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Intact hemispheric specialization for spatial and shape working memory in schizophrenia

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Dr. Philip S. Holzman died before the completion of this manuscript. The authors would like to dedicate this work to his memory

Abstract

Objective: Using functional MRI, we investigated whether, like healthy subjects, patients with schizophrenia show a relative hemispheric specialization in ventrolateral prefrontal cortex (PFC) for spatial and shape working memory (WM). We hypothesized that reduced specialization in schizophrenia would reflect a failure to adopt optimal domain-specific strategies and would contribute to WM deficits.
Methods: Twelve healthy subjects and 16 schizophrenia patients performed spatial and shape WM tasks and a non-WM control task. Direct comparisons of the spatial and shape WM tasks assessed specialization.
Results: Despite deficient WM performance, both patients and controls showed a relative hemispheric specialization in ventrolateral PFC for spatial (right) and shape (left) WM and did not differ in this regard.
Conclusions: The finding of intact hemispheric specialization in ventrolateral PFC suggests that patients employ the same domain-specific strategies as healthy subjects during spatial and shape WM. Rather than reflecting a failure to adopt the optimal strategy, we hypothesize that WM deficits in schizophrenia reflect impairments of executive processes that are required for WM performance regardless of domain. These processes are associated with activity in the dorsolateral PFC, a region that has been repeatedly implicated in studies of WM.

Keywords: Prefrontal cortex; Schizophrenia; Working memory; Hemispheric specialization; Functional neuroimaging; Laterality

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1. Introduction

In schizophrenia, there is abundant evidence of both behavioral impairment and anomalous patterns of brain activity during working memory (WM) performance (c.f. review Manoach, 2003). In addition to being comprised of processes involved in encoding, maintaining, manipulating, and responding to information held "on-line', WM operates on different domains of information. Neuroimaging evidence suggests that there are functional subdivisions within the lateral prefrontal cortex (PFC) for WM processes (Cohen et al., 1997; D'Esposito et al., 1999; Manoach et al., 2003; Petrides, 1995). The literature also supports a relative hemispheric specialization by WM domain (e.g., spatial vs. non-spatial), specifically in the ventrolateral rather than dorsolateral PFC (c.f. review D'Esposito et al., 1998). We recently reported that, compared to shape WM, spatial WM gave rise to increased *right* ventrolateral PFC activity in healthy subjects (Manoach et al., 2004). In contrast, relative to spatial WM, shape WM gave rise to *left* ventrolateral PFC activity. The patterns of performance and brain activation suggested that different processing strategies were used for spatial and shape WM. The present study used these same tasks to examine hemispheric specialization of the lateral PFC for spatial and shape WM in schizophrenia. Hemispheric specialization is presumed to reflect the deployment of specific processing strategies in response to task demands. We hypothesized that PFC hemispheric specialization would be absent or reduced in schizophrenia and that this, along with impaired task-performance, would reflect a failure to adopt the optimal strategy for WM performance. This hypothesis is consistent with a previous fMRI study that found an absence of PFC lateralization comparing verbal and spatial WM performance in schizophrenia (Walter et al., 2003) and with the extensive evidence of reduced lateralization of function in schizophrenia as measured by both behavioral (c.f. reviews: Satz and Green, 1999; Sommer et al., 2001a) and functional neuroimaging studies (e.g., Gur and Chin, 1999; Menon et al., 2001; Sommer et al., 2001b).

The spatial and shape WM tasks employed in the present study used identical stimuli and had the same motor response requirements. They used relatively low WM loads and emphasized WM maintenance rather than manipulation requirements. Because the spatial and shape WM tasks were presented in separate runs, they also minimized task-switching requirements. The rationale for minimizing manipulation, task-switching, and the requirement to manage supra-capacity WM loads is that these executive requirements may all engage the PFC regardless of the domain of information being represented (D'Esposito et al., 1998; D'Esposito et al., 2000; Fletcher and Henson, 2001; Sohn et al., 2000) and for this reason may obscure specialization. In addition we wanted the tasks to be simple enough that patients with schizophrenia could perform significantly better than chance. Thus, the paradigm employed allowed us to test functional specialization for spatial vs. 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 the potential influences of manipulation, task-switching, and processes related to excessive task difficulty (e.g., disengagement, error processing, and guessing).

To test the hypothesis of reduced ventrolateral PFC hemispheric specialization in schizophrenia, we directly compared the spatial and shape WM tasks. We first looked for regions activated in common by both groups and then tested for between group differences. These two comparisons determine which PFC areas have a differential response for domain-specific task demands (e.g., represent locations vs. shape features) in both groups and whether the groups differ in specialization. We also compared each WM task to a non-WM control task, also with identical sensorimotor requirements, to test the hypothesis that reduced specialization in schizophrenia would occur in the context of equal or greater dorsolateral PFC activation for WM, consistent with the findings of previous work (Walter et al., 2003).

2. Materials and methods

2.1. Subjects

The schizophrenia sample was comprised of 16 outpatients (Table 1). Two patients had not taken any antipsychotic medication for six or more weeks. Fourteen patients had been maintained on stable doses

Table 1
Means, standard deviations, and group comparisons of demographic data and rating scale scores

Subject characteristics	Healthy subjects ($n=12$)	Schizophrenia subjects ($n=16$)	t	p
Age	35 ± 10	42 ± 11	1.69	0.10
Sex	8 M/4 F	14 M/2 F	$\phi=0.25$	0.35
Handedness (Edinburgh)	88 ± 10	90 ± 9	0.67	0.51
Parental SES*	1.9 ± 1.2	2.4 ± 1.1	$z=1.4$	0.18
Age of onset		25 ± 8	Level of	
Length of illness (years)		18 ± 10	severity	
BPRS		16 ± 9	Minimal	
PANSS positive		13 ± 4	Mild	
PANSS negative		14 ± 3	Mild	
SANS		26 ± 9	Minimal	

*A lower score denotes higher status.

of antipsychotic medications for at least six weeks: two took conventional agents, two took both conventional and atypical agents, and nine took atypical antipsychotics. One patient was in a blinded drug study and took either a conventional or atypical antipsychotic. Diagnoses were confirmed with Structured Clinical Interviews for DSM-IV (First et al., 1997) administered by an experienced psychiatrist. Clinical status was characterized with the Brief Psychiatric Rating Scale (Overall and Gorham, 1962), the Positive and Negative Syndrome Scale (Kay et al., 1987), and the Scale for the Assessment of Negative Symptoms (Andreasen, 1983). Twelve healthy control subjects, without personal history of psychiatric illness or family history of schizophrenia spectrum disorders, were recruited from the community with poster advertisements. The findings from the healthy subjects were the topic of a previous report (Manoach et al., 2004).

All subjects were screened to exclude substance abuse or dependence within the past six months, a history of head injury resulting in sustained loss of consciousness and/or cognitive sequelae, neurological illness, and any disorder affecting cerebral metabolism.

All subjects endorsed strong right-hand preference as determined by a laterality score of 70 or above on the modified Edinburgh Handedness Inventory (White and Ashton, 1976). The schizophrenia group showed a trend to be older than the healthy group but did not differ in sex, handedness, or parental socioeconomic status (SES) (Hollingshead, 1965). All subjects gave written informed consent. The study was approved by the human subjects committees at Massachusetts General Hospital and the Massachusetts Department of Mental Health.

2.2. Cognitive tasks

The stimuli for spatial and shape WM tasks and the control task were ten Attneave shapes (Attneave and Arnoult, 1956) that could appear in any of ten possible locations on the screen. These shapes were irregular polygons that were selected to have low recognition and association values to inhibit the use of verbal mnemonic strategies (Vanderplas and Garvin, 1959). The locations were also difficult to verbalize since they did not fall on a grid or form any recognizable spatial configuration. The WM and control tasks are depicted and described in Fig. 1 and its legend.

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, grouped together to minimize task-switching requirements. The total experiment time was approximately 40 min. Half of the subjects performed the spatial blocks first and half performed the shape blocks first. The presentation background was black and the shapes were presented in blue for the spatial task, magenta for the shape task, and gray for the control task. 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. Prior to 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.

2.3. Analysis of behavioral data

We analyzed percent errors with repeated measures ANOVA with Group (schizophrenia and healthy) as a factor and Task (spatial and shape) and WM Load (two or three targets) as repeated measures. Pairwise comparisons were evaluated with Tukey–Kramer tests. Latencies for correct trials were analyzed with

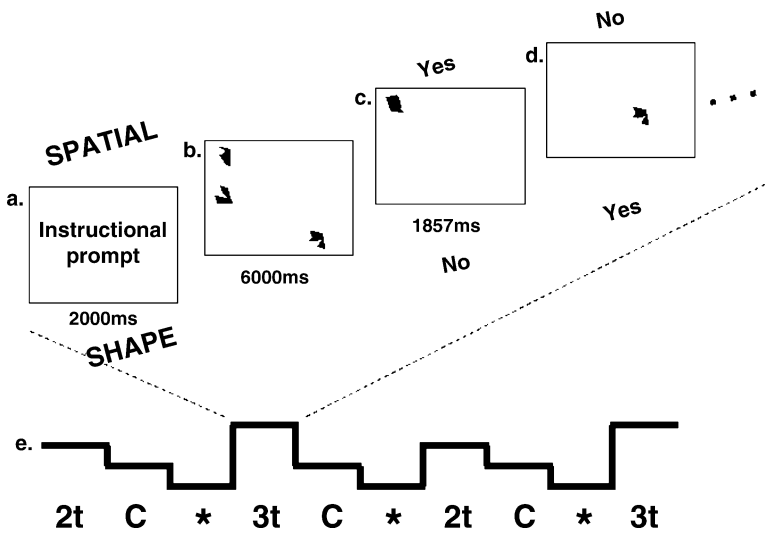

Fig. 1. a) All of the tasks began with an instructional prompt (2000 ms) consisting of "Learn Where" for the spatial task; "Learn What" for the shape task; and "Which Side" for the control task. b) For the WM tasks, this prompt was followed by a set of either two or three target shapes (6000 ms) appearing 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 2 blocks of the high and low load WM conditions (2t and 3t), 3 blocks of the control condition (C) and 3 periods of fixation (*). The fixation baseline condition consisted of an asterisk that flashed at 2 s intervals in order to maintain the subjects' visual attention and gaze. The order of the blocks was the same across runs.

randomized block ANOVA with Group, Task and Load as factors and subjects nested within group as the random factor. Pairwise comparisons were evaluated with contrasts.

2.4. 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 Tesla 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 $3.13 \times 3.13 \times 5$ mm) were acquired interleaved. Four images at the beginning of each scan were acquired and discarded to allow longitudinal magnetization to reach equilibrium.

2.5. fMRI data analysis

The functional data were analyzed using SPM2 (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 SPM's EPI template and spatially smoothed with a three-dimensional isotropic Gaussian filter (8 mm full-width half-maximum). Motion was quantified by computing a maximum displacement metric for each individual based on

translational motion correction parameters in the x, y, and z coordinate axes in millimeters across all six runs (square root (x^2+y^2+z^2)).

Functional data were analyzed in two stages constituting a hierarchical mixed-effects model. In the first stage, a general linear model (GLM) was constructed for each subject's time series data. To form the GLM, neural responses to the instructional prompts, encoding epochs, and probe epochs for the spatial and shape WM tasks at each level of WM load and for the control condition were modeled separately as square waves (i.e., "boxcar" functions). These waveforms were then convolved with a canonical hemodynamic response function to yield regressors that modeled the BOLD response to each condition. The six motion correction parameters for each run were also included in the GLM. Voxelwise parameter estimates for all regressors were estimated using weighted least squares (WLS) within SPM2. Individual subject data were high-pass filtered at an effective cut-off period of 128 s, "pre-whitened" with a fitted autoregressive model (AR(1)), and proportionally scaled to remove temporal fluctuations in global signal.

In the second stage of analysis, contrasts of the parameter estimates from the individual GLMs were entered into an ANOVA model with Group as the between-subjects factor and Task (spatial and shape) and WM Load (2 and 3) as within-subjects factors. These contrasts were based on the comparison of each of the four WM probe epochs (spatial and shape at 2 levels of WM load) to the control condition. The parameters of the ANOVA model were again estimated using WLS in SPM2 and used to form statistical parametric maps of the t-statistic, SPM{T}s.

To identify regional activity common to both groups, we used a highly conservative conjunction approach (Friston et al., 1999) as refined by Nichols et al. (2005) for use at the random effects level. The statistical maps based on these conjunction analyses display voxels that are significantly active in both groups for a particular contrast. Anatomical labeling of regional activity made reference to the Talairach and Tournoux (1988) atlas after adjusting for differences between MNI and Talairach coordinates (http://www.mrc-cbu.cam.ac.uk/Imaging/minispace.html). All group level inferences were made by applying a voxel-level threshold to the SPM{T}s at $p \leq .001$, uncorrected for multiple comparisons.

Given the brief duration of the encoding epochs (6 s), our tasks were optimized to examine activation during the probe epochs (40 s) and the analyses presented are based on the probe epochs only. For the between group comparisons, we ensured that the resulting differences maps revealed positive activation in the group of interest (e.g., healthy), rather than a deactivation in the other group (e.g., schizophrenia), by creating a binary mask of the voxels that were more active in the group of interest in that contrast at a threshold of $p \leq .05$ and limiting our analysis to these voxels.

2.6. Specialization by domain

Direct comparisons of spatial and shape WM, collapsed across WM load, were used to identify PFC regions showing specialization based on domain. Conjunction analyses identified regions that were specialized in both groups and between group comparisons identified differences in regional specialization. To ensure that the resulting specialization maps revealed activation associated with the WM task of interest (e.g., spatial), rather than a deactivation in the WM comparison task (e.g., shape), analyses were restricted to voxels that were more active in the WM task of interest relative to the control condition at a threshold of $p \leq .05$. Thus for the between-groups specialization comparisons, two masks were applied to limit activity to both the group and task of interest.

2.7. Spatial and shape WM

Each WM task, collapsed across WM load, was compared to the control condition. Conjunction analyses identified regional activation associated with spatial and shape WM in both groups. Between-groups comparisons identified differences in activation due to spatial and shape WM.

3. Results

3.1. Task performance

One schizophrenia subject has missing behavioral data during scanning due to technical difficulties. Since his WM performance during the practice trials prior to scan-

ning was accurate, he was included in analyses of the imaging data. Performance exceeded chance levels in all task conditions for all subjects (60% or above at $p \leq .05$, exact binomial test). The groups did not differ in performance of the control task (accuracy: $F(1,25)=1.76$, $p=.20$; latency: $F(1,26)=1.88$, $p=.18$). Healthy subjects showed a trend to respond more quickly and were significantly more accurate on the WM tasks (accuracy: $F(1,25)=34.29$, $p<.001$; latency: $F(1,26)=3.93$, $p=.06$) (Fig. 2). The spatial WM task was easier than the shape WM task. It was performed more quickly by both groups ($F(1,26)=1309.58$, $p<.0001$) and more accurately by the schizophrenia group (trend) (healthy: $F(1,11)=2.64$, $p=.13$; schizophrenia: $F(1,14)=3.69$, $p=.08$). Increasing WM load decreased the accuracy and increased the latency of responding in both groups on both tasks (accuracy: $F(1,25)=25.12$, $p<.0001$; latency: $F(1,26)=1309.58$, $p<.0001$). Increasing WM load slowed latencies more for shape than spatial WM (load by task interaction: $F(1,26)=38.02$, $p<.0001$; spatial WM high vs. low load: $t(26)=4.10$, $p=4e-6$; shape WM high vs. low load: $t(26)=12.66$, $p=2e-36$). In the schizophrenia group, the spatial and shape WM tasks were performed with comparable accuracy at a low WM load. Compared to controls, patients showed a disproportionate decline in accuracy with increasing load (schizophrenia: $F(1,14)=24.64$, $p=.0002$; controls: $F(1,11)=5.01$, $p=.05$) but only for shape ($p<.05$) and not spatial WM.

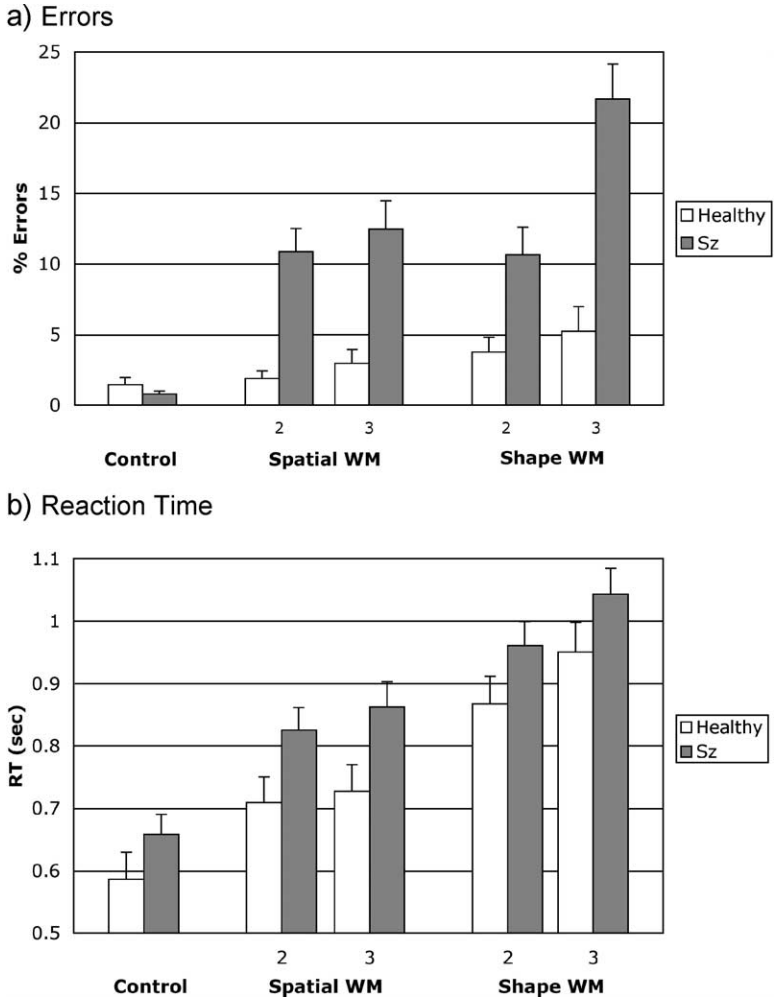

Fig. 2. Means and standard errors of WM task performance for the healthy (white bars) and schizophrenia (gray bars) groups in both the low (two targets) and high (three targets) WM load conditions. a) Accuracy as indicated by percent errors and b) reaction time in seconds.

3.2. Subjective reports of strategy

On the spatial task, 7/12 healthy subjects and 3/16 schizophrenia patients articulated a strategy suggesting that they used the spatial configuration of the shapes on the screen to remember the locations. Three healthy subjects reported relating the locations to defects on the screen and one healthy subject and three schizophrenia patients reported assigning verbal labels to the locations. The remaining subjects had trouble articulating a clear strategy. For the shape task, 11/12 healthy subjects and 6/16 schizophrenia patients reported assigning names to each of the shapes. One healthy subject and two schizophrenia patients reported memorizing the shape features. The remainder of the patients either did not report a strategy or reported an impossible strategy (e.g., "shaded vs. unshaded").

3.3. fMRI findings

3.3.1. fMRI motion

The difference in mean motion between groups was not significant, but schizophrenia subjects were more variable (healthy $1.11 \pm .44$ mm; schizophrenia 1.85 ± 1.57 mm, $t(26) = 1.57$, $p = 0.13$). Examination of the motion plots revealed that there were three outliers that accounted for the increased variability in the schizophrenia group. Omitting these three subjects rendered both mean and SD of the motion metric quite similar to healthy subjects ($1.16 \pm .52$ mm) and did not substantially change the findings. We therefore chose to keep these subjects in the analyses. Group analyses were performed on models that included and excluded individual motion regressors. The findings were not substantially different and only the analyses that included motion regressors are presented.

3.3.2. Specialization by domain

3.3.2.1. Spatial vs. shape WM. Conjunction analysis revealed a relative right hemispheric specialization for spatial vs. shape WM (Fig. 3a; Table 2A) including a small region in the right ventrolateral PFC (BA 44). There were no significant group differences in PFC specialization.

3.3.2.2. Shape vs. spatial WM. The left ventrolateral PFC (BA 44 and 45) was significantly more activated in shape than spatial WM for both groups in the conjunction analysis (Fig. 3b; Table 2B). There were no significant group differences in PFC specialization.

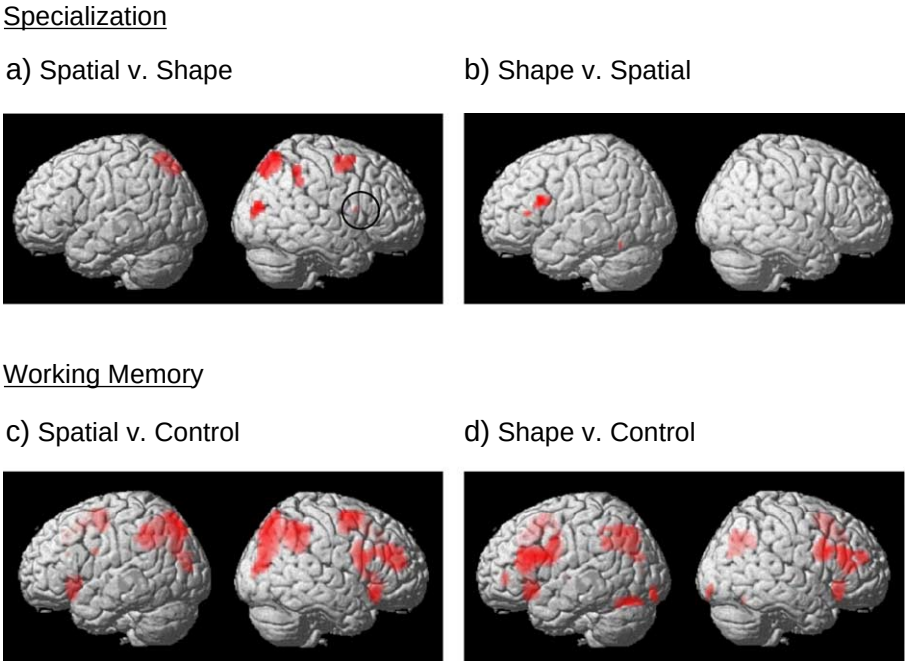

Fig. 3. Renderings of conjunction analysis maps for healthy and schizophrenia groups on the lateral brain surfaces. The intensity of the color indicates depth (e.g., voxels that are 10 mm behind the surface have half the intensity of ones at the surface). Hemispheric specialization for (a) spatial vs. shape WM (the circle highlights an area of common activity in right ventrolateral PFC) and (b) shape vs. spatial WM. Common activation due to working memory for (c) spatial information and (d) shape information.

Table 2
Brain regions showing significant activation in the conjunction and group comparison contrasts

Contrast		BA	Talairach coordinates			z-score
			x	y	z	
A) Spatial>shape conjunction						
Left	Precuneus	7	−12	−63	57	3.29
	Sup. parietal lobule	7	−27	−60	57	3.26
Right	Sup. parietal lobule	7	15	−66	60	4.82
	Mid. frontal g.	6	27	0	54	4.32
	Mid. occipital g.	18	42	−84	18	4.26
	Inf. parietal lobule	40	48	−45	48	3.60
	Inf. frontal g.	**44**	**51**	**9**	**12**	**3.07**
H>SZ						
Left	Sup. parietal lobule	7	−24	−69	57	3.50
	Sup. parietal lobule	7	−9	−69	60	3.48
Right	Inf. temporal g.	37	54	−57	−9	3.63
	Sup. parietal lobule	7	9	−72	60	3.53
SZ>H						
None						
B) Shape>spatial conjunction						
Left	**Inf. frontal g.**	**44**	**−39**	**15**	**21**	**4.16**
	Inf. frontal g.	**45**	**−48**	**27**	**9**	**3.41**
	Fusiform g.	37	−42	−57	−18	3.25
H>SZ						
Left	Claustrum		−27	6	12	3.44
SZ>H						
Right	Mid. frontal g.	6	42	−3	51	3.38
C) Spatial WM conjunction						
Left	**Inf. frontal g.**	**47**	**−30**	**24**	**−9**	**5.90**
	Sup. occipital g.	19	−18	−78	45	5.85
	Inf. parietal lobule	40	−39	−48	39	5.38
	Sup. parietal lobule	7	−27	−75	30	4.84
	Mid. frontal g.	6	−27	−3	51	4.74
	Precentral g.	6	−45	0	24	3.46
	Mid. frontal g.	**46**	**−42**	**27**	**24**	**3.07**
Right	Sup. parietal lobule	7	27	−75	39	6.30
	Sup. occipital g.	19	33	−78	24	5.74
	Inf. frontal g.	**47**	**33**	**24**	**−12**	**5.91**
	Insula		33	21	3	4.32
	Mid. frontal g.	6	30	0	57	5.76
	Med. frontal g.	8	6	15	48	5.65
	Inf. frontal g.	**44**	**54**	**9**	**18**	**4.59**
	Mid. frontal g.	**46**	**48**	**33**	**24**	**4.53**
	Inf. frontal g.	**46**	**45**	**42**	**12**	**4.00**
H>SZ						
Left	Sup. parietal lobule	7	−24	−63	54	3.51
Right	Precuneus	7	15	−60	42	4.25
	Inf. parietal lobule	40	36	−33	33	3.77
	Mid. frontal g.	**44**	**57**	**15**	**33**	**3.73**
	Sup. temporal g.	22	48	−48	9	3.29
	Mid. temporal g.	21	51	−51	0	3.29
SZ>H						
None						
D) Shape WM conjunction						
Left	**Inf. frontal g.**	**47**	**−30**	**24**	**−9**	**6.38**
	Inf. frontal g.	**44**	**−42**	**15**	**24**	**6.12**

Table 2 (*continued*)

Contrast		BA	Talairach coordinates			*z*-score
			x	*y*	*z*	
D) Shape WM conjunction						
Left	Precentral g.	6	−48	0	36	4.27
	Mid. frontal g.	6	−30	0	51	3.69
	Med. frontal g.	6	−3	12	51	5.94
	Cingulate g.	32	−9	18	42	5.57
	Sup. parietal lobule	7	−30	−72	33	5.12
	Mid. occipital g.	19	−30	−75	24	5.08
	Supramarginal g.	40	−30	−57	36	4.88
	Fusiform g.	19	−45	−66	−21	4.97
	Fusiform g.	18	−33	−93	−12	4
	Thalamus		−12	−12	3	3.84
	Mid. frontal g.	**46**	**−42**	**45**	**3**	**3.69**
	Mid. occipital g.	19	−30	−81	9	3.14
Right	Med. frontal g.	8	9	15	48	5.74
	Inf. frontal g.	**47**	**33**	**27**	**−12**	**5.13**
	Inf. frontal g.	**44**	**45**	**9**	**24**	**4.61**
	Inf. frontal g.	**46**	**45**	**33**	**15**	**4.44**
	Mid. frontal g.	**46**	**39**	**48**	**21**	**4.3**
	Sup. parietal lobule	7	33	−66	36	4.28
	Mid. occipital g.	19	33	−75	24	3.95
	Inf. occipital g.	18	30	−96	−9	3.53
	Calcarine g.	17	21	−96	−15	3.14
	Mid. frontal g.	6	36	3	54	3.52
	Thalamus		15	−9	3	3.29
	Fusiform g.	19	45	−63	−21	3.16
H>SZ						
Left	Claustrum		−24	27	6	4.13
	Insula	41	−30	−21	27	4.12
	Posterior cingulate	29	−12	−45	9	3.83
	Hippocampus		−24	−42	0	3.56
	Paracentral lobule	5	−18	−33	48	3.81
	Cingulate g.	24	−18	−3	45	3.42
Right	Caudate		27	−39	6	4.46
	Claustrum		30	0	15	3.74
	Caudate		18	−3	21	3.18
	Mid. frontal g.	6	30	3	36	3.48
	Postcentral g.	3	30	−24	42	3.46
SZ>H						
Left	Cingulate g.	32	0	18	36	4.18
	Sup. temporal g.	38	−48	15	−15	4.07
	Mid. frontal g.	6	−42	0	54	3.63
Right	**Inf. frontal g.**	**47**	**54**	**21**	**−6**	**3.77**
	Mid. frontal g.	6	45	0	51	3.74

Putative Brodmann's areas (BA), Talairach coodinates, 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 millimeters 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. H=healthy group; SZ=schizophrenia group; sup.=superior; inf.=inferior; mid.=middle; med.=medial; and g.=gyrus.

3.3.3. Spatial and shape WM

3.3.3.1. Spatial WM vs. control. Conjunction analysis revealed activation in bilateral dorsolateral and ventrolateral PFC as well as other regions associated with WM including the intraparietal sulcus (IPS) and lateral and medial premotor regions (Fig. 3c, Table 2C). The magnitude and extent of activation tended to be greater in the right hemisphere. Group comparisons revealed that healthy subjects showed significantly increased activity in right ventrolateral PFC (BA 44) and that patients did not show any areas of increased activation.

3.3.3.2. Shape WM vs. control. Both groups showed activation in bilateral dorsolateral and ventrolateral PFC as indicated by conjunction analysis (Fig. 3d; Table 2D). Group comparisons revealed that there were no lateral PFC regions that healthy subjects activated more than schizophrenia subjects and that schizophrenia subjects showed increased activation in right ventrolateral PFC (BA 47).

4. 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 lateralized PFC activation in both groups. This demonstrates that hemispheric specialization depends on task demands, rather than on the nature of the stimuli. The hypothesis that motivated the present study was that a failure to adopt the optimal strategy for domain-specific WM tasks would contribute to deficient WM performance in schizophrenia. We expected this failure to be manifested as reduced relative hemispheric specialization in ventrolateral PFC when spatial and shape WM tasks were compared. Contrary to our hypothesis, patients and controls showed hemispheric specialization in the same ventrolateral PFC regions (right for spatial WM and left for shape WM) and the groups did not differ in this regard. From this we conclude that both healthy and schizophrenia patients employ the same domain-specific processing strategies. In addition, both groups recruited common bilateral dorsolateral and ventrolateral PFC regions for spatial and shape WM performance. This suggests that rather than reflecting a failure to adopt the optimal strategy or to adequately recruit the PFC, WM may be deficient in schizophrenia on the basis of the executive processes that are common to WM tasks, regardless of domain.

In contrast to the relative hemispheric specialization in specific ventrolateral PFC regions, spatial and shape WM performance activated several PFC regions in common in both groups including the dorsolateral PFC. The findings that specific ventrolateral PFC regions show specialization by domain, while dorsolateral PFC regions are engaged for WM regardless of domain, echo the conclusions of a review by D'Esposito et al. (1998). They are also consistent with enduring notions of WM involving a "central executive" and domain-specific subsystems (Baddeley, 1992; Baddeley, 2003). Based on our present findings, we hypothesize that central executive processes subserved by the dorsolateral PFC, rather than domain-specific subsystems, are impaired in schizophrenia. These central executive processes (e.g., manipulation) are diverse and overlap with the concepts of executive function and cognitive control (for reviews see Miller and Cohen, 2001; Stuss and Alexander, 2000). Executive demands during WM tasks are generally associated with increased activity in dorsolateral PFC, while ventrolateral PFC activity is more frequently associated with storage-related processes (see meta-analyses by Owen, 2000; Wager and Smith, 2003). Abnormal function of the dorsolateral PFC is a frequent finding in WM studies in schizophrenia (e.g., Manoach, 2003). In contrast to the dorsolateral PFC, we hypothesize that specific ventrolateral PFC regions play a role in implementing domain-specific storage strategies and that these strategies are intact in schizophrenia as reflected in normal hemispheric specialization.

The nature of these storage strategies is discussed in detail in a previous report (Manoach et al., 2004). Briefly, we propose that, consistent with their self-reports of strategy, subjects in both groups efficiently represented locations as a spatial configuration and that this strategy was implemented automatically, without the need for cognitive control. We further speculate that a region in the right ventrolateral PFC played a critical role in implementing this strategy. This is consistent with findings that structured spatial sequences, that can be represented in WM as configurations, give rise to better performance and greater activation in ventrolat-

eral PFC than unstructured spatial sequences (Bor et al., 2003). We further propose that, compared with the spatial WM task, the novelty of the shape WM task compelled subjects in both groups to use a relatively inefficient strategy (as indicated by their poorer performance). Although we intentionally selected the shapes to be difficult to verbalize, many subjects reported using a verbal-associative mnemonic strategy. It may be that it was the subvocal rehearsal processes associated with this strategy that were associated with left ventrolateral PFC activation in a region that includes Broca's area. 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) and with a recent meta-analysis (Wager and Smith, 2003).

The present findings differ from those of a previous study that reported an absence of PFC lateralization for verbal and spatial WM in schizophrenia using a version of the n-back task (Walter et al., 2003). Although the Walter et al. study reported a lateralized pattern of PFC activity in healthy subjects depending on domain, other studies using the n-back to examine spatial and shape WM have not (Nystrom et al., 2000; Postle et al., 2000). Whether a study finds specialization may depend on both the task requirements and the level of task difficulty. In addition to the maintenance of information, the n-back requires the continuous updating and temporal tagging of the contents of WM. These executive processes are required regardless of domain. One possible explanation of the discrepancy in findings is that, in the prior study, domain specificity might have been obscured in schizophrenia patients by activity attributable to the executive demands of the tasks. The same regions that show domain specificity may also contribute to executive processes. In schizophrenia, these regions may be engaged to a greater degree, regardless of the task domain, in order to compensate for limited WM capacity and this may obscure specialization. The tasks used in the present study were designed to minimize the use of executive processes that have been shown to engage the PFC regardless of the domain of information being represented (D'Esposito et al., 1998; D'Esposito et al., 2000; Fletcher and Henson, 2001; Sohn et al., 2000).

Limitations of the present study include the exclusive focus on activity in the lateral PFC although, clearly, many brain regions participate in these tasks (Table 2, Fig. 3). Furthermore, the task design was optimized to capture activity during the probe epochs of the WM tasks. The probe epochs require the maintenance and mental scanning of the contents of WM, comparison with the probe, and response selection. Although each of these requirements is likely associated with different processes and corresponding patterns of brain activity (e.g., Manoach et al., 2003), the design of the present study does not allow us to discriminate between activity due to maintenance and response processes.

In summary, we present findings of intact relative hemispheric specialization in the ventrolateral PFC for spatial and shape WM in schizophrenia. We interpret this as evidence that both healthy and schizophrenia patients employ domain-specific processing strategies to accomplish these tasks. In spite of indistinguishable lateralized patterns of ventrolateral PFC recruitment, patients showed WM performance deficits. Rather than reflecting a failure to adopt the optimal storage strategy, we hypothesize that poor WM performance reflects deficits in executive processes that are required for WM tasks regardless of domain. These executive processes are thought to be subserved by neural networks involving the dorsolateral PFC, which has been implicated as showing abnormal function in numerous previous studies of WM.

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