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Smooth pursuit and saccadic abnormalities in first-episode schizophrenia

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ABSTRACT

Background. Previous studies of oculomotor dysfunction in schizophrenia have tended to concentrate on abnormalities of smooth pursuit eye tracking in chronic medicated patients. We report the results of a study of smooth pursuit, reflexive and antisaccade performance in drug naive and antipsychotic treated first-episode schizophrenic patients.

Methods. Smooth pursuit and saccadic eye movements were recorded in 36 first-episode schizophrenic patients and 36 controls matched for age and estimated IQ. The schizophrenic patients were divided into drug-naive ($N = 17$) and antipsychotic treated groups ($N = 19$).

Results. Smooth pursuit velocity gain was significantly lower than controls only in the drug-naive patients. The treated patients did not differ significantly from either the controls or the untreated group. In an antisaccade paradigm both treated and drug-naive schizophrenic patients demonstrated an increased number of errors, but only drug-naive patients also demonstrated an increased latency in initiating correct antisaccades.

Conclusions. These impairments are unlikely to be due to a generalized deficit in oculomotor function in the schizophrenic groups, as there were no differences between the groups in saccadic metrics on a reflexive saccade task. The results show that both smooth pursuit and saccadic abnormalities are present at the onset of schizophrenia and are integral to the disorder.

INTRODUCTION

Oculomotor abnormalities, particularly smooth pursuit eye tracking, are one of the most widely studied 'biological markers' of schizophrenia (see Levy, 1994). However, several factors have limited the utility of this research. Many early studies used relatively insensitive electro-oculographic recording techniques and relied on subjective qualitative measures to rate smooth pursuit performance. Another problem stems from inconsistencies in methods of analysing and measuring smooth pursuit performance, making cross study comparison difficult. Finally, most studies have been performed in chronic, medicated schizophrenic populations. It is, therefore, possible that such oculomotor abnormalities may reflect either neurodegenerative brain changes due to chronicity of illness, since oculomotor abnormalities are witnessed in Alzheimer's disease (Fletcher & Sharpe, 1988) and even healthy aged subjects (Moschner & Baloh, 1994), or the effect of medication-related chronic dopaminergic blockade as patients with Parkinson's disease also have deficits in smooth pursuit and saccadic eye movements (Crawford *et al*. 1989; Waterston *et al*. 1996). Indeed, some recent evidence, with healthy volunteers, suggests that smooth pursuit performance may be adversely influenced by antipsychotic medications (King, 1994; Malaspina *et al*. 1994).

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There are relatively few investigations measuring saccadic performance in schizophrenic patients. However, there are several reasons why it might be important to study these in addition to smooth pursuit. First, both systems work together closely and interactively during normal pursuit eye movements. Secondly, the neurological pathways involved in generating saccades in humans are better understood than those involved in generating smooth pursuit eye movements. Thirdly, the basic saccadic metrics (latency, gain, velocity, direction and final eye position) are measured using standard procedures, allowing meaningful cross study comparisons. Fourthly, saccadic paradigms also have the advantage of allowing various attentional, perceptual and cognitive processes to be selectively engaged (Henderson *et al.* 1996). Finally, a number of recent studies have identified abnormalities of saccadic eye movements in schizophrenic patients, particularly in the antisaccade task in which subjects are required to make a saccade to a position directly opposite the target location (Fukushima *et al.* 1990; Crawford *et al.* 1995*a*, *b*; Sereno & Holzman, 1995).

In order to avoid possible contaminating effects of medications and illness duration some previous studies have examined smooth pursuit performance in first-episode schizophrenic patients (Sweeney *et al.* 1992; Lieberman *et al.* 1993; Gooding *et al.* 1994; Maruff *et al.* 1995). These have established that smooth pursuit abnormalities can be observed at presentation. However, differences in the treatment status of the patients, comparison groups and measurement techniques again make conclusions as to the exact nature of the deficit difficult to reach. Furthermore, there are no published studies of saccadic eye movements in first-episode schizophrenic patients.

We, therefore, investigated both smooth pursuit and saccadic eye movements in patients with first-episode schizophrenia in order to examine whether these are fundamental to the disorder. To examine the effect of antipsychotic medication on eye movements, we compared never medicated first-episode patients, with first-episode patients who have received medication for a short period of time. We use standardized measures and a comprehensive test of smooth pursuit (Crawford *et al.* 1995*c*) as well as two tests of saccadic performance – the reflexive, or prosaccade task and the antisaccade task.

METHOD

Subjects

All patients presenting to two NHS Trusts in West London with a first-episode psychotic illness were approached for entry into the study. Those who agreed to participate were assessed by a psychiatrist. Only those who fulfilled DSM-IV criteria for schizophrenia or schizophreniform disorder were included in the study. During the first year of study 36 patients underwent oculomotor testing and their data is presented here. Seventeen of the patients were completely drug-naive at the time of testing. The remaining 19 subjects had received antipsychotic medication for between 2 and 60 days prior to testing. The medicated group were taking a variety of antipsychotic drugs as the consultants responsible for the patients treated them according to their usual practice and were not constrained in their choice of antipsychotic by the study protocol. All patients provided written informed consent. The 36 control subjects were healthy volunteers living in the same community who had no history of psychiatric or neurological disorders in themselves and in their first-degree relatives. The control subjects also denied any history of alcohol or drug abuse. A problem with the recording equipment during one session lead to the results of one control subject being lost. The characteristics of the two groups are summarized in Table 1. The groups were matched for sex ratio, age and estimated pre-morbid IQ (NART; Nelson, 1982).

Apparatus

For saccadic paradigms the target display consisted of four red light-emitting diode (LED) targets (diameter 0·25°) located $\pm 7{\cdot}5°$ and $\pm 15°$ either side of a central fixation LED. The LED

Table 1. *Group characteristics*

	N	Age (range)	NART IQ (range)	Gender (M/F)
Control	36	25·03 (17–35)	108·84 (96–123)	21/14
Drug treated	19	25·37 (16–45)	106·85 (98–121)	15/4
Drug naive	17	27·18 (17–41)	105·62 (89–118)	12/5
P	—	NS	NS	NS

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targets were embedded in a semi-opaque screen and were only visible when illuminated. The smooth pursuit stimulus was a bright red laser spot back projected onto the same translucent screen. The target oscillated horizontally with a triangular waveform of amplitude 22·5°.

Subjects were comfortably seated 1·5 m from the screen with a buzzer located behind their head. Head movements were restrained using an adjustable head rest. All paradigms were conducted in the dark. Eye movements were recorded using a Skalar IRIS infrared limbus reflection device. A hardware anti-aliasing filter (cut-off frequency 200 Hz) was used to filter eye position and the sampling rate was 500 Hz. Stimulus display and data sampling were controlled by a PDP 11/73 computer. Each paradigm was preceded by a calibration trial in which nine equally spaced LED targets with known horizontal positions were illuminated sequentially, the subject being asked to fixate each target in turn.

Procedures

Reflexive paradigm

Each trial consisted of the following sequence: (1) a central fixation LED was illuminated at the beginning of each trial; (2) after 800 ms the fixation LED was extinguished and simultaneously a peripheral target LED was illuminated for 1000 ms and a 200 ms buzzer signal was initiated. Subjects were asked to direct their gaze as quickly and as accurately as possible to the newly illuminated target LED and then return to the central fixation point. The order of targets was varied pseudo-randomly to prevent predictive behaviour. There were 24 trials in all.

Antisaccade paradigm

The stimuli and procedure are identical to the reflexive paradigm. However, the subjects are instructed to move their eyes rapidly towards a position in space equally distant, but in the opposite direction to the peripheral stimulus, i.e. to the mirror image location. An antisaccade error occurs when the subject is 'distracted' by the target appearing and makes a brief reflexive saccade towards it. Subjects typically then make a correct antisaccade in the opposite direction. Subjects performed 24 trials.

In both saccadic paradigms the spatial accuracy or gain (saccadic amplitude divided by target amplitude), peak velocity and latency of the primary saccade were measured, as well as the final eye position (FEP). In addition, the number of antisaccade errors made by all groups were recorded.

Smooth pursuit

The target oscillated horizontally with a triangular waveform of amplitude 22·5°. Four velocities: 10, 20, 30 and 36°/sec were used, and six full cycles recorded at each velocity.

Data analysis

Saccadic analysis was conducted off-line using interactive software which enabled the rejection of artefacts such as blinks. Eye position data was filtered using a Kaiser window low-pass filter. The signal was then differentiated to yield eye velocity. Saccadic detection was based on a velocity criterion of 30°/s in addition to an acceleration across three consecutive samples. Final eye position was measured by taking the mean fixation location during the maximal period of fixation stability after all corrected saccades were completed.

There is considerable controversy surrounding the various ways in which smooth pursuit performance can be quantified (Abel & Ziegler, 1988; Friedman *et al*. 1995). The main function of the pursuit system is to match the velocity of the eyes to that of a moving target. Accordingly, we agree with Stuve *et al*. (1997), that the best assessment of the ability of the smooth pursuit system to perform this task is reflected by the measurement of the ratio of peak eye velocity over target velocity, known as peak velocity gain.

Smooth pursuit analysis was performed using the Eyemap analysis package (Amtech GmbH, Heidelberg). Saccadic movements were identified and excluded from the analysis. In each half cycle the portion of smooth pursuit eye movement having the highest velocity was identified and expressed as peak velocity gain (eye velocity/target velocity). This portion was always collected from the middle third of each half cycle, to avoid acceleration and deceleration transients at the beginning and end of each ramp. Data from leftwards and rightwards movement were kept separate, thus six velocity values were obtained at each target velocity for each direction of movement. For each subject

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the degree of asymmetry between leftwards (L) and rightwards (R) was quantified as an asymmetry factor (A) defined as

$$A = \frac{\text{gain(R)} - \text{gain(L)}}{\text{gain(R)} + \text{gain(L)}}.$$

This factor ranges between -1 and $+1$ with a value of zero indicating no directional preference.

Statistical analyses

Within each measure, outlying data points were identified and removed. Outliers were defined as values either above or below values 1·5 times the interquartile range from the upper and lower limits of that range (the 75th and 25th percentile scores). This procedure resulted in the removal of the anti-saccade error data of two control subjects, the antisaccade latency data of two controls and one drug-naive patient, the anti-saccade gain data of one control, the reflexive saccade latency data of two patients and one control, and the smooth pursuit data of one patient. Data were analysed with analysis of variance (ANOVA). Where a significant main effect of group occurred, planned comparisons were performed. All analyses were repeated with the outliers included and all significant effects remained.

RESULTS

Reflexive saccades

The metrics for the reflexive saccade task are displayed in Table 2. There were no significant differences between any of the three groups on primary saccade gain ($F(2, 68) = 1{\cdot}4$, $P > 0{\cdot}5$), final eye position ($F(2, 68) = 0{\cdot}956$, $P > 0{\cdot}5$) or latency ($F(2, 65) = 0{\cdot}14$, $P > 0{\cdot}5$).

Antisaccades

The groups differed in the number of antisaccade errors ($F(2, 66 = 13{\cdot}98$, $P < 0{\cdot}001$) (Fig. 1). Planned comparisons revealed that both the drug-treated and drug-naive schizophrenics made more antisaccade errors than controls ($t(50) = 5{\cdot}52$, $P = < 0{\cdot}01$ and $t(48) = 3{\cdot}68$, $P < 0{\cdot}01$ respectively). Drug-treated schizophrenics made less errors than drug-naive patients, but the difference was not significant ($t(34) = -1{\cdot}53$, $P = 0{\cdot}14$). The great majority of incorrect reflexive saccades (88·5%) were subsequently corrected with antisaccades by the schizophrenic patients.

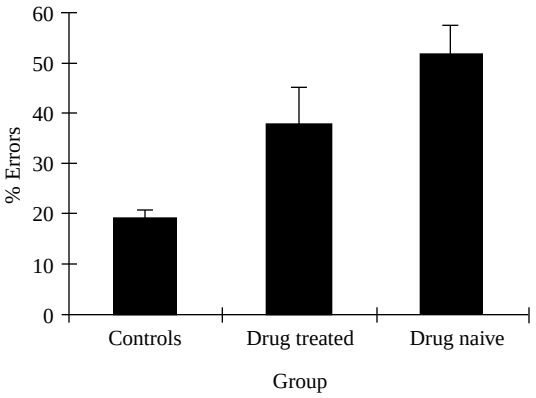


FIG. 1. Antisaccade errors (bars represent standard error).

Table 2. *Reflexive saccade metrics*

	Spatial gain	Final eye position	Latency
Controls (C)	0·92	0·97	194·06
Drug treated (T)	0·87	1·00	195·80
Drug naive (N)	0·88	0·98	190·82
P	NS	NS	NS

Table 3. *Anti-saccade metrics*: (*correct trials*)

	Spatial gain	Final eye position	Latency
Controls (C)	−1·07	−1·13	302·66
Drug treated (T)	−0·84	−1·07	295·91
Drug naive (N)	−0·99	−1·11	352·01
P	C > T	NS	N > C and T

The metrics for correct trials are displayed in Table 3. A significant effect of group was observed for primary saccade gain ($F(2, 67) = 3{\cdot}84$, $P < 0{\cdot}05$). The gain of the primary saccade was lower in the treated group than in the controls ($t(51) = 2{\cdot}97$, $P < 0{\cdot}01$). The difference between the controls and the untreated group, and the untreated group and the treated group were not significant ($t(49) = 1{\cdot}44$, $P = 0{\cdot}16$ and $t(34) = 0{\cdot}93$, $P = 0{\cdot}36$). The final eye positions did not differ significantly between groups ($F(2, 68) = 0{\cdot}19$, $P > 0{\cdot}5$). There was a significant effect of group for correct antisaccade latency ($F(2, 65) = 3{\cdot}72$, $P < 0{\cdot}05$). The latency to respond on correct trials was significantly slower in the untreated group than in both the treated group ($t(33) = -2{\cdot}29$, $P < 0{\cdot}05$) and the controls

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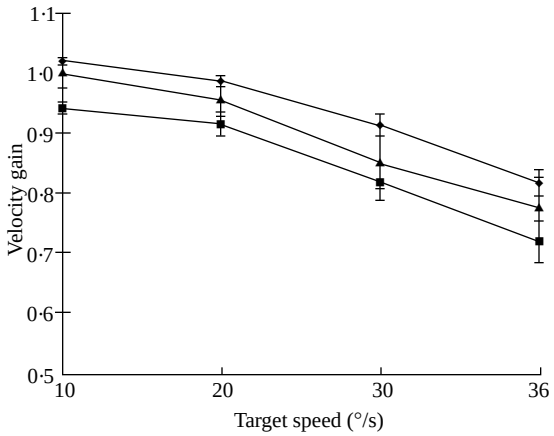


FIG. 2. Smooth pursuit velocity gain (bars represent standard error). (◆, controls; ▲, drug-treated schizophrenics; ■, drug-naive schizophrenics.)

($t(47) = 2{\cdot}91$, $P < 0{\cdot}01$). The latencies of the treated group and the controls did not differ ($t(50) = -0{\cdot}45$, $P = 0{\cdot}65$).

Smooth pursuit

The mean velocity gain at each of the four target speeds for the three subject groups is displayed in Fig. 2. Performance worsened with increasing target speed for all groups, and the gain of patients was lower than that of controls. Analysis of variance (ANOVA) revealed a main effect of target speed ($F(3, 201) = 130{\cdot}21$, $P < 0{\cdot}01$) and a main effect of group ($F(2, 67) = 4{\cdot}54$, $P < 0{\cdot}05$). The interaction was not significant ($F(6, 201) = 0{\cdot}49$). Gain was averaged across target speeds and planned comparisons revealed that the drug-naive group had a significantly lower overall velocity gain than controls ($t(49) = -3{\cdot}06$, $P < 0{\cdot}01$). The gain of the drug-treated group was not significantly different from either the controls ($t(51) = -1{\cdot}84$, $P = 0{\cdot}07$) or from the drug-naive schizophrenics ($t(32) = 1{\cdot}71$, $P = 0{\cdot}25$).

There were no differences between the groups in the asymmetry factor ($F(2, 68) = 1{\cdot}89$, $P = 0{\cdot}16$) with all groups showing very low mean values (0·032, 0·041 and 0·016 for the controls, drug-naive and drug-treated groups respectively).

Relationship between measures of oculomotor performance

Previous studies have demonstrated a relationship between smooth pursuit performance and antisaccade error rate (Sereno & Holzman, 1995; Matsue *et al.* 1994). Accordingly, we performed a Pearson correlation between the average smooth pursuit gain and antisaccade error rate of the patients and controls. The drug-naive and drug-treated schizophrenic patients were combined for this analysis. No significant correlations were found between these two measures in either the controls ($r = 0{\cdot}189$, $P = 0{\cdot}277$ or the schizophrenic patients ($r = -0{\cdot}051$, $P = 0{\cdot}767$).

DISCUSSION

We examined smooth pursuit and saccadic eye movements in patients with schizophrenia or schizophreniform disorder during their first psychotic episode. Both drug-naive and antipsychotic-treated patients were tested. Smooth pursuit velocity gain was significantly lower than controls only in the drug-naive patients. In the antisaccade paradigm both treated and drug-naive schizophrenic patients demonstrated an increased number of errors. Only drug-naive patients also demonstrated an increased latency in initiating correct antisaccades and only drug-treated patients had reduced primary saccade gain compared to controls. There were no differences between the groups on any reflexive saccade metrics.

In the reflexive saccade task, both drug-treated and drug-naive patients performed normally in that they were as quick as controls to initiate an eye movement, the gain of their primary saccades were not hypometric, and their final eye position was highly accurate. This suggests that they were motivated and able to cooperate with the testing procedure. It also suggests that other oculomotor abnormalities cannot be ascribed to either a generalized dysfunction of oculomotor neural systems or to a non-specific effect of antipsychotic medication.

In the antisaccade paradigm, the patients were, again, as accurate as controls regarding the final eye position on correctly performed trials, but they were impaired on other measures. Both patient groups showed increased distractibility by making more reflexive saccades (errors) than controls. This effect was independent of medication status and, importantly, 88·5% of all incorrect reflexive saccades were subsequently

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corrected, indicating that errors were not due to a misunderstanding of the paradigm. Several studies have demonstrated an increased antisaccade error rate in chronic medicated patients (Thaker *et al.* 1989; Fukushima *et al.* 1990; Sereno & Holzman, 1995). Crawford *et al.* (1995*a*) also found this in chronic patients who had not received antipsychotic medication for at least 6 months. We have now extended these findings and demonstrated that increased antisaccade errors can be witnessed at the onset of the clinical manifestations of schizophrenia, and cannot be attributed to medication effects, to more general problems of motivation or to a failure to understand the experimental procedure. This saccadic oculomotor deficit, therefore, appears to be a fundamental abnormality of the disorder.

Evidence suggests that volitional saccades are under the executive control of frontal cortical regions, including the frontal eye fields (Bruce & Goldberg, 1985), the supplementary eye fields (Shook *et al.* 1990) and the dorsolateral prefrontal cortex (DLPFC, Guitton *et al.* 1985). In particular, DLPFC (area 46) appears to be specifically involved in the suppression of reflexive saccades towards the target in antisaccade tasks (Guitton *et al.* 1985; Pierrot-Deseilligny *et al.* 1991). Regarding cognitive explanations of impairment on antisaccade tasks, Henderson and colleagues (1996) suggest that the inability to suppress a biologically prepotent reflexive saccade may reflect a primary deficit in strategic planning. This explanation also agrees with neuropsychological and functional imaging studies of the DLPFC which have shown that this area is critically involved in planning and other strategic processing in non-oculomotor tasks (Baker *et al.* 1996; Owen *et al.* 1996*a*, *b*). There is much evidence to suggest that the DLPFC is especially dysfunctional in schizophrenic patients, and that this mediates their abnormal performance on neuropsychological tests of frontal lobe function such as the WCST, and certain clinical features (see Frith, 1992, 1995).

The differences between the treated and untreated groups on certain measures points to a complex effect of antipsychotic medication on performance in the antisaccade paradigm. The treated patients were significantly faster than the untreated patients in initiating a correct antisaccade suggesting that the medication was having a beneficial effect on performance. This effect may also account for the seemingly reduced error rate in the treated group, although this failed to reach statistical significance. The significance of the decreased primary saccade gain in the treated group is not clear. Since FEP was normal, it does not appear to reflect a deficit in spatial accuracy. It is interesting to note that primary saccade hypometria has also been observed in medicated compared to unmedicated patients with both chronic schizophrenia and manic psychosis (Crawford *et al.* 1995*a*, *b*), as well as in patients with Parkinson's disease (although not on an antisaccade task, Crawford *et al.* 1989). Thus, primary saccade hypometria may be a reflection of antipsychotic drug effects on dopaminergic extrapyramidal motor systems.

Of course, factors other than medication might account for the differences between the treated and untreated groups, although the groups were matched for age, gender and estimated IQ. However, to confirm whether our findings are a reflection of a medication effect, or reflect some other group difference it will be necessary to retest the drug-naive patients once they have been established on medication.

Smooth pursuit eye movements have been studied much more extensively than saccadic performance in schizophrenic patients. The consensus opinion is that patients with chronic schizophrenia have an impairment of smooth pursuit eye tracking, which is perhaps best characterized by a reduction in smooth pursuit velocity gain (eye velocity divided by target velocity) combined with an increase in corrective catch up saccades (Mather, 1985; Levin *et al.* 1988; Moser *et al.* 1990; Abel *et al.* 1991; Friedman *et al.* 1991, 1992, 1995; Litman *et al.* 1994). However, much of this research has been carried out on medicated patients, and there are a number of reasons why antipsychotic medication might be expected to effect smooth pursuit performance. First, the abnormality witnessed in schizophrenic patients can be mimicked by the administration of antipsychotics to normal volunteers (King, 1994; Malaspina *et al.* 1994), although earlier studies have failed to show this (Holzman *et al.* 1975). Secondly, reduced gain has been observed in the early stages of Parkinson's disease (Waterston *et al.* 1996), in which there is a dopamine deficiency in both the

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basal ganglia and cortex, and it is well known that neuroleptic medication can cause parkinsonian symptoms in schizophrenics by blockade of dopamine receptors. Thirdly, in chronic patients, smooth pursuit is worse in those currently taking antipsychotic medication compared to those who have been off medication for at least 6 months (Crawford *et al.* 1995*b*; Kufferle *et al.* 1990), although studies with shorter wash-out periods have failed to demonstrate this (Siever *et al.* 1986; Spohn *et al.* 1988).

Two previous studies have therefore examined smooth pursuit in drug-naive patients. Campion *et al.* (1992) were the first to show that drug-naive patients were as equally impaired as medicated patients. Subsequently, Sweeney and colleagues (1994) demonstrated that drug-naive and drug-free, but previously treated groups of schizophrenic patients had equally reduced smooth pursuit gain compared with controls and that there was no change in this measure following drug therapy in either group. However, the patients in this study had been ill for a mean of 2 years and those of Campion for a mean of 4 years. Studies specifically examining smooth pursuit at the onset of psychosis confirm the presence of reduced velocity gain, but these results are confounded by the inclusion of both treated and untreated patients (Sweeney *et al.* 1992; Lieberman *et al.* 1993). The present study, therefore, clarifies these issues by the demonstration that first-episode drug-naive patients have reduced smooth pursuit velocity gain thus confirming and extending the above findings.

A number of cortical areas are believed to be involved in the control of smooth pursuit eye movements, including the medial temporal visual area (MT) and medial superior temporal visual area (MST), the posterior parietal cortex (PPC) and the frontal eye fields (FEF). It is believed that area MST combines the target motion information with an internally generated signal of eye velocity. The role of the PPC is presumed to be attentional, whereas the FEF may be involved in programming predictive pursuit movements (MacAvoy *et al.* 1991; Morrow & Sharpe, 1995). The frontal eye fields are also believed to be important in antisaccade performance (Rivaud *et al.* 1994; Pierrot-Deseilligny *et al.* 1995). Previous research has found that subjects with poor pursuit tracking also make more antisaccade errors (Matsue *et al.* 1994; Sereno & Holzman, 1995). These findings have been used as further evidence for the contention that schizophrenia is a 'frontal' impairment. However, in our study no such relationship between performance on the two tasks was observed, a result consistent with Gooding *et al.* (1997). These findings, therefore, imply that schizophrenic patients are failing the tasks for different reasons and that different pathophysiological mechanisms may underlie the impairment on these two types of task. We are currently conducting research aimed at further exploring different cognitive deficits which may contribute to low smooth pursuit velocity gain and increased antisaccade error rate in schizophrenic patients.

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