



Hemispheric specialization of the lateral prefrontal cortex for strategic processing during spatial and shape working memory

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Received 3 June 2003; revised 15 October 2003; accepted 15 October 2003

Objective: We investigated whether spatial working memory (WM) is associated with functional specialization of the right prefrontal cortex (PFC) relative to WM for shapes. We designed spatial and shape WM tasks that are relatively easy to perform and that minimize both task-switching and manipulation demands. The tasks use identical stimuli and require the same motor response. **Methods:** We presented 12 subjects with target shapes that appeared in particular locations. Subjects maintained either the location or the shape of the targets in WM and responded to each probe by indicating whether it was a target. During a non-WM control task, subjects indicated whether the probe appeared on the right or left side of the screen. Subjects were scanned with a 3.0 T Siemens scanner and data were analyzed using SPM99. The WM tasks were compared to identify PFC activation that was different for spatial versus shape WM. Each WM task was also compared to the control task. **Results:** compared with shape WM, spatial WM performance was faster and more accurate and was associated with increased right ventrolateral and frontopolar PFC activation. In contrast, compared to spatial WM, shape WM was associated with increased left ventrolateral PFC activity. **Conclusions:** These findings demonstrate hemispheric specialization for spatial versus shape WM in the ventrolateral PFC. The increased activity in the right PFC for spatial WM cannot be attributed to increased task difficulty, the stimuli used, or the response requirements. Rather, we propose that differences in performance and activation reflect the use of configural processing strategies for spatial WM.

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Keywords: Hemispheric specialization; Lateral prefrontal cortex; Strategic processing; Working memory

Introduction

Working memory (WM) is not a unitary construct. It comprises both maintenance and manipulation processes and operates on

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Available online on ScienceDirect (www.sciencedirect.com).

different domains of information (e.g., spatial, verbal, and object features). Neuroimaging evidence suggests that there are functional subdivisions within the lateral prefrontal cortex (PFC) for WM processes (D'Esposito et al., 1999; Petrides, 1995), and possibly also domains (D'Esposito et al., 1998). While some neuroimaging studies demonstrate spatial segregation of PFC activation based on domain (see review by D'Esposito et al., 1998) others provide evidence that the same PFC regions subserve both spatial and nonspatial WM (Nystrom et al., 2000; Owen et al., 1998; Postle et al., 2000a). The literature on single unit recordings in nonhuman primates similarly provides evidence for both anatomical subdivision (Levy and Goldman-Rakic, 1999) and the same neurons participating in WM for both spatial and nonspatial information (Rao et al., 1997). Recent neuroimaging work suggests that domain-related specialization in the PFC reflects the degree of task participation rather than an absolute segregation of function (Haxby et al., 2000; Nystrom et al., 2000).

Identifying the relevant dimensions of functional subdivision within the PFC is an ongoing challenge. In the present study we manipulated both domain (spatial vs. shape) and WM load to determine their effect on patterns of PFC activation. Influenced by a previous behavioral study by Coleman et al. (2002), which, in turn was modeled on work by Smith et al. (1995), we designed WM tasks with identical stimuli and motor response requirements and asked subjects to represent either spatial or shape features at two different levels of WM load. The WM tasks are relatively simple and minimize requirements to manipulate the stimuli while they are held "on-line." Using these tasks, we investigated whether spatial WM is associated with functional specialization of the right prefrontal cortex (PFC) relative to WM for shapes.

The neuroimaging literature on spatial vs. nonspatial WM is extensive. Reviews of this literature support a relative functional specialization in the right PFC for spatial versus nonspatial WM (D'Esposito et al., 1998; Fletcher and Henson, 2001). However, a meta-analytic study suggested that specific regions within the PFC make identical functional contributions to both spatial and nonspatial WM (Owen, 1997). There are several methodological issues that limit the interpretation of the studies reviewed and may

contribute to discrepant findings with regard to functional specialization. These issues were considered in designing the present study and are discussed below.

Many of the studies used different subjects and/or different stimuli to study spatial and nonspatial WM. This nonequivalence makes any resulting differences in activation patterns difficult to attribute to spatial versus nonspatial WM demands as opposed to individual differences or differences in sensory requirements. There are, however, several recent studies that have compared spatial and nonspatial WM in the same subjects using tasks with identical stimuli. These studies are also difficult to reconcile. They report either no segregation in the PFC for locations versus shapes (Postle et al., 2000a; experiments 2 and 3, Postle et al., 2000b) or a relative segregation for spatial WM compared with either shape WM (Nystrom et al., 2000; experiment 3) or face WM (cf. Courtney et al., 1998; Haxby et al., 2000). Few studies have made direct statistical comparisons of activation in spatial vs. nonspatial WM tasks. Instead, many studies have compared the spatial and nonspatial tasks with their respective control tasks and then compared the resulting activation maps (e.g., Postle et al., 2000a). A direct comparison of the WM tasks is necessary to evaluate the significance of activation differences for spatial and nonspatial WM. In addition, because the nature of the control task influences the pattern of activation found, using different control tasks complicates the comparison of the spatial and nonspatial WM maps—it is not clear whether differences reflect domain or control task requirements.

The processing requirements of the tasks employed may also influence whether separate activation is found. Presumably, maintaining and responding to spatial information require different strategic processes than maintaining and responding to shapes. These strategic processes that are specific to spatial versus shape WM may recruit different PFC regions. However, if additional processes are required (e.g., beyond those needed for maintenance and responding), these same PFC regions, that are preferentially recruited for domain-specific WM processes, may also be recruited for these more WM general processes that are not domain-specific. For example, if a region in the right PFC played a role in processes necessary for maintaining spatial, but not shape, features, but also played a role in manipulating information regardless of domain, then the introduction of manipulation requirements might obscure any specialization for spatial versus shape WM. However, this region might be preferentially activated (e.g., show “specialization”) for a spatial versus shape WM task if manipulation requirements were minimized. This supposition is supported by findings that general processing requirements, such as manipulation and task-switching, increase activation in common PFC regions in a diverse tasks, not confined to a particular domain (Duncan and Owen, 2000; Dove et al., 2000; Kimberg et al., 2000; Owen et al., 1996; Postle et al., 1999; Sohn et al., 2000). This suggests that these regions subserve general processing requirements. There is not a one-to-one mapping of a particular process to a particular region (Carpenter et al., 2000) and it is possible that regions that subserve domain-specific processes also contribute to more general processes. If this were the case, the more cognitive processes a task requires, the more likely it is that specialization by domain will be obscured.

Many studies addressing the issue of specialization by domain have employed variations of the n-back task (e.g., Nystrom et al., 2000; Postle et al., 2000a). In addition to the maintenance of information and response processes, the n-back task requires

manipulative processes including temporally tagging and updating the contents of WM. These processes are required regardless of domain. Manipulation engages the PFC more than maintenance (Wagner et al., 2001) even when the tasks are matched for difficulty (D’Esposito et al., 1999; Postle et al., 1999). If manipulation requirements engage the same regions that show domain-specific activation, they may obscure functional specialization. Similarly, the addition of task-switching requirements increases activation in PFC regions (Dove et al., 2000; Sohn et al., 2000). Several recent studies of specialization by domain have employed event-related fMRI designs with randomly intermixed trials of the spatial and nonspatial WM tasks (e.g., (Postle et al., 2000b)). This introduces a greater need for vigilance and imposes task-switching requirements. Task-switching represents another general rather than domain-specific cognitive process that may obscure specialization.

In summary, manipulation and task-switching requirements may lead to increased PFC activation regardless of domain and thereby obscure specialization. The finding of similar activation in PFC regions for spatial and shape WM tasks may reflect general WM processing requirements rather than a lack of specialization by domain. Moreover, manipulation and task-switching requirements may interact with spatial and nonspatial WM demands in an unequal fashion, especially if one task is easier or more dominant (cf. Monsell et al., 2000) and these interactions may also affect the pattern of PFC activation. If this is the case, whether a study finds specialization by domain may depend on the processing requirements of the tasks employed.

The goal of the present study was to determine whether the pattern of lateral PFC activation depends on WM domain type when these general processing requirements are minimized. We designed spatial and shape WM tasks that use identical stimuli and require the same motor responses. The tasks were designed to have minimal manipulative requirements. Because the tasks were presented in a blocked format, they also minimized task-switching requirements. Because the use of high WM loads can result in the use of auxiliary strategic processes to manage increased load in the face of limited storage capacity (Rypma et al., 1999, 2002), the tasks were kept at relatively low load levels (two and three locations or shapes). We compared spatial and shape WM tasks directly to determine which PFC areas are specialized by domain. We also compared each WM task to a single non-WM control task that used identical stimuli to determine which PFC areas were associated with spatial and shape WM. Finally, we varied WM load to determine which PFC regions were sensitive to load. We reasoned that regions that were specialized by domain (i.e., presumably involved in domain-specific maintenance and response processes such as mentally scanning the information represented in WM and comparing it to a probe) would be sensitive to WM load.

Thus, the paradigm employed allowed us to test functional specialization for spatial versus shape WM in a relatively pure manner. It permitted a direct comparison of spatial and shape WM tasks that used equivalent stimuli, required identical motor responses, and minimized manipulation and task-switching requirements. Based on previous findings (D’Esposito et al., 1998; Fletcher and Henson, 2001; Nystrom et al., 2000) and particularly on the results of an investigation using similar stimuli (Smith et al., 1995), we hypothesized that subjects would show a relative hemispheric specialization in lateral PFC for spatial and shape WM (spatial-right; shape-left).

Materials and methods

Subjects

Twelve healthy right-handed subjects (8 male, 4 female, mean age 35 ± 10) were recruited from the hospital community using poster advertisements. All subjects were screened to exclude substance abuse or dependence within the past 6 months, a history of significant head injury resulting in a sustained loss of consciousness and/or cognitive sequelae, current psychoactive medication use, and psychiatric or neurological illness. All subjects were strongly right-handed as determined by a laterality score of 70 or above on the modified Edinburgh Handedness Inventory (White and Ashton, 1976). Subjects had a mean of 18 ± 4 years of education and a mean verbal IQ of 114 ± 8 as estimated by the American National Adult Reading Test (Blair and Spreen, 1989). All subjects gave written informed consent. The study protocol was approved by the Committee on Human Subjects at Massachusetts General Hospital.

Cognitive tasks

The stimuli for spatial and shape WM tasks and the control task were a fixed set of 10 Attneave shapes (Attneave and Arnoult, 1956) that could appear in any of 10 possible locations on the screen. These shapes were irregular polygons that were selected to have low recognition and association values (Vanderplas and Garvin, 1959) to inhibit the use of verbal mnemonic strategies. The locations were also difficult to verbalize since they did not fall on a grid or form any recognizable spatial configuration. Both the shapes and locations, however, could be easily discriminated from one another to emphasize WM rather than visual discrimination requirements. The WM and control tasks are depicted and detailed in Fig. 1. In brief, during the WM tasks subjects were presented with a set of targets (two or three). They were asked to hold in WM either the locations or shapes of the targets. The targets then disappeared and subjects responded to probes by indicating whether they were in the memorized set (a WM-guided response). In the control condition, subjects responded to probes by indicating whether they appeared on the right or left side of the screen (a visually guided response). In the WM and control tasks, response time (RT) and side (right or left) were recorded.

The spatial and shape WM tasks were presented in separate runs and alternated with the control task and fixation. Subjects performed a total of six runs of 5 min 14 s each: three spatial and three shape. The total experiment time was approximately 40 min. Half the subjects performed the spatial blocks first and half performed the shape blocks first. The runs were grouped together by domain type to minimize task-switching requirements. In addition, the color of the stimuli differed according to domain type to enable subjects to associate the color with the task-set so that color would serve as an additional reminder of which task they were performing during scanning. The shapes were presented on a black background in blue for spatial, magenta for shape, and gray for control. Stimuli in PICT format were displayed using Macintosh stimulus presentation software (MacStim[®]) and projected via a Sharp XG-2000 color LCD projector (Osaka, Japan) on a screen positioned on the head coil. Before scanning, subjects practiced until they understood the tasks. They were instructed to respond as quickly and accurately as possible and informed that they would be paid a US\$.05 bonus for each correct response.

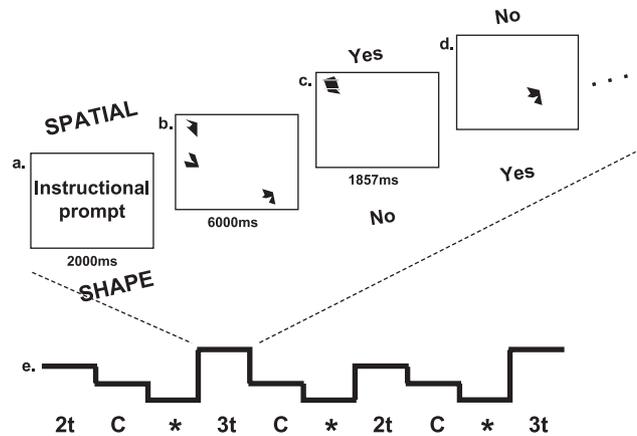


Fig. 1. (a) All of the tasks began with an instructional prompt (2000 ms) consisting of “Learn Where” for the spatial task; “Learn What” for the shape task; and “Which Side” for the control task. (b) For the WM tasks, this prompt was followed by a set of either two or three target shapes (6000 ms) appearing in various locations on the screen. Subjects had to remember either the spatial location or shape of the targets. (c and d) The target set was followed by the presentation of 14 individual probes (1857 ms) with an interstimulus interval of 1000 ms. The subject responded to each probe by indicating whether it appeared in one of the memorized locations regardless of its shape (spatial) or whether the probe was one of the memorized shapes, regardless of its location (shape). In half the trials the probe was a target (a member of the memorized set) and in half the trials the probe was a foil (not a member of the memorized set). Subjects responded by pressing a button box with their right thumb for targets and their left thumb for foils. The non-WM control condition substituted a visually guided for a memory-guided response. Unlike the WM tasks, there was no display of targets (b). Rather the instructional prompt (a) was immediately followed by the presentation of the probes and subjects responded by indicating whether the probe appeared on the right or left side of the screen by pressing the corresponding button. Half the probes appeared on the right and half appeared on the left. (e) Each run of the task contained two blocks of the high and low load WM conditions (2 t and 3 t), three blocks of the control condition (c) and three periods of fixation (*). The fixation baseline condition consisted of an asterisk that flashed at 2-s intervals to maintain the subjects’ visual attention and gaze. The order of the blocks did not vary across runs.

Analysis of behavioral data

We analyzed percent errors with repeated-measures ANOVA with task (spatial, shape, control) and WM load (two or three targets) as repeated measures. Pairwise comparisons were evaluated with Fisher’s Least Significant Difference tests. RTs for correct trials were analyzed with randomized block ANOVA with task and WM load as factors and subjects as the random factor. Pairwise comparisons were evaluated with contrasts.

Image acquisition

Head stabilization was achieved with cushioning and a forehead strap and all subjects wore earplugs to attenuate scanner noise. Images were collected using a 3.0 T Allegra Medical System Magnetom MR modified for echoplanar imaging (Siemens Medical System, Iselin, NJ). Automated shimming procedures were performed and scout images were obtained. T1 and T2 sequences were acquired to assist in slice prescription. Functional images were collected using Blood Oxygen Level Dependent (BOLD) contrast

and a gradient echo T2* weighted sequence (TR/TE/Flip = 2000 ms/30 ms/90°) to measure variations in blood flow and oxygenation. Twenty contiguous horizontal 5 mm slices parallel to the intercommissural plane (voxel size 3.13 × 3.13 × 5 mm) were acquired interleaved. Four images at the beginning of each scan were acquired and discarded to allow longitudinal magnetization to reach equilibrium.

fMRI data analysis

The functional data were analyzed using SPM99 (Wellcome Department of Cognitive Neurology). Data were motion corrected with a six parameter (three translational and three rotational), rigid-body, least-squares realignment routine. They were then spatially normalized to standard Talairach space using an EPI template. Before statistical analysis, the functional data were spatially smoothed with a three-dimensional isotropic Gaussian filter (8 mm full-width half-maximum). A first-order autoregression model [AR (1)] was used to estimate the autocorrelation structure in the individual time-series. Global changes in activity were removed by proportional scaling.

Functional data were analyzed in two stages constituting a random effects model. In the first stage, neural activity for each condition was modeled as a “boxcar” function. These neural response functions were then convolved with a canonical hemodynamic response function to yield regressors that modeled the BOLD response to each condition. The instructional prompts, encoding epochs, and probe epochs were modeled separately for the spatial, shape, and control tasks. These regressors were then combined in a general linear model treating each subject as a fixed effect. Voxelwise parameter estimates for all regressors were estimated using least squares within SPM99. These provide an index of the magnitude of the response for each condition. Effects of interest were tested using linear contrasts of the parameter estimates. In the second stage, these fixed effects, in the form of contrast images, were passed into one-sample *t* tests at each voxel. The resulting statistical parametric map of the *t* statistic, SPM{T}, was used to make inferences at the group level. We used a voxel-level threshold of $P \leq 0.001$, uncorrected for multiple comparisons, and a cluster extent threshold of five contiguous voxels to identify significant activity. Anatomical labeling of regional activity made reference to the Talairach and Tournoux atlas (Talairach and Tournoux, 1988) after adjusting for differences between MNI and Talairach coordinates (<http://www.mrc-cbu.cam.ac.uk/Imaging/minispace.html>).

Our tasks were optimized to examine activation during the probe epochs which involved both maintenance and response processes. We directly compared the spatial and shape probe epochs to determine which PFC regions showed specialization based on domain type. For these comparisons, we ensured that the resulting maps revealed activation that was associated with the WM task of interest (e.g., spatial), rather than a deactivation in the WM comparison task (e.g., shape) by creating a binary mask of the voxels that were more active in the WM task of interest relative to the control condition at a threshold of $P \leq 0.05$ and limiting our analysis to these voxels. Our comparisons of the probe epochs of each WM task versus the control condition (side) identified regional activation associated with spatial and shape WM, respectively. To identify PFC regions sensitive to WM load, we compared the high versus low WM conditions for the spatial and shape WM tasks separately.

Results

Task performance

All of the tasks (control, spatial, and shape) were performed at or near ceiling levels of accuracy by most subjects. There was a significant effect of task on accuracy [$F(2,11) = 4.48, P = 0.02$] and RT [$F(2,11) = 1082.48, P < 0.0001$]. Subjects performed the control task comparably to the spatial task ($P = 0.36$) but more accurately than the shape task ($P = 0.008$). Spatial WM performance showed a trend to be more accurate than shape WM ($P = 0.06$). The control task was performed more quickly than both WM tasks [spatial: $t(11) = 18.99, P < 0.0001$; shape $t(11) = 45.32, P < 0.0001$] and RTs were faster for spatial than shape WM [$t(11) = 29.73, P < 0.0001$] (Table 1).

WM load affected performance of both tasks. Subjects made more errors during the high WM load conditions [$F(1,11) = 5.01, P = 0.05$] and the magnitude of this difference was comparable for spatial and shape WM (Load × Task: $F(1,11) = 0.22, P = 0.65$). With regard to RT, subjects responded more slowly at the high WM load [$F(1,11) = 61.55, P < 0.0001$] and this effect was greater for the shape than the spatial task [Load × Task interaction: $F(1,11) = 24.31, P < 0.001$; spatial WM high vs. low load: $t(11) = 2.07, P = 0.04$; shape WM high vs. low load: $t(11) = 9.00, P = 4e-19$].

In summary, subjects performed the spatial WM task more quickly and accurately (trend) than the shape WM task. In addition, compared with spatial WM, performance of the shape WM task was disproportionately slowed by increasing the WM load.

Subjective reports of strategy

After completing scanning, subjects were asked about their strategies. On the spatial task, most subjects reported using the spatial configuration of the shapes on the screen to remember the locations (e.g., for the high WM load condition one subject reported visualizing a triangle with its vertices at the locations to be recalled). For the shape task, 11 of the 12 subjects reported assigning names to each of the shapes (e.g., using a verbal-associative mnemonic strategy).

Brain activation

Specialization by domain

Spatial versus shape WM. There was a relative right hemispheric specialization for spatial versus shape WM. PFC activation was exclusively in the right hemisphere in ventrolateral and frontopolar regions. The plot of the parameter estimates for the voxel with the maximum *t* statistic within the ventrolateral PFC indicates that activity in this region was not affected by WM load and was specific to spatial WM—it had a greater response to the control task than to shape WM. The plot of parameter estimates in the frontopolar

Table 1

Means and standard deviations of accuracy and RT of the side control task and the spatial and shape WM tasks in both the low (two targets) and high (three targets) WM load conditions

	Side	Spatial WM		Shape WM	
		2 targets	3 targets	2 targets	3 targets
WM load	–				
% correct	98.5 ± 1.7	98.1 ± 1.9	97.0 ± 3.3	96.2 ± 3.6	94.7 ± 6.0
RT (ms)	584 ± 23	710 ± 14	728 ± 15	866 ± 15	948 ± 17

region suggested a nonsignificant response to WM load and deactivation in the shape task. With the exception of the precuneus, other regions activated were exclusively in the right hemisphere and included lateral premotor areas, the superior and inferior parietal lobules, and a posterior region in the middle temporal gyrus (Fig. 2a; Table 2A).

Shape versus spatial WM. The left ventrolateral PFC was significantly more activated in shape than spatial WM. The plot of the parameter estimates suggests an effect of shape WM load (non-

significant) and either a negative or no response to the spatial and control conditions. Other activated regions in the left-hemisphere include medial premotor areas, cingulate, and basal ganglia. Ventral visual association areas and the hippocampus showed bilateral activity (Fig. 2b; Table 2B).

Spatial and shape WM

Spatial WM versus control. This contrast revealed activation in the right dorsolateral and frontopolar PFC and bilateral, right

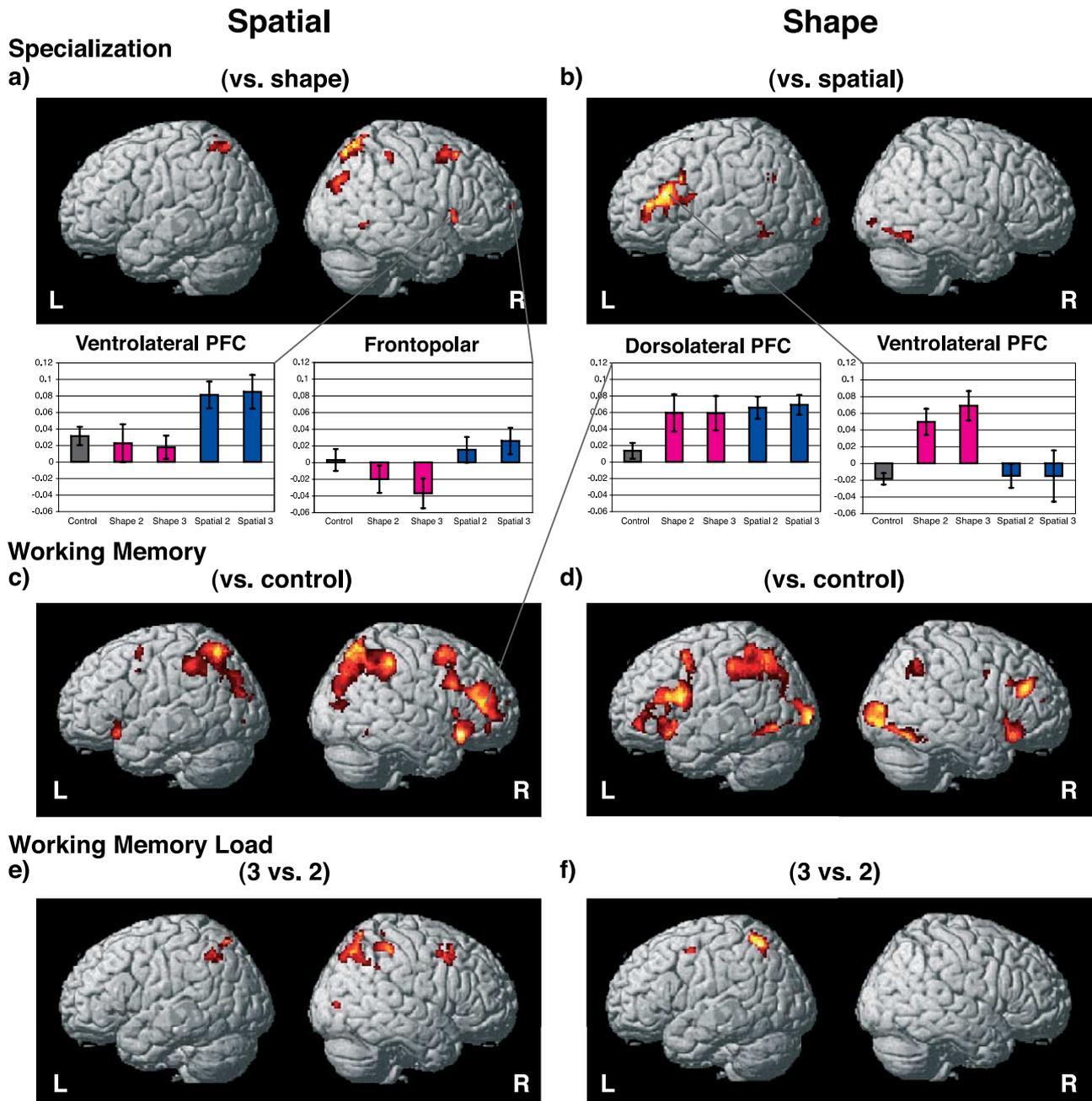


Fig. 2. Renderings of group-averaged statistical parametric maps on the lateral brain surfaces. The first row displays comparisons showing hemispheric specialization by domain: (a) spatial WM vs. shape WM; (b) shape WM vs. spatial WM. The second row displays activity due to spatial and shape WM, respectively; (c) spatial WM vs. control; (d) shape WM vs. control. The third row displays regions that are sensitive to WM load in the spatial (e) and shape (f) WM tasks, respectively. The plots display the parameter estimates with standard error bars for each condition. The estimates are taken from the voxel with the maximum *t* statistic within the activation cluster indicated by the line.

Table 2
Brain regions showing significant activation in the contrasts

Contrast	BA	Talairach coordinates			z score
		x	y	z	
<i>(A) Spatial > shape (masked)</i>					
Left					
Precuneus	7	-4	-51	58	(4.02)
Right					
Superior parietal lobule	7	12	-65	55	(4.47)
Precuneus	7	2	-48	48	(3.91)
Middle temporal gyrus	37	51	-58	1	(4.25)
Superior frontal gyrus	8	38	22	50	(3.91)
Middle frontal gyrus	6	30	8	49	(3.88)
Inferior frontal gyrus*	45	53	18	1	(3.80)
Precuneus	31	18	-61	23	(3.79)
Precuneus	19	42	-70	37	(3.69)
Superior occipital gyrus	19	36	-80	32	(3.57)
Inferior parietal lobule	40	46	-34	51	(3.56)
Superior frontal gyrus*	10	26	63	10	(3.55)
<i>(B) Shape > Spatial (masked)</i>					
Left					
Inferior frontal gyrus*	45	-48	22	21	(4.56)
Inferior frontal gyrus	9	-38	11	27	(4.54)
Inferior frontal gyrus	44	-48	5	16	(4.03)
Insula	13	-38	-5	13	(3.83)
Inferior frontal gyrus	47	-46	39	-2	(3.44)
Superior frontal gyrus (medial)	8	-6	25	43	(4.36)
Superior frontal gyrus (medial)	6	-8	11	55	(3.32)
Caudate		-6	12	10	(4.08)
Angular gyrus	39	-36	-57	32	(3.95)
Nucleus accumbens		-18	-8	-8	(3.91)
Substantia nigra		-16	-20	-6	(3.55)
Hippocampus		-28	-20	-9	(3.35)
Inferior temporal gyrus	37	-46	-51	-6	(3.55)
Precentral gyrus	6	-36	-14	27	(3.55)
Inferior occipital gyrus	18	-20	-95	1	(3.52)
Cingulate gyrus	24	-14	15	27	(3.28)
Cingulate gyrus	24	-14	-4	44	(3.25)
Right					
Fusiform gyrus	37	40	-61	-9	(4.20)
Inferior occipital gyrus	19	44	-76	-5	(4.04)
Hypothalamus		2	-6	-5	(4.11)
Inferior occipital gyrus	18	26	-89	3	(3.60)
Hippocampus		28	-28	-7	(3.40)
<i>(C) Spatial > Control</i>					
Left					
Superior parietal lobule	7	-22	-58	53	(5.25)
Precuneus	7	-8	-56	53	(4.25)
Inferior parietal lobule	40	-42	-39	42	(4.00)
Superior occipital gyrus	19	-24	-79	22	(3.63)
Inferior frontal gyrus	47	-30	21	-11	(4.50)
Middle frontal gyrus	6	-26	2	46	(4.12)
Thalamus		-8	-19	8	(3.32)
Inferior occipital gyrus	19	-42	-82	1	(3.32)
Precentral gyrus	6	-42	6	37	(3.25)
Right					
Inferior frontal gyrus	47	38	23	-11	(5.49)
Superior parietal lobule	7	30	-64	42	(4.58)
Inferior parietal lobule	40	46	-35	46	(4.52)
Middle occipital gyrus	19	44	-77	13	(3.36)
Middle occipital gyrus	18	34	-85	15	(3.19)

Table 2 (continued)

Contrast	BA	Talairach coordinates			z score
		x	y	z	
<i>(C) Spatial > Control</i>					
Middle frontal gyrus*	46	40	39	11	(4.69)
Middle frontal gyrus	10	46	51	1	(4.02)
Middle frontal gyrus	9	48	19	29	(3.73)
Middle frontal gyrus	6	32	11	55	(4.55)
Cingulate gyrus	32	8	22	43	(4.36)
Superior frontal gyrus (medial)	8	10	31	33	(4.18)
Thalamus		6	-17	10	(4.04)
Caudate		16	1	15	(3.82)
Inferior frontal gyrus	45	48	18	3	(3.74)
Thalamus		18	-27	12	(3.54)
Inferior frontal gyrus	10	28	63	10	(3.49)
Middle frontal gyrus	10	46	44	-9	(3.45)
Middle temporal gyrus	37	55	-55	-7	(3.32)
<i>(D) Shape > Control</i>					
Left					
Thalamus		-16	-16	-3	(5.27)
Cingulate Gyrus	32	-12	21	38	(5.06)
Inferior frontal gyrus	44	-50	11	16	(4.74)
Inferior frontal gyrus	45	-32	37	6	(4.72)
Inferior frontal gyrus	47	-30	19	-4	(4.71)
Precentral gyrus	6	-36	4	38	(4.43)
Hippocampus		-26	-24	-6	(4.37)
Insula		-36	9	18	(4.34)
Middle frontal gyrus	11	-32	44	-7	(4.12)
Middle frontal gyrus	6	-24	4	44	(4.05)
Caudate		-6	8	12	(4.03)
Lentiform nucleus		-20	-1	13	(3.72)
Middle frontal gyrus	45	-40	30	15	(3.58)
Inferior parietal lobule	40	-36	-51	36	(4.66)
Middle occipital gyrus	18	-24	-97	7	(4.65)
Superior parietal lobule	7	-34	-54	47	(4.59)
Postcentral gyrus	2	-48	-29	42	(4.26)
Precuneus	7	-14	-66	40	(3.93)
Inferior temporal gyrus	37	-40	-56	-1	(4.35)
Fusiform gyrus	37	-48	-51	-9	(3.84)
Fusiform gyrus	20	-42	-36	-13	(3.52)
Inferior occipital gyrus	18	-30	-76	0	(3.23)
Right					
Inferior frontal gyrus	47	26	23	-8	(4.80)
Insula	13	36	11	16	(3.79)
Middle occipital gyrus	18	32	-87	1	(4.67)
Inferior occipital gyrus	19	42	-78	-5	(4.35)
Fusiform gyrus	19	42	-67	-10	(4.07)
Fusiform gyrus	37	38	-53	-9	(3.85)
Calcarine	17	18	-91	1	(3.53)
Supramarginal gyrus	40	34	-55	32	(4.59)
Superior parietal lobule	7	28	-43	43	(4.55)
Cingulate gyrus	32	14	21	38	(4.56)
Caudate		6	14	7	(4.28)
Middle frontal gyrus	46	50	32	22	(4.38)
Middle frontal gyrus	9	55	23	26	(3.45)
Substantia nigra		8	-16	-9	(4.29)
Hippocampus		30	-26	-5	(4.21)
Thalamus		18	-13	10	(3.71)
Lentiform nucleus		28	2	9	(3.66)
Precentral gyrus	6	40	4	37	(3.65)
Middle frontal gyrus	10	38	47	11	(3.20)

Table 2 (continued)

Contrast	BA	Talairach coordinates			z score
		x	y	z	
<i>(E) Spatial WM Load 3 > 2</i>					
Left					
Lentiform nucleus		–28	6	–5	(3.53)
Inferior parietal lobule	40	–36	–52	45	(3.43)
Superior parietal lobule	7	–20	–61	56	(3.41)
Right					
Inferior parietal lobule	40	50	–34	51	(4.14)
Superior parietal lobule	7	24	–57	64	(3.86)
Middle frontal gyrus	6	40	6	44	(3.79)
Middle frontal gyrus	8	30	18	45	(3.71)
Middle occipital gyrus	19	42	–81	10	(3.52)
Thalamus		28	–27	9	(3.39)
Superior parietal lobule	7	40	–40	63	(3.32)
Inferior parietal lobule	40	42	–45	37	(3.25)
Lentiform nucleus		32	–8	–5	(3.24)
Superior frontal gyrus	6	26	8	51	(3.19)
<i>(F) Shape WM Load 3 > 2</i>					
Left					
Superior parietal lobule	5	–36	–47	61	(4.33)
Superior parietal lobule	7	–40	–58	53	(3.63)
Precentral gyrus	6	–44	0	48	(3.53)
Thalamus		–4	–29	9	(3.27)
Right					
Precuneus	7	4	–49	63	(4.04)
Thalamus		8	–33	7	(3.61)

Putative Brodmann's Areas, Talairach coordinates, and the z scores for the voxel with the maximum *t* statistic within each cluster and for each local maximum that was 12 or more mm apart. If a local maximum fell in the same anatomical location and Brodmann's Area as a global maximum or another local maxima, only the one with the higher *t* statistic was reported. Prefrontal cortex regions are indicated in bold. Indented regions are local maximum within the cluster. An asterisk indicates that the parameter estimates for this voxel have been plotted in Fig. 2.

greater than left, ventrolateral PFC. The plot of the regression coefficients in the right dorsolateral PFC and the activation maps demonstrate that this region was also recruited for shape WM. There was also activation in the superior and inferior parietal lobules, lateral and medial premotor areas, cingulate, basal ganglia, and the thalamus. The magnitude and extent of activation was greater in the right hemisphere (Fig. 2c, Table 2C).

Shape WM versus control. Shape WM was associated with activation in bilateral ventrolateral, right dorsolateral, and left frontopolar PFC. In addition, there was activation in lateral premotor areas, parietal regions, ventral visual association areas, cingulate, basal ganglia, thalamus, and the hippocampus. Activity was generally greater in the left hemisphere (Fig. 2d; Table 2D).

Spatial and shape WM load

Spatial WM load. There were no PFC regions that were significantly more activated in the high versus low spatial WM load condition. Instead, activation was seen in the superior and inferior parietal lobules bilaterally, right lateral premotor areas, the right occipital lobe, bilateral basal ganglia, and the right thalamus (Fig. 2e; Table 2E).

Shape WM load. The PFC was not activated in this contrast. Activated regions included the left superior parietal lobule, right precuneus, left lateral premotor areas, and bilateral thalamus (Fig. 2f; Table 2F).

Discussion

Although the spatial and shape WM tasks used identical stimuli and required identical motor responses, a direct comparison of these tasks gave rise to distinct and highly lateralized patterns of PFC activation. This demonstrates hemispheric specialization by WM domain in these PFC regions. Spatial WM was associated with significantly greater right ventrolateral and frontopolar PFC activation than WM for shapes. This increased PFC activation cannot be attributed to low level sensorimotor requirements, increased task difficulty, or increased time performing the task since performance of the spatial WM task was faster and more accurate. Shape WM, in contrast, was associated with increased activation in the left ventrolateral PFC. These findings demonstrate that hemispheric specialization depends on the nature of the task rather than on the nature of the stimulus.

Our findings of a hemispheric specialization by domain in the ventrolateral PFC, but not in the dorsolateral PFC, echo the conclusions of a review by D'Esposito et al. (1998). In addition to areas that appear to be specialized by domain, the activation maps for spatial and shape WM show similar recruitment of a number of regions. This suggests that these tasks require several WM processes in common. However, the findings of distinct activation for spatial and shape WM suggest that these tasks also require domain-specific prefrontally mediated processing strategies. We hypothesize that the ventrolateral PFC plays a role in implementing these domain-specific strategies. Below, we discuss the nature of the specific strategies that may be required to accomplish the spatial and shape WM tasks.

Spatial WM, the act of maintaining locations on-line, is a task with clear adaptive significance (e.g., for foraging, hunting, escaping predators). Primates are thought to have specialized processing systems for the representation of spatial locations (Leung et al., 2002). In humans, the right hemisphere is dominant for the spatial direction of attention (Mesulam, 1981). Thus, it is not surprising that, compared to shape WM, spatial WM activated a predominantly right hemisphere network, including the right ventrolateral and frontopolar PFC, right lateral premotor areas, and right greater than left parietal regions. The right PFC areas involved in spatial WM were not activated in the shape WM task. We hypothesize that the finding of better performance and predominantly right hemisphere activation during spatial versus shape WM reflects the use of a domain-specific processing strategy for maintaining and responding to spatial information.

With regard to Spatial WM load, with the exception of the PFC, the map of regions that were sensitive to WM load was remarkably similar to the map of regions that were specialized for spatial WM. We interpret the load sensitivity to indicate that these regions are involved in maintaining and responding to spatial information. Given the lack of a significant load effect in the PFC regions showing specialization, we cannot definitively establish that these regions are specialized for WM for locations and shapes rather than more general processing of locations and shapes. However, not all regions that are involved in WM are necessarily sensitive to increases in load. The lack of a load effect in the right

ventrolateral PFC for spatial WM may reflect the use of a cognitive strategy that did not incur a significant increment in cost at the higher level of load.

The exact nature of this strategy is a matter of speculation, but several lines of research are relevant. In studies of numerosity, there is little increment in RT or errors for reporting the number of items present in an array up to about four. This “subitizing” phenomenon has been interpreted to indicate that collections of up to three or four items are represented in parallel, as spatial configurations: two make a line and three form a triangle (e.g., Mandler and Shebo, 1982; Trick and Pylyshyn, 1993). We propose that in the current study, subjects were able to efficiently represent the target locations as a spatial configuration. This is consistent with the subjects’ self-report of strategy. We further speculate that there is little difference in the cost of representing two versus three locations as a configuration and that the right ventrolateral PFC implemented this configural strategy. We account for the significant decrement in performance and increased activation in other brain regions at the higher spatial WM load as reflecting load-sensitive response processes that may have required subjects to break the configuration to compare the locations of each target to that of the probe in a serial fashion. We further hypothesize that activity in right frontopolar cortex played a role in retrieving spatial information for these comparisons (Nyberg et al., 1996).

Our hypothesis regarding the role of the ventrolateral PFC in the use of a configural strategy for spatial WM is consistent with the recent findings of Bor et al. (2003). They reported that structured spatial sequences that could be represented in WM as configurations gave rise to better performance and greater activation in ventrolateral PFC than unstructured spatial sequences. In their study, however, the ventrolateral PFC activation was bilateral, right greater than left. The difference in laterality between the two studies may reflect differences in the comparison tasks. In the present study, the comparison task involved shape WM, while in the study of Bor et al. (2003), it involved WM for unstructured spatial sequences.

There may be no such analogous specialized processing system and/or strategy for the representation of abstract shapes, a relatively novel task with no clear adaptive significance. Note that we refer to our task as a “shape” rather than “object” WM task because rather than objects, we displayed simple two-dimensional shapes that are always shown in the same orientation. In contrast, objects have unique identities, are linked to semantic memory, are experienced in a number of contexts, and are seen in many different orientations. Primates routinely categorize objects such as trees and faces, but the actual shape of an object on the retina continually changes as one interacts with or moves around it. The representation of objects is abstracted beyond the specific details of sensory inputs allowing them to be generalized to new circumstances (Miller et al., 2003). In other words, when we automatically perceive objects as members of categories, we generally look past their actual shape, unless we intend to sketch them from one or another perspective, an activity that requires training. For this reason, in the real world, it is adaptive to retain object constancy rather than shape constancy (Coleman et al., 2002). The novel abstract shape stimuli of the current study are likely represented differently in the brain than are objects such as trees or faces. In fact, there is evidence that the extrastriate regions involved in object recognition (image features) differ from those that respond to lower level features that define a shape (Kourtzi and Kanwisher, 2001). Because of its novelty (and lack of ecological validity), the shape WM task may have compelled subjects to use a relatively inefficient strategy (as indicated by their poorer perfor-

mance). Although we intentionally selected our shapes to be difficult to verbalize, almost all subjects reported using a verbal-associative mnemonic strategy. It may be that it was this strategy that was associated with left ventrolateral PFC activation in a region that includes Broca’s area and in the hippocampus. Our findings and hypotheses regarding the left ventrolateral PFC are consistent with those of a previous study of shape WM that used similar stimuli (Smith et al., 1995).

One would expect activation associated with a verbal mnemonic strategy to be sensitive to increments in WM load. The parameter estimates of activity in the left ventrolateral PFC suggest that this is the case (Fig. 2b). However the difference between loads was not significant and a larger sample may be necessary to definitively demonstrate this effect.

On the basis of our findings, we propose that right ventrolateral PFC specialization for spatial WM reflects the use of a configural strategy and the left ventrolateral specialization for shape WM reflects the use of a verbal mnemonic strategy. However, this hemispheric specialization may be obscured if these same regions are recruited for more general WM processes. This may explain why we found distinct lateral PFC patterns of activation for spatial versus shape WM while some other studies have not (Nystrom et al., 2000; Postle et al., 2000a). These previous studies employed the n-back task, which in addition to maintenance, requires manipulative processes including the updating and temporal tagging of the contents of WM. These processes are required regardless of the domain of information being represented. In addition, the difficulty of the n-back task may encourage the recruitment of several complementary processing strategies. There appears to be a common network of PFC regions, including areas in the dorsolateral and ventrolateral PFC, that show increased activation in response to increases in diverse cognitive demands (e.g., an increase in WM load, response conflict), regardless of domain (Duncan and Owen, 2000). Perhaps because the tasks employed in the current study were relatively easy and minimized manipulation requirements, they gave rise to evidence of hemispheric specialization in the ventrolateral PFC and other brain regions.

A limitation of the present study is that maintenance and response processes were not temporally separated and their hemodynamic responses could not be distinguished. Separated maintenance and response epochs cause distinct patterns of regional activity that presumably reflect the different processes they require (e.g., Cohen et al., 1997; Leung et al., 2002; Manoach et al., in press; Rowe and Passingham, 2001). Some of these processes are probably required for both spatial and shape WM and others may be domain-specific. Because we were not able to separate and examine these component processes, we may have missed domain-specific regional activation. For example, in the present study, the right dorsolateral PFC was activated for both spatial and shape WM. This may reflect its role in response selection, a general process that is required by both WM tasks (Rowe and Passingham, 2001; Rowe et al., 2000). The right dorsolateral PFC activation due to response selection may have masked domain-specific activation due to maintenance. Had we designed the WM tasks to separate the maintenance and response epochs, it is possible that we would have detected hemispheric specialization in the right dorsolateral PFC and/or other regions for processes involved in maintaining spatial information. However, the hypothesis of a dorsolateral PFC role in maintenance would be inconsistent with previous neuroimaging and lesion studies that suggest that the DLPFC plays a greater role in preparing a response based on information stored in

WM than in storage itself (e.g., Leung et al., 2002; Manoach et al., in press; Petrides, 2000; Rowe and Passingham, 2001; Rowe et al., 2000).

In summary, in the same group of volunteers, using spatial and shape WM tasks with identical stimuli, we demonstrated that spatial WM gives rise to greater right ventrolateral PFC activation than a more difficult shape WM task. We propose that this hemispheric specialization reflects the use of configural processing strategies for spatial WM. The exact nature of this strategy and the role of the PFC in implementing it remain to be defined. More generally, identifying the relevant dimensions of PFC functional specialization may depend on understanding the component processes of the tasks that these regions subservise and the basic computations that they perform. These computations are likely to be quite general given the diversity of tasks that have been shown to activate these regions (Duncan and Owen, 2000).

Acknowledgments

This work was supported by the National Institute of Mental Health (K23MH01829, R01 31340, PO1 31154), the National Center for Research Resources (P41RR14075), and the Mental Illness and Neuroscience Discovery (MIND) Institute. The authors wish to thank Mary Foley for her technical assistance and Earl Miller for his thoughtful remarks.

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