Using Neurophysiological Markers of Genetic Risk to Define the Boundaries of the Schizophrenia Spectrum Phenotype

by Matthew T. Avila, Helene M. Adami, Robert P. McMahon, and Gunvant K. Thaker

Abstract

There is considerable evidence that schizophrenia spectrum personality (SSP) disorders mark genetic risk for schizophrenia. Use of the spectrum phenotype in genetic and neurophysiological studies may prove informative. However, the degree to which the current diagnostic criteria correspond with genetic risk is unclear. This can be assessed by observing how measures of liability among SSP subjects change as a function of diagnostic criteria. In this study the generalized estimating equation method was used to assess changes in eye-tracking performance among SSP and non-SSP family and community groups employing various diagnostic criteria. Eye-tracking deficits among SSP relatives remained statistically higher compared with the other groups across progressively more liberal SSP criteria. The results suggest that fewer traits than are used in clinical diagnoses can effectively identify the spectrum phenotype among relatives of schizophrenia patients. Thus, reduced criteria may be used in research to increase "high risk" sample size and power to detect neurophysiological and genetic differences. Our results provide suggestive evidence that the use of clinical criteria in research may, in fact, underidentify at-risk individuals—potentially distorting genetic and neurophysiological findings.

Keywords: Schizophrenia, schizophrenia spectrum, diagnostic criteria, genetic risk, neurophysiological marker, phenotype.


Several investigators have suggested that the study of schizophrenia spectrum personality disorders (SSPDs) may serve to clarify the genetic causes and related neurophysiological deficits associated with schizophrenia (e.g., Lichtermand et al. 2000; Tsuang 2001). Extensive evidence from family studies suggests a relationship between schizophrenia and spectrum disorders (see Battaglia and Torgerson 1996 for a review). This evidence includes reported increases in the prevalence of schizotypal personality disorder among relatives of patients with schizophrenia (e.g., Kendler et al. 1984, 1994; Baron et al. 1985), higher rates of schizophrenia among relatives of individuals diagnosed with schizotypal personality (Battaglia et al. 1991, 1995; Thaker et al. 1993; Kendler and Walsh 1995), and increased prevalence of schizophrenia in the offspring of schizotypal parents whose spouses also have schizotypal personality (Baron et al. 1983). A similar but weaker relationship between paranoid and schizoid personality disorders and schizophrenia is suggested in some studies (Kendler and Gruenberg 1984; Baron et al. 1985; Battaglia et al. 1995; Kendler and Walsh 1995). Although these data clearly indicate a familial association between SSPD and schizophrenia, they provide only indirect support for the hypothesis that these disorders share a common genetic basis. Direct evidence of genetic continuity comes from a recent study by Pulver et al. (2000), who found that stratification of families based on the presence of SSPD in linkage analysis (i.e., restricting the analysis to only those families where both SSPD and schizophrenia were present) resulted in a significantly higher lod score for chromosome 8p21.

Consistent with a shared genetic etiology, studies of neurocognitive and neurophysiological functioning have found similar deficits among patients with schizophrenia and individuals with SSPD (Siever 1985; Battaglia and Torgersen 1996). These similarities include deficits in attention (Keefe et al. 1997; Chen et al. 1998), information processing—e.g., event-related potentials (Cadenhead et al. 2000; Niznikiewicz et al. 2000), and eye-tracking performance (e.g., Clementz et al. 1990, 1995; Siever et al. 1994; Thaker et al. 1996a; O'Driscoll et al. 1998). The
degree to which these neurophysiological findings can be attributed to schizotypy, familial relationship to schizophrenia, or both is currently unresolved (Thaker 2000). However, several studies find that deficits are more likely to occur or are more pronounced among relatives of patients with schizophrenia exhibiting spectrum traits compared with unaffected family members and nonfamilial cases of SSPD (Condray and Steinhauser 1992; Thaker et al. 1996a, 1998; Kimble et al. 2000). In contrast, several lines of evidence suggest that spectrum disorders in the absence of a family history of schizophrenia are heterogeneous in their origins (Squires-Wheeler et al. 1988; Stanley et al. 1990; Kendler et al. 1993; Lyons et al. 1994) and not necessarily related to schizophrenia (Thaker et al. 1996b).

Thus, there is converging evidence from family, genetic, and neurophysiological studies that SSPD, particularly in the presence of schizophrenia, marks the genetic liability to schizophrenia. Growing support for this view has been accompanied by important changes in study conceptualization and design. For example, several investigators have recommended the inclusion of the SSPD phenotype in formal genetic analyses (e.g., Maier et al. 1994; Faroane et al. 1995; Thaker et al. 1996a). The results of Pulver's (2000) restricted linkage analysis and other molecular genetic studies employing the spectrum phenotype (e.g., Ekelund et al. 2000) highlight the potential power of this new strategy in searching for regions of interest in the genome. Assessment and inclusion of SSPD status are also likely to increase the power to detect group differences in neurophysiological and cognitive studies of nonpsychotic relatives.

The success of these strategies is predicated on a high degree of correspondence between the clinical phenotype and the presence of genes conferring risk for schizophrenia. However, the diagnostic criteria used to define these phenotypes (e.g., DSM-III-R and DSM-IV; American Psychiatric Association 1987, 1994) were developed primarily as a clinical indicator of pathology with less emphasis on the identification of genetic risk. Thus, in biological terms it remains unclear how effectively our current diagnostic systems define the boundary of the spectrum phenotype for the purposes of genetic and neurobiological studies of schizophrenia. For example, schizophrenia appears inconsistent with the reported prevalence of negative symptoms (a significant component of both the schizoid and schizotypal phenotype) among relatives of schizophrenia patients (Kety et al. 1994; Maier et al. 1994). Although this is explained, in part, by the use of hierarchical methods for calculating risk rates in which a person meeting the diagnosis for both disorders would be included only in the schizotypal group, it also suggests that DSM criteria for schizoid personality may be too stringent. Siever et al. (1993) and others (e.g., Thaker et al. 1993, 1996a) have suggested that the schizophrenia spectrum may, in fact, extend beyond our current criteria. That is, likely genetic carriers who exhibit spectrum symptoms do not necessarily demonstrate the required number of traits in any one spectrum category (i.e., schizotypal, schizoid, or paranoid) to receive a formal clinical diagnosis. If this assertion is correct, the use of formal DSM criteria can potentially distort neurophysiological and genetic differences—for example, by including nonpsychotic relatives with spectrum traits in unaffected categories.

One way to examine this issue is to observe changes in group performance on a putative liability marker using various diagnostic thresholds for SSPD. To examine the effects of lowering diagnostic thresholds we utilized two eye-tracking measures: (1) smooth pursuit gain during target masking and (2) the ratio of leading saccadic to smooth pursuit eye movements. Both measures, which tap specific components of the smooth pursuit response, have been shown when compared with more global assessments of eye-tracking performance to better differentiate patients and relatives from healthy controls, and are therefore thought to more accurately reflect genetic liability for schizophrenia (Ross et al. 1998, 1999, 2000; Thaker et al. 1998; Avila et al. 2002).

In an attempt to enhance the identification of "affected" relatives in neurophysiological and genetic studies of schizophrenia, several researchers reduce the number of required spectrum traits by one more (e.g., Squires-Wheeler et al. 1989; Siever et al. 1994; Battaglia et al. 1995; Thaker et al. 1996a). The purpose of the present study is to test the validity of this practice by examining the change in eye-tracking performance among SSPD and non-SSPD relatives and community controls using reduced criteria. Because DSM minus one criteria are most frequently employed in studies of schizophrenia, we focus on the comparison between these criteria and DSM-III-R.1 Exploratory analyses are also performed using further trait reductions to identify how far one can relax DSM criteria before eye-tracking differences among SSPD groups are significantly reduced. Observed changes in both the pattern and magnitude of group differences may have important implications for how we define and treat SSPD status in future genetic and neurobiological studies of schizophrenia.

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1 Minus 1 criteria are similar to the number of traits required by DSM-III criteria. The change from DSM-III to DSM-III-R involved the addition of a ninth trait and a subsequent increase in the threshold from 4 to 5. Interestingly, there was no psychometric reason for changing the trait threshold—only a rationale for adding a trait based on clinical content.
Methods and Materials

Research Volunteers

Participant recruitment. All participants gave written informed consent in accordance with University of Maryland Institutional Review Board guidelines. First-degree biological relatives of schizophrenia patients attending inpatient and outpatient programs at the Maryland Psychiatric Research Center (MPRC) were recruited through letters and MPRC family seminars. First-degree relatives were ascertained from independent families in all but five cases. The diagnosis of index probands was verified using the Structured Clinical Interview for DSM-III-R Diagnosis (SCID-III-R) (Spitzer et al. 1990).

Community volunteers were recruited through newspaper advertisements. In order to recruit community participants with spectrum traits, one set of advertisements sought individuals who had experienced magical thinking, perceptual distortions, social isolation, or lack of social drive—see Kunkel et al. (1998) for details on recruitment of spectrum community participants.

Clinical assessments. The SCID-III-R and Structured Interview for DSM-III-R Personality Disorders (SIDP-R) (Pfohl et al. 1989) were used to assess Axis I and Axis II disorders. Modified Family History Research Diagnostic Criteria (FH-RDC) (Andreasen et al. 1986) were used to rule out positive history for psychotic disorders in the families of community volunteers. We modified the FH-RDC by adding probe questions to increase the sensitivity of detecting schizophrenia and related disorders (Adami et al. 1990). Masters- and doctoral-level trained clinicians conducted all interviews. Diagnostic information was reviewed in a best estimate diagnostic meeting. Where additional information was required to make a diagnosis, SIDP-R informant interviews were also conducted. Informant interviews were done for approximately 10 percent of the participants. Each participant was given lifetime DSM-III-R Axis I and Axis II diagnoses. Interrater reliabilities (measured using a kappa statistic) exceeded 0.81 for all instruments.

Rating individual spectrum traits. Rating the presence or absence of individual spectrum traits was accomplished using a 1–7 scale based on the extended ratings scale developed by Chapman et al. (1976). We have developed a manual with anchors to assist in ratings (manual is available upon request from M.T.A.). The following general guidelines were used: a symptom definitely absent was rated a 1; a symptom probably absent was rated a 2; and a symptom probably present was rated a 3. These scores correspond to a rating of 0 on the SIDP-R. A symptom definitely present but mild in severity (i.e., did not significantly interfere with functioning or cause distress) was rated a 4, while a symptom definitely present accompanied by mild functional impairment and/or distress was rated a 5. These correspond to a rating of 1 on the SIDP-R. Finally, symptoms of moderate and marked severity were given ratings of 6 and 7, respectively. These correspond to a rating of 2 on the SIDP-R. In keeping with the goal of identifying covert liability rather than overt pathology, a symptom was considered to be present if the rating was 4 or more. Thus, the current rating system may identify individuals with SSPD who do not exhibit functional impairment, thereby limiting its application to research settings. Interrater reliabilities for paranoid-, schizoid-, and schizotypal-summed scores were excellent (intraclass correlation coefficients [ICCs] > 0.88). On most of the individual items, interrater reliabilities were good (> 0.80); however, on three items, ICCs were suboptimal (0.64 and 0.50 for paranoid items 00A5 and 00A6, respectively, and 0.76 for the schizotypal item 22A7). Interrater reliabilities for diagnoses of the three personality disorders based on full and reduced DSM-III-R criteria ranged from 0.81 to 1.00 (kappa).

Participant groups. Participants with a current or lifetime Axis I diagnosis (except those with a single, past episode of major depression that did not require pharmacological treatment, or those with a history of substance abuse ending at least 6 months prior to the study) were excluded. Community participants with a family history of psychotic disorders according to FH-RDC were also excluded. Research volunteers were grouped according to family status (family vs. community) and spectrum diagnosis. Use of DSM-III-R SSPD criteria yielded a sample composed of 53 non-SSPD and 17 SSPD family members, and 49 non-SSPD and 25 SSPD community participants. Clinical and demographic information are shown in table 1 for the groups defined according to both DSM-III-R and DSM-III-R minus one criteria (the most common threshold reduction seen in the literature).

Ocular Motor Data Acquisition and Analysis. Both the eye-tracking task and ocular motor data acquisition and analyses have been described in detail previously (see Thaker et al. 1998). Briefly, a target was presented on a 15-inch flat monitor. A foveal-petal step-ramp was presented followed by target motion in a horizontal plane, back and forth, at a constant velocity. One sweep across the monitor (from −12° to +12° visual angle) constituted a ramp. After approximately three to four ramps, the target was unpredictably masked (blanked out) for 500 ms. Targets were originally presented at three velocities (9.4°, 14.0°, and 18.7°/sec). In the present study, only data from target velocities previously shown to maximally discriminate groups are presented (Thaker et al. 1998).
Eye-movement data were obtained using an infrared technique (at a sampling rate of 333 Hz and time constant of 4 ms) and 16-bit analogue-to-digital converter. The digital data were filtered offline using a low pass filter at a cutoff frequency of 75 Hz. Eye-movement records were analyzed using interactive software (Igor, Wavemetrics, Lake Oswego, OR). Saccades were identified based on velocity (>35°/sec) and acceleration (>600°/sec²) criteria. Saccades and blinks were removed and replaced with linearly interpolated data points.

**Eye-Movement Measures.** The following eye-movement measures were examined: (1) Predictive pursuit gain, which is a measure of eye movements during the mask designed to assess predictive response based on extra-retinal motion processing (Thaker et al. 1996b, 1998; Barnes et al. 2000); and (2) the ratio of leading (i.e., anticipatory) saccadic eye movements to smooth pursuit eye movements during visible target motion. Predictive pursuit gain and the leading saccade ratio were chosen based on data from several studies suggesting their superior sensitivity and specificity in identifying putative genetic risk (Avila et al. 2002).

**Predictive pursuit gain.** Predictive pursuit gain was calculated from eye-movement data in the mask. When the mask occurs during a ramp, the eye continues to move at the same velocity as before the mask for about 130 to 170 milliseconds—presumably still influenced by the previous closed-loop response. After this initial period, there is a 35 to 50 percent reduction in eye velocity—marking the transition to predictive pursuit (Becker and Fuchs 1985; Thaker et al. 1998). This transition point was identified by algorithm using eye data filtered at 20 Hz. The average eye velocity between the transition point and the end of the mask was used to calculate predictive pursuit gain (mask eye velocity divided by target velocity).

**Leading saccades.** Duplicate eye-movement records (filtered at 75 Hz) in which saccades were left intact were used to measure leading saccades. Saccades were identified using Igor Pro and verified by visual inspection (intrater reliability exceeded 0.95 [ICC]) according to the following criteria: saccades were classified as leading only if they (1) occurred in the direction of the target motion, (2) either began and ended ahead of the target or increased position error by 100 percent, and (3) were followed by at least a 50 ms interval of eye velocity less than 50 percent of target velocity. These criteria are based on the work of Ross and colleagues (Ross et al. 1998). Leading saccades were indexed by the percentage of total artifact-free eye movements due to leading saccades—calculated by dividing the time spent in leading saccades by the total time in pursuit and multiplying this ratio by 100.

**Statistical Analyses**

**Family status × spectrum diagnosis.** Analyses of variance (ANOVA) were used to verify that eye-tracking performance was consistent across the three spectrum categories (i.e., schizoid, paranoid, and schizotypal). These analyses were conducted using both DSM and DSM minus one criteria. The results of these analyses are shown in table 2. Briefly, main effects of SSPD diagnosis were not significant in all cases except leading saccade scores—where individuals meeting full DSM criteria for schizotypal personality disorder showed significantly lower leading saccade scores compared with individuals meeting paranoid and/or schizoid diagnoses only. None of the family status by diagnosis interactions were significant. The mean number of traits for the 56 cases meeting DSM minus one criteria (called MINI below) was 8.3 ± 2.4. Fifty-two of the 56 spectrum cases had traits associated...
Table 2. Comparison of Eye-Tracking Performance in Community and Family Participants Meeting Paranoid and/or Schizoid vs. Schizotypal Criteria a,b

<table>
<thead>
<tr>
<th>DSM-III-R c,d</th>
<th>paranoid and/or schizoid</th>
<th>schizotypal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community spectrum (n = 25)</td>
<td>0.67 ± 0.21</td>
<td>0.67 ± 0.19</td>
</tr>
<tr>
<td>Family spectrum (n = 17)</td>
<td>0.47 ± 0.16</td>
<td>0.42 ± 0.07</td>
</tr>
<tr>
<td>MIN1 e,f</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Community spectrum (n = 30)</td>
<td>0.70 ± 0.21</td>
<td>0.62 ± 0.21</td>
</tr>
<tr>
<td>Family spectrum (n = 26)</td>
<td>0.45 ± 0.15</td>
<td>0.45 ± 0.11</td>
</tr>
</tbody>
</table>

a. Means and standard deviation are presented for predictive pursuit gain (p. gain) and the leading saccade ratio (saccade).
b. 2 (family vs. community status) by 2 (paranoid/schizoid vs. schizotypal diagnosis) analyses of variance were used to determine whether eye-tracking performance differed as a function of spectrum category.
c. (DSM/Gain) Main effect of family status (family group exhibited lower pursuit gain scores), F(1,35) = 9.8, p = .004; No effect of DSM diagnosis, F(1,35) < 1.0, p = .75; No family status by diagnosis interaction, F(1,35) < 1.0, p = .70.
d. (DSM/Saccade) No effect of family status, F(1,37) < 1.0, p = .63; Main effect of DSM diagnosis (subjects with a schizotypal diagnosis exhibited lower saccade scores), F(1,37) = 8.1, p = .007; No family status by diagnosis interaction, F(1,37) < 1.0, p = .58.
e. (MIN1/Gain) Main effect of family status (family group exhibited lower pursuit gain scores), F(1,48) = 14.8, p < .0005; No effect of diagnosis, F(1,48) < 1.0, p = .43; No family status by diagnosis interaction, F(1,48) < 1.0, p = .48.
f. (MIN1/Saccade) Main effect of family status (family group exhibited lower saccade scores), F(1,51) = 4.0, p = .05; No effect of diagnosis, F(1,51) < 1.0, p = .95.

with more than one spectrum category (e.g., both schizoid and schizotypal traits). The lack of differences in eye-tracking performance across the three spectrum categories and the common co-occurrence of traits from the different categories among individual cases support the hypothesized association between neurophysiological abnormalities and schizophrenia spectrum categories. Thus, in subsequent analyses, participants were classified as "SSPD" if they met criteria for any of the SSPD diagnoses.

Each participant was classified as either SSPD or non-SSPD using five different definitions: (1) DSM-III-R criteria (DSM); (2) DSM-III-R criteria with trait thresholds reduced by one (MIN1); (3) DSM-III-R with trait thresholds reduced by two (MIN2); (4) DSM-III-R with trait thresholds reduced by three (MIN3); and (5) DSM SSPD diagnosis based on the presence of any one spectrum trait (ANY).

To assess the impact of changes to DSM SSPD criteria on observed differences in eye-tracking performance between SSPD relatives and the other groups, we adapted Sullivan-Pepe’s method for comparing the strength of univariate associations with a single disease outcome among different risk factors (Sullivan-Pepe et al. 1999). For each participant, five observations were generated—one corresponding to each method of defining SSPD. Using the SAS GLM (General Linear Model) procedure (SAS Institute 1997), the following model was tested: eye-tracking score = group (i.e., family status × SSPD diagnosis) + definition of SSPD + group × definition of SSPD. A significant group × definition interaction was interpreted as evidence that the magnitude of the differences among the groups’ eye-tracking performances differed according to how SSPD was defined. The test of the main effect of groups compared the linear combination of eye-tracking scores (i.e., aggregated across definitions of SSPD) in each of the four groups. Post hoc tests were used to compare eye-tracking performance in family SSPD participants to that of participants in the other groups. To take into account the correlations among repeated observations from the same participants, models were fitted using the generalized estimating equations (GEE) method (Liang and Zeger 1986). The primary analysis compared DSM-III-R criteria to MINI criteria. Exploratory analyses were also performed using all five definitions of SSPD to identify how far the criteria could be relaxed before eye-tracking differences among SSPD groups were significantly reduced. The two eye-tracking measures, predictive pursuit gain and leading saccade ratio, were analyzed separately. Table 3 lists the group means and standard deviations for each eye-tracking measure based on the five definitions of SSPD.

Results

Does the Use of MINI Criteria Affect Group Differences?

Predictive pursuit gain. Type 3 GEE analysis of the group × SSPD definition interaction did not achieve statistical significance (χ²(3) = 6.84, p = 0.077). Thus, reducing diagnostic thresholds by one did not significantly change the pattern or magnitude of group differences in parameter estimates based on predictive pursuit gain. The
linear combination of predictive pursuit gain scores was significantly different among the groups ($\chi^2(3) = 13.36, p = 0.003$). Least squares mean differences indicated that the family SSPD group exhibited lower combined scores (indicating poorer eye-tracking performance) compared with the family non-SSPD group ($\chi^2(1) = 4.19, p = 0.04$), the community SSPD group ($\chi^2(1) = 16.65, p < 0.001$), and the community non-SSPD group ($\chi^2(1) = 10.20, p = 0.01$). These results are illustrated graphically in the boxed area of figure 1.

**Leading saccades.** The group $\times$ SSPD definition interaction for leading saccades was not statistically significant ($\chi^2(3) = 7.36, p = 0.061$)—suggesting that group differences in the leading saccade ratio did not change after applying MINI criteria. Combined leading saccade scores did not significantly differentiate the groups ($\chi^2(3) = 5.78, p = 0.12$). These results are illustrated graphically in the boxed area of figure 1.

The absence of significant group $\times$ SSPD interactions supports the validity of using MINI criteria. However, one should note that both interactions were marginally significant ($p = 0.08$ and $0.06$), and thus a tentative description of them may be informative. Post hoc analyses of the group $\times$ SSPD definition interaction suggests a statistical difference in predictive pursuit gain between the family non-SSPD and family SSPD groups at MINI criteria ($\chi^2(1) = 6.14, p = 0.01$) compared with no statistical effect for these groups using DSM criteria ($\chi^2(1) = 2.31, p = 0.13$). For leading saccades, statistical differences emerged between family SSPD and family non-SSPD ($\chi^2(1) = 4.02, p = 0.05$), family SSPD and community non-SSPD ($\chi^2(1) = 5.43, p = 0.02$), and family SSPD and community SSPD ($\chi^2(1) = 6.17, p = 0.01$) at MINI criteria. These differences were not evident using DSM criteria ($\chi^2(1) < 1.00, p = 0.73; \chi^2(1) = 3.34, p = 0.07; \chi^2(1) = 2.06, p = 0.15$ respectively).

**Pattern of Differences Across All Diagnostic Schemes**

**Predictive pursuit gain.** Analysis of residual predictive pursuit gain including all definitions of SSPD (DSM to ANY) yielded a significant main effect of group ($\chi^2(3) = 13.11, p = 0.004$)—thus the linear combination of pursuit gain scores was significantly different among the groups. The family SSPD group exhibited significantly lower (poorer) combined pursuit gain scores compared with community SSPD ($\chi^2(1) = 16.50, p < 0.001$) and community non-SSPD ($\chi^2(1) = 8.71, p = 0.003$) groups. The family non-SSPD group exhibited significantly lower gain scores compared with the community SSPD group ($\chi^2(1) = 5.23, p = 0.02$), but not compared to the community non-SSPD group ($\chi^2(1) < 1.00, p = 0.37$). The group $\times$ SSPD definition interaction was not statistically significant ($\chi^2(12) = 18.19, p = 0.11$) aggregating across all definitions of SSPD.

**Leading saccades.** The test of the linear combination of leading saccade scores was not statistically significant ($\chi^2(3) = 7.17, p = 0.067$). Thus aggregated across all definitions of SSPD, leading saccades did not significantly differentiate the groups. The group $\times$ SSPD definition interaction was also not statistically significant ($\chi^2(12) = 17.65, p = 0.13$).

**Discussion**

The continued presence of a putative marker of risk (in this case eye-tracking deficit) among SSPD relatives despite the application of more liberal diagnostic criteria (MINI) suggests that fewer traits are required than are cur-

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Table 3. Mean and Standard Deviations for Eye-tracking Measures in Each Diagnostic Scheme

<table>
<thead>
<tr>
<th></th>
<th>DSM-III-R</th>
<th>MIN1</th>
<th>MIN2</th>
<th>MIN3</th>
<th>ANY</th>
</tr>
</thead>
<tbody>
<tr>
<td>community SSPD</td>
<td>(n)</td>
<td>25</td>
<td>37</td>
<td>34</td>
<td>48</td>
</tr>
<tr>
<td>predictive pursuit gain</td>
<td>0.62±0.20</td>
<td>0.64±0.21</td>
<td>0.67±0.23</td>
<td>0.64±0.22</td>
<td>0.63±0.21</td>
</tr>
<tr>
<td>leading saccades</td>
<td>0.80±1.05</td>
<td>0.70±0.98</td>
<td>0.65±0.94</td>
<td>0.60±0.91</td>
<td>0.63±0.87</td>
</tr>
<tr>
<td>community non-SSPD</td>
<td>(n)</td>
<td>49</td>
<td>44</td>
<td>41</td>
<td>32</td>
</tr>
<tr>
<td>predictive pursuit gain</td>
<td>0.58±0.18</td>
<td>0.59±0.17</td>
<td>0.56±0.14</td>
<td>0.58±0.14</td>
<td>0.57±0.14</td>
</tr>
<tr>
<td>leading saccades</td>
<td>0.73±0.91</td>
<td>0.79±0.94</td>
<td>0.84±0.96</td>
<td>0.93±0.98</td>
<td>0.96±1.07</td>
</tr>
<tr>
<td>family SSPD</td>
<td>(n)</td>
<td>17</td>
<td>26</td>
<td>33</td>
<td>44</td>
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<tr>
<td>predictive pursuit gain</td>
<td>0.46±0.14</td>
<td>0.45±0.13</td>
<td>0.49±0.15</td>
<td>0.50±0.15</td>
<td>0.49±0.15</td>
</tr>
<tr>
<td>leading saccades</td>
<td>1.31±1.22</td>
<td>1.71±1.91</td>
<td>1.49±1.78</td>
<td>1.53±1.68</td>
<td>1.47±1.64</td>
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<tr>
<td>family non-SSPD</td>
<td>(n)</td>
<td>53</td>
<td>44</td>
<td>37</td>
<td>26</td>
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<tr>
<td>predictive pursuit gain</td>
<td>0.53±0.18</td>
<td>0.55±0.18</td>
<td>0.54±0.19</td>
<td>0.55±0.21</td>
<td>0.56±0.21</td>
</tr>
<tr>
<td>leading saccades</td>
<td>1.16±1.54</td>
<td>0.89±1.01</td>
<td>0.93±1.05</td>
<td>0.62±0.66</td>
<td>0.64±0.70</td>
</tr>
</tbody>
</table>

a. Mean and standard deviations for the 4 groups are presented for each diagnostic scheme.
b. Changes in sample size for each diagnostic scheme are indicated for each group.
Figure 1. Group differences in eye tracking across definitions of SSPD

Boxed area highlights the DSM v. MINI comparison.

Note. — com = community; fam = family.

currently employed by DSM to effectively identify the spectrum phenotype. In practical terms, the data validate the practice of reducing criteria in order to increase “high risk” sample size and subsequently increase the power to detect group differences in neurophysiological studies. For example, in the present study, the use of MINI criteria increased the family SSPD sample size from 17 to 26 (table 2). The fact that neurophysiological “performance” was unaffected by the change in criteria also suggests that the nine cases added to the affected group were, in fact, affected. Thus, in theoretical terms, the use of MINI criteria may be useful in reducing the number of false negatives made when attempting to identify individuals at genetic risk based on the presence of spectrum traits. The addition of affected cases would serve to increase the power of genetic analyses. Results of the present study suggest that this can be done without increasing false positives.

Preliminary support for this increasing sensitivity can be seen in figure 1, which shows that group eye-tracking performances are relatively stable across the different definitions of SSPD. This pattern is confirmed statistically by the presence of group differences on the
linear combinations of eye-tracking scores aggregated across SSPD definitions. For the predictive pursuit gain measure, combined scores significantly differentiated SSPD relatives from the community groups, but did not differentiate non-SSPD relatives from non-SSPD community participants. Although not statistically significant ($p = 0.067$), the pattern of differences in the combined leading saccade scores was similar—based on least squares differences, SSPD relatives exhibited higher combined scores compared with all other groups, while non-SSPD relatives were not significantly different from the community groups.

Interestingly, it appears that even the presence of one SSPD trait increases the likelihood of carrying risk, as marked by eye-tracking abnormality. For example, if we derive a cut score for normal vs. abnormal eye-tracking performance and graph the percentage of SSPD relatives exhibiting this abnormality across definitions of SSPD (figure 2), we find that there is a relatively high proportion of abnormality among SSPD relatives (ranging from 23 to 33% for predictive pursuit and from 18 to 23% for leading saccades), irrespective of how SSPD is defined. In fact, the SSPD “break” in terms of eye-tracking performance appears to occur between family members exhibiting at

Figure 2. Percentage of SSPD family members exhibiting abnormal eye tracking across definitions of SSPD

Note.—SSPD = schizophrenia spectrum personality disorder

1Cut scores for classifying eye-tracking performance as abnormal were empirically derived using logistic regression analysis. Models were run using family SSPD vs. community as the dichotomous outcome. Cut scores were calculated using the formula $\ln[p/(1-p)] = c + bx$, where b is the eye-tracking measure parameter estimate from the logistic regression, c is the constant from the model, and p is the probability cut score. Probability cut scores yielding approximately 90 percent specificity were chosen for each measure. Cut values for predictive pursuit gain and leading saccades were 0.4025 and 2.031, respectively.
least one spectrum trait and family members without spectrum traits. These data suggest that this way of dividing first-degree relatives may prove informative in future neuropathological studies of schizophrenia.

Analyses of the marginally significant group by definition interactions for the DSM vs. MINI comparison provide another reason to consider the use of reduced criteria in neuropathological studies. Here we see that the conclusions drawn about the relationships between eye-tracking abnormalities, familial association with schizophrenia, and the presence of SSPD are different depending on the criteria used. For example, using DSM criteria, one might conclude that familial association, rather than familial association in the presence of SSPD, is related to abnormalities in predictive pursuit (i.e., family SSPD and family non-SSPD were not different from each other on this measure using DSM criteria). However, using MINI criteria, one might suggest that familial association and the presence of SSPD interact such that family non-SSPD groups perform worse than controls, and family SSPD groups perform worse than family non-SSPD. The latter conclusion based on MINI criteria is consistent with studies that have found that deficits are more likely to occur or are more pronounced among relatives of patients with schizophrenia exhibiting spectrum traits compared with unaffected family members (Condray and Stein-hauer 1992; Thaker et al. 1996a, 1998; Kimble et al. 2000).

Conclusions

Although preliminary, the findings of the present study have important implications for how we define the spectrum phenotype in future genetic and neuropathological studies of schizophrenia. Our data suggest that reduced criteria may prevent the exclusion of likely genetic carriers from affected groups—leading to an increase in at-risk sample sizes. Conversely, this strategy may prevent the inclusion of at-risk individuals in family groups assumed to be psychiatrically healthy and therefore at lower risk. The former misclassification could lead to a failure to find significant associations between SSPD diagnoses and schizophrenia (for example, in the case of schizoid and/or paranoid personality disorders); or a failure to find significant associations between SSPD and neuropathological deficits, while the latter misclassification could lead to an overestimation of impaired neuropathological functioning in "normal" family members.

References


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