ORIGINAL ARTICLE

Dorsolateral Prefrontal Cortex Activity During Maintenance and Manipulation of Information in Working Memory in Patients With Schizophrenia

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Context: It remains unclear whether altered regional brain physiological activity in patients with schizophrenia during working memory tasks relates to maintenance-related processes, manipulation-related (ie, executive) processes, or both.

Objective: To examine regional functional activations of the brain during maintenance- and manipulation-related working memory processing in patients with schizophrenia and in healthy comparison subjects.

Design: Functional images of the brain were acquired in 11 schizophrenic patients and 12 healthy control subjects (matched for age, sex, handedness, and parental education) during 2 spatial working memory paradigms, one contrasting maintenance-only processing with maintenance and manipulation processing and the other contrasting parametrically varying maintenance demands.

Results: Patients and controls showed activation of a large, spatially distributed network of cortical and subcortical regions during spatial working memory processing. When task demands required explicit manipulation of information held in memory, controls recruited right dorsolateral prefrontal cortex (Brodmann areas 45 and 46) to a significantly greater extent than patients. A similar effect was observed for the larger memory set sizes of the memory set size task. No other brain regions showed activation differences between groups for either task. These differences persisted when comparing activation maps for memory set sizes in which the 2 groups were equivalent in behavioral accuracy and when comparing subgroups of patients and controls matched for behavioral accuracy on either task.

Conclusions: Physiological disturbances in the dorsolateral prefrontal cortex contribute differentially to patients' difficulties with maintaining spatial information across a brief delay, as well as with manipulating the maintained representation. These differences persisted when comparing conditions in which the 2 groups were equivalent in behavioral accuracy.

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WORKING MEMORY disturbances are a robust correlate of schizophrenia[1-4] and are featured in several prominent theories of the pathophysiology of the disorder.[5-9] Nevertheless, it remains unclear whether particular aspects of working memory are differentially affected in schizophrenia and whether these deficits can be traced to physiological disturbances in particular components of working memory circuitry. Systematic parsing of working memory processes and related circuitry using well-validated paradigms drawn from basic research on the cognitive neuroscience of working memory[10-12] is critical to efforts to develop more specific models of the neurobiological processes mediating disturbed cognition in schizophrenia and their remediation[5,13] and to identify genes contributing to particular aspects of the schizophrenia phenotype.[14-17]

Several lines of evidence suggest that the working memory processes associated with maintenance of information across a brief delay are at least partially dissociable functionally and anatomically from those involved in the active use or manipulation of the maintained information.[10,12,18] Such a dissociation was observed in the domain of verbal working memory by D'Esposito et al,[12] who found differential activation of dorsolateral prefrontal cortex (DLPFC) when subjects were required to reorder a string of letters during the delay period compared with when they were required to maintain the letter string in its original sequence. Other work suggests that the degree to which any region in the working memory network is recruited during a particular task may depend on the relative maintenance and ma-

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nipulation demands of that task.[10,18,19] It was recently demonstrated that, in the domain of spatial working memory, increasing memory set size is associated with increased activation throughout the working memory network, including DLPFC, parietal cortex (PAR), anterior cingulate cortex (ACC), and frontal eye fields.[18] However, the transfer function relating magnetic resonance signal change to memory load differed by cortical area, with some regions (DLPFC and PAR) showing a linear increase in activity with increasing memory set size and with other areas (eg, ACC) showing activation only when memory demands were highest. Manipulation of the spatial representation during the delay (in this case, by mental rotation) was associated with significantly increased activation compared with maintenance-only processing in the same regions that were activated in the memory set size paradigm. A direct comparison of the magnitude of activation between the 2 tasks revealed significantly increased activity in DLPFC during the manipulation paradigm compared with the memory set size paradigm. This pattern suggests that maintenance and manipulation processes are supported by all components of the working memory network, with DLPFC supporting a greater functional specialization for manipulation processes.[18]

Consistent with theories that postulate a critical role of DLPFC dysfunction in schizophrenia, these patients show profound deficits in tasks requiring manipulation of information.[2,20,21] Nevertheless, they are also impaired on simple maintenance or storage tasks,[1,22] even when between-group perceptual differences are minimized.[3,4] In a recent behavioral study,[23] prior findings of maintenance-related working memory deficits were replicated in patients with schizophrenia using delayed-response tasks that parametrically varied the amount of information to be maintained. Performance declined linearly with increasing memory set size in patients and control subjects, and to equivalent degrees. However, patients' performance was differentially poorer when subjects simultaneously maintained and manipulated information during the delay than when they maintained the same information without an explicit requirement to manipulate it.[23] These results suggest that, while storage and executive aspects of working memory are impaired in schizophrenic patients, the executive aspects are more severely affected. This pattern is not merely because of the increased difficulty of the manipulation condition, because no such differential deficit was observed with increasing memory set size. The finding also does not appear to be caused by a psychometric artifact,[24] as there were equivalently high reliability estimates and equivalent observed score variances across the 2 task conditions.[23]

In this study, we applied the 2 spatial working memory task paradigms just described[18,23] during functional magnetic resonance imaging (MRI) of clinically stabilized schizophrenic patients and of matched healthy comparison subjects. Our goals were to determine whether DLPFC activity differs between patients and controls when maintenance demands are increased parametrically, when manipulation demands are added to the basic maintenance task, or both. Based on prior functional neuroimaging studies,[25-28] it appears likely that, in any given task paradigm, whether the patients' DLPFC activation is higher or lower compared with controls reflects a complex interaction between the comparative task difficulty experienced by the subjects, the mental effort required to perform the task, and the subjects' motivation to exert effort. Therefore, we also sought to determine the nature of any differences in regional brain activation when comparing patients and controls on conditions in which the 2 groups show equivalent behavioral accuracy.

METHODS

SAMPLE

Eleven schizophrenic patients and 12 healthy controls, matched for age (mean ± SD age, 27.1 ± 7.0 and 29.2 ± 6.9 years, respectively; $F = 0.56$, $P < .46$), sex (36% and 15% female, respectively; $\chi^2 = 1.39$, $P = .23$), handedness (10% and 8% left-handed, respectively; $\chi^2 = 0.02$, $P = .89$), and parental education (mean ± SD, 14.8 ± 2.2 and 13.2 ± 3.8 years, respectively; $F = 1.25$, $P < .23$), were recruited to participate in the functional MRI experiments. All participants provided written informed consent for the study, as approved by the institutional review board at the University of California, Los Angeles. All participants met the *DSM-IV*[29] criteria for schizophrenia as determined by the Structured Clinical Interview for *DSM-IV*[30] and were clinically stable outpatients receiving atypical antipsychotic medications (risperidone in 9 patients and olanzapine in 2 patients) in the Aftercare Research Program at the time of examination. We excluded subjects (patients and controls) with a neurological disorder, significant and habitual substance use in the past 6 months, mental retardation, and insufficient fluency in English to complete neurocognitive tasks.

TASK PARADIGMS

Participants performed 2 spatial delayed-response tasks, the first contrasting maintenance and manipulation of spatial information and the second contrasting maintenance of parametrically increasing memory loads (**Figure 1**). Detailed descriptions of the tasks are provided elsewhere.[18,23] Briefly, in task 1, subjects were presented 2 trial types, maintenance only and maintenance and manipulation. In the maintenance-only trials, subjects were shown 3 pseudorandomly positioned target circles. After a delay, 3 probe circles appeared, and subjects determined if these new circles were in the same locations as the target set. During the delay period of the maintenance and manipulation trials, subjects were instructed to "flip" the locations of the target circles over the horizontal meridian. When the probe circles appeared, subjects determined if the locations of the probe stimuli matched the inverted target stimuli. In task 2, subjects were shown an array of 1, 3, 5, or 7 target circles positioned pseudorandomly around a central fixation. After a fixed delay, subjects were shown a single probe circle and were asked to determine if the probe was in the same position as one of the target circles. To minimize a potential encoding by set size interaction, target stimuli were presented for 2 seconds, allowing subjects to fully encode the target array even on the highest memory load levels. For both tasks, half of the trials were true positive, and half were true negative.

MRI SCANNING PROCEDURES

All scanning was carried out on a 3-T General Electric (Waukesha, Wis) MRI scanner in the Brain Mapping Center of the Neuropsychiatric Institute, University of California, Los Angeles. Before each functional study, a high-resolution axial T2-

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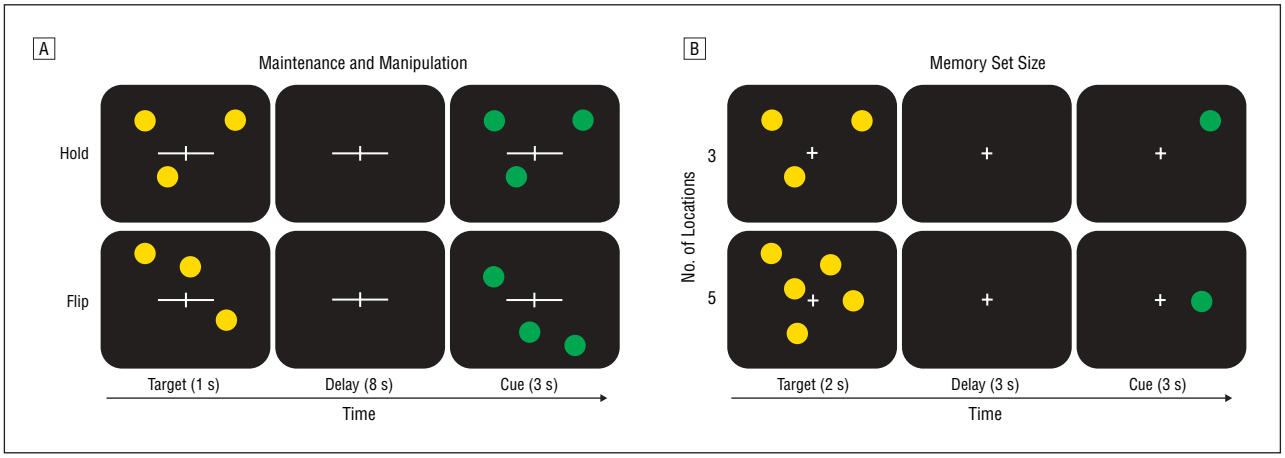

Figure 1. Example trials used during functional magnetic resonance imaging assessment. During scanning, similar trials were grouped into 27-second blocks (3 trials) interspersed with 15-second rest periods. A, In task 1, each trial lasted 9 seconds, and subjects performed 18 trials per condition. In total, task 1 included 12 blocks of trials and lasted 8 minutes 9 seconds. B, In the task 2 depicted, subjects were asked to remember 3 and 5 locations during a fixed 3-second delay. Each trial in task 2 lasted 9 seconds, and subjects performed 12 trials per memory set size (48 in total). Task 2 included 16 blocks of trials and lasted 10 minutes 57 seconds. Yellow circles indicate targets; green circles, probes; and crosshatches, central fixation.

weighted image was obtained and used for anatomical reference (repetition time, 3000 milliseconds; echo time, 41 milliseconds; flip angle, 90º; 30 axial sections; acquisition matrix size, 128×128 pixels; 30-cm field of view, 1.6 mm×1.6-mm in-plane resolution, and 5.0-mm through-plane resolution). Functional imaging used a gradient echo, echoplanar sequence sensitive to the blood oxygenation level–dependent signal[31] acquiring 16 sections parallel to the anterior commissure–posterior commissure plane (repetition time, 3000 milliseconds; echo time, 45 milliseconds; voxel size, 3.125×3.125×4.00 mm; and a 1-mm gap). Through a mirror mounted on the head coil, subjects observed task stimuli back-projected via an LCD projector on a screen placed at the subjects' feet. Behavioral responses (button presses and reaction times) were recorded through a handheld response box.

ANALYSIS OF BEHAVIORAL DATA

Accuracy and reaction time data for each experiment were entered in separate analyses of variance (ANOVAs) testing for main effects of group (patients and controls) and condition (flip, hold, and memory set size). Significant main effects and interactions were decomposed using *t* tests.

FUNCTIONAL MRI ANALYSIS

To combat potential motion artifacts, each blood oxygenation level–dependent image in a time series underwent a 3-dimensional coregistration (6-parameter rigid body) to the middle data point in the time series. Data were smoothed with a nonlinear algorithm designed to preserve image structure by smoothing adjacent voxels thought to be of the same tissue type (5-mm kernel).[32] Each data set was subjected to a multiple regression analysis, using a prewhitening technique[33] to account for the intrinsic temporal autocorrelation of blood oxygenation level–dependent imaging.[34] Initial overall ANOVAs were conducted on each task separately and on the combined data set to assess for group×condition, group×set size, and group×task interaction terms. These higher-order effects were then decomposed for simple effects in follow-up voxel-based analyses using *t* tests. For each intracranial voxel, least squares coefficients were generated independently reflecting each task condition.[35] Statistical images were created for the flip and "hold" conditions of the first task and each memory set size (1, 3, 5, or 7 locations) of the second task. Contrasting these statistical images with the resting state and with each other allowed for testing hypotheses concerning maintenance vs manipulation processing and effects of increasing memory set size.

To facilitate multisubject analysis, a common space brain was defined that approximated the mean size, shape, and orientation of all subjects' (patients and controls) higher-resolution T2-weighted images combined.[36] This approach does not completely eliminate the effects of differential amounts of spatial distortion in taking patients' and healthy subjects' brains into a common space for multisubject analyses, but it provides better control for these issues than an approach in which only healthy subjects' brains are used in creating the anatomical template. Based on the parameters created from the higher-resolution image, statistical images created for each subject were normalized in this common space (12-parameter model). Higher-level multisubject analysis used a mixed-effects model with subjects as a random effect (Functional Magnetic Resonance Imaging of the Brain Software Library's Local Analysis of Mixed Effects [FLAME][37]) and provided *t* images reflecting activation patterns in each diagnostic group separately and an image representing between-group differences for each contrast described in the previous paragraph. To reduce the size of the search space, group statistical images were masked with an image reflecting activation on both tasks vs rest (union of each group for each task). Statistical images were "thresholded" based on the magnitude (minimum *t* value, 3.3) and extent (cluster significance, $P<.05$) of activation.[38,39] To make the results from these group comparisons comparable to others in the literature, the common space brain was normalized into a standard stereotactic space.[40]

To expand on the voxel-level analysis, a region of interest (ROI) analysis was conducted focusing on brain regions of greatest theoretical relevance to working memory dysfunction in schizophrenia (right DLPFC, PAR, and ACC). The location and extent of the ROIs were set functionally according to the conjunction of the thresholded ($P>.05$) task vs rest maps for both tasks in both groups (4 maps in total) (**Table**). The functional regions of interest were based on the conjunction of the 4 thresholded statistical maps as follows: patients' task 1 vs rest, patients' task 2 vs rest, controls' task 1 vs rest, and controls' task 2 vs rest. Therefore, the exact location and extent of these regions were determined by all of the subjects on both tasks (an omnibus contrast). Given that the anatomical definitions for

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Table. Areas of Brain Activation

Functional Region of Interest	Maintenance and Manipulation Task: Volume, mm³	Maintenance and Manipulation Task: Center of Mass*	Memory Set Size Task: Volume, mm³	Memory Set Size Task: Center of Mass*	Brodmann Area
Bilateral parietal and occipital	37 031	0, −61, 41	63 552	−5, −55, 41	18, 19, 39, 40, 7
R prefrontal	5735	48, 20, 19	4452	46, 17, 23	13, 47, 45, 46, 9
R inferior frontal	659	43, 41, 5	. . .	. . .	10, 46
L dorsolateral prefrontal	1877	45, −17, 24	1800	−42, 27, 28	9, 46
Anterior cingulate	2954	1, 3, 42	7306	1, 6, 41	32, 6
Bilateral subcortical	R: 2456	18, 13, 5	119	17, −3, 9	. . .
	L: 4807	−17, 13, 6	4303	−17, −9, 5	
L insular	1622	−31, 22, 4	. . .	. . .	3
Bilateral sensory motor	R: 916	26, −10, 48	3217	26, −5, 47	6
	L: 584	−31, −9, 44	2226	−22, −10, 46	
L motor	805	−45, 0, 28	. . .	. . .	6, 9

Abbreviation: L, left; R, right; ellipsis, not applicable.
*Talairach coordinates x, y, and z, respectively.

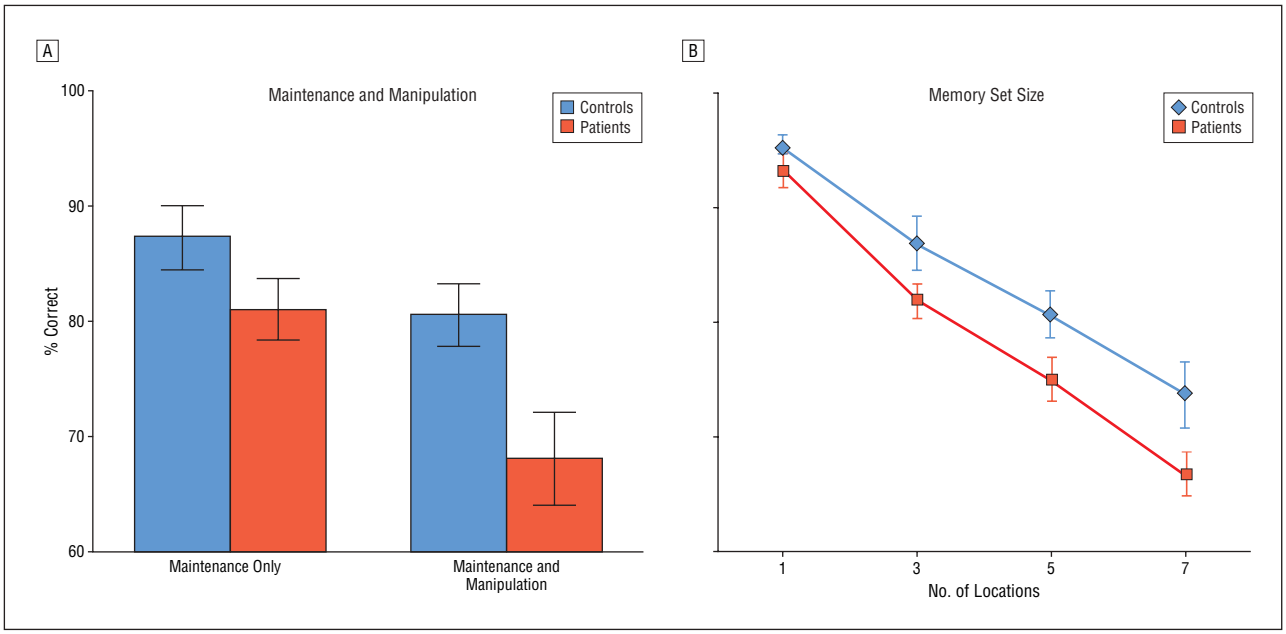

Figure 2. Behavioral performance in the maintenance and manipulation (A) and memory set size (B) tasks. Schizophrenic patients performed worse than healthy control subjects when faced with explicit manipulation requirements or when asked to maintain more than a single location. Data are given with SEM values.

the brain regions of theoretical interest for spatial working memory (right DLPFC, PAR, and ACC) are heterogeneous, an advantage of defining functional ROIs is that only those portions of anatomy associated with the task in the subjects at hand are examined. However, this approach biases one's results toward null results (type II errors) in that only those voxels found active in both groups and across conditions are included. Therefore, voxels that are strongly associated with one task condition but not another or voxels that are represented in only one group would not be included in the conjunction ROIs. For every subject, percentage signal change maps contrasting each cognitive condition with rest were generated separately. Functionally defined ROIs were morphed back into native (subject) space, and the mean value from all voxels within each region was determined. These values were then entered into separate ANOVAs for each task. For task 1, a 2×3×2 ANOVA modeling the effects of diagnostic group (patients and controls), ROI (right DLPFC, PAR, and ACC), and task condition (maintenance only and maintenance and manipulation) was performed. For task 2, a 2×3×4 ANOVA modeling the effects of diagnostic group, ROI, and task condition (memory set size, 1, 3, 5, or 7) was performed. Main effects or interactions were decomposed with region- or condition-specific models.

RESULTS

BEHAVIORAL PERFORMANCE

In task 1, patients performed worse than controls overall ($F_{1,17}$=5.92, P<.02), and subjects in both groups performed worse in the maintenance and manipulation trials compared with the maintenance-only trials of the first task ($F_{1,17}$=19.92, P<.001) (**Figure 2**A). The patients' performance was differentially lower than that of the con-

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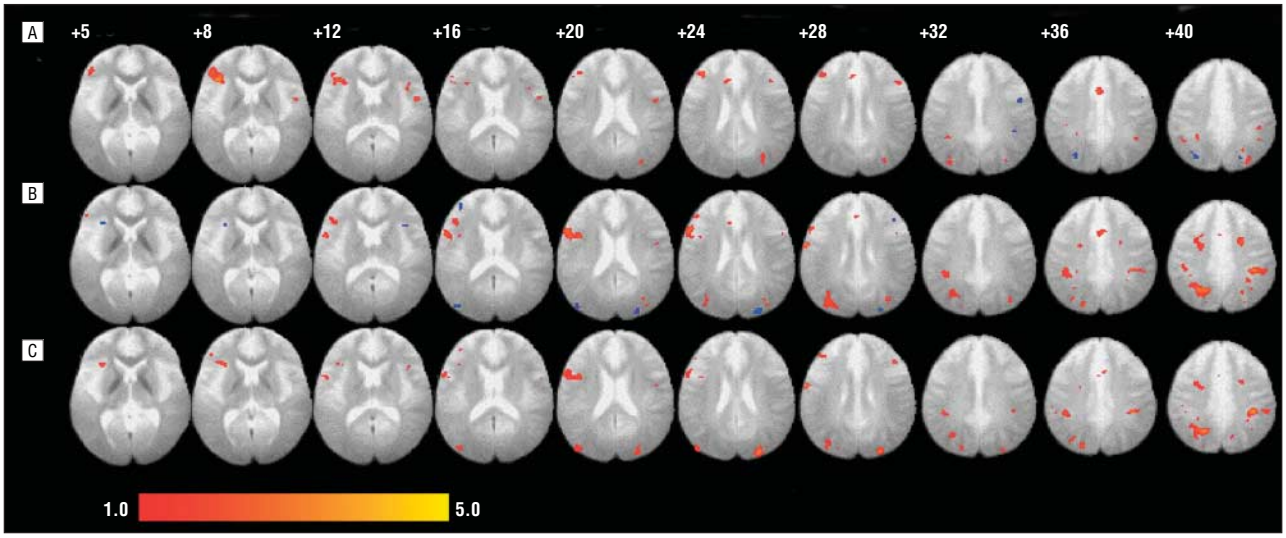

Figure 3. Statistical maps of analysis of variance results showing voxels in which group (controls vs schizophrenic patients) interacted significantly with condition in task 1 (A), with memory load in task 2 (B), and with task across the 2 experiments (C). The top row of numbers indicates the z coordinates in the Talairach space; the scale at the bottom, F statistic.

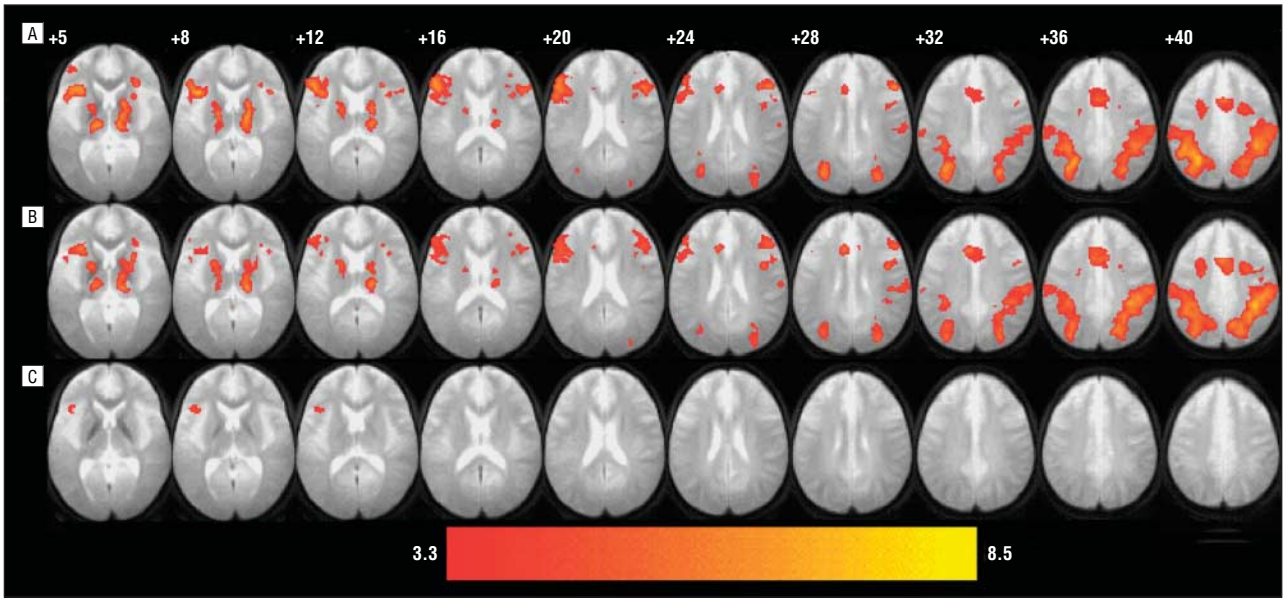

Figure 4. Statistical maps showing regional brain activation for task 1 in which maintenance and manipulation were associated with significantly higher activation than maintenance only in healthy control subjects (A), in schizophrenic patients (B), and in controls compared with patients (C). The top row of numbers indicates the z coordinates in the Talairach space; the scale at the bottom, *t* statistic.

trols in the maintenance and manipulation trials compared with the maintenance-only trials ($F_{1,17}=6.04$, $P<.02$). Group reaction times did not significantly differ ($F_{1,12}=4.17$, $P<.06$). In task 2, as the number of memoranda to be maintained increased, performance decreased in both groups ($F_{3,19}=70.18$, $P<.001$) (Figure 2B). However, although patients performed worse than controls overall ($F_{1,21}=6.15$, $P<.02$), their performance was not differentially affected by increasing memory set size compared with controls ($F_{3,19}=0.75$, $P>.50$). Reaction times for patients and controls did not significantly differ ($F_{1,13}=2.95$, $P<.11$). These behavioral results are consistent with those reported previously among larger samples of patients and controls.[23] There were no group differences or group × condition interactions in terms of β index, a measure of response bias (ie, $\log\beta=0.5[Z^2(\text{false alarms})-Z^2(\text{hits})]$, on either task ($P>.27$ for all).

VOXEL-LEVEL FUNCTIONAL MRI ANALYSIS

The overall ANOVAs detected voxels in the frontal cortex that showed significant sensitivity to the group × condition interactions in task 1, task 2, and across tasks 1 and 2 (**Figure 3**). To decompose these higher-order effects, follow-up *t* test analyses were performed to evaluate task-related activations within each group and between the 2 groups for task 1 (**Figure 4**) and task 2 (**Figure 5**). Groupwide analysis revealed a network of 9 spatially distinct brain regions involved in the maintenance and manipulation task compared with rest in con-

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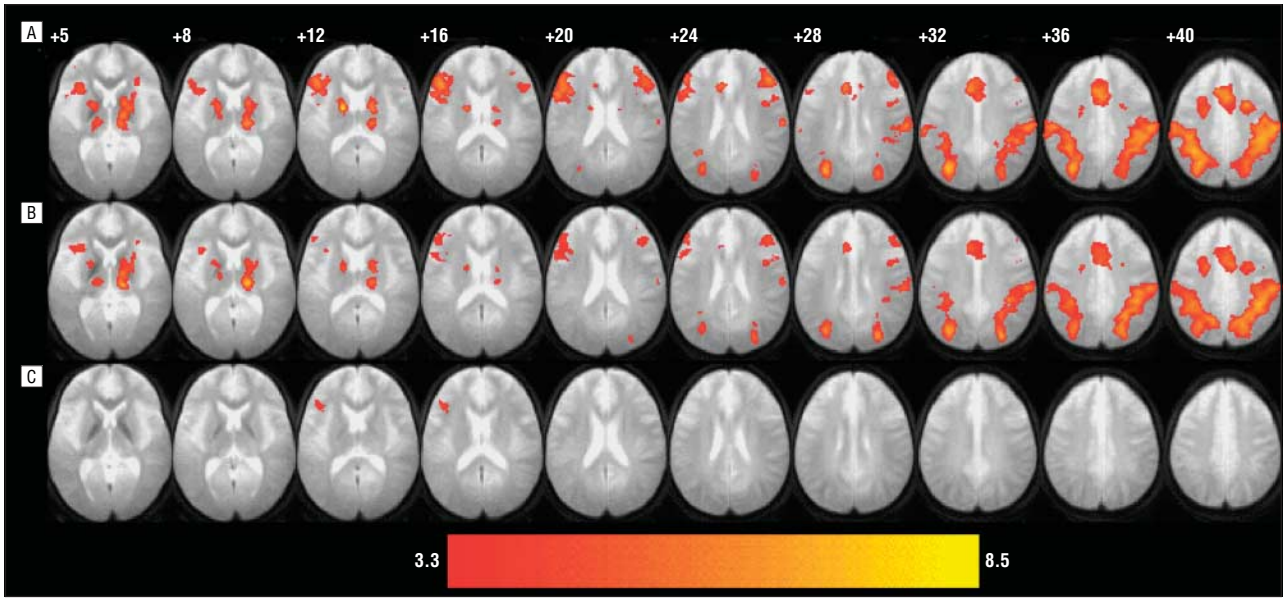

Figure 5. Statistical maps for task 2 in which regional brain activation increased with increasing memory set size in healthy control subjects (A), in schizophrenic patients (B), and in controls compared with patients (C). The top row of numbers indicate the z coordinates in the Talairach space; the scale at the bottom, *t* statistic.

trols (Figure 4A) and in patients (Figure 4B) (Table). These regions included the following: (1) a bilateral posterior region extending from the middle occipital gyrus to the inferior and superior parietal lobules; (2) a right prefrontal region, including the insula and dorsolateral and ventrolateral prefrontal cortex; (3) a right inferior frontal region smaller and more anterior to region 2; (4) a left dorsolateral prefrontal region within the left middle frontal gyrus; (5) a portion of ACC; (6) bilateral subcortical regions, including the thalamus, putamen, and caudate; (7) a left insular region, including the anterior portion of the insula extending into the inferior frontal gyrus; (8) bilateral sensory motor areas extending from the superior portion of the middle frontal gyrus to the most anterior portion of the precentral gyrus; and (9) a left motor area, including precentral and inferior frontal gyri. The regions implicated in the memory set size task (ie, contrasting all set sizes vs rest) in controls (Figure 5A) and patients (Figure 5B) are similar to those associated with the maintenance and manipulation task (Figure 4), except that the anterior inferior frontal region (region 3) was not implicated in the memory set size task, activation in the larger right prefrontal region (region 2) did not reach the inferior extent that was observed in the maintenance and manipulation task, and the left insular and motor regions were not significantly active in the memory set size task vs rest contrast. These results are consistent with previous work using these paradigms in an independent sample of healthy subjects scanned at a lower MRI field strength.[18]

A comparison of group activation maps indicated that, when task demands required explicit manipulation of information held in memory, controls recruited a right hemisphere region at the junction of Brodmann areas 45 and 46 (center of mass [Talairach coordinates x, y, and z, respectively], 42, 20, and 13) to a significantly greater extent than patients (Figure 4C). A similar but slightly more anterior and superior region (Brodmann area 46; center of mass, 42, 23, and 20) differentiated groups for the larger memory set sizes (5 and 7 locations) of the memory set size task (Figure 5C). No other brain regions showed activation differences between groups for either task (Figures 4C and 5C). Given the conservative statistical thresholding requirements for voxel-based analyses,[38] to protect against type II error, a second functional ROI analysis was performed using the areas of cortex nominated by the task vs rest contrasts.

ROI-BASED ANALYSIS

Across all ROIs, subjects in both groups showed higher levels of activation during the maintenance and manipulation trials compared with the maintenance-only trials of the first task ($F_{1,17}$=38.19, P<.001) (**Figure 6**). Although the main effect of diagnostic group was not significant ($F_{1,17}$=0.00, P<.90), there were significant group × region ($F_{2,16}$=5.18, P<.01) and group × condition ($F_{2,16}$=6.35, P<.02) interactions, indicating that patients recruited different brain regions to different extents for different conditions compared with controls. A significant group × condition interaction was observed for right DLPFC ($F_{1,16}$=4.60, P<.04), such that, while patients and controls showed similar levels of activation for the maintenance-only trials ($F_{1,17}$=0.49, P<.50), the controls recruited this region for the maintenance and manipulation trials to a substantially greater extent than the patients ($F_{1,17}$=5.67, P<.02). In contrast, the level of activation in ACC for patients for the maintenance-only trials was higher than for controls ($F_{1,17}$=10.61, P<.005). This difference was not apparent in the maintenance and manipulation condition, in which controls recruited this region to the same extent as patients ($F_{1,17}$=0.31, P<.60). There were no noticeable group differences for the parietal region ($F_{1,17}$=0.08, P<.80).

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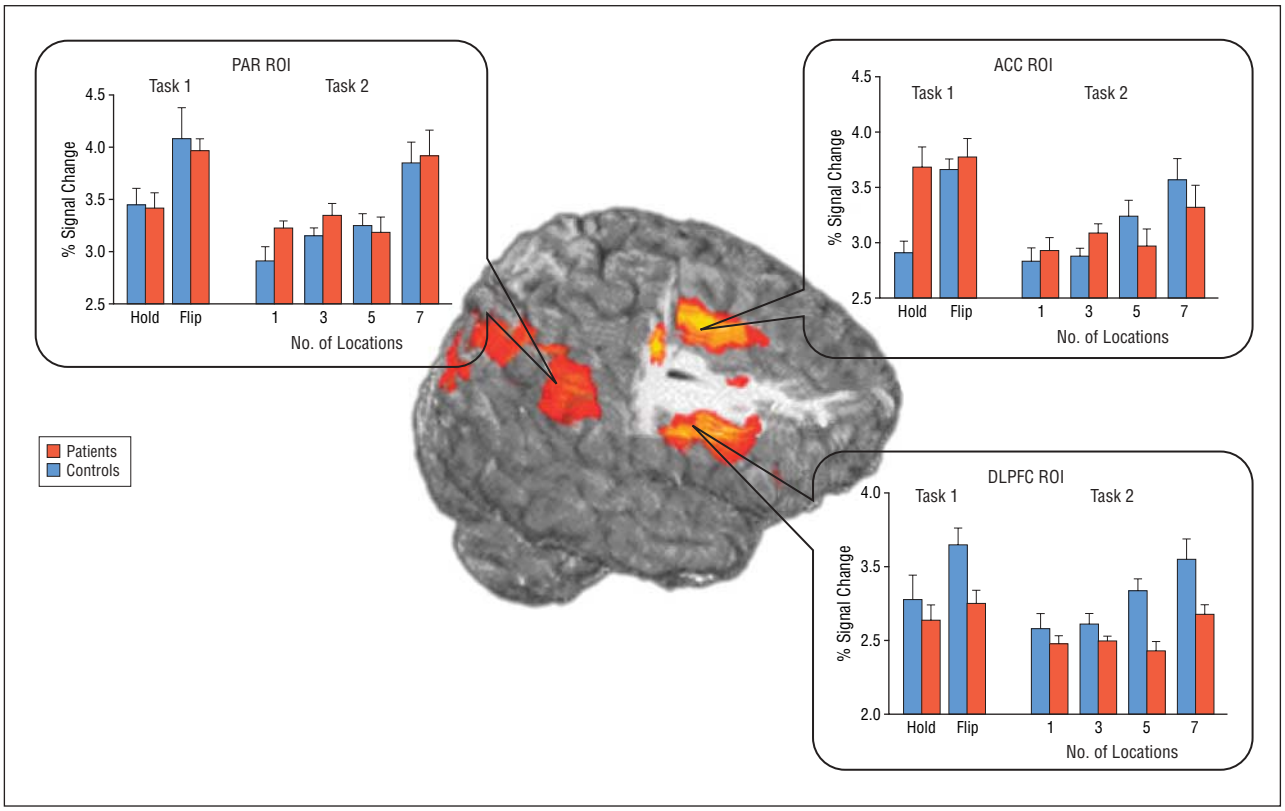

Figure 6. Region of interest (ROI)–based analysis of differences in regional brain activity during 2 spatial working memory tasks between schizophrenic patients and healthy control subjects. The controls activated the dorsolateral prefrontal cortex region to a significantly greater degree than the patients in the manipulation condition (flip) of the first task and in the larger memory set sizes (5 and 7 locations) of the second task. PAR indicates parietal cortex; ACC, anterior cingulate cortex; and DLPFC, dorsolateral prefrontal cortex. Data are given with SEM values.

In task 2 (varying maintenance requirements), as the number of memoranda increased, the activation levels increased in both groups in each ROI ($F_{3,19}=30.59$, $P<.0001$) (Figure 6). A similar pattern for the first and second tasks arose with regard to diagnostic group differences. Although the main effect of group was nonsignificant ($F_{1,21}=0.32$, $P<.60$), significant group × region ($F_{2,20}=5.18$, $P<.01$) and group × set size ($F_{3,19}=4.42$, $P<.007$) interactions were observed, such that under different degrees of memory load, patients recruited brain regions differently than controls. For DLPFC, significant main effects of group ($F_{1,21}=5.47$, $P<.02$) and group × set size interaction ($F_{3,19}=6.09$, $P<.004$) indicate that patients recruited this region less and in different ways than controls across set sizes. Indeed, while activation increased with increasing set size for controls ($F_{2,10}=7.33$, $P<.03$), activation levels for the patient group increased only for the largest memory set size. Although patients and controls showed similar levels of activation in the ACC region overall ($F_{1,21}=0.90$, $P<.70$), the activation pattern across set sizes differed in a manner similar to that found in the first task, with patients showing higher than normal activation in ACC for the smaller set sizes and lower than normal activation for the larger set sizes. As with the first task, patients and controls did not differ in parietal activation.

Patients maintaining 5 locations performed similarly to controls maintaining 7 locations (patients, 75.0% and controls, 73.6%; $t_{1,21}=-0.39$, $P<.70$). Despite equivalent performance, when contrasting DLPFC activation of these 2 conditions by group, patients showed significantly less activation in this region than controls ($t_{1,21}=3.45$, $P>.002$). In contrast, ACC and PAR activation levels did not differ between groups for these 2 conditions ($t_{1,21}=1.16$, $P<.30$; and $t_{1,21}=0.36$, $P<.70$; respectively). Identical analyses were performed comparing activation when patients maintained 3 locations vs when controls maintained 5 locations (81.8% vs 80.6%; $t_{1,21}=-0.47$, $P=.60$). The same basic pattern of results emerged in that, while DLPFC activation differed between the 2 groups ($t_{1,21}=2.05$, $P=.05$), ACC and PAR activation did not ($t_{1,21}=-1.02$, $P<.30$; and $t_{1,21}=-1.36$, $P<.10$; respectively).

Additional analyses were performed with subgroups of subjects matched for behavioral performance (task 1: 8 patients and 7 controls, $t=1.06$, $P<.30$; and task 2: 10 patients and 10 controls, $t=1.59$, $P<.13$) to address the potential confound of task performance and group membership. These analyses generally replicated those already described. In particular, even after selecting subjects with similar performance patterns, patients continued to underactivate the right DLPFC region during the maintenance and manipulation condition of task 1 (group × condition interaction: $F_{1,13}=7.94$, $P<.01$) and did not increase activation levels to the same extent as controls with increasing memory set size in task 2 (group × condition interaction: $F_{3,16}=4.64$, $P<.02$).

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COMMENT

Despite the fact that the present working memory paradigms were associated with activation of a large, distributed set of brain regions in patients and controls, voxel-based analyses revealed group differences in activation only in the region of DLPFC, with patients showing significantly less activation in this region when explicit manipulation requirements were present and at larger memory set sizes. This pattern argues for differential relevance of disturbances in this region in explaining the spatial working memory deficits observed in schizophrenia and has implications for the nature of these deficits, as discussed further herein.

Previous findings are in conflict as to whether activation of DLPFC is lower or higher than normal in schizophrenic patients during working memory processing.[41] Among the many possible sources of the discrepant findings, variations in task difficulty have received the most attention. One advantage of a task design with parametrically varying memory load is that physiological activity can be evaluated across several levels of task difficulty in the same samples. In controls, the blood oxygenation level–dependent signal in the DLPFC region appears to increase with increasing memory load,[42] but on some tasks activation appears to asymptote (and may decline) at the highest memory load levels.[43] Patients appear to reach peak activation of the working memory system at a lower processing load than controls.[44] Therefore, at least on certain tasks at low levels of difficulty, schizophrenic patients may use greater prefrontal resources but achieve lower accuracy compared with controls (ie, "inefficiency"), while at higher levels of difficulty patients may fail to sustain the prefrontal network that processes the information, achieving even lower accuracy as a result.[45] The results of the present study are consistent with this perspective with respect to the failure to sustain prefrontal activation at higher levels of task difficulty but not with respect to hyperactivation of DLPFC at lower levels of difficulty. It remains to be determined whether this pattern would be observed at a difficulty level below the minimum used in our tasks.

The patient-control differences in DLPFC activation found in this study persisted when comparing conditions in which patients' behavioral performance was matched with that of controls. If there were no group differences in activation once performance was equated, the initial differences in activation might then be explained by secondary factors such as motivation or mental effort. Comparing activation across levels of the task in which patients and controls achieved similar behavioral accuracy does not necessarily result in equating the 2 groups for these factors, but it provides a stronger basis for inferring that the activation differences are not likely to be completely determined by them. Abnormally high DLPFC activation in patients at the same level of behavioral accuracy as controls may be understood in light of the inefficiency model described in the previous paragraph. The same model may apply, albeit in a less straightforward way, to evidence of abnormally low DLPFC activation at the same level of behavioral accuracy as controls, in that patients may engage in more diffusely distributed, lower-magnitude network activation to achieve the same behavioral output.[46] Investigation of this possibility will require much larger sample sizes than those used in this study and should be a focus of future work.

Because DLPFC activity was reduced in patients compared with controls in both task paradigms, it appears that disturbances in this region may contribute to patients' difficulties with maintaining spatial information across a brief delay, as well as with manipulating the maintained representation. Together with prior evidence that explicit manipulation requirements activate DLPFC to a significantly greater degree than parametric variations in memory load in healthy subjects,[18] these findings lead to the prediction that patient-control differences in DLPFC activation will be larger with greater degrees of manipulation requirements in a given working memory task.

It could be argued, however, that the hypofrontality observed in the patient group in this study reflects a generalized deficit rather than deficits associated with the maintenance and manipulation demands of the task paradigms used. A generalized deficit model predicts that, as task difficulty increases, with all other factors being equal, the degree of patient impairment (relative to the performance of the control group) should increase. This pattern was observed in regard to the maintenance and manipulation task, in which the presence of explicit manipulation requirements was associated with a greater decrement in performance among patients than controls. However, in the memory set size paradigm, both groups declined in accuracy with an increasing number of spatial locations to be maintained, to equivalent degrees. Therefore, while task difficulty remains a critical issue in interpreting the patient-control differences in brain activation and behavioral performance, at least some component of the hypofrontality observed among the patients in this study appears to reflect mnemonic processes specifically engaged in the 2 task paradigms rather than a generalized deficit. The behavioral evidence of differential deficit in the maintenance and manipulation condition compared with the maintenance-only condition does not appear to be caused by a psychometric artifact,[24] as equivalently high reliability estimates and observed score variances have been demonstrated across these conditions in a larger sample of healthy subjects from which the present control subjects were drawn.[23]

It is possible that the disproportionate deficit in manipulation-related memory processing in the patients results from a deficit in mental manipulation of spatial information rather than from inefficiency in simultaneous maintenance and manipulation of information across a delay. Ideally, a control condition requiring only a manipulation operation without a mnemonic component could be constructed. However, building a purely nonmnemonic manipulation task may be difficult, because such a task would still require encoding the stimulus in working memory before any transformation process. Nevertheless, it may be possible to vary the degree to which the representation maintained in working memory can be updated with information from sensory regions during the process of mental transformation,

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thereby assessing the effects of transformation across a continuum of maintenance requirements.

The use of a blocked design format did not allow us to determine whether decreased DLPFC activity in the patients was specific to the delay periods of the working memory task paradigms. In view of prior work using simpler sensory stimuli and more discrete trial events, involvement of this region during the encoding and retrieval phases of a delayed-response task seems likely.[4,46] In addition, in the manipulation task it is possible that, against the instructions given, subjects could have performed the required transformation while the stimulus was still on the screen (or, less likely, during the response phase). A deficit in encoding or the use of a different encoding strategy could account for deficits in subsequent maintenance and manipulation processes in working memory in patients with schizophrenia. To resolve these ambiguities, future experiments using single-trial (event-related) variants of the tasks are needed to separately evaluate brain activity during the 3 information-processing stages (encoding, delay, and retrieval). This format would also enable a trial structure in which subjects are not made aware of the manipulation requirements in a maintenance and manipulation trial until after the encoding period, and it would allow a better basis on which to control for the effects of case-control behavioral performance differences in the comparison of neuroimaging data between groups (eg, by analyzing correct-only trials).

The results of this study and those of the previous report evaluating these same tasks in an independent sample of controls scanned at a lower field strength[18] argue against a strict functional-anatomical distinction between maintenance-related processes and manipulation- or central executive–related processes. In both studies, the regions showing increases in activity in the maintenance and manipulation condition compared with the maintenance-only condition, including DLPFC, were largely the same regions that were more active with increasing memory set size. This overlap is perhaps not surprising when one considers that tasks without explicit manipulation requirements involve central executive–related processes and that conditions requiring manipulation of the working memory probably tax maintenance-related functions to a greater extent than delayed-response tasks without such a requirement. Nevertheless, the previous study demonstrated a quantitative increase in the magnitude of DLPFC activation required for explicit manipulation of internally held information compared with increasing maintenance demands without the explicit requirement of manipulation. Most important, DLPFC was the only region that showed sensitivity to this effect and, as already noted, was the only region in which there were activation differences between patients and controls on these tasks. This pattern reinforces our conclusion that DLPFC may play an important role in the pathophysiology of maintenance-related and manipulation-related working memory deficits in schizophrenia.

Our findings with respect to activation of ACC in healthy subjects is consistent with prior work suggesting that ACC is uniquely sensitive to variations in task difficulty irrespective of the executive components of a task.[47,48] Although it is tempting to apply an inefficiency analysis to the patient data in this region, such an analysis is consistent with the results of the maintenance and manipulation experiment but not those of the memory set size experiment. Activation patterns in the parietal region were strikingly similar across tasks and groups, except that patients showed more activation when maintaining a single location than controls. This finding is somewhat at odds with previous work that has shown similar reductions in parietal and DLPFC activation in schizophrenia during working memory or executive function tasks[28,49] and may reflect that, compared with healthy subjects, a greater degree of mental effort is required for patients to maintain a single location. Nevertheless, the regions of the PAR recruited in the present behavioral challenges were somewhat different from those in the previous reports. Given that activity in anterior and posterior regions occurs in a time-locked fashion at the single-neuron level in primate models of spatial working memory,[50] and in view of the fact that gray matter density is reduced in both regions in schizophrenic patients,[51] the relationship between DLPFC and parietal functioning in schizophrenia merits further study.

Finally, all patients in this study were medicated and in a remitted state clinically. Treatment with atyptical antipsychotic drugs has been associated with improved working memory and increases in DLPFC activation.[52] Taken together, these considerations suggest that reduced DLPFC activity during maintenance and manipulation and with larger memory set sizes reflects an enduring vulnerability to schizophrenia[53] and that additional treatments will be necessary to achieve normalization of these brain systems.

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