

## ORIGINAL PAPER

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## Eye movement deficits in schizophrenia

### Investigation of a genetically homogenous Icelandic sample

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**Abstract** *Background* Deficits in antisaccade (AS) and smooth pursuit eye movements (SPEM) are promising endophenotypes in genetic studies of schizophrenia. The Icelandic population lends itself ideally to genetic studies due to its ethnic homogeneity and well-documented genealogy. The primary aim of this study was to assess AS and SPEM performance in a large Icelandic sample. Additional aims were to investigate the relationship between AS and SPEM task performance and to assess internal consistency, within-session performance changes and effects of SPEM target velocity on performance. *Method* Patients with schizophrenia ( $N = 118$ ) and healthy controls ( $N = 109$ ) matched for age and gender underwent infrared oculographic assessment of AS and SPEM (at target velocities of 12°, 24° and 36°/s). *Results* On the AS task patients displayed significantly more reflexive errors, longer latency, increased intra-individual latency variability, and reduced amplitude gain compared to controls. On the SPEM task, patients had significantly lower velocity gain and more frequent saccades during pursuit at all velocities, but group differences in velocity gain increased with increasing target velocity. Internal consistency of performance was high for all variables in both groups (Cronbach's alpha  $>0.77$  for AS and  $>0.85$  for SPEM) except for AS spatial error in

patients (alpha = 0.38). A moderate association was found between AS and SPEM performance. By and large, patients and controls showed similar patterns of systematic within-session performance changes. *Conclusions* Our findings confirm the existence of robust eye movement deficits in schizophrenia in a large sample. These measures may be studied as endophenotypes in future studies of potential schizophrenia risk genotypes in the genetically homogenous Icelandic population.

**Key words** schizophrenia · smooth pursuit · antisaccades · endophenotype · genetics

### Introduction

There is strong evidence for involvement of genetic factors in the etiology of schizophrenia. However, the identification of causative genes is complicated by the considerable variability of symptoms and disease course between individuals with schizophrenia. Studying endophenotypes, i.e., biological or behavioral features thought to be more direct expressions of disease related genes than the clinical phenotype, may circumvent this problem and facilitate genetic studies of schizophrenia [3, 51].

Impairments on antisaccade (AS) [11, 17, 19, 39] and smooth pursuit eye movements (SPEM) [30, 33, 49, 50] are well-studied schizophrenia endophenotypes. The AS task requires the subject to generate a rapid eye movement (saccade) to a location opposite of a peripheral visual stimulus. All studies of AS eye movements in schizophrenia have demonstrated more frequent reflexive errors (glances towards the target) in patients than controls [35]. Most studies have found AS latency (time interval between target movement and eye movement) to be prolonged

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in schizophrenia [37, 44] and there is evidence for decreased AS amplitude gain [17, 19, 37]. In the SPEM task the subject follows a slowly moving visual stimulus. Schizophrenia patients have lower velocity gain and more frequent saccades than healthy individuals [50].

Support for the validity of AS and SPEM endophenotypes comes from studies showing that healthy relatives of schizophrenia patients perform worse than subjects with no family history of psychosis [11, 28]. Furthermore, performance is stable over time [7, 18] and twin studies indicate that AS and SPEM performance is considerably heritable [40, 54]. Taken together, these findings suggest that SPEM and AS deficits are promising schizophrenia endophenotypes. Additionally, research using oculomotor tasks has contributed to our understanding of the impairments in cognitive functions in schizophrenia and their pathophysiology [4, 58].

The present study aimed to add to this body of evidence in three ways. First, we aimed to replicate the observation of performance deficits in schizophrenia by studying a large and genetically homogenous Icelandic sample. Second, we explored interrelationships between AS and SPEM variables to determine whether these endophenotypes index overlapping or separate genetic factors. Third, we wished to investigate performance characteristics such as intra-individual variability, internal consistency, within-session changes and SPEM target velocity.

Concerning interrelations between AS and SPEM, neuropsychological and brain imaging studies indicate that these deficits may be based on prefrontal cortex dysfunction [6]. Studies investigating correlations between AS and SPEM task performance have provided inconsistent findings. While some have found an association [56, 68, 70] others have not [34, 62]. This issue is of importance, because a correlation would raise the possibility that the deficits may be related to common vulnerability genes for schizophrenia. This question is best studied in large samples in order to avoid failures to detect small correlations due to low power.

Internal consistency is an important reliability marker and provides a measure of the stability of task performance within one session. This measure has to our knowledge been systematically addressed in only two previous studies of AS and SPEM. For SPEM, high internal consistency was found in healthy [18] and schizophrenia subjects [8]. For AS, a study showed high consistency in healthy individuals [18]; however, this has not been studied in schizophrenia.

Relatedly, relatively few neurocognitive and psychophysiological studies have addressed systematic within-session performance changes (e.g., improvement or deterioration within one session) or intra-individual performance variability (e.g., dispersion) in schizophrenia. By reporting the mean performance

of a testing session that involves a series of trials it is possible that some important abnormal characteristics related to within-session performance changes or variability are missed. The importance of studying intra-individual performance variability in psychiatric populations has been demonstrated in recent neuropsychological studies [36], where variability measures provided considerably larger group effect sizes [45] and were better able to distinguish clinical groups [2] than the mean or median. Regarding oculomotor tasks, previous studies on healthy subjects have shown some within-session performance changes, which have been related to factors such as learning (improvement) and fatigue or boredom (deterioration) [18, 73]. Systematic within-session changes in AS and SPEM and intra-individual variability on saccadic tasks have to our knowledge not been studied in schizophrenia.

A final issue that will be addressed here concerns effects of target velocity on SPEM performance in schizophrenia. Schizophrenia patients and their relatives show impaired motion perception, which correlates with SPEM performance [10]. It has been suggested that deficits in processing internal representations of target motion contribute to abnormal SPEM [79]. At faster target velocities it becomes more difficult to correct retinal mismatch between target velocity and eye velocity. This correction probably depends on a corrective feedback loop, where an internal representation (extraretinal signal) of target motion activates the pursuit system [47]. Furthermore, recent functional magnetic resonance imaging (fMRI) studies have shown reduced activity in motion processing pathways in extrastriate [48] and medial superior temporal cortex, frontal eye field, supplemental eye field and anterior cingulate during SPEM in schizophrenia [31]. In the current study SPEM performance was assessed at three different target velocities in order to progressively tax the pursuit system.

This study represents the largest single-centre case-control study of AS and SPEM in schizophrenia and may thus provide important information on the reliability of eye movement measures and whether and how effects of time and target velocity on performance may differ between patients and controls. From a genetic point of view, there are several advantages of conducting this research in Iceland. First, the nation was an isolated island population up until the late twentieth century and is therefore relatively genetically homogenous [27]. Secondly, there is a reliable genealogy database containing records on approximately half of the adult population ever living in Iceland (716,000 individuals). Finally, access to population and medical records is excellent.

We hypothesized that schizophrenia patients would perform worse than healthy subjects on AS and SPEM. We expected at best moderate relationships between AS and SPEM performance. We also explored

within-session performance changes and we expected greater group differences in SPEM with increasing target velocity.

## Method

### Subjects

Demographic and clinical data are summarized in Table 1. Schizophrenia patients were recruited from the Division of Psychiatry at Landspítali-University Hospital in Reykjavik. This is the main psychiatric center in the country, where over 90% of all schizophrenia patients in Iceland are treated. The treating psychiatrists introduced the study to patients and obtained permission for researchers to contact them. Of 272 patients approached, 78 were excluded because they were too ill or because of significant co-morbidity. Seventy-four patients declined participation. One patient withdrew consent and one patient was excluded due to being of non-Icelandic descent. Data were collected from the remaining 118 patients. Diagnoses were confirmed by experienced psychiatrists according to Research Diagnostic Criteria (RDC) [75] using the Schedule of Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) [74].

Over 90% of patients were taking antipsychotic medications (14.0% typical, 51.3% atypical and 28.7% both typical and atypical). Approximately a third (28.7%) was on clozapine. The majority of patients were smokers (73.9%). Patients' current symptom levels were assessed using the positive and negative syndrome scale (PANSS) [41].

Healthy controls ( $N = 113$ ) were recruited from the local community. They were screened for history of axis I psychiatric disorders using the MINI Neuropsychiatric Interview [71]. Those who had first or second-degree relatives with schizophrenia or other psychotic disorder were excluded. Four controls were excluded because they had second-degree relatives with schizophrenia leaving 109 subjects for eye movement testing. Twenty-one percent of the controls were smokers.

Subjects with a history of neurological illness (e.g., stroke, seizures, Parkinson's disease), eye abnormalities, head injury (causing loss of consciousness), and substance abuse/dependence in the past 12 months were excluded. All participants were Icelandic, between 18 and 55 years of age and provided written, informed consent. The Icelandic Scientific Ethics Committee approved the study.

### Eye movements

Eye movements were recorded using infrared oculography (IRIS 6500; Skalar Medical BV, Delft, The Netherlands). Recordings were taken from the left eye and sampled at 500 Hz. Participants were seated in a chair 57 cm from a 17-in. monitor. Head movements were minimized using a chinrest. A white circular target ( $0.3^\circ$ ) was presented on a black background. Tasks were administered in the following order: prosaccade, AS, fixation and SPEM. Each task was preceded by a 3-point calibration trial ( $0^\circ$ ,  $\pm 12^\circ$ ).

Each prosaccade trial began with the target in the central location ( $0^\circ$ ) for a random duration of 1,000–2,000 ms. The target then stepped to one of four peripheral locations ( $\pm 6^\circ$ ,  $\pm 12^\circ$ ) where it remained for 1,000 ms. Each peripheral location was used 15 times, resulting in a total of 60 trials presented in random order. Four practice trials were carried out. Participants were instructed to keep their eyes on the target and follow it as accurately as possible.

In the AS task, the target movements were identical to those in the prosaccade task. However, on this occasion participants were instructed to look at the target while in the central position and redirect their gaze to the exact mirror image location of the target as soon as it moved to the side.

In the fixation task the target remained stationary in each of three locations for 20 s each. The first target location was randomly right or left ( $\pm 12^\circ$ ), the second location was central ( $0^\circ$ ), the third location was the peripheral location that had not been used in the first trial ( $\pm 12^\circ$ ), and the final location was again central ( $0^\circ$ ). Participants were instructed to focus their gaze on the target as accurately as possible.

For SPEM, a triangular target waveform was employed three times at  $12^\circ$ ,  $24^\circ$  and  $36^\circ/s$ , respectively. The target appeared in the central position ( $0^\circ$ ) and then moved horizontally to  $\pm 12^\circ$ , where it reversed abruptly and moved to the opposite side. The direction of the first ramp was random (right or left). The first ramp (from  $0^\circ$  to  $\pm 12^\circ$ ) was considered practice and was not included in the analyses. A total of 16.5 half-cycles were run at each target velocity. Participants were instructed to keep their eyes on the target as closely as possible.

For AS, prosaccade and fixation data analysis, Eyemap 2.1 (AMTech GmbH, Weinheim, Germany) was used. SPEM analysis was carried out using purpose-written routines in LabView. All data were scored blind to group status by one rater (MH) and confirmed by a second rater (UE). Inter- and intra-rater reliabilities were high ( $r = 0.95$ – $0.99$ ).

For AS it was not possible to analyze data from ten patients and four controls due to poor quality. This was either because of difficulties the subjects had in performing the task or due to excessive

**Table 1** Demographic and clinical data

|   | Patients $N = 118$ | Controls $N = 109$ |
|---|--------------------|--------------------|
| Age (mean [SD] years)                             | 41.2 [9.8]         | 40.8 [9.1]         |
| Sex (% males)                                     | 73.7%              | 62.4%              |
| Ethnicity (% native Icelandic)                    | 100%               | 100%               |
| Smoking (% smokers)                               | 73.9%              | 21.1%              |
| Age of illness onset (mean [SD] years)            | 22.9 [5.3]         | –                  |
| Illness duration (mean [SD] weeks)                | 940.6 [512.3]      | –                  |
| PANSS negative symptoms score (mean [SD])         | 20.5 [7.3]         | –                  |
| PANSS positive symptoms (mean [SD])               | 15.0 [5.7]         | –                  |
| PANSS general psych. (mean [SD])                  | 37.9 [10.7]        | –                  |
| PANSS total score (mean [SD])                     | 73.4 [20.8]        | –                  |
| Conventional antipsychotic medications (%)        | 16 (13.9)          | –                  |
| Atypical antipsychotic medications (%)            | 59 (51.3)          | –                  |
| Both conventional and atypical antipsychotics (%) | 33 (28.7)          | –                  |
| No medications (%)                                | 7 (6.1)            | –                  |
| Clozapine (%)                                     | 33 (28.7)          | –                  |

Note: PANSS Positive and negative syndrome scale

head movements and eye blinking during the task. Saccades were automatically detected on minimum amplitude ( $1^\circ$ ), velocity ( $30^\circ/s$ ) and latency (100 ms) criteria. The rater individually categorized saccades that had been identified by the software.

A correct AS trial occurred when the participant performed a primary saccade in the direction opposite to the peripheral target. A reflexive error was counted when the participant performed a primary saccade towards the peripheral target. A corrective saccade was counted when an error was followed by a saccade in the opposite direction.

A number of dependent variables were derived. The reflexive error rate reflects the percentage of error trials over the total number of valid trials. Latency of correct AS was defined as the time (ms) from target appearance to saccade initiation. AS amplitude gain was calculated as the primary saccade amplitude divided by target amplitude multiplied by 100. Spatial accuracy of correct AS was assessed using the measure of spatial error. Spatial error was obtained by calculating, for each saccade, the percentage of residual error. This is obtained by subtracting the target amplitude from the saccade amplitude and dividing the result by the target amplitude calculated residual error. The absolute value of this term reflects the residual error and is then averaged across all saccades and multiplied by 100. A perfectly accurate saccade thus attracts a spatial error score of 0% and higher scores denote greater spatial error. The percentage of corrective saccades (over the total number of error trials) was also established. For latency, amplitude gain, and spatial error the individual standard deviation was calculated as a measure of intra-individual performance variability.

Finally, these dependent variables were calculated for the total 60 trials as well as for four sub-segments of equal length including approximately 15 trials each. This was done in order to address systematic within-session performance changes.

Prosaccade data from five patients and one control were not used due to poor quality. Prosaccade latency (ms), amplitude gain (%) and spatial error (%), were calculated based on the same criteria as in the AS task. Incorrect prosaccades (subject not following target) were counted. As for the AS task the means and individual standard deviations of these dependent variables were determined for the 60 trials and also for each of four sub-segments of equal length.

SPEM data from two patients and one control for velocity gain and six patients for saccade frequency were not analyzed due to poor quality. Pursuit velocity gain data from one control was not correctly obtained. Velocity gain was calculated by dividing mean eye velocity by target velocity. This was done for sections of pursuit (excluding saccades and eye blinks) during the central half of each ramp excluding the first and last quarters to avoid pursuit initiation and slowing at target turnarounds. These scores were time-weighted and subsequently averaged. Saccades that occurred during SPEM were automatically identified on the basis of minimum amplitude ( $1^\circ$ ) and velocity ( $30^\circ/s$ ). The number of saccades was established at each target velocity and divided by the duration of pursuit at each target velocity to yield measures of saccadic frequency (N/s). Velocity gain and saccade frequency was also calculated for four sub-segments of equal length (approximately four half-cycles each).

For fixation, three patients and one control had poor quality data, which were not analyzed. The frequency of saccades during fixation (N/s) was calculated based on the previously described criteria of minimum amplitude and velocity. Saccade frequency was also calculated for each of the four equally long sub-segments representing the two peripheral and two central target locations.

### Statistical analysis

Statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS) version 11 (SPSS Inc. Chicago, IL, USA). Level of significance was set to  $P < 0.05$ . Outliers were identified using box plots and all extreme values (more than 3 box-lengths from edge of box) were removed. Distributions of oculomotor variables were assessed for normality using the

skewness index. If positively ( $>1$ ) or negatively ( $<1$ ) skewed, variables were transformed using square root or square transformations, respectively.

Group differences on oculomotor variables were investigated using analysis of variance (ANOVA) with each oculomotor variable as dependent variable and Group (patients vs. controls) as independent variable.

Relationship between AS and SPEM variables was evaluated using Pearson correlation. Correlations were first carried out in the combined sample (patients, controls) and then in each group separately.

Internal consistency of task performance was measured using Cronbach's coefficient alpha [14]. Cronbach's coefficient alpha is an index of the average correlation among all items of a psychometric instrument. The alpha coefficient ranges from 0 to 1 and the higher the score, the more reliable the instrument is. The coefficient was calculated using sub-scores of eye movement recordings from the four equally long consecutive sub-segments of each task.

Within-session performance changes were investigated using repeated measures ANOVA for each eye movement variable with TaskDuration (four time segments described above) as within-subject factor and Group (patients, controls) as between-subject factor. Mauchly's test was considered for each ANOVA to evaluate assumptions of sphericity. If assumptions of sphericity were violated, Greenhouse-Geisser epsilon corrections of degrees of freedom were used.

Repeated measures ANOVA was used for evaluating effects of target velocity on SPEM and Velocity-by-Group interactions with velocity ( $12^\circ$ ,  $24^\circ$  and  $36^\circ/s$ ) as within-subjects factor and Group (patients, controls) as between subjects factor.

Relationships between oculomotor variables and PANSS scores, age of illness onset and illness duration were analyzed using Pearson correlation. Effects of smoking and type of antipsychotic medication on eye movement variables were compared using ANOVA with Smoking Status (smokers, non-smokers) and Antipsychotic (typical, atypical, both, none) as independent variables.

## Results

Data from 118 patients (mean age = 41.2, standard deviation = 9.80, 73.7% male) and 109 controls (mean age = 40.8, standard deviation = 9.10, 62.4% male) were analyzed. The groups were matched on sex ( $\chi^2 = 2.61$ ;  $df = 1$ ;  $P = 0.11$ ) and age ( $t = 0.30$ ;  $df = 221$ ;  $P = 0.77$ ) (Table 1). Descriptive statistics and effect sizes for oculomotor variables are shown in Table 2. Extreme values (outliers) were removed from the dataset for prosaccade: two patients and two controls, AS: two patients and two controls, SPEM: one patient and four controls and fixation: ten patients and three controls.

The following variables were skewed (skewness index): AS latency standard deviation (SD) (1.49), AS spatial error SD (1.64), AS correction ( $-3.05$ ), prosaccade spatial error (1.30), prosaccade spatial error SD (1.24), SPEM  $36^\circ/s$  saccade frequency (1.44) and fixation saccade frequency (1.92). Inferential statistical analyses were done on transformed variables. Table 2 shows the untransformed data.

### Prosaccade

The average rate of incorrect prosaccades (subject not following target) was only 0.47% (SD = 1.32) for pa-



**Table 2** Descriptive statistics and effect sizes of eye movement variables

| Variable                             | Patients       | Controls       | Effect size (d) |
|--------------------------------------|----------------|----------------|-----------------|
| Prosaccade                           | <i>N</i> = 113 | <i>N</i> = 108 |                 |
| Error rate (%)                       | 0.47 (1.3)     | 0.22 (0.8)     | 0.23            |
| Amplitude gain (%)                   | 92.2 (11.3)    | 94.5 (9.4)     | -0.22           |
| Variability of amplitude gain (%)    | 17.7 (7.2)     | 14.8 (5.4)     | 0.46            |
| Latency (ms)                         | 187.8 (29.6)   | 177.3 (20.4)   | 0.41            |
| Variability of latency (ms)          | 38.2 (13.8)    | 30.4 (9.4)     | 0.66            |
| Spatial error (%)                    | 17.6 (8.1)     | 14.5 (5.5)     | 0.47            |
| Variability of spatial error (%)     | 11.9 (4.9)     | 9.7 (3.6)      | 0.51            |
| Antisaccade                          | <i>N</i> = 108 | <i>N</i> = 105 |                 |
| Error rate (%)                       | 60.4 (21.7)    | 29.8 (20.2)    | 1.46            |
| Correction rate (%)                  | 91.5 (11.5)    | 97.8 (5.5)     | -0.70           |
| Amplitude gain (%)                   | 92.9 (29.2)    | 106.6 (28.5)   | -0.47           |
| Variability of amplitude gain (%)    | 46.5 (19.3)    | 46.7 (18.8)    | -0.01           |
| Latency (ms)                         | 330.8 (77.0)   | 292.1 (41.5)   | 0.63            |
| Variability of latency (ms)          | 74.6 (37.3)    | 55.7 (19.3)    | 0.64            |
| Spatial error (%)                    | 43.7 (13.2)    | 40.3 (14.1)    | 0.25            |
| Variability of spatial error (%)     | 29.8 (14.1)    | 30.0 (13.5)    | -0.01           |
| Fixation                             | <i>N</i> = 115 | <i>N</i> = 108 |                 |
| Frequency of saccades (N/s)          | 0.09 (0.10)    | 0.04 (0.07)    | 0.58            |
| Smooth pursuit                       | <i>N</i> = 116 | <i>N</i> = 108 |                 |
| Velocity gain at 12°/s (%)           | -92.5 (10.8)   | -96.1 (8.2)    | -0.38           |
| Velocity gain at 24°/s (%)           | -83.8 (15.3)   | -92.9 (11.9)   | -0.66           |
| Velocity gain at 36°/s (%)           | -66.3 (20.1)   | -79.7 (15.7)   | -0.74           |
| Frequency of saccades at 12°/s (N/s) | 1.53 (0.57)    | 1.16 (0.52)    | 0.68            |
| Frequency of saccades at 24°/s (N/s) | 2.35 (0.80)    | 1.87 (0.77)    | 0.61            |
| Frequency of saccades at 36°/s (N/s) | 3.00 (0.99)    | 2.60 (0.81)    | 0.44            |

Note: Data represent means (SD)

tients and 0.22% (SD = 0.79) for controls showing that subjects were generally able and willing to perform the task.

There were significant between-group differences for prosaccade latency ( $F[1,214] = 9.94$ ;  $P = 0.002$ ) and spatial error ( $F[1,214] = 9.86$ ;  $P = 0.002$ ). Patients had significantly longer saccade latency and greater spatial error than controls. There were also significant group differences in the intra-individual variability (SD) of prosaccade amplitude gain ( $F[1,214] = 11.38$ ;  $P = 0.001$ ), latency ( $F[1,214] = 23.89$ ;  $P < 0.001$ ) and spatial error ( $F[1,214] = 12.61$ ;  $P < 0.001$ ). Patients had larger individual performance variability on these variables. No significant difference was seen for prosaccade amplitude gain ( $F[1,214] = 1.41$ ;  $P = 0.27$ ).

Internal consistency of performance was high for all variables in both patients and controls (all Cronbach's alpha > 0.85).

There was a significant TaskDuration effect on prosaccade amplitude gain ( $F[3,191] = 17.05$ ;  $P < 0.001$ ) but no TaskDuration-by-Group interaction ( $P = 0.21$ ). The effect was linear with gain scores decreasing (i.e., becoming more hypometric) over the 4 time segments ( $P < 0.001$ ).

There was a TaskDuration effect ( $F[3,191] = 4.88$ ;  $P = 0.002$ ) and a TaskDuration-by-Group interaction ( $F[3,191] = 2.77$ ;  $P = 0.04$ ) on prosaccade latency. The TaskDuration effect was a quadratic effect with latency decreasing after the first quarter and then increasing ( $P = 0.004$ ). There was also a cubic effect ( $P = 0.01$ )

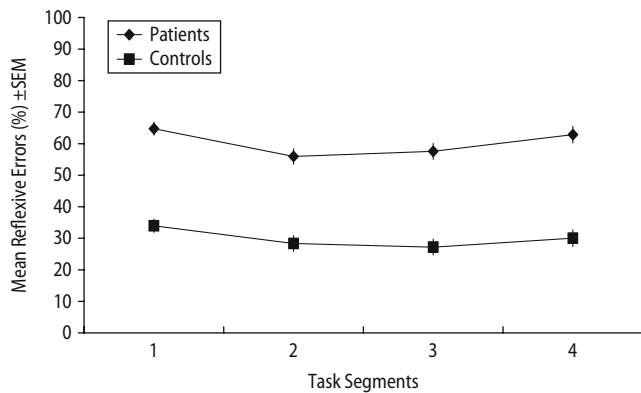
with latency decreasing again in the last quarter in patients. The interaction was due to a general decrease in latency over time in controls ( $P = 0.01$ ) whereas in patients latency increased in the last quarter.

There was a significant TaskDuration effect on prosaccade spatial error ( $F[3,191] = 11.43$ ;  $P < 0.001$ ) but no TaskDuration-by-Group interaction ( $F[3,191] = 0.22$ ;  $P = 0.84$ ). A linear increase in spatial error in the third and fourth quarters was found in both groups ( $P < 0.001$ ) and also a small cubic effect with an initial small decrease in the second quarter and then a steep increase ( $P = 0.02$ ). There were no significant TaskDuration effects on the variability of prosaccade latency, amplitude gain or spatial error (all  $P > 0.05$ ).

### ■ Antisaccade

The average rate of corrections (initiation of an AS after an error) was 97.8% (SD = 5.5) for controls and 91.5% (SD = 11.5) for patients.

Significant group differences were present for reflexive error rate ( $F[1,208] = 106.91$ ;  $P < 0.001$ ), amplitude gain ( $F[1,208] = 8.55$ ;  $P = 0.004$ ), latency ( $F[1,208] = 19.76$ ;  $P < 0.001$ ) and latency SD ( $F[1,208] = 20.49$ ;  $P < 0.001$ ). Patients displayed significantly more reflexive errors, reduced (i.e., hypometric) amplitude gain, and longer and more variable latency than controls. Spatial error ( $F[1,208] = 3.58$ ;  $P = 0.06$ ), spatial error



**Fig. 1** Antisaccade reflexive error rate by group and task segment. Each task segment corresponds to 15 consecutive trials

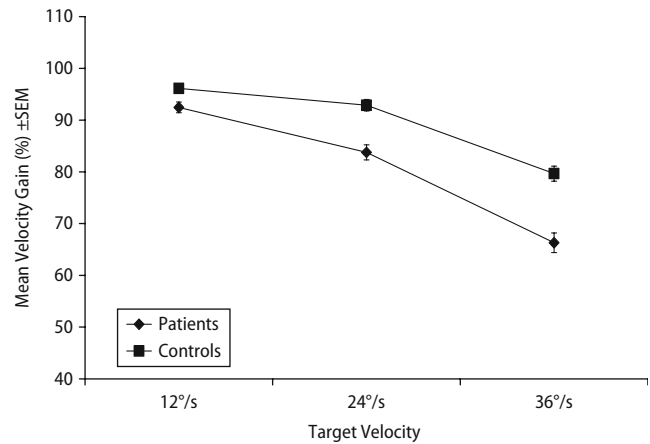
SD ( $F[1,208] = 0.032$ ;  $P = 0.86$ ), and amplitude gain SD ( $F[1,208] = 0.01$ ;  $P = 0.92$ ) did not differ significantly between groups.

Internal consistency was high for all AS variables in both patients and controls ( $>0.77$  and  $>0.80$ , respectively) except for spatial error in patients (0.38).

There was a significant TaskDuration effect on reflexive error rate ( $F[3,198] = 12.09$ ;  $P < 0.001$ ) but no TaskDuration-by-Group interaction ( $F[3,198] = 1.01$ ;  $P = 0.39$ ). The effect was quadratic with error rates decreasing in the second quarter and then increasing in the third and fourth quarters ( $P < 0.001$ ) (Fig. 1). A significant TaskDuration effect was found on AS amplitude gain ( $F[3,175] = 5.57$ ;  $P = 0.001$ ) but no TaskDuration-by-Group interaction ( $F[3,175] = 1.49$ ;  $P = 0.22$ ). The effect was mainly linear with gain decreasing with time ( $P = 0.006$ ). There was also a quadratic effect ( $P = 0.02$ ) with an increase in gain in the fourth quarter in patients. A TaskDuration effect was found on AS latency ( $F[3,171] = 2.73$ ;  $P = 0.049$ ) and there was also a TaskDuration-by-Group interaction ( $F[3,171] = 2.86$ ;  $P = 0.04$ ). The main effect was linear with latency increasing with time ( $P = 0.04$ ). The interaction was due to a cubic effect in patients with latency increasing in the second quarter, decreasing in the third and finally increasing again in the fourth quarter ( $P = 0.01$ ). There were no significant TaskDuration effects on spatial error ( $F[3,175] = 1.32$ ;  $P = 0.27$ ) or the variability of gain ( $F[3,169] = 1.88$ ;  $P = 0.14$ ), latency ( $F[3,169] = 0.34$ ;  $P = 0.79$ ) and spatial error ( $F[3,169] = 1.49$ ;  $P = 0.22$ ).

### ■ Smooth pursuit

A repeated measures ANOVA showed a significant main effect of Velocity on SPEM gain ( $F[2,444] = 291.32$ ;  $P < 0.001$ ), a significant effect of Group ( $F[1,222] = 29.64$ ;  $P < 0.001$ ), and a significant Velocity-by-Group interaction ( $F[2,444] = 14.69$ ;  $P < 0.001$ ). These effects indicate that gain deteriorated with velocity, patients had lower pursuit gain than



**Fig. 2** Smooth pursuit velocity gain by group and target velocity

controls and group differences increased with increasing target velocity (Fig. 2).

For SPEM saccade frequency there was a significant effect of Velocity ( $F[2,430] = 422.56$ ;  $P < 0.001$ ) a significant effect of Group ( $F[1,220] = 23.77$ ;  $P < 0.001$ ), but no significant Velocity-by-Group interaction ( $F[2,440] = 0.27$ ;  $P = 0.74$ ). This result shows that saccade frequency increased with target velocity and that patients made more saccades than controls but the group difference was not affected by target velocity.

Internal consistency of performance was high for all variables in both groups ( $>0.85$ ).

Analysing effects of TaskDuration on SPEM, no significant effect was found on velocity gain at 12°/s ( $F[3,222] = 2.15$ ;  $P = 0.11$ ) but there was a significant effect at 24°/s ( $F[3,223] = 3.70$ ;  $P = 0.015$ ) and 36°/s ( $F[3,224] = 5.18$ ;  $P = 0.002$ ). The effect at 24°/s was quadratic with velocity gain increasing in the second quarter and then decreasing ( $P = 0.02$ ). At 36°/s the effect was mainly cubic with velocity gain increasing in the second quarter, decreasing in the third and finally increasing in controls in the fourth quarter ( $P = 0.001$ ). There was also an overall linear decrease with time ( $P = 0.02$ ). There was a TaskDuration-by-Group interaction only at 36°/s ( $F[3,224] = 3.51$ ;  $P = 0.02$ ). This interaction was both quadratic ( $P = 0.03$ ) and linear ( $P = 0.04$ ) due to an increase in velocity gain in the second quarter and a decrease in the third and fourth quarters in patients.

A significant TaskDuration effect was found on saccade frequency during SPEM at all three target velocities (all  $P < 0.001$ ) but no TaskDuration-by-Group interactions (all  $P > 0.05$ ). The TaskDuration effect was linear at all three velocities with saccade frequency decreasing over the duration of the task (all  $P < 0.001$ ). There was also a quadratic effect with an increase in saccade frequency in the fourth quarter in controls at 12°/s ( $P = 0.002$ ) and 24°/s ( $P < 0.001$ ) and a small cubic effect at 12°/s ( $P = 0.03$ ) due to an increase in the third quarter in patients.

## ■ Fixation

Patients made significantly more saccades during fixation than controls ( $F[1,209] = 17.72$ ,  $P < 0.001$ ). Internal consistency of performance was high for both patients and controls ( $>0.85$ ). No significant Task-Duration effect was found on saccade frequency ( $F[3,225] = 0.45$ ;  $P = 0.66$ ).

## ■ Relationship between AS and SPEM

There were a number of moderate but statistically significant correlations between AS and SPEM measures in the combined sample. Higher AS reflexive errors were associated with lower SPEM velocity gain at  $24^\circ/s$  ( $r = -0.27$ ;  $P < 0.001$ ) and  $36^\circ/s$  ( $r = -0.34$ ;  $P < 0.001$ ). The error rate was also associated with increased SPEM saccade frequency at all target velocities (all  $r > 0.23$  and  $P < 0.001$ ). Increased AS latency was associated with decreased SPEM velocity gain at all target velocities (all  $r < -0.25$  and  $P < 0.001$ ) and higher saccade frequency at  $12^\circ/s$  ( $r = -0.26$ ;  $P < 0.001$ ) and  $24^\circ/s$  ( $r = -0.13$ ;  $P = 0.03$ ). AS spatial error correlated with SPEM velocity gain at  $36^\circ/s$  ( $r = -0.15$ ;  $P = 0.04$ ) and saccade frequency at  $12^\circ/s$  ( $r = 0.15$ ;  $P = 0.03$ ) indicating that less accurate AS performance was associated with lower velocity gain and increased saccade frequency during SPEM. There were no significant correlations between AS amplitude gain and SPEM variables.

In patients, longer AS latency was associated with decreased SPEM velocity gain at all target velocities (all  $r < -0.22$ ; all  $P < 0.02$ ). No other correlations were significant.

In controls, increased AS reflexive error rate was associated with lower SPEM velocity gain at  $36^\circ/s$  ( $r = -0.22$ ;  $P = 0.028$ ) and with higher saccade frequency at  $24^\circ/s$  ( $r = 0.20$ ;  $P = 0.047$ ) and  $36^\circ/s$  ( $r = 0.20$ ;  $P = 0.038$ ). Longer AS latency was associated with lower SPEM velocity gain at all three target velocities (all  $r < -0.20$ ; all  $P < 0.05$ ) and with higher saccade frequency at  $12^\circ/s$  ( $r = 0.27$ ;  $P = 0.006$ ).

## ■ Relationships with clinical variables

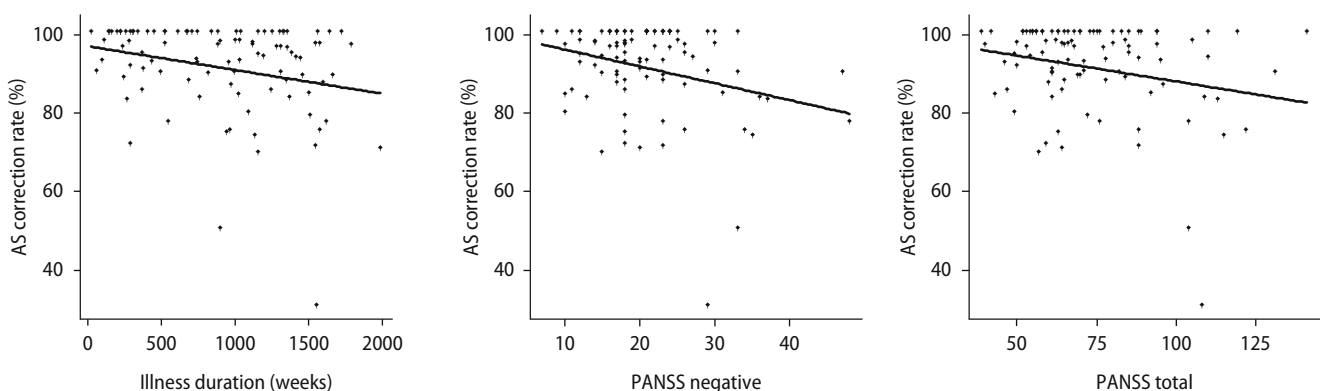
Patients' age at onset of illness did not correlate with any eye movement variable (all  $P > 0.05$ ). While controlling for age, duration of illness correlated with AS correction rate ( $r = -0.27$ ;  $P = 0.008$ ), SPEM velocity gain at  $24^\circ/s$  ( $r = -0.36$ ;  $P < 0.001$ ) and  $36^\circ/s$  ( $r = -0.34$ ;  $P < 0.001$ ) and number of fixation saccades ( $r = 0.23$ ;  $P = 0.02$ ). Longer duration of illness was associated with lower AS correction rate (see Fig. 3), lower SPEM gain and a larger number of fixation saccades.

AS correction rate was the only eye movement variable, which correlated significantly with PANSS scores (negative scale score;  $r = -0.29$ ,  $P = 0.005$ , and total score;  $r = -0.24$ ,  $P = 0.02$ ); patients with higher negative and total PANSS scores had a lower correction rate (see Fig. 3).

ANOVA of patients taking different antipsychotic medications (typical, atypical, both, none) did not show any significant effects of medication type on eye movements (all  $P > 0.12$ ). Due to the unique pharmacology of clozapine patients taking the drug were compared to those who were not. No significant effect of clozapine was found (all  $P > 0.07$ ). There were no effects of smoking (all  $P > 0.1$ ).

## Discussion

This is a study of eye movements in a large sample of schizophrenia patients and healthy controls belonging to the genetically homogenous population of Iceland. It is the largest single centre case-control study examining both AS and SPEM. The main purpose was to confirm and validate the well-known observation of eye movement deficits in schizophrenia. Additionally, we examined the relationship between AS and SPEM and investigated measures of systematic and random performance variability. The next step of this work is to study in this unique Icelandic sample the relationship between eye movement endophenotypes and recently described schizophrenia risk genotypes [26, 67].



**Fig. 3** Relationship between antisaccade (AS) correction rate and three clinical variables: illness duration ( $r = -0.27$ ;  $P = 0.008$ ), PANSS negative syndrome scale ( $r = -0.29$ ;  $P = 0.005$ ) and PANSS total score ( $r = -0.24$ ;  $P = 0.02$ )

On the AS task patients were found to have significantly higher error rate, lower amplitude gain and longer and more variable latency than healthy subjects. During SPEM, velocity gain was significantly lower and saccade frequency higher. The largest effect size in the study was observed for reflexive errors in the AS task.

This present study replicates all previous studies of AS in schizophrenia, which have found increased rates of reflexive error rates in schizophrenia compared to healthy controls [5, 35]. The study strongly supports that schizophrenia patients have difficulty inhibiting reflexive saccades during the AS task, which may be related to lack of inhibitory control in prefrontal cortex [58] or an impaired ability to appropriately activate a volitional AS response [66]. The finding of longer latency of correct AS in patients than healthy controls, replicates what a number of previous studies have demonstrated [23, 37, 44] and suggests a deficit in volitional response generation [65]. Additionally, patients had increased standard deviations of AS latencies, in agreement with recent evidence of increased intra-individual variability in schizophrenia [36]. Interestingly, however, variability of spatial accuracy measures (AS amplitude gain SD and AS spatial error SD) was not significantly increased compared to controls, suggesting that the deficit in intra-individual performance variability on the AS task in schizophrenia may be specific to temporal but not spatial variability of responses.

Several previous studies have found decreased AS amplitude gain in patients with schizophrenia [37, 59]. The ability to match saccade amplitude to target amplitude depends on sensorimotor processes involved in transforming the covertly encoded visual target location into a motor output, a process that requires a shift in signal processing from intraparietal sulcus to frontal eye field [55]. Although patients in the present study were found to have significantly lower amplitude gain than controls the difference was due to the fact that the controls had a mean gain of  $-107\%$  (overshooting) and the patients had a mean gain of  $-93\%$  (undershooting). The mean gain scores of the two groups were therefore equally far (in opposite directions) from the perfect gain score of  $-100\%$ . The measure of spatial error, which provides a spatial accuracy score independent of hypo- or hypermetria, consequently did not differ between groups. It is unclear what the primary AS spatial accuracy deficit in schizophrenia is; however, the present data in conjunction with previous studies [17, 19, 29, 34, 37] suggest that volitional saccades are most commonly of smaller amplitudes compared to controls.

Concerning the prosaccade task, patients had significantly longer latency, higher spatial error and more variable amplitude gain, latency and spatial error than controls. Previous studies of prosaccade eye movements in schizophrenia have provided

inconsistent findings. Most studies have found no significant differences in prosaccade latency and spatial accuracy between patients and controls, suggesting that basic saccadic mechanisms are intact in schizophrenia [11, 13, 37, 46, 76]. However, other studies have demonstrated prolonged latency [20, 53] and reduced accuracy [9, 69] in patients.

Patients also made significantly more saccades during fixation than controls. Previous studies of visual fixation in schizophrenia have obtained conflicting results. While some studies have found fixation to be normal [24, 43], others have not [1, 15]. The contradictory findings of prosaccade and fixation studies in schizophrenia may possibly be attributed to heterogeneity in subject populations and methods of data analysis between studies.

On the SPEM task patients had significantly lower velocity gain and higher saccade frequency than controls at all three target velocities, replicating what most studies using similar methods have found [22, 34, 63, 78]. Recent fMRI studies have shown that schizophrenia patients have decreased activity in extraretinal motion processing pathways during SPEM [31] and also compensatory activity increase in the prefronto-thalamo-cerebellar circuit [61].

Although both AS and SPEM deficits have been proposed as endophenotypes in schizophrenia and both have been related to frontal brain dysfunctions [6] it has not been established whether they reflect the same risk genes. Only a few studies have investigated the association between AS and SPEM measures and results have been inconsistent. While some have found higher reflexive error rate on the AS task to correlate with worse performance on the SPEM task [56, 68, 70] others have not [34, 62]. In the present study only moderate associations were found between the two tasks. Associations that were observed in the combined group were not always significant in each group. We would like to argue therefore that the two measures are likely to tap largely separate sources of genetic risk.

All oculomotor variables displayed very good internal consistency, except AS spatial error in patients. This finding is similar to what has previously been reported in studies of AS and SPEM in healthy subjects [18] and SPEM in schizophrenia patients [8]. The high internal consistency of these measures indicates that inter-individual differences in performance are consistent throughout the session and that these can be reliably measured.

Some systematic within-session changes in performance were observed in both patients and controls. The AS reflexive error rate first decreased and then increased in both groups, which may indicate that it took subjects some time to adapt to the task and improve, but towards the end fatigue was starting to have an effect. A similar effect of time on reflexive error rate was found in a study of healthy males [73]. The present study extends these findings by showing



that this effect is also present in schizophrenia patients, thus representing a process that may be unimpaired in schizophrenia.

AS amplitudes became smaller over time in both groups, indicating that AS hypometria might be related to task duration. This suggests that longer task duration may increase demands on sensory-motor pathways involved in processing the target location information into a motor response. Effects on saccade amplitudes were previously described [60]. Mosimann et al. found that making saccades volitional through instructions led to hypometric amplitudes. Together, this pattern suggests that an increased volitional component (or effort) may be related to saccade hypometria; whether these factors account for the hypometric antisaccade amplitudes in schizophrenia patients and their relatives [17, 19] remains to be investigated further.

There was a moderate increase in AS latency with time in both groups. This increase in reaction time may have been related to fatigue.

Similar to AS, prosaccade amplitudes decreased with time. The TaskDuration effect on prosaccade latency was quadratic with a shorter reaction time in the second segment, which may have been due to effects of practice, followed by a slower response possible because of fatigue. There was a TaskDuration-by-Group interaction due to a linear decrease in latency in controls indicating a stronger improvement effect in controls.

SPEM velocity gain generally decreased with time. There was an interaction effect at the fastest velocity because of an increase in gain in the second quarter but then a linear decline in patients. This effect may be ascribed to increasing fatigue or boredom with time, which affected patients more than controls. Saccade frequency decreased with time in both groups, which may be a fast learning effect allowing subjects to optimally stabilize their gaze on the target. A comparable reduction in catch-up saccades was found in healthy subjects in a study by Ettinger et al. [18].

Overall, therefore, some within-session performance changes were found in both patients and controls, which are most likely related to effects of practice and fatigue. These changes were for the most part similar in patients and controls and the only variables showing TaskDuration-by-Group interactions were prosaccade and AS latency and SPEM gain at the fastest target velocity; for these variables patients displayed greater variability in performance over time than controls.

SPEM performance deteriorated with increasing target velocity in both groups and for velocity gain this effect was significantly stronger in patients than controls. A similar interaction was found in a previous study comparing velocity gain in chronic schizophrenia patients, first episode patients and healthy controls at four target velocities (10, 20, 30 and 36°/s)

[32]. The present findings therefore support previous suggestions of a motion processing deficit in schizophrenia [10] and add to the evidence that the difference in SPEM velocity gain between patients and controls increases with increasing target velocity.

In the present study only AS correction rate correlated weakly with symptom scores. Higher total and negative scale scores were associated with lower correction rate. An association between negative symptoms and performance, on both AS [12, 80] and SPEM [38, 57, 77] was demonstrated previously. However, there are also several studies, which have not found this association [21, 25, 37, 64].

Patients' age at illness onset did not correlate with eye movement performance. However, longer duration of illness was associated with lower correction rate on the AS task, decreased SPEM velocity gain and increased rate of saccades during fixation. Although most previous studies have not found a significant association between SPEM and duration of illness or number of hospitalizations [21, 38, 42], there are studies which have found worse SPEM with higher age at onset of psychosis [72, 77] and longer duration of illness [52]. No relationship was found between AS and SPEM performance and type of antipsychotic medication.

The only eye movement measure which was associated with more than one clinical variable was the AS correction rate. The fact that there were few and only weak associations between clinical variables and other measures of eye movement performance suggests that these oculomotor deficits are likely to represent relatively state-independent endophenotypic markers of schizophrenia.

No effects of smoking on eye movements were observed in this study. Several recent studies have shown that nicotine use improves performance on several neurocognitive tasks including AS and SPEM [16]. In those studies nicotine administration was experimentally manipulated and eye movements were measured within minutes of nicotine use and following abstinence.

In conclusion, this study confirms the existence of significant deficits in AS and SPEM in schizophrenia in a large sample. Only moderate relationships were found between AS and SPEM performance. Internal consistency was high for all measures and similar within-session performance changes were observed in both groups for most variables. Most clinical variables did not correlate with AS and SPEM performance. These eye movement measures can therefore function as valid endophenotypes in future studies of potential schizophrenia risk genotypes in the genetically homogenous Icelandic population.

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