

Dorsolateral Prefrontal Cortex Activity During Maintenance and Manipulation Of Information in Working Memory in Patients with Schizophrenia

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Abstract

Background: It remains unclear whether altered regional brain physiologic activity in schizophrenia patients during working memory tasks relates to maintenance-related processes, manipulation-related (i.e., 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 healthy comparison subjects.

Methods: Functional images of the brain were acquired on 11 schizophrenic patients and 12 healthy comparison subjects (matched for age, gender, and parental socioeconomic status) during two spatial working memory paradigms, one contrasting maintenance-only processing with maintenance-plus-manipulation processing and the other parametrically varying maintenance demands.

Results: Both 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, healthy subjects recruited right dorsolateral prefrontal cortex (BA 45 & 46) to a significantly greater extent than patients with schizophrenia. 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 on which the two 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 DLPFC contribute differentially to patients' difficulties with maintaining spatial information across a brief delay as well as with

manipulating the maintained representation. These differences in activation are not accounted for by group differences in mental effort, task difficulty, or motivation.

Introduction

Working memory disturbances are a robust correlate of schizophrenia¹⁻⁴ 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 memory¹⁰⁻¹² 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 and colleagues,¹² who found differential activation of dorsolateral prefrontal cortex (DLPFC) when subjects were required to re-order a string of letters during the delay period compared to 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 manipulation demands of that task.^{10, 18, 19} We 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, anterior cingulate (AC), and frontal eye fields.¹⁸ However, the transfer function relating MR signal change to memory load differed by

cortical area, with some regions (DLPFC and parietal cortex) showing a linear increase in activity with increasing memory set size and other areas (e.g., AC) 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 in the same regions that were activated in the memory set-size paradigm. Direct comparison of the magnitude of activation between the two tasks revealed significantly increased activity specifically in the DLPFC during the manipulation paradigm compared with the memory set size paradigm. This pattern suggests that both maintenance and manipulation processes are supported by all components of the working memory network, with the DLPFC supporting a relatively 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 on 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, we replicated prior findings of maintenance-related working memory deficits in patients with schizophrenia using delayed response tasks that parametrically varied the amount of information to be maintained.²³ Performance declined linearly with increasing memory set size in both patients and controls, 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 both storage and executive aspects of working memory are impaired in schizophrenic patients, the executive aspects are more severely affected.

In this study we applied the two spatial working memory task paradigms described above^{18,23} during functional magnetic resonance imaging (fMRI) of first-episode schizophrenia patients and matched healthy comparison subjects. Our goals were to determine whether DLPFC activity differs between patients and comparison subjects when maintenance demands are increased parametrically, when manipulation demands are added to the basic maintenance task, or both. Based on prior functional neuroimaging studies, it appears likely that in any given task paradigm, whether patients' DLPFC activation is higher or lower compared to normal subjects 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.²⁴⁻²⁷ Thus, we also sought to determine the nature of any differences in regional brain activation when comparing patients and controls on conditions in which the two groups show equivalent behavioral accuracy.

Subjects and Methods

Sample. Eleven schizophrenia patients and 12 healthy comparison subjects matched on age (27.1+7.0, 29.2+6.9, $F=0.56$, $p<0.46$), sex (36% and 15% female, $\chi^2=1.39$, $p=0.23$), handedness (10% and 8% left handed, $\chi^2=0.02$, $p=0.89$) and parental education (14.8+2.2, 13.2+3.8, $F=1.25$, $p<0.23$), were recruited to participate in the functional MRI experiments. All participants provided written informed consent for the study, as approved by the UCLA Institutional Review Board. All participants met DSM-IV²⁸ criteria for schizophrenia as determined by the Structured Clinical Interview for DSM-IV²⁹ and were clinically stable outpatients receiving atypical antipsychotic medications (9 Risperidone; 2 Olanzapine) in the

Aftercare Research Program at time of examination. We excluded subjects (patients and controls) with presence of a neurological disorder, significant and habitual substance use in the past 6 months, mental retardation, and insufficient fluency in English to validly complete neurocognitive tasks.

Task Paradigms. Participants performed two spatial delayed response tasks, the first contrasting manipulation and maintenance of spatial information and the second contrasting maintenance of parametrically increasing memory loads. Detailed descriptions of the tasks are provided elsewhere.^{18,23} Briefly, in Task 1, subjects were presented two trial types: maintenance only (“hold”) and maintenance plus manipulation (“flip”). In the maintenance only trials (20 total), subjects were shown 3 pseudo-randomly positioned target circles (1 second). After a 6-second delay, 3 probe circles appeared and subjects determined if these new circles were in the same locations as the target set (3-second fixed response interval). During the delay period of maintenance plus manipulation trials (20 total), subjects were instructed to “flip” the locations of the target circles over the horizontal meridian (demarcated by a horizontally-elongated fixation point). When the 3 probe circles appeared, subjects determined if the locations of the probe stimuli matched the inverted target stimuli.

On Task 2, subjects were shown an array of 1, 3, 5, or 7 target circles positioned pseudo-randomly around a central fixation (12 trials per memory set size). After a 3-second fixed delay, subjects were shown a single probe circle and asked to determine if the probe was in the same position as one of the target circles (3-second fixed response interval). 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 load levels. For both tasks, half of the trials

were true positive and half were true negative. During scanning, trials of a similar condition were grouped into 24-second blocks and interspersed with 15-second rest periods.

Scanning Procedures. All scanning was carried out on a 3 Tesla General Electric (Waukesha, WI) MRI scanner in the Brain Mapping Center of the Neuropsychiatric Institute, UCLA. Prior to each functional study, a high-resolution axial T2 weighted image was obtained and used for anatomical reference (TR = 3000 ms, TE = 41 ms, flip angle 90, 30 axial slices, FOV 24 cm²). Functional imaging utilized a gradient echo, echoplanar sequence sensitive to the BOLD signal³⁰ acquiring 16 slices parallel to the AC-PC plane (TR = 3000 ms, TE = 45 ms, voxel size of 3.125 x 3.125 x 4.00mm, and a 1mm gap (FOV=200 cm)). Through a mirror mounted on the head coil, subjects observed task stimuli back-projected via an LCD projector onto a screen placed at the subjects' feet. Behavioral responses (button presses and reaction times) were recorded through a hand-held response box.

Analysis of Behavioral Data. Accuracy and reaction time data for each experiment were entered into to separate MANOVAs testing for main effects of group (patient, control) and condition (flip, hold; memory set size). Significant main effects and interactions were decomposed using t-tests.

Functional Image Analysis. To combat potential motion artifacts, each BOLD image in a time series underwent a 3D co-registration (6 parameter rigid-body) to the middle data point in the time series. Data were smoothed with a non-linear algorithm designed to preserve image structure by smoothing adjacent voxels thought to be of the same tissue type (5 mm kernel).³¹ Each data set was subjected to a multiple-regression analysis, using a pre-whitening technique³² to account for the intrinsic temporal autocorrelation of BOLD imaging.³³ For each intra-cranial voxel, least-squares coefficients were generated independently reflecting each task condition.³⁴

Statistical images were created for the flip and hold conditions of the first task and each memory set size (1, 3, 5, 7) of the second task. Contrasting these statistical images with resting state and with each other allowed for testing hypotheses concerning manipulation vs. maintenance processing and effects of increasing memory set size.

To facilitate multi-subject analysis (and control for differential amounts of spatial distortion in taking patient and healthy subject's brains into the common space for multi-subject analyses), a common space brain was defined which approximated the average size, shape and orientation of all subjects' (patients and controls) higher resolution T2 weighted images, combined.³⁵ Based on the parameters created from the higher resolution image, statistical images created for each subject were normalized into this common space (12 parameter model). Higher-level multi-subject analysis utilized a mixed effects model (FLAME³⁶) and provided t-images reflecting activation patterns in each diagnostic group separately and an image representing between group differences for each contrast described above. To reduce the size of the search-space, group statistical images were masked with an image reflecting activation on both tasks verses rest (union of each group for each task). Statistical images were thresholded based on the magnitude ($t=3.3$) and extent (cluster significance $p<0.05$) of activation.^{37, 38} To make the results from these group comparisons comparable with others in the literature, the common space brain was normalized into a standard stereotactic space.³⁹

To expand upon the voxel level analysis, a region of interest (ROI) analysis, focusing on brain regions of greatest theoretical relevance to working memory dysfunction in schizophrenia (right DLPFC, PAR and ACC), was conducted. The location and extent of the ROIs were set functionally, according to the conjunction of the thresholded task vs. rest maps for both tasks in both groups (see Table 1). The mean percent signal change from rest within each region was

determined for each subject. Data were entered into ANOVAs modeling effects of diagnostic group, ROI and task condition. Main effects or interactions were decomposed with region- and/or condition-specific models.

Results

Behavioral Performance. On Task 1 (Figure 1A), subjects in both groups performed worse on the maintenance plus manipulation trials compared with the maintenance alone trials of the first task ($F(1,17)=19.92$, $p > 0.001$). Patients performed worse than controls overall ($F(1,17)=5.92$, $p > 0.02$), but their performance was differentially lower on maintenance plus manipulations trials compared with maintenance only trials ($F(1,17)=6.04$, $p > 0.02$). On Task 2 (Figure 1B), as the number of memoranda to be maintained increased, performance decreased in both groups ($F(3,19)=70.18$, $p > 0.001$; Figure 1B). However, while patients performed worse than controls overall ($F(1,21)=6.15$, $p > 0.02$), their performance was not differentially affected by increasing memory set size compared with controls ($F(3,19)=0.75$, $p > 0.5$). These behavioral results are consistent with those reported previously on larger samples of patients and controls.²³

Voxel-Level fMRI Analysis. Group wide analysis revealed a network of 9 spatially distinct brain regions involved in the manipulation and maintenance task compared with rest (Figure 2A-D and Table 1). These regions included: 1) a bilateral posterior region extending from the middle occipital gyrus to the inferior and superior parietal lobules; 2) a right prefrontal region including insula and dorsolateral and ventrolateral prefrontal cortex; 3) 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 anterior cingulate cortex; 6) bilateral

subcortical regions including 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 precentral gyrus; 9) a left motor area including precentral and inferior frontal gyri.

The regions implicated in the memory set sizes task (i.e., contrasting all set sizes vs rest) are strikingly similar to those associated with the manipulation and maintenance task, with the exceptions that the anterior inferior frontal region (region #3) was not implicated in memory set-size task, activation in the larger right prefrontal region (region #2) did not reach the inferior extent that was observed in the manipulation and maintenance task, and the left insular and motor regions were not significantly active in the memory set size task versus rest contrast.

These results are highly consistent with our previous work using these paradigms in an independent sample of healthy subjects scanned at a lower MRI field-strength.¹⁸

Comparison of group activation maps indicated that when task demands required explicit manipulation of information held in memory, healthy subjects recruited a right-hemisphere region at the junction of BA 45 & 46 (Center of Mass (CM): -42, -20, 13) to a significantly greater extent than patients with schizophrenia (see Figure 2E). A similar but more anterior and superior region (CM: -42, -23, 20; BA 46) differentiated groups for the larger memory set sizes (5 and 7 locations) of the memory set-size task (see Figure 2F). No other brain regions showed activation differences between groups for either task (e.g. Figure 2E-F).

Given the conservative statistical thresholding requirements for voxel-based analyses,³⁷ to protect against type II error, a second functional region of interest (ROI) analysis was performed using the areas of cortex nominated by the task vs. rest contrasts described above.

ROI Based Analysis. Across all ROIs, subjects in both groups showed higher levels of activation during the maintenance plus manipulations trials compared with the maintenance alone trials of the first task ($F(1,17)=38.19, p > 0.001$; see Figure 3). Although the main effect of diagnostic group was not significant ($F(1,17)=0.0, p > 0.9$), there were significant group x region ($F(2,16)=5.18, p > 0.01$) and group x condition ($F(2,16)=6.35, p > 0.02$) interactions, indicating that patients recruited different brain regions to different extents for different conditions compared with healthy subjects. A significant group x condition interaction was observed for right DLPFC ($F(1,16)=4.60, p > 0.04$), such that while patients and controls showed similar levels of activation for the maintenance-only trials ($F(1,17)=0.49, p > 0.5$), healthy subjects recruited this region for the maintenance-plus-manipulation trials to a substantially greater extent than the patients ($F(1,17)=5.67, p > 0.02$). In contrast, the level of activation in the ACC for patients for maintenance-only trials was higher than for the healthy subjects ($F(1,17)=10.61, p > 0.005$). This difference was not apparent in the maintenance-plus-manipulation condition, in which healthy subjects recruited this region to the same extent as patients ($F(1,17)=0.31, p > 0.6$). There were no noticeable group differences for the parietal region ($F(1,17)=0.08, p > 0.8$).

On Task 2 (varying maintenance requirements), as the number of memoranda increased, activation levels increased in both groups in each ROI ($F(3,19)=30.59, p > 0.0001$; Figure 3). A similar pattern for the first and second tasks arose with regards to diagnostic group differences. While the main effect of group was non-significant ($F(1,21)=0.32, p > 0.6$), significant group x region ($F(2,20)=5.18, p > 0.01$) and group x set size ($F(3,19)=4.42, p > 0.007$) interactions were observed, such that under different degrees of memory load, patients recruited brain regions differently than did healthy subjects. For the DLPFC, a significant main effect of group ($F(1,21)=5.47, p > 0.02$) and group x set size interaction ($F(3,19)=6.09, p > 0.004$) indicate that

patients recruited this region less and in different ways than healthy subjects across set sizes. Indeed, while activation steadily increased with increasing set size for healthy subjects ($F(2,10)=7.33, p>0.03$), 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 ($F(1,21)=0.90, p>0.7$), the activation pattern across set sizes differed in a manner similar to that found in the first task: patients showed higher than normal activation in the ACC for the smaller set sizes and lower than normal levels of activation for the larger set sizes. As with the first task, patients and healthy subjects did not differ in parietal activation.

Patients maintaining 5 locations perform similarly to healthy subjects maintaining 7 locations (patients 75.0%; healthy subjects 73.6%; $t(1,21)=-.39, p>0.7$). Despite equivalent performance, when contrasting the DLPFC activation of these two conditions by group, patients showed significantly less activation in this region than healthy subjects ($t(1,21)=3.45, p>0.002$). In contrast, ACC and PAR activation levels did not differ between groups for these two conditions ($t(1,21)=1.16, p>0.3$; $t(1,21)=0.36, p>0.7$, respectively).

Additional analyses were performed with subgroups of subjects matched for behavioral performance (Task 1: 8 patients, 7 controls, $t=1.06, p<0.30$; Task 2: 10 patients, 10 controls, $t=1.59, p<.13$), to address the potential confound of task performance and group membership. These analyses generally replicated those described above. In particular, even after selecting subjects with similar performance patterns, patients continued to under-activate the right DLPFC region during the maintenance and manipulation condition of Task 1 (group x condition interaction: $F(1,13)=7.94, p<0.01$) and did not increase activation levels to the same extent as healthy subjects with increasing memory set size on Task 2 (group x condition interaction: $F(3,16)=4.64, p<0.02$).

Comment

The results of this study help to resolve ambiguity concerning involvement of the DLPFC in working memory dysfunction in schizophrenia in three key ways. First, despite the fact that a large, distributed set of brain regions was activated in both groups, voxel-based analyses revealed group differences in activation only in the region of the DLPFC. This pattern argues for differential relevance of disturbances in this region in explaining the spatial working memory deficits observed in schizophrenia. Second, because DLPFC activity was reduced in the patients compared with controls in both task paradigms, it appears that disturbances in this region 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 the 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 the greater the degree of manipulation requirements in a given working memory task. Third, importantly, these differences in DLPFC activation persist even when comparing conditions in which patients and controls have equivalent levels of performance (and thus, presumably, experienced the tasks as comparably difficult), indicating that the physiologic disturbance in this region is unlikely to be explained entirely by group differences in mental effort, task difficulty, or motivation.

Both groups activated a complex spatially distributed network of regions for each task. Three of these regions were studied in more detail in ROI analyses. Activation patterns in the parietal region were strikingly similar across tasks and groups, with the exception that patients

showed relatively more activation when asked to maintain a single location than healthy subjects. 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^{27, 40} and may reflect that compared to normals, a relatively greater degree of mental effort is required for the patients to maintain one location. Nevertheless, the regions of the parietal cortex recruited in the current behavioral challenges were somewhat different than 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,⁴¹ and in view of the fact that gray matter density is reduced in both regions in patients with schizophrenia,⁴² the relationship between DLPFC and parietal functioning in schizophrenia merits further study.

In the maintenance-only trials of the first task, patients with schizophrenia showed significantly more anterior cingulate activation than healthy subjects (see Figure 3). As noted above, patients tended to show relatively more ACC activation when maintaining 3 or fewer locations than healthy subjects, but less ACC activation when maintaining 5 or more locations. Although patients activated the ACC to a greater degree than healthy subjects in maintenance-only trials of the first task, the pattern of ACC activation relative to DLPFC activation was tightly coupled for both groups. Prior work suggests that the ACC is uniquely sensitive to variations in task difficulty irrespective of the executive components of a task.^{43, 44} In view of this pattern, our findings suggest that patients find smaller set sizes more difficult than healthy subjects, who may need to exert less mental effort at those load levels due to more efficient maintenance processes.

Because the task paradigms in this study used a blocked trial design format, we were not able to determine whether reduced DLPFC activation in the patients was specific to processes

occurring during the delay period, rather than the encoding or retrieval periods. Experiments using single-trial (event-related) variants of the tasks are needed to isolate processes specific to the delay period.

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Figure Captions

Figure 1. Behavioral Performance on the maintenance and manipulation (A) and memory set size (B) tasks. Patients with schizophrenia performed worse than healthy subjects when faced with explicit manipulation requirements or when asked to maintain more than a single location.

Figure 2. Statistical maps showing regional brain activation during two spatial working memory tasks in healthy subjects and patients with schizophrenia. Panels A, B, and E, show voxels in which maintenance and manipulation was associated with significantly greater activation than maintenance only in healthy subjects (A), in patients with schizophrenia (B), and in healthy subjects compared with patients (E). Panels C, D, and F show the corresponding maps for activation that increased with increasing memory set size in healthy subjects (C), in patients with schizophrenia (D), and in healthy subjects compared with patients (F).

Figure 3. Region of interest based analysis of differences in regional brain activity during two spatial working memory tasks between patients with schizophrenia and healthy comparison subjects. The healthy subjects activated the DLPFC region to a significantly greater degree than the patients in the manipulation condition (flip) of the first task and in the higher memory set sizes (5 & 7 locations) of the second task.

Figure 1

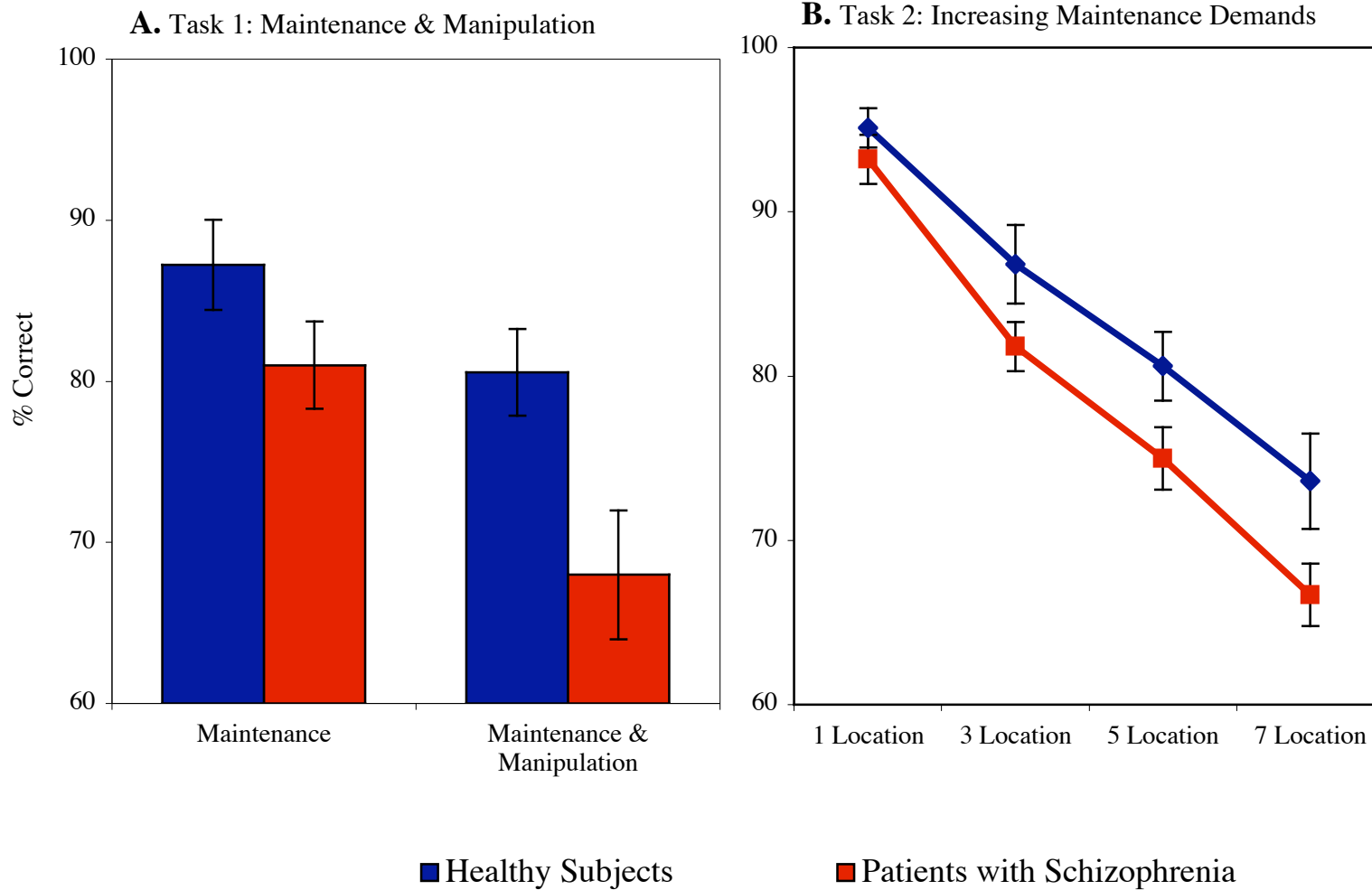


Figure 2

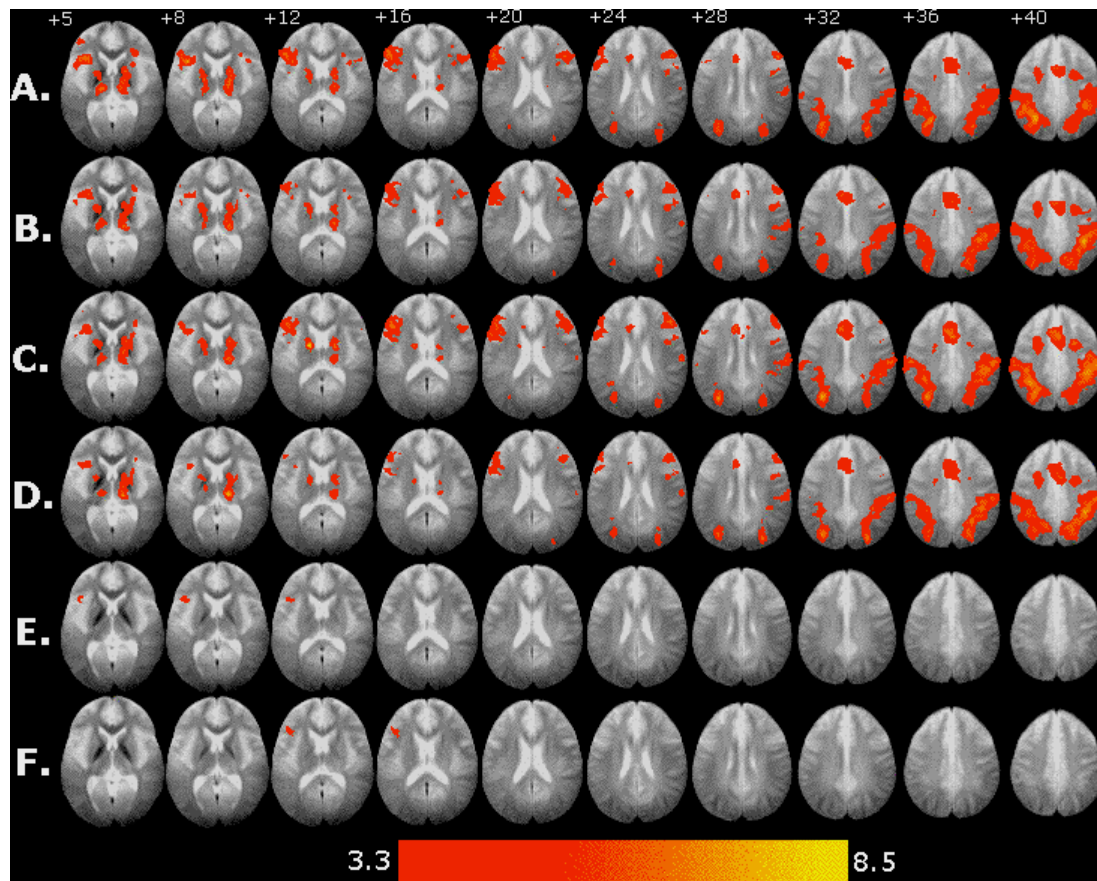


Figure 3

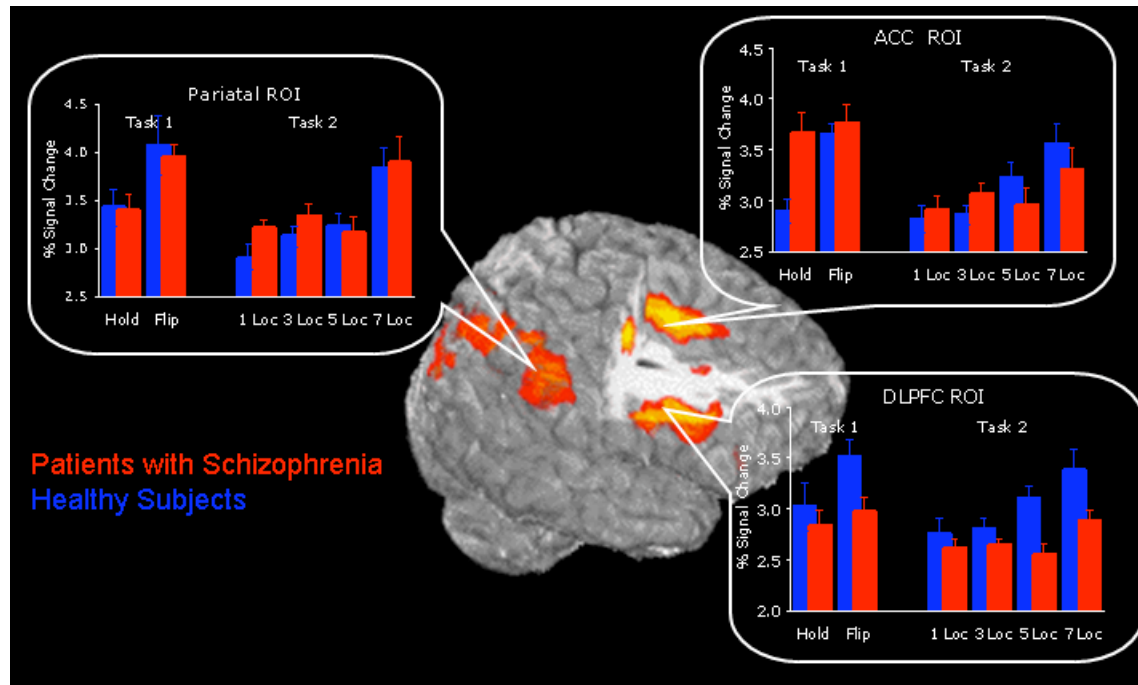


Table 1. Areas of Activation

<i>Functional ROI</i>	<i>Maintenance & Manipulation Paradigm</i>		<i>Memory Set Size Paradigm</i>		<i>Brodman Region</i>
	Volume	Center of Mass	Volume	Center of Mass	
Bilateral Parietal/Occipital	37031	2, 63, 34	63552	7, 57, 35	18, 19, 39, 40, & 7
Right Prefrontal Region	5735	-41, -22, 14	4452	-45, -19, 23	13, 47, 45, 46, 9
Right Inferior Frontal	659	-42, -44, 9	-	-	10 & 46
Left DLPFC	1877	43, -23, 26	1800	42, -28, 29	9 & 46
Anterior Cingulate	2954	0, -1, 41	7306	0, -5, 41	32, 6
Bilateral Subcortical Regions	R: 2456	-17, 10, 3	1190	-17, 0, 9	NA
	L: 4807	17, 11, 3	4303	16,7,3	
Left Insular Region	1622	31, -25, 4	-	-	3
Bilateral SMA	R: 916	-25, 11, 46	3217	-25, 7, 46	6
	L: 584	32, 10, 42	2226	22, 11, 44	
Left Motor Area	805	44, 0, 27	-	-	6 & 9

Center of Mass = Talairach coordinate (x, y, z); Volume = mm³; R=right; L=left