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

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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 Card 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...
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 (Callcott 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; Schulberg 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 semi-structured 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, inter slicethickness 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 × 256 × 12 image matrices (resolution: 1.21 × 1.21 × 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.
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 x 192 matrix; acquired resolution = 1.5 x 0.9 x 1.2 mm. The reconstructed image was a 124 x 256 x 256 matrix (resolution: 1.5 x 0.9 x 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>
<thead>
<tr>
<th>Subject group</th>
<th>Age</th>
<th>Education</th>
<th>NART IQ</th>
<th>Parental SES</th>
<th>Handedness*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 13)</td>
<td>42.46 ± 3.93</td>
<td>14.65 ± 1.03</td>
<td>113.92 ± 7.27</td>
<td>104-125</td>
<td>2.79 ± 0.64</td>
</tr>
<tr>
<td></td>
<td>37-49</td>
<td>14-17</td>
<td>7.54 ± 0.64</td>
<td>2-4</td>
<td>14-39</td>
</tr>
<tr>
<td>Schizophrenic (n = 11)</td>
<td>44.55 ± 4.61</td>
<td>13.82 ± 1.66</td>
<td>110.45 ± 9.65</td>
<td>88-124</td>
<td>2.82 ± 0.98</td>
</tr>
<tr>
<td></td>
<td>37-49</td>
<td>11-17</td>
<td>7.45 ± 0.98</td>
<td>2-5</td>
<td>14-22</td>
</tr>
</tbody>
</table>

* Fourteen to 32 signified right-handedness and 50 to 70 left-handedness.

TABLE 1
Demographic Data (Mean and Standard Deviation) for Subject Groups

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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 x 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).

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...
ROI's. 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; Callcott 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 (Jönides 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 impairments in working memory 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
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. 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.
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. 3—Continued**

![Image](image_url)
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.
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 × ROI × 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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