Smooth Pursuit Eye Movements in Schizophrenia and Attentional Dysfunction: Adults with Schizophrenia, ADHD, and a Normal Comparison Group

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Background: Smooth pursuit eye movement (SPEM) abnormalities are found in schizophrenia. These deficits often are explained in the context of the attentional and inhibitory deficits central to schizophrenia psychopathology. It remains unclear, however, whether these attention-associated eye movement abnormalities are specific to schizophrenia or are a nonspecific expression of attentional deficits found in many psychiatric disorders. Adult attention-deficit/hyperactivity disorder (ADHD) is an alternative disorder with chronic attentional and inhibitory dysfunction. Thus, a comparison of SPEM in adult schizophrenia and adult ADHD will help assess the specificity question.

Methods: SPEM is recorded during a 16.7° per second constant velocity task in 17 adults with ADHD, 49 adults with schizophrenia, and 37 normal adults; all groups included individuals between ages 25–50 years.

Results: Smooth pursuit gain and the frequency of anticipatory and leading saccades are worse in schizophrenic subjects, with normal and ADHD subjects showing no differences on these variables.

Conclusions: Many attention-associated SPEM abnormalities are not present in most subjects with ADHD, supporting the specificity of these findings to the attentional deficits seen in schizophrenia. Biol Psychiatry 2000;48:197–203 © 2000 Society of Biological Psychiatry

Key Words: Schizophrenia, attention-deficit/hyperactivity disorder, eye movements, smooth pursuit, saccades

Introduction

More than 90 years ago, Diefendorf and Dodge (Diefendorf and Dodge 1908) first reported that individuals with schizophrenia had difficulty tracking a predictably moving object. Abnormal eye tracking, one of the most frequently studied and consistently reproduced psychophysiologic abnormalities associated with schizophrenia (Levy et al 1993), may help refine the neurophysiologic description of schizophrenia (Ross et al 1998b) and facilitate genetic studies of schizophrenia (Clementz 1998). Ocular tracking of a moving target, commonly referred to as smooth pursuit eye movements (SPEM), requires the coordinated activation of both smooth pursuit and saccadic systems (Gaymard and Pierrot-Deseiligny 1999). The roles of each of these eye-movement abnormalities in producing the eye-tracking abnormalities in schizophrenia have yet to be fully determined.

SPEM abnormalities often can be at least partially normalized with attention enhancement techniques (Rosenberg et al 1997), and at least one of the pathologic components of SPEM performance, task-inappropriate intrusion of anticipatory saccades, has been conceptualized as a failure of inhibitory control (Friedman et al 1992; Rosenberg et al 1997; Ross et al 1996; Strik et al 1992). Attentional and inhibitory control subjects thus appear to play a major role in the SPEM abnormalities seen in schizophrenia. Despite this focus on the interplay between attentional and inhibitory processes, there has been only minimal exploration of SPEM in another chronic psychiatric disorder of attentional and inhibitory dysfunction—attention-deficit/hyperactivity disorder (ADHD). A primary deficit in ADHD is a failure in response inhibition (Barkley 1997), a deficit that can be identified in saccadic eye-movement tasks (Ross et al 1994) in a manner similar to that found in schizophrenia (Ross et al 1998b). If SPEM abnormalities associated with schizophrenia are due to nonspecific attentional dysfunction, individuals with ADHD should demonstrate similar SPEM abnormalities. Reports have been contradictory as to whether perfor-
mance during a SPEM task is abnormal in children with ADHD (Bala et al 1981; Bylsma and Pivik 1989; Jacobsen et al 1996; Shapira et al 1980). There is no published literature on SPEM performance in adult ADHD and no published reports that include information on anticipatory saccades in ADHD individuals of any age. This study compares adults with schizophrenia, adults with ADHD, and a comparison group of normal subjects on a smooth pursuit eye movement task.

Methods and Materials

Subjects

Because normal aging can impact SPEM performance (Hutton et al 1993; Kanayama et al 1994; Kuechenmeister et al 1977; Larsby et al 1988; Ross et al 1999a; Sharpe and Sylvester 1978; Spooner et al 1980), all subjects were restricted to individuals between ages 25 and 50 years. Seventeen adult ADHD subjects were recruited from an adult outpatient clinic for ADHD. All subjects were recruited early in the diagnostic process. None had received stimulant medications for at least 10 years before enrollment in this study. All subjects were assessed using DSM-IV criteria (American Psychiatric Association 1994) via the structured clinical interview for DSM-IV (First et al 1997). The recruitment process identified individuals with chronic schizophrenia who were maintained with stable symptoms on an outpatient basis. Schizophrenic subjects were excluded for neurologic illness (e.g., seizures), substance abuse or dependence within the last 6 months, and current major depression. This process produced SPEM recordings from 49 schizophrenic and 37 normal subjects for analysis. We have previously reported on many of these subjects (Ross et al 1998b, 1999a, 1999b).

ADHD, schizophrenic, and normal groups did not differ on age; however, there was a significant difference in gender (Table 1). No male-female differences exist on any eye-movement variable reported in this study.

Smooth Pursuit Eye Movements

Subjects were seated 43 cm in front of a video monitor on which a small target was displayed against a black background in an otherwise dark room. The subjects’ heads were stabilized with a bite bar and head rest. Horizontal eye movements were recorded using an infrared photoelectric limbus detection eye-tracking device, which is accurate to within 0.25° of visual angle and has a time constant of 4 msec. The analog output of the device was sampled at 500 Hz using a 12-bit analog-to-digital converter. There are no reported data assessing left-right differences in the dependent eye-movement measures employed in this study, but because disconjugate gaze is likely absent in most subjects, both eyes should be tracking the target in a similar manner. Our experience suggests that minimizing calibration time decreases the time subjects must maintain head position and improves the quality of the recording. Therefore, data were collected only from the eye for which the most rapid and accurate calibration could be obtained.

For the smooth pursuit eye-movement task, the target moved horizontally back and forth over 30° with a constant velocity of 16.7° per sec and a 1.4-sec fixation period between ramps, a “trapezoidal pattern.” Subjects were told to “keep your eyes on the target wherever it goes.”

All eye-movement data were analyzed with a computerized pattern-recognition program, and computer-analyzed results were confirmed with visual inspection by an experienced eye-movement evaluator (RR). Software-generated dependent mea-

| Table 1. Demographics for Adults with Attention-Deficit/Hyperactivity Disorder (ADHD), Schizophrenia, and a Normal Comparison Group |
|---|---|---|---|---|---|
| | ADHD group | Schizophrenic group | Normal group | Statistic | Probability |
| N | 17 | 49 | 37 | | |
| Male/female | 10/7 | 36/13 | 15/22 | | |
| Age (years) | 37 ± 7 | 38 ± 7 | 37 ± 7 | $\chi^2 = 9.5$ | .009 |

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ures have excellent test-retest reliability (Roy-Byrne et al. 1995). This analysis system has been described elsewhere (Radant and Hommer 1992; Ross et al. 1996) and will be described briefly here. Raw data consist of eye position and target position for each 2 msec of recorded tracking. Eye movements were divided into discrete segments, and then each segment was classified as saccade, smooth pursuit, or artifact. Saccades were identified on the basis of peak velocity (greater than 35°/sec), initial acceleration (greater than 2000°/sec²), and duration (≥9 msec). Segments not meeting velocity and acceleration criteria were considered smooth pursuit or fixation. Artifactual segments caused by eye blinks and head movements show distinct morphology and were removed from the analysis by the pattern recognition software. Gain for a given interval of smooth pursuit was defined as mean eye velocity divided by target velocity. Global smooth pursuit gain was defined as the mean gain, weighted for time, of all intervals of true smooth pursuit (Abel et al. 1991). Intervals defined as saccades are not included in computing smooth pursuit gain. During trapezoidal tasks, eye movements during fixation or within 250 msec of a change in target motion were discarded from the analysis because these movements may not represent normal pursuit (Lisberger and Pavelko 1989).

Lowered smooth pursuit gain can occur secondary to either impairment in the smooth pursuit system or as a compensatory mechanism to task-inappropriate saccades that intrude on otherwise normal pursuit (Abel and Ziegler 1988; Clementz and Sweeney 1990). Thus, it has been suggested that smooth pursuit gain is a global measure of task performance (Radant and Hommer 1992).

Catch-up saccades were used as the dependent measure of smooth pursuit system performance. Catch-up saccades function to significantly reduce error between foveal gaze and target location and compensate for poor smooth pursuit system performance (eye velocity below that of target velocity). Saccades, which are in the same direction as target motion and begin and end behind the target, are defined as catch-up saccades. In addition, saccades that are in the same direction as target motion but that begin behind target location and end ahead of target location are also classified as catch-up saccades if post-saccadic position error is ≤50% of presaccadic position error (i.e., the saccade functions to dramatically decrease the mismatch between visual gaze and target location).

One type of task-inappropriate saccade, which intrudes on otherwise normal smooth pursuit, is the anticipatory saccade. Anticipatory saccades must 1) be in the direction of target motion, 2) either begin and end ahead of target location or increase position error by 100%, and 3) be followed by a 50 msec interval of eye velocity less than 50% of target velocity. This definition of anticipatory saccades is based on analyses of parameters that maximize differences between schizophrenic subjects and normal subjects (Ross et al. 1999b, in press). Many authors also include a minimum amplitude criterion when defining anticipatory saccades, generally greater than 4–5° (Abel and Ziegler 1988; Clementz and Sweeney 1990). We traditionally have not included an amplitude criterion in our definition of anticipatory saccades and shall continue in this article to include anticipatory saccades of all amplitudes within the definition of anticipatory saccades. To allow comparison with other accounts, however, we also shall subdivide anticipatory saccades into large anticipatory saccades (with amplitudes greater than 4°) and leading saccades (Ross et al. 1999b).

Smooth pursuit, catch-up saccades, and anticipatory saccades account for more than 90% of eye movements during smooth pursuit tracking (Litman et al. 1994; Radant and Hommer 1992). Other components (e.g., square wave jerks, backup saccades, etc.) constitute only a small portion of smooth pursuit tracking and generally do not differ between schizophrenic subjects and control subjects (Litman et al. 1994; Radant and Hommer 1992). Some saccades begin behind the target, end in front of the target, and do not dramatically increase or decrease position error. These saccades do not meet the definition for either catch-up or anticipatory saccades and are not considered here.

Saccades generally are reported as frequency measures, that is, the number of each saccadic subtype divided by artifact-free recording time. The problem with this approach is that frequency measures do not include information about the amplitudes of saccades. A single large saccade may have a similar effect on global tracking as several small saccades will have. In addition to frequency data, we report the percentage of total eye movements accounted for by each saccadic subtype, a measure mathematically identical to multiplying frequency by mean amplitude. Thus, the percentage of total eye movements accounted for by each saccadic subtype includes amplitude information along with frequency information in the same dependent measure (Olincy et al. 1998; Ross et al. 1993, 1996, 1997, 1998b). Because amplitude criteria are included in the definition of large anticipatory and leading saccades, these two variables shall only be reported as frequency variables.

Statistical Analysis

Comparisons between groups were made with an analysis of variance (ANOVA), with post hoc least-squared differences between groups. In addition, effect sizes (Cohen 1988) for comparisons between the schizophrenic and normal groups, the schizophrenic and ADHD groups, and the ADHD and normal groups were computed for each eye-movement variable. Effect sizes of 0.2–0.49 were considered small, 0.5–0.79 moderate, and greater than or equal to 0.8 large. Differences in effect size of greater than 0.2 were considered notable.

Results

Table 2 shows results for each eye-movement variable. A significant effect of group was found for each eye-movement measure, with post hoc analyses demonstrating differences between the schizophrenic and normal groups on all measures. Significant differences between schizophrenic and ADHD groups were found in gain and the frequencies of anticipatory and leading saccades. Significant differences between the ADHD and normal groups were only identified for the percentage of total eye movements due to smooth pursuit.

Comparisons between the schizophrenic and normal groups produced moderate (the frequency of catch-up...
saccades and the frequency of large anticipatory saccades) to large (all other SPEM measures) effect sizes. The largest effect sizes were for frequency of anticipatory saccades (1.53), frequency of leading saccades (1.46), gain (1.24), and the percentage of total eye movements due to smooth pursuit (1.11).

Five comparisons between the schizophrenic and ADHD groups produced effect sizes that would be considered small (<0.5) or below: frequency of catch-up saccades, percentage of total eye movements due to smooth pursuit, percentage of total eye movements due to catch-up saccades, percentage of total eye movements due to anticipatory saccades, and frequency of large anticipatory saccades. Moderate effect sizes were produced for smooth pursuit gain. The frequency of anticipatory saccades and the frequency of leading saccades produced large effect sizes for comparisons between the schizophrenic and ADHD groups.

With one exception, effect sizes were notably lower (difference in effect size >0.2) for schizophrenic and ADHD group comparisons than for the schizophrenic and normal group comparisons. The one exception is frequency of leading saccades, which produced similar large effect sizes (1.31–1.46) for comparisons between both the schizophrenic and normal groups and the schizophrenic and ADHD groups.

**Discussion**

Schizophrenic adults performed more poorly than did normal adults on each of the SPEM measures examined. This sample contains some individuals who have been discussed in previous reports and thus cannot be considered a replication; however, this is the largest sample of schizophrenic subjects and normal subjects we have published in this age range, suggesting these differences remain even within larger groups. Additionally, the broad range of eye-movement deficits is consistent with what has been reported elsewhere (Clementz and Sweeney 1990; Litman et al 1994; Radant and Hommer 1992; Sweeney et al 1994).

Impaired motion perception (Chen et al 1999a, 1999b) and impaired ability to match eye velocity to target velocity (Ross et al 1996; Farber et al 1997) may contribute to impaired SPEM abnormalities in schizophrenia; however, a major contributor to schizophrenia-associated SPEM abnormalities is, by experimental and theoretical argument, associated with attentional deficits. One focus of this study was to determine whether these attentional findings are associated with the specific types of attentional deficits found in schizophrenia or with nonspecific attentional deficits that might be present in any adult with attentional and inhibitory deficits. Adults with ADHD were chosen as a comparison group with chronic deficits in these areas.

Three eye-movement measures were significantly more abnormal among the schizophrenic patients than among the ADHD patients: gain, frequency of anticipatory saccades, and frequency of leading saccades. The ADHD group did not differ from the normal group on any of these three measures. This suggests that the general attentional

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### Table 2. Smooth Pursuit Performance in Adults with Attention-Deficit/Hyperactivity Disorder (ADHD), Schizophrenia, and a Normal Comparison Group

<table>
<thead>
<tr>
<th></th>
<th>ADHD group</th>
<th>Schizophrenic group</th>
<th>Normal group</th>
<th>F(2,100)</th>
<th>Probability</th>
<th>Post hoc&lt;sup&gt;a&lt;/sup&gt;</th>
<th>d (S–N)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>d (S–A)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>d (A–N)&lt;sup&gt;b&lt;/sup&gt;</th>
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<tbody>
<tr>
<td><strong>Global performance</strong></td>
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<tr>
<td>Gain</td>
<td>0.923 ± 0.112</td>
<td>0.829 ± 0.139</td>
<td>0.968 ± 0.061</td>
<td>16.7</td>
<td>0.00001</td>
<td>N,A &gt; S</td>
<td>1.24</td>
<td>0.71</td>
<td>0.56</td>
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<tr>
<td>% due to smooth pursuit&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.704 ± 0.107</td>
<td>0.641 ± 0.154</td>
<td>0.782 ± 0.78</td>
<td>13.9</td>
<td>0.0005</td>
<td>N &gt; A,S</td>
<td>1.11</td>
<td>0.43</td>
<td>0.89</td>
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<td><strong>Smooth pursuit performance</strong></td>
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<td>Catch-up saccades (#/min)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>59.0 ± 21.8</td>
<td>71.8 ± 33.4</td>
<td>50.5 ± 21.5</td>
<td>6.3</td>
<td>0.003</td>
<td>S &gt; N</td>
<td>0.74</td>
<td>0.41</td>
<td>0.40</td>
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<tr>
<td>% due to catch-up saccades&lt;sup&gt;e&lt;/sup&gt;</td>
<td>11.5 ± 4.0</td>
<td>13.6 ± 5.9</td>
<td>8.8 ± 3.5</td>
<td>10.2</td>
<td>0.0009</td>
<td>S &gt; N</td>
<td>0.96</td>
<td>0.38</td>
<td>0.74</td>
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<tr>
<td>Amplitude catch-up saccades&lt;sup&gt;f&lt;/sup&gt;</td>
<td>2.5 ± 0.9</td>
<td>2.3 ± 0.6</td>
<td>2.1 ± 0.5</td>
<td>2.4</td>
<td>0.10</td>
<td>—</td>
<td>0.36</td>
<td>0.30</td>
<td>0.62</td>
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<td><strong>Anticipatory saccades</strong></td>
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<td>(ant sac)</td>
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<tr>
<td>Ant sac (#/min)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>11.6 ± 12.8</td>
<td>31.9 ± 20.0</td>
<td>8.0 ± 6.3</td>
<td>29.0</td>
<td>0.000000</td>
<td>S &gt; N,A</td>
<td>1.53</td>
<td>1.10</td>
<td>0.41</td>
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<tr>
<td>% due to ant sac&lt;sup&gt;e&lt;/sup&gt;</td>
<td>7.9 ± 15.4</td>
<td>10.5 ± 10.5</td>
<td>3.1 ± 4.5</td>
<td>5.9</td>
<td>0.004</td>
<td>S &gt; N</td>
<td>0.87</td>
<td>0.22</td>
<td>0.52</td>
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<td><strong>Specialized saccades</strong></td>
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<td>Leading saccades&lt;sup&gt;d&lt;/sup&gt;</td>
<td>4.5 ± 4.9</td>
<td>22.5 ± 15.6</td>
<td>4.8 ± 4.1</td>
<td>32.1</td>
<td>0.000000</td>
<td>S &gt; N,A</td>
<td>1.46</td>
<td>1.31</td>
<td>0.07</td>
</tr>
<tr>
<td>Large ant sac</td>
<td>6.6 ± 11.9</td>
<td>7.8 ± 10.3</td>
<td>3.0 ± 5.0</td>
<td>3.0</td>
<td>0.05</td>
<td>S &gt; N</td>
<td>0.57</td>
<td>0.11</td>
<td>0.46</td>
</tr>
</tbody>
</table>

All values are means ± SD.
<sup>a</sup>Post hoc tests are least-squared differences: S, schizophrenia, A, ADHD, N, normal.
<sup>b</sup>Effect size (d) as defined by Cohen (1988): S-N, Schizophrenic group versus normal group comparison; S-A, schizophrenic group versus ADHD group comparison; A-N, ADHD group versus normal group comparison.
<sup>c</sup>% denotes the percent of total artifact-free eye movement due to smooth pursuit or a specific saccadic subtype.
<sup>d</sup>/min denotes the number of saccades per minute of artifact-free recording.
and inhibitory dysfunction associated with ADHD does not translate into major SPEM abnormalities in the majority of ADHD patients. Nonetheless, for two of these three measures (gain and frequency of anticipatory saccades), the effect sizes are notably larger for the comparisons between the schizophrenic and normal groups than for comparisons between the schizophrenic and ADHD groups. This is primarily attributable to a subgroup of ADHD subjects who performed abnormally (for example, see results for gain in Figure 1). Heterogeneity of eye movement performance also has been found among schizophrenic subjects (Holzman et al 1984, 1988).

One SPEM measure, the frequency of leading saccades, produced similar effect sizes for both schizophrenic-normal comparisons (1.46) and schizophrenic-ADHD comparisons (1.31). Leading saccades are a subset of anticipatory saccades. While tracking a moving object, there is a natural tendency to generate a saccade and move the eye ahead of current target location. For example, while watching a car skid across an icy intersection, an individual frequently will generate a saccade along the projected path of the car to determine if and what the car might hit. These anticipations of car movement are termed “anticipatory saccades.” The target tracking task employed in this study is simple and highly predictable. As phase lag during this task approaches zero, this task elicits predictive smooth pursuit. Anticipatory saccades, although rare in normal adult subjects, do occur during this task. This suggests that even in this simple task, saccadic anticipation of target motion is a normal process. The SPEM tasks used in the study of schizophrenia includes the instruction to “keep your eye on the target,” thus requiring the subject to inhibit the tendency to use saccades to anticipate target motion. The failure to inhibit anticipatory saccades has been proposed as a marker of genetic risk for schizophrenia because it is present in adults with schizophrenia and their relatives (Whicker et al 1985; Rosenberg et al 1997; Ross et al 1998b). The lack of an increase in anticipatory saccades in relatives of depressed patients (Rosenberg et al 1997) has argued for the possible specificity of this marker. One of the major problems on research with this marker, however, has been some disagreement on whether amplitude criteria should be included in the definition. Although a number of authors have argued for a minimum amplitude criteria of 4–5° (Abel et al 1991; Clementz and Sweeney 1990), other labs have suggested that there is no a priori reason to assume that anticipatory saccades cannot include saccades of smaller amplitudes (Radant and Hommer 1992; Ross et al 1999b). Fortunately, Strik et al (1992) provided a possible solution to this issue when they classified saccades solely based on amplitude criteria; they found that saccades less than 4° were closely related to another pathophysiologic dysfunction characterized in schizophrenia: reduced amplitude of the auditory N100 event-related potential. They argued that larger saccades represented a nonspecific attentional dysfunction. This finding raised the possibility that saccades with amplitudes greater than 4° represent a different physiologic process than those with amplitudes less than 4°. The results from the current study support the application of this hypothesis to anticipatory saccades. Large anticipatory saccades (amplitudes >4°) occur significantly more often in schizophrenic subjects than in normal subjects, replicating previous work (Litman et al 1994; Rosenberg et al 1997); however, they do not differ between schizophrenic subjects and ADHD subjects, and the schizophrenic-ADHD effect size, at 0.11, is below what is considered to be even a small physiologic effect (Cohen 1998). Thus, as predicted by Strik et al (1992), the frequency of large anticipatory saccades appears to be a nonspecific effect of attentional dysfunction. Conversely, leading anticipatory saccades (anticipatory saccades with amplitudes 1–4°) are significantly elevated in schizophrenia relative to both ADHD and normal subjects, and there appears to be no notable difference between ADHD subjects and normal subjects (effect size 0.07, see Figure 2) on this variable. For leading saccades, the effect size is similar in schizophrenic-normal comparisons and schizophrenic-ADHD comparisons, supporting the specificity of this finding to schizophrenia.

In summary, as a group, ADHD subjects did not significantly differ from normal subjects on the majority of SPEM measures used in this study. Nonetheless, for most measures, a few ADHD subjects performed very poorly. ADHD subjects were identified based on a semi-
structured evaluation by a single investigator (RGR), without interrater reliability assessment; however, subjects identified as meeting criteria for ADHD also scored poorly on the Wender self-report scale, a scale associated with ADHD in adults (Ward et al 1993), suggesting that a majority of these subjects likely had ADHD. Additionally, ADHD subjects and schizophrenic subjects were not matched for severity of attentional dysfunction, and it can be assumed that, on average, the schizophrenic subjects demonstrated more severe psychopathology. The generally lower level of psychopathology in the ADHD subjects (relative to the schizophrenic subjects) cannot be entirely ruled out as a contributor to the generally normal range of SPEM performance exhibited by the ADHD subjects. Nonetheless, nonpsychotic relatives of schizophrenic probands also show SPEM abnormalities, and in particular anticipatory saccade abnormalities, similar to the psychotic probands (Whicker et al 1985; Ross et al 1998b). Thus, SPEM and anticipatory saccade abnormalities appear to reflect genetic vulnerability rather than severity of disease.

One of the goals of determining the specificity of SPEM abnormalities to schizophrenia is assessing the possible utility of SPEM abnormalities as a genetic risk marker in family linkage studies. ADHD is a common disorder in the population (Biederman 1998) and is likely to occur in many families used for linkage analyses. The present results suggest that the percentage of leading saccades is unlikely to be elevated as the result of general attentional dysfunction, thus allowing the inclusion of ADHD family members in genetic studies.

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References


