Elevated Antisaccade Error Rate as an Intermediate Phenotype for Psychosis Across Diagnostic Categories

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Background: Elevated antisaccade error rate, reflecting problems with inhibitory behavioral control, is a promising intermediate phenotype for schizophrenia. Here, we consider whether it marks liability across psychotic disorders via common or different neurophysiological mechanisms and whether it represents a neurocognitive risk indicator apart from the generalized cognitive deficit. Methods: Schizophrenia (n = 267), schizoaffective (n = 150), and psychotic bipolar (n = 202) probands, their first-degree relatives (n = 304, 193, 242, respectively), and healthy controls (n = 244), participating in the Bipolar-Schizophrenia Network on Intermediate Phenotypes consortium, performed antisaccade and prosaccade tasks and completed a neuropsychological battery. Results: Antisaccade error rate was elevated in proband groups with greatest deficit observed in schizophrenia and was unrelated to symptoms and antipsychotic treatment. Increased error rate was also observed among relatives, even those without history of psychosis or psychosis spectrum personality traits. Relatives’ deficits were similar across proband diagnoses. Error rate was familial and remained elevated in proband and relative groups after accounting for generalized cognitive impairment. Speed of attentional shifting, indexed by prosaccade latency, was similarly influenced in all groups by manipulations that freed vs increasingly engaged attention systems and was inversely associated with antisaccade error rate in all but schizophrenia probands. Conclusions: These findings indicate that elevated antisaccade error rate represents an intermediate phenotype for psychosis across diagnostic categories, and that it tracks risk beyond that attributable to the generalized cognitive deficit. The greater severity of antisaccade impairment in schizophrenia and its independence from attention shifting processes suggest more severe and specific prefrontal inhibitory control deficits in this disorder.

Key words: schizophrenia/schizoaffective disorder/bipolar disorder/endophenotype/family study

Introduction

Despite the significant heritability of psychotic disorders, the identification of genes conferring liability has remained a major challenge. Intermediate phenotypes, or endophenotypes, are biobehavioral characteristics that are more proximal to actions of genes than clinical syndromes and thus may aid in identifying genetic risk factors. They mark illness liability in subgroups of patients and distinguish diagnosis-specific liability from factors that track along a clinical dimension, such as psychosis. Gottesman and Gould1 proposed that useful intermediate phenotypes are associated with an illness, state-independent, heritable, present among unaffected family members to a greater degree than the general population, and cosegregate with illness within families. The multiple similar characteristics observed across schizophrenia and psychotic bipolar disorder including overlapping diagnoses among lineages5–7 and shared risk genes8,9 highlight the importance of evaluating putative intermediate phenotypes across these diagnoses.

Elevated error rate on the antisaccade task, which reflects decreased inhibitory behavioral control, is a promising neurocognitive intermediate phenotype for schizophrenia.10–14 There is a robustly elevated error rate among...
schizophrenia probands,15–19 demonstrated heritability,20 and increased error rate among relatives21–27; although negative findings among relatives have been reported.28–33 Elevated error rate has been observed in schizoaffective34 and bipolar probands,21,24,34–37 yet performance among relatives of these patient groups and familiality within these pedigrees has not been established. Therefore, it remains unknown whether elevated antisaccade error rate is a candidate intermediate phenotype that marks liability for schizophrenia or for psychosis more broadly.

Another question is whether increased antisaccade error rate tracks the broad cognitive impairment in psychosis38–39 or if it represents a specific deficit in inhibitory control. As suggested previously,40,41 specific deficits that are dissociable from generalized impairment may be useful for linkage to genetic and molecular markers and thus could increase a measure’s value as an intermediate phenotype. The linkage between ocular motor and attentional neural systems,42,43 and the well-established neurophysiology underlying successful antisaccade performance from monkey and human neuroimaging studies,44–47 provides a strong preclinical basis for interpreting the neural circuitry implications of antisaccade errors. One well-characterized aspect of antisaccades is the inverse relationship between latencies on prosaccade tasks, which reflect the speed of overt attentional shifting to visual targets, and inhibitory errors on the antisaccade task.17,48 Essentially, the faster one visually orients the less time one has to suppress antisaccade errors. This permits examination of the degree to which problems in inhibitory control result from alterations in attentional shifting processes, as has been demonstrated in untreated schizophrenia,19,49 or an independent dysfunction of prefrontally mediated inhibitory behavioral control.

The Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) is a multisite consortium designed to characterize intermediate phenotypes across schizophrenia, schizoaffective, and psychotic bipolar diagnoses. Here, we report antisaccade findings from the B-SNIP consortium and in so doing: (1) evaluate the validity of antisaccade performance as an intermediate phenotype across psychotic diagnoses, (2) determine if antisaccade errors are a trait separable from the generalized cognitive deficit, and (3) evaluate whether attentional mechanisms contribute to inhibitory errors differentially across disorders.

Methods

Participants

Schizophrenia (n = 267), schizoaffective (n = 150), and psychotic bipolar (n = 202) probands, their first-degree relatives (nR = 304, 193, 242, respectively), and healthy controls (nC = 244), participating in the B-SNIP consortium, completed antisaccade and prosaccade tasks and the Brief Assessment of Cognition in Schizophrenia (BACS) test battery,50 a measure of global neuropsychological functioning (table 1). B-SNIP recruitment is described elsewhere.51 All subjects met the following inclusion criteria: (1) age 15–65, (2) no history of intellectual disability (Wide Range Achievement Test-4th Edition [WRAT-IV] Reading standard score > 65), (3) no history of neurologic disorders, including head injury, (4) no history of substance abuse within the last month or substance dependence within the last 6 months, and (5) negative urine toxicology on assessment day. Control subjects met additional criteria: (1) no personal or family history (first degree) of psychotic or bipolar disorders, (2) no history of recurrent mood disorder, (3) no lifetime history of substance dependence, and (4) no history of significant psychosis spectrum personality traits defined by meeting full or within one criteria of a cluster A diagnosis using the Structured Interview for DSM-IV Personality (SIDP-IV).52 Institutional review boards at each site approved the study.

All subjects underwent a diagnostic interview using the Structured Clinical Interview for DSM-IV.53 Relatives without history of psychosis and controls were administered the SID-P. Relatives who met full or within one criteria of a cluster A diagnosis were considered to have elevated psychosis spectrum personality traits. Diagnoses were made by a consensus process at each site led by a senior clinician that included reviews of the structured interviews, psychiatric and medical histories, and available medical records. Proband symptom ratings were completed using the Positive and Negative Symptom Scale,54 the Montgomery Asberg Depression Rating Scale,55 and the Young Mania Rating Scale56 (table 2).

Testing Procedures

Participants performed prosaccade and antisaccade tasks under identical conditions at each site (see online supplementary materials). The prosaccade task consisted of 3 blocks of 32 trials in which the timing of the central fixation crosshair was experimentally manipulated to extinguish simultaneously with (no gap condition), 200 ms before (gap condition) or 200 ms after (overlap condition) the peripheral target appearance at either 10 or 15° from center. Subjects were instructed to make a prosaccade to the peripheral target when it appeared. The antisaccade task consisted of 4 blocks of 20 overlap trials with the same target displacements as the prosaccade task. The overlap condition was used because it has been shown to be most sensitive to relatives’ deficits.21 Subjects were instructed to not look to the peripheral target but instead immediately look to the mirrored location in the opposite hemifield. Eye movement recordings were analyzed using software developed in our laboratory,17,48 and each trial’s measurements were reviewed by technicians blinded to subject characteristics. Prosaccade latency was recorded as a measure of the speed of attentional shifting.
### Table 1. Demographic Characteristic of Control, Proband, and Relative Groups

<table>
<thead>
<tr>
<th></th>
<th>Control (1)</th>
<th>Probands</th>
<th>Scz (2)</th>
<th>SczA (3)</th>
<th>BP (4)</th>
<th>Relatives</th>
<th>Scz (5)</th>
<th>SczA (6)</th>
<th>BP (7)</th>
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<tr>
<td></td>
<td>(N = 244)</td>
<td>(N = 267)</td>
<td>(N = 150)</td>
<td>(N = 202)</td>
<td>(N = 304)</td>
<td>(N = 193)</td>
<td>(N = 242)</td>
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<tr>
<td>Mean (SD)</td>
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<tr>
<td>Age</td>
<td>37.3 (12.5)</td>
<td>35.6 (12.7)</td>
<td>36.1 (11.7)</td>
<td>35.8 (12.9)</td>
<td>43.3 (15.1)</td>
<td>40.2 (16.4)</td>
<td>40.5 (15.8)</td>
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<tr>
<td>N (%)</td>
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<tr>
<td>Male gender</td>
<td>103 (42.2)</td>
<td>181 (67.8)</td>
<td>63 (42.0)</td>
<td>75 (37.1)</td>
<td>97 (31.9)</td>
<td>60 (31.1)</td>
<td>89 (36.8)</td>
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<td>Race</td>
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<tr>
<td>Caucasian</td>
<td>165 (67.6)</td>
<td>131 (49.1)</td>
<td>85 (56.7)</td>
<td>158 (78.2)</td>
<td>169 (55.6)</td>
<td>124 (64.3)</td>
<td>194 (80.2)</td>
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<tr>
<td>African American</td>
<td>61 (25.0)</td>
<td>123 (46.1)</td>
<td>63 (42.0)</td>
<td>38 (18.8)</td>
<td>121 (39.8)</td>
<td>65 (33.7)</td>
<td>40 (16.5)</td>
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<tr>
<td>Other</td>
<td>18 (7.4)</td>
<td>13 (4.9)</td>
<td>2 (1.3)</td>
<td>6 (3.0)</td>
<td>14 (4.6)</td>
<td>4 (2.1)</td>
<td>8 (3.3)</td>
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<td></td>
</tr>
<tr>
<td>WRAT-IV Reading</td>
<td>103.4 (13.6)</td>
<td>95.2 (15.8)</td>
<td>96.7 (15.1)</td>
<td>102.2 (13.3)</td>
<td>97.7 (14.7)</td>
<td>99.3 (15.2)</td>
<td>102.8 (14.1)</td>
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<td>(standard score)</td>
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<tr>
<td>BACS composite (z score)</td>
<td>0.28 (1.06)</td>
<td>-1.42 (1.33)</td>
<td>-1.10 (1.36)</td>
<td>-0.73 (1.26)</td>
<td>-0.30 (1.31)</td>
<td>-0.28 (1.31)</td>
<td>-0.05 (1.14)</td>
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Note: Scz, schizophrenia; SczA, schizoaffective; BP, psychotic bipolar; BACS, Brief Assessment of Cognition in Schizophrenia.

*Hochberg test for post hoc comparison from univariate analysis for continuous variables; Z test for post hoc comparison from chi-square analysis for categorical variables.
Table 2. Medication Treatment and Clinical Characteristics of Proband and Relative Groups

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<tbody>
<tr>
<td>First-generation antipsychotic</td>
<td>50 (18.7)</td>
<td>22 (14.7)</td>
<td>17 (8.4)</td>
<td>2 &gt; 4</td>
<td>5 (1.6)</td>
<td>6 (3.1)</td>
<td>0 (0)</td>
<td>—</td>
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<tr>
<td>Second-generation antipsychotic</td>
<td>225 (84.3)</td>
<td>117 (78.0)</td>
<td>134 (66.3)</td>
<td>2, 3 &gt; 4</td>
<td>38 (12.5)</td>
<td>21 (10.9)</td>
<td>21 (8.7)</td>
<td>—</td>
</tr>
<tr>
<td>Mood stabilizer</td>
<td>41 (15.4)</td>
<td>72 (48.0)</td>
<td>102 (50.5)</td>
<td>2 &gt; 3, 4</td>
<td>16 (5.3)</td>
<td>19 (9.8)</td>
<td>29 (12.0)</td>
<td>—</td>
</tr>
<tr>
<td>Lithium</td>
<td>14 (5.2)</td>
<td>15 (10.0)</td>
<td>56 (27.7)</td>
<td>2, 3 &lt; 4</td>
<td>3 (1.0)</td>
<td>7 (3.6)</td>
<td>8 (3.3)</td>
<td>—</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>101 (37.8)</td>
<td>86 (57.3)</td>
<td>92 (45.5)</td>
<td>2 &gt; 3, 4</td>
<td>65 (21.4)</td>
<td>49 (25.4)</td>
<td>67 (27.7)</td>
<td>—</td>
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<tr>
<td>Stimulant</td>
<td>8 (3.0)</td>
<td>5 (3.3)</td>
<td>20 (9.9)</td>
<td>2 &lt; 4</td>
<td>3 (0.1)</td>
<td>7 (3.6)</td>
<td>16 (6.6)</td>
<td>5 &lt; 6, 7</td>
</tr>
<tr>
<td>Sedative/hypnotic</td>
<td>50 (18.7)</td>
<td>39 (26.0)</td>
<td>54 (26.7)</td>
<td>—</td>
<td>32 (10.5)</td>
<td>19 (9.8)</td>
<td>30 (12.4)</td>
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<tr>
<td>Anticholinergic</td>
<td>43 (16.1)</td>
<td>23 (15.3)</td>
<td>13 (6.4)</td>
<td>2, 3 &gt; 4</td>
<td>7 (2.3)</td>
<td>3 (1.6)</td>
<td>1 (0.4)</td>
<td>—</td>
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<tr>
<td><strong>Clinical Symptom Ratings</strong></td>
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<tr>
<td><strong>PANSS</strong></td>
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<tr>
<td>Positive</td>
<td>16.5 (5.7)</td>
<td>17.8 (5.1)</td>
<td>13.0 (4.3)</td>
<td>2 &lt; 4</td>
<td>2 &lt; 4</td>
<td>2 &lt; 3</td>
<td>4 &lt; 3</td>
<td>—</td>
</tr>
<tr>
<td>Negative</td>
<td>16.7 (6.1)</td>
<td>15.8 (5.0)</td>
<td>12.2 (3.8)</td>
<td>2, 3 &gt; 4</td>
<td>2 &gt; 3</td>
<td>4 &lt; 3</td>
<td>3 &gt; 4</td>
<td>—</td>
</tr>
<tr>
<td>Total</td>
<td>64.7 (17.2)</td>
<td>67.9 (16.2)</td>
<td>54.2 (13.5)</td>
<td>2, 3 &gt; 4</td>
<td>2 &gt; 3</td>
<td>4 &lt; 3</td>
<td>3 &gt; 4</td>
<td>—</td>
</tr>
<tr>
<td>YMRS</td>
<td>5.2 (5.6)</td>
<td>7.0 (6.4)</td>
<td>5.8 (6.7)</td>
<td>2 &lt; 3</td>
<td></td>
<td></td>
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<tr>
<td>MADRS</td>
<td>8.8 (8.0)</td>
<td>14.9 (9.9)</td>
<td>11.0 (9.3)</td>
<td>2 &lt; 4</td>
<td>2 &lt; 3</td>
<td>4 &lt; 3</td>
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</table>

Note: Abbreviations are explained in the first footnote to table 1. PANSS, Positive and Negative Symptom Scale; YMRS, Young Mania Rating Scale; MADRS, Montgomery Asberg Depression Rating Scale.

*a*Hochberg test for post hoc comparison from univariate analysis for continuous variables; Z test for post hoc comparison from chi-square analysis for categorical variables.
under conditions when the attentional fixation system is released (on gap trials) to increasingly engaged (from no gap to overlap trials). The percentage of trials with antisaccade errors was recorded as a measure of failed inhibitory behavioral control.

Statistical Analyses

Linear mixed effects models using SAS Proc Mixed were used to test for differences in group performance, with family membership treated as a random effect. Target displacement and condition block in the prosaccade latency analysis were treated as repeated factors. Age, sex, site, and race were evaluated as potential covariates; those with a statistical contribution to the model \((P < .05)\) were retained. Group effects are emphasized below, with full model effects available in online supplementary materials. Post hoc analyses were corrected using the Tukey-Kramer method. To index the magnitude of performance deficits in each subject group, group differences from controls are reported as effect sizes computed as Glass's delta. Effect sizes are only reported for proband or relative groups' deficits compared to controls. For analyses evaluating effects of relatives' clinical status, BACS performance, and prosaccade latency on antisaccade error rates, mixed effects modeling was repeated with inclusion of these terms. Partial correlational analyses with adjustment for potential covariates examined the association between antisaccade performance and symptom ratings, medication effects (ie, current treatment with a class of medication), and daily chlorpromazine equivalents of antipsychotic treatment.\(^{57}\) Familiality was estimated using a maximum likelihood method in the Sequential Oligogenic Linkage Analysis Routines software (v4.3.1\(^{58}\)) using an ascertainment bias correction because families were recruited through the identification of a psychotic relative with schizophrenia.\(^{59}\) Significance of familiality was determined using a maximum likelihood ratio test of a model in which phenotypic variation explained by family membership was compared to one in which it was not.

Results

Antisaccade Error Rate as an Endophenotype for Psychosis

Findings in Probands and All Relatives. Table 3 contains antisaccade error rates for probands and relatives as a whole (ie, including family members with a lifetime history of psychosis or elevated psychosis spectrum personality traits). The mixed effects model indicated significant effects of group \(F(6,2257) = 28.73, P < .0001\) and target displacement \(F(1,2257) = 945.21, P < .0001\), with greater errors to 10 vs 15° targets. There was no interaction of group with other terms.

Post hoc analyses revealed that all proband groups had elevated error rates compared to controls (figure 1), with schizophrenia probands demonstrating the greatest deficit \((d = 1.05, P < .0001)\), followed by schizoaffective \((d = 0.72, P < .0001)\) and bipolar \((d = 0.60, P < .0001)\) probands. Schizophrenia probands had higher error rate than both bipolar \((P < .0001)\) and schizoaffective \((P = .02)\) probands who did not differ.

Schizophrenia \((d = 0.37, P = .0003)\), schizoaffective \((d = 0.37, P = .003)\), and bipolar \((d = 0.30, P = .01)\) relative groups all had elevated error rates compared to controls (figure 1). There were no significant differences among relatives across diagnostic groups. Schizophrenia \((P < .0001)\), schizoaffective \((P = .01)\), and bipolar \((P = .02)\) proband groups all had higher error rates than their respective relative groups.

Cosegregation of Increased Error Rate With Illness Within Families and Findings in Unaffected Relatives. Additional analyses with relatives were conducted according to their clinical status (ie, those with a lifetime history of psychosis, rela-

| Table 3. Raw Antisaccade Error Rate Among Healthy, Proband, and Relative Groups |
|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
|                   | Probands           |                   | Relative           |                   |                   |                   |                   |                   |                   |
|                   | Control (1)        | Scz (2)           | SczA (3)          | BP (4)            | Scz (5)           | SczA (6)          | BP (7)            |                   |                   |
|                   | \((N = 244)\)      | \((N = 267)\)    | \((N = 150)\)    | \((N = 202)\)    | \((N = 304)\)    | \((N = 193)\)    | \((N = 242)\)    |                   |                   |
| Antisaccade Task  | Mean (SD)          | Mean (SD)         | Mean (SD)         | Mean (SD)         | Mean (SD)         | Mean (SD)         | Mean (SD)         |                   |                   |
| Overall error rate| 18.4 (12.5)        | 44.1 (25.8)       | 35.0 (22.8)       | 31.8 (21.6)       | 28.5 (22.8)       | 27.3 (20.2)       | 25.1 (19.8)       | 1 < all; 2 > 3, 4;|                   |
| \((% of trials)\) |                   |                   |                   |                   |                   |                   |                   | 2 > 5; 3 > 6; 4 > 7 |                   |
| Error rate 10°   | 22.6 (15.2)        | 48.7 (26.2)       | 39.3 (24.7)       | 36.3 (23.6)       | 33.4 (24.6)       | 31.9 (21.7)       | 29.1 (21.7)       |                   |                   |
| \((% of trials)\) |                   |                   |                   |                   |                   |                   |                   |                   |                   |
| Error rate 15°   | 14.3 (11.7)        | 39.2 (26.8)       | 30.8 (22.2)       | 27.0 (20.8)       | 23.4 (22.4)       | 22.5 (19.5)       | 21.0 (20.0)       |                   |                   |
| \((% of trials)\) |                   |                   |                   |                   |                   |                   |                   |                   |                   |

Note: Abbreviations are explained in the first footnote to table 1.

*Reflects significant group effect after post hoc correction based upon a linear mixed effects model including: group, target displacement, race, and site.
elevated psychosis spectrum traits, and those with neither characteristic). The effect of relative clinical status was significant ($F(3,1148) = 16.73, P < .0001$), with relatives with a history of psychosis ($d = 0.86, P < .0001$), elevated psychosis spectrum traits ($d = 0.61, P < .0001$), and those with neither characteristic ($d = 0.30 P < .001$), demonstrating greater error rate than controls (figure 2a). This effect did not differ significantly across schizophrenia, schizoaffective, and psychotic bipolar pedigrees. Error rate among relatives with a lifetime history of psychosis or psychosis spectrum traits did not significantly differ, and both had higher error rates than those without either characteristic ($P < .0001, P < .05$, respectively). Still, significant proportions of unaffected relatives had error rates falling 1–2 SDs above controls (figure 2b). Findings among relatives did not differ when the presence of additional axis I conditions (see table 2) were considered.

**Familiality of Antisaccade Error Rate.** Familiality estimates of antisaccade error rate were significant across
all proband diagnoses ($h^2_{\text{all proband}} = 0.29 \pm 0.06, P = .000003$; $h^2_{\text{schizophrenia}} = 0.32 \pm 0.10, P = .0006$; $h^2_{\text{schizoaffective}} = 0.21 \pm 0.12, P = .03$; $h^2_{\text{bipolar}} = 0.30 \pm 0.21, P = .003$).

Effects of Medications and Symptoms on Error Rate in Probands. There was no association of antipsychotic dose (in chlorpromazine equivalents) and antisaccade error rate ($r = .03, P = .51$). Among schizophrenia probands, treatment with anticholinergic medication was associated with elevated error rate ($r = .18, P = .003$). Among bipolar probands, antidepressant ($r = -.21, P = .004$) or mood stabilizer ($r = -.20, P = .004$) treatments were associated with lower error rate while lithium treatment ($r = .21, P = .003$) was associated with higher error rate. Correlations of symptom ratings and error rate were modest (all $r$ values < .17) and nonsignificant after post hoc correction.

Antisaccade Error Rate and the Generalized Cognitive Deficit

Antisaccade error rates were significantly correlated with BACS composite score in all but schizoaffective probands (see online supplementary materials). After accounting for BACS performance, group differences in antisaccade error rate remained significant ($F(6,2096) = 10.91, P < .0001$). Although significantly attenuated after accounting for the BACS composite score, all proband groups continued to demonstrate elevated error rates compared to controls (schizophrenia: $d = 0.73, P < .0001$; schizoaffective: $d = 0.49, P < .0001$; bipolar: $d = 0.44, P < .0001$). Error rates among relative groups also remained elevated compared to controls after accounting for BACS performance (schizophrenia: $d = 0.29, P = .01$; schizoaffective: $d = 0.30, P = .03$; bipolar: $d = 0.29, P = .03$). However, unlike the case with probands, there was no reduction of deficit after this adjustment, suggesting that the familial antisaccade trait is independent from the generalized cognitive deficit (figure 3). Familiality of antisaccade error rate remained significant after accounting for variation in BACS scores ($h^2 = 0.27 \pm 0.06, P = .00002$).

Speed of Attentional Response and Antisaccade Error Rate

The mixed effects model for prosaccade latency indicated significant effects of trial condition ($F(2,8656) = 3137.11, P < .0001$) and group ($F(6,8656) = 5.00, P < .0001$; see online supplementary tables S1 and S2). There was no interaction between these factors, indicating that the effects of the attention manipulation were similar across groups. As expected, prosaccade latencies increased from gap, to no gap, to overlap conditions. Only schizoaffective relatives had modestly reduced prosaccade latency overall ($d = 0.32, P = .02$).

To evaluate the role of speed of attentional shifting on antisaccade error rate, overall prosaccade latency (ie, averaged across gap, no gap, and overlap trials) as a main and interaction effect with group was added to the mixed model evaluating antisaccade error rate. Findings indicated a significant effect of prosaccade latency ($F(1,2242) = 76.18, P < .0001$) and its interaction with group ($F(6,2242) = 3.19, P = .004$). Follow-up analyses revealed that in all groups other than schizophrenia probands, shorter prosaccade latencies were associated with increased antisaccade error rate ($P$ values < .003; see online supplementary figure S1). The lack of relationship between prosaccade latency and antisaccade error rate

![Fig. 3. Effect size deficit of antisaccade error rate in proband and relative groups compared to controls before (light bars) and after (dark bars) adjustment for generalized impairment as indexed by the BACS composite scores. Scz, schizophrenia; SczA, schizoaffective; BP, psychotic bipolar; BACS, Brief Assessment of Cognition in Schizophrenia.](https://academic.oup.com/schizophreniabulletin/article-abstract/40/5/1011/1924411/1844411)
among schizophrenia probands was not attributable to medication effects or symptom severity.

Given the dissociation between prosaccade latency and antisaccade error rate among schizophrenia probands, we examined whether familiality estimates of prosaccade latency were similar across diagnoses. Familiality estimates for prosaccade latency were significant within bipolar ($h^2 = 0.26 \pm 0.12$, $P = .01$) and schizoaffective ($h^2 = 0.23 \pm 0.09$, $P = .005$) pedigrees, but not schizophrenia pedigrees ($h^2 = 0.02 \pm 0.11$, $P = .42$).

**Discussion**

We investigated elevated antisaccade error rate as an intermediate phenotype for schizophrenia, schizoaffective, and psychotic bipolar disorders to determine whether this measure marks disorder specific risk or liability across the psychosis spectrum. We found that antisaccade error rate was elevated among all proband and relative groups, including those relatives without history of psychosis or psychosis spectrum personality traits. Antisaccade error rate was comparably familial across disorders and was minimally associated with clinical symptoms and medication treatments. We also considered whether elevated error rate represented a distinct neurobehavioral deficit in inhibitory control or whether it merely reflected the generalized cognitive impairment associated with psychosis. Our findings indicated that error rate is indeed separable from a generalized impairment both in terms of the performance deficit and the extent of variation attributable to shared familial factors accounting for general neuro-psychological impairment. These novel findings indicate that problems with inhibitory behavioral control, as measured by the antisaccade paradigm, constitute a specific trait that is associated with liability for psychosis across disorders and thus support this measure’s utility as an intermediate phenotype for genetic studies across psychotic illnesses.

Our findings extend prior studies of antisaccade performance among relatives of schizophrenia probands to demonstrate comparably increased error rate among schizoaffective and psychotic bipolar disorder relatives and similar familiality of antisaccade deficit in these disorders. To our knowledge, this is the first study to demonstrate the familiality of this deficit across this psychosis spectrum. Estimates of familiality reported here were comparable to those reported for schizophrenia pedigrees from the Consortium on the Genetics of Schizophrenia (COGS) and other family studies. Consistent with the cosegregation criterion for intermediate phenotypes, the magnitude of relatives’ deficit, regardless of proband diagnosis, varied according to the presence of either psychosis or elevated psychosis spectrum personality traits. Yet, even among relatives without either characteristic, error rate was elevated with over 30% of this group falling beyond a SD from controls. This indicates that many relatives express the antisaccade phenotype even when they do not show clinical signs of psychosis spectrum features. In fact, deficits among relatives remained elevated even when considering those who also had no history of mood, anxiety, or substance use disorders.

The increased error rate among relatives of psychosis probands reported here is in contrast to some prior findings with schizophrenia relatives, including those from COGS, which found elevated error rate in schizophrenia probands but not in their parents or siblings. Some of these discrepancies may be attributed to methodological differences such as the timing asynchrony of the central fixation offset and target appearance in antisaccade tasks. This cannot be the case with COGS, however, as both consortia used overlap paradigms and identical target displacements. Indeed both studies report a similar error rate in control and schizophrenia proband groups indicating that the discrepant findings among relatives are not accounted for by procedural differences. Rather, differences in family ascertainment may account for the discordant findings. COGS had more stringent inclusion criteria, requiring participation of an unaffected sibling along with both parents, whereas the current study required only a single first-degree relative for proband eligibility. The COGS recruitment strategy, while one with advantages, may have included more cohesive and functional families and thus resulted in ascertainment of families with lower diathesis for psychosis, a possibility that may be reflected in higher error rate among relatives in the present study.

Unlike findings in probands in which we observed an increase in antisaccade impairment from psychotic bipolar disorder to schizophrenia (with schizoaffective disorder intermediate to those groups), there was no such diagnostic effect observed among relatives. This supports the notion that antisaccade error rate is associated with risk for psychosis in general rather than conferring a disorder specific risk. It also suggests that factors other than those attributable to familial risk associated with antisaccade error rate may account for the increased antisaccade deficit in schizophrenia. This inference is consistent with our observation that only schizophrenia probands failed to demonstrate the inverse relationship between prosaccade latency, a measure speed of attentional shifting, and antisaccade error rate. This was observed in the context of normal prosaccade latency and expected gap-overlap effects in this group. In the setting of schizophrenia, but importantly not familial risk for schizophrenia, the absence of this relationship suggests that inhibitory failures appear to more prominently reflect executive prefrontal control deficits rather than processes related to the speed with which attention systems orient to sensory input. While the familial contribution to inhibitory control deficits appears similar across psychotic disorders, other factors that reduce the familial modulation of attention shifting ability in schizophrenia, reflected

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by the nonsignificant heritability of prosaccade latency in schizophrenia families, and the increased inhibitory control deficits in schizophrenia probands qualitatively distinguish schizophrenia from other psychotic disorders.

We observed no association of antisaccade errors with antipsychotic exposure or dosage, although higher error rate was detected among schizophrenia probands treated with anticholinergics and bipolar probands treated with lithium. Conversely, mood stabilizers and antidepressant treatments were associated with lower error rates among bipolar probands. In a cross-sectional design such as ours, medication effects are difficult to disentangle from illness severity and side-effect vulnerability; polypharmacy further complicates interpretation of medication correlations. Overall, however, medication treatments accounted for less than 5% of the variance in error rate. Additionally, symptom ratings were not related to antisaccade performance in proband groups. While acute psychosis may affect eye movement parameters, this study was designed to minimize psychosis acuity effects by recruiting clinically stable patients, so that phenotypes examined would primarily reflect a trait marker of illness. This is consistent with findings from a recent longitudinal study examining the temporal stability of antisaccade and other neurophysiologic measures in a community sample of schizophrenia probands followed longitudinally.

Increased antisaccade error rate among probands and relatives was not attributable to the generalized neuropsychological impairment in these groups. Effect size of antisaccade deficits and its familiality remained consistently elevated after accounting for the variance attributed to the BACS composite score. This suggests that the impairment in inhibitory control, as measured by the antisaccade task, reflects a specific deficit in voluntary inhibitory control independent from the generalized cognitive impairment associated with risk for psychosis. There has been substantial discussion about the need to distinguish specific vs generalized cognitive deficits for some time with active reconsideration of this issue recently. This point has relevance for consideration of intermediate phenotypes in so far as their utility for elucidating risk along gene-to-phenotype pathways is dependent upon their being related to discrete neurobiological systems and substrates and their adding unique and incremental phenotypic characterization. Otherwise, even if traits meet other endophenotype criteria, their ability to provide new information to advance gene discovery is likely limited. The neurocognitive specificity of elevated antisaccade error rate may thus provide a linkage of impaired inhibitory control related to specific alterations in prefrontal and frontoparietal systems that may be related to specific risk pathways.

Certain limitations of this study may constrain the generalizability of our findings. First, the inclusion criteria for probands including the absence of current substance abuse or significant lifetime dependence and the presence of a family member willing and able to participate, and cooperation with the demands of a rigorous research protocol may limit the representativeness of our sample. Additionally, we restricted controls to those without a personal or family history of psychosis or bipolar disorder, and no elevated psychosis spectrum personality traits. While this permitted comparison of our clinical samples with a control group without illness-related characteristics to estimate the impact of illness on the phenotype, it is a comparison group that is healthier than the general population. We note, however, that even relatives without elevated psychosis spectrum personality traits demonstrated deficits compared to our control group.

The results from the present study provide evidence supporting a role for antisaccade error rate as a neurocognitive intermediate phenotype marking clinical and familial risk for psychotic illness across schizophrenia, schizoaffective, and psychotic bipolar diagnostic categories. While associated with familial risk generally across this spectrum of psychotic disorders, disease-specific deficits resulting from potentially differential mechanisms in schizophrenia probands were also detected. These findings provide further support for measures of behavioral inhibitory control as a useful tool in the search for genetic factors conferring susceptibility to psychosis.

Supplementary Material
Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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Antisaccade Errors as an Intermediate Phenotype for Psychosis


