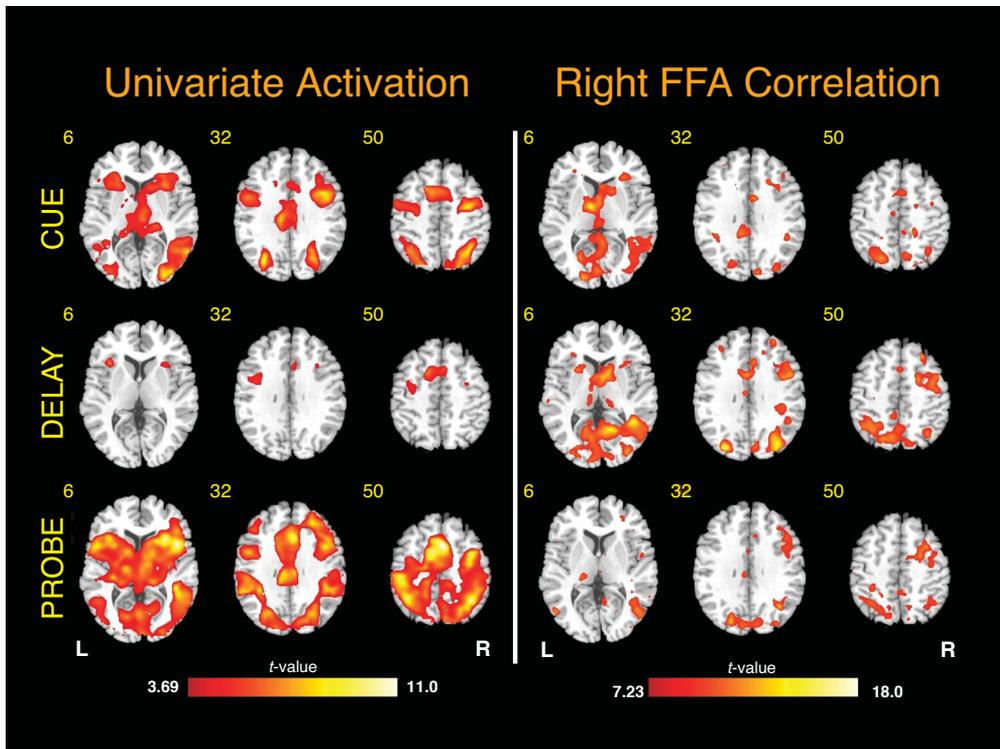


Figure 2. Group-level analysis of the univariate and right fusiform face area (FFA) seed correlation data ($N = 17$) during each stage of the delayed recognition task. The univariate activation maps are displayed at the relatively liberal threshold of $p < .001$ (uncorrected), to illustrate that although some lateral and medial frontal lobe regions are activated during the delay period, these activations are considerably less robust and extensive than those seen in the cue and probe stages. The right FFA seed correlation maps are displayed at a more stringent threshold of $p < .05$ (corrected) and reveal robust correlations throughout all three task stages. Activations from selected slices are shown overlaid on the MNI template brain. The z -coordinates of each slice are shown in yellow in the upper left-hand corner. The color scale indicates the magnitude of the t values.

ter correlation maps were generated in the same manner as the group-level FFA correlation maps.

Region-of-Interest Analyses

To assess the relative contribution of specific cortical regions to the individual processing stages of the task, we quantified the number of voxels surviving our thresholding criteria in a set of six regions of interest (ROIs) taken from the Automated Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002). These ROIs included the right and left middle frontal gyri (MFG), the inferior frontal gyri (IFG), and the fusiform gyri.

RESULTS

Univariate Data

A traditional univariate analysis was performed to compare the overall pattern of activity with the network data obtained from the beta series correlation analysis. At a conservative corrected threshold (see the Method section), univariate analysis revealed significant regions of activation during the cue and probe stages in multiple cortical regions (the MFG, the IFG, the insular cortex, the premotor cortex, the IPS, the ventral temporal cortex, and occipital regions), as well as in the thalamus, but no significant activity was identified in any brain region during the delay stage (data not shown). Given the frequent report of delay period activations in the fMRI literature, we reevaluated the univariate data with a more liberal threshold ($p < .001$, uncorrected for multiple comparisons). This revealed a qualitatively similar, although much more extensive, activity map in the cue and probe stages, but now additionally identified active regions

during the delay stage. These delay period activations included the right IFG bordering on the MFG, the left premotor cortex bordering on the IFG, the right and left dorsal premotor cortices bordering on the MFG, the right and left insular cortices (BA 47/48), the anterior cingulate cortex (ACC), the supplementary motor area (SMA), the right inferior occipital gyrus (BA 18/19), the right thalamus, the right hippocampus, and the right and left globus pallidi (Figure 2). The point of emphasis is the dramatic decrease in the magnitude of univariate activity during the delay period evident at either threshold.

Correlation Data

Beta series correlation analyses were performed for each subject during the three task stages, using the right and left FFA as seeds. Our analyses focus on the correlation data obtained using the right FFA seed, since lesion, electrophysiological, neuroimaging, and behavioral studies have shown the right hemisphere to play a dominant role in the perceptual analysis and recognition of faces (Bentin, Allison, Puce, Perez, & McCarthy, 1996; Hillger & Koenig, 1991; Horovitz, Rossion, Skudlarski, & Gore, 2004; Kanwisher et al., 1997; Landis, Regard, Bliedle, & Kleihues, 1988; Rossion, Joyce, Cottrell, & Tarr, 2003). For the cue and probe periods, the right FFA seed correlation maps revealed a set of regions similar to, but not exactly overlapping with, those described in the univariate analysis (Figure 2). Although a comprehensive description of similarities and differences between the univariate and the correlation data is outside the scope of

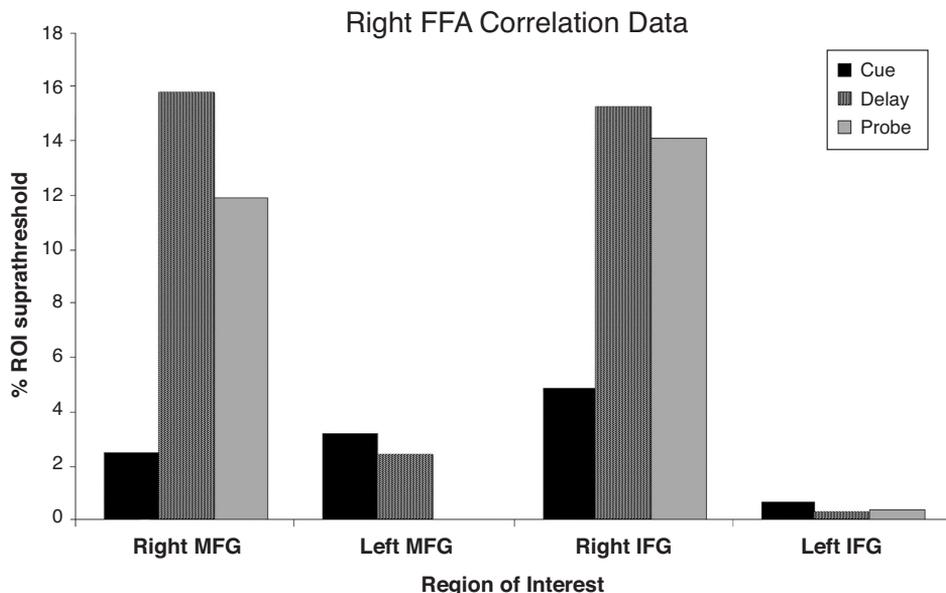


Figure 3. Quantification of right fusiform face area (FFA) correlation effects in the prefrontal cortex. Bars indicate the number of significant voxels present during each stage in four prefrontal regions of interest (ROIs). All data are based on the group-level correlation analysis shown in Figure 2. MFG, middle frontal gyrus; IFG, inferior frontal gyrus.

this article, it is immediately evident that unlike the univariate data, the strength and regional distribution of delay period correlations are comparable to those of the cue and probe stages (Figure 2). In fact, several regions, such as the right MFG, the right IFG, and the right and left fusiform gyri, exhibit a greater number of significantly correlated voxels during the delay stage than during the cue or probe stages (Figure 3, data from fusiform ROIs not shown). The MFG and IFG ROIs also revealed a hemispheric asymmetry in the extent of their correlation with the right FFA. Considerably more voxels in the right-hemisphere PFC ROIs were significantly correlated with the FFA, and it was only in these right-sided ROIs that the number of suprathreshold voxels increased during the delay period (Figure 3).

The delay period network, which is the primary focus of this study, included bilateral regions in the VAC (fusiform gyrus and occipital regions), the PFC (superior frontal sulcus; SFS), the MFG, the IFG, the ACC, the SMA), the IPS, the thalamus, the basal ganglia, the hippocampus, and the cerebellum (Figure 4). For a complete list of the brain regions exhibiting significant correlations with the right FFA seed during the delay period, see Table 1.

Although our analyses focused on the right FFA correlation maps, we also performed a correlation analysis

using the left FFA seed to determine whether the robust delay period correlations we observed in right-hemisphere PFC regions were being driven only by the a right-sided seed. The left FFA delay network map, although exhibiting a slightly different cortical distribution of significantly correlated voxels, essentially identified the same collection of regions (Figure 5). Like the right FFA delay period correlation map, the left FFA map revealed a predominantly right-lateralized network of IFG and MFG regions.

Control Analyses

Several controls were performed to increase our confidence in interpreting the correlation maps. First, we assessed whether the correlation data were associated with a particular univariate activity profile. A comparison between univariate maps revealed cortical regions with both high and low univariate activity that exhibit both high and low correlations (Figure 6, top panel). Second, we investigated whether the delay correlation map was merely a reflection of the cue period correlation map and, thus, a product of interstage signal contamination. Although similar, the delay correlation maps did not reveal the same network as did the cue correlation map. There were regions significantly correlated during delay that were not significantly correlated in the cue stage and regions significantly correlated in the cue stage that were

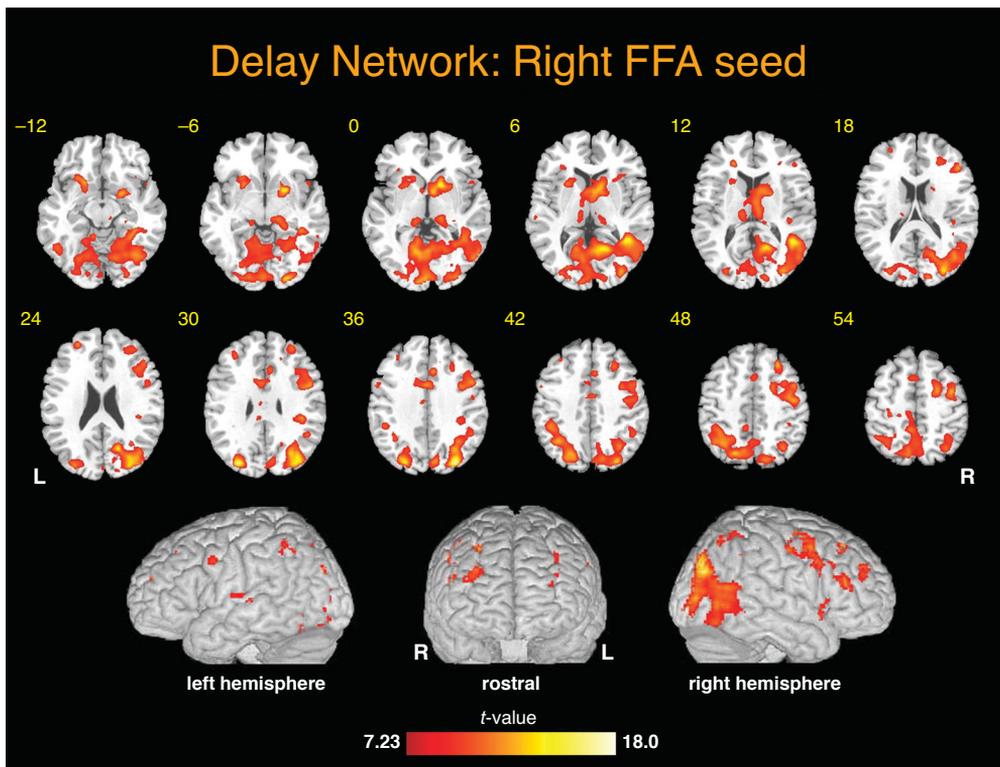


Figure 4. Delay period right fusiform face area (FFA) seed correlation map ($N = 17$). Activations are thresholded at $p < .05$ (corrected) and are shown overlaid on both axial slices and a three-dimensionally rendered MNI template brain. The color scale indicates the magnitude of the t values.

Table 1
Component Regions of the Right Fusiform Face Area Delay Network

Region	Hemisphere	Brodmann's Area	MNI Coordinates			Peak <i>t</i> Value
			<i>x</i>	<i>y</i>	<i>z</i>	
Frontal lobe						
Superior frontal sulcus	R	6/8	26	2	52	10.89
	R	9	30	30	50	12.18
	L	46	-24	50	22	11.56
Middle frontal gyrus	R	6	42	-2	54	11.16
	L	46	-30	38	30	8.69
Inferior frontal gyrus (pars triangularis)	R	45	50	32	20	11.35
	L	47/48	-30	32	4	9.45
Inferior frontal gyrus (pars opercularis)	R	48	54	16	2	8.32
	R	44	48	14	32	9.14
Insula	R	47/48	36	22	4	8.24
	L	11/48	-26	20	-14	10.07
Precentral gyrus	R	6/44	52	32	20	11.27
	R	6/4	48	-10	46	11.26
	L	6/44	-54	4	38	8.83
Middle cingulate gyrus	L	6	-26	-22	58	8.94
	R	32	8	20	40	10.16
	R	23/24	6	-6	42	8.96
Anterior cingulate gyrus	-	24	0	8	32	10.80
Supplementary motor area	-	32/6	4	14	50	8.43
Parietal lobe						
Intraparietal sulcus	R	40	40	-54	56	8.40
	L	7	-18	-69	48	12.16
Inferior parietal lobule	L	40	-36	-44	46	10.75
	R	7/39	36	-64	50	10.08
Angular gyrus	R	39/40	50	-48	38	9.57
	R	19	10	-80	36	10.53
Cuneus	R	18/23	24	-122	24	13.28
Precuneus	-	5	-2	-44	56	10.42
Temporal lobe						
Superior temporal gyrus	L	22	-60	-24	4	8.99
Middle temporal gyrus	R	21	46	-50	10	15.23
Inferior temporal gyrus	L	37	-50	-56	-14	11.42
Fusiform gyrus	R	37	37	-46	-21	13.20
	L	37	-34	-48	-20	11.55
Hippocampus	R	-	20	-28	-4	10.90
	L	-	-14	-30	-6	7.83
Parahippocampal gyrus	R	-	28	-30	-12	7.32
Amygdala	R	34	24	2	-12	11.29
Occipital lobe						
Middle occipital gyrus	R	19	34	-80	36	17.11
	R	19/39	42	-80	28	15.23
	R	18	16	-90	-6	9.67
	L	19	-26	-82	30	16.05
	L	18	-28	-86	10	9.46
Inferior occipital gyrus	R	18/19	26	-92	-6	12.85
Lingual gyrus	L	18	-12	-62	2	12.13
Calcarine	R	17	16	-58	11	14.57
	-	17	0	-92	-2	11.37

not correlated during delay (Figure 6, bottom panel). Lastly, the data were evaluated to determine whether delay correlations might be an artifact of the seed's having a low level of univariate activity, as it does during the delay period. An independent analysis performed with a white matter seed that also exhibited low univariate activity revealed no significant cortical correlations in any of the stages (Figure 5). Further controls of the beta se-

ries correlation method have been performed and published elsewhere (Rissman et al., 2004).

Delay Correlation Subcategories

Regions displaying significant correlations during the delay period can be subdivided into four mutually exclusive categories: significant correlations limited to the delay interval (*d*), those that sustain correlation from the

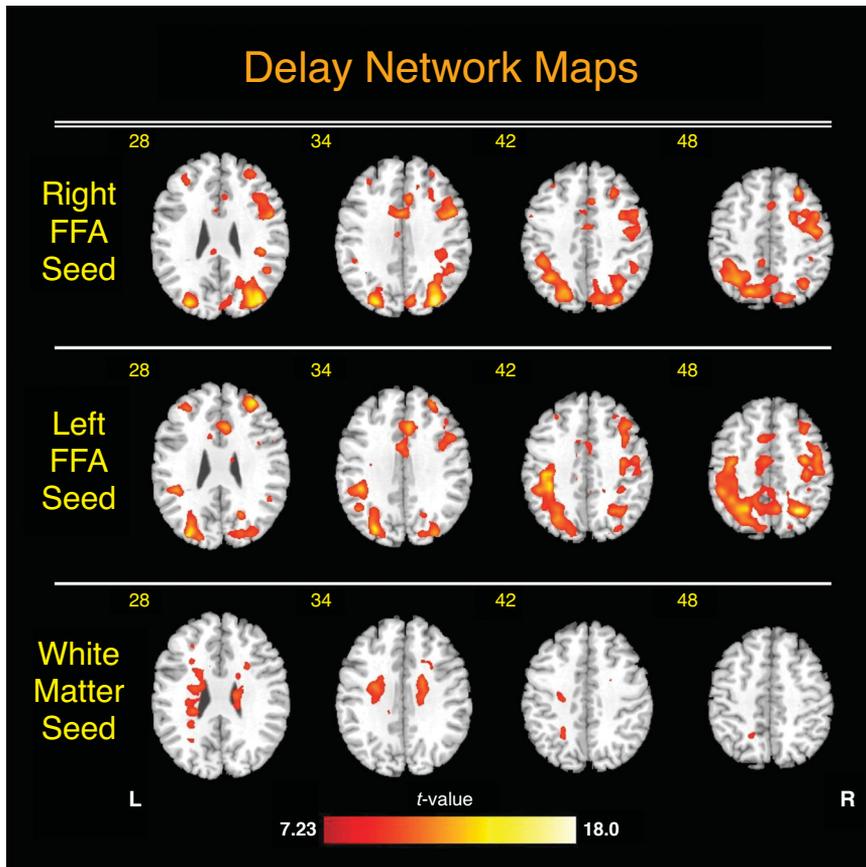


Figure 5. Comparison of correlation data generated with three distinct seeds. The top two panels represent group correlation data from the right and the left fusiform face area (FFA) seeds, respectively. The bottom panel represents group correlation data from a seed chosen in the white matter of the left hemisphere.

cue period into the delay interval (*cd*), those that are significantly correlated only during the delay and probe periods (*dp*), and those that sustain significant correlations throughout the entire delayed recognition task, from cue to delay to probe (*cdp*; Figure 7). At our chosen threshold, many voxels in the PFC were significantly correlated with the right FFA seed during the delay period only. These *d* voxels were especially prominent in the right MFG. In the right IFG and the right premotor cortex, both *d* voxels and *dp* voxels were prevalent, whereas *cd* voxels were most prevalent in the visual cortices, the thalamus, and the caudate. Voxels exhibiting significant correlations that persisted during all the task stages were found in the primary visual cortex, the right lateral inferotemporal cortex, the right thalamus, the bilateral occipitoparietal cortex, and the bilateral IPS.

DISCUSSION

Since its initial discovery over 30 years ago (Fuster & Alexander, 1971, 1973; Kubota et al., 1972), persistent neural activity during the delay interval of a WM task

has represented the hallmark of the neural basis of WM. The ability of the brain to sustain neural activity in the absence of stimulus-driven activity has been extensively characterized at both the single neuron (Funahashi et al., 1989; Fuster, 1973) and the neural population (Courtney et al., 1997; Zarahn, Aguirre, & D'Esposito, 1999) levels, leading to the identification of numerous cortical and subcortical regions exhibiting this phenomenon. Despite the importance of these findings, persistent activity within isolated brain regions is not thought to be the underlying mechanism of information maintenance during the delay period (Fuster, 1995, 1997; Goldman-Rakic, 1988, 1995). Rather, complex interactions between widely distributed nodes of a neural network are believed to engender this emergent property, whether via synaptic reverberations in recurrent circuits (Durstewitz, Seamans, & Sejnowski, 2000; Wang, 2001) or synchronous oscillations between neuronal populations (Engel, Fries, & Singer, 2001; Singer & Gray, 1995). Although studies have been performed to assess how neurons and brain regions interact to facilitate information maintenance (Chafee & Goldman-Rakic, 1998; Constantinidis et al., 2001a;

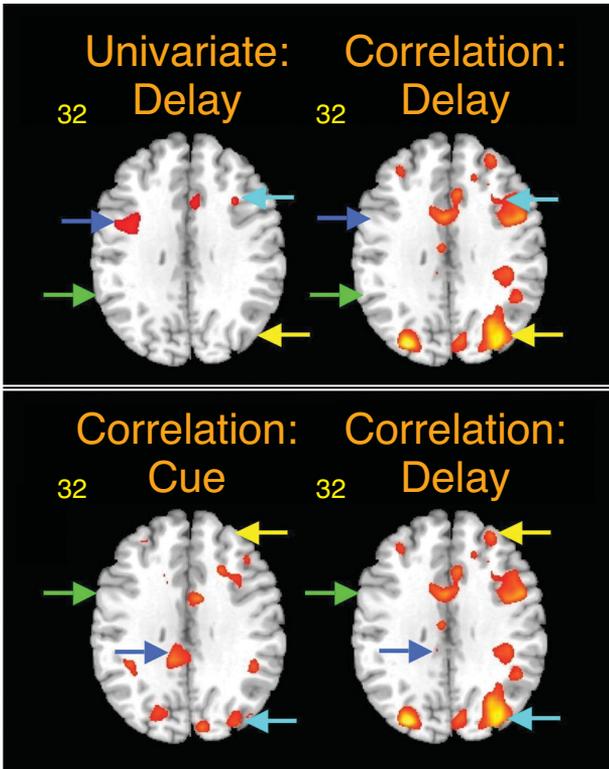


Figure 6. Top: illustration that the seed correlation maps do not merely reveal the same regions as those identified by a standard univariate analysis. The colored arrows indicate examples of regions with high univariate activity but low correlation (dark blue), high univariate activity and high correlation (light blue), low univariate activity but high correlation (yellow), and low univariate activity and low correlation (green). Bottom: illustration that the correlation maps generated from temporally adjacent task stages contain distinct information and that delay period correlations can occur in the presence or absence of significant cue period correlations. The colored arrows indicate examples of regions with high correlation during cue but not during delay (dark blue arrows), high correlation during cue and delay (light blue arrows), low correlation during cue but high correlation during delay (yellow arrows), and low correlation during both cue and delay (green arrows). All the maps are shown at the same thresholds as those used in Figure 2. Correlation maps were generated using the right fusiform face area as the seed.

Funahashi & Inoue, 2000; Fuster et al., 1985; Tallon-Baudry et al., 2001; Tomita et al., 1999), limitations in available methodology have restricted descriptions of the constituent regions of the large-scale network underlying maintenance processes. Here, we utilized fMRI and a recently developed multivariate analysis method, beta series correlations (Rissman et al., 2004), to characterize the pattern of functional connectivity associated with maintaining a visual stimulus representation across the delay interval of a WM task.

Interregional correlations of fMRI time course data have often been interpreted as a measure of functional connectivity between brain regions and the neurons that

made up these regions (Friston et al., 1993). In this study, we capitalized on the variation in neural activity that occurs within a given brain region across multiple trials of the same cognitive task. This variance in activity across trials, which might have otherwise been considered *noise*, became our dependent data, which we used to assess the correlation between brain regions. Thus, our measure of functional connectivity was not based on the time course data themselves, but rather on the trial-to-trial fluctuations in BOLD signal that occur within regions (the beta series) and the correlation of these fluctuations across regions. These beta series correlations served as a reflection of the communication between nodes of a distributed network associated with task performance. Furthermore, the brain regions were identified as nodes of a stage-specific network—cue, delay, or probe—if they exhibited highly correlated activity profiles with a seed region during distinct stages of the task.

The fMRI data utilized in this analysis were pooled from two independent, previously published studies that employed similar delayed recognition paradigms with different groups of subjects (Druzgal & D’Esposito, 2001b; Ranganath & D’Esposito, 2001). These data sets were combined, with the goal of isolating the network specific for their common element, the maintenance of a single face over a short delay interval to guide a subsequent recognition task. Univariate activation maps and seed correlation maps were first derived for each subject individually, and then group-level random effects statistical tests were performed on these maps, pooled across data sets. This pooled analysis has the advantageous property of identifying the voxels that are most consistently activated or correlated across all subjects. However, virtually identical results were obtained by an alternative analysis in which the data sets were analyzed completely independently, and then the group-level *t* maps were conjoined to assess regions of overlap (data not shown).

In this study, we utilized seeds within the VAC for the beta series correlation method, in order to identify the delay network associated with the maintenance of a perceptual representation. Prudent seed selection is an important factor in this technique, essential for the meaningful interpretation of the resulting network maps. The decision to define seeds within the VAC was based on two premises: (1) The representation of a stimulus is maintained within approximately the same posterior cortical regions as those that are optimized for its sensory processing, and (2) when a stimulus is no longer present, its maintenance is supported by distributed connections between that region and other, distant brain regions. Both data sets employed faces as the stimuli in the delayed recognition task, and so a region within the VAC (the FFA) that displayed selectivity for viewing faces (Kanwisher et al., 1997; Puce, Allison, Gore, & McCarthy, 1995) was selected as the perceptual seed. This region has been widely used in fMRI analyses of the stimulus-specific visual association cortex (Druzgal & D’Esposito,

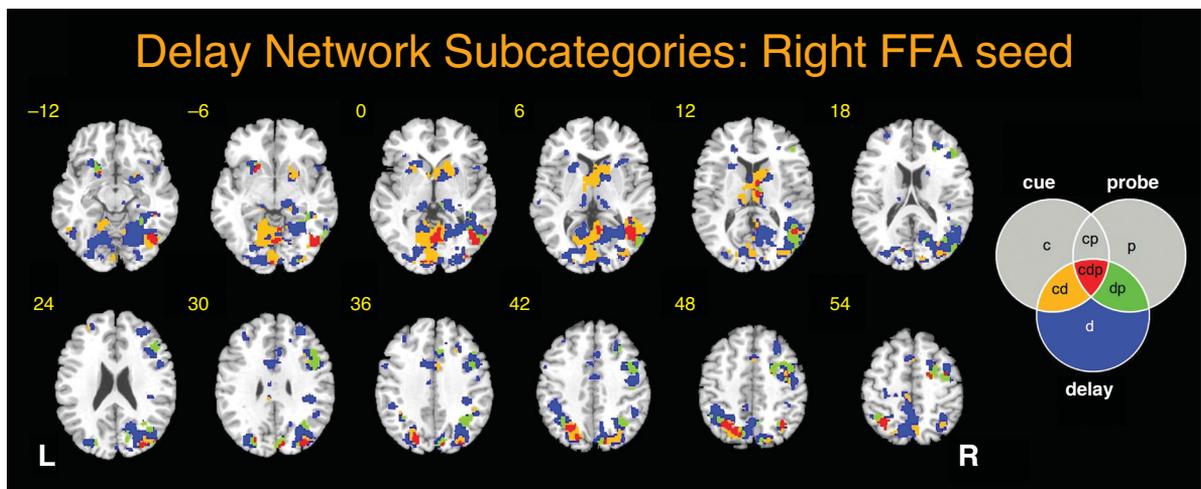


Figure 7. Subclassification of voxels exhibiting significant correlation with the right fusiform face area (FFA) seed during the delay period. All voxels displayed in Figure 4 were color coded on the basis of whether or not they also exhibited significant correlations during the cue and probe stages. Color codes are indicated by the Venn diagram: blue, significant during the delay stage only; orange, significant during the cue and delay stages; green, significant during the delay and probe stages; red, significant during all three task stages.

2003; Lehmann et al., 2004; O'Craven & Kanwisher, 2000; Rossion, Schiltz, & Crommelinck, 2003; Wojculik, Kanwisher, & Driver, 1998). We make no claim that the FFA is a region of the VAC entirely responsible for face representation; rather, it is a component of a distributed VAC network (Haxby et al., 2001; Ishai, Ungerleider, Martin, Schouten, & Haxby, 1999) with relative selectivity for faces and is, thus, likely to be an important node in the face representation network.

Although face-selective voxels can be found in the fusiform gyrus bilaterally in most individuals, we chose to focus this study on right-lateralized FFA seeds, for reasons described in the Results section. However, we also performed a more directed analysis with left-lateralized FFA seeds that revealed a delay network similar to that identified with the right-lateralized seeds, with multiple overlapping components. Despite low univariate delay activity within the FFA seeds, credible and robust network maps were attained during the delay period, so that voxel clusters with high correlations were localized to well-defined cortical and subcortical structures and survived conservative thresholds ($p < .05$, corrected for multiple comparisons in a stringent manner). This delay network map was clearly unique, as compared with the encoding and retrieval correlation maps, and did not exhibit a pattern that was predictable on the basis of the univariate data (i.e., both high and low regions of correlation were identifiable in regions displaying both high and low univariate activity). As a further control, we performed a beta series correlation analysis with a white matter seed that also exhibited low univariate activity and revealed a network map that was entirely limited to the seed and white matter. More extensive validation of

the beta series correlation method has been performed and has been published elsewhere (Rissman et al., 2004).

The general pattern of univariate activity and beta series correlations were strikingly different when compared across the cue, delay, and probe stages of the tasks. As has been observed in many fMRI delayed recognition studies, BOLD signal levels throughout the brain decrease during the delay period when a visual stimulus is no longer present (Curtis et al., 2004; Druzgal & D'Esposito, 2003; Jha & McCarthy, 2000; Ranganath & D'Esposito, 2001). This finding is consistent with single-unit physiology studies revealing that fewer PFC (Chafee & Goldman-Rakic, 1998; Funahashi & Inoue, 2000) and parietal cortex (Chafee & Goldman-Rakic, 1998) neurons exhibit delay interval activity than exhibit cue and probe period activity. Despite this decrease in overall activity levels, significant correlations persist in multiple brain areas during the delay interval, a pattern consistent with what might be expected of an active cognitive process such as maintaining an internal stimulus representation in the absence of stimulus-driven activity.

Our findings of persistent correlations throughout the delay interval in the presence of reduced activity raises the question as to what it means for regions to be highly correlated if they fail to show significant univariate activity. One possibility is that such regions, although exhibiting an overall decrease in activity when the stimulus is absent, contain subpopulations of interconnected neurons that remain active during the delay interval, or even increase in activity (Chafee & Goldman-Rakic, 1998; Funahashi & Inoue, 2000). The BOLD signal is a reflection of the neural activity of a vast population of neurons, so although the activity of a limited subpopula-

tion of neurons may not be substantial enough to generate a strong BOLD signal, it may be enough to synchronize the trial-to-trial fluctuations in BOLD signal and, hence, result in high correlations. Correlation values are a relative measure, reflecting the consistency between regions in their trial-to-trial fluctuations, and are thus a more sensitive measure of delay period processes than are univariate activity measures, which inherently treat trial-to-trial variability as noise. The data presented in this study suggest that the beta series correlation analysis serves as a sensitive indicator of correlated populations of neurons, even in the setting of subthreshold activity. This ability of the beta series correlation method to detect high correlations in the presence of low univariate activity reveals the extensive untapped information contained in fMRI data sets that is not revealed by traditional univariate methods that measure isolated activity levels exceeding a threshold.

Delay Network

All regions identified in this correlation analysis have been previously identified as being involved in WM delay processes by electrophysiological or neuroimaging studies. However, their specific roles have been a matter of debate. The paradigm used in this study was a simple face delayed recognition task. The delay period was thus dominated by the requirement to rehearse a single face for a short period of time. There was minimal monitoring or manipulation of the stimulus representation, spatial memory requirements, or motor response preparation in this task. Despite this, the network map of regions highly correlated with the FFA seed during the delay period revealed many areas that have traditionally been more associated with monitoring/manipulating stimuli (the MFG), spatial memory (parietal cortex, superior frontal sulcus), and motor preparation (the caudate, the pre-SMA, and the premotor cortex). Our functional connectivity data parsimoniously suggest that all of these regions are nodes of a network involved in stimulus representation maintenance, as reflected by their high degree of functional connectivity with the FFA during the delay period. We will explore existing evidence for the role of each of the regions in perceptual maintenance processes and will speculate on their relative contributions as nodes in the stimulus representation network.

Prefrontal cortex. The PFC was the first brain region identified as exhibiting persistent delay activity and, subsequently, has been the most extensively studied. Numerous physiology, functional neuroimaging, and behavioral studies have been performed to elucidate the role of this heterogeneous region in WM processes. Delay-specific PFC activity has been consistently identified in the MFG (Courtney et al., 1997; Postle & D'Esposito, 1999b; Ranganath et al., 2003), the IFG (Courtney et al., 1997; D'Esposito et al., 1998; D'Esposito, Postle, Ballard, & Lease, 1999; Postle & D'Esposito, 1999b; Ranganath et al., 2003), and the superior frontal

sulcus (Courtney, Petit, Maisog, Ungerleider, & Haxby, 1998; Postle & D'Esposito, 1999b; Rowe & Passingham, 2001; Rowe, Toni, Josephs, Frackowiak, & Passingham, 2000). A long-standing goal of WM research has been to understand the role of the PFC during the WM delay interval—specifically, to dissociate its contribution to perceptual memory from that related to motor preparatory processes. This objective has largely been fueled by historical experimental factors. Classically, many WM electrophysiology studies have been performed on awake behaving monkeys and have utilized a delayed response paradigm, in which following a delay interval, animal subjects were required to make a saccadic eye movement or hand reach to a target location that had been presented during the cue stage (Chafee & Goldman-Rakic, 1998; Funahashi et al., 1989; Fuster, 1973; Fuster & Alexander, 1971; Kubota, Iwamoto, & Suzuki, 1974; Niki & Watanabe, 1976). In these tasks, the animal is aware of the correct motor response immediately following the cue and holds this information in mind throughout the delay interval until the response period, when the motor action is performed. Thus, with this paradigm, it has been challenging to dissect the visuospatial, perceptual memory component from the significant motor preparatory component necessary for guiding the forthcoming directed movement. Several single-unit studies, such as those by Goldman-Rakic and colleagues (Constantinidis, Franowicz, & Goldman-Rakic, 2001b; Funahashi, Chafee, & Goldman-Rakic, 1993) and Sawaguchi and colleagues (Sawaguchi & Yamane, 1999) have attempted to dissociate these processes and evaluate the role of the PFC in perceptual maintenance processes. These studies, by manipulating stimulus attributes (Constantinidis et al., 2001b) or utilizing a delayed match-to-sample paradigm (Sawaguchi & Yamane, 1999), have revealed that a subset of PFC neurons exhibit activity specifically associated with visuospatial memory.

In human WM neuroimaging studies, the goal of assessing the PFC's role in perceptual memory during the delay interval has been somewhat more straightforward with the frequent use of delayed recognition tasks, in which a simple buttonpress is made to verify whether the probe stimulus matches or does not match the cue stimulus (Courtney et al., 1997; Jha & McCarthy, 2000; Rypma & D'Esposito, 1999; Zarahn et al., 1999). In these studies, subjects have no prior knowledge of which button they will press until the probe is presented, and so motor preparation is minimal, and the majority of delay period cognitive processes likely support stimulus maintenance. However, unlike monkey WM physiology studies, a major hurdle in studying the delay interval was the need to overcome the dependence of PET and block-design fMRI on cognitive subtraction to evaluate WM, an approach that did not adequately permit dissociation of delay maintenance processes from encoding and response processes (Friston et al., 1996; Zarahn et al., 1999). With the advent of event-related fMRI, the in-

involvement of brain regions during the delay interval could be evaluated in relative isolation from the perceptual cue and the motor response stages (Zarahn et al., 1997b), thus encouraging studies whose aim was to evaluate the role of the PFC in delay processes (Courtney et al., 1997; D'Esposito et al., 1999; D'Esposito et al., 2000; Haxby, Petit, Ungerleider, & Courtney, 2000; Postle, Berger, Taich, & D'Esposito, 2000; Rypma & D'Esposito, 1999). Although motor preparation in the delayed recognition task is less prominent, there is still a motoric, behavioral response linked to the stimulus, and so the long-standing goal of dissecting cognitive processes that are concurrent during the delay interval has persisted in the human fMRI literature. Methods that have been employed in an attempt to assess the role of the PFC in stimulus maintenance include the parametric manipulation of memory load and the use of variable length or prolonged delay periods, intended to selectively influence perceptual memory processes (Cohen et al., 1997; Druzgal & D'Esposito, 2001a, 2003; Jha & McCarthy, 2000; Rypma & D'Esposito, 1999). However, these approaches have yielded mixed results and have not clearly established the PFC as playing a specific role in perceptual maintenance.

In this study, we have provided evidence supporting the role of the PFC in the maintenance of a stimulus representation. Specifically, regions within bilateral MFG and IFG were highly correlated with both the right- and the left FFA seeds. A functional interaction between these regions is supported by previous findings of reciprocal anatomical connections (Petrides & Pandya, 2002; Webster, Bachevalier, & Ungerleider, 1994), as well as by physiological evidence of interregional functional dependence, documented in monkeys with experimentally induced lesions (Fuster et al., 1985; Tomita et al., 1999) and humans with strokes in the PFC (Barcelo et al., 2000). Further analysis of our data to delineate patterns of correlation across the three task stages revealed that the majority of PFC correlations were delay specific, thus supporting a specialized role of these regions in perceptual maintenance (see Figure 7). However, it is important not to overinterpret this finding, since it reflects the relative degree of a stage's correlation contribution and is not an absolute measure. If the statistical threshold were lowered, many PFC regions would demonstrate multistage correlations. This is consistent with single-unit physiology findings that neighboring PFC neurons can exhibit any combination of these stage-related profiles (Chafee & Goldman-Rakic, 1998; Funahashi & Inoue, 2000; Fuster, Bauer, & Jervey, 1982) and, thus, would offer a mixed contribution to population measures such as the BOLD signal.

In general, the networks of brain regions displaying high functional connectivity with the right- and the left FFA seeds during the delay period were highly overlapping. Interestingly, in the PFC, the two FFA correlation maps exhibited the same hemispheric bias, despite the fact

that the seeds were localized to different hemispheres. Both network maps displayed a greater percentage of suprathreshold voxels in the *right* PFC (the MFG, the IFG, and the SFS; see Figures 4 and 5). Hemispheric asymmetry has been reported for almost all cognitive processes, and these data suggest that the right PFC is preferentially involved in the maintenance of a visual stimulus representation. The functional organization of the PFC has been a matter of long-standing debate (D'Esposito et al., 1998; D'Esposito et al., 2000; Goldman-Rakic, Chafee, & Friedman, 1993; Levy & Goldman-Rakic, 2000; Postle & D'Esposito, 2000; Ungerleider, Courtney, & Haxby, 1998). Patricia Goldman-Rakic and others have functionally parcellated the PFC on a dorsal/ventral basis, in which the dorsal PFC is more involved in spatial WM and the ventral PFC in object WM (Courtney et al., 1998; Goldman-Rakic et al., 1993; Levy & Goldman-Rakic, 2000; Munk et al., 2002; Sala, Rama, & Courtney, 2003; Wilson et al., 1993). Another model of functional segregation subdivides the dorsal and the ventral PFC on the basis of cognitive operation, so that the ventral PFC plays a more substantial role in maintenance and the dorsal PFC in manipulation (Petrides, 1994). Although the simple face delayed recognition paradigm used here does not permit unambiguous segregation of these features, our network maps—notably, the right FFA seed map—demonstrate a well-balanced representation of correlations in the MFG and the IFG and pronounced correlations in the SFS, supporting neither of these models of PFC organization. However, the correlation data are consistent with the PFC's being subdivided on a hemispheric basis, with right-PFC regions being more involved in the visual representation network than are their left-PFC homologues (D'Esposito et al., 1998; Postle & D'Esposito, 2000). Baddeley (1986) describes WM as consisting of both a visuospatial sketchpad and a phonological loop, specialized for visual and verbal rehearsal, respectively. Perhaps the traditional distinction of the left hemisphere's being more verbally specialized and the right hemisphere's being more visuospatial applies to the role of the PFC in domain-specific maintenance processes. Future multivariate analyses comparing different delay task paradigms will be necessary to assess whether these data offer a reasonable contribution to theories of the functional organization of the PFC.

Given extensive converging evidence generated across multiple disciplines, the role of the PFC in WM maintenance processes seems largely indisputable, although its specific role has been somewhat controversial (Pochon et al., 2001; Rowe & Passingham, 2001; Rowe et al., 2000). This role is further complicated by the fact that the neural mechanisms underlying the maintenance of a stimulus representation in the absence of stimulus-driven activity remain so poorly understood. Comparisons, however, can be made with the more extensive literature that exists for stimulus representation when a stimulus is present, especially studies that focus on the modulation

of stimulus-driven activity by internal, goal-directed decisions concerning those stimuli. Most of these studies have addressed the characterization of modulation directly within posterior cortical regions. Single-cell recordings in the visual cortex have demonstrated that selective attention can bias the competition among multiple stimuli in favor of a relevant stimulus via neural response enhancement and counteracting the suppressive influences of nearby distracting stimuli (Desimone & Duncan, 1995; Moran & Desimone, 1985). Mostly on the basis of lesion studies and imaging data revealing the consistent coactivation of the PFC during such attention tasks, it has now become widely accepted that higher order association cortices, such as the PFC and the parietal cortex, exert a top-down signal to bias activity in posterior cortical regions (Kastner & Ungerleider, 2000; Miller & Cohen, 2001; Pessoa, Kastner, & Ungerleider, 2003). This same mechanism has often been translated to the role of the PFC and the parietal cortex as top-down modulators when a stimulus is not present. Thus, the neural activity that is observed in primary and association sensory cortices during stimulus-absent paradigms—WM maintenance, visual anticipation, and visual imagery—are believed to be driven by top-down signals from the PFC and the parietal cortex (Ishai, Ungerleider, & Haxby, 2000; Kastner, Pinsk, De Weerd, Desimone, & Ungerleider, 1999; O’Craven & Kanwisher, 2000; Postle et al., 2003). The correlation data presented here contribute to this mechanistic theory by offering more direct evidence of functional connectivity between the PFC and the VAC during information maintenance. This evidence is supportive of the role of long-range projections from the PFC in facilitating the active maintenance of sensory representations stored in posterior cortices (Curtis & D’Esposito, 2003).

Parietal cortex. In addition to its well-characterized role in spatial visual processing (for a review, see Andersen, 1995), posterior parietal cortex neurons in monkeys have been found to exhibit elevated activity during the delay period of spatial WM tasks when evaluated with single-electrode recordings (Chafee & Goldman-Rakic, 1998; Constantinidis & Steinmetz, 1996; Gnadt & Andersen, 1988). In agreement, delay-specific activity localized to the IPS has also been documented in numerous event-related fMRI spatial WM experiments (Curtis et al., 2004; Jha & McCarthy, 2000; Munk et al., 2002; Pessoa et al., 2002; Pochon et al., 2001; Postle & D’Esposito, 1999b; Rowe & Passingham, 2001; Rowe et al., 2000; Sala et al., 2003; Simon et al., 2002). Although most studies have exclusively used spatial delay tasks, studies in which object WM tasks have been utilized have also observed IPS delay activity (D’Esposito et al., 1998; Jha & McCarthy, 2000; Munk et al., 2002; Sala et al., 2003; Simon et al., 2002). Those studies that directly compared spatial with object tasks showed greater activity in the posterior parietal cortex and superior portions of the IPS for spatial tasks (Postle & D’Es-

posito, 1999b; Sala et al., 2003) and greater activity in inferior portions of the IPS for object tasks (Munk et al., 2002; Postle & D’Esposito, 1999b; Sala et al., 2003). In sum, the parietal cortex has a well-documented role in WM delay processes, seemingly greater for spatial than for object-based WM in the superior parietal cortex.

The specific role of the parietal cortex in delay processes has been a matter of debate, largely because of the frequent use of delayed response tasks with a significant motor preparatory component in the delay interval. However, single-unit physiology studies have documented parietal neuron activity both in delayed response tasks, when a saccade to a remembered spatial location was required (Chafee & Goldman-Rakic, 1998; Gnadt & Andersen, 1988), and in delayed recognition tasks, when a match was indicated by a lever release (Constantinidis & Steinmetz, 1996). This issue was also recently addressed by an event-related fMRI study that revealed stronger IPS activity in a delay task with a greater visual memory component, as compared with a delay task with a greater motor preparatory component, thus suggesting an important role for this region in maintaining sensory information (Curtis et al., 2004).

Our data reveal significant correlations between the FFA and the bilateral IPS, both in the inferior and the superior portions, despite the fact that the task was a face recognition paradigm with no explicit spatial requirements and minimal motor preparation. This finding supports a role of the parietal cortex in stimulus representation maintenance, even when spatial memory requirements are minimal, as they are in face recognition, a largely holistic process (Sagiv & Bentin, 2001). Goldman-Rakic and colleagues appreciated the importance of assessing interactions between cortical regions and examined delay activity with single-unit electrodes in the monkey posterior parietal area 7ip and prefrontal area 8a, in order to directly compare activity profiles during the same task in the same subject (Chafee & Goldman-Rakic, 1998). Although their technique did not allow the direct assessment of functional connectivity, a striking similarity in the activity patterns of the neurons in these two regions did suggest an interaction and, in their words, “support[s] a view of cortical function in which neuronal activity patterns are shared and cooperatively generated by interacting areas.” Their observation that neurons in two distinct regions become simultaneously active during task performance is the driving force of the method we utilize here, in which regions that are similarly activated across trials during the same stage display higher correlations. Both of the human equivalents of the cortical regions they studied, parietal area 7 and prefrontal area 8, were identified in this analysis. The high correlation of both of these regions with the FFA seeds implies a high correlation between these regions, consistent with the results of Chafee and Goldman-Rakic, but extending the documented congruence of activity between the parietal and the prefrontal cortices to a larger distributed network of which they are con-

stituents; as the authors speculate, “working memory is associated with increased activity in broadly distributed cortical networks with obligatory prefrontal and parietal components” (p. 2935).

Premotor cortex. The well-established role of the premotor cortex in movement planning and execution has recently been extended to include WM, since electrophysiological evidence revealed that premotor neurons also display mnemonic properties. Specifically, a distinct subset of neurons exhibit sustained delay activity in response to the direction of a planned move (motor preparation), whereas another subset exhibit delay activity responsive to the location of a remembered stimulus (WM; Boussaoud & Wise, 1993a, 1993b). This role of the premotor cortex in mnemonic delay processes has been supported by a recent fMRI study in humans aimed at dissociating the motor preparatory and the WM features of the premotor cortex (Simon et al., 2002). Functional segregation of the dorsal premotor cortex by single-unit recordings and fMRI analysis has revealed a relative specialization of more rostral regions of the dorsal premotor cortex for memory processes (precentral sulcus) and caudal portions for motor preparation (precentral gyrus; Boussaoud, 2001; Simon et al., 2002). Accordingly, we found a relatively greater density of correlations with the right FFA in more rostral regions of the dorsal premotor cortex, consistent with a role in stimulus maintenance or perhaps the integration of the perceptual information with preparation for a motor response. The role of this area in integrating maintenance and response processes may be indicated by its high correlation in both the delay and the probe periods (see Figure 7).

Comparable functional segregation has also been identified in medial premotor areas. An fMRI analysis revealed that the pre-SMA and the ACC exhibit sustained activity during face and spatial WM delay intervals when contrasted with a control task involving simple motor preparation during the delay (Petit, Courtney, Ungerleider, & Haxby, 1998). These regions were distinct from the more caudal SMA and cingulate motor areas that were associated with a simple movement task. These findings thus suggest a more complex role of the pre-SMA and the ACC than simple motor preparation and, as the authors suggest, it reflects either “a state of preparedness for selecting a motor response based on the spatial and object information held on-line” or “an active representation of visual stimuli in working memory” (p. 9436). In our study, both the pre-SMA and the ACC were identified as regions of the delay network highly correlated with the FFA seed. As we have discussed previously, this lends support to the idea that these regions are involved in sensory maintenance or the integration between perceptual information and motor response planning, as Petit et al. suggested. This concept of perception–action integration is the very essence of WM, and it is possible that “motor” regions, such as the premotor cortex, which reveal high correlations during the delay interval with our “perceptual” seeds, may reflect this coupling.

Caudate. The caudate nucleus is another region classically recognized for its role in planning and executing motor action that has now been attributed a more direct role in cognition, including WM processes. The involvement of this subcortical structure has been investigated with selective lesions that document spatial WM deficits (Divac, Rosvold, & Szwarcbart, 1967). Accordingly, neurophysiology (Hikosaka & Sakamoto, 1986) and fMRI studies have localized delay period activity to the caudate nucleus (Lewis, Dove, Robbins, Barker, & Owen, 2004; Postle & D'Esposito, 1999b; Simon et al., 2002), and evidence suggests a preferential involvement in spatial versus nonspatial WM (Postle & D'Esposito, 1999a). In our network analysis, the caudate was revealed to be a site of robust correlations with both FFA seeds, suggesting a role in maintaining the stimulus and perception–motor integration similar to that discussed above for premotor cortical structures.

Thalamus. The thalamus, which acts to gate the flow of information from the environment to specialized processing regions of the cerebral cortex, has also been attributed a role in maintaining information in the absence of stimulus-driven activity. Thalamic involvement in WM processes is based partly on findings that thalamic lesions in both experimental animals and humans result in impaired WM performance (Dagenbach, Kubat-Silman, & Absher, 2001; Isseroff, Rosvold, Galkin, & Goldman-Rakic, 1982; Parker, Eacott, & Gaffan, 1997). However, its specific role in the maintaining of information was elucidated by neurophysiological recordings during the delay period of delayed response tasks, revealing sustained activation in the thalamic mediodorsal nucleus (Fuster & Alexander, 1971, 1973; Tanibuchi & Goldman-Rakic, 2003; Y. Watanabe & Funahashi, 2004). Corroborating fMRI evidence in humans has been limited (Elliott & Dolan, 1999), presumably either because BOLD-induced activity in this region is subthreshold due to a limited population of active neurons during the delay or because most researchers choose to focus on cortical activations, often via ROI analyses, and thus do not evaluate or comment on thalamic activity. A lack of attention to the role of the thalamus in WM is misguided, since persistent delay activity itself may be the product of reciprocal excitation (Alexander & Fuster, 1973; Fuster, 1995; Wang, 2001) or large-scale coherent oscillations (Destexhe, Contreras, & Steriade, 1998; Engel et al., 2001) between the cortex and the thalamus via thalamocortical loops. In our study, the thalamus represents a site of very extensive correlations with the FFA during the delay period, thus supporting its role in maintaining a stimulus representation in the absence of visual stimulation.

Hippocampus. The indispensable involvement of medial temporal lobe structures in maintaining information has most frequently been in reference to their role in long-term memory consolidation (Squire & Zola-Morgan, 1991). However, a vast pool of behavioral and physiological data collected over the last 25 years has firmly established its role in maintaining information over very

brief periods of time. Perhaps the most extensive documentation of this comes from hippocampus and fimbria/fornix lesion studies in rats and monkeys, which demonstrate deficits on both spatial and object WM delay tasks (Lee & Kesner, 2003; Murray, Davidson, Gaffan, Olton, & Suomi, 1989; Olton & Feustle, 1981; Olton, Walker, & Wolf, 1982; Raffaele & Olton, 1988; Wan, Pang, & Olton, 1994; Zola-Morgan & Squire, 1986). Additional support has been obtained by neurophysiological studies with experimental animals, revealing delay-specific sustained activity in the hippocampus of the rat (Wible et al., 1986) and the monkey (Cahusac, Miyashita, & Rolls, 1989; T. Watanabe & Niki, 1985), as well as increased local cerebral glucose utilization in the hippocampus of monkeys engaged in either spatial or object delay tasks (Friedman & Goldman-Rakic, 1988). Delay-specific activity has also been revealed in humans with event-related fMRI (Ranganath & D'Esposito, 2001), although this is not a frequently reported finding, perhaps for the reasons discussed above in the Thalamus section. In our study, bilateral hippocampal correlations with the FFA seed, as well as the parahippocampus and amygdala, were identified, thus supporting the emerging role of medial temporal lobe structures in WM processes and stimulus representation maintenance. The specific contribution of the hippocampus to stimulus maintenance may be either to activate long-term memory networks essential for binding the stimulus representation within the context of preestablished representations (Fuster, 1995) or, perhaps, to subservise incidental consolidation of the stimulus representation into new long-term memories.

Visual cortices. Findings of persistent delay activity in the inferior temporal cortex of monkeys (Fuster, 1990; Fuster & Jervey, 1981; Miller, Li, & Desimone, 1993) and the fusiform cortex in humans (Haxby, Petit, et al., 2000; Postle et al., 2003), coupled with observations of VAC activation during visual imagery (Ishai et al., 2000; O'Craven & Kanwisher, 2000), suggest that the same visual areas involved in perceptual processing of visual stimuli are also involved in establishing its representation in the absence of the stimulus. However, it has also been revealed that the perception of a visual stimulus does not involve activity limited to discrete visual modules, but involves a widely distributed network across multiple visual regions (Haxby et al., 2001; Haxby, Hoffman, & Gobbini, 2000; Ishai et al., 1999). The extension of this logic is that the maintenance of a visual representation also involves a network of regions. Despite the lack of visual stimulation during the delay period, we observed the presence of extensive functional connections between the FFA seed and widespread visual cortices, including the middle and inferior occipital gyrus, the lingual gyrus, and even the calcarine cortex. In addition, in the right fusiform gyrus, this connectivity actually increases in the delay period, as compared with the cue period. A comparable finding has recently been documented

in a study utilizing intracranial electrodes distributed across the VAC of human subjects performing a delayed recognition task (Tallon-Baudry et al., 2001). The investigators observed synchronized oscillatory activity specifically during the delay period between VAC regions separated by several centimeters and concluded that the "results point toward a role of sustained synchronized oscillatory activity between extrastriate areas in the maintenance of an object representation in human visual short-term memory." Our data support this concept that the maintenance of a stimulus representation is distributed across an expanse of the visual cortex.

Conclusions

In this study, we employed a novel multivariate fMRI analysis technique to investigate the neural mechanisms underlying the temporary retention of a visual stimulus representation. Our empirical findings extend maintenance mechanisms from the domain of persistent isolated activity to encompass the concept of persistent functional connectivity. The network of regions we identified has been previously noted to exhibit persistent delay period activity in numerous and diverse single-cell physiology and event-related fMRI studies. We have now revealed a common element across these regions—robust correlations with a seed region in the visual association cortex during the maintenance of a stimulus representation. It is the concerted activity and interaction between these regions within the framework of a distributed system that permits the retention of an internal representation of the stimulus and successful performance of the task.

As was discussed above, physiological and behavioral data suggest that each of these regions may contribute different elements to stimulus maintenance. For example, the hippocampus may serve to activate associated representation networks to establish context, the thalamus may contribute to maintaining persistent activity through reentrant pathways, the premotor cortex and the caudate nucleus may serve to integrate the representation with subsequent behavioral responses, the occipital areas may be the site of perceptual representation, and the PFC may act to bias activity in specific regions of the visual association cortex to maintain the representation. However, definitive allocation of unique functions to discrete modules is not practical or consistent with our current view of brain function, since these regions differ only in their degree of participation in a manner that is dependent on the context of the operation being actively performed (Fuster, 1995, 1997). This is immediately evident by noting that the contribution of so many regions in the network—the premotor cortex, the caudate, the thalamus, and the hippocampus—offers a distinct departure from their traditional roles. A review of the data reveals that these roles are not absolute but, rather, serve a purpose in the framework of the overall process they are actively involved in and the network of which they are integral elements.

Further understanding of this network and the differential contribution of the component regions will require investigating the influence of hypothesis-driven task design manipulations on the functional connectivity between regions, as well as comparing networks across different patient populations in which the functioning of specific network nodes or their connections may be compromised. This goal might also be addressed by comparing network maps attained with different exploratory seeds to assess the presence of distinct networks that might exist concurrently during the delay interval. We also believe that correlational data such as these need to be complemented with techniques that establish the functional necessity of the network nodes, such as reversible lesions induced by cooling (in animals) or transcranial magnetic stimulation (in humans). Lastly, we wish to emphasize the value of continued development of multivariate techniques to explore the interactions between brain regions, essential to furthering our understanding of the neural mechanisms underlying cognitive processes.

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