Antisaccades and Smooth Pursuit Eye Movements in Schizophrenia

Anne B. Sereno and Philip S. Holzman

Saccadic and smooth pursuit eye movements were recorded in schizophrenic patients, nonschizophrenic psychiatric patients, and normal controls. Both schizophrenic subjects and psychiatric controls demonstrated greater increases in error rates and greater delays in generating antisaccades than did normal controls. Schizophrenic patients with impaired smooth pursuit tracking showed greater increases in error rates in the antisaccade task than did schizophrenic patients with normal pursuit. Among psychiatric controls, increased errors on the antisaccade task were unrelated to pursuit performance. The small size of this group, however, reduces the power to detect a relation between smooth pursuit tracking and performance on the antisaccade task. Although most patients were receiving one or more medications, some of which can affect eye movements, medication state in this study did not account for differences we report in dependent variables.

Key Words: Antisaccades, saccades, schizophrenia, smooth pursuit eye movements, prefrontal cortex

Introduction

Although many studies report normal saccadic eye movements in schizophrenic patients (e.g., Iacono et al 1981; Levin et al 1982), previous studies of antisaccade performance have reported that schizophrenic patients show significantly higher error rates and longer latencies than do normal subjects (Fukushina et al 1988; Fukushima et al 1990a; Fukushima et al 1990b; Thaker et al 1989). In an antisaccade task, subjects are instructed not to look at the target when it appears, but instead to look as quickly as possible in the opposite direction. The main difference between an antisaccade and a prosaccade task is the instruction, where to look. Higher error rates and longer latencies suggest that schizophrenic patients have difficulty suppressing reflexive saccades to the target and correctly initiating voluntary saccades to the opposite side.

Smooth pursuit eye movement (SPEM) dysfunctions among schizophrenic patients have been one of the most consistent findings in psychophysiological studies of schizophrenia (Levy et al 1993). There are at least two possible causes of abnormal SPEMs among schizophrenic patients: an impaired smooth pursuit tracking system associated with low gain and increased numbers of compensatory or catch-up saccades (e.g., Abel et al 1991; Levin et al 1988; Yee et al 1987), and saccadic disinhibition associated with increased numbers of noncompensatory saccades or saccadic intrusions (e.g., Cegalis and Sweeny 1979; Holzman et al 1978; Levin 1984a; Mialet and Pichot 1981). It is as yet unclear whether the low gain and increased saccadic eye movements in pursuit are independent phenomena.

An impairment in frontal function has been proposed as a pathophysiological explanation, not only for saccadic intrusions in SPEMs of many schizophrenic patients (Levin...
but also for other prominent clinical features in schizophrenia, such as impairments in attention, motivation, and affect (Levin 1984a). Discussion of a few features of the role of prefrontal cortex in the generation and control of saccades as well as smooth pursuit eye movements is pertinent.

The frontal eye fields (FEFs) are not essential for generating saccadic eye movements, since lesions of FEFs lead only to transient deficits (Schiller et al 1980; Schiller et al 1987). Severe and permanent saccade deficits occur, however, only when FEF and superior colliculus lesions are combined (Schiller et al 1980, 1987). Subtle deficits do appear, nevertheless, following a FEF lesion alone. For example, Daroff and Hoyt (1971) reported that patients with prefrontal lesions have difficulties in looking voluntarily to the contralateral side, and Guittion et al (1982) reported that such lesions result in difficulties in suppressing saccades to contralateral visual stimuli. In an antisaccade task, Guittion et al (1985) demonstrated that frontal lobe–lesioned patients have difficulty both in suppressing reflexive saccades to a target and in initiating voluntary saccades to the opposite side.

Recent studies suggest that in addition to its well-established role in saccadic eye movements, the prefrontal cortex, specifically, the FEF, is involved in the generation of smooth pursuit eye movements (Bruce et al 1985; MacAvoy et al 1991). Although the main sensory processing of a moving visual stimulus in primates seems to occur in parieto-temporal association cortex (Maunsell and Newsome, 1987), persistent pursuit deficits have been described following lesions of the fundus of the FEF in prefrontal cortex of monkeys (Lynch 1987; MacAvoy and Bruce, 1989). Thus, it is possible that both smooth pursuit and saccadic abnormalities may result from a dysfunction of prefrontal cortex.

Previous studies have separately established abnormal performance in antisaccades and smooth pursuit eye movements in schizophrenic patients. No study has yet been undertaken examining the relation of antisaccade and SPEM performance in the same population of schizophrenic patients. This study tests whether schizophrenic patients show deficits in voluntary orienting called for by an antisaccade task, and if so, whether that difficulty is associated with SPEM dysfunctions. Inasmuch as both types of eye movements have been linked to prefrontal cortex, we predict that schizophrenic patients with SPEM dysfunctions will exhibit more errors and longer latencies in an antisaccade task compared with schizophrenic patients with normal SPEMs.

Subjects

Three subject groups were tested: (1) a schizophrenic group (n=17), (2) an affective disorder comparison group (predominantly patients with bipolar affective disorder) (n=11), and (3) a normal control group (n = 14). Subjects were recruited into the study only if they met the following requirements: (1) less than 50 years of age, (2) no evidence of mental retardation, and (3) no evidence of organic brain pathology. Sixteen patients (11 schizophrenic and five affective disorder) were recruited from Medfield State Mental Hospital in Medfield, Massachusetts, and 13 patients (six schizophrenic and seven affective disorder) were recruited from McLean Hospital in Belmont, Massachusetts. The majority of patients were inpatients. Three of the patients in the schizophrenic group and three of the patients in the affective disorder group were outpatients. The 14 normal control subjects consisted of seven subjects recruited from the Medfield area and seven subjects recruited from the Boston area. These subjects were screened for the absence of serious psychiatric or neurologic disorders in themselves and in their first-degree relatives. Patients were recruited if their condition had been diagnosed as either schizophrenia or bipolar affective disorder by the hospital psychiatrist. The diagnoses were independently verified by information gathered from the Structured Clinical Interview for DSM-III-R (SCID), administered by an experienced interviewer. A comprehensive chart review and consultations with the patient's primary clinician provided supplementary information for the diagnostic decision.

Table 1 presents the demographic characteristics of the subjects. The groups did not differ in age, years of education, IQ, gender, or handedness. The patient groups did not differ with respect to age at onset or duration of illness.

All 17 schizophrenic and 10 of the 11 affective disorder patients were taking psychotropic medication. Table 2 summarizes the medication status of the patient groups.

For those readers interested in examining wider associations, these same groups of subjects participated in a set of spatial selective attention tasks (see Sereno and Holzman, 1992; Sereno and Holzman, submitted) and, with the exception of one subject, an express saccade paradigm (see Sereno and Holzman, 1991; Sereno and Holzman, 1993). A preliminary report on how these different findings may relate has appeared in Sereno (1992).
Table 2. Medication Status of Patients

<table>
<thead>
<tr>
<th>Medication</th>
<th>Schizophrenic (n = 17)</th>
<th>Affective (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroleptic</td>
<td>17</td>
<td>9</td>
</tr>
<tr>
<td>Anti-Parkinson</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Anticonvulsant</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Anxiolytic</td>
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<td>2</td>
</tr>
<tr>
<td>Lithium</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>No medication</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Methods

Stimuli

PROSACCADE TASK. The visual display for the prosaccade task was generated on a Macintosh II screen. The target appeared 12° to the left or right of a black fixation point (0.2° in diameter) presented at midline. The target was a filled red circle 0.5° in diameter. Each trial consisted of the following sequence: (1) a blank screen with a central fixation point for 800 msec; (2) a screen presenting the target, which was terminated by (3) an eye movement to the target, and then replaced with a blank screen for 500 msec before the fixation point returned.

ANTISACCADE TASK. The antisaccade task was identical to the prosaccade task, except that the target screen was terminated by an eye movement with equivalent amplitude to the field opposite that of the target.

SMOOTH PURSUIT TASK. A standard test of smooth pursuit eye movements, using an infrared reflected light system, was administered (see Holzman et al 1991). Subjects tracked a target that moved sinusoidally at 0.4 Hz, and their eye movements were recorded.

Apparatus

An ISCAN infrared eye tracking system was used to record the subjects' eye movements during the experiment, while custom software on a Macintosh II presented stimuli on a computer screen, monitored eye movements, and recorded data on accuracy and timing. Eye position was updated 60 times per second. Under optimum conditions, the eye-tracker has a resolution of ±0.5°. A more detailed description of the apparatus has appeared in Sereno and Holzman (1993).

Procedure

There were two testing sessions for the saccade tasks. In session 1, subjects received 20 practice trials and 40 experimental trials on the prosaccade task. These 60 trials were considered practice and were not included in the data analysis. In session 2, subjects performed the pro- and antisaccade tasks (40 trials each), with half the groups receiving the prosaccade task first and the other half the antisaccade task first. Prior to each experiment, there were 20 additional practice trials (i.e., 20 practice trials for the prosaccade task and 20 practice trials for the antisaccade task). After completing the saccade tasks, each subject was given the vocabulary subtest of the Wechsler Adult Intelligence Scale. Finally, a third session was scheduled during which smooth pursuit eye movements were recorded (see below).

Eye movement deviations exceeding 2.3° from the fixation point before the target appeared automatically canceled a trial, which was re-presented later. After target presentation, an eye movement of insufficient amplitude (approximately 7.2° or less) or a failure to make an eye movement within 2500 msec resulted in a time-out beep and the trial was re-presented later. A liberal accuracy criterion was adopted for correct saccades: a radius of 4.8° centered about the target (located 12° to the right or left of a central fixation point). In the antisaccade task, however, this 4.8° window of acceptability for correct saccades was located in the field opposite to that of the target. The occurrence of each correct response and its latency were recorded by the computer. An incorrect eye movement was considered an eye movement of sufficient amplitude (greater than 7.2°) in the opposite direction from the target in the prosaccade task and in the direction of the target in the antisaccade task. In the case of an error, the computer provided immediate feedback (an error beep), recorded the error, and began the next trial. If an eye movement away from the fixation point did not occur within 2500 msec after presentation of the target, the computer beeped, informing the subject that an error was committed, and recorded the error.

Saccade latency was measured as the time from the appearance of the target to the arrival of the eyes at the appropriate target area. This definition of saccade latency measures the saccade response time plus the duration of the saccade. The duration of saccades is quite stereotyped, and for a 12° saccade is approximately 55 msec (see, e.g., Becker 1989). Levin et al (1982) have demonstrated that the dynamic characteristics of saccadic eye movements, including their duration and velocity, are normal in schizophrenic patients.

Results

Scoring

SACCADE TASKS. The distributions of saccade response times (RTs) within group and task were skewed and therefore, for purposes of calculating tests of significance, we used the median RT within task for each subject to carry out the subsequent analyses (Bush et al 1993). Table 3 presents
the group means of the individual subject medians and the standard deviations of those mean values. RTs for incorrect responses (eye movements to the incorrect field) were eliminated prior to obtaining the median RT values for each subject. This procedure removed 2.9% and 16.9% of the data in the saccade and antisaccade tasks, respectively. All data, however, were included in the error analysis.

We separately analyzed error rates and RTs and examined both between-group and within-group differences with respect to quality of SPEM. To compare the performance of subject groups on the antisaccade task, a measure of performance was constructed to control for possible baseline differences on the saccade task. Mean error rate in the prosaccade task was subtracted from the mean error rate in the antisaccade task for each subject. This difference score between the prosaccade and antisaccade tasks was used as a measure of performance decrement incurred on the antisaccade task relative to baseline performance on the prosaccade task. Larger difference scores indicate a greater increase in errors on the antisaccade task. Similar difference scores for each subject were constructed from their median saccadic RTs on the prosaccade and antisaccade tasks (i.e., antisaccade median RT minus prosaccade median RT). Statistical comparisons between groups were performed on these error rate and RT difference scores.

**SPEM TASKS.** The integrity of the smooth pursuit tracking record was independently rated as impaired or normal smooth pursuit tracking by two experienced researchers who were blind to the subjects’ group membership and saccadic performance. Interrater agreement in this laboratory averages more than 95%. SPEM recordings could not be obtained on three subjects, and artifact prevented valid assessment of the records of four subjects, yielding a sample of 15 schizophrenics, 8 affective disorders, and 12 normal control subjects for whom SPEM data could be assessed.

All 12 normal subjects demonstrated normal pursuit tracking. Of the 15 subjects in the schizophrenic group with scorable pursuit records, 5 had normal pursuit and 10 had impaired pursuit. Of the 8 subjects in the affective disorder group with scorable records, 3 had normal pursuit and 5 had impaired pursuit.

**Error Rate**

Table 3 presents mean error rates in the prosaccade and antisaccade tasks. An analysis of variance (ANOVA) was performed on the mean error rate data, which included groups (schizophrenic, bipolar, and normal) as the between-subject factor, and task (prosaccade and antisaccade) as the within-subject factor. This analysis confirmed that there were main effects of group and task, as well as a significant interaction between group and task; respectively, \( F(2,39) = 6.52, p < .004 \), \( F(1.39) = 44.01, p < .0001 \), and \( F(2,39) = 6.95, p < .003 \). Since the analysis includes all three of the subject groups, a series of planned, unpaired, one-tailed Student’s *t*-tests were performed to compare the task effects (using the difference scores) between diagnostic groups.

Both schizophrenic patients and affective disorder patients demonstrate a greater increase in error rate (20.9% and 16.6%, respectively) than normal subjects (3.6%) in the antisaccade task (\( t(29) = 3.67, p < .0005 \) and \( t(23) = 5.29, p < .0017 \), respectively). Schizophrenic patients did not differ

<table>
<thead>
<tr>
<th>Group</th>
<th>Schizophrenic</th>
<th>Affective</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Norm</td>
<td>Imp</td>
</tr>
<tr>
<td>Tracking2</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>17</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Antisaccade task</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT (msec)</td>
<td>484.3</td>
<td>419.5</td>
<td>536.3</td>
</tr>
<tr>
<td>SD</td>
<td>142.6</td>
<td>57.0</td>
<td>164.5</td>
</tr>
<tr>
<td>Errors (%)</td>
<td>24.0</td>
<td>13.5</td>
<td>29.8</td>
</tr>
<tr>
<td>SD</td>
<td>18.1</td>
<td>2.9</td>
<td>19.4</td>
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<tr>
<td>Prosaccade task</td>
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<td></td>
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<tr>
<td>RT (msec)</td>
<td>309.7</td>
<td>296.0</td>
<td>318.5</td>
</tr>
<tr>
<td>SD</td>
<td>25.5</td>
<td>22.3</td>
<td>25.2</td>
</tr>
<tr>
<td>Errors (%)</td>
<td>3.1</td>
<td>2.5</td>
<td>2.8</td>
</tr>
<tr>
<td>SD</td>
<td>3.0</td>
<td>3.5</td>
<td>2.2</td>
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<tr>
<td>Difference (antisaccade–prosaccade task)</td>
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<td></td>
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<tr>
<td>RT (msec)</td>
<td>174.6</td>
<td>123.5</td>
<td>217.8</td>
</tr>
<tr>
<td>SD</td>
<td>139.1</td>
<td>70.1</td>
<td>164.2</td>
</tr>
<tr>
<td>Errors (%)</td>
<td>20.9</td>
<td>11.0</td>
<td>27.0</td>
</tr>
<tr>
<td>SD</td>
<td>16.8</td>
<td>3.8</td>
<td>18.0</td>
</tr>
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</table>

*The integrity of the smooth pursuit tracking record for each subject was independently and qualitatively rated as normal (Norm) or impaired (Imp) smooth pursuit tracking. Seven subjects did not have ratings. Thus, the data from all subjects (All) are included in a separate column.*
Figure 1. Mean saccadic percent error rate difference scores with SE bars (antisaccade minus prosaccade) for schizophrenic and affective disorder subjects with normal and impaired tracking. All normal subjects with pursuit records demonstrated normal tracking. SPEM = smooth pursuit eye movement; SE = standard error.

from affective disorder patients in error rate at a statistically significant level.

We also examined the relation between SPEM quality and performance on the antisaccade task, as measured by mean error rate difference scores (antisaccade minus prosaccade). Since all normal subjects demonstrated normal pursuit, normal subjects were not included in this second series of comparisons; however, their data are included in Figure 1 for reference.

As shown in Figure 1, schizophrenic patients with impaired tracking showed a greater increase in error rate (27%) on the antisaccade task than did schizophrenic patients with normal tracking (11%), t(13) = 1.93, p < .038. For affective disorder patients, impaired tracking was not associated with greater errors on the antisaccade task t(6) = 0.45, p > .33. Schizophrenic patients with impaired tracking did not show a significantly greater increase in errors on the antisaccade task than did affective disorder patients with impaired tracking (27% vs. 18.5%), t(13) = 0.87, p > .20.

Saccade Response Time

Table 3 presents the group means of the individual subject RT medians on both the prosaccade and antisaccade tasks as well as the mean of the median difference scores for the three groups. An analysis of variance was performed on the median RT data, which again confirmed that there were main effects of group and task, as well as a significant interaction between group and task; respectively, F(2, 39) = 7.09, p < .0025, F(1, 39) = 49.72, p < .0001, and F(2, 39) = 5.58, p < .0075. Again, a series of planned, unpaired, one-tailed t-tests were performed to compare the task effects (using the difference scores) between diagnostic groups.

Schizophrenic patients had a significantly larger median RT difference score (175 msec) than normal subjects (45 msec), t(29) = 3.40, p < .001. Affective disorder patients also had a significantly larger median RT difference score (173 msec) than did normal subjects (45 msec), t(23) = 4.32, p = .001. Schizophrenic and affective disorder patients did not differ with respect to median RT difference scores.

Figure 2 presents group means of the median RT difference scores for those subjects with normal and impaired SPEM. Normal subjects’ data are included in this figure for reference. As illustrated in Figure 2, schizophrenic patients with impaired SPEM showed a nonsignificant tendency for a greater increase in saccade latency on the antisaccade task than did schizophrenic patients with normal SPEM, t(13) = 1.21, p > .12. There was also no relation between impaired tracking and a greater increase in saccade latency on the antisaccade task among affective disorder patients, t(6) = 0.07, p > .47.
Analytic Procedures

For dealing with skewed distributions, most statistics texts recommend a log transformation of the data. Bush et al. (1993) also report simulation results consistent with this recommendation: The log transformation led to a benefit over the raw mean scores and was superior (as measured by statistical power) in every case to the other transformations they applied to the raw scores. Hence, to determine whether our specific data analytic procedures affected the findings, we performed a series of analyses on our data, manipulating whether or not we transformed the data (log transformation), whether or not we trimmed the data, and whether or not we used difference scores. The results of these different analytic procedures were remarkably consistent and suggest that the findings we report are not due to the particular statistical techniques we have used.¹

Medication Effects

To address whether or not medication effects played a role in these results, we examined the effects of lithium, anticonvulsants, and anxiolytics on saccade error rates, saccadic RT, and integrity of smooth pursuit. We tested for any medication effects in the dependent variables, first by combining the data from all patients, and then for any effects within either the schizophrenic group or the affective disorder group alone. In our sample, no significant medication effects were found.

Discussion

Our results are consistent with those of Fukushima and colleagues (1988, 1990a, 1990b) in finding both increased latencies and increased error rates among schizophrenic patients on an antisaccade task. Medication effects do not seem to be a significant contaminating variable in the present findings. Although typical neuroleptics do not seem to affect saccade latency (Crawford et al. 1990) or pursuit integrity (Holzman et al. 1975; Levy et al. 1984), lithium has been shown to degrade SPEM and has been associated with increased saccadic events during pursuit (Levy et al. 1985; Holzman et al. 1991). Previous work has shown that anticonvulsants and anxiolytics can also affect eye movements (for review, Abel and Hertle, 1988). In our sample, however, lithium, anticonvulsants, and anxiolytics did not significantly affect saccade error rates, saccadic RT, or integrity of smooth pursuit, and thus cannot account for the differences that we report.

In addition to reporting increased latencies and increased error rates among schizophrenic patients on an antisaccade task, however, we found that affective disorder patients also show increased latencies and errors on an antisaccade task that are statistically commensurate with those shown by schizophrenic patients. This result differs from that reported by Fukushima et al. (1990b), who found that 11 out of 13 patients with affective disorders showed normal performance in an antisaccade paradigm. Our results agree with those of Feil et al. (1991), who reported that schizophrenic, affective disorder, and nonpsychotic depressive patients all show increased numbers of errors on an antisaccade task compared with normal subjects. In our study, neither error rate nor saccadic latency differentiated schizophrenic from affective disorder patients. There are several differences between the present study and that of Fukushima et al. (1990b) that may help explain the discrepant findings.

One difference between the studies concerns the nature of the illness in the affective disorder group. In the present study, the predominant diagnosis of the affective disorder group was a bipolar disorder (eight of 11). It is noteworthy that the two affective disorder patients who differed from normal performance in the Fukushima et al. (1990b) study had conditions diagnosed as a bipolar disorder.

Another difference between the present study and that of Fukushima et al. (1990b) may be that the majority of our patients in both the schizophrenic and affective disorder groups were inpatients; in Fukushima et al.'s study, the majority of the schizophrenic patients were inpatients, but the majority of affective disorder patients were outpatients. Furthermore, the age of onset of illness for subjects in our affective group was unusually early. These considerations suggest that this group of affective disorder patients may have been more severely ill than those tested in the Fukushima study. We therefore cannot rule out the possibility that performance on the antisaccade task in the affective disorder group may be sensitive to state-related factors.

Although our data suggest that deficit performance on an antisaccade task is not specific for schizophrenia, we also find that only among schizophrenic patients is there a confluence of SPEM performance and antisaccade performance, such that impaired SPEM is associated with increased errors on the antisaccade task. Impaired SPEM is
related to the presence of schizophrenia and is not associated to the severity of the condition (Holzman et al 1974). The finding that a large percentage of first-degree relatives of schizophrenic patients demonstrate the same dysfunction further reinforces the idea that SPEM abnormalities are not dependent on the severity of the condition. Hence, this specificity of deficit on the antisaccade task for schizophrenic patients with impaired SPEMs not only argues against a generalized deficit among schizophrenic patients but also is consistent with a pathophysiological explanation that may involve a prefrontal dysfunction.

The small size of the affective disorder subgroups (three and five) compared with the schizophrenic subgroups (five and 10) reduces the power, and thus the likelihood, of finding a statistically significant difference between normal and impaired trackers. Although the affective disorder subgroups were smaller, it is important to note that for the affective disorder group, normal and impaired trackers showed little difference in errors (5.2% compared with 16.0% for schizophrenic patients) and little difference in median RT difference (10.2 msec compared with 94.3 msec for schizophrenic patients). The present findings may not have enough power to determine whether or not affective disorder patients show a relation between smooth pursuit tracking and performance on the antisaccade task; however, the data do suggest that they differ qualitatively from the schizophrenic group.

It is important to know whether antisaccade deficits represent more than state-related factors, and, at least in schizophrenic patients, whether they truly indicate more enduring trait variables. As with the history of SPEM studies in schizophrenia, one avenue of research would be to examine the patients’ first-degree relatives (e.g., Holzman et al 1984; Holzman et al 1988). Further, it will be important to explore whether performance on the antisaccade task is related to specific quantitative measures of smooth pursuit, such as the number of saccadic intrusions (noncorrective saccades), the number of catch-up saccades, or the gain of smooth pursuit.

The present results support the hypothesis that schizophrenic patients with abnormal SPEM show a deficit on a task of voluntary orienting, as represented in this study by the antisaccade task. Both antisaccade difficulty and impaired eye tracking in schizophrenic patients are consistent with a prefrontal dysfunction hypothesis of schizophrenia.

References


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