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Functional Neuroanatomy of Auditory Working Memory in Schizophrenia: Relation to Positive and Negative Symptoms

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Functional brain imaging studies of working memory (WM) in schizophrenia have yielded inconsistent results regarding deficits in the dorsolateral prefrontal (DLPFC) and parietal cortices. In spite of its potential importance in schizophrenia, there have been few investigations of WM deficits using auditory stimuli and no functional imaging studies have attempted to relate brain activation during auditory WM to positive and negative symptoms of schizophrenia. We used a two-back auditory WM paradigm in a functional MRI study of men with schizophrenia ($N = 11$) and controls ($N = 13$). Region of interest analysis was used to investigate group differences in activation as well as correlations with symptom scores from the Brief Psychiatric Rating Scale. Patients with schizophrenia performed significantly worse and were slower than control subjects in the WM task. Patients also showed decreased lateralization of activation and significant WM related activation deficits in the left and right DLPFC, frontal operculum, inferior parietal, and superior parietal cortex but not in the anterior cingulate or superior temporal gyrus. These results indicate that in addition to the prefrontal cortex, parietal cortex function is also disrupted during WM in schizophrenia. Withdrawal-retardation symptom scores were inversely correlated with frontal operculum activation. Thinking disturbance symptom scores were inversely correlated with right DLPFC activation. Our findings suggest an association between thinking disturbance symptoms, particularly unusual thought content, and disrupted WM processing in schizophrenia.

INTRODUCTION

Schizophrenia is characterized by broad range of cognitive impairments (Heinrichs *et al.,* 1998). Working memory (WM), the ability to hold and manipulate information online in the brain (Baddeley *et al.,* 1974; Goldman-Rakic, 1994; Smith *et al.,* 1999), is among the most significantly disrupted cognitive functions in schizophrenia (Goldman-Rakic, 1994; 1991; Spindler *et al.,* 1997; Salame *et al.,* 1998; Stone *et al.,* 1998). The component processes involved in WM—encoding, rehearsal, storage, and executive processes on the contents of stored memory—represent key cognitive operations of the human brain. Smith and Jonides (Smith *et al.,* 1999) have argued that analysis of WM is critical for understanding not only memory systems, but thought itself. Goldman-Rakic (1994) has hypothesized that WM dysfunction may be a fundamental feature of formal thought disorder, a predominant positive symptom of schizophrenia.

Functional and structural neuroimaging in subjects with schizophrenia suggests that cognitive deficits result from prefrontal pathophysiology (Weinberger *et al.,* 1996; Shenton *et al.,* 1997; Nestor *et al.,* 1998; McCarley *et al.,* 1999). Regional cerebral blood flow (rCBF) studies have found evidence for decreased prefrontal cortex blood flow ("hypofrontality") in subjects with schizophrenia (Weinberger *et al.,* 1988), with the largest decreases occurring during cognitive tasks involving executive function (Young *et al.,* 1998). A number of previous imaging studies of prefrontal cortex deficits in schizophrenia have used neuropsychological tasks that have a WM component (Schroeder *et al.,* 1994; Volz *et al.,* 1997, 1999; Andreasen *et al.,* 1992). Although these studies have found deficits in prefrontal cortex function in schizophrenia, they have used tasks, such as the Wisconsin Cart Sorting Test, which are generally quite complex and engage a number of cognitive processes that are unrelated to WM per se.

More recently, researchers have focused attention on tasks that are generally considered to involve the core operations underlying WM (Carter *et al.,* 1998). These tasks can be generally categorized into two types (1) delayed matching to sample tasks involving WM delays of 3–5 s and (2) *n*-back tasks generally involving shorter delays (Gevins *et al.,* 1993). For example, one study (Stevens *et al.,* 1998) used auditory word and tone recognition in a delayed matching to sample task design and found decreased fMRI activation in subjects with schizophrenia in the lateral frontal cortex and

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anterosuperior temporal gyrus, but not in the dorsolateral prefrontal cortex (DLPFC) or parietal cortex. However, Manoach *et al.* (1999) found no decrease in prefrontal cortex activation in subjects with schizophrenia during digit matching to sample. Instead, they found greater activation in subjects with schizophrenia than in control subjects in the left DLPFC, but did not in the right DLPFC. Using a visual 2-back task designed specifically to manipulate contents of WM, Carter *et al.* (1998) found significantly decreased PET activation in the right DLPFC and right posterior parietal cortices of subjects with schizophrenia. An fMRI study using a similar visual 2-back task also found less DLPFC activation in subjects with schizophrenia (Callicott *et al.*, 1998). Both of these studies used visual stimuli with WM delays of 2 s. Overall, functional imaging studies of WM in schizophrenia have yielded variable and conflicting results. These inconsistencies may be related to differences in paradigm and type of operations involving WM. The delayed matching to sample tasks generally emphasize prefrontal cortex function during delay (Elliott *et al.*, 1999), while the *n*-back WM tasks involve delay as well as more dynamic updating of information via executive functions of the prefrontal cortex (Cohen *et al.*, 1997; Smith *et al.*, 1999). More detailed analysis of auditory processing by Javitt *et al.* (1997) have suggested that auditory WM deficits in schizophrenia may not be dependent on the duration for which memory traces are retained.

Attempts to relate cognitive and behavioral deficits in schizophrenia have focused on the characterization of symptom types, such as the dichotomy between positive and negative symptoms (Toomey *et al.*, 1997). The positive symptoms of schizophrenia include disorganization of thinking and planning, and loss of ability to distinguish between real and imagined events as exemplified by hallucinations and delusions (Liddle *et al.*, 1994; Carpenter *et al.*, 1994). The negative symptoms include blunted affect, poverty of speech and content, avolition and apathy, social withdrawal, and anhedonia (Andreasen, 1982). More recently, investigators have used correlational and factor analytic approaches to examine in greater detail the interrelationships between positive and negative symptoms (Andreasen *et al.*, 1999). These studies have suggested that positive symptoms can be further subdivided into two distinct dimensions—psychosis and disorganization (Andreasen *et al.*, 1986; Liddle, 1987; Lenzenweger *et al.*, 1989; Schuldberg *et al.*, 1990; Arndt *et al.*, 1991; Minas *et al.*, 1992).

Dimensional and categorical approaches to investigation of the psychopathology of schizophrenia have relied on a number of specific rating scales. Of these, the Brief Psychiatric Rating Scale (BPRS) (Overall *et al.*, 1988) has been widely used to examine schizophrenia symptomatology both in clinical and research settings (Bishop *et al.*, 1983; Faustman, 1994; Lauriello *et al.*, 1998; Cabeza *et al.*, 2000). The BPRS provides a reliable measure of both the positive and negative symptoms (broadly defined) as well as the more distinct dimensions that researchers have now begun to investigate in greater detail, including psychosis, conceptual disorganization, withdrawal-retardation, and anxiety-depression. The BPRS is more widely used across a range of psychiatric disorders, it provides a potential for generalizing the present results beyond schizophrenia (Dell'Osso *et al.*, 2000; Varner *et al.*, 2000). Although there exists a fairly extensive clinical characterization of these dimensions in schizophrenia, research on the neural correlates of underlying deficits has been limited.

Frontal lobe dysfunction is known to be associated with the negative symptoms of schizophrenia (Breier *et al.*, 1991). However, a recent behavioral study that parsed out different components of frontal lobe function found that positive symptoms are related to frontal executive tasks, whereas negative symptoms are related to mental tracking tasks that require motoric and dexterous manipulation (Zakzanis, 1998). Although a number of rest state rCBF studies (Shioiri *et al.*, 1994; Suzuki *et al.*, 1992; Wolkin *et al.*, 1992) have investigated the effect of positive and negative symptoms on hypofrontality, few neuroimaging studies to date have examined the relation between symptoms and brain activation during cognitive activation paradigms. Andreasen *et al.* (1992) reported that decreased activation during a Tower-of-London task was observed only in subjects with high scores for negative symptoms. McGuire *et al.* (1998) found that verbal disorganization, a feature of thought disorder, correlated inversely with temporal, cingulate, and frontal activation. Further, subjects with schizophrenia predisposed to hallucinations activated temporal and frontal regions less than non-hallucinating patients with schizophrenia or controls (McGuire *et al.*, 1996).

To date, no study has investigated auditory verbal WM in schizophrenia using an *n*-back task. In the present study we used fMRI to specifically examine brain activation in schizophrenia in several prefrontal and parietal cortex areas known to be involved in WM and further examined the relationship of the activation to BPRS scores. In order to control for factors unrelated to WM, we compared activation between WM and a closely matched control condition. We hypothesized that, compared to control subjects, patients with schizophrenia would perform worse and have significantly reduced activation in the DLPFC, ventrolateral prefrontal cortex and inferior parietal cortex (D'Esposito *et al.*, 1998; Smith *et al.*, 1998; Owen, 1997). We also investigated brain activation in the anterior cingulate since it has been linked to executive control of the WM system (D'Esposito *et al.*, 1995) and is thought to be involved in cognitive deficits in schizophrenia (Dolan *et al.*, 1995). While hypofrontality

across broad regions of the frontal lobe has also been reported in schizophrenia (Buchsbaum, 1990; Andreasen *et al.*, 1992; Weinberger *et al.*, 1996, 1988), the specific involvement of the anterior cingulate in WM deficits in schizophrenia is not known. Thus, the major objectives of this study were to investigate regional brain activation during auditory verbal WM in schizophrenia and to examine the relationships of observed activation abnormalities with symptoms.

MATERIALS AND METHODS

Subjects

Eleven men with schizophrenia (8 outpatients and 3 inpatients), and 13 physically and mentally healthy men recruited from the local community participated in the study after giving informed consent. Subjects were recruited from the VA Palo Alto Health Care System, were in good physical health, and met the DSM-IV criteria for schizophrenia based on a consensus of a research psychiatrist or psychologist performing a clinical interview and a trained research assistant performing the Structured Clinical Interview for DSM-IV (First *et al.*, 1995). All patients were on a stable dose of medication for at least 2 weeks prior to the MRI scan. Exclusion factors were the DSM-IV criteria for Alcohol or Substance Abuse or Dependence within 3 months prior to scanning, a history of head injury with loss of consciousness greater than 30 min, and neurological illness or trauma that could affect the central nervous system. Eight patients were on atypical and three were on typical anti-psychotic medication.

Clinical ratings using the BPRS (Overall *et al.*, 1988) were obtained for patients at or close to the day of the scan (eight subjects were rated on the day of the scan, three were rated within 1 week of the scan). The BPRS is a clinician-rated instrument based on a semistructured interview yielding measures of symptomatology on 18 items. Two trained raters administered the BPRS, and the averages of their ratings were used.

Task

Subjects performed a 2-back continuous performance task (Gevins *et al.*, 1993) involving the numbers zero through nine spoken in a female voice with an ISI of two seconds. In the WM condition, subjects were instructed to press a button with their right hand index finger every time the current number presented was the same as the number presented two stimuli prior. In the control condition, subjects were instructed to respond immediately after hearing the number "3." A sequence of 11 stimuli comprised a single epoch. A total of 12 epochs, 6 of each condition, were alternated (ABAB . . .), beginning with the control condition. The number of responses was balanced across conditions. All subjects were trained with 3 epochs of each condition prior to scanning to ensure that they understood how to do the task.

Due to technical problems, behavioral data was not acquired concurrently with fMRI data. Subjects (10 patients with schizophrenia and 8 normal controls) were brought back several months after the scan and were tested on the same experiment with an identical stimulus sequence. Six subjects could not be located or were unable to return for this second session. There is evidence in the literature to suggest that working memory performance is stable for patients with schizophrenia and control subjects over long time periods (Rund *et al.*, 1995). It was assumed that learning effects would have been lost during this period. Response accuracy and reaction time were recorded.

Behavioral Data Analysis

Subject performance was gauged using reaction time (RT) and sensitivity (d'), a measure of response accuracy that subtracts false-positive responses from hits (also referred to as "risk difference") (Macmillan *et al.*, 1991). d' minimizes bias with subjects who respond to nearly every stimulus.

fMRI Data Acquisition

Images were acquired on a conventional 1.5T GE scanner using a quadrature whole head coil. Subjects lay supine in the scanner with their head restrained using a bitebar (Menon *et al.*, 1997b). Functional images were acquired using a T2*-weighted gradient echo spiral pulse sequence with a temporal resolution of 4 s at 132 time points (TR = 1000 ms, TE = 40 ms, flip angle = 40°, and 4 interleaves) (Glover *et al.*, 1998). At each time point, 12 axial slices, −10 to +62 mm with respect to the anterior commissure, were imaged. Slice thickness was 6 mm, interslice thickness was 0 mm, field of view was 310 mm, with an effective in-plane spatial resolution of 4.35 mm. A single *k*-space image file was written to disk and images reconstructed, by inverse Fourier transform for each of the 132 time points, into $256 \times 256 \times 12$ image matrices (resolution: $1.21 \times 1.21 \times 6$ mm).

The task was programmed using Psyscope (http://poppy.psy.cmu.edu/psyscope) on a Macintosh notebook computer. Onset of scanning and task were synchronized using a TTL pulse delivered to the scanner timing microprocessor board from a "CMU Button Box" microprocessor connected to the Macintosh with a serial cable. Audio signals from the Macintosh were amplified using an audio receiver and transmitted to a piezo-electric speaker placed near the head of the scanner. Sound was piped binaurally to the subjects by means of a plastic headset connected with a plastic tube to a funnel placed over the piezo-electric speaker.

TABLE 1

Demographic Data (Mean and Standard Deviation) for Subject Groups

Subject group	Age	Education	NART IQ	Parental SES	Handedness[a]
Control (n = 13)	42.46 ± 3.93 37–49	14.65 ± 1.03 14–17	113.92 ± 7.27 104–125	2.79[b] ± 0.64 2–4	19.54 ± 7.48 14–39
Schizophrenic (n = 11)	44.55 ± 4.61 37–49	13.82 ± 1.66 11–17	110.45 ± 9.65 88–124	2.82 ± 0.98 2–5	15.50[c] ± 2.64 14–22

[a] Fourteen to 32 signified right-handedness and 50 to 70 left-handedness.
[b] Based on seven subjects.
[c] Based on 10 subjects.

MRI Data Acquisition

High resolution whole brain images were acquired to assist localization of activation foci. These images were acquired using a T1-weighted spoiled grass gradient recalled (SPGR) 3-D MRI sequence with the following parameters: TR = 24 ms; TE = 5 ms; flip angle = 40°; 24 cm field of view; 124 slices in sagittal plane; 256 × 192 matrix; acquired resolution = 1.5 × 0.9 × 1.2 mm. The reconstructed image was a 124 × 256 × 256 matrix (resolution: 1.5 × 0.9 × 0.9 mm).

fMRI Data Processing

fMRI data were pre-processed using SPM96 (http://www.fil.ion.ucl.ac.uk/spm). Images were first corrected for movement using least square minimization without higher-order corrections for spin history (Friston *et al.*, 1996). Images were then normalized to stereotaxic Talairach coordinates (Friston *et al.*, 1995b), resampled every 2 mm using sinc interpolation and spatially smoothed with a uniform three dimensional Gaussian filter with a full width at half maximum of 4 mm.

To determine activation during the WM compared to the control condition, regression analysis, and the theory of Gaussian random fields as implemented in SPM96 was used (Friston *et al.*, 1995c). Voxel-wise t statistics were computed using multivariate linear regression for the individual data of each subject (Worsley *et al.*, 1995). A delayed box-car hemodynamic response function (HRF) was used to determine activation directly related to the difference between the WM and control task conditions. The predictor reference waveform consisted of a series of −1 for images corresponding to the control condition and +1 for images corresponding to the WM condition, convolved with a 6-sec delay Poisson function to take into account delay and dispersion in the hemodynamic response. Low frequency noise was removed with a high pass filter (0.5 cycles/min) applied to the fMRI time series at each voxel. The confounding effects of fluctuations in global mean were removed with a scaling model. A temporal smoothing function (Gaussian kernel corresponding to dispersion of 8 s) was applied to the fMRI time series to enhance the signal to noise ratio. The degrees of freedom were adjusted to take into account autocorrelations in the fMRI time series (Friston *et al.*, 1995a). The t statistics were normalized to Z scores.

ROI Analysis

Statistical analysis of subject groups was conducted using regions of interest (ROIs). Based upon previously published studies (Braver *et al.*, 1997; Cohen *et al.*, 1997; Carter *et al.*, 1998; Jonides *et al.*, 1997), 12 mutually exclusive ROIs were constructed: The left and right hemispheres of the DLPFC (Brodmann Areas (BA) 9/46), inferior parietal cortex (BA 39/40), frontal operculum (BA 44/45), superior parietal cortex (BA 7), and anterior cingulate (BA 24/32); a region not known to be involved in WM, the superior temporal gyrus (STG; BA 22/42), was also included for comparisons. Regions of interest were constructed based upon the parcellation of Brodmann areas in the Talairach stereotaxic system (Talairach *et al.*, 1988).

Group Analysis of Brain Activation

The mean Z score of voxels activated above a Z = 2.33 threshold ($P < 0.01$) was used to measure activation intensity within each ROI. An analysis of variance model was used to investigate differences between groups and ROIs.

Clinical State and Brain Activation

Spearman correlations were used to relate both functional measures with clinical measures in patients with schizophrenia. Four subscales of the BPRS were used (Overall *et al.*, 1972; Faustman, 1994): Thinking Disturbance (assessing positive symptoms), Withdrawal-Retardation (assessing negative symptoms), Hostility-Suspiciousness, and Anxiety-Depression.

TABLE 2

Group Differences in Behavioral Measures

Behavioral measure	Control (n = 8)	Schizophrenic (n = 10)	P
d' (WM condition)	0.832 ± 0.090	0.636 ± 0.150	0.0024
d' (Control condition)	0.997 ± 0.006	0.877 ± 0.176	0.0364
RT (WM condition)	822 ± 55 ms	1107 ± 140 ms	<0.0001
RT (Control condition)	721 ± 37 ms	847 ± 119 ms	0.0057

RESULTS

Demographic Measures

The two groups did not differ significantly in age ($t(22) = -1.196$, $P = 0.244$), years of education ($t(22) = 1.507$, $P = 0.146$), intelligence as indexed by the National Adult Reading Test ($t(22) = 1.004$, $P = 0.327$) (Nelson, 1982), parent/caregiver socioeconomic status ($t(16) = -0.077$, $P = 0.939$) (Hollingshead, 1975), or handedness ($t(21) = 1.624$, $P = 0.119$) (Crovitz *et al.*, 1962) (Table 1).

Behavioral

Patients with schizophrenia performed significantly worse than control subjects and had significantly longer RTs for both the WM and control tasks (Table 2). Repeated measures ANOVA of RT showed a significant Group × Task condition interaction ($F(1,16) = 7.731$, $P = 0.013$), indicating that the patients were significantly more impaired during WM than control conditions (Fig. 1). A similar analysis with d′ showed group and condition effects but no significant interaction ($F(1,16) = 2.069$, $P = 0.170$).

Head Movement during fMRI Scan

Functional brain images were corrected for movement using least square minimization. Mean displacement (root-means-squared) needed to realign the images was used as measure of head movement. Head movement for both control subjects (1.12 ± 0.73 mm) and patients (1.50 ± 1.31 mm) was small and did not differ significantly between groups ($t(22) = -0.887$; $P = 0.385$).

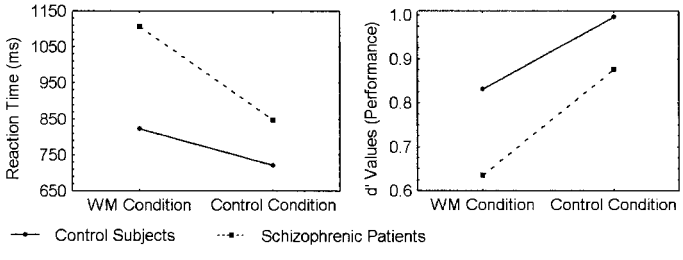

FIG. 1. Behavioral performance in patients with schizophrenia (n = 10) compared to control subjects (n = 8) during the auditory working memory and control conditions.

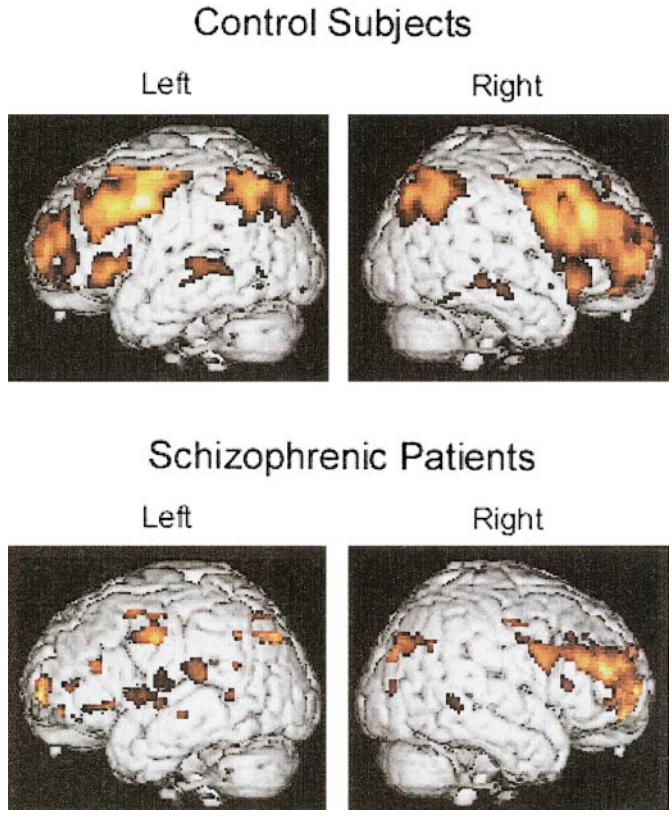

FIG. 2. Surface rendered average group activation the control subjects and patients with schizophrenia. This figure is not a statistical representation of the data—an ROI analysis was used to determine regionally specific group differences.

Group Average Activation

Averaged group data for control subjects and patients are shown in Figs. 2 and 3. These data suggest that patients with schizophrenia had marked deficits in activation in the DLPFC and the inferior parietal lobe. In control subjects, activation foci were found at the following locations in the left DLPFC (Talairach coordinates: 56, 24, 34), right DLPFC (56, 28, 34), left frontal operculum (−58, 24, 2), right frontal operculum (60, 22, 20), left inferior parietal (−46, −58, 42), right inferior parietal (50, −58, 42), left superior parietal (−32, −58, 54), right superior parietal (34, −76, 44), left anterior cingulate (−4, 24, 34), right anterior cingulate (2, 22, 24). Note that these figures do not represent a statistical comparison of the groups. We describe below regional differences in the pattern of activation between groups.

Group Comparison of Activation by ROI

Repeated measures analysis of variance was used to investigate group differences in fMRI activation across

ROIs. Factors used were Group (two levels: control, patient), ROI (five levels: DLPFC, frontal operculum, inferior parietal, superior parietal, anterior cingulate), and Hemisphere (two levels: left, right). Mean values with standard error are illustrated in Fig. 4.

Group differences. Significant effects were found with activation intensity for Group (controls > patients), ROI (DLPFC > inferior parietal > frontal operculum > superior parietal > anterior cingulate), Group × ROI (described below), and Group × Hemisphere (right > left in controls, left = right in patients). Trends toward significance were found for ROI × Hemisphere and Group × ROI × Hemisphere interactions (Table 3). To verify that these results did not arise from systematic group differences in head movement, we conducted a follow-up ANCOVA with the same effects as above, using overall degree of movement as covariate, as suggested by Callicott *et al.* (1998). This procedure yielded results nearly identical to the above ANOVA analysis, with all the same significant effects. The same findings were true when activation in a non-WM region, the STG, was used as a covariate, suggesting that regionally specific group differences do not result from movement.

Follow up analysis of the Group × ROI interaction revealed significantly reduced activation in patients with schizophrenia in the following ROIs: DLPFC ($F(1,22) = 28.163$, $P < 0.001$), frontal operculum ($F(1,22) = 5.201$, $P = 0.033$), inferior parietal ($F(1,22) = 8.391$, $P = 0.008$), and superior parietal ($F(1,22) = 14.151$, $P = 0.001$). Anterior cingulate showed no difference between groups ($F(1,22) = 0.002$, $P = 0.962$).

Group differences in STG. To confirm that group differences in activation did not arise from global reductions in the patients with schizophrenia, we examined activation in the STG. Group differences in activation intensity within this region were not significant ($F(1,22) = 1.530$, $P = 0.229$).

Correlation with symptoms. Thinking Disturbance scores of patients correlated significantly with activation intensity in the right DLPFC (rho = −0.711, $P = 0.014$; Fig. 5), but not in any other ROI. When the individual items on this scale were correlated with right DLPFC activation intensity, unusual thought content showed a significant relationship (rho = −0.648, $P = 0.031$), while hallucinatory behavior (rho = −0.503, $P = 0.115$) and conceptual disorganization (rho = −0.498, $P = 0.119$) did not. Withdrawal-Retardation scores correlated significantly with activation in the left frontal operculum (rho = −0.897, $P < 0.001$; Fig. 6) and right frontal operculum (rho = −0.661, $P = 0.038$; Fig. 6). The Hostility-Suspiciousness and Anxiety-Depression scores showed no significant relationship to activation in any ROI.

DISCUSSION

Although patients with schizophrenia were not significantly different in IQ and a number of demographic variables from control subjects, they showed significant behavioral deficits as well as deficits in brain activation during WM task performance. Patients with schizophrenia were significantly less accurate and slower than control subjects in the 2-back WM task. Additionally, patients were significantly more impaired in the WM condition. Our results are consistent with previous reports of WM deficits in patients with schizophrenia based on other paradigms and stimulus modalities including a visual 2-back WM task (Carter *et al.*, 1998), spatial and object WM (Spindler *et al.*, 1997), and verbal free-recall WM (Flemming *et al.*, 1995; Ganguli *et al.*, 1997). To our knowledge, this is the first demonstration of behavioral deficits during an auditory verbal 2-back WM task in schizophrenia.

Patients with schizophrenia showed significant activation deficits in the left and right DLPFC, left and right inferior parietal cortex, but not the anterior cingulate or the superior temporal gyrus. A significant Group × ROI interaction further underscored the profile of regionally specific deficits in schizophrenia. The most significant differences were found in the DLPFC, inferior and superior parietal cortex, while the frontal operculum showed less significant group differences and the anterior cingulate was not different between groups. Patients with schizophrenia also showed decreased lateralization of activation, in agreement with previous hypotheses (Maher *et al.*, 1998; Crow *et al.*, 1989). Together, these results suggest that the observed decreases in activation do not arise from global deficits in blood flow in schizophrenia patients. Furthermore, head movement during the task was small (1 mm or less in each axis) and did not differ between groups, nor did head movement or STG activation affect observed group differences when used as a covariate, as suggested by Callicott *et al.* (1998). Along with our finding of regionally specific group differences, this suggests that the observed brain activation deficits in schizophrenia patients are related to functional and behavioral differences rather than an artifact arising from differences in head movement.

Patients with schizophrenia showed no deficits in either the left or right STG, suggesting that deficits in early auditory stimulus processing are unlikely to underlie the observed WM deficits in schizophrenia. Rather, our results point to prefrontal and parietal cortex deficits underlying disruptions in the executive and storage components of WM (Smith *et al.*, 1998).

The largest brain activation differences between the groups occurred in the DLPFC, a subregion of the prefrontal cortex that has been implicated in executive functions involved in verbal working memory (Cohen *et al.*, 1997; Smith *et al.*, 1999). Our results suggest that

DLPFC deficits occur in both hemispheres. There were no hemispheric differences in activation in either group of subjects. This is consistent with fMRI studies indicating that both hemispheres, rather than just the left hemisphere, are involved in verbal working memory processing (Rypma *et al.,* 1999; Schumacher *et al.,* 1996). Further, several PET and fMRI studies have shown a correlation between left and right DLPFC activation and increased memory load (Smith *et al.,* 1998).

Although the DLPFC is known to be critically involved in verbal WM, Stevens *et al.* (1998) did not find differences between patients with schizophrenia and controls in this region, a result that they attributed to their task's strong subvocal rehearsal element. Our results converge with previous studies of visual 2-back WM tasks which found decreased DLPFC activation in patients with schizophrenia (Carter *et al.,* 1998; Callicott *et al.,* 1998). The discrepancy in these findings may arise from the fact that the 2-back task may have involved more frequent and dynamic manipulation of the contents of WM compared to the delayed match to sample tasks used by Stevens *et al.* (1998). If this interpretation is correct, these findings would suggest that it is manipulation of WM, compared to maintenance of the contents of WM, which is most affected in the DLPFC of patients with schizophrenia. Patients also showed decreased activation in the frontal operculum, although this deficit was not as large as that in the DLPFC. The left frontal operculum is thought to be involved in the rehearsal and inhibitory processes associated with WM (Smith *et al.,* 1998), while the relative contribution of the right frontal operculum, which appears to have greater deficits in patients with schizophrenia (Fig. 4), is poorly understood (Smith *et al.,* 1999).

Patients with schizophrenia also showed significant activation deficits in the parietal cortex. Differences were found in the inferior as well as the superior parietal lobe. Recent imaging studies suggest that the inferior-posterior parietal cortex is involved in the short-term storage and retrieval of verbal material (Jonides *et al.,* 1998) as well as the active maintenance of phonological stimulus representations (Smith *et al.,* 1998). Furthermore, our finding of conjoint parietal and prefrontal cortex deficits in schizophrenia is consistent with findings from metabolic studies of coactivation in the parietal and prefrontal cortex during working memory (Friedman *et al.,* 1994; Ungerleider *et al.,* 1998). The neuroanatomical connection between the prefrontal and parietal cortices is well documented (Selemon *et al.,* 1988; Cavada *et al.,* 1989). Electrophysiological studies in monkeys have shown changes in firing patterns of prefrontal cortex neurons during WM delay periods when the parietal cortex is cooled (Quintana *et al.,* 1989). Chafee *et al.* (2000) have recently shown that the reciprocal projections between parietal and prefrontal neurons tightly entrains their parallel activation. Together, these findings suggest that deficits in integration of frontal and parietal circuits may underlie working memory deficits in schizophrenia.

Control subjects and patients did not show any differences in the anterior cingulate. The only previous study to examine activation of the anterior cingulate in patients with schizophrenia during a WM task (Stevens *et al.,* 1998) also found no deficits in this region. Previous imaging studies have suggested that anterior cingulate cortex deficits may underlie impairment in verbal fluency (Dolan *et al.,* 1995) and declarative memory (Fletcher *et al.,* 1999). The lack of significant differences in the present study may have arisen from use of a closely matched control condition, thereby resulting in smaller activation in this region (see Fig. 4). The anterior cingulate has been postulated to control inhibition of preprogrammed responses to stimuli, such as in the Stroop task (Smith *et al.,* 1999) and to be involved in detecting and responding to salient target stimuli (Menon *et al.,* 1997a; Posner *et al.,* 1990). In this regard, a potential issue with the control task used in the present experiment as well as other *n*-back working memory studies is worth noting. The control task requires the subject to respond to the number 3. This builds up a preprogrammed response bias to this number. A response bias during the WM condition and response inhibition associated with a "No-Go" type of situation, when it is not an appropriate response target, could be potentially contribute to the activation. However, only 6% of the stimuli during the experimental condition were No-Go stimuli (the number 3) to which the prepotent response bias had been created during the control condition. Thus, it is unlikely that a preprogrammed response bias could have a significant effect on the activation, and group differences in brain activation during the experimental, compared to the control, condition are likely to be dominated by processes related to WM rather than response inhibition. The lack of differential activation of cingulate cortex is noteworthy, as postmortem studies have implicated it in the pathophysiology of schizophrenia (Benes, 1993). The present findings indicate that the anterior cingulate is not the critical locus of auditory working memory disruption in schizophrenia.

This is the first study to investigate the relation between clinical symptoms in schizophrenia and brain activation during an auditory WM task. Our results complement and extend the findings of Carter *et al.* (1996) who suggested that behavioral deficits during the 2-back visuospatial WM were related to negative symptoms. In the present study, negative symptoms, as indexed by the withdrawal-retardation subscale of the BPRS, were associated with left and right frontal operculum activation in patients with schizophrenia. Our results further support the hypothesis of a strong

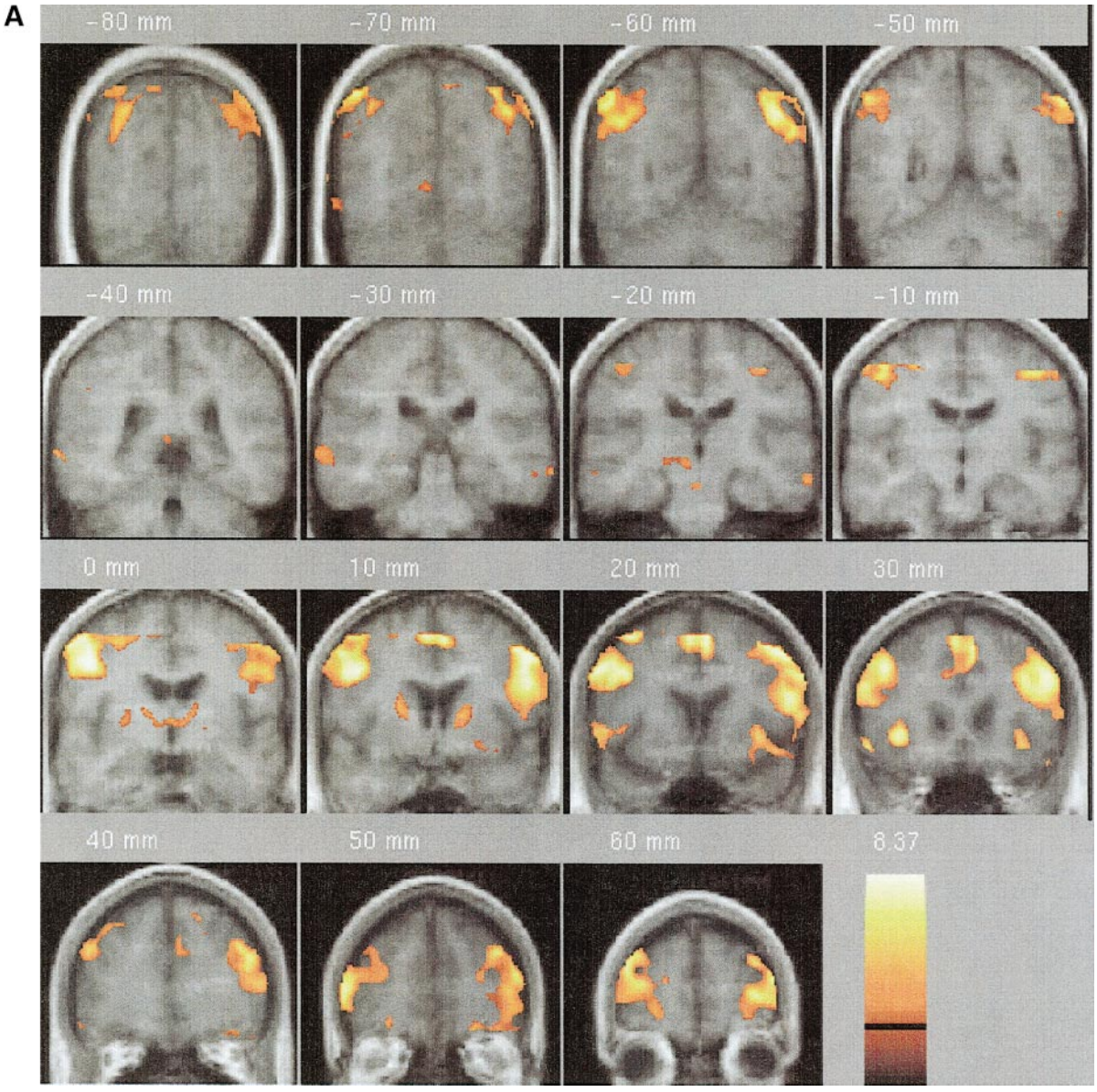

FIG. 3. Averaged group activation for (A) control subjects and (B) patients with schizophrenia ($Z > 2.33$; $P < 0.01$). Activations are shown superposed on the mean T1-weighted normalized structural MRI scans. Coronal slices from $y = -80$ to $+60$ mm are shown.

relationship between the negative symptoms of schizophrenia and prefrontal lobe dysfunction (Mattson *et al.*, 1997). To date the majority of this evidence has been based on neuropsychological assessment during tasks that involve memory and other cognitive functions. Imaging studies have investigated the relation between negative symptoms in schizophrenia and frontal lobe dysfunction mainly with resting state cerebral blood flow using PET and SPECT (Shioiri *et al.*, 1994; Suzuki *et al.*, 1992; Wolkin *et al.*, 1992). These studies have generally shown that decreased frontal brain activity is associated with the severity of negative symptoms in schizophrenia. Our results are in good agreement with the findings of Andreasen *et al.* (1992), who reported decreased PET activation in the prefrontal cortex during the Tower-of-London task only in patients with high scores for negative symptoms. The present fMRI findings suggest that negative symptoms may be more specifically related to frontal operculum dysfunction in schizophrenia. In particular, left frontal operculum dysfunction may be related to poverty of speech because this region, which encompasses classical Broca's language area, is known to be involved in speech production and rehearsal.

Positive symptoms, indexed by the thinking disturbance subscale of the BPRS, were associated with the intensity of right DLPFC activation. The correlation was strongest with unusual thought content and non-

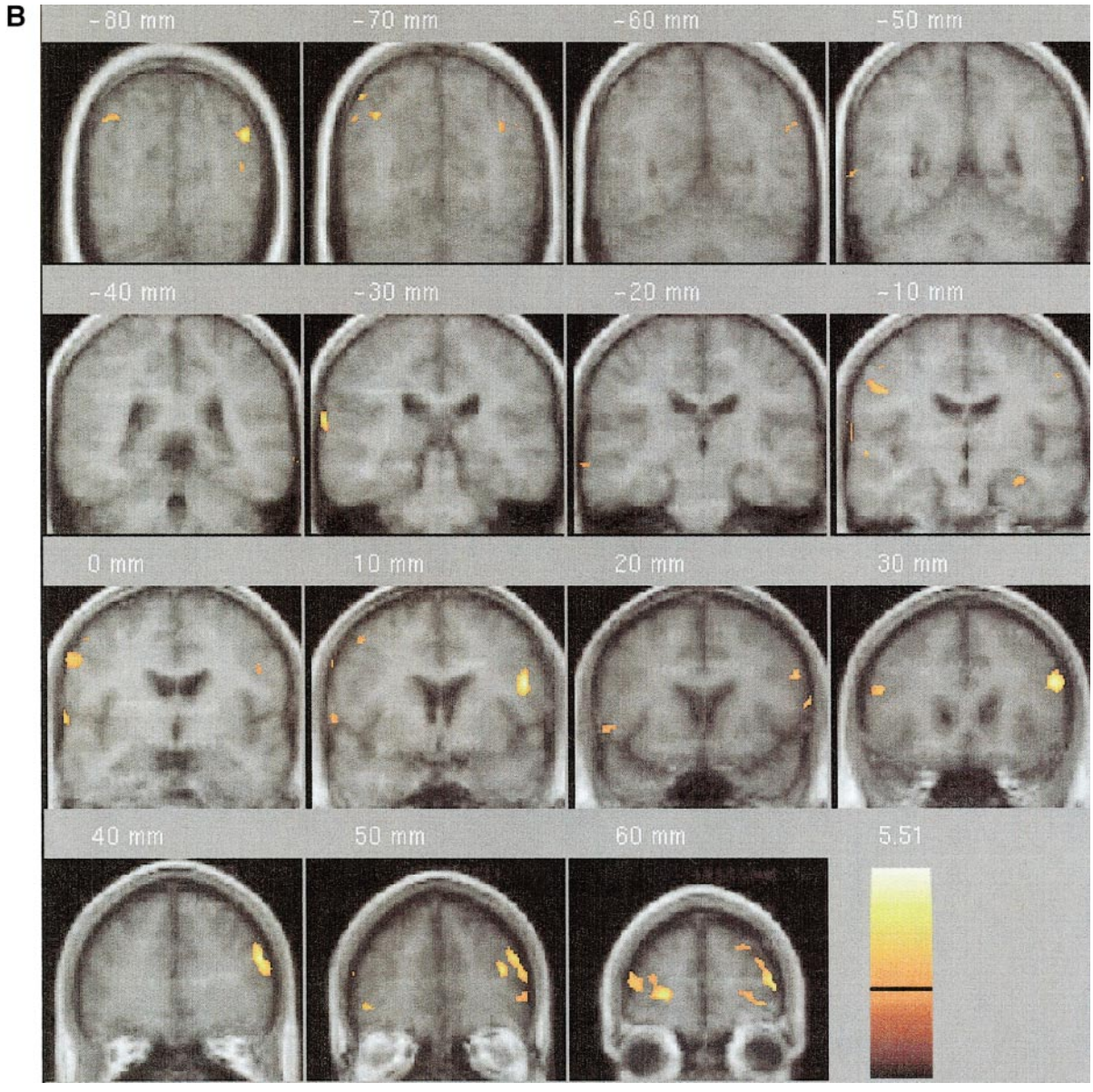

FIG. 3—*Continued*

significant with conceptual disorganization or hallucinatory behavior. Our results are in agreement with McGuire *et al.* (1998), who reported an inverse correlation between thought disorder and baseline PET levels in the right middle frontal gyrus (Brodmann area 9). Our results are also in agreement with behavioral studies which have linked frontal lobe executive cognitive tasks to positive symptoms (Zakzanis, 1998; Morrison-Stewart *et al.*, 1992), and previous research has found a relationship between thought disorder and tests of verbal memory and working memory in patients with schizophrenia (Nestor *et al.*, 1998). These results suggest that unusual thought content, such as delusional thinking, might interfere with WM-related activation. Previous imaging studies of positive symptoms have generally focused on hallucinations using speech or verbal imagery or on formal thought disorder. These studies have shown that functional and structural dysfunction is related to deficits in the superior and middle temporal gyri (Shenton *et al.*, 1992; Turetsky *et al.*, 1995; McGuire *et al.*, 1996, 1998). Positive symptoms have also been linked to the temporal cortex in schizophrenia in rCBF resting state studies (Klemm *et al.*, 1996). In the present study, no activation deficits were found in the STG in patients with schizophrenia. The present study does not access STG function directly because auditory stimuli were completely balanced between WM and control conditions. Thus, no relation was found between STG activation and thinking disturbance, which includes hallucina-

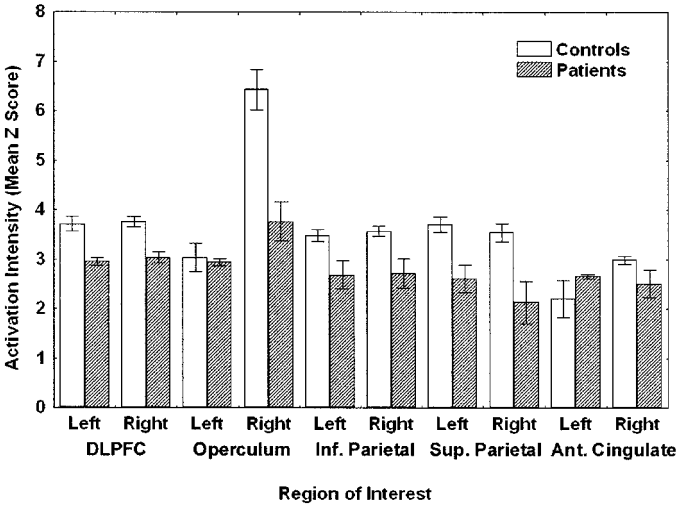

FIG. 4. Activation intensity, as measured by mean *Z* score in each ROI, in control subjects and patients with schizophrenia.

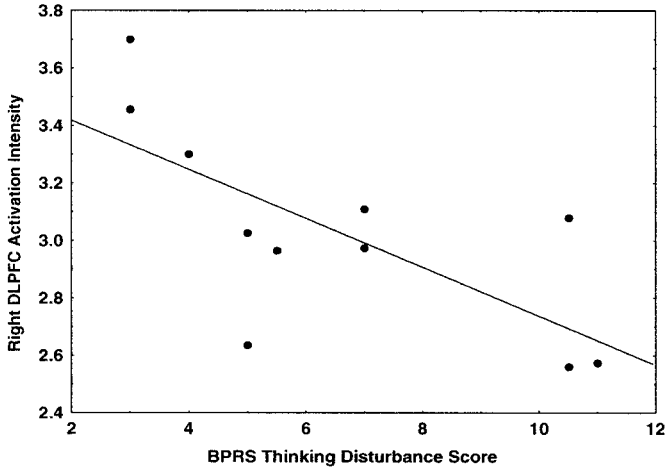

FIG. 5. Scatterplot of activation intensity in the right DLPFC, as measured by mean *Z* score and thinking disturbance (positive symptom) subscale scores for patients with schizophrenia.

tory behavior. The evidence in this study for a common DLPFC neural substrate for working memory and thinking disturbance supports the hypothesis originally proposed by Goldman-Rakic (1987, 1999).

The right DLPFC is thought to be more involved in intentional than incidental memory (Rugg *et al.*, 1997). There has been speculation that the right DLPFC is involved in successful memory retrieval (Rugg *et al.*, 1996) and memory retrieval attempt (Wagner *et al.*, 1998). We suggest that thinking disturbance symptoms, particularly unusual thought content, interfere with the conscious, effortful, processing of the contents of WM, disrupting activation and impeding cognitive performance. These results, together with previous and current findings of right DLPFC deficits underlying WM dysfunction in schizophrenia, support the hypothesis that WM deficits and thinking disturbance symptoms share similar neural substrates. There is some evidence to suggest that psychotropic medication can cause "hypoperfusion" in patients with schizophrenia (Sabri *et al.*, 1997), however, subjects in the present study were all being treated with a stable dose of anti-psychotic medication, and therefore it is unlikely that the present finding of an inverse correlation between right DLPFC and thinking disturbance is due to differences in medication status. The lack of correlation in the DLPFC with withdrawal-retardation is equally notable and warrants further investigation.

Although frontal lobe dysfunction is widely suspected to underlie negative symptoms of schizophrenia (Breier *et al.*, 1991), a number of studies have failed to find specific relation between negative symptoms and performance on specific cognitive tasks. For example, Morrison-Stewart *et al.* (1992) failed to find correlations between frontal lobe neuropsychological test performance and negative symptoms. In their study of chronic patients with schizophrenia, Wolkin *et al.* (1992) reported that while the severity of negative symptoms was a strong predictor of global cognitive abilities, it was a poor predictor for tasks assessing memory and planning functions (WCST and Category Retrieval). Our results suggest that positive and negative symptoms may be related to specific components of cognitive deficits, as correlations with symptom severity were regionally specific. Further studies are needed to investigate the relation between specific cognitive operations and specific symptoms in different brain regions.

All patients in the present study were medicated, and different types of antipsychotic medication were used. Possible confounding effects of medication on fMRI activation in specific brain regions is somewhat difficult to address given the lack of adequate information in this area. Typical and atypical anti-psychotic medication have been shown to have different effects on fMRI signal during a motor task (Braus *et al.*, 1999); decreased activation was seen in sensorimotor cortices (contra- and ipsilateral) in subjects with schizophrenia

TABLE 3

Results of ANOVA

	Activation intensity		
Effect	*df*	*F*	*P* level
Group	1, 22	13.9889	0.0011*
ROI	4, 88	6.9469	0.0001*
Hemisphere	1, 22	0.4361	0.5159
Group × ROI	4, 88	4.4559	0.0025*
Group × hemisphere	1, 22	9.1992	0.0061*
ROI × hemisphere	4, 88	2.2129	0.0740
Group × ROI × Hemisphere	4, 88	2.2998	0.0650

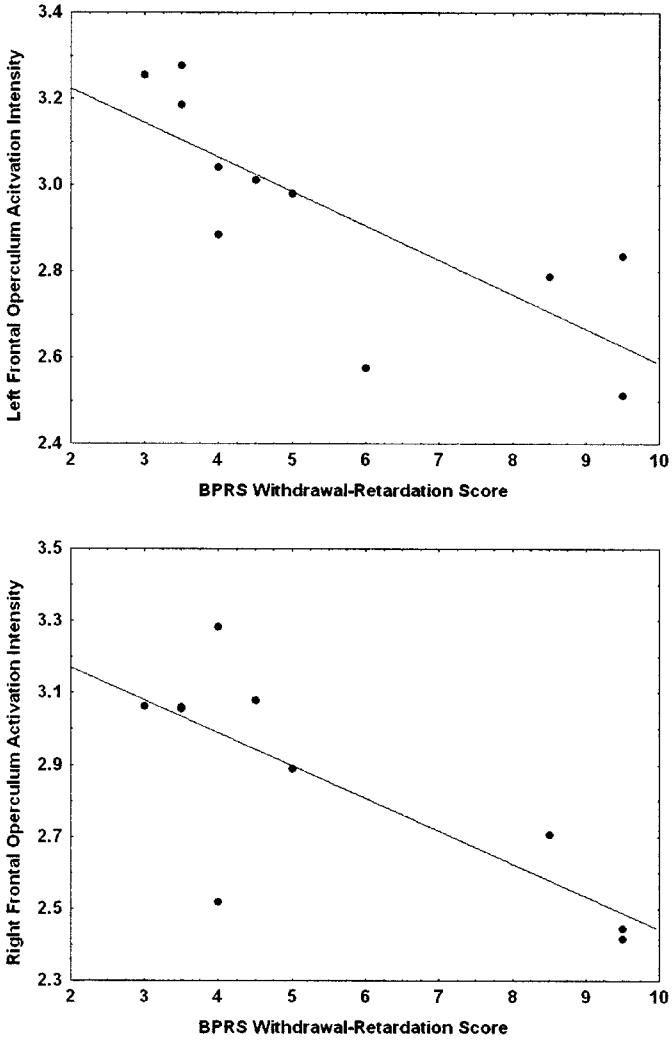

FIG. 6. Scatterplot of activation intensity in the left and right operculum, as measured by mean *Z* score versus withdrawal-retardation (negative symptom) subscale scores for patients with schizophrenia.

under stable medication with typical, but not atypical, antipsychotics. There have been few studies of the precise effects of specific drugs on fMRI activation during complex cognitive tasks. In one of the few studies to date, Honey *et al.* (1999) found that during a WM task, risperidone (an atypical antipsychotic) increased fMRI activation in right prefrontal cortex, SMA, and posterior parietal cortex, compared with a baseline on typical antipsychotic drugs; no such effects were noted in the patients whose medication status remained unchanged. The increased activity during risperidone treatment was not associated with improvement in working memory, perhaps because of the ease of the task which the patients were already performing at normal levels while receiving typical antipsychotic drugs (Meltzer *et al.*, 1999). Only 3 of the 11 patients in the present study were on typical medication and it is unlikely that the effects of medication itself are the major cause of the decreased activation seen in the target brain regions in the present study.

Finally, we address limitations and potential extensions of the present study. With regard to the scanning acquisition, 4 s per image during a task with a 2-s ISI would not seem to be ideal sampling of brain activity during a complex task involving several processes. The block design makes this less of an issue, but it is worth pointing out. More rapid event-related approaches are now needed to determine which basic processes underlying WM are more affected in schizophrenia. It should also be noted that patients with schizophrenia were also mildly impaired in the control condition, raising the possibility that some of the group differences arise from differences in the control, rather than the experimental, condition. This is an important issue that warrants further investigation. On the other hand, the strategy taken in the present study was to investigate the Group $\times$ ROI $\times$ Task interaction. This interaction showed significant effects on both the patterns of brain activation as well as performance measures (both accuracy and reaction time). Given the loud fMRI scanning environment, performance of auditory WM task could be impaired, particularly in a distractible patient population. Although the ROIs used in this study are not as precise as parcellation of individual anatomical maps, the present methodology has strength in being highly replicable (e.g., Stevens *et al.*, 1998).

In summary, patients with schizophrenia showed behavioral deficits and a regionally specific profile of functional activation deficits in the prefrontal and parietal cortex regions during WM. No WM related deficits were found in the anterior cingulate or the superior temporal gyrus. The pattern of activation indicates that patients with schizophrenia showed the most significant deficits in neural systems underlying maintenance, storage, and rapid updating of the contents of WM components of WM. Deficits in frontal operculum activation were related to the severity of withdrawal-retardation symptoms and deficits in right DLPFC activation were related to the severity of thinking disturbance symptoms. Our findings suggest that combining functional activation with symptom ratings can provide new insight into the neural correlates of cognitive deficits in schizophrenia.

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REFERENCES

Andreasen, N. C. 1982. Negative symptoms in schizophrenia. Definition and reliability. *Arch. Gen. Psychiatry* **39:** 784–788.

Andreasen, N. C., and Grove, W. M. 1986. Evaluation of positive and negative symptoms in schizophrenia. *Psychiatrie Psychobiolgie* **I:** 108–121.

Andreasen, N. C., Nopoulos, P., O'Leary, D. S., Miller, D. D., Wassink, T., and Flaum, M. 1999. Defining the phenotype of schizophrenia: Cognitive dysmetria and its neural mechanisms. *Biol. Psychiatry* **46:** 908–920.

Andreasen, N. C., Rezai, K., Alliger, R., Swayze, V. W. d., Flaum, M., Kirchner, P., *et al.* 1992. Hypofrontality in neuroleptic-naive patients and in patients with chronic schizophrenia. Assessment with xenon 133 single-photon emission computed tomography and the Tower of London. *Arch. Gen. Psychiatry* **49:** 943–958.

Arndt, S., Alliger, R. J., and Andreasen, N. C. 1991. The distinction of positive and negative symptoms. The failure of a two-dimensional model. *Br. J. Psychiatry* **158:** 317–322.

Baddeley, A. D., and Hitch, G. 1974. Working memory. In *The Psychology of Learning and Motivation* (G. E. Bower, Ed.), pp. 47–89. Academic Press, New York.

Benes, F. M. 1993. Neurobiological investigations in cingulate cortex of schizophrenic brain. *Schizophr. Bull.* **19:** 537–549.

Bishop, R. J., Golden, C. J., MacInnes, W. D., Chu, C. C., Ruedrich, S. L., and Wilson, J. 1983. The BPRS in assessing symptom correlates of cerebral ventricular enlargement in acute and chronic schizophrenia. *Psychiatry Res.* **9:** 225–231.

Braus, D. F., Ende, G., Weber-Fahr, W., Sartorius, A., Krier, A., Hubrich-Ungureanu, P., *et al.* 1999. Antipsychotic drug effects on motor activation measured by functional magnetic resonance imaging in schizophrenic patients. *Schizophren. Res.* **39:** 19–29.

Braver, T. S., Cohen, J. D., Nystrom, L. E., Jonides, J., Smith, E. E., and Noll, D. C. 1997. A parametric study of prefrontal cortex involvement in human working memory. *Neuroimage* **5:** 49–62.

Breier, A., Schreiber, J. L., Dyer, J., and Pickar, D. 1991. National Institute of Mental Health longitudinal study of chronic schizophrenia. Prognosis and predictors of outcome. *Arch. Gen. Psychiatry* **48:** 239–246.

Buchsbaum, M. S. 1990. The frontal lobes, basal ganglia, and temporal lobes as sites for schizophrenia. *Schizophren. Bull.* **16:** 379–389.

Cabeza, I. G., Amador, M. S., Lopez, C. A., Gonzalez de Chavez, M. 2000. Subjective response to antipsychotics in schizophrenic patients: Clinical implications and related factors. *Schizophren. Res.* **41:** 349–355.

Callicott, J. H., Ramsey, N. F., Tallent, K., Bertolino, A., Knable, M. B., Coppola, R., *et al.* 1998. Functional magnetic resonance imaging brain mapping in psychiatry: Methodological issues illustrated in a study of working memory in schizophrenia. *Neuropsychopharmacology* **18:** 186–196.

Carpenter, W. T., Jr., and Buchanan, R. W. 1994. Schizophrenia. *N. Engl. J. Med.* **330:** 681–690.

Carter, C., Robertson, L., Nordahl, T., Chaderjian, M., Kraft, L., and O'Shora-Celaya, L. 1996. Spatial working memory deficits and their relationship to negative symptoms in unmedicated schizophrenia patients. *Biol. Psychiatry* **40:** 930–932.

Carter, C. S., Perlstein, W., Ganguli, R., Brar, J., Mintun, M., and Cohen, J. D. 1998. Functional hypofrontality and working memory dysfunction in schizophrenia. *Am. J. Psychiatry* **155:** 1285–1287.

Cavada, C., and Goldman-Rakic, P. S. 1989. Posterior parietal cortex in rhesus monkey: II. Evidence for segregated corticocortical networks linking sensory and limbic areas with the frontal lobe. *J. Comp. Neurol.* **287:** 422–445.

Chafee, M. V., and Goldman-Rakic, P. S. 2000. Inactivation of parietal and prefrontal cortex reveals interdependence of neural activity during memory-guided saccades. *J. Neurophysiol.* **83:** 1550–1566.

Cohen, J. D., Perlstein, W. M., Braver, T. S., Nystrom, L. E., Noll, D. C., Jonides, J., *et al.* 1997. Temporal dynamics of brain activation during a working memory task. *Nature* **386:** 604–608.

Crovitz, H. F., and Zener, K. A. 1962. Group test for assessing hand and eye dominance. *Am. J. Psychol.* **75:** 271–276.

Crow, T. J., Ball, J., Bloom, S. R., Brown, R., Bruton, C. J., Colter, N., *et al.* 1989. Schizophrenia as an anomaly of development of cerebral asymmetry. A postmortem study and a proposal concerning the genetic basis of the disease. *Arch. Gen. Psychiatry* **46:** 1145–1150.

D'Esposito, M., Aguirre, G. K., Zarahn, E., Ballard, D., Shin, R. K., and Lease, J. 1998. Functional MRI studies of spatial and nonspatial working memory. *Brain Res. Cogn. Brain Res.* **7:** 1–13.

D'Esposito, M., Detre, J. A., Alsop, D. C., Shin, R. K., Atlas, S., and Grossman, M. 1995. The neural basis of the central executive system of working memory. *Nature* **378:** 279–281.

Dell'Osso, L., Pini, S., Tundo, A., Sarno, N., Musetti, L., and Cassano, G. B. 2000. Clinical characteristics of mania, mixed mania, and bipolar depression with psychotic features. *Compr. Psychiatry* **41:** 242–247.

Dolan, R. J., Fletcher, P., Frith, C. D., Friston, K. J., Frackowiak, R. S., and Grasby, P. M. 1995. Dopaminergic modulation of impaired cognitive activation in the anterior cingulate cortex in schizophrenia. *Nature* **378:** 180–182.

Elliott, R., and Dolan, R. J. 1999. Differential neural responses during performance of matching and nonmatching to sample tasks at two delay intervals. *J. Neurosci.* **19:** 5066–5073.

Faustman, W. O. 1994. Brief Psychiatric Rating Scale. In *The Use of Psychological Testing for Treatment Planning and Outcome Assessment* (M. E. Maruish, Ed.), pp. 371–401. Lawrence Erlbaum, Hillsdale, NJ.

First, M. B., Spitzer, R. L., Gibbon, M., and Williams, J. B. W. 1995. *Structured Clinical Interview for DSM-IV Axis I Disorders—Patient Edition (SCID-I/P)*, Version 2.0. Biometrics Research Department, New York State Psychiatric Institute, 722 W 168th Street, New York, NY 10032.

Fleming, K., Goldberg, T. E., Gold, J. M., and Weinberger, D. R. 1995. Verbal working memory dysfunction in schizophrenia: Use of a Brown-Peterson paradigm. *Psychiatry Res.* **56:** 155–161.

Fletcher, P., McKenna, P. J., Friston, K. J., Frith, C. D., and Dolan, R. J. 1999. Abnormal cingulate modulation of fronto-temporal connectivity in schizophrenia. *Neuroimage* **9:** 337–342.

Friedman, H. R., and Goldman-Rakic, P. S. 1994. Coactivation of prefrontal cortex and inferior parietal cortex in working memory tasks revealed by 2DG functional mapping in the rhesus monkey. *J. Neurosci.* **14:** 2775–2788.

Friston, K. J., Holmes, A. P., Poline, J. B., Grasby, P. J., Williams, S. C., Frackowiak, R. S., *et al.* 1995a. Analysis of fMRI time-series revisited. *Neuroimage* **2:** 45–53.

Friston, K. J., Ashburner, J., Frith, C. D., Poline, J. B., Heather, J. D., and Frackowiak, R. S. J. 1995b. Spatial registration and normalization of images. *Hum. Brain Mapp.* **2:** 165–189.

Friston, K. J., Holmes, A. P., Worsley, J. P., Poline, C. D., Frith, C. D., and Frackowiak, R. S. J. 1995c. Statistical parametric maps in functional imaging: A general linear approach. *Hum. Brain Mapp.* **2:** 189–210.

Friston, K. J., Williams, S., Howard, R., Frackowiak, R. S., and Turner, R. 1996. Movement-related effects in fMRI time-series. *Magn. Reson. Med.* **35:** 346–355.

Ganguli, R., Carter, C., Mintun, M., Brar, J., Becker, J., Sarma, R., Nichols, T., and Bennington, E. 1997. PET brain mapping study of

auditory verbal supraspan memory versus visual fixation in schizophrenia. *Biol. Psychiatry* **41:** 33–42.

Gevins, A., and Cutillo, B. 1993a. Spatiotemporal dynamics of component processes in human working memory. *Electroencephalogr. Clin. Neurophysiol.* **87:** 128–143.

Glover, G. H., and Lai, S. 1998. Self-navigated spiral fMRI: interleaved versus single-shot. *Magn. Reson. Med.* **39:** 361–368.

Goldman-Rakic, P. S. 1987. Circuitry of the frontal association cortex and its relevance to dementia. *Arch. Gerontol. Geriatr.* **6:** 299–309.

Goldman-Rakic, P. S. 1991. Prefrontal cortical dysfunction in schizophrenia: The relevance of working memory. In *Psychopathology and the Brain* (B. J. Carroll and J. E. Barret, Ed.), Raven Press, New York.

Goldman-Rakic, P. S. 1994. Working memory dysfunction in schizophrenia. *J. Neuropsychiatry Clin. Neurosci.* **6:** 348–357.

Goldman-Rakic, P. S. 1999. The physiological approach: Functional architecture of working memory and disordered cognition in schizophrenia. *Biol. Psychiatry* **46:** 650–661.

Heinrichs, R. W., Zakzanis, K. K. 1998. Neurocognitive deficit in schizophrenia: A quantitative review of the evidence. *Neuropsychology* **12:** 426–445.

Hollingshead, A. B. 1975. *Four Factor Index of Social Status.* Yale Univ. Press, New Haven, CT.

Honey, G. D., Bullmore, E. T., Soni, W., Varatheesan, M., Williams, S. C., and Sharma, T. 1999. Differences in frontal cortical activation by a working memory task after substitution of risperidone for typical antipsychotic drugs in patients with schizophrenia. *Proc. Natl. Acad. Sci. USA* **96:** 13432–13437.

Javitt, D. C., Strous, R. D., Grochowski, S., Ritter, W., and Cowan, N. 1997. Impaired precision, but normal retention, of auditory sensory ("echoic") memory information in schizophrenia. *J. Abnorm. Psychol.* **106:** 315–324.

Jonides, J., Schumacher, E. H., Smith, E. E., Koeppe, R. A., Awh, E., Reuter-Lorenz, P. A., *et al.* 1998. The role of parietal cortex in verbal working memory. *J. Neurosci.* **18:** 5026–5034.

Jonides, J., Schumacher, E. H., Smith, E. E., Lauber, E. J., Awh, E., Minoshima, S., *et al.* 1997. Verbal working memory load affects regional brain activation as measured by PET. *J. Cogn. Neurosci.* **9:** 462–475.

Klemm, E., Danos, P., Grunwald, F., Kasper, S., Moller, H. J., and Biersack, H. J. 1996. Temporal lobe dysfunction and correlation of regional cerebral blood flow abnormalities with psychopathology in schizophrenia and major depression—A study with single photon emission computer tomography. *Psychiatry. Res.* **68:** 1–10.

Lauriello, J., Mathalon, D. H., Rosenbloom, M., Sullivan, E. V., Faustman, W. O., Ringo, D. L., Lim, K. O., and Pfefferbaum, A. 1998. Association between regional brain volumes and clozapine response in schizophrenia. *Biol. Psychiatry* **43:** 879–886.

Lenzenweger, M. F., Dworkin, R. H., and Wethington, E. 1989. Models of positive and negative symptoms in schizophrenia: An empirical evaluation of latent structures. *J. Abnorm. Psychol.* **98:** 62–70.

Liddle, P., Carpenter, W. T., and Crow, T. 1994. Syndromes of schizophrenia. *Br. J. Psychiatry* **165:** 721–727.

Liddle, P. F. 1987. The symptoms of chronic schizophrenia. A re-examination of the positive–negative dichotomy. *Br. J. Psychiatry* **151:** 145–151.

Macmillan, N. A., and Creelman, C. D. 1991. *Detection Theory: A User's Guide.* Cambridge Univ. Press, New York.

Maher, B. A., Manschreck, T. C., Yurgelun-Todd, D. A., and Tsuang, M. T. 1998. Hemispheric asymmetry of frontal and temporal gray matter and age of onset in schizophrenia. *Biol. Psychiatry* **44:** 413–417.

Manoach, D. S., Press, D. Z., Thangaraj, V., Searl, M. M., Goff, D. C., Halpern, E., *et al.* 1999. Schizophrenic subjects activate dorsolateral prefrontal cortex during a working memory task, as measured by fMRI. *Biol. Psychiatry* **45:** 1128–1137.

Mattson, D. T., Berk, M., and Lucas, M. D. 1997. A neuropsychological study of prefrontal lobe function in the positive and negative subtypes of schizophrenia. *J. Genet. Psychol.* **158:** 487–494.

McCarley, R. W., Wible, C. G., Frumin, M., Hirayasu, Y., Levitt, J. J., Fischer, I. A., *et al.* 1999. MRI anatomy of schizophrenia. *Biol. Psychiatry* **45:** 1099–1119.

McGuire, P. K., Silbersweig, D. A., Wright, I., Murray, R. M., Frackowiak, R. S. J., and Frith, C. D. 1996. The neural correlates of inner speech and auditory verbal imagery in schizophrenia: Relationship to auditory verbal hallucinations. *Br. J. Psychiatry* **169:** 148–163.

McGuire, P. K., Quested, D. J., Spence, S. A., Murray, R. M., Frith, C. D., and Liddle, P. F. 1998. Pathophysiology of "positive" thought disorder in schizophrenia. *Br. J. Psychiatry* **173:** 231–235.

Meltzer, H. Y., Park, S., and Kessler, R. 1999. Cognition, schizophrenia, and the atypical antipsychotic drugs. *Proc. Natl. Acad. Sci. USA* **96:** 13591–13593.

Menon, V., Ford, J. M., Lim, K. O., Glover, G. H., and Pfefferbaum, A. 1997a. Combined event-related fMRI and EEG evidence for temporal-parietal cortex activation during target detection. *Neuroreport* **8:** 3029–3037.

Menon, V., Lim, K. O., Anderson, J. H., Johnson, J., and Pfefferbaum, A. 1997b. Design and efficacy of a head-coil bite bar for reducing movement-related artifacts during functional MRI scanning. *Behav. Res. Methods Instruments Comput.* **29:** 589–594.

Minas, I. H., Stuart, G. W., Klimidis, S., Jackson, H. J., Singh, B. S., and Copolov, D. L. 1992. Positive and negative symptoms in the psychoses: Multidimensional scaling of SAPS and SANS items. *Schizophren. Res.* **8:** 143–156.

Morrison-Stewart, S. L., Williamson, P. C., Corning, W. C., Kutcher, S. P., Snow, W. G., and Merskey, H. 1992. Frontal and non-frontal lobe neuropsychological test performance and clinical symptomatology in schizophrenia. *Psychol. Med.* **22:** 353–359.

Nelson, H. E. 1982. *The National Adult Reading Scale* (NART). Nelson, Windsor.

Nestor, P. G., Shenton, M. E., Wible, C., Hokama, H., O'Donnell, B. F., Law, S., *et al.* 1998. A neuropsychological analysis of schizophrenic thought disorder. *Schizophren. Res.* **29:** 217–225.

Overall, J. E., and Gorham, D. R. 1988. The Brief Psychiatric Rating Scale (BPRS): Recent developments in ascertainment and scaling. *Psychopharmacol. Bull.* **24:** 97–99.

Overall, J. E., Klett, C. J. 1972. *Applied Multivariate Analysis.* McGraw-Hill, New York.

Owen, A. M. 1997. The functional organization of working memory processes within human lateral frontal cortex: The contribution of functional neuroimaging. *Eur. J. Neurosci.* **9:** 1329–1339.

Posner, M. I., Petersen, S. E. 1990. The attention system of the human brain. *Annu. Rev. Neurosci.* **13:** 25–42.

Quintana, J., Fuster, J. M., and Yajeya, J. 1989. Effects of cooling parietal cortex on prefrontal units in delay tasks. *Brain Res.* **503:** 100–110.

Rugg, M. D., Fletcher, P. C., Frith, C. D., Frackowiak, R. S., and Dolan, R. J. 1996. Differential activation of the prefrontal cortex in successful and unsuccessful memory retrieval. *Brain* **119:** 2073–2083.

Rugg, M. D., Fletcher, P. C., Frith, C. D., Frackowiak, R. S., and Dolan, R. J. 1997. Brain regions supporting intentional and incidental memory: A PET study. *Neuroreport* **8:** 1283–1287.

Rund, B. R., and Landro, N. I. 1995. Memory in schizophrenia and affective disorders. *Scand. J. Psychol.* **36:** 37–46.

Rypma, B., Prabhakaran, V., Desmond, J. E., Glover, G. H., and Gabrieli, J. D. 1999. Load-dependent roles of frontal brain regions in the maintenance of working memory. *Neuroimage* **9:** 216–226.

Sabri, O., Erkwoh, R., Schreckenberger, M., Owega, A., Sass, H., and Buell, U. 1997. Correlation of positive symptoms exclusively to hyperperfusion of hypoperfusion of cerebral cortex in never-treated schizophrenics. *Lancet* **349:** 1735–1739.

Salame, P., Danion, J. M., Peretti, S., and Cuervo, C. 1998. The state of functioning of working memory in schizophrenia. *Schizophren. Res.* **30:** 11–29.

Schroeder, J., Buchsbaum, M. S., Siegel, B. V., Geider, F. J., Haier, R. J., Lohr, J., *et al.* 1994. Patterns of cortical activity in schizophrenia. *Psychol. Med.* **24:** 947–955.

Schuldberg, D., Quinlan, D. M., Morgenstern, H., and Glazer, W. 1990. Positive and negative symptoms in chronic psychiatric outpatients: Reliability, stability, and factor structure. *Psychol. Assess. J. Consult. Clin. Psychol.* **2:** 262–268.

Schumacher, E. H., Lauber, E., Awh, E., Jonides, J., Smith, E. E., and Koeppe, R. A. 1996. PET evidence for an amodal verbal working memory system. *Neuroimage* **3:** 79–88.

Selemon, L. D., Goldman-Rakic, P. S. 1988. Common cortical and subcortical targets of the dorsolateral prefrontal and posterior parietal cortices in the rhesus monkey: Evidence for a distributed neural network subserving spatially guided behavior. *J. Neurosci.* **8:** 4049–4068.

Shenton, M. E., Kikinis, R., Jolesz, F. A., Pollak, S. D., LeMay, M., Wible, C. G., Hokama, H., Martin, J., Metcalf, D., Coleman, M., *et al.* 1992. Abnormalities of the left temporal lobe and thought disorder in schizophrenia: A quantitative magnetic resonance imaging study. *N. Engl. J. Med.* **327:** 604–612.

Shenton, M. E., Wible, C. G., and McCarley, R. W. 1997. *A Review of Magnetic Resonance Imaging Studies of Brain Abnormalities in Schizophrenia.* Marcel Dekker, New York.

Shioiri, T., Kato, T., Inubushi, T., Murashita, J., and Takahashi, S. 1994. Correlations of phosphomonoesters measured by phosphorus-31 magnetic resonance spectroscopy in the frontal lobes and negative symptoms in schizophrenia. *Psychiatry Res.* **55:** 223–235.

Smith, E. E., and Jonides, J. 1998. Neuroimaging analyses of human working memory. *Proc. Natl. Acad. Sci. USA* **95:** 12061–12068.

Smith, E. E., and Jonides, J. 1999. Storage and executive processes in the frontal lobes. *Science* **283:** 1657–1661.

Spindler, K. A., Sullivan, E. V., Menon, V., Lim, K. O., and Pfefferbaum, A. 1997. Deficits in multiple systems of working memory in schizophrenia. *Schizophren. Res.* **27:** 1–10.

Stevens, A. A., Goldman-Rakic, P. S., Gore, J. C., Fulbright, R. K., Wexler, B. E. 1998. Cortical dysfunction in schizophrenia during auditory word and tone working memory demonstrated by functional magnetic resonance imaging. *Arch. Gen. Psychiatry* **55:** 1097–1103.

Stone, M., Gabrieli, J. D., Stebbins, G. T., and Sullivan, E. V. 1998. Working and strategic memory deficits in schizophrenia. *Neuropsychology* **12:** 278–288.

Suzuki, M., Kurachi, M., Kawasaki, Y., Kiba, K., and Yamaguchi, N. 1992. Left hypofrontality correlates with blunted affect in schizophrenia. *Jpn. J. Psychiatry. Neurol.* **46:** 653–657.

Talairach, J., and Tournoux, P. 1988. *Co-Planar Stereotaxic Atlas of the Human Brain.* Thieme, New York.

Toomey, R., Kremen, W. S., Simpson, J. C., Samson, J. A., Seidman, L. J., Lyons, M. J., *et al.* 1997. Revisiting the factor structure for positive and negative symptoms: Evidence from a large heterogeneous group of psychiatric patients. *Am. J. Psychiatry.* **154:** 371–377.

Turetsky, B., Cowell, P. E., Gur, R. C., Grossman, R. I., Shtasel, D. L., and Gur, R. E. 1995. Frontal and temporal lobe brain volumes in schizophrenia. Relationship to symptoms and clinical subtype. *Arch. Gen. Psychiatry* **52:** 1061–1070.

Ungerleider, L. G., Courtney, S. M., and Haxby, J. V. 1998. A neural system for human visual working memory. *Proc. Natl. Acad. Sci. USA* **95:** 883–890.

Varner, R. V., Chen, Y. R., Swann, A. C., and Moeller, F. G. 2000. The Brief Psychiatric Rating Scale as an acute inpatient outcome measurement tool: A pilot study. *J. Clin. Psychiatry* **61:** 418–421.

Volz, H., Gaser, C., Hager, F., Rzanny, R., Ponisch, J., Mentzel, H., *et al.* 1999. Decreased frontal activation in schizophrenics during stimulation with the Continuous Performance Test—A functional magnetic resonance imaging study. *Eur. Psychiatry* **14:** 17–24.

Volz, H. P., Gaser, C., Hager, F., Rzanny, R., Mentzel, H. J., Kreitschmann-Andermahr, I., *et al.* 1997. Brain activation during cognitive stimulation with the Wisconsin Card Sorting Test—A functional MRI study on healthy volunteers and schizophrenics. *Psychiatry Res.* **75:** 145–157.

Wagner, A. D., Desmond, J. E., Glover, G. H., and Gabrieli, J. D. 1998. Prefrontal cortex and recognition memory. Functional-MRI evidence for context-dependent retrieval processes. *Brain* **121:** 1985–2002.

Weinberger, D. R., and Berman, K. F. 1988. Speculation on the meaning of cerebral metabolic hypofrontality in schizophrenia. *Schizophren. Bull.* **14:** 157–168.

Weinberger, D. R., and Berman, K. F. 1996. Prefrontal function in schizophrenia: Confounds and controversies. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* **351:** 1495–1503.

Wolkin, A., Sanfilipo, M., Wolf, A. P., Angrist, B., Brodie, J. D., and Rotrosen, J. 1992. Negative symptoms and hypofrontality in chronic schizophrenia. *Arch. Gen. Psychiatry* **49:** 959–965.

Worsley, K. J., and Friston, K. J. 1995. Analysis of fMRI time-series revisited—Again. *Neuroimage* **2:** 173–181.

Young, D. A., Zakzanis, K. K., Bailey, C., Davila, R., Griese, J., Sartory, G., *et al.* 1998. Further parameters of insight and neuropsychological deficit in schizophrenia and other chronic mental disease. *J. Nerv. Ment. Dis.* **186:** 44–50.

Zakzanis, K. K. 1998. Neuropsychological correlates of positive vs. negative schizophrenic symptomatology. *Schizophren. Res.* **29:** 227–233.