Schizophrenic Subjects Activate Dorsolateral Prefrontal Cortex during a Working Memory Task, as Measured by fMRI

Dara S. Manoach, Daniel Z. Press, Venkatassen Thangaraj, Meghan M. Searl, Donald C. Goff, Elkan Halpern, Clifford B. Saper, and Steven Warach

Background: *Neuroimaging studies of schizophrenic subjects performing working memory (WM) tasks have demonstrated a relative hypoactivity of prefrontal cortex compared with normal subjects.*

Methods: *Using functional magnetic resonance imaging (fMRI), we compared dorsolateral prefrontal cortex (DLPFC) activation in 12 schizophrenic and 10 normal subjects during rewarded performance of a WM task. Subjects performed a modified version of the Sternberg Item Recognition Paradigm (SIRP), a continuous performance, choice reaction time (RT) task that requires WM. We compared a high WM load condition with a nonWM choice RT condition and with a low WM load condition.*

Results: *Schizophrenic subjects performed the tasks better than chance but worse than normal subjects. They showed greater activation than normal subjects in the left DLPFC but did not differ in the right DLPFC or in the control region. In the schizophrenic group, left DLPFC activation was inversely correlated with task performance, as measured by errors.*

Conclusions: *These findings contrast with previous studies that demonstrated task-related hypofrontality in schizophrenia. Task parameters that may contribute to this difference are discussed. We hypothesize that the performance and activation differences we observed are also manifestations of prefrontal dysfunction in schizophrenia. They reflect inefficient functioning of the neural circuitry involved in WM.* Biol Psychiatry 1999;45:1128–1137

Key Words: Schizophrenia, prefrontal cortex, working memory, functional magnetic resonance imaging, neuropsychology, functional brain mapping

Introduction

Although the neuroanatomic underpinnings of schizophrenia remain controversial, a wealth of clinical data indirectly implicates dysfunction of the prefrontal cortex. Cognitive deficits and negative symptoms of schizophrenia resemble prefrontal dysfunction. In particular, schizophrenic patients show working memory (WM) deficits (Park and Holzman 1992). The anatomic components of the hypothetical neural network subserving WM are not completely understood, but, on the basis of converging lines of evidence from nonhuman primates and from neuroimaging studies of humans (Friedman and Goldman-Rakic 1994; Petrides et al 1993b), the dorsolateral prefrontal cortex (DLPFC) is thought to play a critical role.

WM is a cognitive psychological construct that refers to the process of actively holding information "on-line" and manipulating it in the service of guiding behavior (Baddeley 1992). It is hypothesized to be a temporary store whose contents are continually updated, scanned, and manipulated in response to immediate information-processing demands. WM is a critical component of normal cognition and is impaired in schizophrenia (Park and Holzman 1992). Some investigators have hypothesized that many of the cognitive deficits in schizophrenia stem from deficient WM processes that lead to a failure to guide behavior on the basis of internalized representations such as schemata and ideas (Cohen et al 1996; Goldman-Rakic 1991). Such a failure could lead to behaviors that are stimulus-bound (rather than guided by context), stereotypic, and perseverative.

Neuroimaging studies of schizophrenic subjects performing WM tasks have demonstrated "task-related hypofrontality" (Callicott et al 1998; Weinberger and Berman 1996; Yurgelun-Todd et al 1996). Compared with normal subjects, schizophrenic subjects show a relative physiological hypoactivity of the prefrontal cortex. These findings have been challenged as a possible artifact of task performance (Ebmeier et al 1995). Poor performance may reflect poor effort or motivation, the use of an inappropri-

From Beth Israel Deaconess Medical Center (DSN, DZP, VT, MMS, CPS, SW); and Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts (DCG,EH).

Address reprint requests to Dara S. Manoach, Behavioral Neurology Unit, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Boston, MA 02215.

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Table 1. Means, SDs, and Group Comparisons of Demographic Data and Rating Scale Scores (*z* value is the result of a nonparametric Mann-Whitney *U* comparison)

Subject characteristics	Normal subjects ($n = 10$)	Schizophrenic subjects ($n = 12$)	t	p
Age	37.7 ± 11.0	42.4 ± 5.2	1.33	.20
Laterality score	77.0 ± 17.8	75.8 ± 44.3	0.08	.94
Education (years)	15.4 ± 2.2	10.8 ± 3.4	3.70	.001[a]
Estimated verbal IQ	119.6 ± 5.1	105.3 ± 14.4	2.97	.008[a]
Parental SES	2.4 ± 1.1	3.3 ± 1.1	$z = 1.85$	.07
Age of onset		22.8 ± 6.3	Level of	
Length of illness (years)		19.7 ± 5.9	severity	
BPRS		19.8 ± 4.0	minimal	
PANSS negative		20.1 ± 4.3	mild to moderate	
PANSS positive		12.6 ± 3.4	minimal to mild	
AIMS		1.9 ± 2.1	minimal to mild	
Simpson-Angus		1.1 ± 1.2	minimal	

[a] significant at $p = .05$; SES, socioeconomic status; BPRS, Brief Psychiatric Rating Scale; PANSS, Positive and Negative Syndrome Scale; AIMS, Abnormal Involuntary Movement Scale.

ate strategy, or that the task was too difficult, and for these reasons result in hypofrontality (Frith et al 1995). When a task is too difficult, subjects may engage cognitive and affective processes that are unrelated to WM. These may include error monitoring, attempts at compensation, disengaging from the task, feeling overwhelmed, and guessing. In the current study, we attempted to address these issues to determine whether schizophrenic subjects are able to activate the DLPFC during WM performance. We employed a task that constrains strategy by requiring WM to succeed, yields objective measures of performance, and enables schizophrenic subjects to perform better than chance. We also provided a financial incentive for correct responses to enhance motivation.

Another potential limitation of some previous neuroimaging studies is that group-averaging methodologies were employed. Because schizophrenic patients are heterogeneous on many measures of brain structure and function, group averaging may mask individual differences in prefrontal activation. We measured activation with functional magnetic resonance imaging (fMRI), which allows an evaluation of DLPFC activation in individual subjects. fMRI provides an indirect measure of task-related changes in regional cerebral perfusion.

We employed the Sternberg Item Recognition Paradigm (SIRP) (Sternberg 1966), modified for fMRI (Manoach et al 1997), to examine task-related differences in DLPFC activation in normal versus schizophrenic subjects. The SIRP is a continuous performance, choice reaction time (RT) task that requires WM and reliably activates the DLPFC in normal subjects (Manoach et al 1997). The task requires subjects to memorize a set of digits. The subjects are then presented with single digits and must respond by indicating whether the digit presented is a target (a member of the memorized set) or a foil (not a member of the memorized set). Accurate responses are predicated upon a temporarily stored representation of the targets that must be maintained in WM for the duration of the trial. We manipulated the WM load by varying the number of targets. Based on our previous experience with the SIRP (Goff et al 1995; Goff et al 1996), we choose a "high" WM load condition that schizophrenic subjects found challenging but could perform significantly better than chance. We compared the high WM load condition with a choice RT condition that did not require WM to examine changes in DLPFC perfusion as a function of WM. We also compared the high WM load with a "low" WM load condition, which had fewer targets but was identical in all other respects, to ensure that our findings in the first comparison could not be attributed to differences in the baseline task that are not related to WM. Our hypothesis was that schizophrenic subjects would not show task-related hypofrontality and that their DLPFC activation would be related to task performance.

Methods and Materials

Subjects

Table 1 reports subject demographic and descriptive information. We studied a total of 13 male schizophrenic outpatients and 10 male normal subjects. The data from 1 schizophrenic subject were discarded, prior to analysis, due to excessive susceptibility artifact in the functional images that affected the regions of interest. The remaining cohort of 12 schizophrenic subjects was recruited from an urban mental health center. Diagnoses were confirmed with Structured Clinical Interviews for DSM-III-R (Spitzer et al 1992), and subjects with concurrent axis I disorders were excluded. All schizophrenic subjects had been maintained on stable doses of antipsychotic medications for at least 6 weeks, 7 subjects on atypical and 5 subjects on conventional agents.

Symptomatology was characterized with the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham 1962) and the Positive and Negative Syndrome Scale (PANSS) (Kay et al 1987). Movement abnormalities were characterized with the Abnormal Involuntary Movement Scale (National Institute of Mental Health 1974) and the Simpson-Angus Rating Scale (Simpson and Angus 1970). Ten normal subjects without a history of psychiatric or neurological disease were recruited from the hospital community to form a control group. All subjects were screened to exclude a history of major head trauma, significant medical or neurological illness, and substance abuse or dependence within the past 6 months. All normal subjects and 11 of the 12 schizophrenic subjects were right-handed, as determined by a laterality score of 70 or more on the modified Edinburgh Handedness Inventory (White and Ashton 1976). Subject groups were matched for age and laterality score. Compared with the schizophrenic subjects, normal subjects had more years of education, higher estimated verbal IQs as measured by the American National Adult Reading Test (Blair and Spreen 1989), and showed a trend toward having a higher parental socioeconomic status, as determined by the Hollingshead Index (Hollingshead 1965). All subjects gave written informed consent, and the experimental protocol was approved by the Committee on Clinical Investigations at Beth Israel Deaconess Medical Center and at the Massachusetts Department of Mental Health.

Tasks

Experimental tasks were controlled by a Macintosh PowerBook 180c using Macintosh stimulus presentation software (MacStim®). Prior to scanning, subjects practiced until their performances indicated that they understood the tasks. They were instructed to respond as quickly and accurately as possible and informed that they would be paid a 5 cent bonus for each correct response. Stimuli were projected onto a screen. Subjects lay in the scanner and viewed the screen through a mirror positioned on the head coil. Subjects responded with thumb triggers in either hand. The triggers were attached via a fiber optic connection to the PowerBook mouse port so that response RT and side (right or left) were recorded.

In the high WM load condition (5t), subjects were presented with five target digits to remember. This was followed by stimulus trials, during which they responded to individual digits that appeared on the screen by pressing with the right thumb (R) if the digit was a target and the left thumb (L) if it was a foil. The low WM load condition (2t) was identical to the 5t condition, except that there were only two target digits to remember. In the baseline condition (Arrows), which did not require WM, subjects responded to the display of arrows pointing right and left by pressing the corresponding trigger.

Each of the three conditions was presented seven times in a counterbalanced order. Each run of a condition lasted 64 sec and included a 10-sec pause at the beginning for instructional prompts and presentation of targets, during which no scanning took place. Each run consisted of 20 stimulus trials of either digits or arrows. For half the trials, the correct response was an R response and for the other half, an L response. Each trial lasted 2750 msec, including a random interstimulus interval, which ranged from 150–1000 msec. The total experiment time was 22 min and 40 sec.

Image Acquisition

Images were obtained with a whole-body 1.5-T Siemens Medical System Magnetom MR modified for echoplanar imaging (Erlangen, Germany). A circularly polarized head coil was used for excitation/receiving. A vacuum-compressed surgical pillow minimized head motion. A three-dimensional volume ($1.25 \times 1.25 \times 2.0$ mm voxel size) for anatomical localization was acquired using a magnetization prepared, rapid acquisition gradient echo pulse sequence. Blood oxygenation level-dependent, contrast functional images were acquired for each run of a condition with a gradient echo, echoplanar imaging pulse sequence (TE: 64 msec; TR: 2.16 sec; 25 acquisitions per run; 240 mm field of view). Eight contiguous 8-mm axial slices were placed parallel to the intercommissural plane to cover the frontal cortex ($3.75 \times 1.875 \times 8.0$ mm voxel size).

Image Analysis

The raw T2* weighted images were corrected for motion (x, y, z rotations and translations) using a least squares algorithm (iMIPS, Pembroke, Massachusetts) that corrupted the top and bottom slices. We calculated an index of motion that consisted of the median of the product of the summed corrected rotations and the summed corrected translations across all of the functional scans for each subject. The first three acquisitions of each run were eliminated to attain steady-state magnetization. The data were smoothed using a Gaussian filter (element size: 5 voxels). We identified voxels with task-related signal changes (which we will refer to as "activation") using cross-correlation analyses comparing voxel signal intensities with an idealized boxcar waveform (Bandettini et al 1993). We compared the high WM load condition with the control condition (5t versus Arrows) and with the low WM load condition (5t versus 2t). We used a threshold of $r = .22$ to identify significantly activated voxels in the DLPFC and a control region. This threshold was calculated based on the 308 observations of each voxel and corresponds to a significance level at each voxel of .00005, which provides an overall p-value of .05 for the approximately 1000 voxels in the DLPFC in each hemisphere. Only voxels with positive signal changes were analyzed and reported. Anatomic images were registered and resliced to the orientation and voxel size of the functional images for anatomic localization of activated voxels in the correlation maps.

DLPFC Definition and Analysis

Unlike that of other primates, the human prefrontal cortex is not bounded by definitive sulcal landmarks. The term DLPFC is frequently used to refer to Brodmann's areas 9 and 46, both of which are activated in WM tasks (Petrides et al 1993a; Petrides et al 1993b). We developed anatomic criteria to include portions of these regions, based on a study of their cytoarchitectonic definition (Rajkowska and Goldman-Rakic 1995). The regions

Table 2. Working Memory Task Performance Means, SDs, and *t*-Tests for Percent Correct Responses and Reaction Time

	Condition	Normal subjects ($n = 10$)	Schizophrenic subjects ($n = 12$)	t, p
Percent correct	Arrows	98.6 ± 1.4	93.4 ± 10.0	$t = 1.63$, $p = .12$
	2t	98.1 ± 1.5	89.5 ± 11.8	$t = 2.96$, $p = .03$[a]
	5t	96.2 ± 2.8	76.3 ± 15.6	$t = 3.96$, $p = .0008$[a]
Reaction time (sec)		($n = 7$)[b]	($n = 11$)[b]	
	Arrows	.460 ± .057	.573 ± .099	$t = 3.15$, $p = .006$[a]
	2t	.555 ± .106	.696 ± .125	$t = 3.30$, $p = .005$[a]
	5t	.705 ± .129	.865 ± .173	$t = 3.03$, $p = .008$[a]

[a] significant at $p \leq .05$
[b] RT data is missing for three normal subjects and one schizophrenic subject.

were drawn on each subject's resliced anatomic images without reference to the functional data. The anterior and posterior boundaries of the DLPFC were defined by planes that were placed perpendicular to the intercommissural plane. The placement of the planes was determined by a neurologist (Daniel Z. Press) blind to subject identity and using objective criteria. To exclude the frontal pole, the anterior plane was placed at the point one third, from the rostral tip of the genu of the corpus callosum to the frontopolar hemispheric margin on the midsagittal view. The posterior plane was defined for each hemisphere using three-dimensional renderings of the lateral brain surfaces. It was placed at the point where the anterior ascending ramus of the Sylvian fissure joins the posterior horizontal ramus of the Sylvian fissure. This point can be reliably identified in morphometric studies (Caviness et al 1996) and was chosen to exclude the premotor cortex. The DLPFC regions were drawn on individual slices, within the boundaries defined by the planes, to include the lateral superior and middle frontal gyri and the bordering superior, middle, and inferior frontal sulci.

We also defined a control region in an effort to rule out the possibility that group differences in DLPFC activation represented a more global activation difference. The control region was drawn on each slice that contained DLPFC and consisted of the whole slice, excluding the right and left DLPFC regions. The regions were combined across slices to create three region of interest (ROI) masks: right and left DLPFC and control (slices minus DLPFC). The right and left DLPFC were considered separately to test for group differences in the laterality of activation. Whereas the schizophrenic subjects' ROI masks were, on average, smaller than those of the normal subjects, these differences approached significance only for the control mask ($t = 3.20$, $p = .09$).

We superimposed each ROI mask on the correlation maps to derive quantitative indices of activation for each comparison (5t versus Arrows and 5t versus 2t). Our primary index was the value of the voxel with the maximum correlation coefficient (max voxel), which is a measure of the peak signal intensity change within the mask, scaled by the error variance, regardless of whether it met the significance threshold. We derived the following three additional indices to determine the consistency of our findings with the max voxel index. The mean correlation coefficient of the activated voxels within the mask (active mean) provided a measure of the magnitude of suprathreshold voxels. When a mask did not contain suprathreshold voxels, this index could not be computed and we substituted the value of the max voxel, since excluding subjects with the least activation can bias group comparisons by inflating the mean activation for the group. The mean correlation coefficient for all the voxels in the mask (ROI mean) provided a measure of signal intensity change in the entire region. Since the DLPFC is large and functionally heterogeneous, we expected that this value would be close to zero and that activation differences might be diluted. Finally, we measured the proportion of ROI voxels with significant activation (percentage of voxels). This index is influenced by both the magnitude and spatial extent of activation.

Data Analysis

Behavioral measures, RT and response accuracy, were subjected to repeated measures analyses of variance. Pairwise comparisons were evaluated with *t*-tests. RTs from incorrect trials were excluded. Subject groups were compared on the indices of activation, using both *t*-tests and nonparametric Mann-Whitney *U* tests. The results for both types of analyses were identical with regard to the determination of significance, and we present the findings of the *t*-tests only. We used analyses of covariance with the interaction of the group and the covariate (max voxel) to compare the relation of activation with task performance, as measured by errors and RT in the schizophrenic versus the normal group. We used Spearman's rank correlation coefficients to describe the relationship in each group. A statistic was considered to be significant if its exact two-tailed probability value was ≤.05.

Results

Task Performance

Table 2 reports task performance data and group comparisons. All of the normal subjects and 10 of the 12 schizophrenic subjects performed significantly above chance in all three task conditions. Two of the 12 schizophrenic subjects performed significantly above chance in

Table 3. Number of Subjects Showing Significant DLPFC Activation by Group, Comparison, and Hemisphere

Group	Comparison	Left DLPFC	Right DLPFC	Either DLPFC
Normal	5t versus Arrows	7 (70%)	10 (100%)	10 (100%)
(n = 10)	5t versus 2t	5 (50%)	8 (80%)	8 (80%)
Schizophrenic	5t versus Arrows	11 (92%)	11 (92%)	11 (92%)
(n = 12)	5t versus 2t	11 (92%)	10 (83%)	12 (100%)

DLPFC, dorsolateral prefrontal cortex.

the Arrows and 2t conditions, but not in the 5t condition. These two subjects responded correctly to 56% and 54% of the 5t trials, and a large proportion of their errors (62% and 42%) were failures to respond within the time allotted. Given their performance in the Arrows and 2t conditions, we determined that they may have been responding too slowly in the 5t condition but were engaged in the task nonetheless. On this basis, we did not exclude them from further analyses.

Schizophrenic subjects made significantly more errors than normal subjects ($F[1, 20] = 10.85$, $p = .004$), and there was a significant interaction of condition by diagnosis ($F[2, 40] = 14.24$, $p = .0001$), with schizophrenic subjects making significantly more errors than normal subjects in both WM conditions but not in the Arrows condition. Due to a trigger malfunction, RT data is missing for one schizophrenic and three normal subjects. Schizophrenic subjects had significantly longer RTs than normal subjects ($F[1, 16] = 12.57$, $p = .003$). There was no interaction between condition and diagnosis. Both error rate and mean RT increased significantly as a function of condition from Arrows to 2t to 5t in both groups, as indicated by planned linear contrasts (error rate: normal: $F[1, 19] = 12.98$, $p = .002$; schizophrenic: $F[1, 23] = 24.70$, $p = .0001$; RT: normal: $F[1, 13] = 140.68$, $p = .0001$; schizophrenic: $F[1, 21] = 124.93$, $p = .0001$).

Group Comparisons of Activation

Table 3 reports the number of subjects showing significant activation, divided by group, comparison, and hemisphere. In the 5t versus Arrows comparison, all of the normal and 11 of the 12 schizophrenic subjects showed significant DLPFC activation (either hemisphere). In the 5t versus 2t comparison, 8 of the 10 normal subjects and all of the schizophrenic subjects showed significant DLPFC activation. Table 4 reports means, SDs, and group comparison results for each of the activation indices. In the left DLPFC, schizophrenic subjects showed significantly greater activation than normal subjects in both comparisons, using the max voxel index. Group comparisons of left DLPFC activation using the active mean and mean ROI indices were generally consistent with this finding.

Table 4. Means, SDs, and t-Tests of Group Differences in Activation (findings are presented for each activation index within each ROI mask for the 5t versus Arrows and 5t versus 2t comparisons)

		Left DLPFC				Right DLPFC				Control			
		Max voxel	ROI mean	Active mean	Percent voxels	Max voxel	ROI mean	Active mean	Percent voxels	Max voxel	ROI mean	Active mean	Percent voxels
5t vs. A	N	.30 ± .14	−.02 ± .06	.24 ± .08	4.4 ± 4.9	.37 ± .11	.02 ± .06	.27 ± .03	7.9 ± 10.3	.59 ± .11	.006 ± .04	.30 ± .02	6.2 ± 4.8
	SZ	.45 ± .13	.04 ± .04	.29 ± .05	8.5 ± 2.8	.37 ± .15	.05 ± .08	.27 ± .07	10.7 ± 12.0	.56 ± .15	.02 ± .04	.30 ± .04	6.7 ± 5.4
	t	2.50	2.96	1.90	1.42	0.08	0.81	0.06	0.59	0.59	0.97	0.08	0.22
	p	.02[b]	.008[b]	.07[a]	.17	.94	.43	.95	.56	.56	.35	.94	.83
5t vs. 2t	N	.22 ± .06	−.003 ± .04	.21 ± .04	.59 ± 1.0	.27 ± .07	.01 ± .06	.24 ± .04	2.7 ± 4.8	.44 ± .12	.01 ± .04	.27 ± .02	2.5 ± 3.1
	SZ	.33 ± .14	.03 ± .06	.25 ± .04	6.6 ± 11.8	.32 ± .15	.02 ± .08	.26 ± .05	8.5 ± 14.4	.46 ± .16	.02 ± .05	.27 ± .03	4.8 ± 5.1
	t	2.23	1.39	2.57	1.60	1.02	0.41	0.93	1.21	0.33	0.65	0.10	1.22
	p	.04[b]	.18	.02[b]	.12	.32	.69	.37	.24	.74	.52	.92	.24

[a] statistical trend at $p \leq .10$
[b] significant at $p \leq .05$
DLPFC, dorsolateral prefrontal cortex; ROI, region of interest; vs., versus; A, Arrows.

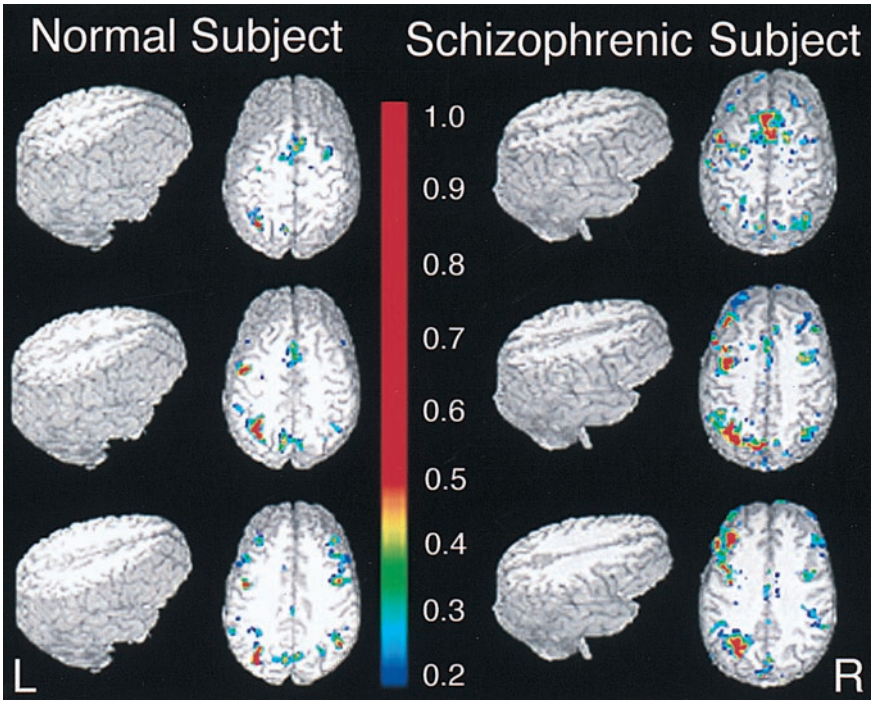

Figure 1. Slice planes and anatomical slices (with the colorized correlation maps of the 5t versus Arrows comparison superimposed on each slice) showing activated voxels in the DLPFC and other regions for a normal and a schizophrenic subject.

Schizophrenic subjects did not differ significantly from normal subjects in the proportion of left DLPFC voxels activated (percentage of voxel index). This index showed a high degree of variability. Schizophrenic and normal subjects were not different in activation in the right DLPFC or control ROI masks in either comparison on any index. Figure 1 shows brain slices with DLPFC activation for two subjects.

Figure 2 depicts left versus right DLPFC activation for each subject. The lateralization of DLPFC activation, as measured by the max voxel index, was quantified by the following equation: (right − left)/(right + left). Lateralization was significantly different in the schizophrenic versus the normal group in the 5t versus Arrows comparison ($t = 3.25$, $p = .004$) and showed a trend in the 5t versus 2t comparison ($t = 1.87$, $p = .08$). Whereas normal subjects tended to show greater right than left DLPFC activation in both comparisons (5t versus Arrows: $t = 1.92$, $p = .09$; 5t versus 2t: $t = 2.28$, $p = .05$), schizophrenic subjects tended to show greater activation in the left than the right DLPFC in the 5t versus Arrows comparison ($t = 2.10$, $p = .06$), but not in the 5t versus 2t comparison ($t = .14$, $p = .89$). Excluding the one left-handed schizophrenic subject from these analyses did not change the findings.

Relation of DLPFC Activation to Task Performance

Using analyses of covariance with an interaction of group with the covariate (max voxel), we compared the relation of activation in the 5t versus Arrows comparison with task performance in the subject groups. The relation of left DLPFC activation to errors in all three conditions was significantly different for the schizophrenic versus the normal group (5t: $F[1, 18] = 4.33$, $p = .05$; 2t: $F[1, 18] = 8.81$, $p = .008$; Arrows: $F[1, 18] = 4.94$, $p = .04$). In the schizophrenic group, left DLPFC activation was

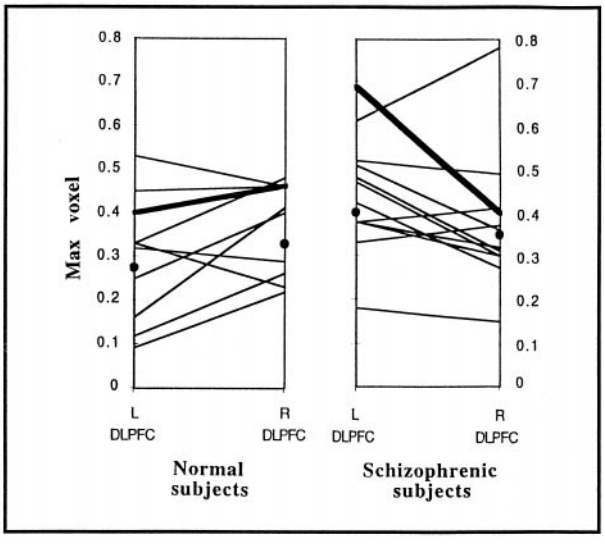

Figure 2. Left (L) and right (R) dorsolateral prefrontal cortex (DLPFC) activation in the 5t versus Arrows comparison, as measured by the max voxel index. Each line represents a subject. The two thicker lines represent the subjects whose brain slices are shown in Figure 1. The black circles on the y-axes represent group means.

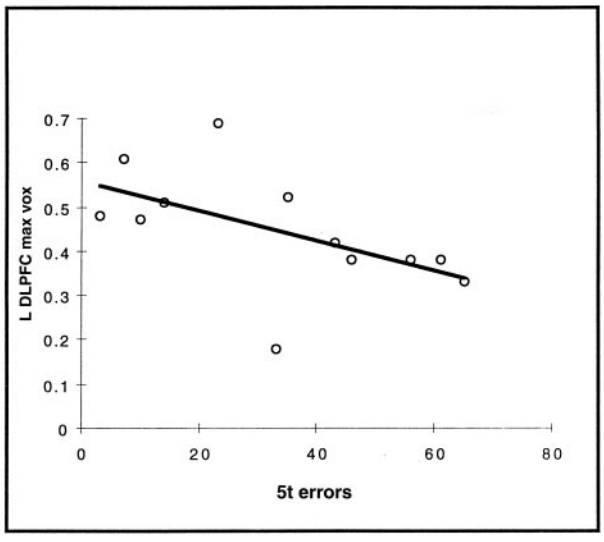

Figure 3. Scatter plot and regression line for the schizophrenic group, illustrating the relation of 5t errors to left (L) dorsolateral prefrontal cortex (DLPFC) activation (as measured by the max voxel index in the 5t versus Arrows comparison).

inversely correlated, with errors in all three conditions (Arrows: rho = −.65, $p = .03$; 2t: rho = −.73, $p = .01$; 5t: rho = −.64, $p = .03$). In the normal group, left DLPFC activation was not related to errors (Arrows: rho = .15, $p = .66$; 2t: rho = .20, $p = .54$; 5t: rho = .25, $p = .45$). There were no significant relations between errors and activation in the right DLPFC or in the control ROI mask in either group. RT was not related to activation in any of the ROI masks in either group, and analyses of covariance did not reveal group differences in the relations of RT to activation in any of the ROI masks. Figure 3 plots the relation of 5t errors to left DLPFC activation in the schizophrenic group.

Analysis of Control Variables

Because the activation indices were derived from correlation coefficients, the finding of increased left DLPFC activation in the schizophrenic group could reflect either a greater change in signal intensity in the high WM load condition relative to the baseline condition (Arrows or 2t) or a decreased error variance of signal intensity. To distinguish between these possibilities, for each subject we computed the SD of signal intensity for the repeated measurements taken within each condition for each ROI mask. There were no significant group differences in error variance. Thus, the group difference in left DLPFC activation reflects a difference in the magnitude of signal intensity change.

With regard to the motion index, schizophrenic and normal subjects were not significantly different within any condition or across all of the scans ($t = .04$, $p = .97$). When we correlated the motion index with activation in the 5t versus Arrows comparison, we found no significant correlations in any ROI mask in the schizophrenic group. In the normal group, there was a significant inverse correlation in the control mask (rho = −.66, $p = .05$), but not in the DLPFC masks (left DLPFC: rho = .13, $p = .70$; right DLPFC: rho = −.25, $p = .46$). Although the schizophrenic and normal groups were not different with regard to the motion index, we cannot rule out the possibility that motion may have led to increased variance of signal intensity and therefore decreased the power to detect significant activation in the control mask of the normal group. Visual inspection of the motion-corrected data did not reveal significantly activated voxels at the edge of the brain that might suggest motion artifact in either group.

Years of education and estimated verbal IQ were not correlated with activation in the 5t versus Arrows comparison in any ROI mask in either group. Schizophrenic subjects taking conventional antipsychotics did not differ in activation in any ROI mask from those taking atypical antipsychotics. Negative symptoms showed a trend toward being inversely related to left DLPFC activation (rho = −.51, $p = .09$), but not to activation in the right DLPFC or control masks. Neither general psychopathology (BPRS) nor positive symptoms were related to activation in any of the ROI masks.

Discussion

In the current study, schizophrenic subjects activated the right DLPFC as much as normal subjects and the left DLPFC significantly more than normal subjects during performance of a WM task. These findings contrast with the literature that demonstrates task-related hypofrontality in schizophrenia. We propose that this difference is a function of task parameters, including the level of task demand, the requirement that subjects adopt a DLPFC-mediated strategy, the expectation that subjects respond to every item, and the reward for correct responses.

In previous studies, poor effort or motivation, or the use of a task that was too demanding, may have contributed to poor task performance and hypofrontality in the schizophrenic group. In the current study, the level of task demand (WM load) was chosen to be sufficiently challenging but not overwhelming for the schizophrenic group. In addition, because the task constrains strategy—correct responses are predicated on the maintenance of an internal representation of the targets during the stimulus trials—the better-than-chance performance of the schizophrenic subjects indicates that they engaged WM. It may be this "holding on-line" that critically depends on the DLPFC.

The task demand to respond to every item may have ensured that subjects engaged WM and therefore the DLPFC for the duration of the scanning period. Finally, subjects were rewarded for correct responses. Although we did not compare rewarded with unrewarded performance, we hypothesize that the reward enhanced DLPFC activation, task performance, and motivation. In monkeys performing spatial-delayed response tasks, DLPFC neurons involved in retaining information in WM are responsive to reward; they show more activity during delay periods when a preferred reward is anticipated than when it is not (Watanabe 1996).

The finding of equal or increased task-related DLPFC activation in schizophrenic versus normal subjects is not unprecedented. A previous study reported equal or greater left DLPFC activation in schizophrenic subjects during accurate performance of a verbal fluency task (Frith et al 1995). In a recent study of word-stem cued recall, schizophrenic subjects showed decreased right hippocampal but increased right prefrontal activation (Heckers et al 1998). Their performance indicated that the experimental manipulation was effective and that they were able to perform the tasks. In the current study, schizophrenic subjects performed significantly worse than normal subjects but significantly better than chance. Both subject groups showed the expected increments in error rate and RT across the three conditions of increasing WM load. Taken together, these findings highlight the importance of measuring performance to ensure that subjects are engaged in the task, able to perform it accurately, and responsive to the experimental manipulations.

The current findings raise questions about the relation of activation to task demand. Schizophrenic subjects performed significantly worse than normal subjects but showed increased activation of the left DLPFC. Their error rates and RT suggest that they worked longer and harder than normal subjects to accomplish the same task. Their increased activation may reflect this increased demand. This hypothesis is consistent with recent findings in normal subjects of increased DLPFC activation in response to increased WM demands (Barch et al 1997; Braver et al 1997). Within the schizophrenic group, however, increased error rate (suggesting increased demand) was associated with decreased left DLPFC activation. This finding seems to contradict the hypothesis that increased WM demands lead to greater DLPFC activation. One possible explanation for this seeming contradiction is that DLPFC activation may reflect WM demand only up to the point at which the demands begin to outstrip WM capacity. This is supported by the recent finding that DLPFC activation and task performance decline when processing demands are excessive (Goldberg et al 1998). In the schizophrenic subjects who made the most errors, the WM demands may have been excessive. In these subjects, decreased activation and performance may reflect greater DLPFC dysfunction, which renders it less able to subserve WM. For the normal subjects, who performed near ceiling levels with regard to errors, there was no relation between performance and activation, which may reflect this restriction of range.

This hypothesized nonlinear relationship between DLPFC activation and WM demand leads us to speculate about our findings had we used a higher WM load (e.g., six or seven targets). The higher WM load may have been too demanding for schizophrenic subjects, resulting in a breakdown of their performance and hypofrontality, relative to normal subjects. For the normal subjects, the increased demand may have made the task more challenging but not overwhelming, leading to increased errors and increased DLPFC activation. Clearly, the relation of activation to performance and task demand is complex, especially in the context of pathology. It may involve a number of variables (i.e., the possibility of recruiting compensatory neural circuitry) that the current study did not address.

If the subject groups were matched for WM performance, one might expect that they would show equal DLPFC activation. Although this type of matching was not possible in the current study, on a posthoc basis, we exploited the fact that the schizophrenic subjects' performances in the 2t condition were closer to the normal subjects' performances in the 5t condition than were their performances in the 5t condition. The groups were matched for RT, but schizophrenic subjects still made significantly more errors ($t = 2.07$, $p = .05$). We compared activation (max voxel) for schizophrenic subjects in the 2t versus Arrows comparison with that of normal subjects in the 5t versus Arrows comparison. Schizophrenic subjects were not different from normal subjects in right or left DLPFC activation and activated the left and right DLPFC equally. This is consistent with the hypothesis that the schizophrenic group's greater recruitment of the left DLPFC in the 5t versus Arrows comparison reflects increased WM demands.

Schizophrenic and normal subjects showed a different pattern of lateralized DLPFC activation. Consistent with our previous study, normal subjects activated the right more than the left DLPFC in both comparisons, although in the previous study this observation was not quantified (Manoach et al 1997). Schizophrenic subjects, in contrast, showed left more than right DLPFC activation in one comparison and did not show laterality differences in the second. These findings, although intriguing, were not anticipated and need to be replicated. They may reflect the use of different strategies to represent the targets in the two groups or, as proposed above, increased WM demands

for the schizophrenic subjects. The reason that increased demand may be associated with greater left, but not right or bilateral DLPFC activation in the schizophrenic group is unclear. It may be specific to the task employed. It would be interesting to determine whether normal subjects would also show increased left DLPFC activation with a higher WM load.

Several additional factors must be considered in evaluating the finding of equal or greater DLPFC activation in schizophrenic versus normal subjects in relation to the literature that demonstrates task-related hypofrontality. Although several previous studies have tested acutely ill inpatients (Berman et al 1986; Rubin et al 1991; Weinberger et al 1986), the current sample consisted of chronic outpatients with minimal to moderate symptomatology. Hypofrontality, however, has also been demonstrated in inpatients who were similar to the current sample with regard to symptom ratings (PANSS positive and negative) but had a shorter duration of illness (Callicott et al 1998) and in schizophrenic outpatients (symptom ratings and duration of illness were not presented) (Yurgelun-Todd et al 1996). Nor are medication differences likely to account for the discrepant findings. Task-related hypofrontality has been observed in schizophrenic subjects taking antipsychotics, either conventional or atypical, and in unmedicated and neuroleptic-naive subjects (Andreasen et al 1992; Berman et al 1986; Callicott et al 1998; Weinberger et al 1986). In the current study, subjects taking conventional versus atypical antipsychotics did not differ with regard to activation; however, this subgroup comparison was limited by lack of power. It is important to note that the groups were not matched for years of education or estimated verbal IQ; however, neither variable was correlated with activation in either group. Subject groups did not differ with regard to motion, and motion was not related to DLPFC activation in either group. Finally, although a task-components analysis is beyond the scope of this paper, it is possible that the SIRP differs in critical components from tasks employed in previous studies. The performance measures, however, strongly suggest that the SIRP taps an aspect of WM in which schizophrenic patients are deficient. Hypofrontality has been demonstrated during performance of a range of tasks that require WM (Andreasen et al 1992; Callicott et al 1998; Weinberger et al 1986).

The nature of WM dysfunction in schizophrenia remains unclear. Do the performance and activation differences of schizophrenic subjects reflect a quantitatively less efficient neural system or a qualitative abnormality? Do schizophrenic subjects activate the same WM circuitry, or do they compensate for dysfunction by activating different DLPFC subregions and WM circuitry? We were not able to address these issues in the current study. In ongoing work, we are examining activation differences in DLPFC subregions and in other brain regions involved in WM (Manoach et al 1998).

Although this study did not demonstrate hypofrontality, prefrontal dysfunction remains a meaningful explanatory construct in schizophrenia. Findings from neuropsychological, eye movement, and clinical studies implicate prefrontal dysfunction in schizophrenia. We hypothesize that the performance and activation differences reported here are another manifestation of prefrontal dysfunction. They reflect inefficient functioning of the neural circuitry involved in WM.

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