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Smooth pursuit eye movements of patients with schizophrenia and affective disorder during clinical treatment

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Abstract *Background* Smooth pursuit eye movement dysfunctions are considered a biological indicator for vulnerability to schizophrenia. This study examines test-retest stability of specific eye movement variables such as velocity gain and different saccadic categories. *Methods* Smooth pursuit eye movements of 27 schizophrenic patients and 30 patients with major depression were examined three times during clinical treatment using high-resolution infrared oculography. Forty-one normal controls were retested after four weeks. *Results* Intraclass correlation coefficients as a measure for retest-stability were highly significant in each group for all time-points, except for anticipatory saccades in schizophrenics. No significant correlations were found between psychopathological status, neuroleptic medication and eye movement variables. *Conclusions* Our results indicate that the most important measures of eye tracking performance in psychiatric patients are not significantly influenced by neuroleptic medication or clinical state and are stable across time.

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Introduction

Since the report of Holzman et al. (1973) smooth pursuit eye movement (SPEM) dysfunction in schizophrenia has been replicated numerous times. It is now considered one of the best biological indicators of genetic liability to schizophrenia (Iacono and Clementz 1992). To have utility as a trait marker indicating vulnerability, SPEM dysfunction should be stable over time and insensitive to neuroleptic and clinical status. If it were dependent on variable factors, e. g. psychopathology, it could perhaps qualify as an episode marker but could not signify an underlying vulnerability to the illness. It might be, therefore, particularly important to look at stability during treatment because significant changes in neuroleptic dose and psychopathology occur at this time.

There are only a few studies reporting test-retest findings, despite the importance of this issue. Retest reliability coefficients ranged from 0.45 to 0.81 (Bartfai et al. 1985, Holzman et al. 1974, Rea et al. 1989, Shagass et al. 1974). Using a global qualitative assessment of eye movement performance, Rea et al. (1989) reported a test-retest correlation coefficient of 0.57 in nine medicated schizophrenics over a period of one month. Gooding et al. (1994), using root mean square (RMS) error scores, found a test-retest correlation of 0.68 in 38 first-episode schizophrenic patients over a period of 9.5 months. Campion et al. (1992) found no significant test-retest difference for mean values of gain and saccades. Retest correlation coefficients ranged from 0.58 to 0.91 in different subtypes of schizophrenic patients. Most of the above mentioned studies used global measures to assess quality of SPEM.

Recent research has emphasized the need to use more specific and neurophysiologically defined measures of

eye movement dysfunctions such as pursuit gain and saccadic categories. Part of the data presented here have been published and shown that SPEM-dysfunction in schizophrenia is mainly and specifically due to an increase of catch-up saccade rate which in itself is secondary to position errors caused by a mismatch of velocities of stimulus and eye (Flechtner et al. 1997). The present study examines therefore test-retest stability in schizophrenic and depressed patients over the course of their clinical treatment using specific parameters such as gain (ratio eye velocity/target velocity) and different saccadic categories.

Methods

Subjects

Forty-four schizophrenic patients, 34 patients with major depression and 42 controls participated in the study. Diagnoses were made according to DSM III-R criteria (APA 1987). Normal controls had no personal or familial history of psychiatric disease. Exclusion criteria for all subjects were: age under 18 or above 65, history of substance dependence or recent substance abuse, signs of organic brain disease, neurological or ophthalmologic illnesses, evidence of mental retardation.

The group with major depressive disorder had a higher mean age (46.9 ± 11) than the schizophrenic patients (30.7 ± 7.2) and normal subjects (34.3 ± 10.9). The female/male ratio was higher in the depressed patients (25/9) than in schizophrenic patients (16/27) and in normals (22/20).

After complete description of the study to the subjects, written informed consent was obtained. Controls were examined two times (T0, T1) with a four-week interval in between. In patients clinical assessments and eye movement recordings were performed shortly after admission to the hospital (T0), four weeks later (T1) and again shortly before discharge (T2). Mean interval between T0 and T1 was 28.3 ± 3.6 days, mean interval between T0 and T2 was 96 ± 55.9 days. The interval between T1 and T2 was not fixed beforehand. The last eye movement recording (T2) took place shortly before discharge in a state of clinical recovery. While in the hospital schizophrenic patients were treated with neuroleptics. Five patients were treated with clozapine, the rest with typical neuroleptics. Three schizophrenic patients also received anticholinergic medication. Four depressed patients received serotonine reuptake inhibitors, the rest tricyclic antidepressants. Six patients were treated additionally with lithium and three with carbamazepine.

Between measurements, several patients dropped out of the study for various reasons. Most patients left the clinic suddenly on their own accord before they could be reexamined. At T1, we had 27 schizophrenic patients, 30 depressed patients and 41 controls. At T2, there were 20 schizophrenic patients and 18 depressed patients.

The following clinical rating scales were used to obtain detailed description of psychopathological status: the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham 1962), the Schedule for the Assessment of Negative Symptoms (SANS) (Andreasen 1984), the Schedule for the Assessment of Positive Symptoms (SAPS) (Andreasen 1984), the Hamilton Depression Rating Scale (Hamilton 1967), and the Rating Scale for Extrapyramidal Side-Effects (EPS) (Simpson et al. 1970). For every patient a detailed history of medication and of the previous course of illness was obtained.

Procedures

Subjects were seated comfortably in a quiet, darkened room. A headrest was used to inhibit head movements. Smooth pursuit eye movements were induced using a red laser light spot that moved sinusoidally in the horizontal plane at a frequency of 0.4 Hz across ± 10°of visual angle. Subjects were instructed to follow the target carefully at all times. Eye movements were recorded with high-resolution infrared oculography (AMTech, Eye tracker 3). Data were digitized online at 250 Hz. Before each trial, the system was calibrated by asking the subject to look at the center and ± 10°. Every single recording was visually inspected on the computer monitor and blinks and artifacts were cut out. We rejected $^3/_4$ of the first sinus because initiation of pursuit is different from maintenance of pursuit. Saccades were detected automatically. All intervals with a velocity greater than 30° per second above the stimulus velocity were automatically identified as saccades. The beginning of each saccade was then automatically determined by the intercept of a line drawn through the average velocities for 5 ms before and after. All intervals were visually inspected and classified as saccades or artifacts without knowledge of the subject's group membership. Saccades as small as 0.2°could readily be detected.

We examined several oculomotor parameters as an index of oculomotor functioning: pursuit gain, catch-up saccades, anticipatory saccades, square wave jerks. Pursuit gain measures how accurately the eye matches target velocity during smooth pursuit and was calculated as the ratio of eye velocity to target velocity. We calculated gain using data ± 400 ms around the peak velocity in each direction of each cycle. This means that we cut off the end-points of the sinus, because at low velocities the variability of gain values and the risk of errors increase. Periods of low or zero velocity after anticipatory saccades were not included in the gain calculation. Likewise, all non-pursuit eye movements, e. g. blinks and saccades were cut out. For determining gain, we used each point of measurement without filtering or smoothing transformation and calculated then a mean gain. A gain of less than 1.0 means that pursuit velocity is slower than target velocity. In that case, the eyes fall behind the target and the resulting position error is corrected by catch-up saccades, which take the eyes from a position behind the target to the target. All saccades that started behind the stimulus and decreased position error were classified as catch-up saccades. Inappropriate saccades that can occur during pursuit are saccadic intrusions. They are functionally independent of the pursuit system and the eyes leave the target during pursuit. The most common ones are square wave jerks (SWJ), which are small pairs of saccades in opposite directions, separated by an intersaccadic interval of 200–450 ms. During this time, pursuit continues practically uninterrupted. Anticipatory saccades (AS) have larger amplitudes (often above 5°) and take the eyes ahead of the stimulus. Saccades in the direction of the target motion that increased position error were classified as AS. After an AS, pursuit gain values drop sharply because of reduced eye velocity, until the stimulus has caught up. Sometimes a back-up saccade occurs after an AS which is directed towards the target and contrary to the target motion.

Statistics

Because there were moderate but significant correlations (up to 0.57) between age and most eye movement variables we used age-adjusted values. To test for mean differences between time points we used a repeated measures analysis of variance (MANOVA). We carried out two MANOVAS. One with the patients who had observations at T0 and T1 and the second comprising patients who had observations at all three time points (T0, T1, T2). To assess test-retest reliability we computed intraclass correlation coefficients (ICC) (Bartko 1991).

Results

Patients who were lost at follow-up

In the schizophrenic group out of 44 patients at T0, 27 were retested at T1 and 20 at T2. In the depressed patient group out of 34 at T0, 31 were retested at T1 and 20 at T2. In both patient groups there was no statistically significant difference between dropouts and non-dropouts in terms of age, sex, acute psychopathology, number of

Table 1 Gain and saccade rates (saccades/min) at different measurements. Age adjusted mean and ± SD of subjects studied at each time point

	Schizophrenics			Depressed			Controls	
	T0	T1	T2	T0	T1	T2	T0	T1
Gain	0.91±0.07	0.88±0.07	0.84±0.13	0.92±0.08	0.94±0.07	0.9±0.14	0.96±0.04	0.98±0.04
CUS	109.1±34.3	100±34.8	104.9±42	92.1±27	90.1±29.8	91.9±42.8	82.5±22.7	80.7±21
AS	9.3±9	10.7±8.2	11.3±13.8	7.8±11.3	8.7±12.8	11.2±18.2	3.9±7	3.3±5.3
BS	5.0±6.2	4.0±4.6	3.1±4.7	4.4±8.6	4.9±8.8	6.4±11.9	3.1±6.6	2.6±4.7
SWJ	9.6±9.9	15.8±14.1	10.3±11.6	14.7±18.3	16.3±16.3	13.1±9.4	9.2±10.3	9.3±9.5

CUS Catch-up saccades; *AS* Anticipatory saccades; *BS* Back-up saccades; *SWJ* Square wave jerks.

hospital admission, duration of illness, life-time CPZ medication, or daily smoked cigarettes.

Eye movement variables

Table 1 displays means and standard deviations for all measures and time points. The MANOVAS for each eye movement variable across the different time points showed a non-significant main effect for "time". There was no significant mean difference between all time points in any group and for all eye movement measures.

Table 2 shows ICC for gain and the different saccadic categories between all time points. The ICC for gain, catch-up saccades and square wave jerks between all time points were highly significant ($p < 0.001$) for all groups. ICC for anticipatory saccades (AS) and back-up saccades (BS) were highly significant for all time points in the depressed patients and the normal control group. Only ICC for AS and BS were non-significant in the schizophrenic group for all time points except the ICC for T1:T2 for AS which was significant.

Clinical status and medication over time

After initial examination (T0) at the time of admission to hospital, reassessment of psychopathology was performed about 28 days later (T1) and again shortly before discharge, on average 96 days later (T2). In both patient groups, there was a significant reduction of overall quantity of psychopathology. We carried out a MANOVA using time as a repeated measures factor and global scores of different rating scales as dependent variables. There was a significant main effect for time in schizophrenic patients for global BPRS scores, $F(2,15) = 67$, $p < 0.0001$ (Fig. 1), the SAPS $F(2,15) = 42$, $p < 0.0001$ (Fig. 1) and the SANS $F(2,15) = 16$, $p < 0.0001$. In depressed patients there was also a significant effect for scores of the Hamilton depression rating scale, $F(2,12) = 62$, $p < 0.0001$ (Fig. 1). At the same time neuroleptic doses increased significantly in schizophrenic patients, $F(2,15) = 44$, $p < 0.0001$ (Fig. 1).

To determine whether there was any relationship between clinical status and smooth pursuit performance we correlated eye movement measures with psychopathological rating scores. At no time point (T0, T1, T2) did we find significant correlations between eye movement measures, acute psychopathology, duration of illness, number of hospital admissions and scores for extrapyramidal side effects in either patient group. There were also no significant correlations between eye movement measures and neuroleptic or antidepressant medication at any time point. There was no significant difference between patients receiving lithium and non-lithium treatment. Although there was a tendency for schizophrenics treated with clozapine to have a higher frequency of catch-up saccades, numbers were too small as to allow a definitive conclusion. Cumulative neuroleptic dosage prior to hospital treatment did not correlate significantly with eye movement measures.

Table 2 Intraclass correlation coefficients (ICC) for gain and mean saccade frequency at T0, T1, T2

	Schizophrenics			Depressed			Controls
	T0:T1	T1:T2	T0:T1:T2	T0:T1	T1:T2	T0:T1:T2	T0:T1
Gain	0.64	0.81	0.76	0.88	0.81	0.89	0.71
CUS	0.73	0.83	0.84	0.74	0.80	0.83	0.79
AS	0.21*	0.63	0.40*	0.75	0.69	0.73	0.90
BS	0.28*	0.18*	0.22*	0.84	0.69	0.77	0.90
SWJ	0.64	0.71	0.77	0.74	0.74	0.77	0.74

CUS Catch-up saccades; *AS* Anticipatory saccades; *BS* Back-up saccades; *SWJ* Square wave jerks. ICC marked * are statistically non-significant, all others are highly significant: $p < 0.001$

Stable versus unstable pursuit

We calculated the absolute value of the difference of catch-up saccades between T0 and T1 for each subject. Unstable pursuit was then defined as two SD beyond the mean difference of the controls. Of the whole sample 14.3% had unstable pursuit. Seven (25.9%) schizophrenic patients, five (16.7%) patients with affective disorder and two (4.9%) normal controls displayed unstable pursuit. The schizophrenic group contained a significantly higher proportion of subjects with unstable pursuit than controls, Fisher's Exact Test (two-tail), $p = 0.024$, but not than the affective disorder patient group, Fisher's Exact Test (two-tail), $p = 0.52$. Controls and affective disorder patients did not differ signifi-

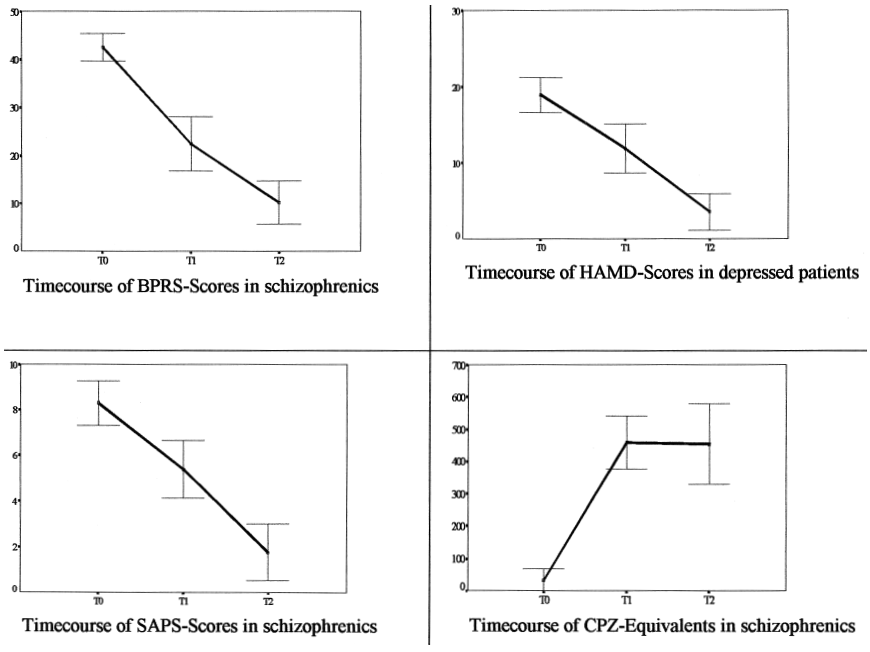

Fig. 1 Timecourse of psychopathology and neuroleptic dosage (*BPRS* Brief Psychiatric Rating Scale; *HAMD* Hamilton Depression Rating Scale; *SAPS* Schedule for the Assessment of Positive Symptoms; *CPZ* Chlorpromazine Equivalents; *T0* shortly after hospital admission; *T1* ca. four weeks later; *T2* ca. three months after admission).

cantly on the proportion of subjects with unstable pursuit, Fisher's Exact Test (two-tail), $p = 0.12$.

Patients with stable pursuit ($n = 84$) did not differ significantly from patients with unstable pursuit ($n = 14$) in terms of mean age, sex, duration of illness, number of hospital admissions, life-time CPZ-dosage, daily smoked cigarettes, or severity of psychopathology at T0 or T1 (Mann-Whitney U Tests, all n. s).

Predicting retest performance

A stepwise multiple regression analysis was conducted with catch-up saccade frequency as the dependent variable to evaluate to what extent retest performance could be predicted. The value at each previous testing was entered first because it accounted for the largest proportion of variance in the retest performance. No other variable was entered afterwards because no clinical or psychopathological variable yielded a significant increment in the squared multiple correlation. The procedure did not reveal any variable that could significantly predict retest performance after the effects of the previous catch-up saccade frequency were partialed out.

Discussion

The highly significant ICC indicate a good test-retest stability over a period of about three months for all oculomotor parameters, except AS and BS in the schizophrenic group. This stability is especially noteworthy because during the same time there was a significant reduction of overall quantity of psychopathology and a significant increase of daily psychotropic medication in both patient groups. These changes of clinical status did not have a measurable effect on the studied oculomotor variables. There were no significant correlations suggesting an association between clinical status including daily medication and eye movement variables. Therefore, we conclude that psychopathological status and acute neuroleptic medication do not affect the studied eye movement variables to a significant extent. This conclusion is consistent with findings of other studies (Spohn et al. 1988; Katsanis & Iacono 1991; Gooding et al. 1994).

To assess the reliability of eye movement parameters most studies calculated Pearson's correlation coefficients. Bartko (1991) argues that this is an inappropriate measure of reliability because it measures 'linear association' but not 'agreement' between two measurements as does the intraclass correlation (ICC). Except for anticipatory saccades and back-up saccades, the ICC for all of our eye movement variables across all groups between the different time points were significant. This means that the agreement between time points within a subject is high. The multiple regression analyses show that the strongest factors predicting retest performance are values of the same oculomotor parameter at an earlier time point. Recently it has been shown that catch-up saccades are the oculomotor component that is specific to schizophrenia (Flechtner et al. 1997). Our results indicate that catch-up saccades are stable across time. This is important because the catch-up saccade rate seems to constitute the key eye movement variable for assessing smooth pursuit performance in schizophrenics.

Correlations between time points for anticipatory saccades and back-up saccades are high in normals, low to moderate in depressives and mostly non-significantly low in schizophrenics. This means that anticipatory saccades and the subsequently generated back-up saccades do not have a sufficient reliability in schizophrenics to

qualify as a trait characteristic. Anticipatory saccades are functionally not part of smooth pursuit and are not informative of the accurateness of the smooth pursuit system itself but are probably more related to factors such as attention or cooperation. The discrepancy of reliability coefficients between schizophrenics and the other two groups could therefore be explained by varying attentional statuses of schizophrenic patients who are known to have attentional deficits (Nuechterlein and Dawson 1984).

It is of interest to note that there are subjects whose eye movement variables vary over time and that can be classified as having instable pursuit. In our sample, we found 14.3% of all subjects to have unstable pursuit while 25.9% in the schizophrenic group had unstable pursuit. In other words 74.1% of schizophrenic patients had stable pursuit. Using RMS errors Gooding et al. (1994) found 13% of schizophrenics and 10% of a sample including patients with schizophrenia, affective disorder and normals to have unstable pursuit.

If SPEM dysfunction is to be used as a biological indicator for vulnerability to schizophrenia, it is important to show to what extent SPEM dysfunction remains stable in each individual. Our data suggest a good test-retest stability for catch-up saccades and gain. Because within-subject values can vary over time to a certain extent, although group mean values remain stable, further studies are needed to determine prevalence rates of patients with stable SPEM dysfunction.

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