

Relation of Prefrontal Cortex Dysfunction to Working Memory and Symptoms in Schizophrenia

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Objective: The dorsolateral prefrontal cortex has been implicated in both working memory and the pathophysiology of schizophrenia. A relationship among dorsolateral prefrontal cortex activity, working memory dysfunction, and symptoms in schizophrenia has not been firmly established, partly because of generalized cognitive impairments in patients and task complexity. Using tasks that parametrically manipulated working memory load, the authors tested three hypotheses: 1) patients with schizophrenia differ in prefrontal activity only when behavioral performance differentiates them from healthy comparison subjects, 2) dorsolateral prefrontal cortex dysfunction is associated with poorer task performance, and 3) dorsolateral prefrontal cortex dysfunction is associated with cognitive disorganization but not negative or positive symptoms.

Method: Seventeen conventionally medicated patients with schizophrenia and 16 healthy comparison subjects underwent functional magnetic resonance imaging while performing multiple levels of the "n-back" sequential-letter working memory task.

Results: Patients with schizophrenia showed a deficit in physiological activation of the right dorsolateral prefrontal cortex (Brodmann's area 46/9) in the context of normal task-dependent activity in other regions, but only under the condition that distinguished them from comparison subjects on task performance. Patients with greater dorsolateral prefrontal cortex dysfunction performed more poorly. Dorsolateral prefrontal cortex dysfunction was selectively associated with disorganization symptoms.

Conclusions: These results are consistent with the hypotheses that working memory dysfunction in patients with schizophrenia is caused by a disturbance of the dorsolateral prefrontal cortex and that this disturbance is selectively associated with cognitive disorganization. Further, the pattern of behavioral performance suggests that dorsolateral prefrontal cortex dysfunction does not reflect a deficit in the maintenance of stimulus representations per se but points to deficits in more associative components of working memory.

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Schizophrenia has long been considered a disease of brain function that is reflected in a host of cognitive impairments in addition to the classic symptoms on which the diagnosis is based. For example, patients with schizophrenia show a range of cognitive deficits, particularly in measures of memory and executive functions (1), and differences in brain structure (2) and functional activity in regions thought to support such functions (3). Emphasis has been placed on the dorsolateral prefrontal cortex and its relation to working memory (3–6), a set of cognitive processes involved in actively maintaining and manipulating information in the mind in order to guide behavior (e.g., reference 7) and critical to high-level cognition (e.g., language, problem-solving, and reasoning). The relevance of working memory dysfunction to schizophrenia is evident in aspects of its symptoms, including formal thought disorder (8) and attentional disturbances (9–12), as might be predicted given the role of working memory in aspects of attention and goal-directed behavior. Accordingly, several

behavioral studies have pointed to links between dorsolateral prefrontal cortex dysfunction, working memory, and cognitive disorganization, reflected in symptoms of poor attention and conceptual disorganization (10, 11, 13, 14).

The dorsolateral prefrontal cortex has been implicated in both working memory and the pathophysiology of schizophrenia. Evidence for the role of the dorsolateral prefrontal cortex in working memory comes from a variety of clinical and experimental domains, including human neuropsychological and cognitive psychological studies (7), brain lesion and functional brain imaging studies (15–17), and lesion and physiological studies in nonhuman primates (6, 18). Evidence for a role of the dorsolateral prefrontal cortex in the pathophysiology of schizophrenia also comes from a variety of domains. For example, patients typically show deficits on tests sensitive to frontal lobe damage, such as the Wisconsin Card Sorting Task (19), and on the Stroop (11) and delayed-response tasks (20, 21). Studies using brain imaging techniques have also

demonstrated structural (2) and resting (22) functional abnormalities of the dorsolateral prefrontal cortex. Resting studies of brain activity have yielded mixed findings regarding the dorsolateral prefrontal cortex and schizophrenia, but more recent studies using functional neuroimaging methods coupled with neuropsychological or cognitive psychological tasks (4, 23, 24) have more reliably demonstrated evidence of dorsolateral prefrontal cortex dysfunction in subjects with schizophrenia.

Although considerable evidence implicates the dorsolateral prefrontal cortex in the pathophysiology of schizophrenia, a direct link between working memory dysfunction and deficits in brain activity remains elusive. This is, in part, because a number of functional neuroimaging studies of schizophrenia that ostensibly focus on working memory suffer from several important limitations.

First, much of the research has used experimental tasks such as the Wisconsin Card Sorting Task because of their sensitivity to frontal lobe function in traditional neuropsychological testing. Although these tasks clearly tap working memory, they engage other cognitive processes (e.g., learning, reinforcement) in addition to those typically considered central to working memory. The use of such tasks has been an important step in identifying specific cognitive processes and brain regions that may be disturbed in schizophrenia, but their complexity makes it difficult to disentangle working memory from other cognitive processes, thereby making it difficult to determine links between working memory deficits and prefrontal dysfunction in schizophrenia. The use of such complex tasks also makes it difficult to choose appropriate control tasks for use in “subtractive” image analysis methodology, further complicating inferences that can be drawn regarding working memory deficits and brain activity (25).

A second issue concerns the interpretation of activation differences in the face of group differences in task performance. It has been argued that, since patients with schizophrenia generally perform poorly on many cognitive tasks (26), hypofrontality or other abnormal task-evoked brain activity reflects a generalized secondary phenomenon or deficit, such as inattention or lack of engagement, and that such activation differences are merely “artifacts” of these nonspecific factors (27, 28) (compare with reference 29).

The primary aim of the present study was to build on previous findings and begin addressing these limitations by exploiting the advantages of functional magnetic resonance imaging (fMRI) and parametrically manipulating working memory load. By varying working memory load in a graded fashion, it becomes possible to selectively identify the brain circuitry supporting working memory in healthy subjects in a “dose-response” fashion. Thus, we can evaluate dysfunction within this circuitry in patients with schizophrenia by assessing neural activity at multiple levels of task demand and behavioral performance. Parametric manipulation has been shown to evoke graded changes in neural activity associated with working mem-

ory (15, 16, 30) and, more recently, has been shown to differentiate patients with schizophrenia from healthy subjects during both working memory (31) and retrieval from long-term memory (32).

We acquired fMRI data while patients with schizophrenia and healthy comparison subjects performed several levels of the “n-back” task, which we (15, 16) and others (30) have shown both systematically manipulates behavioral performance associated with verbal working memory and activates the cortical circuitry underlying verbal working memory, including the dorsolateral prefrontal cortex. We predicted that if working memory and dorsolateral prefrontal cortex dysfunction are functionally linked, patients and healthy comparison subjects would differ most in dorsolateral prefrontal cortex activation when they also differed in task performance. In contrast, we predicted that brain regions supporting other aspects of task performance that are not critical to working memory function (e.g., stimulus encoding or response execution) would not differentiate the groups, providing a critical “internal activation standard” (33). Finally, we predicted that dorsolateral prefrontal cortex dysfunction would correlate selectively with cognitive disorganization and that regions not showing activation deficits related to working memory would not show such a relationship.

Method

Participants

Participants were 17 clinically stable outpatients diagnosed with schizophrenia and 16 demographically matched healthy comparison subjects recruited from the community (Table 1). Eleven of the 17 patients and 10 of the 16 comparison subjects were men; six patients and six comparison subjects were women. To reduce the heterogeneity of the patient group, only patients who had been maintained on fixed doses of conventional injectable neuroleptics for at least 2 months before the study were included, and most participated within 5 days before the end of their injection cycle. Medical record review and structured clinical interview (with the Structured Clinical Interview for DSM-IV [SCID] [35]), conducted by a Ph.D.-level clinical psychologist (W.M.P.) and/or a trained research assistant, confirmed DSM-IV diagnoses of schizophrenia; absence of psychiatric symptoms in comparison subjects was also confirmed by the SCID.

The patients’ clinical state was assessed by using the Positive and Negative Syndrome Scale (34) on the day of testing. Ratings were completed either by a Ph.D.-level clinical psychologist (W.M.P.) or a trained researcher who regularly participated in training and reliability sessions. Symptoms were grouped into three “syndromes” according to the three factors suggested by Liddle (36)—reality distortion, poverty, and disorganization (Table 1). Intraclass correlations (37) established for interrater reliability during reliability sessions were 0.95, 0.95, and 0.94 for reality distortion, poverty, and disorganization, respectively.

All participants were right-handed, and none had a history of brain trauma, seizure disorder, ECT, mental retardation, or substance abuse or dependence within the past 6 months. All participants were paid for their participation. Before experimental sessions, patients were acclimated in an MRI simulator for at least 15 minutes, and all participants practiced the tasks until it was evident that they understood the instructions. Practice also served to

TABLE 1. Demographic Characteristics of Patients With Schizophrenia and Healthy Comparison Subjects Participating in a Functional Magnetic Resonance Imaging Study of Working Memory

Characteristic ^a	Patients (N=17)			Comparison Subjects (N=16)		
	Mean	SD	Range	Mean	SD	Range
Age (years)	36.5	7.5	24–51	36.5	6.9	26–47
Education	13.6	2.2	—	15.0	2.4	—
Parental education (years) ^b	13.0	2.3	—	13.3	2.7	—
Mean age at onset (years)	22.6	4.0	—			
Duration of illness (years)	13.9	8.4	—			
Schizophrenia symptom syndrome ^c						
Reality distortion	2.64	0.84	1.3–4.0			
Poverty	2.40	0.62	1.2–3.4			
Disorganization	2.21	0.68	1.0–3.3			

^a Patients and healthy comparison subjects did not differ on any demographic variable ($t < 1.80$, $df = 16$, $p > 0.08$).

^b Averaged across mother's and father's education, neither of which significantly differed as a function of group ($t < 1.00$, $df = 31$, $p > 0.50$).

^c Symptom ratings from the Positive and Negative Syndrome Scale have been collapsed into three symptom syndromes described elsewhere (13, 14, 34, 36). Reality distortion (positive symptoms): hallucinations, delusions, unusual thought content; poverty (negative symptoms): blunted affect, emotional withdrawal, passive social avoidance, motor retardation, lack of spontaneity; and disorganization: conceptual disorganization, mannerisms and posturing, difficulty abstracting, poor attention.

reduce the influence of task-strategy development on brain activity. After complete description of the study, written informed consent was obtained from all participating subjects.

Tasks

Participants performed a sequential-letter memory task—the *n*-back task (15, 16). This task parametrically varied working memory load—0, 1, and 2 items for patients and 0, 1, 2, and 3 items for comparison subjects. Patients were not subjected to the 3-back task to minimize scanner time and reduce potential movement artifact. In the 0-back condition, the target was any letter that matched a prespecified letter (e.g., “X”). In the 1-back condition, the target was any letter that was identical to the one immediately preceding it (i.e., one trial back). In the 2-back and 3-back conditions, the target was any letter that was identical to the one present two and three trials back, respectively. Stimulus encoding and response demands are constant across conditions; only the requirements to maintain and update increasingly greater amounts of information at higher loads differ.

Pseudorandom sequences of single consonants were presented centrally on a visual display mounted in the scanner (500-msec duration, 3500-msec interstimulus interval). Subjects responded with a dominant-hand button press to each stimulus, pressing one button to targets (33% of trials) and another to nontargets. In each trial block, a number of stimuli were nontarget repeats that were included as foils (e.g., 1-back repeats in the 2-back task). Conditions were run in blocks of 72 seconds (18 stimuli) during which scans were acquired, with six blocks for each load condition. Order of task conditions was randomized across subjects.

Image Acquisition

Scanning took place in a conventional 1.5-T GE Signa whole-body scanner, and a standard radiofrequency head coil was used. Functional images were acquired in the axial plane by using a two-interleave T2*-weighted spiral-scan pulse sequence (TR=2000 msec, TE=35 msec, flip angle=80°, field of view=24 cm) (38) and were composed of isotropic voxels (3.75 mm³) acquired at 26 contiguous locations parallel to the anterior commissure-posterior commissure line. Scan acquisition was time-locked to each stimulus onset, and the duration of each scan spanned the entire 4-second duration of each trial. The first three trials of each block were discarded to allow for “loading” of working memory at the outset of the task. Structural images were obtained with a standard T1-weighted pulse sequence before functional scanning.

Task Performance Analysis

Reaction time and signal detection measures (39)—*d'* (sensitivity) and beta (response criterion)—characterized the pattern of behavioral responding, which is not adequately reflected in overall accuracy. To test the a priori hypothesis that patients would perform worse than comparison subjects only at higher load levels, planned one-tailed, between-group, pairwise comparisons were made at each working memory level.

Image Analysis

Following reconstruction, images were normalized to a common mean and movement-corrected by using six-parameter automated image registration (40). Each subject's structural images were then coregistered to a common reference by using 12-parameter automated image registration and smoothed by using a three-dimensional Gaussian filter (8-mm full width at half maximum) to accommodate between-subject differences in brain anatomy. Imaging data were analyzed with voxel-wise, mixed-model, two-group by three-load analyses of variance (ANOVAs) (subject= random factor). Follow-up contrasts of signal intensity in statistically identified regions were made by using between-group tests of linear and quadratic trend. A significance level of $p < 0.005$ and an 8-voxel three-dimensional contiguity (41) were used as thresholds for statistical maps. Anatomical localization of suprathreshold activity was determined by overlaying activation maps onto the reference structural image and transforming them into standard reporting coordinates (42) by using AFNI software (43).

A potential criticism of fMRI studies in schizophrenia is that increased movement among patients creates artifacts that impair detection of cortical activation. This seems unlikely in the present study because significant differences in activation were limited to specific cortical regions and a specific task condition. Nevertheless, we evaluated this possibility by analyzing each of the six incremental movement measures using group-by-load ANOVAs. A main effect of group emerged for the roll measure ($F = 6.96$, $df = 1, 31$, $p < 0.02$). Consequently, we conducted two additional pixel-wise group-by-load ANOVAs on the fMRI data: one excluded two patients who contributed most to group differences in movement; the second retained all subjects but excluded images during and immediately before and after any movement parameter exceeded two standard deviations above the mean of any measure for comparison subjects. No significant group differences remained in the movement measures, and image analyses for both movement mitigation approaches yielded a pattern of statistical results that was identical to those already described.

TABLE 2. Performance on Working Memory Task of 17 Patients With Schizophrenia and 16 Healthy Comparison Subjects as a Function of Memory Load^a

Performance Measure and Working Memory Load	Comparison Subjects		Patients	
	Mean	SD	Mean	SD
Reaction time (msec)				
0-back	572.0	103.2	657.4	114.4
1-back	696.9	135.9	768.7	187.1
2-back	819.8	150.0	897.6	197.6
3-back	888.4	185.6	—	—
Target-detection sensitivity (d')				
0-back	3.32	0.36	3.12	0.83
1-back	2.66	1.24	2.51	0.82
2-back	2.40	0.77	1.90	0.75
3-back	2.11	0.59	—	—
Response criterion (beta)				
0-back	4.24	2.03	3.13	2.33
1-back	2.94	1.97	3.07	2.47
2-back	3.06	1.73	2.01	1.51
3-back	2.97	2.27	—	—
Proportion of errors by trial type ^b				
Targets				
1-back	0.19	0.07	0.22	0.08
2-back	0.17	0.07	0.26	0.08
Foils				
1-back	0.16	0.18	0.25	0.17
2-back	0.12	0.18	0.22	0.18
Nonfoils				
1-back	0.08	0.06	0.18	0.07
2-back	0.11	0.16	0.09	0.02

^a Working memory was assessed with a sequential-letter task. In the 0-back condition, the target was any letter that matched a prespecified letter. In the 1-back condition, the target was any letter that was identical to the one immediately preceding it. In the 2-back condition, the target was any letter identical to the one two trials back. In the 3-back condition, the target was a letter identical to that three trials back; the patients with schizophrenia were not given the 3-back condition.

^b Foils on the 2-back task are 1-back matches; foils on the 1-back task are 2-back matches.

Results

Task Performance

Neither *d'* nor beta (Table 2) significantly differentiated the groups at the 0-back and 1-back loads, but both measures were significantly lower in patients than comparison subjects at the 2-back load ($t \geq 1.88$, $df=31$, $p < 0.04$). Thus, patients were less able than comparison subjects to detect targets accurately and were more willing to respond to stimuli as targets at the highest load. Also, the two groups exhibited an equivalent number of responses overall in that they showed an equal proportion of “no responses” at all load levels. Finally, reaction times were significantly longer for patients than comparison subjects at the 0-back level ($t=2.25$, $df=31$, $p < 0.02$), but the groups did not differ at the 1-back or 2-back levels.

Imaging Data

Voxel-wise group-by-load ANOVAs (Table 3) revealed significant load main effects in a network of regions previously shown to be engaged by verbally mediated working memory (Figure 1). All load main effects reflected mono-

TABLE 3. Brain Regions in 17 Patients With Schizophrenia and 16 Healthy Comparison Subjects That Showed Significant Clusters in Voxel-Wise ANOVAs of Group and Working Memory Load

Analysis and Region of Signal Change	Brodmann's Area	Coordinates ^a			z score ^b
		x	y	z	
Load main effect					
Middle frontal gyrus	6				
Right		27	2	47	4.43
Left		-25	2	57	3.65
Anterior cingulate gyrus	32	-2	16	10	4.34
Middle frontal gyrus	46/9				
Right		38	27	24	4.94
Left		-36	38	23	4.90
Inferior frontal gyrus	44				
Right		49	10	23	5.27
Left		-47	7	23	4.73
Parietal cortex	39/40				
Right		42	-56	38	4.94
Left		-37	-52	38	4.84
Insula	—				
Right		35	15	8	4.38
Left		-40	10	10	5.10
Thalamus	—	-2	-15	13	4.38
Group main effect					
Anterior cingulate gyrus	32	-14	42	15	2.93
Group-by-load interaction					
Right middle frontal gyrus	46/9	43	27	27	3.49

^a From the atlas of Talairach and Tournoux (42).

^b Determined from the voxel showing the maximal F value in each cluster.

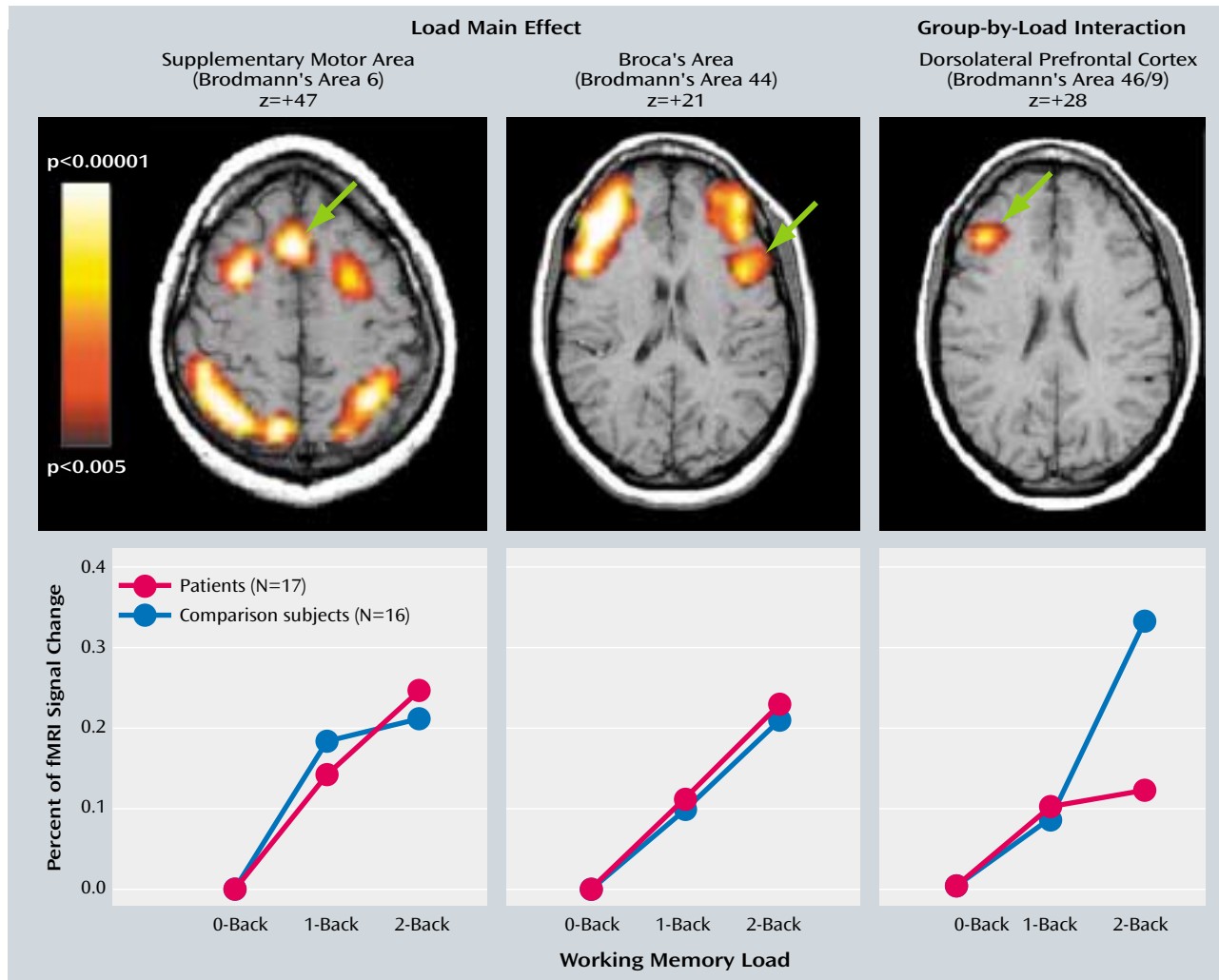
tonically increasing or decreasing activity; only increases are discussed here. The main effect of group revealed that activity in the subgenual region of the anterior cingulate gyrus was greater in patients than comparison subjects, but not as a function of load. More importantly, the predicted group-by-load interaction emerged in the dorsolateral prefrontal cortex (Figure 1). Compared with healthy subjects, patients with schizophrenia showed a negligible increase in signal intensity in the right dorsolateral prefrontal cortex at the 2-back compared with the 0-back and 1-back loads, but both groups showed equivalent increases from the 0-back to 1-back loads. Analysis of signal intensity within the right dorsolateral prefrontal cortex cluster yielded a significant interaction of group with both the linear ($t=3.67$, $df=31$, $p < 0.001$) and quadratic ($t=2.57$, $df=31$, $p < 0.02$) trends over load.

A second potential criticism is that poorer task performance by patients confounds interpretation of activation differences (44, 45); that is, patients may not activate the dorsolateral prefrontal cortex because they are not performing the task rather than because of any intrinsic dorsolateral prefrontal cortex dysfunction. The finding that the two groups did not differ in the number of no-response trials argues against this possibility.

Relationship Between Dorsolateral Prefrontal Cortex Activity and Task Performance

Correlations for each group separately between prefrontal cortex activity and measures of task performance, collapsed across working memory load levels, yielded a

FIGURE 1. Brain Regions of Patients With Schizophrenia and Healthy Comparison Subjects in Which Activity Increased Monotonically as a Function of Working Memory Load, Group-by-Load Interaction in Dorsolateral Prefrontal Cortex, and Change in Signal Intensity^a



^a The z values in the upper panel indicate the superior-inferior locations of the slices shown (according to the atlas of Talairach and Tournoux [42]) (left=right, right=left). The signal intensity values shown in the lower panel reflect the signal intensity averaged across all voxels in the statistically defined cluster. Working memory was assessed with a sequential-letter task. In the 0-back condition, the target was any letter that matched a prespecified letter. In the 1-back condition, the target was any letter that was identical to the one immediately preceding it. In the 2-back condition, the target was any letter identical to the one two trials back.

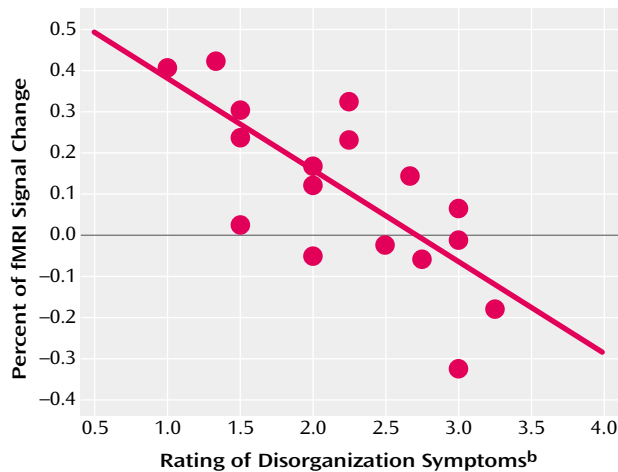
significant positive relationship with beta for the comparison subjects ($r=0.53$, $df=15$, $p<0.04$), but not the patients ($r=0.12$, $df=16$, $p>0.60$). This finding suggests that a more stringent response criterion was associated with increased prefrontal cortex signal intensity in the healthy subjects but not in the patients.

To demonstrate a link between dorsolateral prefrontal cortex dysfunction and target-detection sensitivity (d'), participants were grouped according to whether or not they exhibited increased right dorsolateral prefrontal cortex activity in the 2-back versus the 0-back condition. The change in d' across these levels was then assessed by using a one-tailed t test. No comparison subject showed less activity in the 2-back than in the 0-back condition; five of the 17 patients did. Patients with less activity at the 2-back

than the 0-back load showed significantly greater d' decrement (-1.78) than patients who showed activity increases from the 0-back to the 2-back load (-0.99) ($t=1.73$, $df=15$, $p=0.05$).

The fMRI data were also analyzed after matching the groups on behavioral performance (d')—0-back, 1-back, and 3-back levels for comparison subjects and 0-back, 1-back, and 2-back levels for patients. Under these conditions, no brain regions showed a significant group-by-load interaction at $p<0.005$ or at a more liberal threshold of $p<0.01$, providing additional evidence that group differences in task performance were associated with the observed group differences in dorsolateral prefrontal cortex activity.

FIGURE 2. Relationship Between Disorganization Symptoms and Change in Signal Intensity in Right Dorsolateral Prefrontal Cortex as a Function of Working Memory Load for 17 Patients With Schizophrenia^a



^a Working memory was assessed with a sequential-letter task. In the 0-back condition, the target was any letter that matched a pre-specified letter. In the 1-back condition, the target was any letter that was identical to the one immediately preceding it. In the 2-back condition, the target was any letter identical to the one two trials back. The signal change shown here is the percent change of the 2-back from the 0-back condition.

^b Includes conceptual disorganization, mannerisms and posturing, difficulty abstracting, and poor attention from the Positive and Negative Syndrome Scale (34).

Relationship Between Dorsolateral Prefrontal Cortex Activity and Symptoms

Correlation analyses conducted between the three symptom syndromes and fMRI signal change from 0-back to 2-back load levels in the right dorsolateral prefrontal cortex yielded a significant correlation only for disorganization ($r=-0.74$, $df=16$, $p<0.0007$) (Figure 2): increased disorganization was associated with decreased signal intensity change. This relationship was specific to the dorsolateral prefrontal cortex and disorganization; correlations between each of the three symptom syndromes and signal intensity change in supplementary motor and Broca's areas were not significant.

Discussion

Medicated patients with schizophrenia, compared with healthy subjects, failed to exhibit task-related activity increases in the dorsolateral prefrontal cortex at the highest level of working memory load, consistent with the hypothesis of working-memory-related dorsolateral prefrontal cortex dysfunction in schizophrenia. Additionally, the reduced dorsolateral prefrontal cortex activation was associated with both poorer task performance and cognitive disorganization symptoms and emerged only at a level of working memory load that distinguished patients from healthy subjects on task performance.

These results complement previous findings of dorsolateral prefrontal cortex dysfunction using the n-back task (4, 31, 41). However, the present study employed a parametric approach with larger samples and found significant differences between groups in brain activity only when behavioral performance distinguished between the groups. The difference in dorsolateral prefrontal cortex activity persisted after we controlled for differences that might arise from movement artifact and was not sustained after groups were matched on task performance, providing additional support for a relationship between dorsolateral prefrontal cortex activity and working memory deficits.

Of particular note is the finding that significant load-related group differences were observed only in the dorsolateral prefrontal cortex and not in other regions typically engaged during verbally mediated working memory, namely, Broca's area and the supplementary motor and posterior parietal cortices. This suggests that not all of the circuitry critical to verbal working memory is dysfunctional in patients, demonstrates some degree of specificity for dorsolateral prefrontal cortex dysfunction, and provides a critical "internal activation standard" (33). Further, the fact that the two groups did not differ on overall frequency of behavioral responding, even at the highest level of working memory load, minimizes the possibility that lack of behavioral engagement underlies the group differences in prefrontal activation. Given the entirety of findings, these results implicate a strong link between dorsolateral prefrontal cortex dysfunction and working memory deficits in conventionally medicated patients with schizophrenia. They also point to an association between cognitive disorganization and dorsolateral prefrontal cortex dysfunction.

What might be the particular aspect of working memory subserved by the dorsolateral prefrontal cortex and deficient in patients with schizophrenia? According to an influential theory (7), working memory comprises three dissociable components subserved by different but interacting cortical regions: a modality-specific buffer for storage of phonological codes (subserved largely by parietal regions), rehearsal processes to refresh these codes (subserved largely by the supplemental motor and Broca's areas), and a set of executive or associative processes to manipulate the buffer's contents in the service of higher cognitive functions (subserved by the dorsolateral prefrontal cortex). In view of this model, the absence of group differences in parietal and Broca's/supplementary motor area activation suggests that pure storage and rehearsal components are not deficient in patients. Instead, more executive functions supported by the dorsolateral prefrontal cortex are implicated.

Detailed consideration of the pattern of task performance can further illuminate potential working memory component-processing deficits implied by the imaging data. Specifically, both the patient and comparison groups showed a higher proportion of false alarms on foil trials

(i.e., nontarget repeats) compared with nonfoil (i.e., non-repeat) trials and did not differ in error rates on target trials (Table 2). This suggests that patients adequately maintained trace representations of stimulus identity and points to a potential associative deficit—coding or maintaining sequential order information. The 2-back task requires maintaining the target-set n-back stimulus representations and coding and maintaining temporal position in the sequence, but the 0-back and 1-back tasks do not, since only a single letter must be kept in mind at any given time.

The groups showed equal levels of dorsolateral prefrontal cortex activity and performance at load levels that did not require temporal sequencing but differed in both when sequencing was required. This overall pattern is consistent with the hypothesis that maintenance and rehearsal are intact in schizophrenia but more associative processes (e.g., temporal coding) are dysfunctional, reflected in patients' impaired ability to make appropriate use of the maintained information to guide behavior. This suggestion is also consistent with findings pointing to a role for the right dorsolateral prefrontal cortex in maintenance of not only the intrinsic content of stimuli but also the temporal order of their occurrence (46).

An alternative but not mutually exclusive interpretation of the observed dorsolateral prefrontal cortex deficit is that it reflects "capacity constraints." That is, as working memory load increases and more attentional resources are required to maintain and manipulate the contents of working memory, capacity limitations are approached and expressed in impaired performance (30, 31, 45). Thus, patients may reach capacity limitations at lower load levels than healthy subjects, manifest by an inability to enhance dorsolateral prefrontal cortex activity as the limit is approached or exceeded.

Recent observations using modern neuroanatomical techniques to examine postmortem brain tissue in schizophrenia (2, 47, 48) have confirmed the presence of dorsolateral prefrontal cortex abnormalities that may contribute to the dorsolateral prefrontal cortex dysfunction described here. Among these findings are observations of reduced cortical thickness and increased neuronal density, suggestive of a loss of neuropil in dorsolateral prefrontal cortex (2), and reduced thalamic innervation of dorsolateral prefrontal cortex layer-three pyramidal cells (47). In the light of our current finding of normal activation in the inferior frontal cortex of patients with schizophrenia, it is intriguing that a recent study (48) demonstrated that the increased cell density was specific to the dorsolateral prefrontal cortex (Brodmann's area 9) and that normal cell densities were observed in Brodmann's area 44. It is unclear whether these and other anatomical

findings reflect primary disturbances in the intrinsic circuitry of the dorsolateral prefrontal cortex, changes secondary to other factors such as altered thalamocortical connectivity, or both. However, these neuroanatomical data converge with results such as those of the present study to suggest that dorsolateral prefrontal cortex dysfunction is a reliable finding and may manifest its behavioral expression in impaired working memory function and disorganization.

The results of the present study differ in some ways from those of several previous studies. First, at least one study (20) observed a relationship between negative symptoms and working memory. Importantly, patients in this study were unmedicated, but all of the patients in the present study and our previous behavioral studies implicating a link between working memory and disorganization were receiving maintenance doses of conventional antipsychotic medications. This discrepancy may suggest that measurement of negative symptoms in unmedicated patients provides a purer measure of negative symptoms than measurement in medicated patients and enhances the ability to detect relationships among working memory, the prefrontal cortex, and negative symptoms. Additionally, the relationship between working memory and negative symptoms observed by Carter et al. (20) was obtained by using a spatial (rather than verbal) working memory task. Clarification of the relationship between prefrontal cortex activity and symptoms clearly requires additional study.

Second, although a task analysis points to deficits in temporal coding, maintenance of sequential-order information, or both, a study that explicitly tapped these functions (49) did not prompt activation in the dorsolateral prefrontal cortex, revealing instead patient hypoactivity in Broca's area. Among the critical task differences between these studies, however, is the constant requirement to update information over the course of a trial block in the present study, which was absent from the "span" tasks used by Stevens et al. (49) and which may account for the differences.

In summary, our findings point to a specific deficit in the right dorsolateral prefrontal cortex linked to working memory in patients with schizophrenia that is selectively associated with cognitive disorganization symptoms. Decomposition of task components suggests that dorsolateral prefrontal cortex dysfunction is associated with more executive aspects of working memory, such as coding of temporal order, rather than processes involved in maintenance of stimulus representations per se. Future studies using tasks designed to assess coding and maintenance of order information more systematically will be necessary to evaluate this hypothesis more thoroughly.

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