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# Working and Long-Term Memory Deficits in Schizophrenia: Is There a Common Prefrontal Mechanism?

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This study tested the hypothesis that dorsolateral prefrontal cortex deficits contribute to both working memory and long-term memory disturbances in schizophrenia. It also examined whether such deficits were more severe for verbal than nonverbal stimuli. Functional magnetic resonance imaging was used to assess cortical activation during performance of verbal and nonverbal versions of a working memory task and both encoding and recognition tasks in 38 individuals with schizophrenia and 48 healthy controls. Performance of both working memory and long-term memory tasks revealed disturbed dorsolateral prefrontal cortex activation in schizophrenia, although medial temporal deficits were also present. Some evidence was found for more severe cognitive and functional deficits with verbal than nonverbal stimuli, although these results were mixed.

A large literature on cognitive function in schizophrenia suggests that individuals with this illness display deficits in several different cognitive domains, including deficits in working memory (WM) and long-term memory (LTM). Deficits in WM have often been hypothesized to reflect a disturbance in prefrontal cortex (PFC) function (D'Esposito et al., 1998), whereas deficits in LTM (i.e., encoding or retrieval) have often been hypothesized to reflect a disturbance in medial temporal cortex hippocampal function (Heckers et al., 1998). However, among individuals with schizophrenia, it is not yet clear that disturbances in WM and LTM truly represent two distinct cognitive deficits associated with different neurobiological substrates. An alternative, potentially more parsimonious, hypothesis is that a disturbance in PFC function contributes to deficits in both WM and LTM among individuals with schizophrenia (Goldberg, Weinberger, Pliskin, Berman, & Podd, 1989). The goal of the current study was to test this hypothesis using functional magnetic resonance imaging (fMRI) to assess the patterns of cortical function and dysfunction associated with the performance of both WM and LTM tasks in individuals with schizophrenia and controls.

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WM has been defined as the ability to temporarily maintain and manipulate information on-line (Baddeley & Della Sala, 1996). A growing number of studies suggest that individuals with schizophrenia show deficits on tasks designed to measure WM (Barch & Carter, 1998; Cohen, Barch, Carter, & Servan-Schreiber, 1999; Gold, Carpenter, Randolph, Goldberg, & Weinberger, 1997; Goldberg, Patterson, Taqqu, & Wilder, 1998; Park & Holzman, 1992, 1993; Stone, Gabrieli, Stebbins, & Sullivan, 1998; Wexler, Stevens, Bowers, Sernyak, & Goldman-Rakic, 1998). Further, several researchers have suggested that WM deficits may be the fundamental cognitive defect present in schizophrenia and that the neurobiological substrate of such WM deficits is a disturbance in PFC function (Cohen & Servan-Schreiber, 1992; Goldman-Rakic, 1991; Weinberger & Gallhofer, 1997). For example, the literature on cognitive functional neuroimaging suggests that individuals with schizophrenia fail to appropriately activate PFC during performance of WM tasks. In fact, a number of studies suggest a particular disturbance in the activation of dorsolateral regions of PFC (i.e., middle frontal gyrus, BA 46/9; Andreasen et al., 1992; Barch et al., 2001; Berman, Torrey, Daniel, & Weinberger, 1992; Berman, Zec, & Weinberger, 1986; Callicott et al., 1998, 2000; Carter et al., 1998; Manoach et al., 1999; Menon, Anagnoson, Mathalon, Glover, & Pfefferbaum, 2001; Perlstein, Carter, Noll, & Cohen, 2001; Volz et al., 1997; Weinberger, Berman, & Illowsky, 1988; Weinberger, Berman, & Zec, 1986; Weinberger et al., 1996), although other regions of PFC are also sometimes disturbed (e.g., BA 44/45; Stevens, Goldman-Rakic, Gore, Fulbright, & Wexler, 1998; Volz et al., 1997; Weinberger et al., 1986, 1988, 1996).

The evidence concerning deficits in WM and PFC in schizophrenia continues to grow. However, it is clear that individuals with schizophrenia also show deficits in cognitive domains other than WM, such as at least some aspects of LTM function (Aleman, Hij, de Haan, & Kahn, 1999; Danion, Rizzo, & Bruant, 1999; Gold, Randolph, Carpenter, Goldberg, & Weinberger, 1992; Goldberg et al., 1993; Hutton et al., 1998). LTM refers to the ability to encode or retrieve newly learned information. Several studies suggest that LTM is more seriously disturbed than general intel-

lectual ability (McKenna et al., 1990; Tamlyn et al., 1992) or other cognitive functions (Saykin et al., 1991, 1994) in schizophrenia. In fact, some researchers have argued that LTM deficits also constitute a core cognitive deficit in schizophrenia (Clare, McKenna, Mortimer, & Baddeley, 1993; McKay et al., 1996). Further, it has been argued that the pattern of LTM deficits found in individuals with schizophrenia is similar to those seen in individuals with structural abnormalities of the medial temporal lobes, and that such LTM deficits in schizophrenia may be linked to disturbances in these same structures (Fletcher et al., 1998).

It is possible that deficits in WM and LTM represent two distinct domains of cognitive dysfunction in schizophrenia, each with a separate neuroanatomical substrate. However, an alternative hypothesis is that poor performance on tasks measuring both LTM and WM in schizophrenia may reflect a common disturbance in PFC function, which in turn causes deficits in executive functions that can impair performance on both WM and LTM tasks (Carter & Barch, 2000; Goldberg et al., 1989). Several lines of evidence are consistent with this hypothesis. First, the particular pattern of LTM deficits shown by individuals with schizophrenia is more consistent with the cognitive profiles of individuals with frontal lesions than of individuals with medial temporal cortex hippocampal lesions (Goldberg et al., 1989). For example, some studies have shown that individuals with schizophrenia are more impaired on recall tasks than recognition memory tasks (Calev, 1984a; Goldberg et al., 1989; Koh, 1978; Paulsen et al., 1995; Rizzo, Danion, Van Der Linden, & Grange, 1996; Rushe, Woodruff, Murray, & Morris, 1998). Such a pattern is more common with frontal-lobe lesions than with temporal-lobe lesions (Shimamura, Janowksy, & Squire, 1991) and may reflect an inability to effectively use organizational and retrieval strategies rather than a primary deficit in the ability to encode new memories (O'Reilly, Braver, & Cohen, 1999). In addition, among individuals with schizophrenia, recall performance benefits from the addition of explicit cues to organize the information at encoding (Koh, 1978), as well as from additional cues at retrieval (Sengel & Lovallo, 1983). Again, this pattern of LTM performance is characteristic of individuals with frontal lesions (Gershberg & Shimamura, 1995).

A second line of evidence is the fact that the literature on the empirical relationship between LTM deficits and either structural or functional disturbances in medial temporal cortex (hippocampus) in schizophrenia has been somewhat mixed. This statement is not meant to deny the body of evidence suggestive of structural changes in temporal cortex, including hippocampus (Csernansky et al., 1998; R. E. Gur et al., 2000; McCarley et al., 1993; Nelson, Saykin, Flashman, & Riordan, 1998; Shenton, Dickey, Frumin, & McCarley, 2001; Shenton et al., 1992; Suddath, Christison, Torrey, Casanova, & Weinberger, 1990). Nevertheless, although some studies have found associations between LTM deficits and structural or functional deficits in medial temporal cortex/hippocampus (R. E. Gur, Jaggi, Shtasel, Ragland, & Gur, 1994; R. E. Gur et al., 2000; Heckers et al., 1998; McCarley et al., 1993; Weinberger, Berman, Suddath, & Torrey, 1992), several others have not (Andreasen et al., 1996; Crespo-Facorro et al., 1999; Ganguli et al., 1997; Nohara et al., 2000; Ragland et al., 1998, 2001; Torres, Flashman, O'Leary, Swayze, & Andreasen, 1997). Further, some studies have found correlations between neuropsychological measures of LTM deficits and volume reductions in dorsolateral prefrontal cortex (DLPFC; Baare et al., 1999; Seidman et al., 1994) rather than medial temporal regions (Seidman et al., 1994). Thus, the schizophrenia literature has not consistently found a relationship between LTM deficits and medial temporal cortex disturbances, and in fact has demonstrated some evidence for correlations between LTM disturbances and frontal deficits.

The growing neuroimaging literature on memory processes in healthy adults provides a third line of evidence consistent with the hypothesis that frontal dysfunction may contribute to LTM deficits in schizophrenia. This literature demonstrates that encoding and retrieval may be just as dependent on PFC function as medial-temporal cortex hippocampal function. For example, a recent review by Buckner concluded that there was very consistent evidence that encoding, retrieval, and WM tasks all activate at least one common region of PFC: an area within inferior frontal gyrus (BA 44/6; Buckner & Koutstaal, 1998). It is important that a recent event-related study by Wagner and colleagues (Wagner et al., 1998) demonstrated that activation in left inferior, frontal gyrus (including BA 44/6), as well as activation in parahippocampal gyrus (e.g., BA 37), was greater for words that were later correctly remembered than for those that were not correctly remembered. Further, both WM and retrieval tasks activate two additional regions of PFC: one in DLPFC (BA 46/9) and one in anterior frontal gyrus (BA 10; MacLeod, Buckner, Miezin, Peterson, & Raichle, 1998).

A secondary but related goal of this study was to assess the material specificity of WM and LTM deficits in schizophrenia, as well as to determine whether any laterality differences exist in cortical dysfunction in schizophrenia. A number of researchers have suggested that schizophrenia is characterized by a left-lateralized cortical dysfunction (Crow, 1990; R. E. Gur, 1978). Consistent with this hypothesis, several studies have found greater left- than right-hemisphere structural (Shenton et al., 1992) and functional (R. C. Gur & Gur, 1995; Siegal et al., 1993) changes in schizophrenia, although other studies have not (Nelson et al., 1998; Suddath et al., 1990). In addition, a number of studies have found greater deficits in schizophrenia with verbal than nonverbal materials (Cannon et al., 1994; R. E. Gur et al., 1994; Saykin et al., 1994; Wexler et al., 1998), whereas others have found equally severe deficits with verbal and nonverbal materials (Blanchard & Neale, 1994; Calev, 1991; Calev, Korin, Kugelmass, & Lerer, 1987; Cornblatt, Lenzenweger, & Erlenmeyer-Kimling, 1989; Hoff, Riordan, O'Donnell, Morris, & DeLisi, 1992; Sullivan, Shear, Zipursky, Sagar, & Pfefferbaum, 1997).

The hypothesis that patients with schizophrenia may show material-specific or lateralized disturbances in brain function is in part based on research demonstrating relative material-specific laterality effects in some regions of the brain. For example, the encoding of words elicits relatively greater left than right activation in both PFC (BA 44/6; Kelley et al., 1998) and medial temporal cortex/hippocampus (Kelley et al., 1998; Martin, Wiggs, & Weisberg, 1997; Milner, 1971), whereas encoding of nonnameable faces elicits relatively greater right- than left-sided activation in these same regions (Braver et al., 2001; Kelley et al., 1998). However, activation in DLPFC (i.e., BA 46/9) tends to be bilateral or right sided for both verbal and nonverbal materials (D'Esposito et al., 1998). Thus, if deficits in WM and LTM in schizophrenia are primarily associated with a disturbance in DLPFC function, then one would expect these cognitive deficits to be equally severe

for verbal and nonverbal materials, because this region of PFC seems to be important for processing both types of material.

The goals of the current study were twofold. Our first goal was to test the hypothesis that PFC dysfunction contributes to both WM and LTM deficits in individuals with schizophrenia. To do this, we conducted fMRI in participants with schizophrenia during the performance of three tasks: (a) intentional encoding into LTM, (b) retrieval from LTM, and (c) WM. We predicted that participants with schizophrenia would show behavioral deficits in both WM and LTM and that these deficits would be strongly correlated. Further, we predicted that both WM and LTM deficits would be associated with disturbed activation of the same region of PFC, namely DLPFC. The second goal of this study was to determine whether deficits in WM and LTM in schizophrenia are equally severe for verbal and nonverbal materials. To test this hypothesis, we used both verbal (words) and nonverbal (nonnameable faces) versions of the encoding, retrieval, and WM tasks. As described above, we predicted that participants with schizophrenia would not show material-specific (e.g., greater verbal than nonverbal deficits) or hemispheric-specific dysfunction during the performance of either WM or retrieval tasks if the primary neurobiological mechanism was a disturbance in DLPFC function (BA 46/9).

## Method

### *Participants*

Participants were 38 individuals with schizophrenia, diagnosed according to the criteria of the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM–IV*; American Psychiatric Association, 1994), and 48 healthy controls. The participants with schizophrenia were all clinically stable inpatients at the St. Louis Metropolitan Psychiatric Center (MPC) or outpatients recently released from MPC. All participants were medicated and had been recruited through an ongoing related structural imaging protocol conducted by John G. Csernansky. The controls were recruited from the same community as the individuals with schizophrenia, through local advertisements. Controls were excluded if they had any lifetime history of Axis I psychiatric disorder or any first-order family member with a psychotic disorder. Potential participants (either patient or control) were also excluded for (a) meeting *DSM–IV* criteria for substance abuse (severe) or dependence (any type) at any time within the past 3 months; (b) the presence of any clinically unstable or severe medical disorder, or a medical disorder that would confound the assessment of psychiatric diagnosis or make participation in the research protocol unsafe; (c) present or past head injury with documented neurological sequelae or causing loss of consciousness; and (d) meeting *DSM–IV* criteria for mental retardation (mild or greater in severity). The demographic and clinical characteristics of both participant groups are shown in Table 1. All patients with schizophrenia were medicated, with 79% taking atypical and 21% taking typical antipsychotics. As such, only a small percentage (17%) were taking anticholinergic medications. The controls had higher levels of educational attainment than did the participants with schizophrenia, $t(84) = 3.45$, $p < .01$, but the groups did not differ significantly on age, $t(84) = 0.1$, $p > .50$; years of parent education (to match approximately for socioeconomic status), $t(84) = 1.1$, $p > .20$; gender, $\chi^2(2, N = 86) = 2.8$, $p > .20$; and handedness, $\chi^2(2, N = 86) = 1.2$, $p > .50$.

Schizophrenia and control diagnoses were determined using the Structured Clinical Interview for *DSM–IV* (SCID–IV; Spitzer, Williams, Gibbon, & First, 1990). The structured interviews were conducted by a MSW-level research assistant who had completed SCID–IV training and who regularly participated in ongoing diagnostic training sessions at the MPC. The SCID–IV interviewer had access to all data from present and past MPC hospital records, corroborative personal sources (e.g., family), and records from other hospitals. In addition, a semistructured interview was performed by an expert clinician (in most cases, John G. Csernansky), also using *DSM–IV* criteria. This expert clinician also had access to all available medical records and collaborative sources but was unaware of the results of the SCID–IV interview. The participant's final diagnosis was determined by a consensus meeting between the SCID–IV interviewer and the expert clinician.

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 & Gorham, 1962). Ratings were completed by a research assistant who regularly participated in training and reliability sessions with Deanna M. Barch and John G. Csernansky. 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 (Brekke, DeBonis, & Graham, 1994; Shatasel et al., 1992; Silver et al., 1993; Van der Does, Linszen,

Table 1
*Demographic and Clinical Characteristics of Study Participants*

| | Mean | | Standard deviation | |
|---|---|---|---|---|
| Characteristic | Healthy controls | Participants with schizophrenia | Healthy controls | Participants with schizophrenia |
| Age (years) | 36.5 | 36.3 | 11.2 | 10.3 |
| Sex (% male) | 46 | 63 | | |
| Parent's education (years) | 13.6 | 12.8 | 3.2 | 2.9 |
| Education (years) | 15.1 | 12.9 | 2.3 | 3.2 |
| Handedness (% right) | 96 | 92 | | |
| Age of first hospitalization | | 23.2 | | 6.2 |
| Length of illness (years) | | 13.0 | | 11.5 |
| BPRS total | | 20.8 | | 7.5 |
| Mean SAPS global item score | | 1.0 | | 0.8 |
| Mean SANS global item score | | 1.5 | | 0.8 |
| Poverty symptoms | | 11.4 | | 5.0 |
| Disorganization | | 4.9 | | 3.2 |
| Reality distortion | | 6.4 | | 4.8 |

*Note.* BPRS = Brief Psychiatric Rating Scale; SAPS = Scale for the Assessment of Positive Symptoms; SANS = Scale for the Assessment of Negative Symptoms.

Dingemans, Nugter, & Scholte, 1993) and the SANS/SAPS (Andreasen, Arndt, Alliger, Miller, & Flaum, 1995): (a) Reality Distortion, $\alpha = .84$, includes hallucinations and unusual thought content from the BPRS and hallucinations and delusions from the SAPS; (b) Disorganization, $\alpha = .48$, includes conceptual disorganization, mannerisms and posturing, and disorientation from the BPRS and inappropriate affect, positive formal thought disorder, and bizarre behavior from the SAPS/SANS; and (c) Poverty Symptoms, $\alpha = .73$, includes emotional withdrawal, motor retardation, and blunted affect from the BPRS and anhedonia–asociality, avolition–apathy, alogia, and affective flattening from the SANS. Handedness (see Table 1) was assessed using the Edinburgh Inventory (Oldfield, 1971).

### *Tasks and Materials*

All participants were scanned while performing three tasks. Each task was performed twice, once with verbal stimuli and once with nonverbal stimuli (see below). The first task assessed WM function and was the 2-back version of the N-back task. 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 4 blocks of trials, with each block containing 16 trials (see Figure 1). Within each 16 trials, one third were targets and two thirds were nontargets. In numerous studies, this task has been shown to reliably produce activation in both BA 46/9 and BA 44/6 (Braver et al., 1997; Cohen et al., 1994, 1997; Spitzer et al., 1996). Further, this task has been used previously with schizophrenia participants, and it elicits predicted deficits in both PFC activation and behavioral performance (Carter et al., 1998; Weinberger et al., 1996).

The second task was an intentional encoding task. Participants were presented with a series of stimuli and told to pay careful attention to each item because they would receive a memory test later. To equate for the motor responding required in the other two tasks (and to ensure participants were attending to the stimuli), participants were told to press two adjacent buttons (the same two buttons used in the WM and recognition tasks) as soon as the stimulus appeared. As with the WM task, stimuli were presented in 4 blocks, with 16 trials in each block. To ensure that stimulus parameters were similar across the WM and encoding tasks, participants saw the same number of repeated stimuli during the encoding task as they did during the WM task. The third task was a yes–no recognition task. Participants were presented with a series of stimuli and told to press one

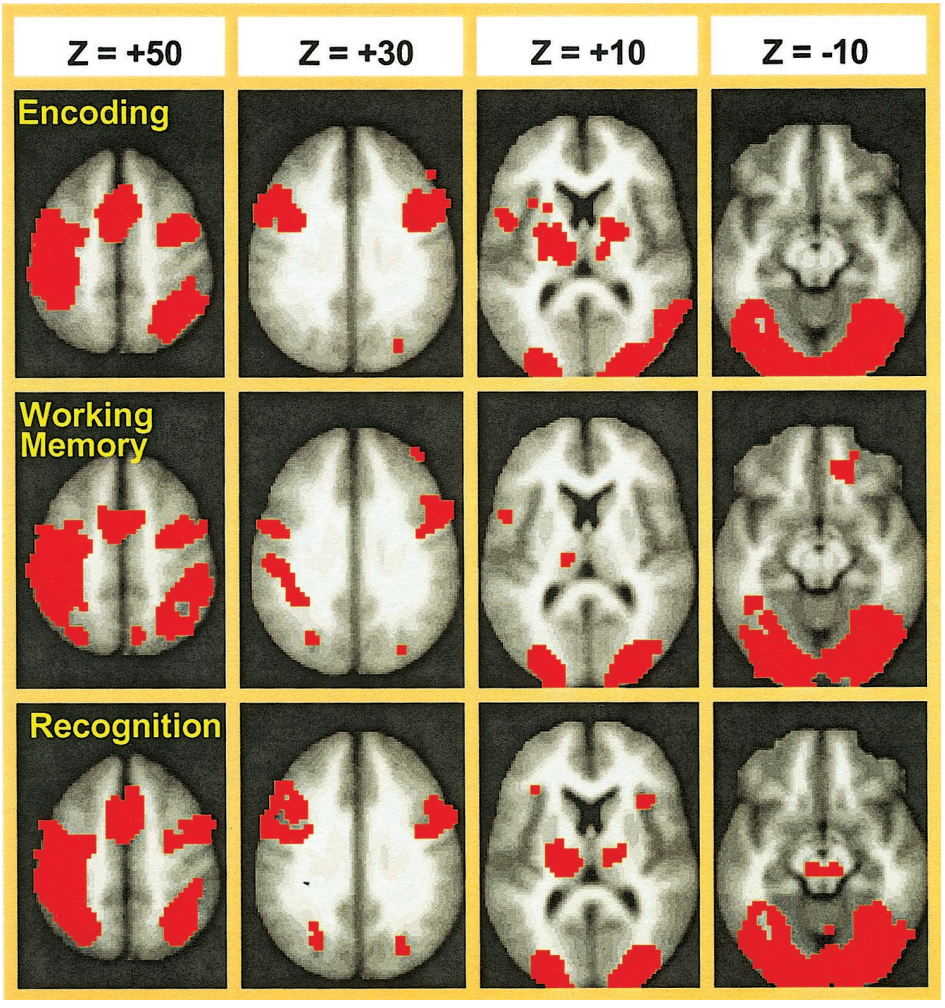


*Figure 1.* Brain regions demonstrating significant task-related activity in both controls and individuals with schizophrenia for each of the three tasks. The right side of the image is the right side of the brain; the left side of the image is the left side of the brain.

button if the stimulus had been seen during either of the two previous tasks (WM or encoding) and another button if the stimulus was new. As with the other two tasks, stimuli were presented in 4 blocks of 16 trials. Half of the stimuli were old and half were new; of the old stimuli, half were seen during the WM task and half were seen during the encoding task.

Stimuli for the verbal tasks were concrete visually presented words, 3–10 letters in length, presented in 48-point Geneva font. Stimuli for the nonverbal tasks were nonnameable faces. These are the same stimuli used in a number of prior studies (Braver et al., 2001; Kelley et al., 1998). For both words and faces, stimuli were separated into two lists, and the list used for the encoding versus the WM task was counterbalanced so that half the participants received List 1 during encoding and List 2 during the WM task, with the opposite order for the remaining participants. Tasks with the same stimulus type were grouped together, and the order in which participants received either the verbal or nonverbal tasks was counterbalanced across participants. The encoding and WM tasks were always performed before the recognition task. However, the order in which participants performed the WM versus encoding task was counterbalanced across participants. These counterbalancing procedures allowed us to control for any confounding effects of stimuli, time on task, head movement, scanner drift, and so on.

Participants performed each task in a run lasting 255 s (6 runs total). Each run included 4 task blocks and 3 fixation blocks interleaved in alternating order with the task blocks. Task blocks lasted 40 s and fixation blocks lasted 25 s. Each of the 16 items in a task block was presented for 2 s followed by a 500-ms interstimulus interval. During fixation blocks, a cross-hair appeared continuously, and participants were told to fixate. Visual stimuli were generated by an Apple PowerMac (Cupertino, CA) and PsyScope (Pittsburgh, PA; Cohen, MacWhinney, Flatt, & Provost, 1993) and projected to participants with a Sharp LCD projector (Mahwah, NJ) onto a screen positioned at the head end of the bore. Participants viewed the screen through a mirror attached to the top of the magnetic resonance (MR) head coil. A fiber-optic key press interfaced with the PsyScope button box was used to record the participant's behavioral performance.

### *Scanning*

All scanning was performed on the 1.5T Siemens VISION system (Erlangen, Germany) 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*; time to repetition [TR] = 2,500 ms, time to echo [TE] = 50 ms, field of view [FOV] = 24 cm, flip = 90°). During each functional run, 102 sets of 16 contiguous axial images, 8 mm thick, 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). Structural images were acquired using a coronal MP-RAGE 3D T1-weighted sequence (TR = 10 ms, TE = 4 ms, flip = 8°; voxel size = 1 × 1 × 1.2 mm). These structural images were used for between-subjects registration (as described below) and anatomic localization.

### *Data Analysis*

*fMRI data.* The fMRI data were reconstructed into images and then normalized across runs by scaling whole-brain signal intensity to a fixed value (Bandettini, Jesmanowiz, Wong, & Hyde, 1993). The fMRI data was then aligned to correct for head motion using a 6-parameter rigid-body rotation and translation correction (Friston, Jezzard, & Turner, 1994; Snyder, 1996; Woods, Cherry, & Mazziotta, 1992). This algorithm for head movement correction provided two sets of estimated movement parameters that could be used to examine group differences in movement. The first set was the difference of the current 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). Between-subjects analyses were conducted by coregistering participants' structural images to a reference brain using a 12-parameter rotation, translation, and expansion–contraction algorithm (Woods et al., 1992; Woods, Mazziotta, & Cherry, 1993) and then blurring the images with an 8-mm full-width half-maximum Gaussian filter. This method is identical to that used for MR-based coregistration of positron emission tomography (PET) data (Wiseman, Nichols, Dachille, & Mintun, 1996; Woods et al., 1993), and it provides a straightforward method for conducting quantitative group comparisons. The fMRI signal was then analyzed using appropriately designed analysis of variance (ANOVA) and *t*-test techniques. For all analyses, participants 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 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. A cluster-size threshold of 9 contiguous voxels and a per-voxel alpha of 0.005 was chosen, corresponding to a corrected whole-brain false-positive rate of approximately .05. Some of the analyses presented below were conjunction analyses, in which we required multiple effects to be significant simultaneously. When two or more effects were required to be significant, a *p*-value threshold of .05 was required for each effect, leading to a combined significance of either .0025 (.05 × .05) or .000125 (.05 × .05 × .05).

*Behavioral data.* Accuracy and median reaction times (RTs) were examined for the WM tasks and the recognition tasks. Due to technical difficulties, data files for 1 control and 1 patient were missing for the word WM task, as were the data files for 1 control and 1 patient for the word recognition task. Correlations between accuracy and RTs for each task were examined separately for controls and participants with schizophrenia to ensure that speed–accuracy trade-offs were not driving any significant effects. All correlations were negative (faster RT associated with higher accuracy) or nonsignificant, suggesting that speed–accuracy trade-offs were not having a major influence on our results. The data from the WM tasks (both RT and accuracy) and the recognition tasks (both RT and accuracy) were analyzed using two-factor ANOVAs, with group (schizophrenia, control) as a between-subjects factor and material (verbal vs. nonverbal) as a within-subjects factor. Correlations between performance in the WM and recognition tasks were examined separately for each group, using Pearson's product–moment correlations.

## Results

### *Behavioral Data*

*Working memory.* The ANOVA for accuracy in the WM tasks indicated significant main effects of group, $F(1, 82) = 14.13$, $p < .001$, and material, $F(1, 82) = 7.38$, $p < .01$, but no Group × Material interaction, $F(1, 82) = 0.001$, $p > .90$. As expected, participants with schizophrenia performed significantly worse than controls (see Table 2), but were equally impaired with verbal and nonverbal materials. All participants performed better with words than faces. The ANOVA for RTs indicated no significant main effect of group, $F(1, 82) = 1.13$, $p > .20$, and no Group × Material interaction, $F(1, 82) = 0.01$, $p > .90$, although there was a main effect of material type, $F(1, 82) = 4.07$, $p < .05$. As shown in Table 2, all participants had faster RTs for words than faces. Participants with schizophrenia did tend to respond more slowly than controls. However, the large degree of variability in the RTs likely influenced the lack of significant differences.

*Recognition.* The ANOVA for accuracy in the recognition tasks indicated significant main effects of group, $F(1, 81) = 27.25$,

Table 2
*Participant Performance on Working Memory and Recognition Tasks*

| Task | Mean | | Standard deviation | |
|---|---|---|---|---|
| | Healthy controls | Participants with schizophrenia | Healthy controls | Participants with schizophrenia |
| Working memory | | | | |
| Words | | | | |
| Accuracy | .92 | .84 | .08 | .15 |
| Reaction time | 855 | 913 | 258 | 316 |
| Faces | | | | |
| Accuracy | .89 | .82 | .09 | .11 |
| Reaction time | 930 | 972 | 267 | 254 |
| Recognition | | | | |
| Words | | | | |
| Accuracy | .79 | .70 | .09 | .12 |
| Reaction time | 943 | 1,105 | 241 | 389 |
| Faces | | | | |
| Accuracy | .70 | .62 | .08 | .08 |
| Reaction time | 1,098 | 1,114 | 217 | 264 |

*Note.* Reaction times are expressed in milliseconds.

$p < .001$ and material, $F(1, 81) = 37.87$, $p < .001$, but no Group × Material interaction, $F(1, 81) = 0.21$, $p > .50$. As expected, participants with schizophrenia performed significantly worse than controls (see Table 2) but were equally impaired with verbal and nonverbal materials. All participants performed better with words than faces. The ANOVA for RTs demonstrated no main effect of group, $F(1, 81) = 2.75$, $p = .10$, but a significant main effect of material, $F(1, 81) = 9.54$, $p < .01$, and a significant Group × Material interaction, $F(1, 81) = 6.83$, $p < .05$. Planned contrasts to follow up on the Group × Material interaction demonstrated that participants with schizophrenia were slower than controls for words, $F(1, 81) = 5.52$, $p < .05$, but not for faces, $F(1, 81) = 0.17$, $p > .50$. In addition, RTs for controls were significantly slower for faces than for words, $F(1, 81) = 18.73$, $p < .001$; among participants with schizophrenia, RTs did not differ significantly between words and faces, $F(1, 81) = 0.10$, $p > .50$.

*Cross-task and cross-material correlations.* The hypothesis that both WM and LTM deficits in schizophrenia reflect a disturbance in PFC function suggests that performance across the two domains should be correlated, at least among participants with schizophrenia. Consistent with this hypothesis, recognition and WM performance were positively correlated for both words, ($r = .44$, $p < .01$) and faces ($r = .38$, $p < .05$) among participants with schizophrenia. Among controls, recognition and WM performance were positively correlated for faces, ($r = .55$, $p < .001$) but not for words ($r = .01$, $p > .50$). Fisher's *r*-to-*z* transformations indicated that the correlation between WM and recognition performance for words was significantly larger among participants with schizophrenia than among controls, $z = 1.98$, $p < .05$. However, the correlations did not differ between groups for face performance, $z = -.97$, $p > .50$. We next examined whether performance for words and faces was associated. In the recognition tasks, performance for words and faces was not significantly correlated among either controls ($r = .16$, $p > .10$) or participants with schizophrenia ($r = .21$, $p > .10$). However, in the WM tasks, performance for words and faces was strongly correlated for both controls ($r = .58$, $p < .01$) and participants with schizophrenia ($r = .72$, $p < .01$).

## *fMRI Data*

*Intact activation as a function of task.* We began by examining regions of task-related activation that were intact among individuals with schizophrenia in each of the three tasks, irrespective of material type. Identifying such intact task-related activation in at least some brain regions is a critical first step in that it will provide a baseline against which to interpret the specificity of any functional activation deficits found in individuals with schizophrenia. We defined a region of intact activation as one that showed significant task-related activation in both groups, with no significant differences in the degree of task-related activity across groups. We used two criteria to identify intact task-related activation among individuals with schizophrenia. First, for each task, we identified regions that were significantly active in both individuals with schizophrenia and controls, using "conjunction" analyses conceptually similar to those described by Friston and colleagues (Friston, Holmes, Price, Buchel, & Worsley, 1999). Specifically, we conducted paired *t* tests on all voxels (separately for each group) and examined only those voxels that demonstrated significantly greater activation during the task period than during fixation. We then excluded regions from this analysis if they showed significantly greater activity in one group or the other, defined as a *p* value of less than .05 for a Group (patient, control) × Condition (task, fixation) interaction. Regions of activation that met both of these criteria for each of the three tasks are shown in Figure 1. In each of the three tasks, individuals with schizophrenia demonstrated intact activation of a number of similar regions, including visual cortex, primary motor and somatosensory cortex, supplementary motor cortex, bilateral inferior frontal gyrus, bilateral insula, and bilateral superior parietal cortex.

*Regions demonstrating impaired activity in schizophrenia for both WM and LTM tasks.* We next examined regions of activation that differed significantly between controls and individuals with schizophrenia in both the WM and LTM tasks, irrespective of material type. To do so, we again used conjunction analyses in which we conducted two-way ANOVAs (separately for each task)

with diagnostic group as a between-subjects factor and condition (task, fixation) as a within-subjects factor. We then examined those voxels that demonstrated Group × Condition interaction in two or more tasks. We chose this approach to analysis because we thought it unlikely to bias us toward or against finding regions that showed either impaired activity in only one task or impaired activity in multiple tasks. As shown in Figure 2 and Table 3, five regions demonstrated significant task-related group differences in all three tasks. As predicted, one of these regions was in right DLPFC, in which controls demonstrated greater task-related activation than individuals with schizophrenia in all three tasks. In fact, for the recognition and WM tasks, the largest effect sizes for group differences were in this right DLPFC region. However, controls also displayed significantly greater activation than individuals with schizophrenia for all three tasks in left and right parietal cortex and left brain stem. In the supplementary motor cortex region, individuals with schizophrenia displayed greater activity than controls in all three tasks.

There was only one region, visual cortex, that displayed Group × Condition interaction for both encoding and recognition but not working memory (Figure 2 and Table 3). In this region, participants with schizophrenia displayed greater task-related activity than controls. There was also one region, left hippocampus/parahippocampal gyrus, that displayed task-related group differences in both encoding and working memory, with greater activity among controls (Figure 2 and Table 3). Last, there were six regions that displayed task-related group differences in both recognition and working memory. In five of these, including brain stem, basal ganglia, thalamus, and medial PFC, controls demonstrated greater activity than participants with schizophrenia. In the remaining region, left somatosensory cortex, participants with schizophrenia displayed greater task-related activity than controls. Planned contrasts were used to determine whether group differences in task-related activity in all of these regions were present for both word and face stimuli. For all but one region (left hippocampus), significant group differences were present for both word and face stimuli (all $p$s $< .05$). In the left hippocampal region, group differences in task-related activity were present for word stimuli ($p < .001$) but not face stimuli ($p > .20$).

*Regions demonstrating impaired activity in schizophrenia only in WM or LTM.* We next examined whether there were any additional regions displaying significant Group × Condition interactions in only one of the tasks. There were no additional regions (other than the ones identified above) that demonstrated Group × Condition interactions for either the encoding or recognition tasks alone. However, there were a number of additional regions (see Table 4) that displayed significant Group × Condition interaction only for the WM tasks, including regions in left and right DLPFC, right-anterior and posterior hippocampus, left and right superior PFC, and left and right precuneus. Planned contrasts indicated that the group differences in task-related WM activity were significant for both verbal and nonverbal stimuli in all regions, all $p$s $< .05$, except for the right posterior hippocampal region (significant only for word stimuli).

*Gender effects.* We next examined whether any of the regions demonstrating group differences in any of the tasks showed further

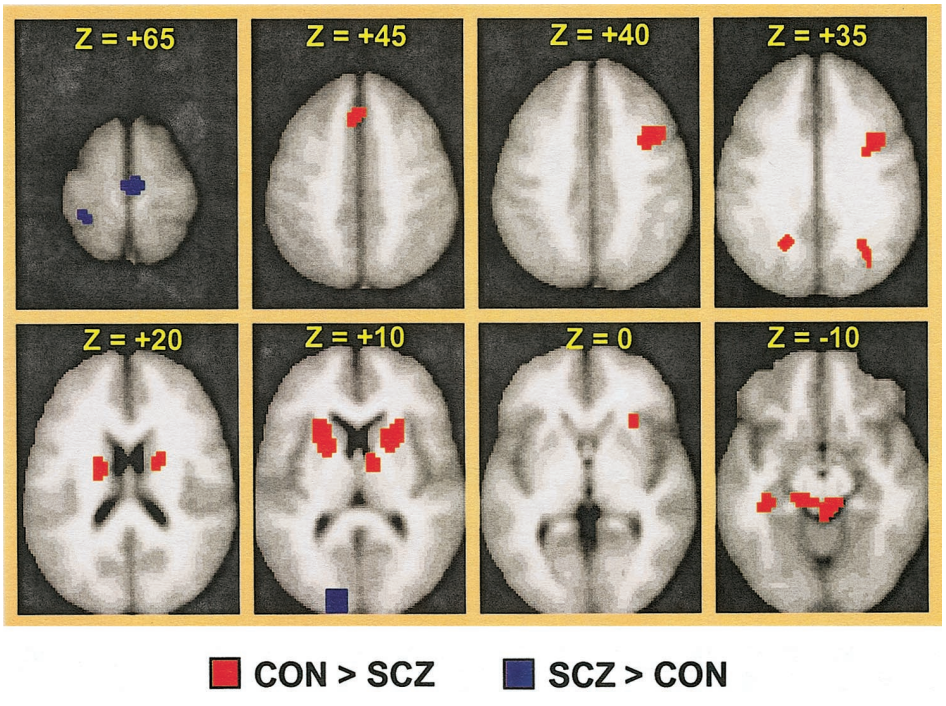


*Figure 2.* Brain regions demonstrating significant Group × Condition interaction. Regions shown in red are ones in which controls demonstrated greater task-related activation than individuals with schizophrenia. Regions shown in blue are ones in which individuals with schizophrenia demonstrated greater task-related activation than controls. The right side of the image is the right side of the brain; the left side of the image is the left side of the brain. CON = controls; SCZ = participants with schizophrenia.

Table 3
*Regions Demonstrating Group × Condition Interactions in Two or More Tasks*

| Task/region of interest | Brodmann's area | $X^a$ | $Y^a$ | $Z^a$ | Peak $F$ value | Effect size[b] | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Encoding | Recognition | WM |
| All three tasks (encoding, WM, and recognition) | | | | | | | | |
| Brainstem | | −7.5 | −33 | −15 | 11.8 | .43* | .41* | .46** |
| Right parietal cortex | 7 | 28.5 | −63 | 30 | 15.0 | .47** | .48** | .62*** |
| Left parietal cortex | 7 | −19.5 | −60 | 27 | 18.7 | .39* | .54** | .59*** |
| Right dorsolateral prefrontal cortex | 9 | 37.5 | 6 | 39 | 22.5 | .35* | .69*** | .72*** |
| Supplementary motor cortex | 6 | 1.5 | −21 | 63 | 14.2 | −.36* | −.58*** | −.55*** |
| Encoding and recognition | | | | | | | | |
| Left visual cortex | 17/18 | −13.5 | −90 | 12 | 11.3 | −.53*** | −.56*** | −.34 |
| Encoding and WM | | | | | | | | |
| Left hippocampus | | −31.5 | −36 | −12 | 18.9 | .40* | .28 | .49** |
| Recognition and WM | | | | | | | | |
| Brainstem | | 4.5 | −36 | −18 | 16.5 | .30 | .39* | .59*** |
| Left basal ganglia (putamen) | | −19.5 | 6 | 9 | 12.2 | .31 | .46** | .62*** |
| Right basal ganglia (caudate nucleus) | | 25.5 | 15 | 6 | 13.5 | .21 | .49** | .53*** |
| Thalamus | | 7.5 | −6 | 12 | 10.5 | .14 | .48** | .44** |
| Medial superior prefrontal cortex | 8 | −1.5 | 24 | 45 | 11.6 | .24 | .37* | .49** |
| Left somatosensory cortex | 5 | −25.5 | −39 | 63 | 12.2 | −.31 | −.58** | −.55** |

*Note.* WM = working memory.
[a] *X*, *Y*, and *Z* are coordinates in a standard stereotactic. [b] Positive effect size values indicate greater activation in controls; negative values indicate greater activation in patients.
* $p < .05$. ** $p < .01$. *** $p < .001$.

interactions with gender. Only one region showed such an interaction ($p < .05$), the left visual cortex region, which demonstrated greater activity in patients than controls. This greater activity was significant only for female patients.

*Additional analyses of DLPFC and medial temporal regions.* The goals of this study were primarily focused on examining the role of PFC and hippocampus in both WM and LTM performance in individuals with schizophrenia. Thus, we wished to explore further the nature of the activation patterns in the DLPFC and hippocampal regions identified as showing group differences in both the WM and LTM tasks. We began by examining the pattern of activation in these regions as a function of task and material type. To do so, we computed percentage-change scores, [task–fixation/fixation] × 100, for each participant for each region (averaging across all voxels within a region), and conducted separate two-way ANOVAS in each group, with task (encoding, recognition, WM) and stimulus type (word, face) as within-subjects factors. In the left hippocampal region (see Figure 3), controls demonstrated a main effect of stimulus type, $F(1, 47) = 6.01$, $p < .05$, with greater activity for words but no significant main effect of task or Task × Stimulus Type interaction. Participants with schizophrenia did not demonstrate any significant main effects or interactions in this region. Thus, participants with schizophrenia failed to show the same modulation by stimulus type shown by controls in this left hippocampal region. In the right DLPFC region demonstrating significant group effects in all three tasks, controls demonstrated significant main effects of task, $F(2, 94) = 6.31$, $p < .01$, and stimulus type, $F(1, 47) = 12.1$, $p < .01$,

Table 4
*Regions Demonstrating Group × Condition × Task Interaction*

| Region of interest | Brodmann's area | $X^a$ | $Y^a$ | $Z^a$ | Peak $F$ value | Effect size | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Encoding | Recognition | Working memory |
| Right hippocampus | | 25.5 | −24 | −9 | 13.6 | .12 | .30 | .67*** |
| Right hippocampus | | 37.5 | −45 | 3 | 13.6 | .07 | .12 | .55*** |
| Left operculum | | −34.5 | 9 | 15 | 14.7 | −.12 | .23 | .65*** |
| Left dorsolateral prefrontal cortex | 46/10 | −37.5 | 36 | 9 | 12.8 | −.04 | .01 | .51** |
| Right dorsolateral prefrontal cortex | 9 | 40.5 | 33 | 30 | 15.1 | .07 | .13 | .62*** |
| Left dorsolateral prefrontal cortex | 9 | −34.5 | 18 | 33 | 11.6 | .06 | .24 | .59*** |
| Left precunneus | 7 | −7.5 | −60 | 36 | 14.5 | .09 | .09 | .57*** |
| Right precuneus | 7 | 10.5 | −60 | 39 | 14.4 | .09 | .08 | .61*** |
| Right dorsolateral prefrontal cortex | 9 | 31.5 | 6 | 39 | 16.0 | .12 | .21 | .62*** |
| Right superior prefrontal cortex | 8 | 7.5 | 27 | 42 | 12.3 | .09 | .22 | .56*** |
| Left superior prefrontal cortex | 8 | −43.5 | 6 | 45 | 14.1 | .09 | .19 | .63*** |

[a] *X*, *Y*, and *Z* are coordinates in a standard stereotactic.
* $p < .05$. ** $p < .01$. *** $p < .001$.

but no Task × Stimulus Type interaction. As shown in Figure 3, planned contrasts indicated that controls demonstrated significantly greater activity in the WM ($p < .05$) and recognition ($p < .05$) tasks than in the encoding tasks, and significantly greater activity for faces than words. Participants with schizophrenia also demonstrated a significant main effect of stimulus type in this region, $F(1, 37) = 6.93$, $p < .05$, with greater activity for faces than words (Figure 3) but no main effect of task or Task × Stimulus Type interaction. Thus, although participants with schizophrenia displayed the same modulation by stimulus type as controls in this right PFC region, they failed to show the same modulation by task demands as shown by controls.

We next examined whether individual differences in brain activity in these regions were correlated across tasks. If WM and LTM share common processes supported by DLPFC and hippocampus, then one would predict that such correlations should be present. Among controls, the magnitude of DLPFC activity was significantly correlated across all three tasks ($.37 \leq r \leq .60$; all $p$s $< .05$) and the magnitude of hippocampal activity was correlated across all three tasks ($.33 \leq r \leq .58$; all $p$s $< .05$). Among patients with schizophrenia, DLPFC activity during WM and recognition were strongly correlated ($r = .47$, $p < .005$). However, DLPFC activity during encoding was not significantly correlated with activity during WM ($r = .23$, $p = .16$) or recognition ($r = .24$, $p = .14$), which may reflect the restricted range of DLPFC activity during encoding among patients with schizophrenia. However, the magnitude of hippocampal activity in patients with schizophrenia was significantly correlated across all three tasks ($.34 \leq r \leq .51$; all $p$s $< .05$).

We next examined whether individual differences in activation in any of the regions showing group differences in all three tasks were associated with individual differences in performance. To do so, we computed correlations between task performance for recognition and WM and activity in these regions, separately for each group. None of these correlations was significant. We also computed similar correlations with task performance for each of the other regions demonstrating significant Group × Condition interactions (i.e., brain stem, thalamus, basal ganglia, parietal cortex) but again did not find any significant relationships between individual differences in activity and individual differences in behavioral performance. We next examined whether activity in any of the regions showing group differences in all three tasks were correlated across tasks (i.e., was BA 46/9 activity in WM correlated with BA 46/9 activity in recognition?).

*Intact material-specific activations in schizophrenia.* We next examined intact regions of activation among participants with schizophrenia that showed greater activity for one material or the other, irrespective of task. We did not conduct this analysis separately for each task, because our prior work suggested that material effects were not task specific (Braver et al., 2001). To identify such regions, we again performed conjunction analyses in which we conducted ANOVAs on all voxels (separately for each group) and examined only those voxels that demonstrated significant Condition (task, fixation) × Material (word, face) interactions independently for each group. As can be seen in Figure 4, participants with schizophrenia showed patterns of activity associated with face processing very similar to those found in previous studies (Braver et al., 2001; Kelley et al., 1998). Specifically, both groups demonstrated greater task-related activity for faces than words in right inferior PFC, right fusiform gyrus, right temporal–parietal cortex, and primary visual cortex. However, the only region that demonstrated greater task-related activity for words than faces in both groups was in bilateral primary visual cortex. None of these regions showed any further interactions with gender.

*Impaired material-specific activation patterns in schizophrenia.* We next examined regions of activation that differed significantly between groups as a function of material type. To do so, we conducted voxel-wise ANOVAs with group (schizophrenia, control) as a between-subjects factor and condition (task, fixation) and material (face, word) as within-subjects factors. No voxels demonstrated a significant Group × Condition × Material interaction. This was somewhat surprising, as previous research has found that

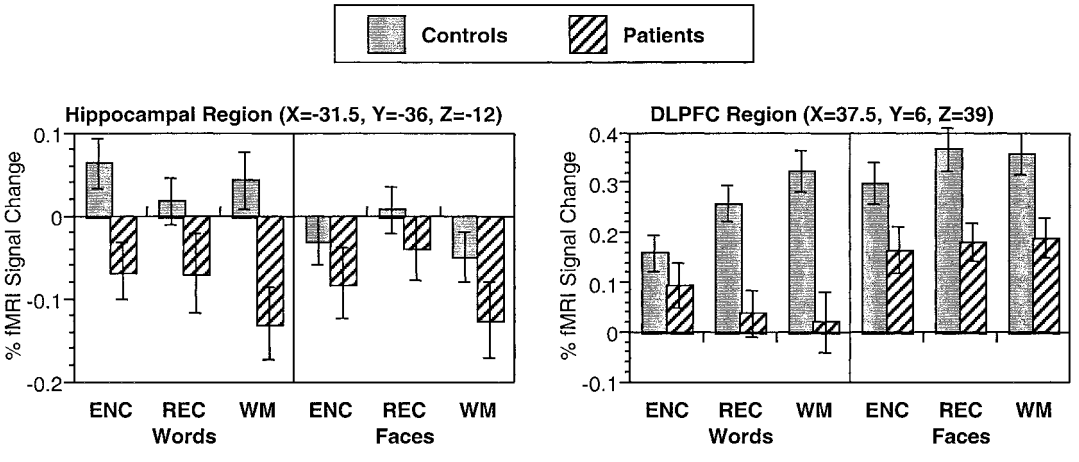


*Figure 3.* Patterns of activation as a function of task and stimulus type for the prefrontal cortex and hippocampal regions showing reduced activation among individuals with schizophrenia during performance of both working memory and long-term memory tasks. The graphs plot the percentage change from fixation to task, [(task − fixation)/fixation] × 100, for each task and stimulus type. DLPFC = dorsolateral prefrontal cortex; ENC = encoding; REC = recording; WM = working memory; fMRI = functional magnetic resonance imaging.

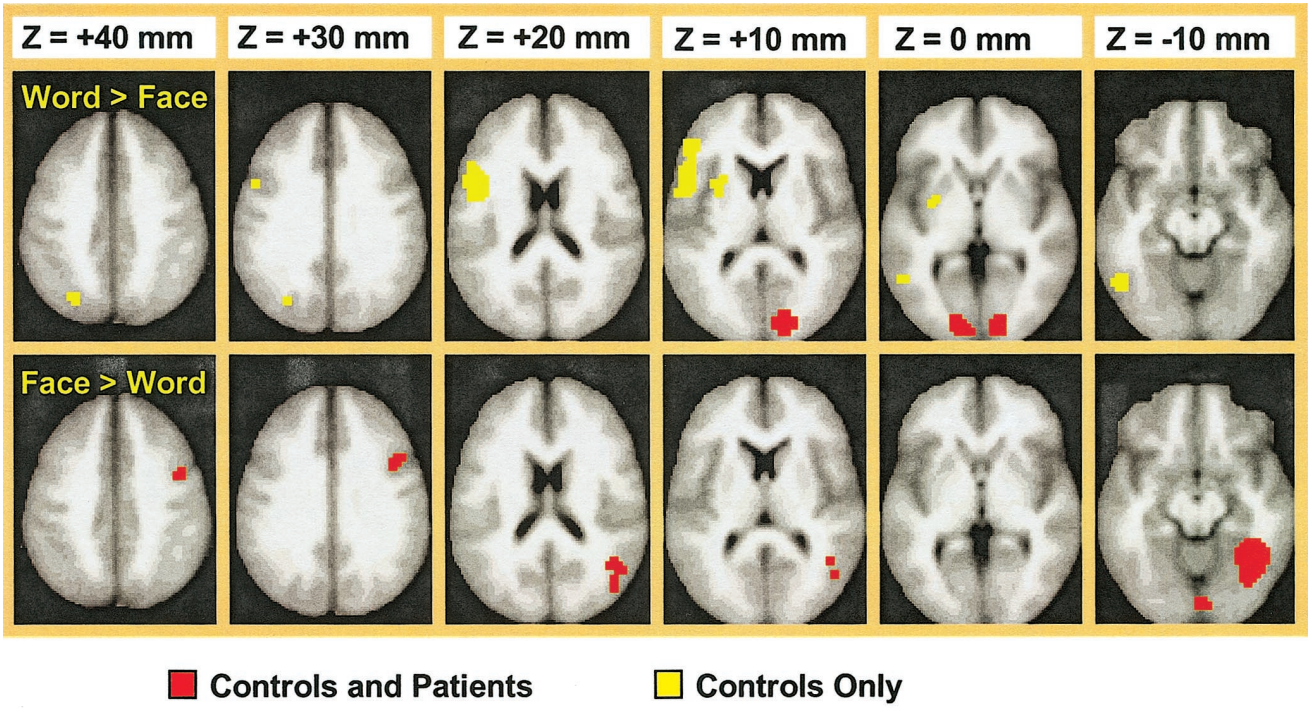


*Figure 4.* Brain regions demonstrating significant Condition × Stimulus Type interactions. Regions shown in red show significant material selectivity effects in both controls and individuals with schizophrenia. Regions shown in yellow demonstrate significant material selectivity effects only among controls. The right side of the image is the right side of the brain; the left side of the image is the left side of the brain.

left inferior PFC demonstrated significantly greater activity for words than faces (Braver et al., 2001; D'Esposito et al., 1998; Kelley et al., 1998). Such a region was not identified as either intact among both groups or as showing a significant difference between groups. Thus, we went back and examined those regions that demonstrated significantly greater activation for words than faces among controls only. As shown in yellow in Figure 4, in addition to visual cortex, controls demonstrated significantly greater activity for words than faces in left inferior PFC, left parietal cortex, and left temporal cortex. When we examined the pattern of activation among participants with schizophrenia in these regions (Figure 5), we found that patients also tended to show greater activation for words than faces in left inferior PFC and left parietal cortex, though these effects were not significant. Participants with schizophrenia did not show greater activity for words than faces in left temporal cortex. None of these regions showed any further interactions with gender.

*Potential confounds.* A potential criticism of fMRI studies in schizophrenia is that increased movement among participants with schizophrenia creates artifacts that impair the detection of cortical activation. Indeed, as can be seen in Figure 6, participants with schizophrenia tended to have higher movement on all estimated

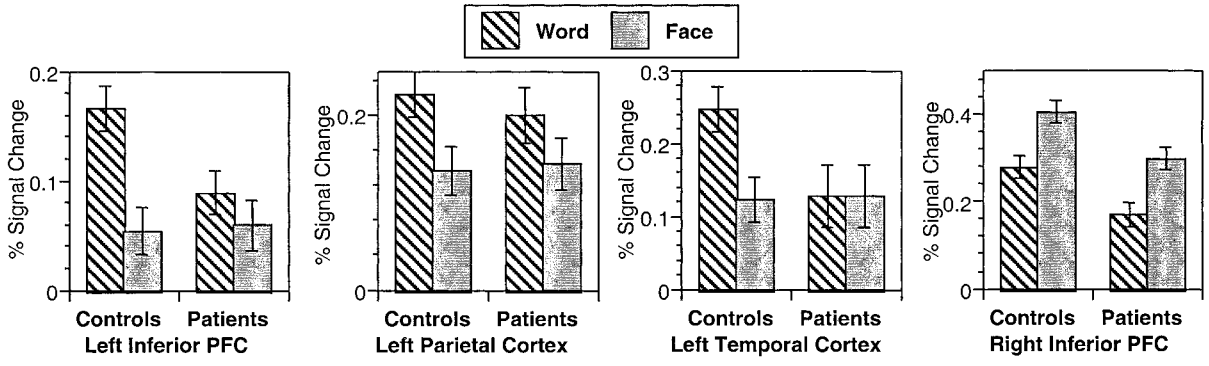


*Figure 5.* Patterns of task-related activation as a function of stimulus type. The graphs plot the percentage change from fixation to task, [(task − fixation)/fixation] × 100, for each stimulus type. PFC = prefrontal cortex.

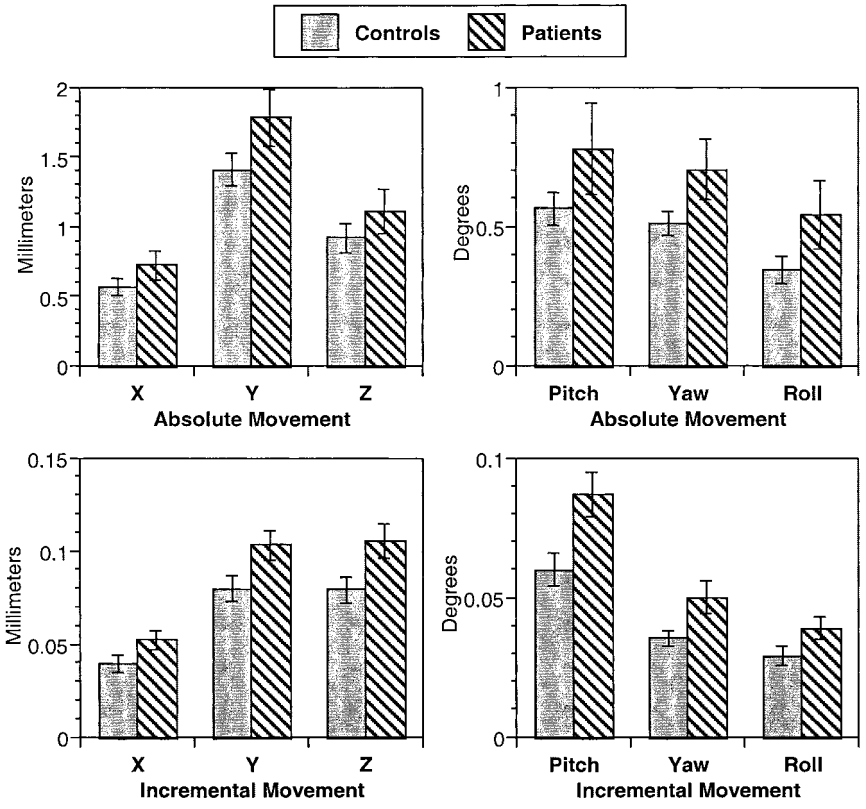


*Figure 6.* Graphs plotting the absolute values of the estimated movement for controls and individuals with schizophrenia. *Absolute movement* refers to the difference of the current image from the reference image (the first image acquired). *Incremental movement* refers to the difference of the current image from the immediately preceding image.

movement parameters, with significant group differences for incremental movement in *Y*, $t(84) = 2.3$, $p < .05$; *Z*, $t(84) = 2.2$, $p < .05$; pitch, $t(84) = 2.7$, $p < .01$; and yaw, $t(84) = 2.3$, $p < .05$. We also examined signal-to-noise ratios (SNR = *M*/*SD*) for the fMRI data using a two-way ANOVA with group (control, patient) as a between-subjects factor and slice (1–16) as a within-subjects factor. This analysis indicated no main effect of group, but did show a Group × Slice interaction, $F(15, 1260) = 2.021$, $p < .05$, with participants with schizophrenia demonstrating lower SNR in the middle slices. Thus, we examined whether the group differences in task-related activation found in the previous analyses were still present in a subgroup of controls ($n = 43$) and participants with schizophrenia ($n = 28$) matched for movement, variance, and SNR. These two subgroups did not differ on any of the 12 movement parameters (all *p*s > .7) and also did not differ in image SNR (controls: $M = 231$, $SD = 66$; participants with schizophrenia: $M = 239$, $SD = 64$) or image standard deviations (controls: $M = 2.4$, $SD = .90$; participants with schizophrenia: $M = 2.2$, $SD = .66$). However, repetition of the analyses conducted above in this subgroup of controls and participants with schizophrenia matched for movement still revealed significant effects in all of the regions of interest (ROIs) showing Group × Condition interactions, with the same patterns as found for the total sample. Thus, group differences in activation did not appear to be an artifactual result of increased movement on the part of participants with schizophrenia.

A second potential criticism is that the poorer behavioral performance on the part of participants with schizophrenia confounds the interpretation of any observed activation differences (Weinberger & Berman, 1996; Weinberger et al., 1996). To address this issue, we examined whether the group differences in task-related activation were still present in a subgroup of controls ($n = 29$) and participants with schizophrenia ($n = 25$) matched for behavioral accuracy. Group × Condition interactions remained significant in all but two of the ROIs. The right and left precuneus regions that displayed Group × Condition interactions only in the WM tasks no longer demonstrated significant group differences in this subset of controls and participants with schizophrenia matched for behavioral performance. Thus, group differences in activation in all of the PFC regions, and most of the non-PFC regions, did not appear to be an artifactual result of decreased behavioral performance on the part of participants with schizophrenia.

## Discussion

The primary goal of this study was to test the hypothesis that disturbances in PFC function contribute to deficits in both WM and LTM function among individuals with schizophrenia. Consistent with this hypothesis, a major finding was that the same region of right DLPFC demonstrated impaired activation in individuals with schizophrenia during performance of both WM and LTM

tasks. This finding of impaired DLPFC activation associated with LTM deficits in schizophrenia is consistent with the growing cognitive neuroscience literature on the role of PFC in LTM function (Cabeza & Nyberg, 2000), as well as the results of a number of previous neuroimaging studies of LTM function in schizophrenia (Ganguli et al., 1997; R. E. Gur et al., 1994; Hazlett et al., 2000; Heckers et al., 1999; Nohara et al., 2000; Ragland et al., 2001). Although this right DLPFC region was not the only one to display impaired activation during both WM and LTM performance in schizophrenia, this result demonstrates that LTM deficits in schizophrenia may be as strongly associated with DLPFC disturbances as are WM deficits. Further, we did not find any regions that demonstrated impaired activation among individuals with schizophrenia in the LTM but not WM tasks, even though this study had one of the largest sample sizes for any functional neuroimaging study in schizophrenia. However, we did find disturbed activation in a hippocampal/parahippocampal gyrus region during performance of the verbal encoding task. A surprising finding was that activation in this hippocampal region was equally impaired during performance of the verbal WM tasks. In addition, we found that performance on the WM and recognition tasks was strongly correlated among individuals with schizophrenia. Taken together, these results are consistent with the hypothesis that WM and LTM deficits in individuals with schizophrenia reflect common cognitive and neurobiological mechanisms, which include a disturbance in DLPFC function. Nonetheless, the findings suggest that functional abnormalities of medial temporal cortex are also present in schizophrenia but that such disturbances also contribute to both LTM and WM deficits. Each of these results will be discussed in more detail below.

Our finding of impaired right DLPFC function for both WM and LTM performance among individuals with schizophrenia suggests that we need to move away from thinking of cognitive deficits in schizophrenia as specific to either WM or LTM and instead focus on processes supported by particular brain systems that may play a role in many cognitive domains. For example, in prior work, we have suggested that a critical role of DLPFC is the representation and maintenance of context information needed to guide behavior (Barch et al., 2001; Cohen et al., 1999). Our prior work suggests that context maintenance strongly activates left DLPFC (Barch et al., 1997), and we have found impaired left DLPFC activation associated with impaired context processing in medication-naïve individuals with schizophrenia (Barch et al., 2001). However, the region of impaired DLPFC activation during performance of both WM and LTM tasks in the current study was in the right hemisphere, in a location very similar to that identified in four previous studies using variants of the N-back task in schizophrenia (Callicott et al., 1998; Carter et al., 1998; Menon et al., 2001; Perlstein et al., 2001). Individuals with schizophrenia did demonstrate impaired left DLPFC activation in the current study, but only during the WM tasks. This finding is interesting in itself, given that in the N-back task prior stimuli serve as context for deciding how to respond to the current stimulus, necessitating the maintenance of context information. The encoding and recognition tasks do not have as explicit a demand for the maintenance of context, and thus they did not activate this region even among controls. Prior WM studies in schizophrenia have suggested that impaired right DLPFC activation reflects a disturbance in the manipulation components of WM (Menon et al., 2001; Perlstein et al., 2001). However, performing a recognition task (which does not have explicit manipulation demands) engages this region as much as performance of WM tasks with high manipulation demands among controls. Further, among individuals with schizophrenia, activity in this region is equally impaired during performance of both recognition and WM tasks. Such results are not consistent with the hypothesis that right DLPFC is specifically involved in the manipulation of information in WM.

An alternative possibility is that right DLPFC is involved in the selection and maintenance of an appropriate strategy for the task at hand, which is important for almost all cognitive tasks. In verbal encoding tasks, one can phonologically rehearse the words or make semantic connections among words. Similarly, in verbal WM tasks, one can actively rehearse the words phonologically or use a more familiarity-based strategy. With nonverbal stimuli, one can try to use a familiarity-based strategy or try to verbally label the stimuli and use the verbal labels as mnemonic cues. Some strategies are more effective than others. In LTM encoding tasks, semantic encoding promotes better memory than phonological or orthographic encoding. In WM tasks, active rehearsal is more effective than relying on familiarity, especially if the task contains nontargets as well as targets that repeat (as our version of the task did). If the right DLPFC is involved in the selection and maintenance of most effective strategies, then individuals with schizophrenia should show impairments in choosing the effective strategies. Consistent with this hypothesis, a number of previous verbal encoding studies in schizophrenia have found that individuals with schizophrenia fail to spontaneously use effective encoding and retrieval strategies, such as semantic chunking (Brebion, Amador, Smith, & Gorman, 1997; Calev, 1984a, 1984b; Calev et al., 1987; Calev, Venables, & Monk, 1983; Gold et al., 1992).

In the current study, we could examine whether there was evidence that individuals with schizophrenia were more likely than controls to use a familiarity-based strategy for the WM task. Specifically, we could examine error rates for nonrepeated nontargets and repeated nontargets (items previously presented, but not two trials previously). If individuals with schizophrenia are relying more on familiarity than are controls, then they should be more likely to false alarm to these repeated nontargets. Consistent with this hypothesis, a two-way ANOVA with group and trial type (nonrepeated nontargets, repeated nontargets) indicated a Group $\times$ Trial Type interaction, $F(1, 84) = 6.44$, $p < .05$. All participants performed worse on repeated than nonrepeated nontargets, and individuals with schizophrenia performed worse than controls on both nonrepeated nontargets (controls: $M = .96$, $SD = .07$; individuals with schizophrenia: $M = .91$, $SD = .13$) and repeated nontargets (controls: $M = .71$, $SD = .26$; individuals with schizophrenia: $M = .53$, $SD = .26$). However, group differences were clearly greater for repeated nontargets (effect size = .69) than nonrepeated nontargets (effect size = .45). These behavioral data are consistent with the hypotheses that individuals with schizophrenia were using a less effective strategy for performance of the WM tasks and that right DLPFC deficits in schizophrenia may reflect a disturbance in the ability to select effective strategies. However, future research will need to more directly examine the role of right DLPFC in strategy selection among individuals with schizophrenia.

The hypotheses of this study were primarily focused on the role of PFC dysfunction in the cognitive deficits displayed by individ-

uals with schizophrenia. However, an unexpected finding was a region of left hippocampal/parahippocampal gyrus that also displayed impaired activation in individuals with schizophrenia during both WM and encoding tasks with word stimuli. Further, we found a region of right medial temporal cortex that demonstrated disturbed activation only in the WM task. The finding of impaired hippocampal activation during performance of a verbal encoding task is consistent with a hypothesized role for medical temporal disturbances in LTM deficits among individuals with schizophrenia (R. E. Gur et al., 1994; Heckers et al., 1998) and with the literature on structural abnormalities in this region. However, the medial temporal activation found during in WM is more novel. Again, a focus on the processes that might be subserved by the medial temporal cortex may help to explain these findings. Numerous researchers have suggested that medial temporal regions are involved in the encoding of information, a process likely engaged by any task that requires the need to remember information, including intentional encoding and both low- and high-load WM tasks. As such, the difference between the results of the current study and those of prior studies may reflect the nature of the "control" task used as a baseline comparison.

In previous N-back studies in schizophrenia, performance in conditions with high WM load was compared with performance in conditions with low WM load (Callicott et al., 1998; Carter et al., 1998; Menon et al., 2001; Perlstein et al., 2001). In the current study, disturbed hippocampal activation among individuals with schizophrenia during WM performance was evident if one compared performance of the 2-back task with fixation. However, we would not have found group differences in activation in left hippocampus during WM performance if our comparison had been of activity in WM versus activity during encoding (which could be considered a condition with low WM load), because left hippocampas activity in controls was as great or greater during encoding performance as during WM performance. Similarly, the right hippocampal regions that only demonstrated impaired activation during WM would not have shown up in a comparison of WM with encoding or retrieval. Although group differences in these right hippocampal regions were significant only in the WM task, these regions did not demonstrate significant Group $\times$ Task interactions. Thus, previous WM studies in schizophrenia may not have identified impaired hippocampal activation if activity in controls did not differ between high- and low-load WM conditions. Taken together, the results of the current study and prior studies are consistent with the hypothesis that medial temporal regions play a role in the encoding of information, a cognitive process that may be engaged by both low- and high-load WM tasks as well as explicit encoding tasks. If this hypothesis is correct, and individuals with schizophrenia have disturbances in the function of medial temporal regions, such disturbances should be present in any task condition that requires the encoding of information, regardless of the WM load.

In addition to disturbances in DLPFC and hippocampus, we also found regions in brain stem, basal ganglia, thalamus, and parietal cortex that also demonstrated impaired activation during performance of both LTM tasks (either or both encoding and recognition) and WM tasks. All of these are regions are ones typically activated by the performance of both WM and LTM tasks in healthy individuals and, together with regions of PFC and hippocampus, probably form an integrated circuit necessary for the performance of a range of cognitive tasks. Findings of impaired activation among individuals with schizophrenia in all of these regions during performance of both LTM and WM tasks again suggests that there is a common neurobiological disturbance that contributes to cognitive deficits in multiple domains in this disorder. Further, such results suggest that although both DLPFC and hippocampus are clearly involved, individuals with schizophrenia display disturbances in the ability to engage a network of brain regions that support cognitive performance. Future research will need to determine how abnormalities in the functional activation of these different brain regions are associated in schizophrenia. For example, it will be important to determine whether impaired activation in one or more of these regions reflects the downstream effects of primary deficits in other regions (e.g., DLPFC, hippocampus) as opposed to a fundamental disturbance in the functional or structural integrity of the region.

A secondary goal of this study was to assess the material specificity of WM and LTM deficits in schizophrenia, as well as to determine whether any laterality differences exist in cortical dysfunction in this disorder. On this question, the results of this study were somewhat mixed. Individuals with schizophrenia were equally impaired in terms of accuracy in both verbal and nonverbal WM and recognition performance, but they did have slower RTs than controls for words but not faces in the recognition task. Thus, the behavioral data provide some evidence for greater verbal than nonverbal recognition-memory deficits among individuals with schizophrenia, but no evidence for greater verbal than nonverbal WM deficits in this population. In terms of cortical dysfunction, individuals with schizophrenia displayed impaired activation of right DLPFC for both words and faces during both WM and LTM performance, a result that is consistent with previous research suggesting that dorsolateral regions of PFC typically do not show material specificity effects (D'Esposito et al., 1998). However, the impairments in left hippocampal activation were present only for word stimuli, as this region was not activated by face stimuli for controls. Further, individuals with schizophrenia displayed the same pattern of material specificity effects as controls for faces but failed to show greater activation for words than faces in several regions that typically show enhanced activation for verbal stimuli (Braver et al., 2001; Kelley et al., 1998), including left inferior PFC, left parietal cortex, and left temporal cortex. Taken together, these results suggest that although impaired behavioral performance and cortical activation among individuals with schizophrenia are present for both verbal and nonverbal stimuli, there may be relatively greater impairment in left hemisphere cortical activity associated with verbal memory processes (R. E. Gur & Chin, 1999; R. E. Gur et al., 1994).

A potential confound in many neuroimaging studies of individuals with psychiatric disorders is the issue of medication status. All individuals with schizophrenia in the current study were on antipsychotic medications, primarily atypicals (approximately 80%). As such, some or all of the reduced cortical activation could have reflected medication effects rather than primary deficits associated with schizophrenia. However, a number of studies in unmedicated and never-medicated individuals with schizophrenia have also found impaired activation in many of the same regions we identified, including DLPFC (Andreasen et al., 1997; Barch et al., 2001; Berman et al., 1986). Such results suggest that at least some

of the patterns of impaired task-related cortical activation found in the current study were not simply the result of medication effects.

In summary, the findings of this study support the hypothesis that disturbances in DLPFC function in schizophrenia contribute to deficits in both WM and LTM function in this illness. As such, these results highlight the need to stop thinking of LTM deficits in schizophrenia as solely the result of abnormalities in the medial temporal cortex. In particular, we have suggested that impaired right DLPFC activation in schizophrenia may contribute to disturbances in the ability to select and maintain task-appropriate strategies, a cognitive process relevant to task performance in multiple domains. This hypothesis will need to be directly tested in future behavioral and neuroimaging studies in schizophrenia. At the same time, however, our results also suggest the need to consider how disturbances in medial temporal cortex might contribute to deficits in both WM and LTM in schizophrenia. Further, future research will need to determine how abnormalities in DLPFC and medial temporal cortex, as well as other brain regions, are related in schizophrenia. For example, it will be important to determine whether impaired activation in one or more of these regions reflects the downstream effects of primary deficits in other regions as opposed to a fundamental disturbance in the functional or structural integrity of a region.

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