A Specific Deficit in Context Processing in the Unaffected Siblings of Patients With Schizophrenia

Angus W. MacDonald III, PhD; Michael F. Pogue-Geile, PhD; Melissa K. Johnson, BA; Cameron S. Carter, MD

Background: Understanding the biological basis of complex, heritable illnesses such as schizophrenia is facilitated by sensitive and functionally specific measures of intermediate processes. Context processing is a theoretically motivated construct associated with executive function. Impairments in this process have been associated with dysfunction of the prefrontal cortex. In the present study, we evaluated whether a specific deficit in context processing could be associated with the unexpressed genetic liability to schizophrenia.

Methods: Twenty-four patients with schizophrenia, 24 unaffected siblings and 36 control subjects completed a version of the AX task with (1) a condition that required context processing and (2) an expectancy condition in which intact context processing could lead to errors.

Results: Patients and unaffected siblings performed relatively worse in the context processing condition, whereas controls performed relatively worse in the expectancy condition. A double dissociation between siblings and controls (F = 9.5, P < .005) constituted strong evidence of a specific deficit in context processing associated with a familial or genetic liability to schizophrenia. Preliminary evidence of high diagnostic efficiency was also noted (specificity, 38%; and sensitivity, 100%).

Conclusions: Context processing deficits have been associated with dorsolateral prefrontal cortex dysfunctions in schizophrenia. Such a dysfunction may occur even when genetic liability to schizophrenia is unexpressed clinically. The present method of demonstrating a double dissociation may be a useful approach to exploring endophenotypes related to specific cognitive and neural processes that can be measured in ways sensitive to subtle group differences.

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The generalized deficit confound is important to address in family studies of schizophrenia. First, the confound is a source of noise for molecular genetic studies that use endophenotypes. The purpose of an endophenotype is to increase statistical power to detect liability genes by identifying gene carriers who do not manifest clinical symptoms. However, this potential gain in power may be offset if the endophenotype is merely sensitive to heterogeneous causes of generalized deficits (which include lower intelligence, differences in motivation and other personality factors, or deficits in other cognitive processes). Specific deficits should be easier than generalized deficits to relate to neural structures, neurotransmitter systems, or genetic polymorphisms. Second, identifying a specific deficit may allow task manipulations to amplify the signal associated with a particular cognitive process, thereby increasing our ability to detect the unexpressed genetic liability to schizophrenia in future studies. Finally, specific impairments may be useful targets for potential preventative treatments.

The most popular solution to the generalized deficit confound has been to match tasks of interest with control tests on properties such as difficulty, observed variance, and reliability, thereby equating the tasks to be compared for discriminating power. Two studies that have used such matching strategies in the unaffected adult relatives of patients with schizophrenia have not yielded significant effects. Another approach is to isolate specific deficits by including within the experiment internal controls that constrain the interpretation of the impaired cognitive process. The most powerful internal control is one that results in a double dissociation. In this case, psychometric properties are not matched across condition. Instead, the experimental group performs worse because of the task demands in one condition, while the control group performs worse on a second condition. The present study used such an approach to study the theoretically motivated construct of context processing.

Context processing refers to the adaptive control of current behavior through the use of prior context information. Context information might include the processing of a sequence of stimuli, such as a sentence; a specific prior stimulus, such as a cue; and a set of task instructions. Context processing is conceptualized as consisting of 2 intertwined components, representation and maintenance. Representation refers to the process of constructing and using the context information to control behavior. Maintenance refers to the short-term storage of the context representation to control behavior even after a delay. Thus, context processing can be classified as an executive function that subsumes aspects of other cognitive constructs, including response inhibition, selective attention, cognitive control, and working memory. Previous research on context processing in the general population has demonstrated that this construct can be modeled as top-down support for task-specific processes using a simple connectionist architecture, and that representation and maintenance of information are associated with dorsolateral prefrontal cortex function. Patients with schizophrenia show context processing deficits that correlate with the prominence of disorganization symptoms. These deficits seem to be related to a circumscribed dorsolateral prefrontal cortex dysfunction in long-term–medicated and medication-naive patients, and can be modeled as a dopamine dysfunction that interferes with top-down support.

In developing a task sensitive to subtle, but specific, context processing deficits in the unaffected relatives of patients, we modified the expectancy AX (trial type) task used in recent studies of patients with schizophrenia. In this task, an X is only a target when it follows an A. We strengthened the automatic, or default, pattern of responding by making most trials AX pairs, thus establishing that As were generally followed by targets and Xs were generally valid targets. Three exception trial types were included: AX, BX, and BY pairs (where B was any non-A cue and Y was any non-X probe). This expectancy manipulation tested participants' ability to use the context of the cue to overcome their automatic target response to the probe: AX false alarms increased if the A cue was strongly represented because Y violated the expectation that A is generally followed by a valid probe (X); and BX false alarms increased if the B cue was weakly represented because, although nothing following a B could be a target, X was generally a valid probe. False alarms in all conditions, including the AX and BY conditions, increased in the presence of a generalized deficit. The interval between the cue and the probe was also varied from no delay to a short delay. This allowed us to partially disentangle the 2 components of context processing, representation and maintenance. Both conditions required context representation, but maintenance was required more in the delay condition.

The present study evaluated whether context processing deficits are characteristic of the unexpressed liability to schizophrenia. Specifically, we tested the hypothesis that patients with schizophrenia and their unaffected siblings would show more errors and slower reaction times (RTs) in the BX relative to the AX condition. We hypothesized that this effect would increase when the cue was followed by a delay. Furthermore, we hypothesized that the expectancy AX task would be diagnostically efficient, in the sense that it would be useful in identifying individuals more likely to express schizophrenia-related genes.

METHODS

SUBJECTS

Twenty-four medicated patients with schizophrenia or schizoaffective disorder, 1 unaffected sibling of each patient, and 36 control subjects participated. The demographic characteristics of the final sample are summarized in Table 1. Thirty-one outpatients at Western Psychiatric Institute and Clinic, Pittsburgh, volunteered to participate based on a DSM-IV medical record diagnosis of schizophrenia or schizoaffective disorder that was verified using the Structured Clinical Interview for DSM-III-R. For each patient, we attempted to recruit 1 full sibling between the ages of 18 and 45 years who had not previously been diagnosed as having a psychotic disorder. Only patients with a participating full sibling were included in the analysis; of all potential patient families, 4 could not be reached, 1 refused, and 2 could not confirm full sibling status. There were no demographic, symptom, or functioning differences be-
tween patients who were included and those who were not. Controls were recruited through newspaper advertisements. Controls were invited to participate if they were between the ages of 18 and 45 years, had no history of psychosis, and were similar to the group of patient siblings in parental educational level. The reading section of the Wide Range Achievement Test III was given to all subjects as a measure of general intellectual ability, and the results are also reported in Table 1. There were no significant differences across the groups for any demographic variables, although patients showed a strong trend toward less education relative to controls.

Siblings and controls were screened for lifetime psychiatric symptoms or disorders using the Structured Clinical Interview for DSM-III-R: Non-patient Edition and the Structured Interview for DSM-III Personality Disorders–Revised diagnosed as having any features according to DSM-IV, and rated on current psychiatric symptoms according to the Brief Psychiatric Rating Scale and the Positive and Negative Syndrome Scale. Interviews were conducted by one of us (A.W.M.) and a research assistant, both of whom participated in regular drift prevention training throughout the study. A total of 10 controls and siblings (17% of the sample) were used for diagnostic ratings, and 13 additional patients (5 of whom participated in the study, or 21% of the sample) were included for reliability on symptom measures. There was no agreement across raters (κ=0.74 for agreement across all diagnostic categories) and strong reliability for symptom ratings (Positive and Negative Syndrome Scale disorganization items intraclass correlation coefficient [ICC], 0.84; positive symptom items ICC, 0.87; negative symptom items ICC, 0.75; Brief Psychiatric Rating Scale total ICC, 0.94; and Global Assessment Scale ICC, 0.91). There were no significant (P>.10 for all) differences between siblings and controls for history of mood disorders (3 [12%] of 24 vs 2 [6%] of 36), anxiety disorders (4 [17%] of 24 vs 2 [6%] of 36), substance use disorders (4 [17%] of 24 vs 4 [11%] of 36), or any Axis I disorder (8 [33%] of 24 vs 7 [19%] of 36). Cluster A personality disorders were only observed in siblings (paranoid personality disorder, 2 siblings [8%] [P=.09]; schizoid personality disorder, 1 sibling [4%] [P=.21]; schizotypal personality disorder, 1 sibling [4%] [P=.34]; and any cluster A personality disorder, 3 siblings [12%] [P=.06]). Although this was not significantly different from controls, secondary analyses were conducted without these subjects. As reported in Table 1, there were no significant differences between siblings and controls for ratings of current psychiatric symptoms, whereas patients showed significant impairment across all symptoms.

### EXPECTANCY AX TASK

The AX-CPT was modified from a previous version and extensively repiloted in an initial sample. The task was performed on a personal computer (Macintosh; Apple Computer Inc), with white letters on a dark background appearing one at a time. Subjects identified targets and nontargets with a button press using separate fingers on the same hand according to the conditional A then X rule previously described. Subjects were instructed to respond as quickly and accurately as possible and were told that everyone makes some mistakes because speed is important. The experimenter remained in the testing room and repeated the instruction again during the session. In both counterbalanced conditions, the cue (A or non-A) duration was 1000 milliseconds, and the probe (X or non-X) duration was 500 milliseconds.

### ANALYSES

Analyses for all variables were performed first in controls to determine the nature of normative performance. For the between-group analysis, a 4×2×3 mixed-effects repeated-measures analysis of variance was conducted on the error data, with trial type (AX, AY, BX, or BY) and delay condition (immediate or delay) as within-subject factors and group (patient, sibling, or control subject) as the between-subject factor. Greenhouse-Geisser (G-G) corrections were used to control for violations of the sphericity assumption.

### Table 1. Sample Characteristics: Selected Demographic and Symptom Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (n = 24)</th>
<th>Siblings (n = 24)</th>
<th>Control Subjects (n = 36)</th>
<th>Test Value</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>36.8 (9.2)</td>
<td>35.8 (7.7)</td>
<td>33.6 (8.4)</td>
<td>F,2.81 = 1.09</td>
<td>.34</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>54</td>
<td>29</td>
<td>42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minority, %†</td>
<td>21</td>
<td>21</td>
<td>22</td>
<td></td>
<td>.21</td>
</tr>
<tr>
<td>WRAT III (raw score)</td>
<td>47.0 (7.3)</td>
<td>48.9 (5.8)</td>
<td>49.9 (4.8)</td>
<td>F,2.81 = 1.71</td>
<td>.19</td>
</tr>
<tr>
<td>Education, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject</td>
<td>14.0 (2.4)</td>
<td>14.6 (2.7)</td>
<td>15.6 (2.8)</td>
<td>F,2.81 = 2.96</td>
<td>.06</td>
</tr>
<tr>
<td>Parent</td>
<td>12.7 (3.0)</td>
<td>12.7 (3.0)</td>
<td>13.0 (1.8)</td>
<td>F,2.81 = 0.28</td>
<td>.76</td>
</tr>
<tr>
<td>PANSS composite score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive component</td>
<td>6.7 (3.0)</td>
<td>3.0 (2.0)</td>
<td>3.0 (0.2)</td>
<td>F,2.81 = 39.20</td>
<td>&lt;.001†</td>
</tr>
<tr>
<td>Negative component</td>
<td>9.3 (4.6)</td>
<td>5.3 (5.1)</td>
<td>5.8 (1.2)</td>
<td>F,2.81 = 7.38</td>
<td>&lt;.005‡</td>
</tr>
<tr>
<td>Disorganization component</td>
<td>7.5 (3.4)</td>
<td>5.2 (3.0)</td>
<td>4.9 (1.1)</td>
<td>F,2.81 = 7.41</td>
<td>&lt;.005‡</td>
</tr>
<tr>
<td>BPRS total score</td>
<td>30 (8)</td>
<td>20 (4)</td>
<td>18 (2)</td>
<td>F,2.81 = 39.00</td>
<td>&lt;.001‡</td>
</tr>
<tr>
<td>GAS score</td>
<td>64 (15)</td>
<td>89 (21)</td>
<td>95 (3)</td>
<td>F,2.81 = 36.10</td>
<td>&lt;.001‡</td>
</tr>
</tbody>
</table>

Abbreviations: BPRS, Brief Psychiatric Rating Scale; GAS, Global Assessment Scale; PANSS, Positive and Negative Syndrome Scale; WRAT, Wide Range Achievement Test.

*Data are given as mean (SD) unless otherwise indicated.
†The value for patients was greater than the values for siblings and control subjects (Student-Newman-Keuls post hoc analysis, P<.05). The other comparisons were not significant.
‡The value for patients was greater than the values for siblings and control subjects (Student-Newman-Keuls post hoc analysis, P<.05).
The expectancy AX task yielded error and RT data for 4 different trial types in 2 different delay conditions across 3 different groups. Table 2 summarizes error and d’-context data, and Table 3 summarizes correct trial RT and RT interference data across the different trial types, delays, and groups, along with the univariate effect sizes. We present controls data first, followed by between-group contrasts. Finally, we examine whether this instrument can efficiently identify siblings and controls.

### RESULTS

Analyses of the error data, correct trial RT data, and secondary measures were initially performed in controls to evaluate the normative pattern of performance. For the error data, there was a main effect of trial type (G-G $F_{1,105}=22.66, P<.001$ (increased AY errors); and delay $F_{1,105}=25.27, P<.001$ (increased delay errors)); (2) Two-way interactions. Group by trial type $G-G F_{1,105}=4.50, P<.005$ (increased patient and sibling BX errors) (see text); group by delay, not significant; and trial type by delay $G-G F_{2,20,105}=14.23, P<.001$ (increased delay AX and BX errors). (3) Three-way interaction. Group by trial type by delay $G-G F_{4,62,243}=2.55, P<.05$ (increased sibling delay AX errors and increased patient immediate BY errors).

<table>
<thead>
<tr>
<th>Measure</th>
<th>Patients (n = 24)</th>
<th>Siblings (n = 24)</th>
<th>Control Subjects (n = 36)</th>
<th>Patients vs Control Subjects $^*$</th>
<th>Siblings vs Control Subjects $^*$</th>
<th>Patients vs Siblings $^+$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Errors‡</td>
<td>AX</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Immediate</td>
<td>0.04 (0.04)</td>
<td>0.01 (0.01)</td>
<td>0.06 (0.01)</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>Delay</td>
<td>0.16 (0.16)</td>
<td>0.05 (0.07)</td>
<td>0.06 (0.05)</td>
<td>0.16</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td>AY</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Immediate</td>
<td>0.18 (0.22)</td>
<td>0.07 (0.12)</td>
<td>0.16 (0.20)</td>
<td>0.10</td>
<td>−0.15</td>
</tr>
<tr>
<td></td>
<td>Delay</td>
<td>0.12 (0.13)</td>
<td>0.11 (0.14)</td>
<td>0.14 (0.14)</td>
<td>−0.15</td>
<td>−0.21</td>
</tr>
<tr>
<td></td>
<td>BX</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Immediate</td>
<td>0.15 (0.23)</td>
<td>0.07 (0.18)</td>
<td>0.01 (0.05)</td>
<td>0.84</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td>Delay</td>
<td>0.26 (0.32)</td>
<td>0.23 (0.36)</td>
<td>0.06 (0.39)</td>
<td>0.94</td>
<td>0.62</td>
</tr>
<tr>
<td></td>
<td>BY</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Immediate</td>
<td>0.06 (0.11)</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.02)</td>
<td>0.76</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td>Delay</td>
<td>0.04 (0.12)</td>
<td>0.02 (0.06)</td>
<td>0.00 (0.02)</td>
<td>0.46</td>
<td>0.45</td>
</tr>
<tr>
<td>d’-Context§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Immediate</td>
<td>3.00 (0.91)</td>
<td>3.61 (0.67)</td>
<td>3.87 (0.29)</td>
<td>1.46</td>
<td>0.47</td>
</tr>
<tr>
<td></td>
<td>Delay</td>
<td>1.96 (1.12)</td>
<td>2.83 (1.30)</td>
<td>3.32 (0.68)</td>
<td>1.28</td>
<td>0.51</td>
</tr>
</tbody>
</table>

Abbreviations: AX, a trial type in which A precedes X; AY, a trial type in which A precedes Y (any non-A probe); BX, a trial type in which B (any non-A probe) precedes X; BY, a trial type in which B precedes Y; d’-context, the normalized proportion of trials in which participants used context to distinguish target signals relative to the proportion of trials in which they fail to use context to distinguish nontarget signals.

$^*$Positive values (Cohen’s $d$) reflect better performance in controls.

$^+$Better performance in siblings.

$‡$Data are given as mean (SD) for the “Patients,” “Siblings,” and “Control Subjects” columns. The between-group error analysis is as follows. (1) Main effects. Group $F_{1,105}=7.82, P<.005$ (increased patient errors); trial type Greenhouse-Geisser (G-G) $F_{1,105}=22.66, P<.001$ (increased AY errors); and delay $F_{1,105}=25.27, P<.001$ (increased delay errors). (2) Two-way interactions. Group by trial type $G-G F_{1,105}=4.50, P<.005$ (increased patient and sibling BX errors) (see text); group by delay, not significant; and trial type by delay $G-G F_{2,20,105}=14.23, P<.001$ (increased delay AX and BX errors). (3) Three-way interaction. Group by trial type by delay $G-G F_{2,20,105}=82.39, P<.05$ (increased in the immediate condition). (4) Delay by group contrasts. Finally, we examine whether this instrument can efficiently identify siblings and controls.

**CONSULTS**

Discriminant functions were calculated to evaluate how effectively these measures separated siblings from controls. Finally, we conducted an exploratory diagnostic efficiency analysis to determine what cut points would provide adequate sensitivity and specificity for molecular genetic analyses.

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tion (F\(_{1,35}=21.32, P<.001\)), with more errors on AY trials, as well as an interaction between trial type and delay (F\(_{1,35}=4.81, P=.35\), with increased BX errors with delay. Similarly, ‘d’-context was significantly better in the immediate condition (F\(_{1,35}=30.69, P<.001\)).

Correct trial RT analyses recapitulated the pattern observed in the error data. Again, there was the predicted main effect of trial type (G-G F\(_{1,27,101}=230.11, P<.001\)), with longer RTs on correct AX trials and shorter RTs on BX trials. The effect of delay was highly significant (F\(_{1,35}=101.24, P=.001\), with the immediate condition faster than the delay condition, although the interaction between trial type and delay was not significant (P = .41). A priori contrasts of the AY and BX conditions showed a strong effect (F\(_{1,35}=278.28, P<.001\)), with AY trials being slower. As with errors, this important effect did not interact with delay. As in the comparison of correct RTs, RT interference in controls showed a main effect of trial type (F\(_{1,35}=278.27, P<.001\)), with AY trials slower than AX trials (positive interference) and BX trials slightly faster than AX trials. This effect did not interact with delay.

Thus, a normative pattern of performance is characterized by a high level of AY errors and slower RTs in both delay conditions and a moderate, but significant, increase in AX and BX errors with delay. These data are consistent with the interpretations that AY errors and slower RTs result from normal intact context processing.

**GROUP COMPARISONS**

Error data, correct trial RT data, and secondary measures were subsequently included in between-group analyses. Error analyses are reported in Table 2 and illustrated in Figure 1. As predicted, there was a significant group effect and a group-by-trial type interaction. A priori contrasts of overall AY and BX errors across groups showed the predicted differences between patients and controls (F\(_{1,81}=14.70, P<.001\)) and between patients and siblings (F\(_{1,81}=8.50, P<.01\)), but no overall performance difference between siblings and controls (F\(_{1,81}=0.41, P=.52\)). The interaction of AY and BX trials with group was significant when comparing patients with controls (F\(_{1,81}=10.73, P<.005\)) and siblings with controls (F\(_{1,81}=9.58, P<.005\), but there was no interaction of trial type and group in patients and siblings (F\(_{1,81}=0.27, P=.87\)). These effects were due to increased BX errors in parallel for patients and siblings and increased AY errors in controls relative to siblings (Figure 1A). This predicted pattern of contrast effects provides strong interpretive leverage for describing the nature of context-

### Table 3. The RTs on Correct Trials and Effect Sizes for the Expectancy AX Task

<table>
<thead>
<tr>
<th>RT Measure</th>
<th>Patients (n = 24)</th>
<th>Siblings (n = 24)</th>
<th>Control Subjects (n = 36)</th>
<th>Patients vs Control Subjects†</th>
<th>Siblings vs Control Subjects†</th>
<th>Patients vs Siblings‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correct analyses§</td>
<td></td>
<td></td>
<td></td>
<td>AX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate</td>
<td>432 (75)</td>
<td>393 (54)</td>
<td>340 (57)</td>
<td>1.38</td>
<td>0.95</td>
<td>0.60</td>
</tr>
<tr>
<td>Delay</td>
<td>546 (97)</td>
<td>496 (86)</td>
<td>418 (83)</td>
<td>1.42</td>
<td>0.92</td>
<td>0.55</td>
</tr>
<tr>
<td>AY</td>
<td></td>
<td></td>
<td></td>
<td>Immediate</td>
<td>610 (101)</td>
<td>551 (54)</td>
</tr>
<tr>
<td>Delay</td>
<td>668 (79)</td>
<td>613 (74)</td>
<td>575 (80)</td>
<td>1.17</td>
<td>0.49</td>
<td>0.72</td>
</tr>
<tr>
<td>BX</td>
<td></td>
<td></td>
<td></td>
<td>Immediate</td>
<td>549 (163)</td>
<td>432 (153)</td>
</tr>
<tr>
<td>Delay</td>
<td>664 (139)</td>
<td>514 (148)</td>
<td>416 (108)</td>
<td>1.99</td>
<td>0.76</td>
<td>1.04</td>
</tr>
<tr>
<td>BY</td>
<td></td>
<td></td>
<td></td>
<td>Immediate</td>
<td>471 (96)</td>
<td>372 (89)</td>
</tr>
<tr>
<td>Delay</td>
<td>574 (80)</td>
<td>473 (98)</td>
<td>392 (83)</td>
<td>2.23</td>
<td>0.89</td>
<td>1.13</td>
</tr>
<tr>
<td>Interference data¶</td>
<td></td>
<td></td>
<td></td>
<td>AX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate</td>
<td>178 (97)</td>
<td>158 (60)</td>
<td>182 (65)</td>
<td>-0.05</td>
<td>-0.38</td>
<td>0.25</td>
</tr>
<tr>
<td>Delay</td>
<td>122 (87)</td>
<td>117 (55)</td>
<td>157 (55)</td>
<td>-0.48</td>
<td>-0.73</td>
<td>0.07</td>
</tr>
<tr>
<td>BX</td>
<td></td>
<td></td>
<td></td>
<td>Immediate</td>
<td>116 (172)</td>
<td>39 (118)</td>
</tr>
<tr>
<td>Delay</td>
<td>77 (169)</td>
<td>22 (129)</td>
<td>-9 (57)</td>
<td>0.68</td>
<td>0.31</td>
<td>0.37</td>
</tr>
</tbody>
</table>

**Abbreviations:** AX, a trial type in which A precedes X; AY, a trial type in which A precedes Y (any non-A probe); BX, a trial type in which B (any non-A probe) precedes X; BY, a trial type in which B precedes Y; RT, reaction time; RT interference, (mean RT for the trial type) − (mean RT for AX trials).

§Positive values (Cohen’s d) reflect better performance in controls.

†Better performance in siblings.

‡Better performance in siblings.

§The between-group RT analysis is as follows. (1) Main effects. Group F\(_{2,80}=35.77, P<.001\) (slower RTs in patients and siblings); trial type G-G F\(_{3,240}=4.10, P<.05\) (slower AY delay RTs). (2) Two-way interactions. Group by trial type G-G F\(_{2,80}=7.78, P<.01\) (slower patient and sibling AX, BX, and BY RTs) (see text); group by delay, not significant; and trial by delay G-G F\(_{2,80}=4.72, P<.05\) (slower RTs in patients and siblings); trial type F\(_{1,80}=29.27, P<.001\) (slower delay RTs). (3) Three-way interaction. Group by trial type by delay, not significant.

¶The between-group RT interference analysis is as follows. (1) Main effects. Group F\(_{2,80}=91.73, P<.001\) (more interference in patients); trial type F\(_{1,80}=91.37, P<.001\) (more AY interference); and delay F\(_{1,81}=6.63, P<.05\) (more immediate interference). (2) Two-way interactions. Group by trial type F\(_{2,80}=9.77, P<.01\) (less BX interference in controls) (see text); group by delay, NS; and trial by delay, NS. (3) Three-way interaction. Group by trial type by delay, NS.

- Positive values (Cohen’s d) reflect better performance in controls.

**Interpretive leverage for describing the nature of context-
processing impairments. The lack of an overall error effect between siblings and controls and the highly significant disordinal (x-shaped) interaction with trial type is suggestive of a double dissociation. In fact, controls made significantly more AY errors (t
57.62 =−2.03, P =.05), while siblings made significantly more BX errors (t
25.48 =2.16, P =.05) (both 2-tailed tests for unequal variances). The difference between subjects’ BX and AY errors was a useful metric that capitalized on this double dissociation, and subtracted out generalized deficits that were measured in both conditions. As expected, there were large mean differences on BX−AY between controls and both patients and siblings (effect sizes, 0.88 and 0.80, respectively), but patients were nearly equal to siblings (effect size, 0.05) (Figure 1B). The 3-way interaction in the omnibus tests was not interpretable (Table 2).

An analysis of the secondary measure, d’-context, is also reported in Table 2. Again, a group effect was observed such that patients were less sensitive than controls or siblings (F
1,81 =12.00, P =.005, for both) and siblings tended to be less sensitive than controls (F
1,80 =3.46, P =.06).

Correct RT analyses are reported in Table 3. There were the predicted group differences and a group–by–trial type interaction that largely recapitulated the error effects: contrasts showed that patients were generally slower than siblings (F
1,80 =18.71, P <.001), siblings were generally slower than controls (F
1,80 =13.08, P =.005), and patients and siblings were significantly slower than controls on BX relative to AY trials (F
1,80 =19.24 and 4.99, respectively; P =.05 for both). There were also large effect size differences between groups on all but AY trials.

Reaction time interference data are particularly important for comparing groups with different baseline RTs and are also reported in Table 3 and illustrated in Figure 2. Most important, there was again the predicted main effect of group, which again interacted with trial type: contrasts showed that patients had more overall interference than either siblings or controls (F
1,80 =4.88 and 8.95, respectively; P <.05 for both), whereas siblings and controls did not differ; however, patients and siblings showed more BX interference, whereas controls showed more AY interference (F
1,80 =19.24 and 4.99, respectively; P <.05 for both), while patients and siblings did not show differences in interference between trial types.

The same pattern of effects was observed when 3 siblings with Axis II diagnoses were removed (eg, the group-
by–trial type interaction for errors was G-G $F_{1,78} = 4.51$ [$P < .005$] and the contrast of siblings and controls on AY vs BX trials was $F_{1,78} = 9.54$ [$P < .005$]). In another set of subsequent analyses, other diagnoses were entered as covariates into a $4 \times 2 \times 3$ analysis of covariance and the effects remained similar (eg, for all group–by–trial type interactions for errors, $F > 4.4$ [$P < .005$]; and for the contrast of siblings and controls on AY and BX trials, $F > 7.9$ [$P < .005$]). Thus, the pattern of results seemed closely tied to the genetic liability to schizophrenia and not to the sporadic occurrence of psychiatric symptoms in the healthy samples.

To summarize, across several distinct measures of impairment, patients showed a generalized deficit (poorer performance across all trials) in addition to a context processing impairment (poorer performance on BX trials relative to other trial types, especially AY trials). Siblings of patients showed a context processing impairment but not a generalized deficit. In contrast to patients and their siblings, controls performed worst on AY trials, presumably because they were being misled by their expectation of the probe. This suggests intact context processing. The context processing impairments in patients and their siblings occurred when the cue was immediately followed by the probe, as well as when there was a delay.

### Predicting Group Membership

Exploratory discriminant functions were used to determine which measures or combinations of measures were more effective in separating the control and sibling groups. The BX–AY errors and BX – AY RTs were also examined to capitalize on the disordinal interaction while preserving $d_1$ values. The most effective measure when entered alone was the mean of BX errors (68.3% correctly classified; sensitivity, 41.7%; specificity, 86.1%; Wilks $\Lambda = 0.89$; $P < .05$) and the RT for delay BX trials minus delay AY trials (66.1% correctly classified; sensitivity, 47.8%; specificity, 77.8%; Wilks $\Lambda = 0.91$; $P < .05$). Other BX–AY difference scores and RTs significantly, but less effectively, classified cases ($P < .05$), whereas $d'$-context did not significantly ($P = .11$) classify cases. Using multiple variables to separate groups did not significantly improve these classifications.

Diagnostic efficiency analyses were conducted to identify optimal cut points maximizing correctly classified siblings, or sensitivity, relative to correctly rejected controls, or specificity. A cut point of mean BX–AY errors greater than 0.20 showed 21% sensitivity at 100% specificity ($\chi^2 = 8.18$, Fisher exact test $P < .01$). A cut point of mean BX–AY RT greater than 32 showed 33% sensitivity at 100% specificity ($\chi^2 = 13.85$, Fisher exact test $P < .001$). A combination of these criteria led to 38% sensitivity at 100% specificity ($\chi^2 = 15.88$, Fisher exact test $P < .001$). These are post hoc analyses and, therefore, require replication. Nevertheless, they demonstrate that this version of the expectancy AX task, used as either a continuous or a dichotomous measure, may be a sensitive and specific probe of an endophenotype related to the genetic liability to schizophrenia.

Patients with schizophrenia and their unaffected siblings were compared with controls on an expectancy version of the AX task to test the hypothesis that context processing is a specific deficit associated with genetic liability. Siblings and patients performed better on AY relative to BX trials, which implied worse context processing, whereas controls performed better on BX relative to AY trials, which implied better context processing. The pattern of disordinal interactions between siblings and controls constituted strong evidence of a specific deficit in context processing associated with a familial, and probably a genetic, liability to schizophrenia. The observation that there was no main effect for performance indicates that our interpretation was not confounded by factors such as a general performance deficit, recruitment bias, speed-accuracy trade-off differences, or differences in vigilance. Any of these may have led to an increase in errors and/or RT interference across conditions rather than the pattern of strengths and deficits observed in siblings. This pattern was observed even after removing individuals with schizophrenia-spectrum disorders and variance associated with other Axis I psychopathological features.

Several studies have demonstrated impaired performance on continuous performance test paradigms in the relatives of patients with schizophrenia. Continuous performance tests that combine several sources of difficulty by including encoding, updating, and storage task demands have led to a consistent robust effect size of around 0.90.11-13 This success has pointed the way, but has not yet established a specific deficit associated with genetic liability to schizophrenia. Two other studies have attempted to establish specific deficits in the relatives of patients with schizophrenia using tasks that required processing information in the face of distraction. One study18 found no difference between adult relatives when comparing a shorter digit span task with distractors with a longer digit span task without distractors that was psychometrically matched (a specific deficit was reported in high-risk adolescents using a similar task40). In another study,17 patients’ relatives were not differentially impaired on a task that required repeating aloud audibly presented phrases in the presence of distractors compared with a matched task that only required repeating unpredictable words. The present study suggests that task manipulations that lead to better and worse performance in different task conditions may be a powerful strategy for establishing specific deficits, particularly when comparing psychiatrically healthy groups. Thus, the comparison of AY hits with BX false alarms was more sensitive than the comparison of AX hits with BX false alarms (the components of $d'$-context). In this regard, the finding that RT differences on AX and BY trials showed as large between-group effects as did RTs on BX trials remains somewhat curious. On the one hand, this suggests that generalized deficits, as measured by correct RTs, can obscure the relative size of the specific context processing impairment. On the other hand, differential impairments on BX trials remained even after AX differences were subtracted away in the interference analysis.
This suggests that RT difference scores may be a useful way to observe interpretable specific deficits.

One hypothesis that was not supported was that patients and their siblings would be more impaired after a delay. Consistent with some previous work, the present findings suggest that context processing deficits occur immediately and are not only due to the context representation degrading more rapidly in patients and siblings over the interval examined in the present paradigm. One might speculate that a longer delay would have resulted in significant effects.

The present study was also unable to address questions about the variation observed within the sibling group. Supplementary mixture analyses did not provide strong evidence either for or against a commingling of distinct subgroups. These questions remain important issues to address in future family studies.

Functional neuroimaging studies suggest that representing and maintaining a cue to overcome an automatic response, as in the current task, involves the dorsolateral prefrontal cortex and that this region is dysfunctional in patients with schizophrenia. Preliminary data from one study that used functional magnetic resonance imaging and a working memory task that required storage and executive processes showed that the unaffected siblings of patients were also impaired in activating this region of the cortex. Thus, there is early suggestive evidence that the specific deficits associated with the liability to schizophrenia may involve abnormal gene expression related to the function of the dorsolateral prefrontal cortex. Methods such as those illustrated herein could be used to test this hypothesis directly.

In conclusion, the present study evaluated context processing, a specific theoretically derived cognitive function, in the unaffected relatives of patients with schizophrenia. The modification of a classic task proved to be sensitive to subtle group differences, while at the same time retaining specificity to processes that have previously been localized to a particular region of the brain. It seemed that context processing was robustly related to the genetic liability to schizophrenia. Such translational cognitive neuroscience research may play an important role in the development of sophisticated tools for investigating the complex genetics of schizophrenia.

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REFERENCES


**Correction**

Error in Acknowledgment. In the article titled “Forty Years of Neurotransmitters: A Personal Account,” published in the November issue of the ARChives (2002;59:983-994), on page 993, the first 4 lines in column 1 should have read “Presented in part as the History of Neuroscience lecture at the Society for Neuroscience annual meeting, San Diego, Calif, November 13, 2001, to mark the award (shared with Michael Rutter, MD, FRS).”