

Prefrontal Cortex Function in Nonpsychotic Siblings of Individuals with Schizophrenia

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Background: Cognitive dysfunction is a hallmark feature of schizophrenia. In recent years, it has been proposed that impairments in attention, working memory and executive function may all reflect an underlying deficit in context processing. In individuals with schizophrenia, deficits in context processing have been associated with functional impairments of the dorsolateral prefrontal cortex (DLPFC).

Methods: We used a variation of the continuous performance task, the AX-CPT, to test the hypothesis that genetic high-risk individuals (full siblings of individuals with schizophrenia) have deficits in context processing and abnormal activation of the DLPFC as compared to community controls.

Results: Siblings of individuals with schizophrenia made significantly more B-X errors on the AX-CPT, indicative of a deficit in context processing. They also showed task-related hyper-activation in a number of brain regions, including the DLPFC.

Conclusions: Inefficient hyper-activation of the DLPFC may underlie deficits in context processing and contribute to the genetic vulnerability for developing schizophrenia.

Key Words: Context processing, DLPFC, executive function, fMRI, genetic high-risk, schizophrenia

Individuals with schizophrenia display deficits in several domains of cognitive functioning. In a meta-analysis, Heinrichs and Zakzanis (1) concluded that this group exhibits deficits in intelligence, memory, attention, spatial ability, language function and executive function. In recent years, it has been proposed that impairments in at least some of these domains, such as attention, working memory, and executive function, in schizophrenia can be explained in terms of a underlying deficit in context processing (2,3). Furthermore, deficits in context processing have been associated with deficits in activation of the dorsolateral prefrontal cortex (DLPFC) (4). The results of several studies in individuals with schizophrenia support an association between deficits in context processing and abnormalities of prefrontal cortex function (5–7). The goal of the current study was to test the hypothesis that nonpsychotic siblings of individuals with schizophrenia also show deficits in context processing and prefrontal activation.

Context processing has been conceptualized as the ability to represent and maintain information and use it effectively to guide behavior (3). Contextual information can include a specific stimulus, processing of previously presented stimuli or even task instructions (8). Moreover, context processing can sub serve other cognitive functions that are often treated as independent: attention (selection and support of task-relevant information for processing), active memory (on-line maintenance of task-relevant information), and inhibition (suppression of task-irrelevant information). When a task involves a delay between a cue and a later contingent response, it is assumed that a working memory function is involved. However, in the context model, the mechanism used to represent context information also underlies the

maintenance of task-relevant information against the interfering and cumulative effects of noise over time. Under these conditions, context representations serve an attentional function by selecting task-relevant information for processing over other potentially competing sources of information.

Research suggests that contextual representations are processed and maintained in the DLPFC. Functional imaging studies have shown that tasks involving working memory, selective attention and certain forms of inhibition increase activity in the DLPFC (9,10). Further, tasks specifically designed to assess the representation and maintenance of context also elicit DLPFC activity (4,5,11–13).

A task frequently used to measure context processing is a variation of the continuous performance task known as the AX-CPT (2). In this task, participants are presented with consecutive pairs of letters that appear individually on a computer screen. The first letter of each pair is referred to as the 'cue' and the second letter of the pair is referred to as the 'probe.' Participants are instructed to make a target response to the probe X but only if it follows the cue A, and a nontarget response to every other letter. There are three possible nontarget trials: B-X (where B refers to any nonA cue), A-Y (where Y refers to any nonX probe), and B-Y (where B refers to any nonA cue and Y refers to any nonX probe). A majority of the trials (70%) are A-X trials and the remaining 30% are split evenly among the other three nontarget trial types. A correct response to X depends upon maintaining the "context" provided by the cue (A or not-A).

The high frequency of target A-X trials creates two biases. The first is to make a target response to an X probe, since this is the correct response on most trials. On B-X trials, context provided by the B cue must be used to inhibit this bias to make a target response to X (which would lead to a false alarm). The second bias is to make a target response after an A cue, since most of the time an X follows the A cue. Theoretically, on trials in which A is not followed by X, this predictive aspect of context actually creates the tendency to false alarm. Thus, intact context representation should hurt performance on A-Y trials but help performance on B-X trials, as the context provided by the cue (not A) prepares one to make the correct nontarget response to a subsequent X probe. In contrast, individuals with impaired context processing should show worse B-X than A-Y perfor-

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Received November 16, 2006; revised May 4, 2007; accepted May 10, 2007.

mance. Although theory dictates an inverse correlation between A-Y and B-X performance, MacDonald *et al.* (14) reported that A-Y and B-X errors were uncorrelated in a large, general population sample. However, Braver *et al.* (15) found a strong inverse correlation between A-Y and B-X reaction times (RTs) after controlling for overall RTs. This finding supports the theoretical notion that individuals with intact context processing may be slower on A-Y trials in order to overcome the predictive aspect of the A cue, which could lead them astray.

A number of independent replications have shown that patients with schizophrenia make significantly more B-X errors compared to controls (2,3) and to nonpsychotic depressed patients (7), but do not differ in AY errors. Such results have been found in both medicated and unmedicated patients (16,17). Studies using tasks other than the AX-CPT to measure context processing have also found deficits among individuals with schizophrenia (18–21). Further, context processing deficits in schizophrenia patients are associated with abnormal activation of the DLPFC (5–7), again in both medicated and unmedicated patients (22,23).

Context processing deficits have also been found among individuals thought to be at increased genetic risk for developing schizophrenia. Barch *et al.* (8) reported context processing deficits in individuals with schizotypal personality disorder, a schizophrenia spectrum disorder (24–26). MacDonald *et al.* (27) found that nonpsychotic relatives of individuals with schizophrenia had increased B-X errors whereas controls had increased A-Y errors. Research has also shown that the nonpsychotic relatives of individuals with schizophrenia show altered activation in the prefrontal cortex during working memory tasks (28–32). Further, recent work by Macdonald (31) on a variant of the AX-CPT found reduced cue-related activation (B cues in particular) in DLPFC among first degree relatives of a mixed group of individuals with schizophrenia and schizoaffective disorder.

In the present study, we tested the specific hypothesis that nonpsychotic siblings of individuals with schizophrenia show context processing deficits (i.e., more B-X errors) and impaired DLPFC function while performing the AX-CPT task compared to community controls.

Methods and Materials

Participants

Participants were recruited through the Conte Center for the Neuroscience of Mental Disorders (CCNMD) at Washington University in St. Louis and included: 30 siblings of individuals with schizophrenia (14 males, 16 female) and 92 healthy participants (39 male, 53 female). The control group was actually comprised of 46 sibling pairs. Similarities and/or differences between controls and their siblings were not the focus of this paper, and all results reported below remained significant when the siblings were compared just to control siblings as well as to the full sample of controls. Thus, we combined controls and their siblings into a single group of controls to simplify the description and presentation of analyses and results.

Individuals with schizophrenia were recruited from local inpatient and outpatient treatment facilities in St. Louis. Diagnoses for all participants were determined using the Structured Clinical Interview for *DSM-IV* (SCID) (33). If the participant met criteria for schizophrenia, his/her full sibling was invited to join the study (siblings). Siblings were excluded for lifetime history of Axis I psychotic disorders (including bipolar), but not other Axis I disorders. Control participants were recruited using local ad-

vertisements in the St. Louis community. Exclusion criteria for controls included the presence of a lifetime history of any Axis I psychiatric disorder or any first-degree relative with a psychotic disorder. All potential participants (i.e., siblings and controls) were also excluded for: (a) meeting *DSM-IV* criteria for substance abuse or dependence within the past 6 months, (b) presence of any clinically unstable or severe medical disorder, or a medical disorder that would confound the assessment of psychiatric diagnosis or render research participation dangerous, (c) head injury with documented neurological sequelae or resulting in loss of consciousness and (d) meeting *DSM-IV* criteria for mental retardation (mild or greater in severity).

Demographic information is displayed in Table 1. Controls had significantly more Caucasian participants than siblings [$X^2(1) = 6.26, p < .05$], but the two groups did not differ significantly on gender [$X^2(1) = .17, p = \text{ns}$]. The groups also did not differ significantly on age [$t(120) = -1.44, p = \text{ns}$], years of education [$t(120) = .35, p = \text{ns}$], years of parent education [$t(118) = -.72, p = \text{ns}$], or handedness [$t(119) = -.81, p = \text{ns}$]. Handedness was assessed using the Edinburgh Handedness Inventory (34). All participants were administered the Vocabulary subtest of the Wechsler Adult Intelligence Scale—third edition (35) as a proxy for general intellectual functioning. The groups were not significantly different on this measure [$t(119) = 1.2, p = \text{ns}$].

Procedures

Participants performed two blood oxygen level-dependent runs of the AX-CPT task. Each task block consisted of target and nontarget trials that appeared intermixed in a pseudorandom sequence. Trial frequency was as follows: 70% A-X, 10% B-X, 10% A-Y, 10% B-Y, which replicates those used in most previous AX-CPT studies (4,15,16,22,36,37). We also manipulated the delay over which participants had to maintain the context (e.g. cue) information.

Stimuli were presented centrally for 500 msec. The delay between cue offset and probe onset was 1000 msec in the short-delay condition and 5000 msec in the long-delay condition. The inter-trial interval varied inversely with delay and condition: 5000 msec from probe offset in the short-delay condition and 1000 msec from probe offset for the long-delay condition. Participants had 1300 msec to respond; responses made after that time were not recorded. Trials were presented to participants blocked, with one run of short-delay trials and one run of long-delay trials; order was counterbalanced across participants. Each run consisted of task blocks (10 trials each, three repetition times (TRs) per trial, a total of 30 TRs) and three fixation blocks (10 TRs each), plus four additional TRs at the beginning and end of each block. Participants received a total of 60 trials (30 with a short

Table 1. Demographic Characteristics of Study Participants

Characteristic	Controls (n = 92)		Siblings (n = 30)	
	M	SD	M	SD
Age (years)	20.2	3.4	21.3	3.5
Gender (% male)	42.4	—	46.7	—
Race (% Caucasian) ^a	78.3	—	63.3	—
Education (years)	13.0	2.5	12.8	2.9
Parental Education (years)	14.9	2.2	15.2	2.4
WAIS-III Vocabulary	11.7	3.1	10.9	3.5
Handedness rating	62.1	47.8	70.0	42.7

M, mean; SD, standard deviation; WAIS, Wechsler Adult Intelligence Scale.

^aControls > Siblings.

Table 2. Required Conditions for Effects of Interest

Main Effect of Delay	
1.	The region demonstrated varied activity across all participants during the long vs. short delay conditions.
2.	The region did not demonstrate a group by delay interaction.
3.	The region demonstrated main effects of delay within each group separately, using a paired sample <i>t</i> test comparing long and short delays.
Main Effect of Group	
1.	The region demonstrated different task-related activity in siblings vs. controls.
2.	The region did not demonstrate a group by delay interaction.
3.	The region demonstrated a significant effect of task in at least one group, defined as a one-sample <i>t</i> test comparing the average of the long and short delays to 0.
Group by Delay Interaction	
1.	The region demonstrated task-related activity that differed between groups as a function of delay.
2.	The region demonstrated a significant effect of delay in at least one group, assessed using paired-sample <i>t</i> tests comparing long and short delays.

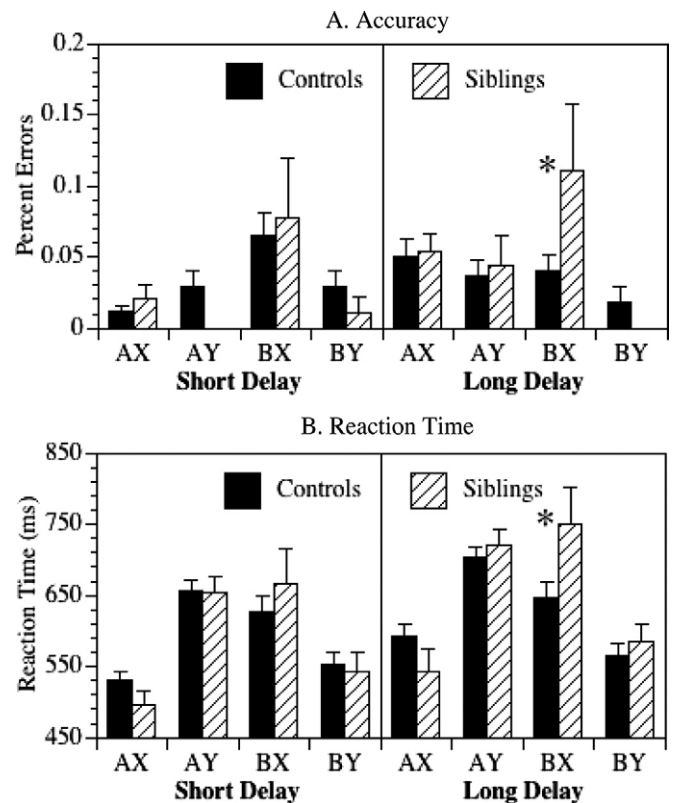
delay and 30 with a long delay). Prior to administering the AX-CPT, participants were read standardized instructions and administered a block of practice trials. This ensured that participants understood the instructions and were performing appropriately.

Scanning was performed on the 1.5T Siemens VISION system (Erlangen, Germany) at the Research Imaging Center of the Mallinckrodt Institute of Radiology at the Washington University School of Medicine. Functional images were collected using an asymmetric spin-echo echo-planar sequence sensitive to blood oxygenation level-dependent contrast (T2*) (TR = 2500 msec, echo time = 50 msec, field of view = 24 cm, flip = 90°). During each functional run, 128 sets of oblique axial images were acquired parallel to the anterior-posterior commissure plane (3.75 × 3.75 mm in plane resolution). Nineteen 7 mm thick slices were acquired in each image. Structural images were acquired using a coronal 3D T1-weighted sequence magnetization prepared rapid gradient echo (TR = 9.7 msec, echo time = 4 msec, flip = 10°; voxel size = 1 × 1 × 1.2 mm). These structural images were used for between subject registration and anatomic localization.

Preprocessing of the functional magnetic resonance imaging data included: 1) compensation for slice-dependent time shifts, 2) elimination of odd/even slice intensity differences due to interpolated acquisition, 3) realignment of data acquired in each subject within and across runs to compensate for rigid body motion (38), 4) intensity normalization to a whole brain mode value of 1000 and 5) spatial smoothing with an 8-mm full width half maximum Gaussian kernel. Functional data were transformed into stereotaxic atlas space (39) by computing a sequence of affine transforms and resampled to 3 mm cubic voxels. Methods for movement correction and cross subject registration are analogous to the linear methods used in automated image registration (40). For each participant, we estimated the magnitude of task-related activation in each voxel with a general linear model using a box-car function convolved with a canonical hemodynamic response, with separate estimates for each delay condition. These estimates were then entered into analyses of variance (ANOVAs) and *t* tests (described below) that treated subjects as a random factor.

Imaging Analyses

Our *a priori* hypotheses were focused on the DLPFC. We therefore created an anatomical mask for DLPFC based on criteria provided by Rajkowski and Goldman-Rakic (41) and used a less conservative statistical threshold for voxels in this region of interest. However, we used a more conservative statistical threshold for all voxels outside of the DLPFC, given that we did not have specific *a priori* hypotheses about these regions. A multi-step approach was used to identify brain regions showing our effects of interest (see below) on the AX-CPT. This approach involved the application of multiple statistical tests, with each test set at a relatively low statistical threshold. We have used this type of approach in a number of previous studies (22,42) and believe it optimizes the trade-off between false positive protection (type 1 error) and sensitivity/power (type 2 error). In order for a brain region to be considered significant, every voxel within that region had to be statistically significant (defined as $p < .02$ within the DLPFC, $p < .005$ outside the DLPFC) for each test required for a given effect. These analyses were designed so that any voxel meeting criteria in all statistical tests would have an α level of at least .0004 within the DLPFC (.000025 outside the DLPFC) for the inference that the voxel demonstrated all of the required patterns simultaneously, though this value is likely an overestimate of the α level given nonindependence in the error terms of the statistical contrasts. This approach does not change the significance level for any individual test (43), but does impact inferences about the likelihood of all tests being significant simultaneously. In addition, we only considered a region to be significant if it contained a cluster of nine or more contiguous voxels. This cluster size requirement

**Figure 1.** Error rate and reaction times on AX-CPT. CPT, continuous performance task.

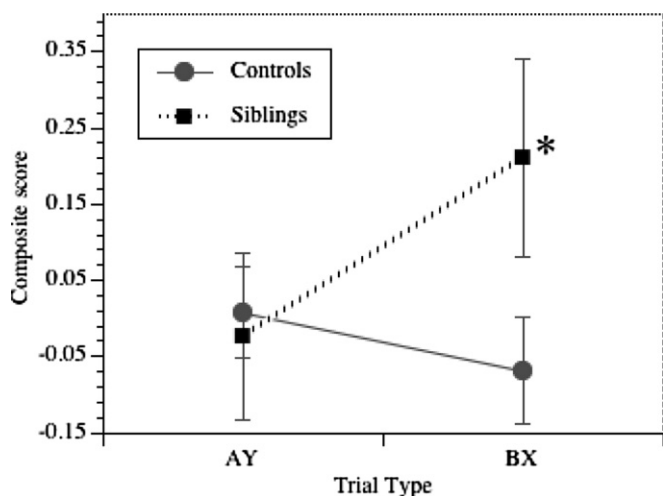


Figure 2. Group by trial type interaction.

provides further protection against type 1 error rates (44,45) and was chosen based on Monte Carlo simulations.

We were interested in identifying regions showing one of the following three effects: main effect of delay, main effect of group or group by delay interaction. To identify these regions, we computed a voxel-wise repeated measures ANOVA with group as a between-subject factor, delay as a within-subject factor and task minus fixation magnitudes as the dependent measure. See Table 2 for the computation of these effects.

Behavioral Analyses

Behavioral performance on the AX-CPT was evaluated using both errors and reaction times to correct trials. A composite score was computed for each of the four trial types by averaging z-scored error and RT data. All analyses reported below were conducted using this composite variable, unless otherwise noted. Applying signal detection theory, a *d'* measure was also com-

puted using correct A-X responses as hits and B-X responses as false alarms (separately for long and short delays). We termed this measure *d'*-context because we believe it to be more sensitive to context processing than a traditional *d'* measure which would also include A-Y errors (2).

Results

Behavioral Analyses

Raw data for errors and RTs across all trial types are presented in Figure 1. A repeated measures ANOVA, with group as a between-subject factor and delay and trial-type as within-subject factors, revealed no main effect of delay [$F(1, 120) = .72, p = ns$] or a significant delay by group interaction [$F(1, 120) = 2.79, p = ns$]. The main effect of trial-type was also not significant [$F(3, 360) = .91, p = ns$], but the group by trial-type interaction was significant [$F(3, 360) = 3.50, p < .05$]. Planned contrasts revealed that the group by trial-type interaction for the B-X condition was significant at a trend level [$F(1, 120) = 3.63, p = .06$]. Follow-up *t* tests confirmed that siblings performed worse than controls in the long delay condition [$t(120) = -2.5, p < .05; d = .40$] but not in the short delay condition [$t(120) = -.80, p = ns$]. Planned contrasts also revealed that siblings were significantly worse on the B-X than A-Y condition compared to controls, who did not differ on these trial types [$F(1, 120) = 5.1, p < .05$] (Figure 2).

An independent samples *t* test for *d'*-context revealed no significant differences between controls and siblings on this measure, either in the short [$t(120) = 1.3, p = ns$] or the long delay [$t(120) = 1.5, p = ns$] conditions.

Imaging Analyses

We began by examining regions that showed a main effect of delay in both groups. Consistent with prior research, we found regions in bilateral DLPFC that showed increased activity in the long versus short delay conditions (see Table 3 and Figure 3). In addition, we found that regions in bilateral cerebellum, bilateral insula, bilateral precentral gyrus, left middle frontal gyrus and left

Table 3. Regions Showing a Main Effect of Delay

Region of Interest	Brodmann's Area	# Voxels	Talairach Coordinates			z-value	Effect Size
			x	y	z		
Activation: Long > Short							
R DLPFC	9	118	+40	+25	+34	4.25	.44
R DLPFC	9	60	+30	+42	+21	3.60	.45
L DLPFC	9	64	-41	+26	+30	4.04	.36
L Middle Frontal Gyrus	6	58	-3	-3	+58	4.25	.42
R Precentral Gyrus	6	13	+47	-1	+43	3.44	.37
L Precentral Gyrus	6	19	-29	-16	+55	3.62	.34
L Inferior Parietal	40	51	-43	-53	+47	4.73	.53
R Temporal Lobe	37	11	+45	-43	-12	3.60	.39
R Insula	13	30	+36	+16	+8	3.98	.42
L Insula	13	37	-44	+11	+4	3.70	.42
R Cerebellum		20	+26	-37	-43	3.98	.48
L Cerebellum		10	-14	-37	-25	3.25	.42
Deactivation: Short > Long							
L DLPFC	8	15	-14	+46	+42	3.07	.32
R Middle Temporal Lobe	39	28	+44	-75	+21	3.55	.42
L Posterior Cingulate	23	39	-7	-57	+17	3.73	.47
R Postcentral Gyrus	3	11	+37	-33	+64	3.47	.39
L Precuneus	31	12	-15	-51	+32	3.80	.44

Effect sizes reported as absolute values. DLPFC, dorsolateral prefrontal cortex; L, left; R, right.

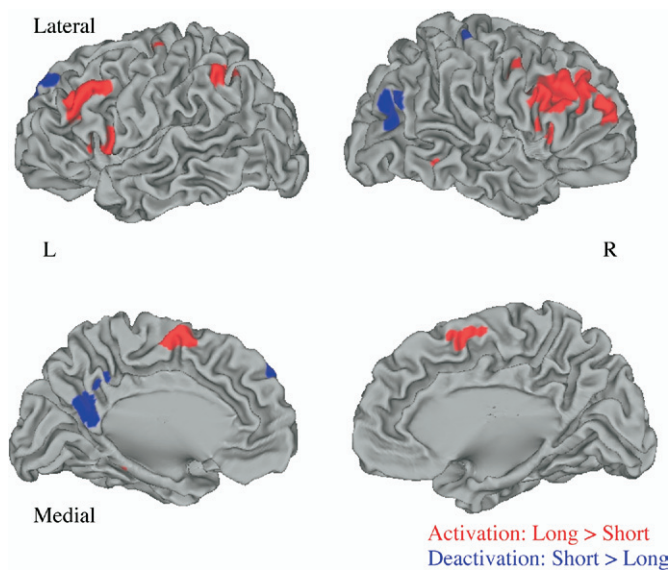


Figure 3. Regions showing a main effect of delay.

inferior parietal lobe also showed greater activity at the long delay condition. Regions in the left precuneus, left posterior cingulate, right postcentral gyrus, and right middle temporal lobe were identified as showing greater deactivation at the short versus the long delay. Effect sizes ranged from .32 to .53.

Next, we examined regions that showed a main effect of group (see Table 4 and Figure 4). Regions in which siblings showed greater general task-related activity than controls included bilateral DLPFC, bilateral precentral gyrus, right superior and inferior frontal gyri, right superior and inferior parietal lobes, right medial temporal gyrus, right insula, right caudate, right claustrum, right cerebellum, and left thalamus. Effect sizes ranged from .40 to .67.

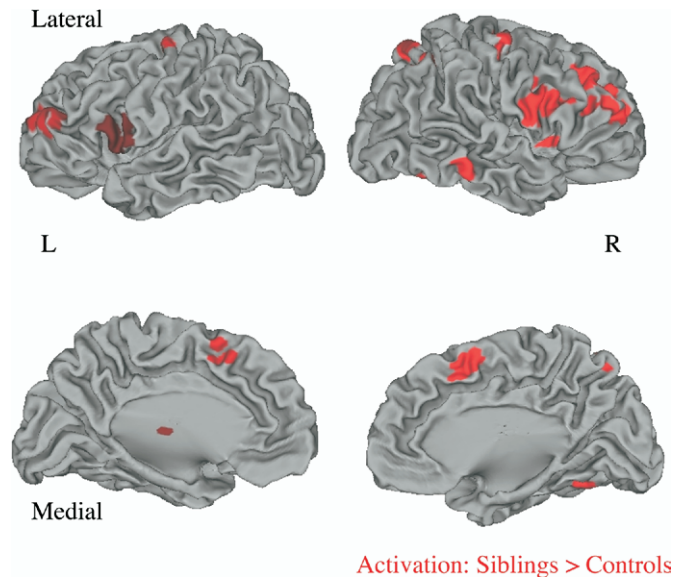


Figure 4. Regions showing a main effect of group.

We also examined regions that showed a group by delay interaction (see Table 5 and Figure 5). The pattern observed in right DLPFC was for siblings to show greater activation than controls during the short delay and for controls to show greater activation during the long delay. There was one region in left middle frontal gyrus that showed a different pattern: siblings showed greater deactivation than controls during the long delay but greater activation than controls during the long delay. Effect sizes ranged from .58 to .75.

Discussion

This study compared AX-CPT task performance and functional activation in siblings of individuals with schizophrenia and

Table 4. Regions Showing a Main Effect of Group

Region of Interest	Brodmann's Area	# Voxels	Talairach Coordinates			z-value	Effect Size
			x	y	z		
Activation: Sibling > Control							
R DLPFC	9	169	+29	+36	+25	3.75	.61
R DLPFC	46	9	+45	+18	+26	2.63	.40
L DLPFC	10	31	-29	+47	+20	3.49	.53
R Inferior Frontal Gyrus	44	68	+53	+7	+22	4.14	.63
R Superior Frontal Gyrus	6	51	+1	+9	+52	3.56	.58
R Precentral Gyrus	6	21	+41	-1	+33	3.07	.54
R Precentral Gyrus	6	55	+30	-14	+57	3.83	.67
L Precentral Gyrus	44	55	-52	+10	+9	4.21	.67
L Precentral Gyrus	6	26	-30	-15	+64	4.17	.67
R Inferior Parietal	7	10	+35	-57	+46	3.04	.53
R Superior Parietal	7	22	+18	-68	+57	3.64	.60
R Middle Temporal Gyrus	21	15	+64	-33	-12	3.38	.52
R Insula	9	9	+38	+13	+1	2.97	.49
R Caudate	16	16	+30	-31	+6	3.93	.61
R Claustrum	16	16	+27	+10	+15	3.18	.53
L Thalamus	15	15	-14	-22	+5	3.40	.57
R Cerebellum	36	36	+8	-33	-49	3.91	.61
R Cerebellum	13	13	+31	-57	-20	3.33	.54

Effect sizes reported as absolute values.
DLPFC, dorsolateral prefrontal cortex; L, left; R, right.

Table 5. Regions Showing a Group by Delay Interaction

Region of Interest	Brodmann's Area	# Voxels	Talairach Coordinates			z-value	Effect Size
			x	y	z		
Activation: Short - Sibling > Control, Long - Control > Sibling							
R DLPFC	10	11	+26	+51	+24	2.78	.58
R DLPFC	9	18	+43	+13	+36	3.02	.63
Deactivation: Short - Sibling > Control, Long - Control > Sibling							
R Middle Frontal Gyrus	6	11	-30	+4	+62	3.64	.75

Effect sizes reported as absolute values.

DLPFC, dorsolateral prefrontal cortex; R, right.

community controls. Data support the hypothesis that siblings' performance was significantly worse than controls' in the B-X condition. Siblings and controls did not differ significantly in the A-Y condition, but planned contrasts revealed that siblings made significantly more B-X than A-Y errors. This pattern has been previously reported in patients with schizophrenia (2,3,16,17) and is indicative of deficits in context processing. Data are consistent with other reports of context processing deficits in first-degree relatives of schizophrenia patients (14,27,31).

Analysis of imaging data confirmed that both controls and siblings showed greater task-related activation in DLPFC during the long delay condition, consistent with the hypothesis that DLPFC plays a role in maintaining context over a delay period. Imaging results also revealed that as a group, siblings showed greater task-related activation than controls in DLPFC and other regions. However group by delay analyses demonstrated that siblings showed greater activation only during the short-delay condition. During the long-delay condition, DLPFC was more active in controls than in siblings.

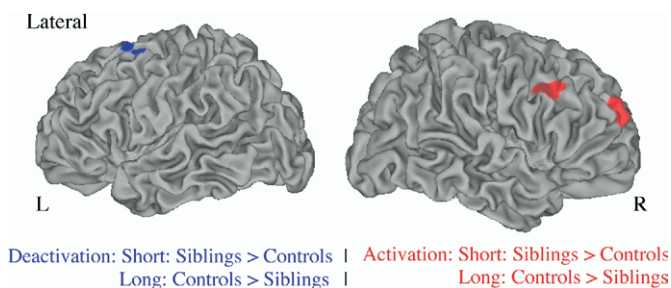
Task related hyper-activation in siblings is consistent with findings in the schizophrenia literature of enhanced task-related activity during performance of working memory tasks (30,46–50). Some researchers have suggested that hyper-activation during cognition in schizophrenia is related to inefficient processing in the face of increased task demands (51,52). According to this hypothesis, the theoretical response of the DLPFC is represented as an inverted U-shaped curve. Individuals with schizophrenia and healthy controls are theorized to have separate curves, where schizophrenia patients reach the peak of the inverted U sooner than controls, thus demonstrating hyper-activation at lower working memory loads. Our data suggest that DLPFC was more active in siblings during the short delay condition but more active in controls during the long delay condition. Siblings also made more B-X errors during the long delay. This pattern of performance suggests that siblings also show hyper-activity while performing a relatively low-demand task; when demands are high, activity decreases and perfor-

mance suffers. Thus, in this model, the curve for siblings could theoretically lie between that for patients and healthy controls. Manoach (52) proposed that the 'inverted U-shaped model' can be called upon to resolve discrepant findings about task-related hypo- versus hyper-activation in the schizophrenia literature. This 'inverted U hypothesis' has gained empirical support from a study of individuals with schizophrenia, where some such individuals performed as well as healthy controls on the two-back version of the n-back task and showed hyper-activation of the DLPFC, while others performed worse than controls and showed hyper-activation of the DLPFC (51).

Our results support the hypothesis that inefficient processing of context information and hyper-activation of the DLPFC may be related to genetic vulnerability for schizophrenia. In our sample of siblings, we found evidence of hyper-activation of a number of regions, including the DLPFC, and significant performance deficits in the B-X condition. These findings are consistent with previous reports of hyper-activity in DLPFC and other regions among relatives of individuals with schizophrenia in studies using more traditional working memory paradigms (28–30,32).

We have interpreted hyper-activation during AX-CPT as inefficient processing. It is possible that differences in strategy use could also account for the significant differences in brain activity in controls and siblings. Braver, Gray, and Burgess (53) have proposed two types of cognitive control strategies for tasks such as AX-CPT: proactive and reactive. A proactive strategy would require one to pay attention to the cue as it appears and prepare for a response to the subsequent probe, whereas a reactive strategy involves minimal processing of the cue information at the time of presentation but requires reactivation of the cue information when the probe appears. Previous research suggests that there are age differences in strategy use (15,36). Paxton *et al.* (54) have argued that a proactive strategy might be more effective and efficient since it maximizes correct responses on most (i.e., A-X) trials. Thus, it is possible that siblings may be using a different (i.e., reactive) strategy than controls. However, such a strategy is arguably less efficient than a proactive strategy, which may be used by controls.

Another alternative to the inefficiency hypothesis is the compensation hypothesis, which suggests that an increase in activity is related to response-related activity rather than cue-maintenance. Support for this hypothesis comes from a recent study by MacDonald *et al.* (31), who found subtle reductions in prefrontal activity for relatives following cue presentation and an increase following the probe. A limitation of the present study was its 'blocked' design, which made it difficult to examine functional changes related to different cue and probe presentations. Future event-related designs with AX-CPT in high-risk samples may be better able to investigate how these individuals process cue-related information. An event-related design would

**Figure 5.** Regions showing a group by delay interaction.

also allow investigation of brain activity during specific events, such as presentation of B cues versus A cues or responses to targets.

It is notable that we observed significant performance deficits of a moderate effect size on B-X trials, even though we used a relatively few number of B-X trials. We did not find overall performance differences across trials in siblings and controls. Nonetheless, we observed significant group differences of moderate to large effect sizes in brain activity related to context processing. Such results suggest that functional magnetic resonance imaging adds to our ability to detect and characterize cognitive abnormalities related to the genetic liability for schizophrenia. Follow-up data on genetically high-risk participants may also shed light on the power of subtle neurocognitive and neurophysiologic deficits to predict conversion to full blown schizophrenia.

We wish to thank the individuals with schizophrenia and their families who participated in this work. In addition, we thank the staff of the Administration and Assessment Core at the Washington University Conte Center for the Neuroscience of Mental Disorders.

This work was supported by a National Alliance for Research on Schizophrenia and Depression Young Investigator's award, National Institute of Mental Health Grants MH60887 and MH56584, and the Conte Center for the Neuroscience of Mental Disorders (MH071616).

The authors declare they have no conflicts of interest, financial or otherwise, to disclose.

- Heinrichs RW, Zakzanis KK (1998): Neurocognitive deficit in schizophrenia: A quantitative review of the evidence. *Neuropsychologia* 12:426–445.
- Servan-Schreiber D, Cohen JD, Steingard S (1996): Schizophrenic deficits in the processing of context: A test of a theoretical model. *Arch Gen Psychiatry* 53:1105–1113.
- Cohen JD, Barch DM, Carter C, Servan-Schreiber D (1999): Context-processing deficits in schizophrenia: Converging evidence from three theoretically motivated cognitive tasks. *J Abnorm Psychol* 108:120–133.
- Barch DM, Braver TS, Nystrom LE, Forman SD, Noll DC, Cohen JD (1997): Dissociating working memory from task difficulty in human prefrontal cortex. *Neuropsychologia* 35:1373–1380.
- MacDonald AW 3rd, Carter CS (2003): Event-related fMRI study of context processing in dorsolateral prefrontal cortex of patients with schizophrenia. *J Abnorm Psychol* 112:689–697.
- Perlstein WM, Dixit NK, Carter CS, Noll DC, Cohen JD (2003): Prefrontal cortex dysfunction mediates deficits in working memory and prepotent responding in schizophrenia. *Biol Psychiatry* 53:25–38.
- Holmes AJ, MacDonald A, Carter CS, Barch DM, Stenger VA, Cohen JD (2005): Prefrontal functioning during context processing in schizophrenia and major-depression: An event related fMRI study. *Schizophr Res* 76:199–206.
- Barch DM, Mitropoulou V, Harvey PD, New AS, Silverman JM, Siever LJ (2004): Context-processing deficits in schizotypal personality disorder. *J Abnorm Psychol* 113:556–568.
- Goldman-Rakic PS (1996): The prefrontal landscape: Implications of functional architecture for understanding human mentation and the central executive. In: Roberts AC, Robbins TW, Weiskrantz L (eds), *The prefrontal cortex: Executive and cognitive functions*. Oxford: Oxford University Press, pp 87–103.
- Jonides J, Smith EE (1997): The architecture of working memory. In Rugg MD (ed), *Cognitive neuroscience*. Cambridge, MA: The MIT Press.
- Braver TS, Cohen JD, Servan-Schreiber D (1995): Neural network simulations of schizophrenic performance in a variant of the CPT-AX: A predicted double dissociation. *Schizophr Res* 15:110.
- Cohen JD, Forman SD, Braver TS, Casey BJ, Servan-Schreiber D, Noll DC (1994): Activation of the prefrontal cortex in a nonspatial working memory task with functional MRI. *Hum Brain Mapp* 1:293–304.
- Sylvester CY, Wager TD, Lacey SC, Hernandez L, Nichols TE, Smith EE, *et al.* (2003): Switching attention and resolving interference: fMRI measures of executive functions. *Neuropsychologia* 41:357–370.
- MacDonald AW, Goghari VM, Hicks BM, Flory JD, Carter CS, Manuck SB (2005): A convergent-divergent approach to context processing, general intellectual functioning, and the genetic liability to schizophrenia. *Neuropsychologia* 19:814–821.
- Braver TS, Satpute AB, Rush BK, Racine CA, Barch DM (2005): Context processing and context maintenance in healthy aging and early stage dementia of the Alzheimer's type. *Psychol Aging* 20:33–46.
- Barch DM, Carter CS, MacDonald A, Braver TS, Cohen JD (2003): Context processing deficit in schizophrenia: Diagnostic specificity, 4-week course, and relationships to clinical symptoms. *J Abnorm Psychol* 112:132–143.
- Javitt DC, Shelley A, Silipo G, Lieberman JA (2000): Deficits in auditory and visual context-dependent processing in schizophrenia. *Arch Gen Psychiatry* 57:1131–1137.
- Stratta P, Daneluzzo E, Bustini M, Prosperini P, Rossi A (1999): Schizophrenic patients use context-independent reasoning more often than context-dependent reasoning as measured by the Cognitive Bias Task (CBT): A controlled study. *Schizophr Res* 37:45–51.
- Condray R, Steinhauer SR, Cohen JD, van Kammen DP, Kasperek A (1999): Modulation of language processing in schizophrenia: effects of context and haloperidol on the event-related potential. *Biol Psychiatry* 45:1336–1355.
- Titone D, Levy DL, Holzman PS (2000): Contextual insensitivity in schizophrenic language processing: evidence from lexical ambiguity. *J Abnorm Psychol* 109:761–767.
- Niznikiewicz MA, O'Donnell BF, Nestor PG, Smith L, Law S, Karapellou M, *et al.* (1997): ERP assessment of visual and auditory language processing in schizophrenia. *J Abnorm Psychol* 106:85–94.
- Barch DM, Carter CS, Braver TS, McDonald A, Sabb FW, Noll DC, *et al.* (2001): Selective deficits in prefrontal cortex regions in medication naive schizophrenia patients. *Arch Gen Psychiatry* 50:280–288.
- MacDonald A, Carter CS, Kerns JG, Ursu S, Barch DM, Holmes AJ, *et al.* (2005): Specificity of prefrontal dysfunction and context processing deficits to schizophrenia in never-medicated patients with first-episode psychosis. *Am J Psychiatry* 162:475–484.
- Cadenhead KS (2002): Vulnerability markers in the schizophrenia spectrum: implications for phenomenology, genetics, and the identification of the schizophrenia prodrome. *Psychiatr Clin North Am* 25:837–853.
- Baron M, Gruen R, Rainer J, Kane J, Asnis L, Lord S (1985): A family study of schizophrenic and normal control probands: Implications for the spectrum concept of schizophrenia. *Am J Psychiatry* 142:447–455.
- Kety SS, Wender PH, Jacobsen B, Ingraham LJ, Jansson L, Faber B, *et al.* (1994): Mental illness in the biological and adoptive relatives of schizophrenic adoptees. Replication of the Copenhagen Study in the rest of Denmark. *Archives of General Psychiatry* 51:442–455.
- MacDonald AW, Pogue-Geile MF, Johnson MK, Carter CS (2003): A specific deficit in context processing in the unaffected siblings of patients with schizophrenia. *Arch Gen Psychiatry* 60:57–65.
- Callicott JH, Egan MF, Mattay VS, Bertolino A, Bone AD, Verchinski B, *et al.* (2003): Abnormal fMRI response of the dorsolateral prefrontal cortex in cognitively intact siblings of patients with schizophrenia. *Am J Psychiatry* 160:709–719.
- Thermenos HW, Seidman LJ, Breiter H, Goldstein JM, Goodman JM, Poldrack R, *et al.* (2004): Functional magnetic resonance imaging during auditory verbal working memory in nonpsychotic relatives of persons with schizophrenia: A pilot study. *Biol Psychiatry* 55:490–500.
- Brahmbhatt S, Haut K, Csernansky JG, Barch DM (2006): Neural correlates of verbal and nonverbal working memory deficits in individuals with schizophrenia and their high-risk siblings. *Schizophr Res* 87:191–204.
- MacDonald A, Becker TM, Carter CS (2006): Functional magnetic resonance imaging study of cognitive control in the healthy relatives of schizophrenia patients. *Biol Psychiatry* 60:1241–1249.
- Seidman LJ, Thermenos HW, Poldrack R, Peace NK, Koch JK, Faraone SV, *et al.* (2006): Altered brain activation in dorsolateral prefrontal cortex in adolescents and young adults at genetic risk for schizophrenia: An fMRI study of working memory. *Schizophr Res* 85:58–72.
- Spitzer RL, Williams JB, Gibbon M, First MB (1990): *User's guide for the structured clinical interview for DSM-III-R: SCID*. Washington D. C.: American Psychiatric Press.

34. Oldfield RC (1971): The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia* 9:97–113.
35. Wechsler D (1997): *Wechsler Adult Intelligence Scale - Third Edition*. San Antonio: The Psychological Corporation.
36. Braver TS, Barch DM, Keys BA, Carter CS, Cohen JD, Kaye JA, *et al.* (2001): Context processing in older adults: Evidence for a theory relating cognitive control to neurobiology in healthy aging. *J Exp Psychol Gen* 130: 746–763.
37. Braver TS, Cohen JD (2001): Working memory, cognitive control, and the prefrontal cortex: Computational and empirical studies. *Cognit Process* 2:25–55.
38. Ojemann J, Akbudak E, Snyder A, McKinsty R, Raichle M, Conturo T (1997): Anatomic localization and quantitative analysis of gradient refocused echo-planar fMRI susceptibility artifacts. *Neuroimage* 6:156–167.
39. Talairach J, Tournoux P (1988): *Co-planar stereotaxic atlas of the human brain*. New York: Thieme.
40. Woods RP, Grafton ST, Watson JDG, Sicotte NL, Mazziotta JC (1998): Automated image registration: II. intersubject validation of linear and nonlinear models. *J Comput Assist Tomogr* 22:153–165.
41. Rajkowski G, Goldman-Rakic PS (1995): Cytoarchitectonic definition of prefrontal areas in the normal human cortex: II. Variability in locations of areas 9 and 46 and relationship to the talairach coordinate system. *Cereb Cortex* 5:323–337.
42. Braver T, Reynolds J, Donaldson D (2003): Neural mechanisms of transient and sustained cognitive control during task switching. *Neuron* 39:713–726.
43. Nichols T, Brett M, Andersson J, Wager T, Poline JB (2005): Valid conjunction inference with the minimum statistic. *Neuroimage* 25:653–660.
44. Forman SD, Cohen JD, Fitzgerald M, Eddy WF, Mintun MA, Noll DC (1995): Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. *Magn Reson Med* 33:636–647.
45. McAvoy MP, Ollinger JM, Buckner RL (2001): Cluster size thresholds for assessment of significant activation in fMRI. *Neuroimage* 13:S198.
46. Schneider F, Habel U, Reske M, Kellermann T, Stocker T, Shah NJ, *et al.* (2006): Neural correlates of working memory dysfunction in first-episode schizophrenia patients: An fMRI multi-center study. *Schizophr Res* 89:198–210.
47. Callicott JH, Bertolino A, Mattay VS, Langheim FJ, Duyn J, Coppola R, *et al.* (2000): Physiological dysfunction of the dorsolateral prefrontal cortex in schizophrenia revisited. *Cereb Cortex* 10:1078–1092.
48. Manoach DS, Press DZ, Thangaraj V, Searl MM, Goff DC, Halpern E, Saper CB, Warach S (1999): Schizophrenia subjects activate dorsolateral prefrontal cortex during a working memory task, as measured by fMRI. *Biol Psychiatry* 45:1128–1137.
49. Manoach DS, Gollub RL, Benson ES, Searl MM, Goff DC, Halpern E, *et al.* (2000): Schizophrenic subjects show aberrant fMRI activation of dorsolateral prefrontal cortex and basal ganglia during working memory performance. *Biol Psychiatry* 48:99–109.
50. Thermenos HW, Goldstein JM, Buka SL, Poldrack RA, Koch JK, Tsuang MT, *et al.* (2005): The effect of working memory performance on functional MRI in schizophrenia. *Schizophr Res* 74:179–194.
51. Callicott JH, Mattay VS, Verchinski BA, Marengo S, Egan MF, Weinberger DR (2003): Complexity of prefrontal cortical dysfunction in schizophrenia: more than up or down. *Am J Psychiatry* 160:2209–2215.
52. Manoach D (2003): Prefrontal cortex dysfunction during working memory performance in schizophrenia: reconciling discrepant findings. *Schizophr Res* 60:285–298.
53. Braver TS, Gray JR, Burgess GC (2007): Explaining the many varieties of working memory variation: Dual mechanisms of cognitive control. In Conway AR, Jarrold C, Kane M, Miyake A, Towse J (eds), *Variation in working memory*. Oxford: Oxford University Press.
54. Paxton JL, Barch DM, Storaandt M, Braver TS (2006): Effects of environmental support and strategy training on older adults' use of context. *Psychol Aging* 21:499–509.