Selective Deficits in Prefrontal Cortex Function in Medication-Naive Patients With Schizophrenia

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Background: Previously we proposed that dorsolateral prefrontal cortex (PFC) supports a specific working memory (WM) subcomponent: the ability to represent and maintain context information necessary to guide appropriate task behavior. By context, we mean prior task-relevant information represented in such a form that it supports selection of the appropriate behavioral response. Furthermore, we hypothesized that WM deficits in schizophrenia reflect impaired context processing due to a disturbance in dorsolateral PFC. We use functional magnetic resonance imaging to examine PFC activation in medication-naive, first-episode patients with schizophrenia during a WM, task-isolating context processing.

Methods: Fourteen first-episode, medication-naive patients with schizophrenia and 12 controls similar in age, sex, and parental education underwent functional magnetic resonance imaging during performance of an A-X version of the Continuous Performance Test.

Results: Patients with schizophrenia demonstrated deficits in dorsolateral PFC activation in task conditions requiring context processing but showed intact activation of posterior and inferior PFC. In addition, patients demonstrated intact activation of the primary motor and somatosensory cortex in response to stimulus processing demands.

Conclusions: These results demonstrate selectivity in dorsolateral PFC dysfunction among medication-naive first-episode patients with schizophrenia, suggesting that a specific deficit in PFC function is present at illness onset, prior to the administration of medication or the most confounding effects of illness duration. Furthermore, these results are consistent with the hypothesis that WM deficits in patients with schizophrenia reflect an impairment in context processing due to a disturbance in dorsolateral PFC function.

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DISTURBANCES in prefrontal cortex (PFC) functioning have long been implicated in schizophrenia and have been linked to working memory (WM) deficits.[1] Working memory is typically defined as the ability to temporarily maintain and manipulate information on-line.[2] Several lines of research support a link between PFC and WM dysfunction in schizophrenia[3-19] (for contrasting evidence, see the articles by Manoach et al[17] and Fletcher et al[20]). However, many studies have examined large areas of PFC, combining subregions that may be functionally distinct.[9,13,15,16] Thus, it is not clear whether all or only certain subregions of PFC show disturbed patterns of cognition-related activation in schizophrenia. Additionally, most functional imaging studies have chosen tasks based on their sensitivity to frontal lobe dysfunction (eg, Wisconsin Card Sorting Test)[16,19] or used tasks that tap multiple components of WM,[9,14,15] making it difficult to determine which specific processes are disturbed in schizophrenia.

Considerable controversy exists about what functions specific regions of PFC carry out in support of WM. Several researchers have argued that ventral regions (ie, Brodmann area [BA] 44, BA 45, and BA 47) subserve pure maintenance functions, whereas dorsolateral (DL) PFC (ie, DLPFC; BA 46, BA 9) is involved in manipulating the contents of WM.[21-23] In contrast, Goldman-Rakic[24] has argued that DLPFC supports the maintenance of information. Our hypothesis regarding DLPFC function combines elements of both views. Specifically, we have proposed that DLPFC supports a subcomponent of WM: the ability to represent and maintain context information necessary to guide appropriate task behavior.[25,26] By context, we mean prior task-relevant information represented in a form that supports selection of the appropriate re-

PATIENTS AND METHODS

PARTICIPANTS

Participants were 12 healthy controls and 14 medication-naive first-episode patients with schizophrenia. Controls were recruited through advertisements and evaluated using the non-patient version of the Structured Clinical Interview for *DSM-III-R*.[33] All patients were neuroleptic naive and recruited if they were experiencing any type of psychotic symptom (ie, hallucination, delusion, thought disorder) and it was their first psychiatric hospitalization or contact with outpatient psychiatric services. Patients were scanned as soon as possible after initial contact, typically within 1 to 2 days. Patients were followed longitudinally and confirmed to have a diagnosis of schizophrenia 6 months after their participation in this study. Diagnoses were confirmed by diagnostic conference, including information from the Structured Clinical Interview for *DSM-III-R*,[33] administered by trained research personnel, and thorough medical record review. In addition, the Brief Psychiatric Rating Scale,[34] the Global Assessment Scale, and the Scales for the Assessment of Positive and Negative Symptoms were used to evaluate symptom severity (**Table 1**). Ratings were completed by trained research team personnel, blind to task performance, who regularly participated in evaluation sessions to insure reliability. All ratings were made within 1 week of testing.

Participants were excluded for (1) age (older than 50 years or younger than 14 years); (2) Wechsler Adult Intelligence Scale–Revised full scale IQ lower than 70; (3) non-English native language; (4) lifetime diagnosis of substance dependence or substance abuse within 1 month of testing; (5) neurologic disorders or family history of hereditary neurologic disorder; or (6) pregnancy. Potential controls were excluded if they had (1) lifetime history of axis I disorder or first order family history of a psychotic disorder or (2) treatment with any psychotropic medication within 6 months of testing. Controls were similar to patients regarding age, sex, race, and father's education (as a proxy for socioeconomic status). *t* Tests indicated that controls did not differ from patients with schizophrenia on any of these variables (Table 1). All participants were right-handed and signed informed consent forms in accordance with the University of Pittsburgh, Pittsburgh, Pa, institutional review board.

COGNITIVE TASK

Single letters were presented centrally on a visual display. Trials lasted 10 seconds and included a cue, a delay period, a probe, and an intertrial interval (ITI). Cue and probe durations were 0.5 seconds. In long delay trials, the cue-probe interval was 8 seconds, and the ITI was 1 second. In short delay trials this was reversed, with a 1-second cue-probe interval and an 8-second ITI to control general factors (eg, pace of the task). Subjects responded to every stimulus with their dominant hand, pressing one button for targets and an adjacent button for nontargets. Eleven patients and 8 controls performed the task continuously for blocks made up of 10 trials. The remaining 3 patients and 4 controls performed the task continuously for blocks of 12 trials. Between each block there was a brief delay, allowing the subject to rest, and the hemodynamic response to recover. Six blocks were run for each of the 2 delay conditions, pseudorandomly ordered to control for the confounding effects of time on task, head movement, and scanner drift.

IMAGE ACQUISITION

Scanning took place using a whole-body scanner (1.5T GE Signa; General Electric Medical Systems, Milwaukee, Wis) and standard head coil in the University of Pittsburgh Medical School, Pittsburgh, Pa, MR Research Center. Sixteen slices (3.75 mm^3 voxels) were acquired parallel to the anterior commissure-posterior commissure (AC-PC) line. Functional scans were acquired using a spiral-scan pulse sequence.[35] In 11 patients and 8 controls, we used a 2-shot spiral sequence (TR [time to repetition], 1250 milliseconds; TE [time to echo], 35 milliseconds; flip, 40°; field of view, 24 cm), with scanning synchronized with stimulus presentation so that a set of 16 slices was acquired 4 times during each 10-second trial (Figure 1). In the other 3 patients and 4 controls, we used a 4-shot spiral sequence (TR, 640 milliseconds; TE, 35 milliseconds; flip, 40°; field of view, 24 cm); which allowed 8 slices to be acquired every 2.5 seconds. Scanning was again synchronized with stimulus presentation so that 4 scans of 8 slice locations were acquired during each 10-second trial (Figure 1). A first set of 8 locations was scanned for 3 trials, followed by 2 additional sets of 8 different locations, each scanned for 3

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sponse. Context representations can include instructions, specific prior stimuli, or the result of processing a sequence of prior stimuli (eg, a sentence). Thus, we believe that DLPFC plays a role in manipulation by recoding information into context representations. However, we believe that context representations are also actively maintained in DLPFC, a hypothesis supported by prior imaging work.[27] We have also hypothesized that WM deficits in schizophrenia reflect impaired context processing due to disturbed DLPFC function.[26] In behavioral studies, we have observed a highly selective pattern of schizophrenic deficits in task conditions sensitive to context processing.[28-30] However, we have not yet determined whether context processing deficits in schizophrenia are associated with a selective disturbance in DLPFC function.

The current study, using functional magnetic resonance imaging (fMRI), examined PFC activation in medication-naive first-episode patients with schizophrenia during a WM task-isolating context processing: a version of the A-X Continuous Performance Test (AX-CPT).[25,27,29,30] In the AX-CPT, subjects are presented with a sequence of letters and instructed to respond to a prespecified probe (X) only if it follows a particular contextual cue (A). Target (A-X) trials occur frequently (70%), producing (1) a prepotent tendency to make a target response to an X, and (2) an expectancy to make a target response following an A. Thus, context processing can be selectively probed in 2 types of nontarget trials, B-X and A-Y (B and Y refer to the letters used other than A and X). In B-X trials, context is required to inhibit the prepotent tendency to make a target response to the X. In A-Y trials, the context creates an

trials. Slice acquisition order was counterbalanced across subjects and blocks. Individual subject analyses did not indicate differences between results with the 2- and 4-shot sequences, so data from these 2 sequences were combined in the analyses presented in the "Imaging Data" section. T1-weighted structural scans were performed in the same planes as the functional scans for anatomic localization and coregistration of images across subjects.

IMAGE ANALYSIS

Images were movement corrected using a 6-parameter rigid body translation, coregistered to a common reference brain using a 12-parameter algorithm[36] and smoothed using a 3-dimensional Gaussian filter (8-mm full with half maximum) to accommodate between-subject differences in anatomy.

DATA ANALYSIS

Reaction time (RT) and accuracy (normalized using an arcsine transformation[37]) for behavioral data acquired during scanning were analyzed using analyses of variance (ANOVAs) with group as a between-subject factor and trial type and delay as within-subject factors. We also examined a more specific measure of sensitivity to context, referred to as d'-context, which computes d'[38] from A-X hits and B-X false alarms. Since d'-context compares responses to X in the presence of contextual cues indicating a target response (A-X) with a nontarget response (B-X), it provides a more focused measure of sensitivity to context.

For the fMRI data, we conducted group analyses using voxel-wise ANOVAs with subject as a random factor, group as a between-subject factor (control vs patients), and both scan (scans 1-4 within each trial) and delay (short vs long) as within-subject factors. In theory, one could examine all possible main effects and interactions in this design. However, our a priori hypotheses focused on regions demonstrating 1 of the following 4 patterns. (1) The first pattern was a main effect of delay, designed to identify regions responding to the context memory manipulation, by identifying voxels demonstrating greater activity in the long- than short-delay condition. If a region demonstrated a main effect of delay, planned contrasts were conducted to confirm that this effect was significant for both controls and patients. (2) The second pattern was a group × delay

interaction. If a region demonstrated such an interaction, planned contrasts were conducted to confirm that the interaction reflected a significant delay effect in at least 1 of the groups. (3) The third pattern was a main effect of scan. This effect was designed to identify regions showing significant responses to motor and sensory processes, which should be transient events with a specific hemodynamic response shape. Thus, we only examined regions showing a main effect of scan, the activity of which also demonstrated an event-related time course that reflected greater signal during scans 2 and 3 than scans 1 and 4 (taking into account the well-characterized lag in hemodynamic response that results in peak activation occurring approximately 5 seconds after stimulus onset[39,40]). To identify such time courses, we conducted planned contrasts on voxels showing a main effect of scan using inverse quadratic contrast weights (–1, 1, 1, –1). The signal values for each of 4 scans are multiplied by their corresponding contrast weights and then summed for each subject. If activity during scans 2 and 3 is significantly greater than activity during scans 1 and 4, then the summed value is significantly greater than 0 (tested using a t test against 0).[41] As with the main effect of delay, additional planned contrasts were then conducted on any such region to confirm that the inverse quadratic effects of a scan were significant in both patients and controls. (4) The fourth pattern was a group × scan interaction, with planned contrasts conducted to confirm that the interaction reflected a significant scan effect in at least 1 of the groups. Voxel-wise statistical maps were generated for each pattern and then thresholded for significance using a cluster-size algorithm[42] that protects against an inflation of the false-positive rate with multiple comparisons. A cluster-size threshold of 8 voxels and a per-voxel α of .01 was chosen, corresponding to a corrected image-wise false-positive rate of 0.01. Regions showing such effects were overlaid onto the reference structural image and transformed to standard stereotactic space using computer software (Analysis of Functional NeuroImages; R.W. Cox, Medical College of Wisconsin, Milwaukee).[43] We also conducted individual subject analyses (using ANOVAs treating trial as a random factor) to locate regions showing a main effect of delay, using the same significance threshold as the group analyses. These analyses were conducted to insure that any failures to obtain PFC activation in the group analyses among patients did not reflect increased heterogeneity of the location of activation in PFC.

expectancy that an X will occur next, leading to a tendency to false alarm to the probe. Thus, the same failure to represent and maintain context should manifest as an increase in B-X false alarms but no change, or even a decrease, in A-Y false alarms. The B-Y trials serve as a control since performance is unaffected by context processing. We manipulated contextual memory demands by varying the delay between the cue and probe (**Figure 1**).[25,27,29,30] Our task design allowed us to provide internal activation standards among patients,[15] which are needed to establish the validity of fMRI findings in schizophrenia. Specifically, we used event-related methods to track the dynamics of activation during each trial (Figure 1) and identify sensory and motor regions that exhibited transient activation associated with stimulus presentation and/or response execution.

Based on prior work,[25,29,30] we first predicted that patients would show behavioral evidence of selective cognitive deficits involving the active maintenance of context. Second, we predicted that cognitive deficits in patients would manifest in the neuroimaging data as a failure to show increased activity in DLPFC during the long delay.[27] In contrast, we predicted that patients would show intact delay-related activation of posterior and inferior PFC (ie, BA 44, BA 45). This latter hypothesis was based on findings suggesting that patients with schizophrenia are not impaired while performing short-term memory tasks that primarily require verbal rehearsal of items,[29,31] a process commonly associated with the function of BA 44 and BA 45.[32] Lastly, we predicted that patients would show normal activation in motor and somatosensory regions associated with response demands,

Table 1. Clinical and Demographic Characteristics*

	Group	
Characteristic	Normal Controls (n = 12)	Patients With Schizophrenia (n = 14)
Age, y	24.5 (5.6)	23.6 (8.0)
Sex, M, %	75	57
Parent's education, y	16.2 (3.1)	15.5 (2.5)
Education, y	16.8 (3.0)	13.0 (1.6)
Global Assessment Scale	. . .	31.76 (4.70)
Total BPRS	. . .	60.2 (8.3)
SAPS Hallucinations	. . .	2.7 (1.7)
SAPS Delusions	. . .	3.6 (0.9)
SAPS Bizarre behavior	. . .	0.9 (1.3)
SAPS Thought disorder	. . .	3.1 (0.9)
SANS Affective flattening	. . .	2.7 (0.9)
SANS Alogia	. . .	2.6 (0.6)
SANS Avolition	. . .	3.2 (0.8)
SANS Anhedonia	. . .	3.6 (0.6)
SANS Attention	. . .	2.6 (1.0)

*Ellipses indicate not applicable; BPRS, Brief Psychiatric Rating Scale; SAPS, Scale for the Assessment of Positive Symptoms; and SANS, Scale for the Assessment of Negative Symptoms. Values are given as mean (SD) except where indicated.

providing evidence of intact basic somatosensory and motor processing.

RESULTS

BEHAVIORAL DATA

The accuracy of ANOVA (**Table 2**) did not reveal significant main effects of group ($F_{1,24}=2.18$, $P=.11$) or delay ($F_{1,24}=0.3$, $P>.10$) but did indicate a significant trial type main effect ($F_{3,72}=4.6$, $P=.005$), which was moderated by a group × trial type interaction ($F_{3,72}=3.49$, $P=.02$). As predicted, planned contrasts indicated that this interaction reflected (1) worse performance on B-X trials ($t_{24}=2.65$, $P=.01$) and (2) better performance on A-Y trials for patients ($t_{24}=2.96$, $P=.007$); and (3) no B-Y differences ($t_{24}=0.92$, $P=.37$). The RT ANOVA (Table 2) indicated main effects of group ($F_{1,24}=6.5$, $P=.02$; patients slower than controls), delay ($F_{1,24}=8.9$, $P=.006$; long delay slower), and trial type ($F_{3,72}=26.8$, $P<.001$). Again, the trial type main effect was moderated by a group × trial type interaction ($F_{3,72}=3.8$, $P<.01$). Planned contrasts indicated that this interaction reflected (1) slower B-X RTs for patients ($t_{24}=2.2$, $P=.037$), (2) no significant differences on A-Y RTs ($t_{24}=1.6$, $P=.12$), (3) slower B-X than A-Y RTs in patients ($t_{24}=2.6$, $P=.016$), and (4) slower A-Y than B-X RTs in controls ($t_{24}=2.6$, $P=.47$). The group × trial type × delay interactions for accuracy and RT did not reach significance. However, we did find the predicted interaction with delay in d′-context (Table 2). The d′-context ANOVA indicated main effects of group ($F_{1,24}=5.4$, $P=.029$) and delay ($F_{1,24}=18.1$, $P<.001$) and a group × delay interaction ($F_{1,24}=4.1$, $P=.05$). Planned contrasts indicated no significant differences between patients and controls at the short delay ($t_{24}=1.0$, $P=.33$) but significantly decreased d′-context among patients at the long delay ($t_{24}=3.2$, $P=.004$).
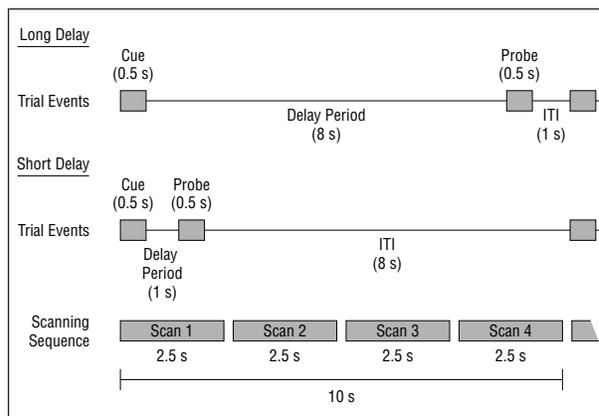

Figure 1. Experimental design. This diagram shows a timeline of the events occurring in each trial in the short and long delay blocks and the timing of scan acquisitions. ITI indicates intertrial interval.

Table 2. Behavioral Data*

	Normal Controls (n = 12)		Patients With Schizophrenia (n = 14)	
Behavior†	Short Delay	Long Delay	Short Delay	Long Delay
Errors				
A-X	2.6 (4.0)	8.3 (11.6)	1.6 (3.8)	22.3 (29.5)
A-Y	12.2 (17.5)	8.0 (10.0)	11.0 (16.9)	0
B-X	5.3 (8.0)	4.2 (7.5)	16.1 (29.2)	16.9 (15.0)
B-Y	2.8 (6.5)	0	2.1 (5.4)	1.2 (4.5)
Reaction time				
A-X	470 (110)	523 (143)	554 (156)	621 (111)
A-Y	632 (113)	686 (146)	722 (121)	779 (147)
B-X	587 (225)	609 (250)	828 (205)	802 (197)
B-Y	497 (157)	571 (160)	623 (121)	652 (122)
d′-Context	3.7 (0.4)	3.4 (0.6)	3.4 (1.0)	2.5 (0.7)

*Values given as mean (SD).
†Working memory task-isolating context processing conducted using a version of the A-X Continuous Performance Test.[25,27,29,30]

IMAGING DATA

We first examined regions showing a main effect of delay. In the group analysis, we observed a network of WM-related regions[21] showing this effect (**Table 3**). Planned contrasts indicated that most of these regions demonstrated significant delay effects in both groups, including bilateral inferior/posterior frontal cortex (**Figure 2**), right parietal cortex, and the anterior cingulate. The 2 right temporal regions demonstrated significant delay effects in patients but marginally significant effects in controls ($P<.10$). Individual subject analyses provided similar results (Table 3). Most patients and controls displayed delay-related activity in anterior cingulate, bilateral inferior frontal, and right parietal cortex, though fewer individual subjects displayed significant activity in the temporal regions.

As predicted, only 1 brain region displayed a significant group × delay interaction. This was located in DLPFC (Table 3 and **Figure 3**), and planned contrasts revealed significantly greater activity in the long compared with short delay among controls ($t_{11}=3.6$, $P<.005$)

Table 3. Regions Exhibiting Significant Delay-Related Activity

Regions of Interest	Brodmann Area	X*	Y*	Z*	Region of Interest, F	Volume, mm³†	No. (%), Healthy Controls‡ (n = 12)	No. (%), Patients With Schizophrenia‡ (n = 14)
Main effect of delay								
Anterior cingulate/supplementary motor area	32, 24	7	17	33	10.88	2844	9 (75)	8 (57)
Right inferior frontal cortex	44, 6	46	11	34	20.88	5520	10 (83)	10 (71)
Left inferior frontal cortex	44, 6	−48	7	20	10.84	1060	10 (83)	11 (79)
Right parietal cortex	40	40	−49	46	17.97	5356	11 (92)	12 (86)
Right temporal cortex	22	61	−39	16	9.32	2492	6 (50)	8 (57)
Right temporal cortex	39	38	−74	18	7.20	645	5 (42)	4 (29)
Group × delay interaction								
Left dorsolateral prefrontal cortex	46, 9	−34	25	26	11.24	472	10 (83)	6 (50)

*X, Y, and Z are coordinates in a standard stereotactic space[44] in which positive values refer to regions right of (X), anterior to (Y), and superior to (Z) the anterior commissure.

†Volume refers to the number of voxels (converted to cubic millimeters) that reached statistical significance in each region of interest.

‡The number of healthy controls and patients with schizophrenia who displayed significant activity in this region in the individual subject analyses.
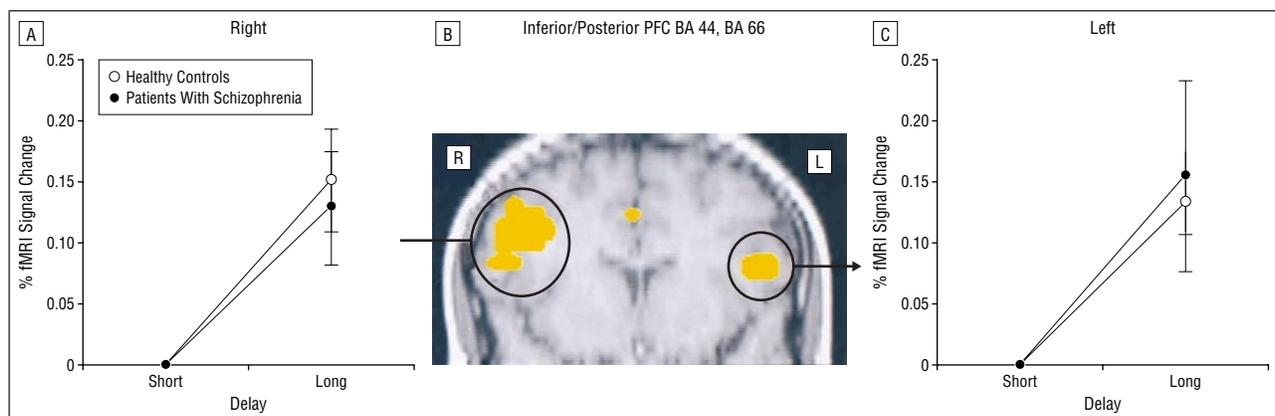

Figure 2. Prefrontal cortex (PFC) regions showing main effect of delay. The functional magnetic resonance image (fMRI) shows PFC regions active in long delay relative to short delay blocks with significant effects in both controls and patients. Insets plot the signal for healthy controls (n = 12) and patients with schizophrenia (n = 14) separately as a percent change from the short delay condition. BA indicates Brodmann area.
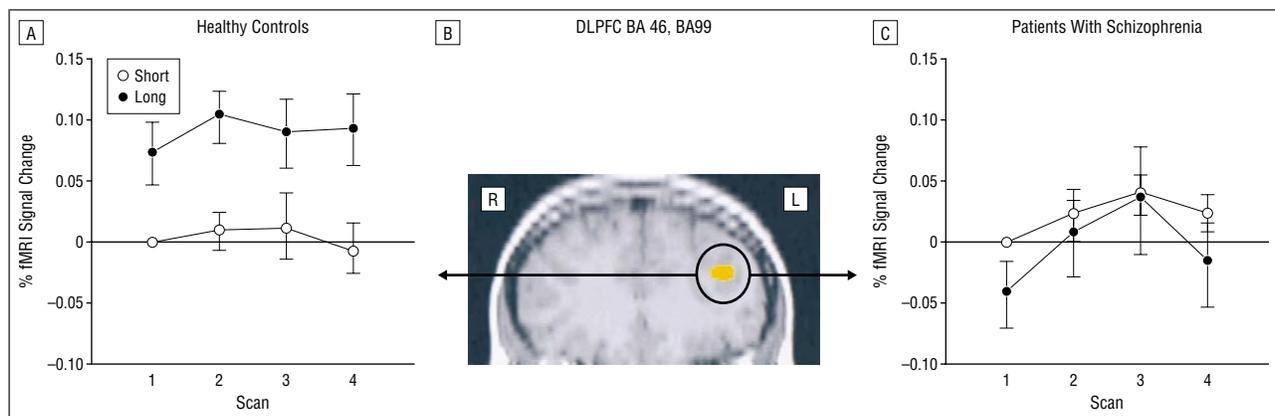

Figure 3. Dorsolateral prefrontal cortex (DLPFC) region showing group × delay interaction. Functional magnetic resonance image (fMRI) shows DLPFC region demonstrating group × delay interaction. Insets plot the signal for healthy controls (n = 12) and patients with schizophrenia (n = 14) separately as a percent change from the first scan of the short delay condition. BA indicates Brodmann area.

but not in patients ($t_{13} = 1.6$, $P > .10$). Moreover, among controls, the temporal dynamics of activity indicated a sustained response over the delay period (manifested as no main effect of scan in the long delay condition, $F_{3,33} = 1.81$, $P > .15$), consistent with the interpretation that this region is actively maintaining the context information provided by the cue. One possibility for this is that patients with schizophrenia did demonstrate DLPFC activation in response to the delay manipulation but simply in a different area than controls. However, no other

Table 4. Regions Exhibiting Significant Scan-Related Activity

Regions of Interest (N = 26)	Brodmann Area	X*	Y*	Z*	Region of Interest, F	Volume, mm³†
Main effect of scan within trial						
Left motor cortex	4	−37	−13	42	53.85	13 772
Right motor cortex	4	49	6	34	31.08	5106
Anterior cingulate/supplemental motor area	32, 8	1	3	43	37.80	8332
Left inferior frontal cortex	44, 6	−51	−18	20	44.87	1728
Left parietal cortex	40, 7	−23	−57	45	12.12	2028
Right parietal cortex	40, 7	32	−57	43	7.17	1412
Group × scan interaction						
Left inferior frontal	44, 6	−52	8	37	5.81	460
Right inferior frontal	44	47	14	29	6.35	576
Posterior cingulate	23	7	−30	24	6.19	1356

*X, Y, and Z are coordinates in a standard stereotactic space[44] in which positive values refer to regions right of (X), anterior to (Y), and superior to (Z) the anterior commissure.
†Volume refers to the number of voxels (converted to cubic millimeters) that reached statistical significance in each region of interest.
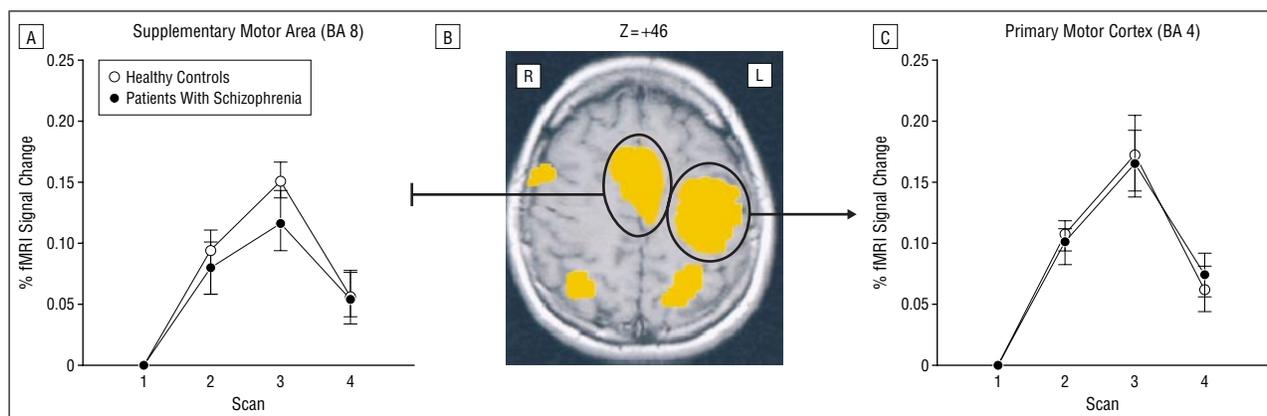

Figure 4. *Representative regions demonstrating significant effects of functional magnetic resonance imaging (fMRI) within trial. Insets plot the signal for healthy controls (n=12) and patients with schizophrenia (n=14) separately as a percent change from the first scan. BA indicates Brodmann area.*

regions anywhere in the brain demonstrated a group × delay interaction with a significant delay effect in patients. Furthermore, analyses examining delay effects in patients with schizophrenia alone did not reveal any significant activity in DLPFC, though they did reveal activation in the bilateral inferior/posterior frontal cortex, parietal cortex, anterior cingulate, and temporal cortex, consistent with the main effect of delay analyses presented in the section. In addition, individual subject analyses indicated that 10 of 12 controls displayed significantly greater activity in the long compared with short delay in DLPFC, while only 6 of 14 patients did (Table 3).

We did not predict that DLPFC activity would interact with trial type, even though we did predict and find such interactions in the behavioral data. This is because we believe that the behavioral trial type interaction reflects the fact that the same deficit in maintaining context information can lead to worse (eg, more B-X errors) and better performance (eg, fewer A-Y errors). Thus, reduced DLPFC activation should be present during all trial types at the long delay, even though its behavioral manifestations may differ across trial types. We were able to examine trial type effects in those individuals scanned with the 2-shot spiral sequence (n=19), though the AX-CPT design provided only a small number of trials for

each nontarget trial type. Consistent with our predictions, the DLPFC did not show a further interaction with trial type (P>.25).

We next examined regions showing significant effects of scan within trial. As given in **Table 4** and **Figure 4**, controls and patients showed response-related activation of motor and somatosensory cortex, with similar amplitude and dynamics. Three additional regions showed a group × scan interaction (Table 4). One region (left posterior frontal cortex) demonstrated significant inverse quadratic effects of scan within trial among patients but not controls, while the other 2 (right inferior frontal and posterior cingulate) showed such effects among controls but not patients.

A potential criticism of fMRI studies in schizophrenia is that increased movement among patients creates artifacts that impair the detection of cortical activation. To explore this possibility, we analyzed the 12 estimated movement parameters (pitch, roll, yaw, X, Y, and Z for absolute and image-to-image movement). Patients differed significantly from controls only on average absolute pitch ($t_{24}=2.03$, $P=.05$) due primarily to increased movement in 2 patients. When these patients were removed, no significant group differences in movement remained ($P>.10$ for all parameters), but the behavioral (eg, d′-context group × delay interaction; $F_{1,22}=4.6$,

P=.04) and imaging effects (eg, DLPFC group × delay interaction; $F_{1,22}$=14.7, P=.001) remained significant. We also examined signal-to-noise ratios in each slice of the imaging data. There were significant signal-to-noise ratio reductions among patients but only in more inferior slices (ie, slices 11-14, Z=+7-18 mm), well below the regions of interest in either PFC or parietal cortex.

A second criticism of fMRI studies in schizophrenia is that the poorer behavioral performance on the part of patients confounds the interpretation of observed activation differences.[9,17] To address this concern we looked at DLPFC activation in a subset of 8 controls and 8 patients roughly matched for performance based on d′-context at the long delay (mean [SD]: controls, 3.14 [0.62]; patients, 3.10 [0.41]). The DLPFC group × delay interaction remained significant in this subset of patients and controls ($F_{1,16}$=11.25, P=.004).

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COMMENT

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The pattern of results obtained in the current study were consistent with our hypothesis that patients with schizophrenia have a specific impairment in the ability to actively represent and maintain context information due to an underlying neurophysiological disturbance in DLPFC. Specifically, patients with schizophrenia demonstrated a specific pattern of both better (fewer A-Y errors) and worse behavioral performance (more B-X errors), suggestive of a deficit in the ability to actively represent and maintain context information. In addition, patients with schizophrenia demonstrated a selective deficit in the ability to appropriately activate DLPFC in response to demands for the maintenance of context. Our results suggested that the observed differences between controls and patients were not due to increased movement or reduced signal-to-noise ratios in the patient data. Since this study was conducted in first-episode medication-naive patients, we can conclude that DLPFC deficits are present at the onset of the first acute exacerbation in this illness and are not due to current or previous medication effects. More importantly, our findings suggest that PFC disturbances among patients with schizophrenia, at least first-episode medication-naive patients, may be somewhat anatomically specific. In particular, we found that more posterior and inferior regions of PFC, such as BA 44, were relatively functionally intact in our sample of patients with schizophrenia, providing critical "internal activation standards" against which to interpret decreased DLPFC activation among patients with schizophrenia. Patients also showed intact response-related activation of motor and somatosensory cortex, with amplitude and dynamics similar to controls.

Such results raise the question of the functional significance of activation in DL vs inferior regions of PFC and have implications for normal cognitive function as well as for the nature of cognitive impairments in schizophrenia. Activation of BA 44 is frequently found in neuroimaging studies of language and verbal WM.[32,45-47] This activity has typically been interpreted as reflecting articulatory planning and covert rehearsal processes.[32,47-49] As such, normal activation in BA 44 among patients is consistent with prior research, suggesting that patients are not impaired while performing tasks for which explicit rehearsal is sufficient to drive performance (eg, span tasks).[31,50] However, the AX-CPT is qualitatively different from some traditional WM tasks. In many such tasks, an articulatory or phonologically based representation of stimuli may be sufficient for correct performance. For example, in the digit-span task, the representation of the digits must be actively maintained in a form that allows them to be correctly repeated back without error. Thus, an ideal representation for this task would be an articulatory or phonologically based one. In contrast, in the AX-CPT, such articulatory or phonologically based representations may be useful or even necessary but not sufficient for correct performance. Instead, performance is critically dependent on transforming the cue into a representational form that carries information regarding the cue's implications for future stimulus evaluation and response, which we refer to as a *context representation*. For example, following a B cue, representing the stimulus in a phonological or articulatory form may not be sufficient. What is also needed is an interpretation of a B cue as indicating that a subsequent X should be associated with a nontarget rather than a target response. It is the representation and maintenance of information in this contextual code that we feel best characterizes the function of DLPFC[25] and which we believe is a key function that is impaired in schizophrenia.[26]

Although our results suggested impaired DLPFC activation but relatively intact activation of BA 44 in patients with schizophrenia, we should note that some prior studies have found disturbed activation of BA 44 in this illness. In particular, a recent study by Stevens et al[51] using word and tone span tasks found hypoactivation of a number of inferior/posterior PFC regions, such as BA 44, BA 6, and BA 45. There are a number of differences between the current study and the study of Stevens and colleagues that may have contributed to the differences in our results. First, and perhaps most importantly, the patients in the study by Stevens and coauthors had received long-term medication, while ours were medication-naive first-episode patients. As such, in future research, it will be important to determine whether illness duration and/or medication effects influence the integrity of BA 44 and BA 45 in schizophrenia. Second, the tasks used in the study by Stevens et al[51] placed a heavy demand on covert rehearsal, as noted by the authors themselves, and may not have strongly tapped the context processing component of WM. Consistent with this task analysis, Stevens and colleagues did not find activation of DLPFC among controls in their study. In contrast, the AX-CPT task used in the current study was specifically designed to tap context processing and may have only placed a moderate demand on covert rehearsal. Thus, another possibility is that the magnitude of BA 44 and BA 45 dysfunction demonstrated by patients with schizophrenia is related to the degree to which the task taxes or is critically dependent on covert rehearsal, a hypothesis that can be investigated in future cognitive and neuroimaging studies. Although we believe our results are consistent with the hypotheses outlined in the introduction, we should also note

some limitations of the current study. First, our patients were experiencing their first contact with the psychiatric system and had not yet experienced any potential confounding effects of antipsychotic medications or repeated hospitalizations. However, prodromal symptoms of schizophrenia can sometimes appear years before the onset of the first acute psychotic episode. Thus, we cannot rule out the possibility that our results may have been influenced by subtle effects of this prodromal period. Second, we did not match our patients and controls on variables such as IQ. This was a deliberate choice, as it has been argued that the development of schizophrenia itself may influence IQ and that matching groups on IQ can lead to nonrepresentative groups of both patients and controls.[52] Nonetheless, in future work it will be important to determine how variables such as IQ are related to both context-processing deficits and DLPFC dysfunction in schizophrenia. Lastly, we have interpreted the results of our study as reflecting disturbances in the ability to represent and maintain context. However, the results of this study itself cannot rule out an alternative interpretation, namely that patients have a deficit in actively maintaining any type of information, not just context representations, over a delay. This alternative hypothesis is consistent with the proposals of Goldman-Rakic[1,24] regarding the function of DLPFC and with data showing deficits on delayed matched to sample tasks among patients with schizophrenia.[6,53] To arbitrate between these alternatives, future research will need to directly compare the role of DLPFC in the maintenance of contextual vs noncontextual information and determine the critical parameters influencing WM deficits in schizophrenia.

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