Prefrontal Cortex Function in Nonpsychotic Siblings of Individuals with Schizophrenia

Zainab Delawalla, John G. Csernansky, and Deanna M. Barch

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

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

ARTICLE IN PRESS

BIOL PSYCHIATRY 2007;xx:xxx

0006-3223/07/$32.00
doi:10.1016/j.biopsych.2007.05.007
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formance. 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 A-Y 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 advertisements 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 [X2(1) = 6.26, p < .05], but the two groups did not differ significantly on gender [X2(1) = .17, p = ns]. The groups also did not differ significantly on age [t(120) = -1.44, p = ns], years of education [t(120) = .35, p = ns], years of parent education [t(118) = - .72, p = ns], or handedness [t(119) = -.81, p = 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 = 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 ms 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 time (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 delay over which participants had to maintain the context (e.g., cue) information.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controls (n = 92)</th>
<th>Siblings (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>20.2 ± 3.4</td>
<td>21.3 ± 3.5</td>
</tr>
<tr>
<td>Gender (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>42.4 ± 46.7</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>57.6 ± 46.7</td>
<td></td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>78.3 ± 63.3</td>
<td></td>
</tr>
<tr>
<td>Non-Caucasian</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education (years)</td>
<td>13.0 ± 2.5</td>
<td>12.8 ± 2.9</td>
</tr>
<tr>
<td>Parental Education (years)</td>
<td>14.9 ± 2.2</td>
<td>15.2 ± 2.4</td>
</tr>
<tr>
<td>WAIS-III Vocabulary</td>
<td>11.7 ± 3.1</td>
<td>10.9 ± 3.5</td>
</tr>
<tr>
<td>Handedness rating</td>
<td>62.1 ± 47.8</td>
<td>70.0 ± 42.7</td>
</tr>
</tbody>
</table>

M, mean; SD, standard deviation; WAIS, Wechsler Adult Intelligence Scale. *Controls > Siblings.
Table 2. Required Conditions for Effects of Interest

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

prior (appropriately) administered a block of practice trials. This ensured that participants were read standardized instructions and 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 x 3.75 mm in plane resolution). Nineteen 7 mm thick slices were acquired in each image. Structural images were acquired using a coronal 3D TI-weighted sequence magnetization prepared rapid gradient echo (TR = 9.7 msec, echo time = 4 msec, flip = 10°, voxel size = 1 x 1 x 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 $\alpha$ level of at least .0004 within the DLPFC (.0000025 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 $\alpha$ 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.
Applying signal detection theory, a d’ measure was also conducted using this composite variable, unless otherwise noted. The z-scored error and RT data. All analyses reported below were computed for each of the four trial types by averaging the 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 computed 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 \( F(1, 120) = .72, p = \text{ns} \) or a significant delay by group interaction \( F(1, 120) = 2.79, p = \text{ns} \). The main effect of trial-type was also not significant \( F(3, 360) = .91, p = \text{ns} \), 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 \( t(120) = -.80, p = \text{ns} \). 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 \( t(120) = 1.3, p = \text{ns} \) or the long delay \( t(120) = 1.5, p = \text{ns} \) 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

![Figure 2. Group by trial type interaction.](https://www.sobp.org/journal)

Table 3. Regions Showing a Main Effect of Delay

<table>
<thead>
<tr>
<th>Region of Interest</th>
<th>Brodmann’s Area</th>
<th># Voxels</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>z-value</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Activation: Long &gt; Short</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R DLPFC</td>
<td>9</td>
<td>118</td>
<td>+40</td>
<td>+25</td>
<td>+34</td>
<td>4.25</td>
<td>.44</td>
</tr>
<tr>
<td>R DLPFC</td>
<td>9</td>
<td>60</td>
<td>+30</td>
<td>+42</td>
<td>+21</td>
<td>3.60</td>
<td>.45</td>
</tr>
<tr>
<td>L DLPFC</td>
<td>6</td>
<td>13</td>
<td>+47</td>
<td>-1</td>
<td>+43</td>
<td>3.44</td>
<td>.37</td>
</tr>
<tr>
<td>L Middle Frontal Gyrus</td>
<td>6</td>
<td>19</td>
<td>+43</td>
<td>+53</td>
<td>+47</td>
<td>4.73</td>
<td>.53</td>
</tr>
<tr>
<td>R Precentral Gyrus</td>
<td>40</td>
<td>51</td>
<td>+45</td>
<td>-3</td>
<td>-12</td>
<td>3.60</td>
<td>.39</td>
</tr>
<tr>
<td>R Insula</td>
<td>13</td>
<td>30</td>
<td>+36</td>
<td>+16</td>
<td>+8</td>
<td>3.98</td>
<td>.42</td>
</tr>
<tr>
<td>L Insula</td>
<td>13</td>
<td>37</td>
<td>+44</td>
<td>+11</td>
<td>+4</td>
<td>3.70</td>
<td>.42</td>
</tr>
<tr>
<td>R Cerebellum</td>
<td>20</td>
<td>26</td>
<td>-37</td>
<td>-43</td>
<td>3.98</td>
<td>.48</td>
<td></td>
</tr>
<tr>
<td>L Cerebellum</td>
<td>10</td>
<td>14</td>
<td>-14</td>
<td>-37</td>
<td>-25</td>
<td>3.25</td>
<td>.42</td>
</tr>
<tr>
<td><strong>Deactivation: Short &gt; Long</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L DLPFC</td>
<td>8</td>
<td>15</td>
<td>-14</td>
<td>+46</td>
<td>+42</td>
<td>3.07</td>
<td>.32</td>
</tr>
<tr>
<td>R Middle Temporal Lobe</td>
<td>39</td>
<td>28</td>
<td>-44</td>
<td>-75</td>
<td>+21</td>
<td>3.55</td>
<td>.42</td>
</tr>
<tr>
<td>L Posterior Cingulate</td>
<td>23</td>
<td>39</td>
<td>-7</td>
<td>-57</td>
<td>+17</td>
<td>3.73</td>
<td>.47</td>
</tr>
<tr>
<td>R Postcentral Gyrus</td>
<td>3</td>
<td>11</td>
<td>+37</td>
<td>-33</td>
<td>+64</td>
<td>3.47</td>
<td>.39</td>
</tr>
<tr>
<td>L Precuneus</td>
<td>31</td>
<td>12</td>
<td>-15</td>
<td>-51</td>
<td>+32</td>
<td>3.80</td>
<td>.44</td>
</tr>
</tbody>
</table>

Effect sizes reported as absolute values.

DLPFC, dorsolateral prefrontal cortex; L, left; R, right.
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.

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 5. Regions Showing a Group by Delay Interaction

<table>
<thead>
<tr>
<th>Region of Interest</th>
<th>Brodmann's Area</th>
<th># Voxels</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>z-value</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Activation: Short - Sibling &gt; Control, Long - Control &gt; Sibling</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R DLPFC</td>
<td>10</td>
<td>11</td>
<td>+26</td>
<td>+51</td>
<td>+24</td>
<td>2.78</td>
<td>.58</td>
</tr>
<tr>
<td>R DLPFC</td>
<td>9</td>
<td>18</td>
<td>+43</td>
<td>+13</td>
<td>+36</td>
<td>3.02</td>
<td>.63</td>
</tr>
<tr>
<td><strong>Deactivation: Short - Sibling &gt; Control, Long - Control &gt; Sibling</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R Middle Frontal Gyrus</td>
<td>6</td>
<td>11</td>
<td>-30</td>
<td>+4</td>
<td>+62</td>
<td>3.64</td>
<td>.75</td>
</tr>
</tbody>
</table>

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 performance suffers. Thus, in this model, the inverted U-shaped model can be used to explain 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 hypo-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...
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.


