fMRI Study of Maintenance and Manipulation Processes Within Working Memory in First-Episode Schizophrenia

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Objective: Working memory, a critical cognitive capacity that is affected in schizophrenia, can be divided into maintenance and manipulation processes. Previous behavioral research suggested that manipulation is more affected than maintenance in patients with chronic schizophrenia. In this study of first-episode schizophrenia patients, the authors evaluated the extent to which the two working memory processes are affected early in the course of schizophrenia.

Method: Study subjects were 11 first-episode schizophrenia patients and 11 matched healthy comparison subjects. Each group performed two verbal working memory tasks while undergoing functional magnetic resonance imaging. One task required maintenance of information; the other required manipulation of information in addition to maintenance.

Results: Under behaviorally matched conditions, both groups activated a predominantly left-sided frontal-parietal network. The manipulation plus maintenance task elicited activation of greater magnitude and spatial extent. With both tasks, patients showed less bilateral dorsolateral prefrontal cortex activation and greater ventrolateral prefrontal cortex activation, relative to the comparison subjects. A group-by-task interaction was observed for activation at the left dorsolateral and ventrolateral prefrontal cortex. The increase in activation when patients engaged in the manipulation plus maintenance task was disproportionately less in the dorsolateral prefrontal cortex and greater in the ventrolateral prefrontal cortex.

Conclusions: These functional neuroanatomical findings add support to earlier suggestions that manipulation of information is selectively more affected than maintenance of information in persons with schizophrenia. They also suggest the presence of interacting regions of dysfunctional and compensatory prefrontal responses in the dorsolateral and ventrolateral prefrontal cortex, respectively, that are more prominent when information is manipulated. This disrupted prefrontal network is present relatively early in the course of schizophrenia.

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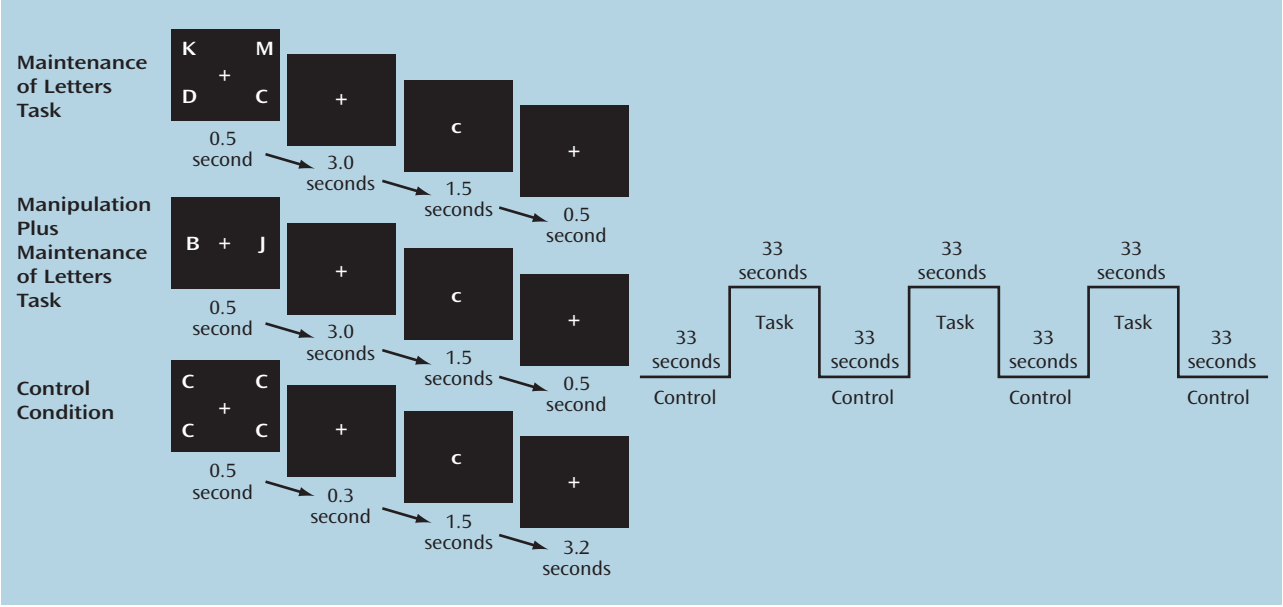
Working memory is a limited-capacity system that enables maintenance and manipulation of information temporarily. It plays an important role in higher-order thinking, language, and goal-directed behavior (1), and it is an important facet of the cognitive dysfunction in schizophrenia (2, 3). A number of neuroimaging studies have sought to uncover the neural basis of working memory deficits in patients with schizophrenia. Reduced dorsolateral prefrontal cortex (i.e., Brodmann's area 46, 9) activation (4, 5), increased activation (6), an absence of differences in activation (7), and a combination of increased and decreased activation (8) have all been described. The anatomically and functionally related ventrolateral prefrontal cortex (Brodmann's area 44, 45, 47) has been reported to show decreased activation in some studies (9) but not in others (4, 8).

These divergent findings could arise from non-disease-related factors, for example, task performance (6, 10), working memory load (6, 8), and the cognitive paradigm used in the study (11). Many previous experiments evaluating working memory engaged the various components of this faculty but did not explicitly attempt to dissociate the effects of the illness on these components. An important goal of the present study was to explore this possibility in terms of the effect on prefrontal activation of the interaction of task component and disease. Illness-related factors such as duration of illness, occupational and social deprivation, and substance abuse are thought to affect brain anatomy and function (12) and may be a further confounder in the effort to define disease-specific working memory dysfunction. Thus, only first-episode schizophrenia patients were evaluated in our study.

One approach that has pointed to specific dorsolateral prefrontal cortex dysfunction is isolation of context processing in working memory (4). Another approach, the one we used in this study, is to consider the maintenance and manipulation processes separately. For a given load, the addition of explicit manipulation requirements results in increased activation, particularly in the dorsolateral prefrontal cortex, in normal individuals (13, 14). (Here, the

FIGURE 1. Sequence and Timing of the Maintenance of Letters and Manipulation Plus Maintenance of Letters Tasks[a]



[a] Adapted with permission from Chee and Choo (19). Copyright 2004 by the Society for Neuroscience.

term "load" refers to the number of items that have to be maintained in working memory [e.g., in a Sternberg-type maintenance task]. "Task complexity" refers to the number of cognitive processes required to perform a task. "Task difficulty" is dependent on one or both of these conditions; when comparing tasks tapping different domains, as in the current study, reaction time and accuracy are used to gauge difficulty.) The dorsolateral prefrontal cortex also has a role in the maintenance of information (15, 16), whereas the left ventrolateral prefrontal cortex and left inferior parietal lobule are thought to participate in rehearsal processes that briefly maintain verbal information (17, 18).

In this study, we used two working memory tasks that evaluated prefrontal function associated with maintenance alone and with manipulation in addition to maintenance (19). We tested working memory using a two-by-two experimental design, with the expectation that prefrontal activation in the dorsolateral prefrontal cortex and ventrolateral prefrontal cortex would diverge more prominently in patients, relative to comparison subjects, particularly in the manipulation plus maintenance task, as suggested by recent behavioral experiments (20).

Method

Patients and Comparison Subjects

To include patients early in the course of the illness, we recruited first-episode psychosis patients and confirmed the diagnosis of schizophrenia at 6-month follow-up. Originally, 16 patients were recruited from among inpatients and outpatients treated in a psychiatric unit of a teaching hospital, which was also a setting for evaluation of community referrals from primary care providers throughout Singapore. Thirteen healthy comparison subjects matched with the patients for gender, age, and educational level were recruited from the surrounding community of staff and students. All subjects were right-handed, as assessed by the handedness inventory (21). After a complete description of the study to the subjects, written informed consent was obtained in accordance with the National University Hospital and Singapore General Hospital institutional review boards.

All healthy comparison subjects were screened by a research physician (W.C.C.) with a standardized questionnaire to exclude those with a past history of psychiatric, neurological, or serious medical disorders; IQ below 70; and drug or alcohol abuse in the last 6 months. First-episode psychosis patients, who met similar criteria, underwent functional magnetic resonance imaging (fMRI) when they were clinically stabilized, as defined by a score of ≤3 on the Clinical Global Impression scale (22). At the time of scanning, all patients had been taking atypical antipsychotic medications for at least 1 month. None received anticholinergic medications. Patients were followed up for at least 6 months after recruitment into the study. The diagnosis of schizophrenia was made according to DSM-IV criteria and was corroborated by a diagnostic conference that included review of information from the Structured Clinical Interview for DSM-IV (23) that had been administered by a research psychiatrist (H.Y.T.) and from all available medical records. In addition, the research psychiatrist administered the Positive and Negative Syndrome Scale (24) and the Global Assessment of Functioning Scale (DSM-IV, p. 32) to assess symptom severity within a week before the fMRI scan. After 6 months of follow-up, three patients were excluded because they met the DSM-IV criteria for other diagnoses (two for schizoaffective disorder and one for brief psychotic disorder). Two patients and two comparison subjects were excluded because of motion artifacts.

Working Memory Tasks

Two working memory tasks were used (Figure 1). The maintenance of letters task evaluated maintenance of information and was adapted from previous work (19, 25). Briefly, four different uppercase letters were presented for 0.5 second, followed by a delay of 3.0 seconds during which a fixation cross was displayed. A

TABLE 1. Characteristics and Behavioral Performance on Working Memory Tasks of First-Episode Schizophrenia Patients and Healthy Comparison Subjects in an fMRI Study of Maintenance and Manipulation of Information

Characteristic and Behavioral Performance	Patients (N=11)		Comparison Subjects (N=11)	
	N	%	N	%
Subject characteristics				
Male gender	5	45.5	5	45.5
	Mean	SD	Mean	SD
Age (years)	25.0	5.5	25.9	6.4
Education (years)	13.6	1.7	14.6	2.3
Duration of untreated psychosis (months)	2.4	3.1		
Time to scan from initiation of treatment (months)	3.5	3.2		
Global Assessment of Functioning Scale score	62.5	8.5		
Positive and Negative Syndrome Scale score				
Positive subscale	10.2	2.7		
Negative subscale	17.5	6.2		
General subscale	28.4	8.2		
Total	56.1	13.7		
	N	%	N	%
Medication				
Patients given risperidone	6	54.5		
Patients given olanzapine	5	45.5		
	Mean	SD	Mean	SD
Dose of risperidone (mg/day)	2.3	0.4		
Dose of olanzapine (mg/day)	11.0	4.2		
Behavioral performance				
Maintenance of letters task[a]				
Omitted responses (%)	3.0	4.0	2.2	3.9
Accuracy (proportion of correct responses)	0.91	0.06	0.95	0.04
Reaction time (msec)	992	34	985	31
Manipulation plus maintenance of letters task[a]				
Omitted responses (%)	5.6	7.4	3.5	5.1
Accuracy (proportion of correct responses)	0.90	0.05	0.93	0.05
Reaction time (msec)	994	163	947	189
Control task[a]				
Accuracy (proportion of correct responses)	0.96	0.05	0.95	0.05
Reaction time (msec)	721	132	684	79

[a] The sequence and timing of the task are illustrated in Figure 1.

lowercase probe letter was then presented for 1.5 seconds, followed by a fixation cross for a further 0.5 second. Subjects signaled a match or a nonmatch by pressing one of two response buttons. Half the probes matched the target letters. The proportion of omitted responses was also recorded. The control condition was designed to match the perceptual and motor elements of the actual task. Four identical uppercase letters appeared for 0.5 second. In order to minimize working memory engagement, a lowercase probe that matched the target in half the trials appeared after a short interval of 0.3 second. Subjects signaled a match or nonmatch by using one of two response buttons.

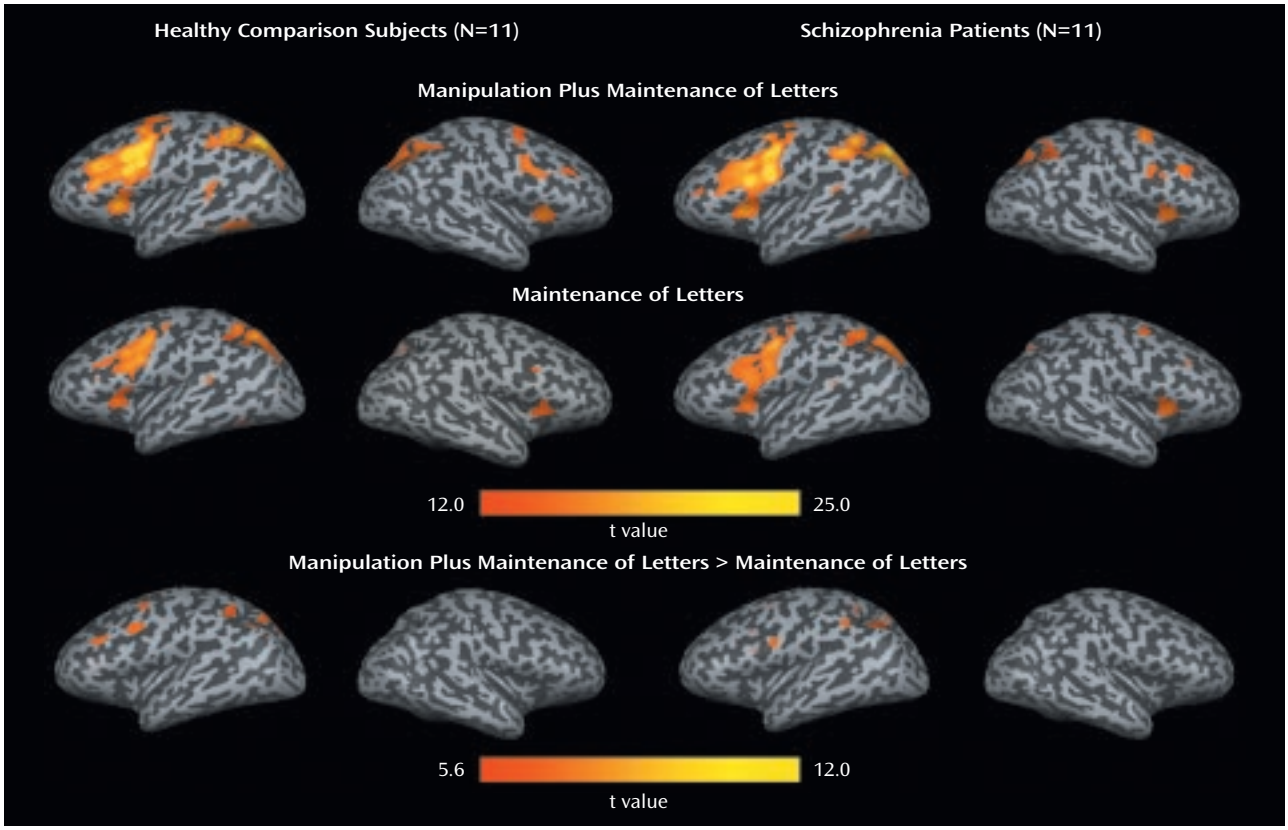
The more complex manipulation plus maintenance of letters task was titrated to engage additional manipulation of items retained in verbal working memory without increasing reaction time or changing accuracy relative to the maintenance of letters task (19). Two different letters were presented, and subjects were instructed to shift each letter forward alphabetically and to keep the results in mind. For example, if "B" and "J" were presented, subjects had to remember "c" and "k" to be able to match them with the probe. Half the trials were matches. Stimulus presentation sequence and timing were identical to that used in the maintenance of letters task. The control condition was identical to that used in the maintenance of letters task.

Before scanning, a practice session was performed outside the scanner to familiarize participants with the tasks and to ensure that task instructions were understood. Task and control blocks each lasted 33 seconds. Each block consisted of six trials (5.5 seconds per trial). Each experimental run consisted of four control blocks alternating with three task blocks. Each participant was presented with three runs of the maintenance of letters task and three runs of the manipulation plus maintenance task. The order of the two tasks was counterbalanced across subjects.

Imaging Procedure

Stimuli were projected onto a screen and viewed by subjects using a rear-view mirror. Subjects registered their responses through a hand-held response box with the right hand. A bite-bar was used to reduce head motion. Images were acquired from a 3.0-T Allegra scanner (Siemens, Erlangen, Germany). A gradient-echo, echo-planar imaging sequence was used (TR=3000 msec, field of view=192×192 mm, 64×64 mm pixel matrix). Thirty-two oblique axial slices with a 3-mm thickness (0.3-mm gap) approximately parallel to the anterior commissure-posterior commissure line were acquired. The sampled brain volume did not consistently include the cerebellum. High-resolution coplanar T_2 anatomical images were also obtained. A further high-resolution anatomical reference image was acquired by using a T_1 three-dimensional magnetization-prepared, rapid acquisition gradient echo image sequence for the purpose of image display in Talairach space.

FIGURE 2. Blood-Oxygen-Level-Dependent Signal Change Reflecting Activation During Working Memory Tasks in Patients With First-Episode Schizophrenia and Healthy Comparison Subjects[a]



[a] Group-level analyses were conducted by using a fixed-effects model (p<0.001, uncorrected).

Image Analysis

Motion correction was performed in-scanner by using PACE (Siemens, Erlangen, Germany). Analysis was performed by using Brain Voyager 2000 version 4.9 (Brain Innovation, Maastricht, Holland). The coplanar T_2 images were used to register the functional data set to the three-dimensional image. The resulting aligned data set was then transformed into Talairach space (26). Mean intensity adjustment and intrasession alignment were performed on the functional images. Gaussian filtering was applied in the spatial domain with a smoothing kernel of 8 mm full width at half maximum for group-level activation maps.

Bearing in mind that performance may confound interpretation of functional imaging data (6, 7), we analyzed only blocks where performance was satisfactory (accuracy >0.65). In each subject, no more than three (of nine) task blocks for each task failed to meet this criterion and were removed; a mean of 1.3 (SD=1.2) blocks were removed for the patients, compared to a mean of 0.4 (SD=0.5) blocks for the comparison subjects (t=2.3, df=20, p<0.05). Group-level analyses were conducted by using a fixed-effects model. Statistical t maps were computed from a general linear model with a single predictor for each task (maintenance of letters, manipulation plus maintenance of letters) by using separate subject predictors. The expected blood-oxygen-level-dependent (BOLD) signal change was modeled by using a gamma function (tau=1.5, delta=2.5) synchronized to blocks of cognitive tasks. Voxels that survived a threshold of p<0.001 (uncorrected) and a minimum cluster size of 50 were considered for group-level analysis. Whole brain voxel-by-voxel analyses for group dependent effects were then performed for each task, as well as for the contrast between tasks (manipulation plus maintenance > maintenance of letters).

In addition, hypothesis-driven region of interest analyses were carried out for the dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, and anterior cingulate. These regions were selected for study because they have been shown in prior studies to be active in working memory operations (13, 27). Voxels within these regions of interest were those in which group differences were present when the contrast (manipulation plus maintenance > maintenance of letters) was compared by using a statistical threshold of p<0.001 (uncorrected) and a fixed-effects analysis. We then obtained parameter estimates from activated voxels within a bounding box with a 15-mm edge centered on the peak voxel. This activation mask was subsequently applied to individual subjects' data, yielding one parameter estimate per subject per region. Analysis of variance was performed on these parameter estimates. A statistical threshold of p<0.05 was applied in this second-level analysis.

Results

Subject Demographics

The 11 patients with first-episode schizophrenia and 11 comparison subjects were matched for age, gender distribution, and years of education (Table 1). At the time of scanning, positive psychotic symptoms were mostly in remission. The duration of psychosis was less than 12 months in all patients and less than 6 months in the majority of patients. All patients had initiated treatment with atypical antipsychotic medications within the previous 3 months.

Behavioral Results

Considering only blocks where performance was satisfactory (accuracy >0.65), performance accuracy on the maintenance of letters task (t=1.5, df=20, p>0.05) and manipulation plus maintenance task (t=1.4, df=20, p>0.05) was similar for the patients and the comparison subjects, as were reaction times (maintenance: t=0.2, df=20, p>0.05; manipulation plus maintenance: t=0.6, df=20, p>0.05) (Table 1). On the control task, accuracy (t=0.3, df=20, p>0.05) and reaction time (t=0.2, df=20, p>0.05) were also similar between groups. The proportion of omitted responses did not differ across groups for either task (maintenance: t=1.1, df=20, p>0.05; manipulation plus maintenance: t=1.9, df=20, p>0.05). Among patients, accuracy and reaction time were similar when performance on the maintenance task was compared to performance on the manipulation plus maintenance task (accuracy: t=1.1, df=10, p>0.05; reaction time: t=1.0, df=10, p>0.05). As in a previous study (19), the comparison group also showed equivalent performance for these two tasks (accuracy: t=1.7, df=10, p>0.05; reaction time: t=0.7, df=10, p>0.05).

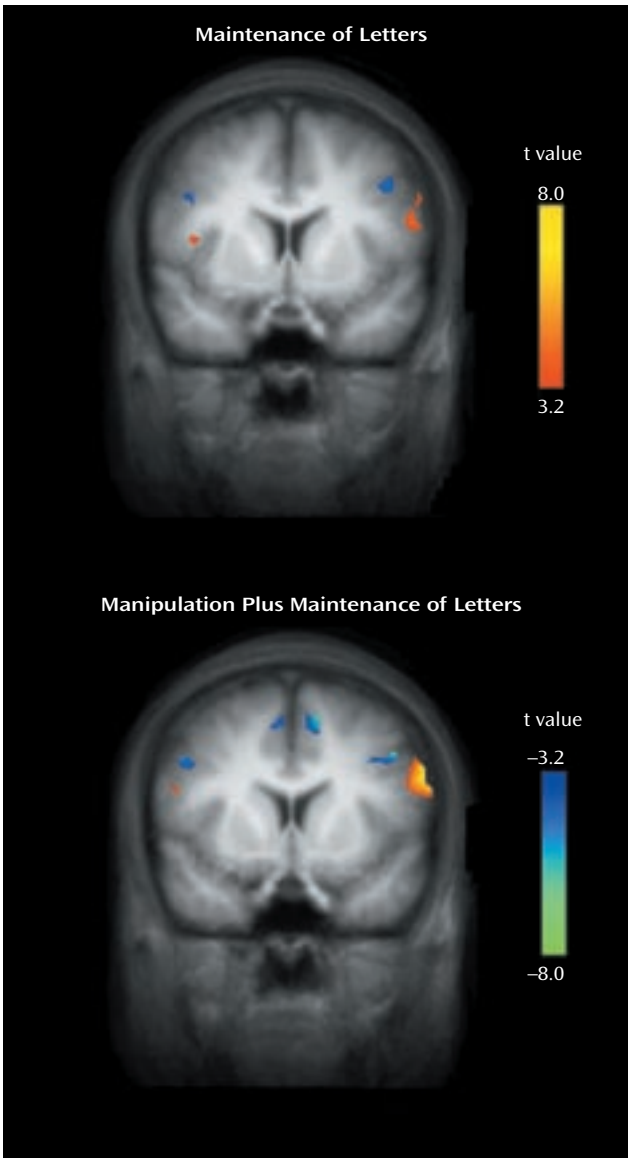
Task-Related Activation

For maintenance of letters, both groups activated a common network of frontal-parietal regions, predominantly on the left side (Figure 2). Regions activated by both groups included the bilateral middle frontal gyri (Brodmann's area 9/46), inferior frontal gyri (Brodmann's area 45), anterior cingulate (Brodmann's area 32), inferior parietal lobule (Brodmann's area 40), insula, and thalamus. The left fusiform gyrus (Brodmann's area 37) and precentral gyrus (Brodmann's area 6) were also activated. Deactivation common to both groups was observed in the medial frontal (Brodmann's area 10) and posterior cingulate (Brodmann's area 31) regions.

The manipulation plus maintenance task and the maintenance task activated similar frontal-parietal regions, but the activations had a greater magnitude and spatial extent in the manipulation plus maintenance task. Both groups activated the bilateral middle frontal gyri (Brodmann's area 9/46), anterior cingulate (Brodmann's area 32), inferior parietal lobule (Brodmann's area 40), precentral gyri (Brodmann's area 6), insula, and thalamus. In addition, the left inferior frontal gyrus (Brodmann's area 44) and fusiform gyrus (Brodmann's area 37) were activated. The medial frontal (Brodmann's area 10) and posterior cingulate (Brodmann's area 31) regions were deactivated in the manipulation plus maintenance task.

With the contrast (manipulation plus maintenance > maintenance of letters) that examines activation in response to the additional manipulation component in the manipulation plus maintenance task, both groups showed relatively greater activation with the manipulation plus maintenance task in the left inferior frontal gyrus (Brodmann's area 44) and the left middle frontal gyrus (Brodmann's area 9/46). The left anterior cingulate (Brodmann's area 32), inferior parietal lobule (Brodmann's area 40), and left precentral gyrus (Brodmann's area 6) also showed relatively greater activation with manipulation plus maintenance task, compared to maintenance task.

FIGURE 3. Differences in Blood-Oxygen-Level-Dependent Signal Change in Prefrontal Regions During Working Memory Tasks Between Patients With First-Episode Schizophrenia (N=11) and Healthy Comparison Subjects (N=11)[a]



[a] Group-level analyses were conducted by using a fixed-effects model (p<0.001, uncorrected). Images show coronal sections at Talairach coordinate y=9 mm. Blue areas indicate regions with relatively less activation in patients; red areas indicate regions with relatively greater activation in patients. Images are shown in radiological convention.

Group Differences in Task Activations

With the maintenance of letters task, patients activated the bilateral middle frontal gyri (Brodmann's area 9) to a lesser extent than the comparison subjects. In contrast, the bilateral inferior frontal gyri (Brodmann's area 44)

TABLE 2. Regions Displaying Peak Differences in Blood-Oxygen-Level-Dependent (BOLD) Activation During Working Memory Tasks Between First-Episode Schizophrenia Patients (N=11) and Healthy Comparison Subjects (N=11)

	Patients < Comparison Subjects					Patients > Comparison Subjects				
Task and Region	Estimated Brodmann's Area	Coordinates[a] x	y	z	Analysis (t)[b]	Estimated Brodmann's Area	Coordinates[a] x	y	z	Analysis (t)[b]
Maintenance of letters task										
Left middle frontal gyrus	9	–42	9	36	5.7					
Right middle frontal gyrus	9	45	10	32	4.6					
Left thalamus	–	–15	–19	16	5.2					
Left inferior frontal gyrus						44	–55	11	22	7.2
Right inferior frontal gyrus						44	54	13	20	4.3
Left precentral gyrus						6	–47	–4	51	5.1
Right insula							32	12	15	4.1
Left inferior parietal lobule						40	–45	–52	45	5.8
Right inferior parietal lobule						40	–47	–52	45	7.4
Manipulation plus maintenance of letters task										
Left middle frontal gyrus	9	–42	34	30	10.6					
Right middle frontal gyrus	9	41	35	22	7.2					
Left anterior cingulate	8	–10	11	51	7.0					
Right anterior cingulate	32	8	16	48	5.5					
Right insula		32	27	4	4.4					
Left insula		–26	22	0	6.4					
Left inferior frontal gyrus						44	–54	4	29	11.2
Right inferior frontal gyrus						44	56	13	23	5.9
Left medial frontal cortex[c]						10	–1	57	21	6.0
Left inferior parietal lobule						40	–52	–44	43	7.6
Right inferior parietal lobule						40	52	–44	48	7.9
Manipulation plus maintenance task > maintenance of letters task										
Left middle frontal gyrus	9	–43	33	32	6.3					
Left anterior cingulate	32	–8	8	53	5.1					
Left inferior frontal gyrus						44	–54	4	29	5.2
Left inferior parietal lobule						40	–55	–41	40	4.4

[a] Coordinates from the stereotaxic atlas of Talairach and Tournoux (26).
[b] Regional peak activation representing BOLD signal change that survived a threshold of p<0.001 (uncorrected) in a fixed-effects analysis.
[c] Denotes deactivation.

were activated to a greater extent in the patients than in the comparison subjects, as were the inferior parietal lobules (Brodmann's area 40) (Figure 3, Table 2). During the manipulation plus maintenance task, patients similarly activated the bilateral middle frontal gyri (Brodmann's area 9) to a lesser extent and the bilateral inferior frontal gyrus (Brodmann's area 44) to a greater extent than the comparison subjects (Figure 3, Table 2). In the medial frontal region (Brodmann's area 10), the patients showed a reduced magnitude of deactivation, relative to the comparison subjects, during the manipulation plus maintenance task.

When the contrast (manipulation plus maintenance > maintenance of letters) was compared across groups to examine activation differences in response to the additional manipulation component of the manipulation plus maintenance task, we found that patients activated the left inferior frontal gyrus (Brodmann's area 44) to a greater extent than the comparison subjects. The left middle frontal gyrus (Brodmann's area 9) and anterior cingulate (Brodmann's area 32) were activated to a lesser extent in the patients (Figure 4). Parameter estimates for these three regions were used for subsequent analysis. The parameter estimate for the left middle frontal gyrus (dorsolateral prefrontal cortex) showed a task-by-group interaction ($F=5.4$, $df=1, 20$, $p<0.05$), in addition to a main effect of task ($F=13.1$, $df=1, 20$, $p<0.005$). The patients had a disproportionately lower increase in dorsolateral prefrontal cortex activity as they engaged in the manipulation plus maintenance task, relative to the maintenance of letters task (Figure 5). The parameter estimate for the left inferior frontal gyrus (ventrolateral prefrontal cortex) also showed a task-by-group interaction ($F=5.9$, $df=1, 20$, $p<0.05$) and a main effect of task ($F=7.2$, $df=1, 20$, $p<0.05$). Here, patients had a disproportionate increase in ventrolateral prefrontal cortex activity as they engaged in the manipulation plus maintenance task, compared to the maintenance of letters task (Figure 5). A task-by-group interaction was found for left anterior cingulate activation ($F=8.0$, $df=1, 20$, $p<0.05$) (Figure 5).

Discussion

We found that both first-episode schizophrenia patients and healthy comparison subjects activated a predominantly left-sided frontal-parietal network, with the manipulation plus maintenance task eliciting activation of greater magnitude and spatial extent, compared to the maintenance task. In the patients, relative to the comparison subjects, both the maintenance and manipulation components of verbal working memory were associated with

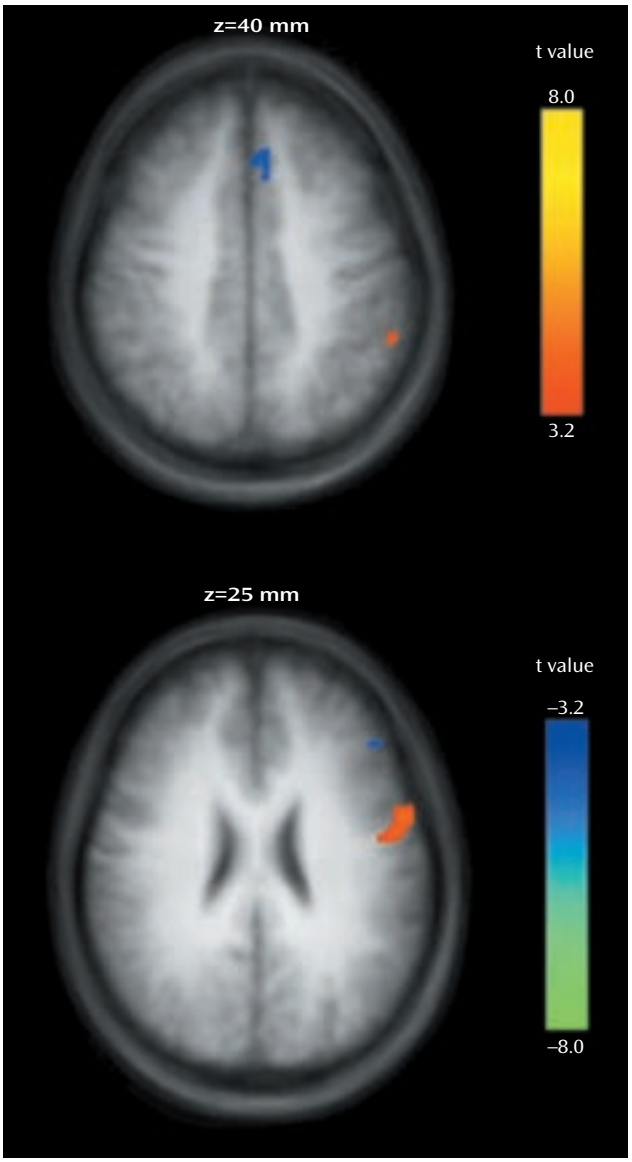
decreased activation in the dorsolateral prefrontal cortex and increased activation in the ventrolateral prefrontal cortex. In addition, these findings were more prominent in the manipulation component, as shown by the group-by-task interactions found for activation in the left dorsolateral prefrontal cortex and ventrolateral prefrontal cortex (Figure 5).

Our finding of relative increases and decreases in prefrontal activation that were accentuated in manipulation versus maintenance tasks in patients adds to recent behavioral data suggesting that while both maintenance and central executive aspects of working memory are impaired in schizophrenia, the central executive aspect is more severely affected (20). Several sources of behavioral findings have also suggested that schizophrenia patients are particularly impaired on tasks requiring executive processes (28, 29). In concert with these studies, a recent study found working memory to be a core deficit that could be rate-limiting for a number of diverse cognitive functions affected in schizophrenia (2). The present study adds functional neuroanatomical evidence to suggest that within working memory processes, manipulation may contribute more to dysfunction in schizophrenia. Supporting the present findings, Honey et al. (30) reported that manipulation processes elicited greater BOLD signal change in a similar frontal-parietal network in healthy subjects exposed to subdissociative doses of ketamine; these findings were obtained in the context of a model of *N*-methyl-D-aspartic acid receptor hypofunction in schizophrenia.

The relatively lower dorsolateral prefrontal cortex activation during manipulation in patients adds support to several pieces of evidence for the importance of the dorsolateral prefrontal cortex in the pathophysiology of schizophrenia (16, 31). Decreased dorsolateral prefrontal cortex activation and dysfunction have been demonstrated in several working memory fMRI studies of chronic schizophrenia (32, 33), as well as first-episode schizophrenia (4). In addition, a proton magnetic resonance spectroscopy study of schizophrenia patients showed that reduced dorsolateral prefrontal cortex *N*-acetylaspartate concentrations correlate with abnormal activation within the working memory network (6). Finally, postmortem studies have shown increased neuronal density in the dorsolateral prefrontal cortex in patients with schizophrenia (34–36).

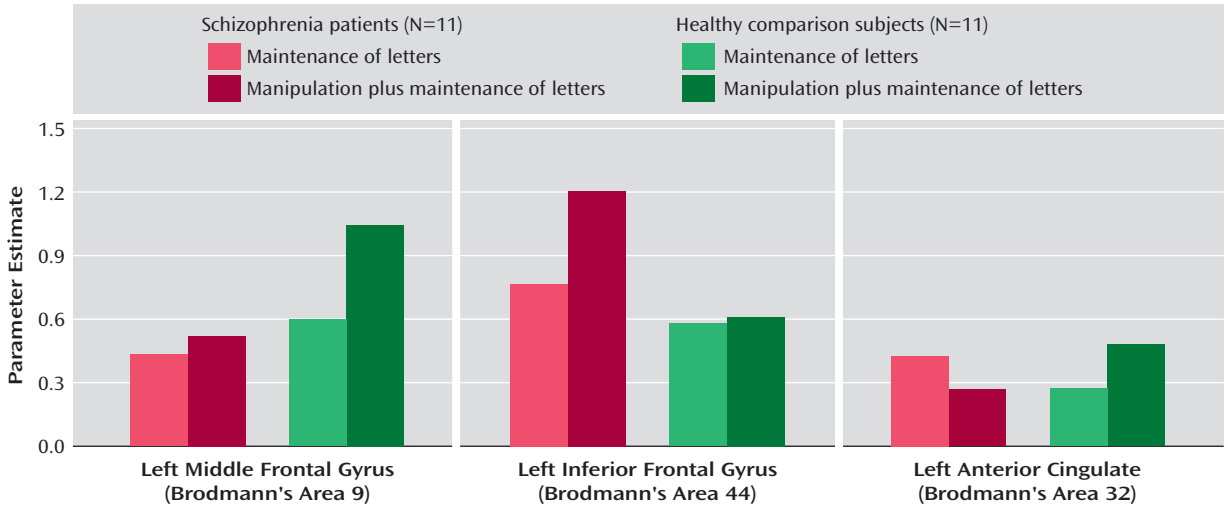
In contrast to relatively decreased dorsolateral prefrontal cortex activation, we found a disproportionate increase in ventrolateral prefrontal cortex activation in first-episode patients during the manipulation task, compared to the maintenance task, suggesting that the ventrolateral prefrontal cortex might serve a compensatory function. Greater ventrolateral prefrontal cortex activation was also observed in another group of schizophrenia patients (8). In healthy subjects, subvocal rehearsal and phonological loop processes are thought to contribute to activation of the left ventrolateral prefrontal cortex in verbal working memory tasks (18, 37). In patients, the relatively greater activation observed might represent the overuse of this strategy in a neural substrate that is compensating for the dysfunctional dorsolateral prefrontal cortex. A synthesis with recent findings of cytoarchitectonic abnormalities selectively at the dorsolateral prefrontal cortex but not the ventrolateral prefrontal cortex (38) further suggests that these activation differences may represent interacting regions of dysfunctional and compensatory neuroplastic activity in the dorsolateral prefrontal cortex and the ventrolateral prefrontal cortex, respectively.

FIGURE 4. Differences in Blood-Oxygen-Level-Dependent Signal Change Showing Effects of Manipulation of Information Between Patients With First-Episode Schizophrenia (N=11) and Healthy Comparison Subjects (N=11)[a]



[a] Group-level analyses were conducted by using a fixed-effects model ($p<0.001$, uncorrected). Effects of manipulation of information were determined in a contrast between tasks (manipulation plus maintenance of letters > maintenance of letters). Blue areas indicate regions with relatively less activation in patients; red areas indicate regions with relatively greater activation in patients. Images are shown in radiological convention.

FIGURE 5. Parameter Estimates Showing Relative Activation in the Left Middle Frontal Gyrus, Left Inferior Frontal Gyrus, and Left Anterior Cingulate During Working Memory Tasks in Patients With First-Episode Schizophrenia and Healthy Comparison Subjects



Although we found relatively increased activation in the ventrolateral prefrontal cortex, others have found no difference (4) or a decrease in activation (9) in this region. These differences may be explained by variations in the study task or in patients' medications or illness duration. For example, a prior study (4) used a context processing task that differed from ours in that the subvocal rehearsal and the phonological loop were not taxed. The patients in the study that reported a decrease in activation (9) were older and had a longer duration of illness, making the results of that study difficult to compare with ours.

Task-specific activity differences in patients versus comparison subjects were also observed in the left anterior cingulate. Whereas the healthy comparison subjects had greater activation in this region during the manipulation task, patients had less activation (Figure 5). Given the close functional relationship between this region and the dorsolateral prefrontal cortex, and its complementary role in cognitive control and conflict monitoring, this reduced activation could contribute to the overall dysfunction in the prefrontal network in schizophrenia (39).

An alternative explanation for our prefrontal activation findings is that they resulted from increased overall working memory load and/or difficulty involved in the manipulation task rather than from the manipulation per se. This explanation is less likely because the maintenance and manipulation tasks yielded similar behavioral results in both the patients and the comparison subjects in our study (see Results) and in an earlier study in which the participants were healthy subjects (19).

The effects of atypical antipsychotic medications, which were taken by all of the patients in our study, deserve mention. We chose to study cognitive deficits after initial stabilization, because deficits that are present at that stage have been demonstrated to be less transient (40), more reflective of the core pathology, and more predictive of functional outcome (41). Although our finding of reduced dorsolateral prefrontal cortex activation is consistent with the findings of an earlier study that included neuroleptic-naive first-episode schizophrenia patients (4), it is possible that medication effects contributed to the increased ventrolateral prefrontal cortex activation, as suggested by an fMRI study showing greater prefrontal cortex activation after substitution of risperidone for haloperidol in patients with schizophrenia (42). This possibility, together with the broader question of prefrontal responses to medications in patients with early illness, is intriguing and warrants future investigation.

Finally, we note that these task-specific prefrontal findings were present in first-episode patients and therefore could have been established relatively early in the course of schizophrenia, at or before the first psychotic episode. These findings are unlikely to be a result of chronic illness and related epiphenomena. Although our findings support the notion that dorsolateral prefrontal cortex dysfunction is already present at the first psychotic episode, additional research will be needed to examine the nature of the ventrolateral prefrontal cortex response in relation to its possible compensatory role in information processing, the effect of parametric variation in task load on these brain activations, and the effect of medications and disease progression. We also need a better understanding of the relationship of these prefrontal findings to neuropsychological and epidemiological findings of cognitive deficits sustained before the onset of psychosis (17, 43–45).

Conclusions

In patients with first-episode schizophrenia, reduced activation in the dorsolateral prefrontal cortex and increased activation in the ventrolateral prefrontal cortex were disproportionately present in tasks involving the ma-

nipulation of information versus the maintenance of information. These results suggest complex interactions between dysfunctional and compensatory responses in the dorsolateral prefrontal cortex and ventrolateral prefrontal cortex, respectively, associated with an overall less effective prefrontal neural strategy. This disruption of the prefrontal network mediating working memory occurs relatively early in the course of schizophrenia and is present at the first psychotic episode.

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