The effect of change in clinical state on eye movement dysfunction in schizophrenia

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Abstract

Measures of eye movement dysfunction have been considered as candidate endophenotypes for the study of genetic liability in schizophrenia. In this respect it is crucial to confirm a clinical state independence of these measures. Twenty people with DSM-IV schizophrenia were assessed using a battery of oculomotor tasks in the acute phase of their disorder without being treated with antipsychotic medication and then again in the remission phase under treatment with antipsychotic medication. The saccade latency in the saccade task, the error rate and antisaccade latency in the antisaccade task, and the frequency of unwanted saccades in the active fixation task were stable in time both at the group level and within each individual, showing no relation to the significant improvement in different psychopathological dimensions of these patients. The root mean square error, gain and saccade frequency in the pursuit task were not stable over time, although again this instability was not related to the changes in psychopathological status of these patients. Finally, the saccade frequency in the active fixation task with distracters was not stable in time and was correlated with changes in specific dimensions of psychopathology. These results provide further evidence that saccade and smooth eye pursuit dysfunction measures are not affected by the substantial change in the clinical state of schizophrenia from the acute phase to remission, and strengthen the current view that they can be used as endophenotypes. On the other hand, active fixation might be state-dependent adding to the evidence against its use as a candidate endophenotype in schizophrenia.

Keywords: Schizophrenia; Psychosis; Eye tracking; Saccade; Antisaccade; Neurophysiology

1. Introduction

The use of oculomotor function tests in psychiatry research has been growing exponentially in the last 35 years since Holzman et al. (1973) rediscovered the eye movement dysfunction (EMD) in schizophrenia that was first described by Diefendorf and Dodge in 1908. The EMD observed in people with schizophrenia opened the possibility to investigate the pathophysiological substrate of this complex disorder and link behavior to brain function. A recent theoretical formulation suggested that biological markers for psychiatric disorders such as EMD in schizophrenia could be used as endophenotypes. An endophenotype is an intermediate variable measuring one aspect of the complex psychiatric disorder and links the phenotype of the disorder to the corresponding genotype. The EMD endophenotypes that can be objectively measured could be used in genetic studies in search of the complex and probably polygenic substrate of schizophrenia.

An endophenotype should be associated with the illness and also it should be observed at a higher rate in non-affected family members than in the general population. Deficits
in smooth pursuit eye movements have been observed in people with schizophrenia [29,40] and their first-degree relatives [28,29,40]. The saccadic eye movements have also been investigated in schizophrenia and the research has focused mainly on antisaccades, which are saccades directed in the opposite direction from that of a visual target. People with schizophrenia produce more errors in their performance in the antisaccade task, have longer antisaccade latencies [8,13,21,31,35,43,49] and also have lower accuracy for antisaccade amplitude than normal controls [17,16]. The same antisaccade performance deficits have been observed in first degree relatives of schizophrenia patients [8,12,13,43,44,55]. Finally, it has been suggested that people with schizophrenia have a deficit in suppressing unwanted saccades compared to healthy subjects in an active visual fixation task [1,2,45] or in an active fixation task with increased inhibitory load, for example by adding distracting targets [14,22,46].

These data then suggest that EMD in the form of deficits in smooth eye pursuit, antisaccades and less so in active fixation could be potential endophenotypes for schizophrenia [4,5,56].

Another criterion used for identifying endophenotypes is state-independence [26]. This means that the endophenotype should manifest in an individual whether or not the illness is active.

Some studies have investigated the temporal stability of EMD in schizophrenia. The quality of smooth eye pursuit as an index of pursuit performance has been described as evidence for stability over time periods as long as two years in schizophrenia patients [9,24,33,34,40]. However, there have been very few investigations of the temporal stability of more precise measures of smooth pursuit in schizophrenia patients such as the gain of pursuit and the number of unwanted saccades [7,20,54]. In recent years the question of temporal stability of EMD has been extended to include the saccadic eye movements such as saccades and antisaccades [6]. More recent studies restricted their focus on the temporal stability of saccade and antisaccade measures of performance in people with schizophrenia [25,27]. In all these studies temporal stability of EMD was measured by comparing group mean values in different time points. In some studies the intra-subject variation of these measures in time was also estimated using either Pearson correlation or the more appropriate intra-class correlation coefficient.

Although temporal stability over time is an indication of state-independence, the question remains whether differences in the illness manifestation have an effect on EMD or not. Thus if EMD complied with the criterion of state-independence it would be expected not to vary with changes in different symptoms such as positive, negative or general psychopathology symptoms of the disorder. This issue has not been adequately addressed in the studies that investigated temporal stability of EMD in schizophrenia as previously discussed. Some studies investigated the correlation of EMD to measures of psychopathology across subjects at a particular time point [25,27].

The question that was addressed in this study was whether a major difference in the manifestation of schizophrenia, such as the difference between acute phase and remission, would be related to specific changes in EMD thus suggesting state-dependence of EMD in schizophrenia.

In order to address this question we collected clinical and oculomotor task performance data (saccade, antisaccade, smooth eye pursuit and active fixation tasks) from a group of 20 patients meeting DSM-IV criteria for schizophrenia in the acute phase of the disease and the remission phase under treatment with antipsychotic medication. Since the major goal of this study was to test the effect of changes in different dimensions of psychopathology on changes in measures of EMD within each patient, the difference in clinical status was maximized by including acutely ill patients requiring hospitalization.

Temporal stability of EMD was measured both at the level of mean difference between assessments and intra-subject variability. Then the specific hypothesis was tested of whether the clinical improvement in different dimensions of psychopathology in these patients, from acute phase to remission, affected the stability of oculomotor performance measures.

2. Methods
2.1. Participants

Twenty male patients meeting DSM-IV criteria for schizophrenia [3] participated in this study (mean age 23.9 years, SD 3.5 years). The mean education level of the participants was 12.85 years (SD 1.84 years). All participants provided written, informed consent. Patients were admitted in the Psychosis Unit of the Psychiatry Department of the National and Kapodistrian University of Athens at Eginition Hospital. Exclusion criteria included the following: organic cerebral illness, mental retardation, any oculomotor dysfunction and drug abuse in the last year before admission, and age over 30 years. Of those included in the study, 4 patients were diagnosed with the first onset of psychosis and had never being medicated before. All other patient participants had received antipsychotic medication at some time during the course of the disorder and underwent a medication wash out period for 5 days before the first assessment for the purposes of this study. Oculomotor tasks and the Positive and Negative Syndrome Scale (PANSS) were administered to the patients at two separate assessments, namely, in the acute antipsychotic-free phase (phase 1) and in the second phase of illness remission (phase 2) after administration of antipsychotic medication for at least 2 months. The mean dose of antipsychotic medication for all patients in chlorpromazine equivalents was 595 mg (SD 350.8 mg).

2.2. Clinical assessment

The clinical assessment of the patients in each one of the two phases was performed by the same trained psychiatrist using the Greek version of the Positive and Negative Syndrome Scale (PANSS) [36,42]. The PANSS total score, positive symptom scale score, negative symptom scale score...
and general psychopathology score were assessed in phase 1 and phase 2 for each patient. The duration of the illness (in months) and the interval between the assessment in phase 1 and the assessment in phase 2 (inter-assessment interval in months) were also used in the analysis as described below.

2.3. Eye movement measurement

Oculomotor tasks were performed in a setup that has been described in detail in previous studies [19,51]. Briefly, a PC-driven setup was used consisting of an adjustable chair for the subject and a specially designed table that had a head holder adjusted at one end and a 17 inch computer monitor mounted at the other end (1 m distance from the head holder). Eye movements were recorded from the right eye using the IRIS SCALAR® infrared device. Stimulus presentation and recording of the responses was accomplished with a program written in Turbo Pascal 7.0 for DOS. A 12-bit A/D converter was used for data acquisition (Advantech® PC-Lab Card 818L). Eye movement data were sampled at 600 Hz and stored in the PC for off-line data processing.

2.4. Saccade, antisaccade task

Each task was preceded by a calibration procedure, with saccades at 5° and 10° to the left and to the right of a central fixation point (white cross; 0.5° × 0.5° wide). During the saccade task the subject initially fixated a target (white cross; 0.5° × 0.5° wide) that could appear either at the center of the screen or at a peripheral position located at 8°, 6°, 4°, or 2° on an imaginary horizontal line, to the right or to the left of the screen center. After a variable period of 1–2 s the first target was turned off and a second identical target appeared either to the left or to the right of the first target. The second target could appear at one of five distances 2°, 4°, 6°, 8° and 10° from the first target to the right or to the left, if possible (for example if the first target was at 8° to the left of the center then only one location was available to the left, the one at 10°). The subject had 1.5 s to respond and then the second target disappeared and the screen was black for a period of 1 s before a new target appeared. Each subject performed 90 trials (18 trials for each first target position).

An antisaccade trial started with the appearance of a central fixation target (white cross; 0.5° × 0.5° wide). After a variable period of 1–2 s, the central target was extinguished and an identical target appeared randomly at one of nine target distances to the right or to the left from the center (2°, 3°, 4°, 5° etc., up to 10°). Participants were instructed to look quickly in the opposite direction from that of the peripheral target and to hold that position until the central fixation target reappeared 1.5 s later. Each participant completed a block of 90 experimental trials.

An interactive PC program (created using the TestPoint® CEC) was used for detection and measurement of saccades from the eye movement record (details are given in Evdokimidis et al. 2002) [19]). We excluded trials with artifacts (blinks, etc.) in the analysis period extending from 100 ms before the appearance of the peripheral target to the end of the first saccade, as well as trials for which an eye movement occurred in the 100 ms period before the appearance of the peripheral target. In addition, we excluded trials with a response latency that was not within the window of 80–600 ms (to avoid including predictive movements). For each subject, the following saccade and antisaccade performance indices were evaluated for the purposes of this study:

1. Median latency in milliseconds for saccades. The median was used instead of the mean latency because the latency distribution is skewed and the median is a better estimate of the central tendency [41].
2. Percentage of antisaccade errors. Since the percentage of errors is a count measure and its distribution is not normal, we used an arcsine transformation for parametric statistical testing [53].
3. Median latency in milliseconds for antisaccades.

2.5. Smooth eye pursuit task

Details on the pursuit task procedure used in this study are given in Smynis et al. 2007 [49]. Briefly, in the pursuit task each subject initially performed a calibration procedure consisting of saccadic eye movements to visual targets (white cross; 0.5° × 0.5° wide) at 10° to the right and 10° to the left of a center target (white cross; 0.5° × 0.5° wide). This cycle was repeated twice and then two more cycles were performed at a distances of 5°. Then the subject was instructed to follow a target (white cross 0.5° × 0.5°) that was moving horizontally on the computer monitor at constant speed. The visual angle of the moving target was ±10° from the center of the screen. We used five speeds (10°/s, 20°/s, 30°/s, 40°/s and 50°/s). The subject completed five cycles for each target speed consisting of the target moving 20° to the left and then 20° to the right at constant speed. The target started moving at a speed of 10°/s. After completion of the five cycles the target increased speed and the subject continued tracking at 20°/s then at 30°/s until all five target speeds were presented. There was no stop between changes in target speed. In this analysis we used data for the first three the target speeds (10–30°/s). The reason for excluding higher speed data was that many subjects changed their strategy and instead of pursuing the stimulus they made large saccadic eye movements anticipating the movement of the target [50].

A PC program written in the laboratory in Delphi 7.0 [50] was used to calculate the root mean square error (RMSE) between the eye position and the target position record at each target speed (10°/s, 20°/s, 30°/s). RMSE is a global measure of pursuit accuracy and increases with increasing dissimilarity between the eye position and the target position. The percentage of total signal duration, where the signal was saturated due to large eye blinks or other artifacts, was calculated for all pursuit records. This percentage of signal with artifacts never exceeded 10% of the total signal duration for all pursuit records and was close to zero for the majority of them, indicating good quality for pursuit records.
Another interactive PC program (created in the laboratory using the TestPoint CEC) was used for detection and measurement of pursuit gain and number of saccades from the eye movement record (details on the program are provided in ref [50]). The program selected a period of 133 ms centered at the point where the target crossed the center of the screen (two periods per run, 10 periods for each target speed). This window was selected in order to measure eye velocity at the primary position [38]. The operator manually discarded the period if an artifact was detected (i.e. a blink). If the period was artifact free then the program computed the instantaneous velocity and derived a median value of it, after scanning all of the period. Then the program identified particular points were the instantaneous velocity exceeded the median value by more than two-fold. The program considered these instances as occurrences of saccadic eye movements and measured their latency from the period onset and their duration. After excluding all time segments with saccades, the remaining pure pursuit segments were marked on the position trace and were used to measure mean velocity (amplitude difference divided by the total segment time) for the segment and finally by dividing the mean velocity with the corresponding target velocity to derive a gain value for the particular segment. For each individual, the following specific smooth eye pursuit performance indices were evaluated:

1. Median pursuit gain at each target speed (10°/s, 20°/s, 30°/s), which was the median of the gain calculated at each measurement period excluding periods with artifacts.

2. Saccade frequency (SF) at each target speed which was the total number of saccades for all measurement periods excluding periods with artifacts divided by the sum of these periods.

2.6. Fixation tasks

The details of the fixation task procedure and analysis are given in a previous report [52]. Briefly, three different fixation tasks of 50 s duration were presented in a random order for each individual. In the first task (visual fixation undistracted) subjects were instructed to fixate a visual target on the center of the computer monitor (white cross; 0.3° × 0.3° wide). In the second task (visual fixation distracted) subjects were instructed to focus their gaze on the central target and ignore targets that might appear to the right or to the left. For each trial four distracting targets (two small, 0.3° × 0.3° wide white crosses and two large, 1° × 1° wide white crosses) presented for a duration of 0.5 s at random intervals. Finally, in the third task (no target fixation) subjects were asked to keep their eyes fixating in the primary position (straight ahead) and avoid making eye movements. Before each active fixation task, a calibration procedure was performed.

An interactive PC program (created using the Test-Point CEC Software) was used for analyzing the eye movement records (for details see ref [52]). The program marked all saccades and eye blinks. For each subject and each fixation task condition we used in this analysis the frequency of saccades, which was the number of saccadic eye movements that were larger than 0.5° divided by the total time in the task.

2.7. Data analysis

We first analyzed the data from the PANSS scale and compared the scores in the patient group between phases 1 and 2 using paired t-tests and computed effect sizes using Cohen’s $d$ [10].

We tested for mean differences in the saccade, antisaccade and fixation task variables between phases 1 and 2 using paired t-tests. A repeated measures ANOVA, with phase and target speed as the repeated measures, was used to test for mean differences in pursuit variables. Paired t-tests were also used to compare the mean RMSE, gain and SF scores for all target speeds between the two phases. When a significant difference between phases 1 and 2 was observed for a particular oculomotor variable, the effect size was calculated using Cohen’s $d$. Finally, the intra-individual variability between phases 1 and 2 was assessed using the intra-class correlation coefficient (ICC). The two-way mixed model for computing the ICC was used that assumes that subject effect is random and the phase effect is fixed.

Difference scores between phases 1 and 2 were computed for each subscale of PANSS, for each subject (PSd, difference score for the positive symptom scale; NSd, difference score for the negative symptom scale; and GSd, difference score for the general psychopathology scale). Difference scores between phases 1 and 2 for each oculomotor variable for each subject were also computed. Then the following linear regression model was applied:

$$\text{oculomotor variable difference score} = a + b \times \text{PSd} + c \times \text{NSd} + d \times \text{GSd} + \epsilon$$

where $a$, $b$, $c$, $d$ are the regression coefficients and $\epsilon$ is the residual error. This regression model tests the dependence of the difference in each oculomotor variable score on the difference in each of the PANSS subscale scores between phase 1 and phase 2. The significance of the regression was assessed using the ANOVA $F$-test for regression. In those cases, the $F$ value was significant, the effect size was calculated using the formula: $d = 2r\sqrt{(1 - r^2)}$ where $r$ is the regression coefficient [11].

A separate linear regression model was used to test the effect of illness duration and inter-assessment interval (independent factors) one each oculomotor variable difference score.

3. Results

The design of this study relied on a basic difference in clinical state between phase 1, which was the acute phase of symptom exacerbation at initial admission to the hospital, and phase 2, in which the symptoms had remitted after hospitalization. This indeed was the case, as can be seen in Table 1.
The differences in PANSS total score and all subscale scores between phases 1 and 2 were highly significant and the effect sizes for these differences were large.

3.1. Saccade, antisaccade task

There was no overall difference between phases 1 and 2 for all saccade and antisaccade variables that were measured, as presented in Table 2. The same table also presents the intraclass correlation coefficients for these variables. The error rate in the antisaccade task showed marginally significant test–retest stability between phases 1 and 2, while the stability of saccade and antisaccade latency was significant.

Table 3 shows the results of the regression analysis. It can be seen that the significant changes in PANSS subscale scores between phases 1 and 2 were not related to changes in saccade latency, antisaccade error rate and antisaccade latency. Finally, the results of the regression analysis using the illness duration and inter-assessment interval showed no significant effect of these parameters on the change of saccade latency, antisaccade error rate and antisaccade latency between the two phases (results not shown).

In conclusion, this analysis confirmed that saccade and antisaccade task parameters were stable between phase 1 (acute phase) and phase 2 (remission phase) and that the large changes in quantitatively measured symptoms between the two phases were not related to changes in these variables.

3.2. Smooth eye pursuit task

Fig. 1 illustrates the mean RMSE for all patients for smooth eye pursuit at the three different target speeds in both phases. RMSE increased significantly with increasing target speed ($F_{2,36} = 10.5, P = 0.0002$). Also, the RMSE in phase 1 was significantly larger than that in phase 2 ($F_{1,19} = 5.62, P = 0.028$) and this difference between the two phases was not dependent on target speed (non-significant interaction of speed by phase: $F_{2,36} = 0.82, P = 0.44$). The effect sizes for RMSE differences between phases 1 and 2 for all target speeds, were medium as presented in Table 4. The ICCs for RMSE between phase 1 and phase 2 for all target speeds were not significant (Table 4).

Fig. 2 illustrates the mean gain for all patients for smooth eye pursuit at the three different target speeds in both phases. Gain decreased significantly with increasing target speed ($F_{2,38} = 15.5, P < 10^{-3}$). Overall the gain did not differ between phases 1 and 2 ($F_{1,19} = 3.22, P = 0.09$) but there was a marginally significant interaction of phase by target speed ($F_{2,38} = 2.98, P = 0.06$). Post hoc comparisons (Tukey's test) confirmed that only at 30°/s the gain was significantly lower in phase 1 than phase 2 ($P = 0.002$). The effect size for this difference was large, as shown in Table 4. The ICCs for gain between phases 1 and 2 were not significant for all target speeds (Table 4).

Finally, Fig. 3 illustrates the mean saccade frequency in pursuit for all patients for smooth eye pursuit at the three different target speeds in both phases. Saccade frequency increased with increasing target speed ($F_{2,38} = 15.5, P < 10^{-3}$). Saccade frequency was marginally significantly different in phase 1 compared to phase 2 ($F_{1,19} = 4.05, P = 0.06$). Also, there was no significant interaction of phase by target speed ($F_{2,38} = 2.17, P = 0.13$). The effect sizes for the differences in saccade frequencies between phases 1 and 2 were small to medium, as shown in Table 4. The ICCs for saccade frequency between phases 1 and 2 were not significant.

### Table 1

<table>
<thead>
<tr>
<th>PANSS scale scores</th>
<th>Phase 1 mean (SD)</th>
<th>Phase 2 mean (SD)</th>
<th>Paired $t_{19}$ ($P$)</th>
<th>Cohen's $d$</th>
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<tbody>
<tr>
<td>Total</td>
<td>119.2 (9.3)</td>
<td>82.85 (10.13)</td>
<td>11.8* $P &lt; 10^{-3}$</td>
<td>3.74</td>
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<td>Positive symptom</td>
<td>32.25 (4.05)</td>
<td>20.1 (3.65)</td>
<td>9.96* $P &lt; 10^{-3}$</td>
<td>3.15</td>
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<tr>
<td>Negative symptom</td>
<td>28 (3.83)</td>
<td>23.2 (3.3)</td>
<td>4.24*</td>
<td>1.34</td>
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<tr>
<td>General psychopathology</td>
<td>58.95 (4.82)</td>
<td>39.95 (5.48)</td>
<td>11.9*</td>
<td>3.68</td>
</tr>
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* $P < 10^{-3}$.

### Table 2

<table>
<thead>
<tr>
<th>Oculomotor variable</th>
<th>Phase 1 group mean (SD)</th>
<th>Phase 2 group mean (SD)</th>
<th>Paired $t_{19}$</th>
<th>ICC</th>
<th>$F$ for ICC</th>
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<tr>
<td>Saccade task</td>
<td></td>
<td></td>
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<tr>
<td>Median latency (ms)</td>
<td>183.5 (36.4)</td>
<td>174.3 (36.6)</td>
<td>1.02</td>
<td>0.55</td>
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<td>Antisaccade task</td>
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<tr>
<td>Error rate (%)</td>
<td>49.1 (29.7)</td>
<td>42.8 (15.8)</td>
<td>1.13</td>
<td>0.53</td>
<td>2.15*</td>
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### Table 3

<table>
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<tr>
<th>Relation of phases 1, 2 PANSS and oculomotor variable differences</th>
<th>$r^2$</th>
<th>$F$</th>
<th>$P$</th>
<th>$b$</th>
<th>$t$</th>
<th>$d$</th>
<th>$SD$</th>
<th>$t$</th>
<th>$b$</th>
<th>$d$</th>
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<tbody>
<tr>
<td>Saccade task</td>
<td>Med latency</td>
<td>0.10</td>
<td>0.6</td>
<td>-0.2</td>
<td>-0.62</td>
<td>-0.27</td>
<td>-0.88</td>
<td>0.5</td>
<td>1.32</td>
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<tr>
<td>Antisaccade task</td>
<td>Error rate</td>
<td>0.19</td>
<td>1.15</td>
<td>0.23</td>
<td>0.73</td>
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<td></td>
<td>Med latency</td>
<td>0.07</td>
<td>0.36</td>
<td>0.13</td>
<td>0.37</td>
<td>0.33</td>
<td>0.95</td>
<td>-0.36</td>
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<td>Smooth eye pursuit task</td>
<td>RMSE 10</td>
<td>0.26</td>
<td>1.93</td>
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<td>-1.21</td>
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<td>-1.85</td>
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<td>RMSE 20</td>
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<td>-0.52</td>
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<td>RMSE 30</td>
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<td>Gain 10</td>
<td>0.19</td>
<td>1.24</td>
<td>0.34</td>
<td>1.12</td>
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<td>Gain 20</td>
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<td></td>
<td>Gain 30</td>
<td>0.23</td>
<td>1.57</td>
<td>0.36</td>
<td>1.21</td>
<td>0.48</td>
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<td>Saccade frequency 10</td>
<td>0.24</td>
<td>1.66</td>
<td>-0.05</td>
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<tr>
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<td>Saccade frequency 30</td>
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<td>0.47</td>
<td>0.02</td>
<td>0.05</td>
<td>0.18</td>
<td>0.58</td>
<td>0.12</td>
<td>0.3</td>
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### Table 4

<table>
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<tr>
<th>Fixation tasks: saccade frequency</th>
<th>Unundistracted</th>
<th>Distracted</th>
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<tr>
<td>$F_{1,19}$</td>
<td>0.24</td>
<td>0.42</td>
<td>0.26</td>
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<tr>
<td>$P$</td>
<td>0.57</td>
<td>0.73</td>
<td>0.66</td>
</tr>
</tbody>
</table>

Bold indicates significant at $P < 0.05$.
for the target speeds of 10°/s and 20°/s while the ICC for 30°/s was significant (Table 4).

Summarizing these results, group differences in smooth eye pursuit performance were observed between phase 1 and phase 2. The performance was overall worse in phase 1 (higher RMSE and lower gain) than in phase 2 and this effect was prominent for high target speeds. Moreover the intra-subject stability of these variables across phases was low.

The question then was whether the group differences in pursuit performance between phases 1 and 2 were related to specific clinical parameter differences between the two phases as assessed with PANSS. The results of the regression analysis of score changes in the three PANSS subscales on the different pursuit variables are shown in Table 3. The change in psychopathology scores were not related to changes in any of the smooth eye pursuit variables measured. The same lack of relation with smooth eye pursuit variables was observed when illness duration and inter-assessment interval were used instead of the PANSS score differences as independent predictors (results not shown).

3.3. Fixation tasks

There were no significant group differences between phase 1 and phase 2 in saccade frequency for the three fixation tasks as shown in Table 5. The ICC for the saccade frequency in the undistracted fixation task was highly significant, while for the other fixation tasks the ICCs were not significant (Table 5).

The regression analysis showed no significant relation of the change in PANSS subscale scores on saccade frequency differences between phases 1 and 2 in the undistracted and no target fixation tasks (Table 3). A significant effect of the change in PANSS scores on saccade frequency differences between phases 1 and 2 was observed in the distracted fixation task (Table 3). The effect size for this effect was 1.7. Furthermore, this effect was specific for the change in negative symptoms and general psychopathology symptom scale scores.

The regression analysis of illness duration and inter-assessment interval on the change in saccade frequency between phases 1 and 2 in the three fixation tasks resulted in non-significant effects (results not shown).

In summary, there was no overall difference in fixation performance between phases 1 and 2, while the intra-subject stability of performance was significant only for the undistracted fixation task. The changes in negative symptoms and
general psychopathology symptoms between phases 1 and 2 were significantly related to a change in fixation performance only in the distracted fixation task.

4. Discussion

In this study we measured performance in a series of eye movement tasks in a group of 20 men suffering from schizophrenia. The question addressed was whether the change in clinical state of the disorder from acute phase to remission affects stability in task performance. In what follows we compare our results with previous findings and draw some conclusions for the state-independence of the different oculomotor variables measured.

4.1. Saccades, antisaccades

Growing evidence in recent years suggests that saccadic eye movement deficits in people with schizophrenia may be regarded as endophenotypes [4,5]. Among the criteria for identifying endophenotypes state-independence has been the focus of a few recent studies.

Group mean saccadic latency was found to remain stable over time in people with schizophrenia in two previous studies [6,25]. This stability over time was also confirmed in this study. The intra-individual stability though of this measure in people with schizophrenia was found to be low in the same studies [6,25]. In contrast to these previous findings, this study showed a significant intra-individual stability (measured using the ICC) for saccadic latency. The difference in intra-subject stability over time between our study and these previous studies might be related to the fact that the inter-assessment interval was much longer in both previous studies [6,25].

The antisaccade error rate and the antisaccade latency were found to remain stable over time as both a group mean and intra-individually in the two aforementioned studies using clinically stable patients under medication [6,25]. In a third study [27] it was found that antisaccade error rate was reduced significantly and the latency for correct antisaccades became faster with repeated measurements while intra-subject stability was significant for both measures (significant ICC). In our study we observed no significant group mean error rate difference from acute phase (test) to remission (retest) and the intra-subject stability was marginally significant ICC. A major difference between our study and the study of Harris and coworkers [27] was that they included medication naïve first episode patients while our sample included patients under psychotic relapse that were medication free at the first test

(with the exception of four first episode patients that were drug naïve).

Two previous studies [25,27] investigated the effect of psychopathology on antisaccade performance by correlating the antisaccade performance with psychopathology variables at different time points and found no significant correlation. Our study added further evidence in support of the state-independence of saccade and antisaccade task parameters. We observed that the dramatic improvement in different dimensions of psychopathology between acute phase (phase 1) and remission (phase 2) was not correlated to a change in these parameters supporting the state-independence criterion for identifying endophenotypes.

4.2. Smooth eye pursuit

Smooth eye pursuit deficit was the first oculomotor disturbance observed in people with schizophrenia [15] and a large amount of evidence over the last 35 years supports its use as a candidate schizophrenia endophenotype [5,56].

A previous study [24] reported that the mean RMSE scores in smooth eye pursuit remained stable over time and the intra-subject stability was significant in a group of drug naïve first episode patients that were retested after initiation of medication and clinical stabilization. In this study RMSE was significantly higher in the acute phase than in the remission phase for our patient group. Also the intra-individual stability of RMSE measured using ICC was not significant. The major difference between the two studies was the use of first episode drug naïve patients in the first phase of the previous study and the use of drug free patients in acute phase after psychotropic relapse in this study.

The question then was whether differences in RMSE observed in this study were correlated with differences in illness manifestation. We tested this hypothesis and found that the improvement in all psychopathological dimensions in these patients from acute phase to remission was not correlated with the significant reduction in RMSE scores observed in the same group of patients between the two phases.

In previous studies, smooth eye pursuit gain was assessed repeatedly in stable medicated patients [6,20]. It was also assessed in non-medicated patients (either medication naïve first episode patients or medication free patients) that were receiving medication at retest [7,54] and it was reported that the group mean gain was stable and the intra-subject stability was significant. In this study, mean pursuit gain was stable for low pursuit speeds while for the high speed of 30°/s the group mean gain at remission was lower than in the acute phase. It should be noted that all the above mentioned studies investigating time stability of pursuit gain in patients used a range of target speeds of 10–20°/s. Thus while our results are in agreement with previous results suggesting overall time stability of pursuit gain at low and medium speeds, our study suggests that this stability might not be present at high pursuit speeds. The intra-subject stability of smooth eye pursuit in patients was found to be significant in previous studies [6,7,20,54], while it was not significant in this study.
The issue of intra-subject stability of pursuit gain has not been solved in normal controls either. One study using low speed pursuit at 10°/s reported very high test–retest reliability in normal volunteers for successive measurements within one day [48] while in a subsequent study the test–retest reliability for pursuit gain in normal volunteers was found to be very low for successive measurements separated by a period of approximately 2 months [18].

The results discussed so far addressed the issue of time stability of smooth eye pursuit gain but the question remains whether the changes in clinical manifestation of the disorder have a specific effect on this parameter. In two previous studies correlation analysis has shown no effect of clinical symptoms on pursuit gain both at test and retest [20,54]. We extended this result and showed that the highly significant improvement in specific dimensions of psychopathology between the acute phase of the disorder and the remission phase did not correlate with changes in smooth eye pursuit gain.

Previous studies showed conflicting results on the time stability of saccade frequency in pursuit in people with schizophrenia. In one study [7] the test–retest reliability of this measure was high for repeatedly tested medicated patients but low for medication naive first episode patients that were tested again after medication and stabilization. In another study [54] the test–retest reliability for saccades was significant both for a drug naïve first episode group and a medication free group of patients that were retested. Finally, in a third study of medicated patients [20] the stability in the frequency of a particular type of saccades was significant (catch up saccades) while for other types of saccades (anticipatory and back up saccades) it was non-significant. Studies of test–retest reliability of saccade frequency in pursuit in healthy individuals have shown good stability within a day [48] and over a 2 month period [18]. This study showed a marginally significant difference in the group mean saccade frequency between acute phase and remission and the effect size of this difference was low for low target speeds and medium for high target speeds. Also this study showed non-significant intra-subject stability of saccade frequency in smooth eye pursuit at low target speeds and significant stability at the high speed. These results would suggest then that the conflicting reports on time stability of saccade frequency in pursuit might be the result of the use of different target speeds among different studies.

This study also showed that the highly significant improvement in specific dimensions of psychopathology between the acute phase of the disorder and the remission phase did not correlate with changes in smooth eye pursuit saccade frequency in these patients.

Summarizing the results on all smooth eye pursuit parameters, it could be argued that time stability of these parameters remains an open issue with conflicting results form different longitudinal studies including the present one. One the other hand, this study clearly showed that differences in these parameters across time cannot be attributed to the manifestation of the disorder thus providing evidence that smooth eye pursuit parameters are state-independent.

4.3. Active fixation

The temporal stability of performance in active fixation tasks has not been studied in people with schizophrenia. This study showed that the mean saccade frequency for the patient group in the all active fixation tasks was stable over time. The intra-subject stability was excellent for the undistracted fixation task but non-significant for the distracted and the no target fixation tasks.

It was also found that the improvement in psychopathology from acute phase to remission was not correlated with changes in performance in the undistracted and not target fixation task while it was significantly correlated with changes in performance in the distracted fixation task as predicted. More specifically, improvement in performance in the distracted fixation task was significantly correlated with improvement of general psychopathology and negative symptoms.

Although it was found in this study that undistracted visual fixation performance displays good temporal stability and is not affected by illness manifestation, there is controversy in the literature as to whether people with schizophrenia display a deficit compared to normal controls in this task, with some studies favoring a difference [2,14,22,45,46] and others not [8,23,37]. On the other hand it has been argued that a deficit in active fixation in schizophrenia emerges in a more demanding condition where distracters are introduced [14,22,46]. This task then could be used as an endophenotype for schizophrenia. This study though showed that performance in this task state-dependent thus limiting its usefulness as an endophenotype.

4.4. Study limitations

A potential limitation of this study was the fact that medication status at onset was variable. Some patients had stopped taking their medication and relapsed, others relapsed under medication and four patients experienced a first psychotic episode and were drug naïve. The 5-day medication free period tried to ameliorate this problem of variable illness manifestation changes on the oculomotor variables. One the other hand, the main focus of the study was the specific effect of illness manifestation changes on the stability over time of these oculomotor variables and we believe that the study design was adequate to address this issue.

Another potential limitation was the inclusion of all male patients in the study. It could be argued that the results could be affected by gender but there are no studies that have shown gender differences regarding the time stability of oculomotor task parameters.

5. Conclusion

In this study we investigated the dependence of eye movement deficits in people with schizophrenia to changes in
clinical status. Integrating our results with those of the few previous studies on this issue we could conclude there is evidence for state-independence both for the saccade, antisaccade task and smooth eye pursuit measures in schizophrenia. This study also provided evidence that active fixation with distracting stimuli that has been used to dissociate patients and controls might be state-dependent on illness manifestation thus adding to previous evidence that excludes active fixation tasks from candidate endophenotypes in schizophrenia.

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References


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