Working Memory and Prefrontal Cortex Dysfunction: Specificity to Schizophrenia Compared with Major Depression

Deanna M. Barch, Yvette I. Sheline, John G. Csernansky, and Abraham Z. Snyder

Background: *A large number of studies suggest the presence of deficits in dorsolateral prefrontal cortex function during performance of working memory tasks in individuals with schizophrenia. However, working memory deficits may also present in other psychiatric disorders, such as major depression. It is not clear whether people with major depression also demonstrate impaired prefrontal activation during performance of working memory tasks.*

Methods: *We used functional magnetic resonance imaging to assess the patterns of cortical activation associated with the performance of a 2-back version of the N-Back task (working memory) in 38 individuals with schizophrenia and 14 with major depression.*

Results: *We found significant group differences in the activation of dorsolateral prefrontal cortex associated with working memory performance. Consistent with prior research, participants with schizophrenia failed to show activation of right dorsolateral prefrontal cortex in response to working memory tasks demands, whereas those with major depression showed clear activation of right and left dorsolateral prefrontal cortex as well as bilateral activation of inferior and superior frontal cortex.*

Conclusions: *During performance of working memory tasks, deficits in prefrontal activation, including dorsolateral regions, are more severe in participants with schizophrenia (most of whom were recently released outpatients) than in unmedicated outpatients with acute nonpsychotic major depression.* Biol Psychiatry 2003; 53:376–384 © *2003 Society of Biological Psychiatry*

Key Words: Schizophrenia, major depression, functional magnetic resonance imaging (fMRI), working memory, cognition

Introduction

A growing literature on cognitive deficits in schizophrenia and their neurobiological correlates suggests that people with schizophrenia have deficits in working memory (WM) that are associated with abnormalities in the activation of the prefrontal cortex, particularly the dorsolateral prefrontal cortex. However, only a few studies have examined whether such WM deficits are specific to schizophrenia or are also present in people with other psychiatric disorders. For example, research on the neurobiological underpinnings of major depression suggest that prefrontal cortex dysfunction may also be present in this disorder, which may in turn contribute to WM deficits. As such, the goal of our study was to use functional magnetic resonance imaging (fMRI) to compare the patterns of cortical activation associated with the performance of both verbal and nonverbal WM tasks in people with schizophrenia and people with major depression.

Typically WM is defined as the ability to temporarily maintain and manipulate information online (Baddeley and Della Sala 1996). A large number of studies have demonstrated that people with schizophrenia demonstrate performance deficits on a wide range of WM tasks (Barch et al 1998, in press; Cohen et al 1999; Gold et al 1997; Goldberg et al 1998; Gooding and Tallent 2001; Park and Holzman 1992, 1993; Stone et al 1998; Wexler et al 1998). Moreover, people with schizophrenia demonstrate abnormalities in the activation of prefrontal cortex during performance of WM tasks. In particular, several studies suggest a disturbance in the activation of dorsolateral regions of the prefrontal cortex (PFC; i.e., middle frontal gyrus, Brodmann's area 46/9; Andreasen et al 1992; Barch et al 2001, in press; Berman et al 1992, 1986; Carter et al 1998; Menon et al 2001; Perlstein et al 2001; Volz et al 1997; Weinberger et al 1988; Weinberger et al 1986, 1996). The most frequent pattern of abnormal dorsolateral PFC activation is a reduction in activation among people with schizophrenia compared with healthy control participants, although a few studies have actually found greater activation of PFC in people with schizophrenia when they perform WM tasks (Callicott et al 1998, 2000; Manoach et al 1999). Furthermore, some studies have identified relationships between the degree of structural abnormality in dorsolateral PFC and cognitive disturbances in people with schizophrenia (Baare et al 1999; Seidman et al 1994). Thus, a wealth of literature supports the presence of

From the Departments of Psychology (DMB), Psychiatry (DMB, YIS, JGC), and Radiology (YIS, AZS), Washington University, St. Louis, Missouri.

Address reprint requests to Deanna M. Barch, Ph.D., Department of Psychology, Box 1125, One Brookings Drive, St. Louis MO 63130.

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dorsolateral PFC deficits in schizophrenia and their role in cognitive deficits in this disorders.

Several recent reports suggest that people with other psychiatric disorders, such as unipolar major depression, also display WM deficits (Landro et al 2001; Merriam et al 1999; Pelosi et al 2000; Sweeney et al 1998). However, these deficits may not be as severe as those found in schizophrenia (Goldberg et al 1993; Merriam et al 1999), and a number of investigators have not found such WM deficits in major depression (Cohen et al 1999; Grant et al 2001; Sweeney et al 2000; Zakzanis et al 1998) or in bipolar disorder (Gooding and Tallent 2001; Park and Holzman 1992). It has been suggested that such WM deficits in major depression also reflect disturbances in prefrontal function (Merriam et al 1999; Purcell et al 1997; Sweeney et al 1998). However, structural and resting blood flow studies in mood disorders have typically identified deficits in more orbital and medial regions of prefrontal cortex, as opposed to dorsolateral PFC (Drevets 2000), although a few studies have identified abnormalities in dorsolateral regions (Dolan et al 1993; Medved et al 2001). To our knowledge, only one previous study has examined brain activation during cognitive challenge in major depression, finding greater impairment in dorsolateral PFC activation during performance of the Wisconsin Card Sorting Task in patients with schizophrenia compared with major depression (Berman et al 1993). However, brain activation during performance of a specific WM task has not yet been compared among people with schizophrenia and those with major depression.

The goal of this study was to compare brain activation, using fMRI, and behavioral performance in people with schizophrenia and with unipolar major depression during performance of both verbal and nonverbal WM tasks. We predicted that participants with schizophrenia would show significantly impaired WM performance and impaired activation of dorsolateral PFC compared with participants with major depression. The inclusion of both verbal and nonverbal WM tasks also allowed us to determine whether differences between diagnostic groups might vary as a function of material type.

Methods and Materials

Participants

Participants included 38 people with DSM-IV-diagnosed schizophrenia, 14 with unipolar major depression, and 49 healthy control subjects. (Data from the same schizophrenia participants were compared with a demographically similar group of healthy controls in Barch et al, in press). The participants with schizophrenia were inpatients ($n = 4$) at the St. Louis Metropolitan Psychiatric Center (MPC) or outpatients recently released from MPC ($n = 34$). (The results were identical when only the outpatients with schizophrenia were compared with subjects with major depression, who were all outpatients.) All participants with schizophrenia were medicated and clinically stable at the time of assessment (i.e., drug treatment had not been changed for at least 2 weeks, and residual symptoms had been minimized). Of the participants with schizophrenia, 79% were taking atypical antipsychotics and 21% were taking typical antipsychotics; only a small percentage (17%) were taking anticholinergic medications. The participants with major depression were all acutely depressed outpatients; 12 of 14 were unmedicated at the time of participation (the two on medications were both taking sertraline). Major depression and healthy control participants were recruited through local advertisements. Control participants were excluded if they had any lifetime history of Axis I psychiatric disorder or any first-degree relative with a psychotic disorder. Potential participants were also excluded for 1) meeting DSM-IV criteria for substance abuse within the last 3 months or dependence at any time within the past 6 months; 2) the presence of any clinically unstable or severe medical disorder or of a medical disorder that would confound the assessment of psychiatric diagnosis or make participation in the research protocol unsafe; 3) present or past neurologic disorders, including any head injury causing loss of consciousness; and 4) meeting DSM-IV criteria for mental retardation (mild or greater in severity). The demographic and clinical characteristics of the participant groups are shown in Table 1. The major depression and healthy control participants had higher personal education than participants with schizophrenia [$F(2,97) = 8.36$, $p < .001$] but did not differ from each other. The groups did not differ significantly on age [$F(2,97) = .12$, $p > .7$], years of parent education [to match approximately for socioeconomic status; $F(2,97) = .35$, $p > .7$], gender [$\chi^2(2) = 2.3$, $p > .3$], or handedness [$\chi^2(2) = 1.1$, $p > .5$].

Diagnoses were determined using the Structured Clinical Interview for DSM-IV (SCID-IV; Spitzer et al 1990). The structured interviews and clinical symptom ratings for schizophrenia and healthy control participants were conducted by an MSW-level research assistant. The research assistant had completed SCID-IV training and regularly participated in ongoing diagnostic training sessions at the Metropolitan Psychiatric Center. The structured interviews for participants with major depression were conducted by a board-certified psychiatrist (YIS). All participants with schizophrenia were assessed clinically using the Scale for the Assessment of Negative Symptoms (SANS; Andreasen 1983a), the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen 1983b), and the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962). Scores on the three major factors (see Table 1) typically found in these scales were used to describe the clinical state of the participants with schizophrenia (Andreasen et al 1995; Brekke et al 1994; Shatasel et al 1992; Silver et al 1993; Van der Does et al 1993). The specific items included in each subscale were as follows: 1) Reality Distortion (alpha = .84); hallucinations and unusual thought content from the BPRS, hallucinations and delusions from the SAPS; 2) Disorganization (alpha = .48); conceptual disorganization, mannerisms and posturing, and disorientation from the BPRS, inappropriate affect, positive formal thought disorder, bizarre behavior from the

Table 1. Demographic and Clinical Characteristics of Participants

	Healthy Control		Major Depression		Schizophrenia	
	M	SD	M	SD	M	SD
Age (in years)	36.5	11.2	37.6	12.0	36.3	10.3
Gender (% male)	46		50		63	
Parent's Education (in years)	13.6[a]	3.2	13.6[a]	3.2	12.8	2.9
Participant's Education (in years)	15.1	2.3	15.6	2.6	12.9	3.2
Handedness (% right)	96		100		92	
Poverty Symptoms					11.36	5.0
Disorganization					4.9	3.2
Reality Distortion					6.4	4.8
Hamilton Depression Rating Scale Total			21.7	6.1		

[a]Significantly different from participants with schizophrenia at $p < .05$

SAPS/SANS; and 3) Poverty Symptoms (alpha = .73); emotional withdrawal, motor retardation, and blunted affect from the BPRS, anhedonia and asociality, avolition and apathy, alogia and affective flattening from the SANS. Participants with major depression were assessed with the Hamilton Depression Rating Scale (Hamilton 1960), with ratings completed by YIS. Handedness (see Table 1) was assessed using the Edinburgh Inventory (Oldfield 1971). All participants signed informed consent forms in accordance with the Washington University Institutional Review Board.

Tasks and Materials

All participants were scanned while performing two runs of a 2-back version of an N-back task. One run was performed with verbal stimuli and one with nonverbal stimuli (described later). In this task, participants saw a sequence of stimuli presented in the center of a computer screen and were told to push one button (target) any time they saw a stimulus that was the same as the stimulus that they saw two trials back and to push a nontarget button otherwise. The stimuli for each task were presented in four blocks of trials, with each block containing 16 trials. Within each 16 trials, one third were targets, and two thirds were nontargets. The stimuli for the verbal task were concrete, visually presented words, 3–10 letters in length, presented in 48-point Geneva font, subtending visual angle of ~6°. The stimuli for the nonverbal task were non-nameable faces that subtended a ~6° visual angle vertically and horizontally (faces of nonfamous people for whom participants would not have an a priori verbal label). All of the faces had either neutral or mildly pleasant expressions. These are the same stimuli used in a number of prior studies (Braver et al 2001; Kelley et al 1998).

Participants performed each task condition in a run lasting 255 sec. As described earlier, each run included four task blocks. In addition, each run included three fixation blocks interleaved in alternating order with the task blocks (there were also four fixation trials at the beginning and end of each run). Task blocks lasted 40 sec, and fixation blocks lasted 25 sec. Each of the 16 items in a task block was presented for 2 sec, followed by a 500 msec interstimulus interval. During the fixation blocks, a crosshair appeared continuously, and participants were told to fixate. Visual stimuli were generated by an Apple PowerMac and PsyScope (Cohen et al 1993) and projected to participants with a Sharp LCD projector onto a screen positioned at the head end of the bore. Subjects viewed the screen through a mirror attached to the top of the magnetic resonance head coil. A fiber-optic, light-sensitive key press interfaced with the PsyScope Button box was used to record participants' behavioral performance.

Scanning

All scanning was performed on the 1.5-T Siemens VISION system at the Research Imaging Center of the Mallinkrodt Institute of Radiology at the Washington University Medical School. Two types of information were acquired in each scan session: functional and structural scans. The functional images were collected in runs using an asymmetric spin-echo echo-planar sequence sensitive to blood oxygenation level–dependent (BOLD) contrast (T2*; repetition time = 2500 msec, echo time = 50 msec, field of vision = 24 cm, flip = 90°). During each functional run, 102 sets of 16 contiguous, 8-mm-thick axial images were acquired parallel to the anterior–posterior commissure plane (3.75 × 3.75 mm in plane resolution), allowing complete brain coverage at high signal-to-noise ratio (Conturo et al 1996). We realize that these dimensions create anisotropic voxels that could lead to partial volume effects in disorders with structural abnormalities, such as schizophrenia and major depression; however, we believe that the benefit of the increased signal-to-noise ratio conferred by the thicker slices outweighed the potential partial volume problems. Structural images were acquired using a sagittal MP-RAGE three-dimensional T1-weighted sequence (repetition time = 10 msec, echo time = 4 msec, flip = 8°; voxel size = 1 × 1 × 1.25 mm). These structural images were used for between-subject registration (as described later) and anatomic localization.

fMRI Data Analysis

Preliminary processing included 1) compensation for systematic slice-dependent time shifts, 2) elimination of systematic odd–even slice intensity differences due to interpolated acquisition, and 3) realignment of all data acquired in each subject within and across runs to compensate for rigid body motion. The head movement correction algorithm provided two sets of estimated movement parameters that we used to examine group differences in movement. The first set was the difference of the current

Table 2. Behavioral Performance by Group

	Healthy Control		Major Depression		Schizophrenia	
	M	SD	M	SD	M	SD
Words						
Accuracy	.92	.08	.96	.04	.84	.15
Reaction time	855	258	793	94	913	316
Faces						
Accuracy	.89	.09	.92	.04	.82	.12
Reaction time	930	267	814	129	976	257

image from the first image acquired (absolute movement). The second set was the difference of the current image from the immediately preceding image (incremental movement). Each fMRI run was intensity normalized (each voxel value multiplied by a fixed constant) to achieve whole-brain signal intensity mode of 1000 (Bandettini et al 1993). Between-subjects analyses were conducted by coregistering participants' structural images to an atlas representative target brain using a 12-parameter rotation, translation, and expansion–contraction algorithm. Atlas transformation of the Echo Planar Imaging (EPI) data were achieved as previously described (Ojemann et al 1997). The atlas representative target was made to conform to the Talairach Atlas (Talairach and Tournoux 1988) using the method of Lancaster et al (1995). The functional imaging data were then spatially blurred with an 8-mm full width half maximum (FWHM) Gaussian filter.

The fMRI signal was then analyzed using appropriately designed analysis of variance (ANOVA) and *t* test techniques. For all of these analyses, subjects were treated as a random factor. The statistical analyses of the fMRI signal were conducted individually for each voxel in the brain, which generated voxelwise statistical maps that were then thresholded for significance using a cluster-size algorithm (Forman et al 1995) that protects against an inflation of the false-positive rate with multiple comparisons (see Results for the specific thresholds used). Specifically, we used a cluster-size threshold of 10 contiguous voxels and a pervoxel alpha of .002, corresponding to a whole brain false-positive rate of approximately .05 (McAvoy et al 2001).

Behavioral Data Analysis

Accuracy and median correct reaction times (RTs) were examined for the verbal and nonverbal WM tasks. The data from the WM tasks (both RT and accuracy) were analyzed using two-factor ANOVAs, with group (schizophrenia, depression, healthy control) as a between-subjects factor and material (verbal vs. nonverbal) as a within-subjects factor.

Results

Behavioral Data

The ANOVA for accuracy in the WM tasks indicated a significant main effect of group [$F(2,95) = 10.9$, $p < .01$] and material [$F(1,95) = 8.9$, $p < .05$], but no group by material interaction [$F(2,95) = .05$, $p > .9$]. (Due to technical difficulties, data files for the word version of the WM task were missing for one participant with schizophrenia and one with major depression.) Post hoc comparisons using Tukey's honestly significant difference indicated that participants with schizophrenia performed significantly worse than participants with major depression and healthy control subjects (see Table 2) but were equally impaired with verbal and nonverbal materials. Participants with major depression and healthy control subjects did not differ significantly. All participants performed better with words than faces. The ANOVA for RTs indicated no main effect of group [$F(2,95) = 2.1$, $p > .1$], no main effect of material type [$F(2,95) = 2.5$, $p > .1$], and no group by material interaction [$F(2,95) = .17$, $p > .8$].

fMRI Data

TASK-RELATED ACTIVATION WITHIN EACH GROUP. We began by examining the regions of the brain that demonstrated significant task-related activity within each group, separately for each material type (words, faces). To do so, we conducted voxelwise *t* tests with condition (task, fixation) as a within-subject factor. As shown in Figure 1, all three groups demonstrated task-related activation in many of the same regions for both the verbal and the nonverbal versions of the task, including bilateral inferior frontal cortex and parietal cortex, as well as motor cortex, visual cortex, and anterior cingulate cortex. The participants with schizophrenia also displayed some evidence of left dorsolateral prefrontal cortex activity. Notably, however, they showed less activity in right dorsolateral prefrontal cortex (which we define as Brodmann's areas 9, 46, or both) than either the participants with major depression or the healthy control participants. In contrast, as shown in Figure 1, participants with major depression demonstrated task-related activation in most of the regions activated by healthy control participants in WM tasks, including bilateral activation of dorsolateral prefrontal cortex. All three groups showed the same general pattern of material sensitivity effects, with relatively greater right inferior frontal and parietal activity for faces, but relatively greater left inferior frontal and parietal activity for words.

MAJOR DEPRESSION VERSUS HEALTHY CONTROL PARTICIPANTS. We next examined whether there were any regions of task-related activation that showed significant group differences between the healthy control and major depression participants. To do so, we conducted voxelwise ANOVAs with group (healthy control, depression) as a between-subject factor and both condition (task,

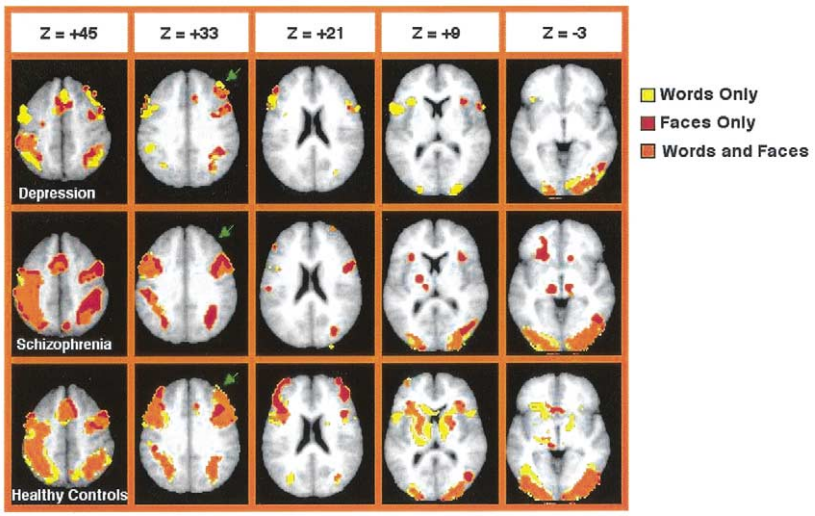

Figure 1. Brain regions demonstrating significant task-related activity in major depression (top panel), schizophrenia (middle panel), and healthy control (bottom panel) participants. As described in the text, these regions of interest are thresholded at $p <$ .002 and 10 contiguous voxels. The green arrow points to right dorsolateral prefrontal cortex (BA 9/46).

fixation) and material type (words, faces) as within-subject factors. As shown in Table 3 and Figure 2, there were four regions that demonstrated a significant group by condition interaction. These regions included bilateral thalamus, right precentral gyrus, and right parietal cortex. In all four regions, the healthy control participants demonstrated significantly greater task-related activation than participants with major depression for both words and faces. In addition, there were two regions that demonstrated significant group by condition by material type interactions. As shown in Table 3, these regions were in right middle temporal gyrus and right superior frontal gyrus. In both of these regions, healthy control participants demonstrated significant task-related activation for words but not faces, whereas participants with major depression demonstrated the opposite pattern.

SCHIZOPHRENIA VERSUS MAJOR DEPRESSION PARTICIPANTS. We next examined whether there were any regions of task-related activation that showed significant group differences between the major depression and schizophrenia groups. To do so, we again conducted voxelwise ANOVAs with group (schizophrenia, depression) as a between-subject factor and both condition (task, fixation) and material type as within-subject factors. We are not reporting on the comparison between healthy control and schizophrenia participants, because this has been reported previously (Barch et al, in press). As shown in Table 4 and Figure 3, there was one region that demonstrated a significant group by condition interaction. This region was in right dorsolateral prefrontal cortex and demonstrated significantly greater task-related activation for both words and faces in major depression compared with schizophrenia participants. In addition, there were two regions that demonstrated significant group by condition by material type interactions, one in right parietal cortex and one in left parietal cortex. In both parietal regions, participants with major depression demonstrated task-related activation for words and not faces, whereas

Table 3. Regions Demonstrating Task-Related Brain Activation Differences between Participants with Major Depression and Healthy Control Participants

Regions of Interest	Brodmann's Area(s)	X[a]	Y[a]	Z[a]	Peak *F* Value	Volume in mm^3	Group Difference Effect Size for Words[b]	Group Difference Effect Size for Faces[b]
Group by Condition								
Right Thalamus		26	−3	18	21.8	105	.82[d]	1.06[d]
Left Thalamus		−23	−9	15	20.9	58	.76[c]	1.03[d]
Right Precentral Gyrus	6	32	−12	39	15.8	14	.88[d]	.80[c]
Right Parietal Cortex	7	23	−60	45	14.9	11	.73[c]	.67[c]
Group by Condition by Material								
Right Middle Temporal Gyrus	21	35	6	−30	19.8	13	.49[c]	−.43[c]
Right Superior Frontal Gyrus	6	11	9	57	14.8	25	.27	−1.1[d]

[a]X, Y, and Z are Talairach coordinates of the centroid of activation.
[b]Positive effect size values indicate greater activation in control participants; negative values indicate greater activation in participants with major depression.
[c]$p < .05$
[d]$p < .005$

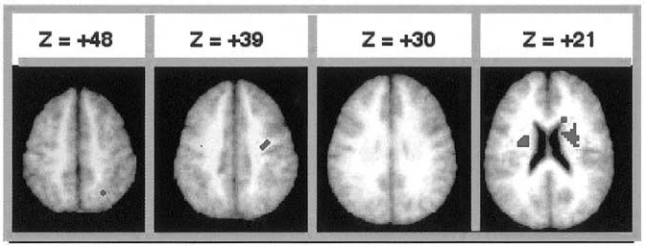

Figure 2. Brain regions demonstrating significantly greater task-related activation for both words and faces in healthy control participants than in participants with major depression. As described in the text, these regions of interest are thresholded at $p < .002$ and 10 contiguous voxels.

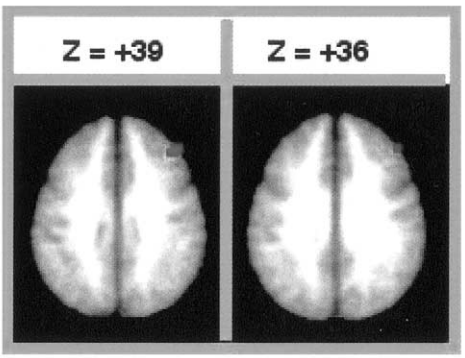

Figure 3. Brain regions demonstrating significantly greater task-related activation for both words and faces in participants with major depression than in those with schizophrenia. As described in the text, these regions of interest are thresholded at $p < .002$ and 10 contiguous voxels.

participants with schizophrenia demonstrated the opposite pattern.

Potential Confounds

A potential problem with fMRI studies in two diagnostic groups is that increased movement among one group (i.e., participants with schizophrenia) creates artifacts that impair the detection of cortical activation. To address this question, we compared the amount of movement shown by the participants with major depression and those with schizophrenia. The two groups did not differ significantly on any of the estimated movement parameters, whether absolute movement (all ts < 1.1) or incremental movement (all ts < 1.7). We also examined signal-to-noise ratios (SNR = mean/SD) for the fMRI data using a two-way ANOVA with group (major depression, schizophrenia) as a between-subject factor and slice (1–16) as a within-subject factor. This analysis indicated no significant main effect of group [$F(1,50) = 2.3$, $p > .10$] or group by slice interaction [$F(15,750) = 1.01$, $p > 3$]. Thus, group differences in activation did not appear to be a consequence of increased movement or decreased SNR on the part of participants with schizophrenia.

Discussion

The primary goal of this study was to examine the hypothesis that deficits in PFC function during performance of WM tasks are specific to schizophrenia compared with major depression. Consistent with this hypothesis, we found that participants with schizophrenia demonstrated impaired behavioral performance on both verbal and nonverbal versions of a WM task compared with participants with major depression. Furthermore, we found significant group differences in activation of dorsolateral PFC for both verbal and nonverbal stimuli. Consistent with prior research, participants with schizophrenia failed to demonstrate activation of right dorsolateral PFC during performance of the N-back task (Perlstein et al 2001; Weinberger et al 1996), although they did show some evidence of left dorsolateral prefrontal activation. In contrast, participants with major depression demonstrated activation of both right and left dorsolateral prefrontal cortex during performance of the N-back tasks, in locations similar to those

Table 4. Regions Demonstrating Task-Related Brain Activation Differences between Participants with Major Depression and Schizophrenia

Regions of Interest	Brodmann's Area(s)	X[a]	Y[a]	Z[a]	Peak F Value	Volume in mm^3	Group Difference Effect Size for Words[b]	Group Difference Effect Size for Faces[b]
Group by Condition								
Right middle frontal gyrus	9	44	30	36	16.08	11	1.09[d]	.68[c]
Group by Condition by Material								
Left parietal cortex	7	−20	−66	57	13.6	15	.49	−.86[c]
Right parietal cortex	40	38	−51	57	17.1	21	.94[d]	−.51

[a] X, Y, and Z are Talairach coordinates of the centroid of activation.
[b] Positive effect size values indicate greater activation in participants with major depression; negative values indicate greater activation in participants with schizophrenia.
[c] $p < .05$
[d] $p < .005$

seen in previous fMRI studies of WM (Braver et al 1997; Cohen et al 1997; Smith et al 1995). We also found significant group differences in the activation of parietal cortex, with schizophrenia participants showing a different pattern of material sensitivity than participants with major depression.

These results provide evidence to support the hypothesis that impairments in dorsolateral PFC function during cognitive task performance are specific to schizophrenia, a critical question that has not yet been adequately addressed in the literature. A number of behavioral studies have demonstrated that impairments in WM performance may be worse among people with schizophrenia than among those with major depression (Cohen et al 1999; Goldberg et al 1993; Merriam et al 1999), and at least one prior study has found impaired dorsolateral activation in schizophrenia compared with depression during Wisconsin Card Sorting Task performance (Berman et al 1993). To our knowledge, however, this is the first study to show that impairments in activation of PFC are also worse among people with schizophrenia than among those with major depression during performance of a task specifically designed to assess WM function. Nonetheless, it should be noted that all of our participants with major depression were nonpsychotic. Moreover, the majority of the participants with major depression were unmedicated, whereas all of the participants with schizophrenia were medicated. As such, it is possible that impairments in prefrontal function during performance of WM tasks is related to either psychosis per se or to the administration of antipsychotic medication. We and others have found disturbed cognitive task performance and dorsolateral PFC activation in unmedicated participants with schizophrenia, however, including both medication naive, first-episode patients schizophrenia (Andreasen et al 1997; Barch et al 2001) and chronic patients withdrawn from medication (Berman et al 1986). Such results suggest that deficits in PFC function in schizophrenia are not simply secondary to the administration of antipsychotic medications. Further research is needed to determine whether impaired prefrontal activation is selective to schizophrenia per se or present in people with other psychotic disorders, such as bipolar disorder with psychotic features or delusional disorder.

Despite some previous reports of WM deficits in people with major depression (Landro et al 2001; Merriam et al 1999; Pelosi et al 2000; Sweeney et al 1998), we found no evidence for any disturbances in WM behavioral performance among our participants with major depression. Furthermore, we found clear evidence for activation of both inferior prefrontal cortex and dorsolateral PFC during performance of WM tasks in these same participants with major depression. Our results are consistent with a number of recent studies suggesting that cognitive deficits are relatively minimal in younger, ambulatory people with major depression (Grant et al 2001; Purcell et al 1997). Cognitive deficits may be more severe in older people with major depression, however, especially if they are chronic and hospitalized (Beats et al 1996; Elliott et al 1996; Palmer et al 1996), and it is possible that we would have found more evidence for deficits in dorsolateral PFC activation among depressed patients if we had studied an older, chronic, or hospitalized sample. Nonetheless, our findings of intact inferior and dorsolateral PFC activity in major depression are not inconsistent with reports suggesting that the primary prefrontal regions disturbed in major depression may be more medial and orbital, including ventral–medial PFC and subgenual regions of anterior cingulate (Drevets 1998; Drevets et al 1997). These regions of frontal cortex have extensive connectivity with limbic regions of the brain involved in emotional processing (i.e., amygdala, hippocampus, hypothalamus, etc.), and there is evidence from both structural and functional imaging studies that such regions are impaired in people with major depression (Drevets 1998; Drevets et al 1997). Furthermore, our results provide additional evidence for the specificity of dorsolateral prefrontal cortex activation deficits to schizophrenia.

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