
Prefrontal Cortex Dysfunction Mediates Deficits in Working Memory and Prepotent Responding in Schizophrenia

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Background: Schizophrenic patients show deficits in working memory (WM) and inhibition of prepotent responses. We examined brain activity while subjects performed tasks that placed demands on WM and overriding prepotent response tendencies, testing predictions that both processes engage overlapping prefrontal cortical (PFC) regions and that schizophrenic patients show reduced PFC activity and performance deficits reflecting both processes.

Methods: Functional magnetic resonance imaging data were acquired while 16 schizophrenic and 15 healthy subjects performed the N-Back task that varied WM load and a version of the AX-CPT that required overriding a prepotent response tendency.

Results: Both tasks engaged overlapping cortical networks (e.g., bilateral dorsolateral PFC, Broca's area, parietal cortex). Increased WM load monotonically increased activity; preparation to override a prepotent response produced greater and more enduring activity. Group differences on each task emerged in a right dorsolateral PFC region: schizophrenic subjects showed lesser magnitude increases under conditions of high WM and prepotent response override demands, with concomitant performance impairments.

Conclusions: Schizophrenic patients exhibit PFC-mediated deficits in WM and preparation to override prepotent responses. Findings are consistent with the operation of a single underlying PFC-mediated cognitive control mechanism and with physiologic dysfunction of the dorsolateral PFC in schizophrenic patients reflecting impairments in this mechanism. *Biol Psychiatry* 2003; 53:25–38 © 2003 Society of Biological Psychiatry

Key Words: Schizophrenia, prefrontal cortex, cognitive control, working memory, response inhibition, functional magnetic resonance imaging

Introduction

Advances in neuroscience theory and methods have supported early conceptions that schizophrenia is a disease of brain function (Kraepelin 1971) associated with a host of cognitive impairments (Bleuler 1950). For example, schizophrenia patients exhibit a range of cognitive deficits, particularly on measures of memory and “executive” functions (e.g., Blanchard and Neale 1994), as well as differences in brain structures (Akil et al 1999; Benes et al 1991; Selemon et al 1999; Selemon and Goldman-Rakic 1999) and activity (Barch et al 2001; Carter et al 1998; Callicott et al 1999; Fletcher et al 1998; Weinberger et al 1986) thought to support these functions. A burgeoning clinical–cognitive neuroscience literature has focused on the role of the prefrontal cortex (PFC) in cognitive impairment in patients with schizophrenia.

The precise nature of PFC-mediated cognitive dysfunction in schizophrenia remains uncertain, however. Much of the recent literature has focused on working memory (WM), a set of cognitive processes involved in actively maintaining and manipulating information in mind to guide task-appropriate behavior (e.g., Baddeley 1986). An increasing number of behavioral studies have demonstrated WM deficits in schizophrenia patients (e.g., Carter et al 1996; Park and Holzman 1992). Functional neuroimaging studies have demonstrated altered dorsolateral PFC (dlPFC) activity during the performance of WM-dependent tasks, with some studies showing reduced dlPFC activity (i.e., “hypofrontality”; Barch et al 2001; Carter et al 1998; Honey et al 2002; Perlstein et al 2001) and others showing increased dlPFC activity (i.e., “hyperfrontality”; Callicott et al 2000; Manoach et al 2000), although the finding of altered dlPFC activity in schizo-

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phrenia patients is not universal (e.g., Manoach et al 1999). Nonetheless, the PFC plays a complex role in high-level cognition (Duncan and Owen 2000; Nauta 1971; Stuss et al 1994), and schizophrenia patients exhibit deficits in a range of executive cognitive functions (Blanchard and Neale 1994; Perlstein et al 1998) associated with alterations in PFC activity (Fletcher et al 1998).

Several theoretical formulations have outlined unified descriptions of PFC-mediated cognitive functions in an attempt to account parsimoniously for the range of cognitive deficits observed in patients with PFC damage or psychopathology associated with PFC dysfunction (Cohen and Servan-Schreiber 1992; Fuster 1997; Kimberg et al 1998; Miller and Cohen 2001; Roberts and Pennington 1996). Most common to these formulations is that the PFC plays a critical role in the active maintenance and use of complex representational information to organize and guide contextually appropriate behavior. As elaborated by Cohen (Braver et al 1999; Cohen and Servan-Schreiber 1992; Cohen et al 1996) and others (Kimberg et al 1998), representations maintained in the PFC include not only information about task-relevant stimuli per se, but also complex “context” representations, a subset of representations within WM that govern how other representations are used. This “context-maintenance” hypothesis proposes that a form of inhibition may reflect the operation of PFC-mediated context maintenance processes and that WM and inhibition reflect the operation of a common underlying cognitive control mechanism supported by the PFC (Cohen and Servan-Schreiber 1992; Miller 2000; Mitchell et al 2002; Roberts et al 1994). The linking of PFC representations to the organization of prospective action is a critical function of the dlPFC (Fuster 1997; Goldman-Rakic 1987), and preparation to overcome contextually inappropriate responses is an important component of this organization. Thus, deficits in a WM system, which may reflect dysfunction in PFC-mediated top-down biasing of contextually appropriate responding, may also manifest as difficulties in resisting prepotent actions (Barch et al 1998; Cohen et al 1999; Gooding and Tallent 2001; McDowell et al 2002; Mitchell et al 2002; Perlstein et al 1998; Roberts et al 1994).

Our research was motivated by these contemporary accounts of PFC function that emphasize a critical role for PFC-mediated cognitive control functions in WM and overcoming prepotent response tendencies. Specifically, we examined behavioral performance and brain activity in schizophrenia patients and healthy comparison subjects on two tasks designed to interrogate processes involved in WM and preparation to override prepotent responses. The following predictions were tested: 1) WM and preparation

Table 1. Mean (SE) Demographic Characteristics of Experiment Participants

Subject Characteristics ^a	Schizophrenia Patients	Healthy Subjects
<i>N</i>	16	15
Age	36.8 (1.9)	36.4 (1.8)
Age Range	24–51	26–47
Gender (men/women)	11/5	9/6
Education	13.7 (.6)	14.9 (.6)
Parental Education ^b	13.1 (.7)	13.5 (.6)
Mean Age Onset	22.8 (1.0)	
Duration of Illness (years)	14.1 (2.2)	
Chlorpromazine Equivalents	175.3 (30.2)	
% Taking Antiparkinsonians	18.8	
% Taking Antidepressants	6.3	
% Taking Benzodiazepines	6.3	
	Symptom Syndrome ^c (mean, range)	
Reality Distortion	2.75 (1.5–4.0)	
Poverty	2.48 (1.2–3.4)	
Disorganization	2.17 (1.0–3.3)	

^aPatients and healthy comparison subjects did not differ on any demographic variable ($t(30) < 1.40$, $p > .17$).

^bAveraged across mother and father education, neither of which significantly differed as a function of group ($t(30) < 1.00$, $p > .5$).

^cSymptom ratings from Positive and Negative Symptom Scale have been collapsed into three symptom syndromes described in Liddle (1987) and Kay et al (1987). Reality Distortion (positive symptoms): hallucinations, delusions, unusual thought content; Poverty (negative symptoms): blunted affect, emotional withdrawal, passive social avoidance, motor retardation, lack of spontaneity; Disorganization: conceptual disorganization, mannerisms and posturing, difficulty abstracting, poor attention.

to override prepotent response tendencies will activate overlapping cortical networks, including the dlPFC and 2) schizophrenia patients will show altered dlPFC activity and task performance deficits reflecting both processes.

Methods and Materials

Participants

Participants were 16 clinically stable outpatients diagnosed with schizophrenia and a group of 15 demographically matched healthy comparison subjects and underwent two functional magnetic resonance imaging (fMRI) scanning sessions. Participants in the study comprise a large subset of those reported in Perlstein et al (2001). Most subjects completed both fMRI sessions within 5–10 days (range = 0–41 days; median = 6.2 days). The demographic and clinical characteristics of participants are shown in Table 1. Depot doses of antipsychotics were converted to average daily chlorpromazine-equivalent doses using the guidelines suggested by Baldessarini (1985); two patients were also receiving daily oral antipsychotics, and these were converted to chlorpromazine equivalents using guidelines suggested by Davis et al (1983). To reduce patient-sample heterogeneity, only patients maintained on fixed doses of conventional injectable neuroleptics for at least 2 months before the study were included, and most participated in the first fMRI session within 5 days

before the end of their injection cycle. Medical record review and structured clinical interview (SCID-IV; First et al 1995), conducted by a PhD-level clinical psychologist (WMP) or a trained research assistant (or both), confirmed DSM-IV (American Psychiatric Association 1994) diagnoses of schizophrenia; absence of psychiatric symptoms in comparison subjects was confirmed by SCID-IV. Clinical state of patients was assessed using the Positive and Negative Symptom Scale (Kay et al 1987) on the day of testing. Ratings were completed either by a PhD-level clinical psychologist (WMP) or a trained research assistant who regularly participated in training and reliability sessions. Symptoms were grouped into three “syndromes” using the three factors suggested by Liddle (1987)—reality distortion, poverty, and disorganization (Table 1). Interrater reliability (Shrout and Fleiss 1979) established during reliability sessions was .95 for reality distortion, .95 for poverty, and .94 for disorganization. All participants were right handed and had no history of brain trauma, seizure disorder, electroconvulsive therapy, 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 a magnetic resonance simulator for at least 15 min, and all participants practiced the tasks until it was evident that they understood the instructions and to reduce the influence of task-strategy development on brain activity. After complete description of the study, written informed consent was obtained in accordance with the University of Pittsburgh Institutional Review Board guidelines.

Stimuli and Task

Behavioral tasks used during scanning were developed on the PsyScope platform (Cohen et al 1993). Subjects performed two tasks in nearly counterbalanced order: the AX-CPT and the N-Back. In both tasks, subjects viewed sequences of letters (500-msec duration) presented singly in the middle of a visual display mounted in the scanner bore and provided dominant-hand button presses. The N-Back task (Cohen et al 1994) is a sequential-letter memory task that parametrically varies WM load among 0, 1, and 2 items. In the 0-back condition, the target was any letter that matched a prespecified letter (e.g., “X”). In the 1- and 2-back conditions, a target was any letter that was identical to the one presented one or two trials preceding it, respectively. Stimulus encoding and response demands were constant across conditions; only requirements to maintain and update increasingly greater amounts of information at higher loads differed. Pseudorandom sequences of single consonants were presented (3500-msec interstimulus interval), and subjects responded to each stimulus, pressing one button to targets (33% of trials) and another to nontargets. Conditions were run in blocks of 18 stimuli during which scans were acquired, with six blocks for each load condition. Order of task conditions was randomized across subjects.

In the AX-CPT (Servan-Schreiber et al 1996), subjects were instructed to respond to a prespecified probe (X) only if it follows a particular contextual cue (A). Target (“AX”) trials occurred frequently (70%); the remaining 30% of trials were divided evenly between three distractor conditions: non-A fol-

lowed by X (“BX” trials); A followed by non-X (“AY” trials); and non-A followed by non-X (“BY” trials). This combined frequency distribution produces a prepotent tendency to make target responses following A cues (ACue condition) and a requirement to overcome the tendency to respond to a subsequent probe as a target following B cues (BCue condition), because A cues signal “probably target, possibly nontarget,” whereas the B cues signal “definitely nontarget.” Trials were presented in blocks, with the delay between cue and probe systematically varied between blocks (1000 msec and 9000 msec). In short delay blocks, there was 1 sec between cue and probes, and 9 sec between the probe and next cue (ITI). In long delay blocks, timing was reversed: the cue-probe delay was 9 sec, and ITI was 1 sec. This delay–ITI distribution maintains an identical duration of trial blocks across both delay blocks. Conditions were run in blocks of 10 cue-probe trials, with five repetitions of each of the two delay conditions randomized across blocks and subjects.

Task Performance Analysis

Reaction time (RT) and error rates were acquired during scanning. Median RTs and error rates for the N-Back task were analyzed using between-group tests of linear and quadratic trend over load. Between-group pairwise comparisons were made at each load level to test our a priori hypothesis that significant group differences in performance would emerge only at the higher load levels. Median RTs and mean error rates for the AX-CPT task were analyzed using separate analyses of variance (ANOVAs) for ACue and BCue types, with group as the between-subjects factor and probe type (X, Y) and delay (short, long) as the within-subject factors. BCue false alarms and ACue commission errors were evaluated separately, because ACues are more sensitive to active maintenance functions, whereas BCues are more sensitive to prepotency effects.

Image Acquisition

Scanning took place in a conventional 1.5-T GE Signa whole-body scanner using a standard head radio-frequency (RF) coil. Functional images were acquired in the axial plane using a two-interleave T2*-weighted spiral-scan pulse sequence (AX-CPT: repetition time [TR] = 1250 msec, echo time [TE] = 35 msec, flip angle = 40°, field of vision [FOV] = 24 cm, 16 slices; N-Back: TR = 2000 msec, TE = 35 msec, flip angle = 80°, FOV = 24 cm, 24 slices; Noll et al 1995) and were composed of isotropic voxels (3.75 mm³) acquired at contiguous locations parallel to the anterior commissure-posterior commissure (AC–PC) line. Scan acquisition was time locked to each stimulus onset, and the duration of each scan spanned the entire duration of each trial. Thus, a scan during the N-Back task yielded a single image volume for each trial and during the AX-CPT task each scan yielded four image volumes for each 10-sec trial, providing four hemodynamic response points during the course of a trial. The first three trials of each block in the N-Back task were discarded to allow for “loading” of WM at the outset of the task. Before functional scanning, T1-weighted structural images were acquired in the same planes as the functional images for anatomical localization and coregistration of images across subjects for groupwise analyses.

Image Reduction and Analysis

Following reconstruction, images were normalized to a common mean and movement-corrected using a six-parameter rigid body translation (Woods et al 1992). Each subjects' structural images were then coregistered to a common reference using a 12-parameter algorithm and smoothed using a three-dimensional Gaussian filter (8-mm full width at half maximum) to accommodate between-subject differences in brain anatomy. Imaging data from each task were analyzed separately using voxelwise ANOVAs, with subject as the random factor. Image preprocessing and voxelwise analyses were conducted using Neuroimaging Software (NIS; <http://kraepelin.wpic.pitt.edu/nis/>).

N-BACK. Functional MRI data for N-Back were analyzed using 2-Group \times 3-Load (0- through 2-back) ANOVAs. Follow-up contrasts on signal intensity in the voxel showing the maximal F -value in statistically identified clusters used between-group tests of linear and quadratic trend over load to identify interactions. Trend analyses also were conducted on these voxels for each group separately to determine if one or both groups showed significant WM load effects.

AX-CPT. For the AX-CPT, voxelwise ANOVAs included group as the between-subject factor and cue type (A, B) and scan within trial (1–4) as within-subject factors. Although one could examine all possible main effects and interactions in this design, our a priori hypotheses focused on regions demonstrating one of the following three patterns: 1) a main effect of cue type identified voxels showing greater activity in the BCue than ACue condition to reveal regions associated with preparing to override a prepotent response tendency; 2) because preparation to override the prepotent response tendency can be manifest as greater intensity or a more prolonged hemodynamic response, we also identified voxels showing a cue type \times scan interaction to test for differential temporal dynamics of the hemodynamic response as a function of cue type; and 3) a group interaction with cue type and cue type and scan. For regions that showed any of these patterns, planned contrasts were conducted on signal intensity in the voxel showing the maximal F value within statistically identified clusters to confirm that the predicted pattern of interest was significant for at least one of the groups.

Voxelwise statistical maps were generated for each pattern of interest and then thresholded for significance using a cluster-size algorithm (Forman et al 1995) 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 .005 were chosen, corresponding to a corrected imagewise false-positive rate of .005. Regions showing such effects were overlaid onto the reference structural image and transformed to standard stereotaxic space (Talairach and Tournoux 1988) using AFNI software (Cox 1996) for reporting purposes.

Results

Behavioral Data

N-BACK. Increased WM load was associated with increased error rates, and with greater errors at higher load

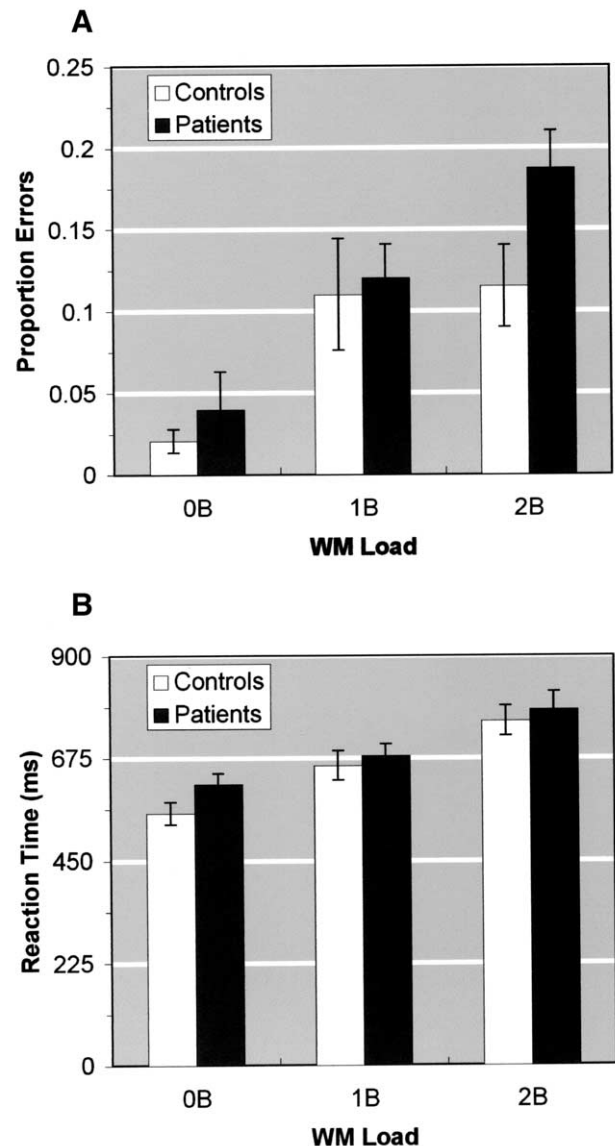


Figure 1. Mean error rates (A) and reaction times (B) on performance for 0- through 2-back loads on the N-Back working memory (WM) task for schizophrenia patients and healthy control subjects. Bars represent ± 1 SE.

levels in patients compared with control subjects (Figure 1). These findings were statistically confirmed by a significant linear trend over load [$t(29) = 6.86, p < .0001$] and a trend-level interaction of group with the quadratic trend over load [$t(29) = 1.71, p < .10$], respectively. Between-group comparisons at each level of WM load revealed that patients committed significantly more errors than comparison subjects only at the highest load level [$t(29) = 2.13, p < .05$]. Reaction times were significantly longer at higher load levels [linear trend over load: $t(29) =$

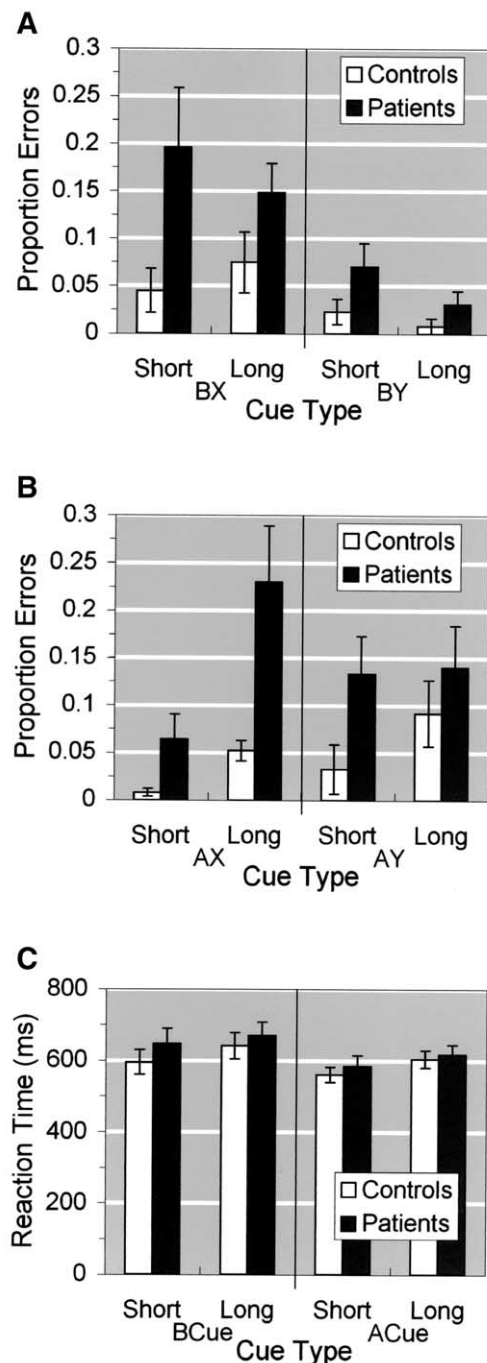


Figure 2. Behavioral performance data for schizophrenia patients and healthy controls on the AX-CPT task as a function of cue type and delay. (A) Probe error rates on B-cue trials (BX, BY), illustrating impairment in patients' ability to inhibit the prepotent response tendency (greater errors in the BX condition). (B) Error rates on ACue trials (AX, AY), illustrating patients' impaired ability to maintain the context information inherent in the cue, as evidenced by increased patient errors at the long delay. (C) Reaction times to probes following ACue and BCue types, collapsed across probe type. Bars represent ± 1 SE.

9.09, $p < .0001$] and did not differ as a function of group at any level of WM load.

AX-CPT. Error-rate data (Figure 2) to BCues indicate that patients were impaired on overriding the prepotent response tendency. Patients made more errors overall [$F(1,29) = 7.75$, $p < .01$], and both groups made more errors to BX than BY trials [$F(1,29) = 12.08$, $p < .002$]. Although the group \times delay interaction was not significant [$F(1,29) = 2.15$, $p = .15$], planned comparisons revealed that patients committed significantly more BCue false alarms than comparison subjects at the short delay [$t(29) = 2.32$, $p < .03$], and only a trend toward more BCue errors at the long delay [$t(29) = 1.87$, $p < .08$]. This suggests that patients were less able than control subjects to use cue information to overcome the prepotent tendency to respond to a subsequent probe, particularly when there was less time between cues and probes to resolve the prepotency signaled by the cue. A more sensitive test of the response-inhibition hypothesis examined responses to only BX trials (collapsed across delay) and revealed that patients committed significantly more false alarms than control subjects [$t(29) = 2.37$, $p < .025$]. A similar analysis of BY-trial errors, which provides a measure of nonspecific response bias and random responding, showed that the two groups did not differ.

ACue errors were significantly greater at the long than short delay [$F(1,29) = 14.33$, $p < .001$], and greater in patients than control subjects [$F(1,29) = 7.66$, $p < .01$]; however, significant group \times cue type \times delay interaction [$F(1,29) = 4.47$, $p < .05$] reflects the finding that the group difference was mainly due to patients' increased AX errors at the long delay (i.e., a context maintenance deficit). Follow-up analyses on AX and AY cue types separately, using group \times delay ANOVAs, support this observation, yielding, for AX stimuli, significant group [$F(1,29) = 7.83$, $p < .01$] and delay [$F(1,29) = 18.27$, $p < .0002$] main effects, and a group \times delay interaction [$F(1,29) = 6.30$, $p < .018$]. A similar analysis of AY trials revealed no significant effects, although relative to performance at the short delay, control subjects' performance worsened at the long delay, whereas patients' performance remained unchanged.

Response times (Figure 2C) were longer to BCues than ACues [$F(1,29) = 17.61$, $p < .0005$] and in the long than short delay [$F(1,29) = 6.99$, $p < .015$]. The latter finding corroborates the error-rate analysis, further suggesting that the probability manipulation was effective in producing a requirement to overcome the prepotent response tendency associated with improbable BCues.

COMPARISON OF AX-CPT AND N-BACK PERFORMANCE. Correlations were conducted to examine relationships between performance on the AX-CPT and N-Back

Table 2. Regions Exhibiting Significant Experimental Effects in the N-Back Task

Region of Interest	Brodmann's Area(s)	X ^a	Y ^a	Z ^a	p Value			
					Load	Group × Load	Control Subjects	Patients
Load main effect								
R SMA	6	33	1	52	< .0001	.0632	< .0001	< .0001
AC	32	5	14	40	< .0001	.4459	.0013	.0008
R dlPFC	46/9	40	36	22	< .0001	.0605	< .0001	.0207
L dlPFC	46/9	-37	37	22	< .0001	.2271	.0004	.0254
R Broca	44	44	15	14	< .0001	.4195	.0002	< .0001
L Broca	44	-39	15	16	< .0001	.8711	.0003	.0017
R PAR	40	43	-55	36	< .0001	.2105	< .0001	.0011
L PAR	40	-35	-52	38	< .0001	.8199	.0009	.0042
Thalamus		1	13	12	< .0001	.3398	< .0001	.0449
Group × Load Interaction								
R dlPFC	46/9	43	27	26	< .0001	.0004	< .0001	.0357

dlPFC, dorsolateral prefrontal cortex; AC, anterior cingulate gyrus; SMA, supplementary motor area; PAR, posterior parietal cortex; R, right; L, left.

^aX, Y, and Z are coordinates in standard stereotactic space (Talairach and Tournoux 1988) in which positive values refer to regions of right (X), anterior to (Y), and superior to (Z) the anterior commissure (AC).

tasks. If WM maintenance and inhibitory deficits are associated, we would predict that these measures would be positively correlated. Thus, behavioral measures included error rates for ACue and BCue types, collapsed across delay for the AX-CPT, and error rates for the 2-Back load level on the N-back.¹ Error rates on the 2-back condition correlated positively and significantly with error rates on both ACue and BCue trials of the AX-CPT ($r_s[30] = .52$ and $.43$, $p_s < .0025$ and $.016$, respectively). Thus, WM performance indexed via the N-back task was related to both WM and inhibitory functions tapped by the AX-CPT task.

Imaging Data

N-BACK. Significant load-related effects were observed in a network of regions (Table 2; Figure 3), including the bilateral dlPFC and parietal regions and Broca's area, the anterior cingulate, and the thalamus. All load main effects reflected monotonically increasing or decreasing activity; only regions showing increases are illustrated in the figure and discussed here. Planned contrasts on signal intensity in these regions confirmed that the load-related increases were significant in both groups. More important, the predicted group × load interaction emerged in the right dlPFC (Figure 3). Both groups showed increased activity from 0- to 1-back, but unlike control subjects, patients failed to show further increases in the 2-back condition.

Analysis of signal intensity within the right dlPFC yielded a significant linear trend over load [$t(29) = 6.82$, $p < .0001$]; however, group significantly interacted with both the linear [$t(29) = 3.29$, $p < .003$] and quadratic [$t(29) = 2.61$, $p < .015$] trends over load. Trend analyses on right dlPFC activity in each group separately revealed a significant linear [$t(14) = 9.45$, $p < .0001$] and quadratic effect [$t(14) = 2.15$, $p < .05$] in control subjects; patients showed only a moderate linear trend [$t(15) = 2.13$, $p = .05$].

AX-CPT. A network of regions that substantially overlapped those identified for the N-Back task exhibited significant cue-type effects, due to greater or more temporally extended activity to BCue than ACue types (Table 3; Figure 4). Cue-type main effects were restricted to the PFC and included bilateral dlPFC (Brodmann's area [BA] 46/9 of the middle frontal gyri, extending to BA45 of the inferior frontal gyri ventrally), left Broca's area (BA44), and midline anterior cingulate and supplementary motor cortex (BA32/6). All frontal regions showing this main effect also interacted with scan, as did regions in the bilateral parietal cortex. Interactions with scan reflected greater magnitude and longer duration responses to BCues than ACues. Planned contrasts on signal intensity in regions showing cue-type main effects confirmed these observations for both groups. Planned contrasts on signal intensity in regions showing a cue type × scan interaction indicated that this effect was significant in all regions in comparison subjects; however, right dlPFC activity was only marginally significant ($p = .06$) in patients.

¹ The 2-back load was used due to restricted range of errors on the 0- and 1-back load levels of the N-Back task.

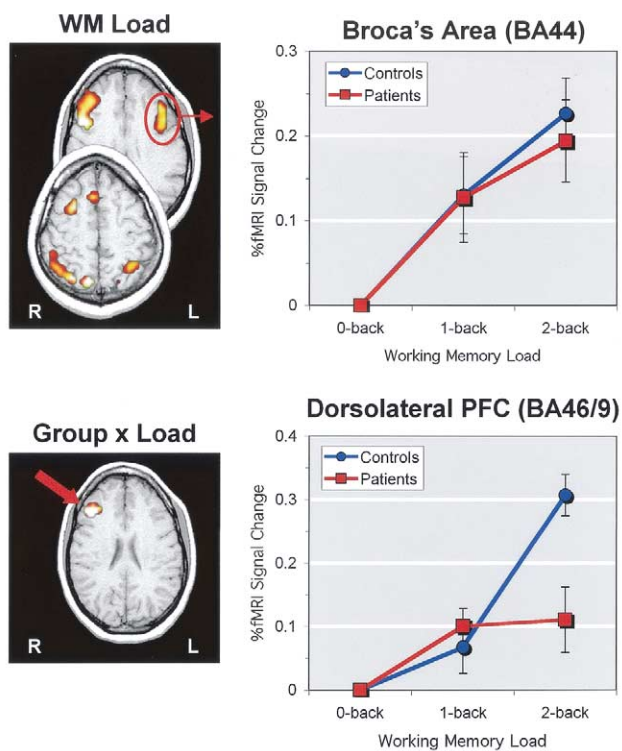


Figure 3. Functional magnetic resonance image (fMRI) slices showing representative regions that exhibited load- (top left) and group \times load-related (bottom left) effects in the N-Back task. Plots to the right reflect signal intensity in Broca's area (BA 44; top right) and the dorsolateral prefrontal cortex (PFC; BA 9/46; bottom right) for healthy comparison and schizophrenia subjects as the percent change in signal intensity from the 0-back condition. Bars represent ± 1 SE.

Next, we examined regions showing effects of group and interactions of group with cue type and scan. No group main effects were observed in regions showing task-related activity. Thus, group main effects were not task related and will not be discussed. No regions showed a group \times cue type interaction wherein activity to BCues was significantly greater than ACues in comparison subjects; however, activity in the right dlPFC showed a significant group \times condition \times scan interaction (Figure 4), indicating that the temporal course of cue-related activity is an important moderator of the group-related effects. Comparison subjects showed greater and more prolonged activity to BCues than ACues; patients showed lesser magnitude BCue-related activity compared with control subjects and did not differentiate between cue types as a function of temporal course within trials. A region of the right parietal cortex showed an identical pattern. Planned contrasts on signal intensity within these two regions revealed significant group \times cue type \times scan interactions [$F(3,87) \geq 6.39$, $ps < .0006$]; the comparison group showed

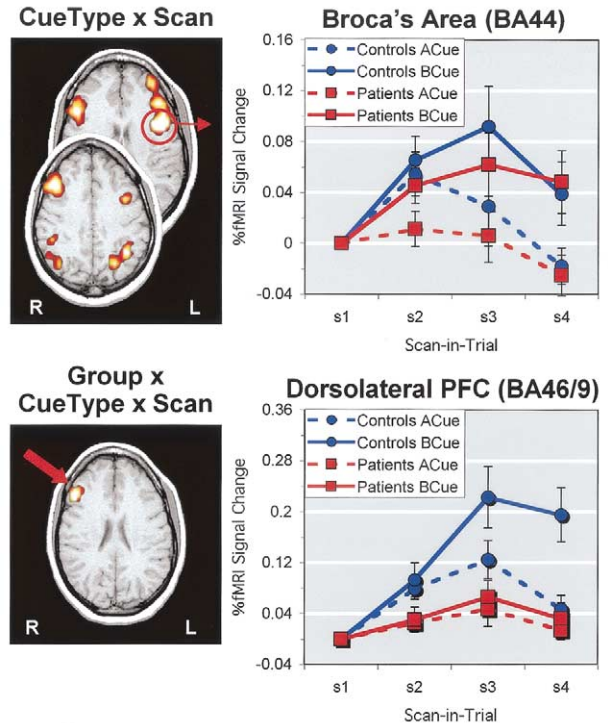


Figure 4. Functional magnetic resonance image (fMRI) image showing representative regions that exhibited effects of cue type \times scan (top left) and group \times cue type \times scan (bottom left) effects in the AX-CPT task. Plots to the right reflect signal intensity for healthy comparison and schizophrenia subjects as the percent change in signal intensity from scan 1 for the ACue and BCue types in Broca's area (top right) and the dorsolateral prefrontal cortex (bottom right). Bars represent ± 1 SE.

significant cue type \times scan interactions in both regions [$F(3,42) \geq 9.77$, $ps < .0001$]; patients did not show significant effects of either type in either region [$F(3,45) \leq .41$, $ps > .74$].

Importantly, additional contrasts revealed that the two groups did not differ in response to ACues, either as a main effect of group or as a group \times scan interaction, but did significantly differ to BCues in the group \times scan interaction [$F(3,87) = 7.69$, $p < .0001$]. The absence of group differences on ACue trials, combined with the finding of significantly poorer patient performance on short compared with long BX trials, suggests that active maintenance of cue representations cannot solely underlie the observed group differences seen in BCue trials (see Discussion).^{2,3}

² Because the two groups differed in error rates on the BCue condition, and more so at the short than the long delay, we examined activity in the right dlPFC to determine if there was a delay-related effect in this condition that paralleled the behavioral data. Thus, we calculated the percent change from scan 4 (the scan reflecting sustained activity) to scan 1 for the BCue condition. A group \times delay analysis of variance yielded a significant main effect of group [$F(1,29) = 11.33$; $p < .0025$; mean \pm SE, control subjects $.195 \pm .035$; patients: $.089 \pm$

Table 3. Regions Showing Significant Experimental Effects in the AX-CPT Task

Region of Interest	Brodmann Area(s)	X ^a	Y ^a	Z ^a	p Value			
					Cue Type ^b	Group Interaction ^c	Control Subjects	Patients
Cue Type Main Effect								
R dlPFC	46/9	43	40	22	.0003 ^{b,d}	.4893	.0019 ^{b,d}	.0379 ^b
L dlPFC	46/9	−28	44	27	.0018 ^{b,d}	.2782	.1347	.0046
L dlPFC	46	−39	25	25	.0014 ^{b,d}	.7706	.0585 ^{b,d}	.0082
AC/SMA	32	1	22	39	.0018 ^d	.8770 ^{c,e}	.0289 ^b	.0269
L Broca	44	−44	4	22	<.0001 ^{bd}	.7531 ^d	.0008 ^b	.0005
Cue Type × Scan Interaction								
R dlPFC	46/9	32	51	29	<.0001 ^{b,d}	.1550	.0005 ^{b,d}	.0558
R dlPFC	46/9	48	23	28	<.0001 ^{b,d}	.3046	.0004 ^{b,d}	.0114
AC/SMA	32	2	40	20	.0002 ^d	.9019	.0147	.0199
L Broca	44	−42	8	25	<.0001 ^{b,d}	.6502	.0011 ^b	.0045 ^b
R PAR	40	42	−50	35	<.0001 ^{b,d,f}	.2854	<.0001 ^b	.0362
L PAR	39/40	−39	−50	34	<.0001 ^{b,d}	.7832	.0036 ^b	.0010 ^b
Group × Cue Type × Scan Interaction								
R dlPFC	46/9	40	24	26	<.0001 ^{b,d}	.0004 ^{c,e}	<.0001 ^b	.7740 ^b
R PAR	40	50	−46	33	.0052 ^{b,d}	.0004	<.0001 ^b	.8631 ^b

dlPFC, dorsolateral prefrontal cortex; AC, anterior cingulate gyrus; SMA, supplementary motor area; PAR, posterior parietal cortex; R, right; L, left.

^aX, Y, and Z are coordinates in standard stereotaxic space (Talairach and Tournoux 1988) in which positive values refer to regions of right (X), anterior to (Y), and superior to (Z) the anterior commissure.

^bIndicates significant ($p < .05$) working memory load-related increases in activity from the N-Back task.

^cIndicates significant ($p < .05$) group × load interaction in activity from the N-Back task.

^dIndicates significant ($p < .05$) linear trend over load in activity from the N-Back task.

^eIndicates significant ($p < .05$) group × linear trend over load in activity from the N-Back task.

^fIndicates significant ($p < .05$) quadratic trend over load in activity from the N-Back task.

Finally, if BCue-related activity reflects preparation to override the prepotent response tendency signaled by the cue, we predict that greater dlPFC activity would be associated with faster probe RTs. Pearson Product–Moment correlations revealed that dlPFC activity (percent change in signal intensity from the mean signal intensity across conditions) significantly and inversely correlated with short-delay BCue median RTs [$r(30) = -.58$, $p < .001$ for both groups combined; $r(14) = -.59$, $p < .025$ for control subjects; $r(15) = -.56$, $p < .025$ for patients; Figure 5]. Faster RTs did not reflect a speed-accuracy tradeoff because RT and error-rates were not systematically correlated. In contrast, dlPFC activity did not signifi-

cantly correlate with ACue-related activity ($ps > .10$), as might be expected if the observed activity more strongly reflects active maintenance of the cue information.

COMPARISON OF AX-CPT AND N-BACK ACTIVATIONS. As predicted, the two tasks activated a highly overlapping cortical network of regions associated with WM and overriding prepotent response tendencies, and schizophrenia patients differed significantly from healthy control subjects in dlPFC activation in both tasks. To more directly determine if the regions showing greater sensitivity to BCues than ACues were also sensitive to changes in WM load, we conducted linear and quadratic trend analyses over load on signal intensity at the voxel showing the maximal F value in regions that exhibited cue-type (or cue type × scan) effects. Results (Table 3) demonstrate that all regions exhibiting cue-type-related effects described earlier also showed significant linear increases in activity with increased WM load. Additionally, activity in the right dlPFC again showed a significant interaction of group with the linear trend over load.

ANALYSIS OF MOVEMENT PARAMETERS. To examine the possibility that movement artifacts impaired the detection of cortical activation in patients, we analyzed the six estimated movement parameters (pitch, roll, yaw, x, y, and

.024] and marginally significant group × delay interaction [$F(1,29) = 3.55$, $p < .07$]. Comparison of each group separately revealed that comparison subjects showed significantly greater activity to the short than long delay [$F(1,14) = 5.81$, $p < .032$; mean ± SE, short: .248 ± .057; long: .142 ± .037], whereas patients did not differ significantly [$F(1,14) = .117$, $p < .73$] between short (.024 ± .037) and long (.040 ± .032) delays.

³ Because the prepotency manipulation would be expected to build over trials, we also examined whether modulation of prefrontal cortex task-dependent activity similarly developed over trials. Trials were divided into first and second halves of the experiment, and the percent change from ACue to BCue was evaluated as a function of experimental half (collapsed across scan in trial). The groups did not significantly differ during the first half of the experiment [$t(31) = 0.63$, $p < .50$; mean ± SE, control subjects: .049 ± .023; patients: .030 ± .019] but did not differ during the second half [$t(29) = 2.87$, $p < .008$; control subjects: .077 ± .020; patients: .002 ± .017]. During the second half, control subjects showed increasing dorsolateral prefrontal cortex activity from BCue to ACue, whereas patients showed decreasing activity.

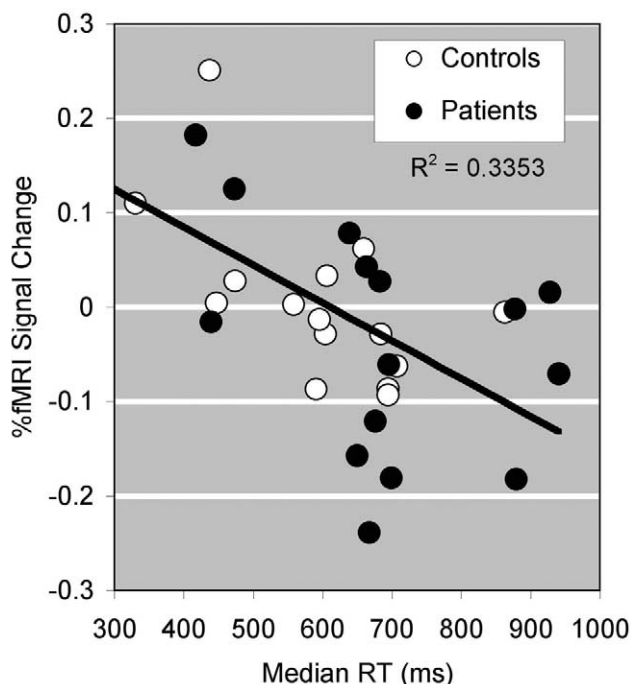


Figure 5. Scatter plot and regression line showing the relationship between median reaction times and functional magnetic resonance image (fMRI) signal intensity to the short BX trials in the right dorsolateral prefrontal cortex region that distinguished patients and comparison subjects. The regression line shown was calculated across subject groups. White represents control subjects, black represents patients.

z for the absolute value of scan-to-scan movement) for each task separately, collapsed across conditions. No significant group differences were found for any of the parameters in either study [Table 4; AX-CPT: $t_s(29) < 1.00$, $p_s > .34$; N-Back: $t_s(29) < 1.42$, $p_s > .17$], suggesting that group-related activation differences cannot be attributed to differential movement in the scanner. Further evidence that movement does not contribute to the observed dlPFC effects is the finding of comparable task-related effects in other brain areas.

Discussion

We sought to determine if processes involved in the active maintenance and manipulation of information in WM and in the preparation to override prepotent response tendencies activate overlapping cortical regions, including the dlPFC, and if schizophrenic patients exhibit altered dlPFC activity during both processes. Analysis of the fMRI data revealed overlapping regions of cortical activation across the two tasks, including regions of the bilateral dlPFC, Broca's area, and parietal cortex. Replicating previous studies using similar versions of the N-Back (Braver et al 1997; Cohen et al 1994, 1997; Jansma et al 2000; Smith and Jonides 1999), WM-related activity in these regions increased monotonically with increased WM load. In the AX-CPT, activity following cues signaling a requirement to override a prepotent response tendency to a subsequent probe was greater in magnitude and more sustained than activity associated with cues signaling a shortly following probable target response. The latter finding converges with those of other neuroimaging studies demonstrating a role for the dlPFC in response inhibition processes (Casey et al 2001; de Zubizaray et al 2000; MacDonald et al 2000b; McDowell et al 2002; Pochon et al 2001).

More central to the aims of the study was the predicted finding that schizophrenia patients exhibit a disturbance in physiologic activation of an overlapping region of the dlPFC under demands for WM and preparation to override a prepotent response, with concomitant selective impairments in task performance. Patients showed less right dlPFC activation than healthy control subjects under conditions of high WM load, replicating previous findings using positron emission tomography and a different subject population (Carter et al 1998) and under conditions requiring preparation to override a prepotent response tendency. Analysis of the behavioral data confirmed that the two tasks were sensitive to both processes of interest and that schizophrenic patients performed more poorly than control subjects when these processes were more heavily called on. The N-Back behavioral results replicate

Table 4. Mean (SE) Estimated Scan-to-Scan Rotational (Degrees) and Translational (mm) Estimated Movement Parameters (Mean of Absolute Values) for Each Group and Task

Parameter ^a	AX-CPT		N-Back	
	Control subjects	Patients	Control subjects	Patients
Pitch	.060 (.011)	.059 (.006)	.053 (.007)	.060 (.011)
Roll	.045 (.011)	.051 (.006)	.027 (.003)	.033 (.003)
Yaw	.031 (.003)	.036 (.004)	.029 (.003)	.033 (.004)
X	.028 (.004)	.033 (.004)	.029 (.007)	.031 (.003)
Y	.042 (.007)	.034 (.003)	.044 (.007)	.041 (.007)
Z	.065 (.007)	.055 (.006)	.051 (.006)	.066 (.011)

^aThere were no significant group differences in any of the estimated movement parameters for either task.

previous findings showing poorer patient performance at higher load levels (e.g., Callicott et al 2000; Carter et al 1998), whereas the AX-CPT findings parallel previous results showing greater BX errors in schizophrenic compared to control subjects (Barch et al 2001; Cohen et al 1999; Stratta et al 2000). Finally, all regions showing sensitivity to the prepotency manipulation were also sensitive to WM load. The overall pattern of results is consistent with the hypotheses that the dlPFC plays a critical role in both WM and preparation to inhibit a prepotent response tendency and provides some support for the hypothesis that WM and inhibition may reflect the operation of a similar PFC-mediated cognitive control mechanism. Notably, our findings indicate a role for dlPFC in both WM and inhibitory processes without introducing a dual-task component (cf., Mitchell et al 2002). The right-lateralized group effect is also consistent with findings of Garavan et al (1999) implicating the right dlPFC in inhibitory control mechanisms.

In certain respects, our imaging results replicate aspects of findings by Barch et al (2001) in providing some measure of specificity of deficits to the dlPFC as opposed to more inferior or posterior frontal regions such as Broca's area (BA44) or the inferior frontal gyrus (BA45; cf., Stevens et al 1998). These authors observed a specific deficit in the left dlPFC when examining delay-related effects (in contrast to the prepotency effect) in an identical version of the AX-CPT in a group of first episode, medication-naïve schizophrenia patients. Specificity to the dlPFC, as opposed to more inferior–posterior regions of the PFC, has also been demonstrated in structural alterations (Selemon et al 1999). In contrast to our finding of dlPFC activity associated with prepotency, Barch et al did not observe dlPFC activity in their analysis of the delay main effect, although this region did emerge as an interaction between group and delay.

Several accounts of PFC function suggest that the dlPFC is critically involved in cognitive control—the top-down biasing of processing in other brain regions to facilitate selection of neural pathways required for task performance (Miller 2000; Miller and Cohen 2001). Computational modeling studies of the AX-CPT (e.g., Braver et al 1999; Servan-Schreiber et al 1996) have supported this hypothesis and also suggest that active maintenance of context information serves to aid in preparing task-appropriate responses to compete with a stronger, but inappropriate, response. Activation of highly overlapping regions of the dlPFC in the two tasks used in our research, combined with abnormal dlPFC activation in schizophrenia patients, is also consistent with this hypothesis. Performance on the AX-CPT task “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” (Barch et al 2001, p. 286). With respect to the prepotent response override function, the cue identity and its contextual implications for future responding must be maintained to disambiguate the target status of the subsequent probe and to bias behavioral activity toward the appropriate response.

Despite evidence provided by our study that is consistent with the predictions outlined in the Introduction, limitations and alternative hypotheses require discussion. Persistent concerns in cognitive studies of schizophrenia are that any observed performance decrements may reflect generalized rather than specific deficits and that any observed differences in brain activation may reflect secondary phenomena such as inattention or lack of engagement (e.g., Chapman and Chapman 1973, 2001). Several factors in our study suggest that patients exhibited a specific set of deficits rather than a generalized deficit over a range of conditions: 1) On the AX-CPT, the groups did not differ in accuracy or RTs to cue stimuli (in contrast to probe stimuli), nor did they differ in response to BY trials, which provide a measure of nonspecific response bias; 2) the groups did not differ in overall frequency of nonresponses in either task; 3) the groups differed in dlPFC activation in the predicted direction and only under the predicted conditions; and 4) the specificity of the location of activation deficits in patients further supports the differential deficit.

The imaging results, at least for the AX-CPT, also cannot be explained by the hypothesis that the BCue condition is more difficult or effortful, because more errors overall were committed to probes following the ACues than BCues. In contrast, brain activity was lesser in magnitude to ACues than to BCues, suggesting that increased BCue activity was not associated with increased task difficulty. Thus, the overall pattern of behavioral and imaging results indicate that the two groups were equally engaged in the tasks and argue against lack of behavioral engagement or nonspecific deficit.

As both tasks require active maintenance in WM, the observed group differences could be attributed to patients' difficulties in maintaining representations of cue identity. Such a deficit cannot solely account for the observed prepotency effect, however, because both A and B cue types provide context that required active maintenance, and the groups did not differ in activity on ACue trials. The finding that the BX condition, which is most sensitive to failures of overriding the prepotent response tendency, had more errors at the short than long delay further suggests that active maintenance did not play a predominant role and that context maintenance requires time to achieve full strength. Additionally, greater BCue-related dlPFC activity was associated with faster probe RTs only

in the BCue condition (particularly at the short delay where BCue errors were greatest), consistent with the hypothesis that greater dlPFC activity is associated with faster responses when overriding the prepotent response tendency.

An additional argument against a primary role for active maintenance can be derived from a more detailed examination of the behavioral data. Specifically, the N-Back consists of several different trial types—targets, foils (nontarget repeats), and nonfoils (nontarget nonrepeats). As discussed by Perlstein et al (2001), false alarms on foil trials are sensitive to the maintenance of a trace representation: they equal error rates on target trials and both exceed error rates on nonfoil trials. Based on this reasoning, we would predict that foil and target errors would selectively correlate with errors on long AX trials but not short BX trials, whereas errors on nonfoil trials should correlate with neither. Analyses of the patient data only (due to restricted range of errors in the control group) support this prediction: Collapsing foil, target, and nonfoil errors each across 1- and 2-back loads revealed significant long-AX error correlations with foil and target errors [$r_{s(15)} \geq .51$, $p_s < .05$] but not with nonfoil errors. In contrast, none of the N-Back trial types correlated significantly with short-BX errors ($p_s > .22$). Thus, despite the fact that WM and inhibition are somewhat confounded in the AX-CPT task, the pattern of behavioral findings, although suggesting a critical role for WM processes in performance of the AX-CPT, does implicate the involvement of other processes as well. Findings of dlPFC-mediated antisaccade deficits in schizophrenia patients similarly support the current interpretation (McDowell et al 2002). Deficits in cue encoding also cannot account for the observed effects, because patients and control subjects did not differ in their accuracy to cue stimuli.

Methodologic constraints using the current AX-CPT also prevent this study from fully dissociating the overlapping hemodynamic responses associated with cue- and probe-related processing. Thus, it could be argued that the dlPFC activity reflects response-related competition or conflict effects rather than, or in addition to, preparation for overriding prepotent response tendencies; however, a recent preliminary report using a version of the AX-CPT with 10-sec cue-probe and interpair intervals similarly observed greater BCue than ACue activity in the dlPFC during the cue-probe delay period (MacDonald et al 2000b). Under these long-delay conditions, the hemodynamic response reflecting preparatory and response-related processes associated with cues and probes, respectively, can be clearly dissociated. The RT-activity correlation, selective to the BX condition, also suggests that the observed dlPFC activity is associated with prepa-

ratory rather than response conflict-related processes. Additionally, response conflict-related activity has been shown to differentially engage anterior cingulate, whereas response preparation is associated with dlPFC activity (MacDonald et al 2000a; Ullsperger and von Cramon 2001; van Veen et al 2001).

One must also examine the AX-CPT in the context of classic motor inhibition tasks, such as the Go/No-Go task (Casey et al 1997; Kawashima et al 1996), which are typically associated with activity in more inferior and medial PFC regions. The PFC activation in our study, although predominantly localized to dorsal regions, did extend to the inferior frontal cortex (BA 45), particularly on the right side. Additionally, the AX-CPT differs from classic Go/No-Go tasks commonly employed in response inhibition literature, in that in the former selection signals are presented on a trial-by-trial basis and require maintenance of these cue-signal representations over a period of delay, and a forced-choice response rather than withholding a response is required. Finally, others have similarly shown dlPFC engagement under demands for response inhibition, particularly when the task contained a strong WM component (e.g., Diamond and Goldman-Rakic 1989; Garavan et al 1999). It should also be noted that few studies have examined activity in the preparatory interval of response inhibition paradigms, focusing instead on the postresponse signal.

Finally, our sample of schizophrenia patients was chronically medicated using conventional antipsychotics. The effects of medication on the cognitive processes of interest remain uncertain, although the behavioral data from Barch et al (2001) for medication-naïve patients was generally similar in pattern to the current data. A post hoc correlational analysis between task performance and imaging data with antipsychotic medication doses revealed no significant associations, replicating previous findings for AX-CPT behavioral performance (Cohen et al 1999). Work by Cohen and colleagues (Braver et al 1999; Cohen et al 1992) has suggested, on the basis of computational modeling studies, that dopamine plays a central role in the maintenance of context information; however, the specific roles of dopamine, and the influence of dopaminergic antagonists in schizophrenia cognitive dysfunction remain poorly characterized.

In conclusion, our findings are consistent with the hypothesis that processes engaged during the active maintenance and manipulation in WM and preparation to override prepotent response tendencies are supported by a highly overlapping cortical network. The findings also strongly suggest that schizophrenia patients exhibit deficits in both processes, with concomitant dysfunction in physiologic activation of the dlPFC. Although these find-

ings are consistent with the hypothesis that WM and overriding prepotent responses may reflect the operation of a common mechanism, future studies are required to more fully examine this hypothesis. Future studies are also required to examine any potential influence of antipsychotic medication on brain activity and the cognitive processes of interest and to exploit the sensitivity to temporal dynamics of fMRI to more clearly tease apart active maintenance, preparatory, and response conflict-related processes in patients with schizophrenia.

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