Neurophysiological correlates of the pathway to the early stages of psychosis
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INCREASED SACCADIC RATE DURING SMOOTH PURSUIT EYE MOVEMENTS IN PATIENTS AT ULTRA HIGH RISK FOR DEVELOPING A PSYCHOSIS

Mirjam J. van Tricht, Dorien H. Nieman, Lo J. Bour, Thijs Boerée, Johannes H. Koelman, Lieuwe de Haan, Don H. Linszen

ABSTRACT

Abnormalities in eye tracking are consistently observed in schizophrenia patients and their relatives and have been proposed as an endophenotype of the disease. The aim of this study was to investigate the performance of patients at Ultra High Risk (UHR) for developing psychosis on a task of smooth pursuit eye movement (SPEM). Forty-six UHR patients and twenty-eight age and education matched controls were assessed with a task of SPEM and psychiatric questionnaires. Our results showed that both the corrective and non-corrective saccadic rates during pursuit were higher in the UHR group. There were however no differences in smooth pursuit gain between the two groups. The saccadic rate was related to positive UHR symptoms. Our findings indicate that abnormalities in SPEM are already present in UHR patients, prior to a first psychotic episode. These abnormalities occur only in the saccadic system.
1. INTRODUCTION

Abnormalities in smooth pursuit eye movements (SPEM) and antisaccade tests are consistently observed in schizophrenia (Holzman, 1987; Levy et al., 2000; Nieman et al., 2000; O’Driscol & Callahan, 2008; Slaghuis et al., 2007; Zanelli et al., 2005) and have also been reported in relatives of patients with schizophrenia (Ettinger et al., 2003; Holzman et al., 1978; Kathmann et al., 2003; O’Driscol et al., 1998; Siever et al., 1990; Sporn et al., 2005). Therefore, eye tracking deficits have been proposed as markers of a genetic vulnerability for schizophrenia, thus as an identifier of the underlying genetic abnormalities of the disorder (Haraldsson et al., 2009; Holahan & O’Driscol, 2005; Holzman, 1987; Lee & Williams, 2000).

In an attempt to identify individuals with an increased risk of developing a psychosis, the term ‘Ultra High Risk’ (UHR) has been suggested (McGorry et al., 2003; Yung et al., 2007). This term is used to indicate a sub threshold syndrome that can be regarded as a risk factor for subsequent psychosis within the next year. Psychosis is however not inevitable. UHR patients show abnormalities on neuro-imaging (Job et al., 2003; Pantelis et al., 2007; Takahashi et al., 2009), neurophysiological (Bramon et al., 2008; Frommann et al., 2008; Ozgürdal et al., 2008; van der Stelt et al., 2005) and neuropsychological (Brewer et al., 2005; Niendam et al., 2007) examinations before a possible psychotic onset, indicating a pre-existing vulnerability to psychosis. To our knowledge, no studies have yet investigated SPEM in patients at UHR of developing a psychosis.

SPEM is the ability to track a moving object with the eyes while keeping that object on or near the fovea (Flechtner et al., 1997; Zanelli et al., 2005). Quantitative parameters for SPEM task performance are usually divided into smooth pursuit gain and the saccadic rate. A reduced pursuit gain, i.e. where pursuit velocity is less than target velocity, has frequently been reported in schizophrenia patients. Additionally, many (Kathmann et al., 2003; Lee and Williams, 2000) but not all (Friedman et al., 1995; Hutton et al., 2001) studies reported increased rates of corrective and non-corrective saccades during pursuit.

The underlying cerebral mechanism of SPEM is complex; many cortical and subcortical areas are involved (for an overview see Leigh & Zee, 2006; Lencer & Trillenberg, 2008). The medial superior temporal (MST) area of V5 plays an important role in the initiation, generation and maintenance of SPEM (Lencer & Trillenberg, 2008; Nuding et al., 2008). In addition, frontal areas, including the frontal eye fields (FEF), the supplementary eye field (SEF), the prefrontal and the premotor cortex and the anterior cingulate are crucial in SPEM. The FEF are thought to be involved in anticipating and predicting the stimulus movement in predicatively moving stimuli (Leigh & Zee, 2006; Nagel et al., 2008), and through inhibition of the superior colliculus in suppressing non-purposive saccades (Shaffer et al., 2003), whereas other frontal areas are responsible for suppressing unwanted saccades, learning and motor planning (Lencer et al., 2004; Lencer & Trillenberg, 2008; Levin, 1984; McDowell et al., 2002; Pierrot-Deseilligny et al., 2004; Ross et al., 1998). Parietal areas have also been proposed to be related to the
suppression of saccades during pursuit (Lencer & Trillenberg, 2008). Finally, the basal ganglia are an important source in the control of non-reflexive saccades, for example by inhibiting the superior colliculus (Shaffer et al., 2003).

In schizophrenia as well as high-risk groups for psychotic disorders (e.g. relatives of schizophrenia patients), imaging studies have revealed brain abnormalities in (pre)frontal lobes (DeLisi et al., 2006; Fusar-Poli et al., 2007; Gogtay et al., 2007; Lacerda et al., 2007). Similar neuroanatomical abnormalities have been demonstrated in UHR patients (Morey et al., 2005; Wood et al., 2008). Given the importance of the frontal lobe, in particular the FEF and SEF, in the prediction and suppression of unwanted saccades during SPEM, abnormalities in smooth pursuit can also be expected in patients at UHR for developing a psychosis.

Abnormalities in SPEM task performance may also be related to psychiatric symptoms in UHR groups, although this relation is still relatively unclear. For instance, studies in schizophrenic patients have reported associations between SPEM and both positive and negative symptoms (Roitman et al., 1997; Solomon et al., 1987). SPEM dysfunction has also been associated with disorganization symptoms (Lee et al., 2001).

The primary aim of the present study was to assess SPEM task performance in a group of subjects at UHR for developing a first psychotic episode. As discussed previously, SPEM dysfunction has been proposed to be a vulnerability marker of schizophrenia. If this is indeed the case, SPEM impairments should also be present in UHR patients before the transition to a first psychotic episode. We expect UHR patients to show impairments on our SPEM task. In line with the SPEM abnormalities reported in schizophrenia patients and their relatives, as discussed above, we expect to find a decreased SPEM gain and an increased rate of both corrective and non-corrective saccades in our UHR group compared to a group of healthy controls. Exploratively, the relationship between SPEM performance and UHR symptoms was evaluated.

2. METHODS
2.1. Participants
2.1.1. UHR group
 Forty-six patients (10 women) with an UHR for developing psychosis were included (Table 1). Thirty-five of these UHR subjects have been described in a previous study of our group, investigating antisaccade abnormalities in an UHR sample (Nieman et al., 2007). The UHR patients were referred to the Academic Medical Center (AMC), Amsterdam, the Netherlands, by psychiatrists and psychologists for a second opinion with the question whether a psychotic development was taking place. The inclusion criteria for the ‘Ultra High Risk’ group were: age between 15 and 35 years, and belong to one or more of the following four groups (as described in McGorry et al., 2003; Yung et al., 2007):
Genetic risk in combination with reduced functioning: subjects who have a first degree relative with a psychotic disorder, or who themselves have a schizotypal personality disorder and who have experienced a significant decrease in functioning during the past year (i.e. 30% reduction of Global Assessment of Functioning (GAF) score for at least 1 month).

Attenuated Positive Symptoms (APS): subjects who have experienced sub threshold, attenuated positive psychotic symptoms, defined by at least 1 of the following symptoms, appearing several times per week for at least 1 week within the last 3 months: unusual thought content/delusional ideas, suspiciousness/persecutory ideas, grandiosity, perceptual abnormalities/hallucinations, disorganized communication and odd behavior/appearance.

Brief limited intermittent psychotic symptoms (BLIPS): subjects who have experienced episodes of frank psychotic symptoms. BLIPS were defined by hallucinations, delusions or formal thought disorders occurring within the last 3 months and resolving spontaneously within 1 week.

And as an extra criterion:

Basic symptoms: presence of at least two of the following nine self-reported disturbed cognitive and perceptive basic symptoms of at least ‘moderate’ severity during the last 3 months: inability to divide attention, thought interference, -pressure and -blockage, disturbances of receptive and of expressive speech, disturbance of abstract thinking, unstable ideas of reference, captivation of attention by details of the visual field, as assessed with the Scale for the Assessment of Basic Symptoms-Prediction List (BSABS-P; Klosterkötter et al. 2001). This extra criterion was added following studies assessing risk factors of a psychotic development over a follow up period of 10 years. Subjective cognitive symptoms are thought to represent such a risk factor (Klosterkötter et al., 2001).

The exclusion criteria were: previous psychotic episode for more than one week (as assessed with the Structured Clinical Interview for Diagnosis, sections B and C (Spitzer et al., 1992), symptoms due to substance abuse (as assessed with the Comprehensive International Diagnostic Interview, sections J and L; WHO, 1993), IQ below 85 (as assessed with the Dutch National Adult Reading Test (NART; Schmand et al., 1991), vision disorders, endocrine disease and known neuropsychological impairment (e.g. closed head injury). Twenty-two of the UHR patients used medication during the neurophysiological assessment. Seven of the UHR patients used atypical antipsychotics (risperidone, olanzapine, quetiapine), three used haloperidol. Furthermore, nine patients used antidepressants and three anxiolytica. One of the UHR patients used lithium and was excluded from the analyses, because some studies have demonstrated associations between SPEM dysfunctions and lithium medication (for an overview see: Leigh & Zee (2006)). Although the relationship between SPEM dysfunction and lithium use has not been replicated consistently (Flechtner et al. 1992), we wanted to ensure that our results are an effect of UHR status rather than of lithium use. For the analyses, UHR subjects were categorized in one of the following medication groups: none, antipsychotic drugs, atypical antipsychotic drugs, antidepressants or ‘other’.
2.1.2. Control group
Twenty-eight participants (13 women) served as a control group for SPEM performance. Exclusion criteria were visual disorders, endocrine disease, psychiatric illness present or in the past, familial history of psychiatric illness (evaluated for first and second degree relatives), known neuropsychological impairment (e.g. closed head injury) and IQ below 85. They were matched as a group on age and education (i.e. the highest level of education ever reached). In the UHR group, subjects may drift downwards in their educational level. If a downward drift occurs, this education estimate is not influenced. The control subjects received a fee for their participation of 40 euros. None of the control subjects used psychoactive medication.

The investigation was carried out in accordance with the latest version of the Declaration of Helsinki. The study design was approved by the Medical Ethical Committee of the AMC. Informed consent of all the participants was obtained after the nature of the procedures had been fully explained.

3. MATERIALS
3.1. Eye movement assessment
3.1.1. Apparatus
Eye movements were recorded using the double magnetic induction method (DMI-method) developed by Bour et al. (2000, 1984). The investigation of eye movements took place in a room that was shielded against optical or acoustical interference. The subject’s head was positioned in a homogeneous alternating primary magnetic field with constant amplitude and stabilized with a head tie and a chin rest. Horizontal as well as vertical eye positions were derived from a secondary magnetic field picked up by a detection coil placed in front of the eye. A golden metallic ring attached to the subject’s eye (anaesthetised with one droplet of 0.4% solution of Oxybuprocainehydrochloride) generates the secondary field and its strength is related to the rotation of the rings. Magnetic field strength is measured with a phase-locked amplitude technique and within the range of −15 to 15°, raw eye signals do not deviate more than 5% from linearity and have an accuracy better than 15 min arcs of visual angle. Both horizontal and vertical eye positions of one eye were recorded, low pass filtered (150 Hz, 12 dB/oct, 2nd order Bessel filter), sampled with a frequency of 500 Hz and computer stored. Given the variability in vertical eye movements even in healthy controls, only horizontal eye movement will be analyzed in this study.

3.1.2. Stimuli
The visual target was a single, red, 0.5° of visual angle in diameter, circular laser-spot of 20 cd/m² luminance, projected on the rear of a white translucent screen by means of a scanning mirror device. Subjects were asked to follow the target, which moved with a
constant velocity of 10°/s from left to right and vice versa, as closely as possible. Extreme target positions were at +/-10°.

For the purpose of stabilization of the target on the retina, the eye position was measured and adjusted with the target position online. To calibrate the eye movements, subjects were asked to perform saccades to an array of vertical and horizontal targets with 10° of visual angle from primary position before each experiment. This cycle was repeated until the target was sufficiently stabilized on the retina. Data calibration and analysis of saccades and smooth pursuit were performed off-line with a program developed by one of the authors in the department of Clinical Neurophysiology of the AMC.

3.1.3. SPEM parameters
The procedure to divide the eye movement signal during pursuit into segments with smooth pursuit and segments with saccades was as follows: first, to find possible candidates for on- and offset of saccades, the signal was down-sampled five times. Subsequently, the second derivative of this down sampled signal was calculated and then rectified. To exclude detection of noise, the value of this signal needed to exceed a fixed threshold criterion (360°/s²), before peak detection took place. Thus, the detected peaks marked sudden transients in eye velocity. Secondly, eye velocity between the successive peaks was calculated based on the original signal values at the peaks and the time difference between the peaks. The original signal was then split up in smooth segments of SPEM and saccadic segments. When the eye velocity between two peaks was smaller than 15°/s or larger than −5°/s, it was considered to belong to a smooth segment of SPEM (ongoing target velocity is 10°/s). The remaining segments were classified as saccadic segments. Eye blinks, registered by an automatic blink detection algorithm, were removed and not included in the analysis. After automatic detection, the experimenters double checked the validity of all events and false positives, while blinded for patient/control status.

3.2. Gain
SPEM gain is defined as the ratio between target velocity and eye velocity. A pursuit response gain of less than one or higher than one means that pursuit velocity is less than target velocity or higher than target velocity, respectively. During the first 50–100 ms after stimulus onset, the pursuit gain is not driven by internal feedback but directly by visual motion information, although after repetition of the target motion presentation there seems to be a build up of anticipation leading to a dependence on both visual information and internal feedback (Calkins et al., 2008). In our study, we excluded the first phase of pursuit initiation, also known as open-loop gain segments. Due to the decrease or increase of velocity, the first 150 ms before and after the turning point also were excluded in the calculation of the eye velocity. By excluding these points we aimed at only assessing predictive pursuit. During open loop segments, or around turning points, pursuit behavior is less predictable, resulting in changes in velocity and an increased saccadic rate. Furthermore, for the gain calculation over the pursuit
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sample a weighted average across all smooth segments of SPEM was used, to prevent short sections of high or low gain having an undue effect. The mean pursuit gain was calculated over 29 ramps.

3.3. Saccades

There are several types of saccadic movements that may intrude on pursuit. In our study, we differentiate between saccades that correct for SPEM deficiencies (corrective saccades) and saccades that disrupt tracking (non-corrective saccades). Corrective saccades are needed to match the fovea with the visual target. Thus, these saccades play a role in the minimization of retinal error, which is defined as the difference between target and eye position (Orban de Xivry & Lefèvre, 2007). Non-corrective saccades were classified as such if they were in the opposite direction of the target, i.e. bringing the eye off target during pursuit. Definitions of the saccadic events used in our study are presented in Figure 1.

Fig. 1. Example of SPEM in an Ultra High Risk (UHR) patient. The following corrective saccades were distinguished: Catch-up saccades (A), defined as saccades in the same direction as target motion, thereby serving to reposition the eye on the target. These saccades are made when the eye is lagging behind a position near or on the target, thereby decreasing position error (Calkins et al., 2008). Back-up saccades (C), defined as saccades taking the eye from a position ahead of the target back to the target, with a direction opposite to the target movement. Two types of non-corrective saccades were distinguished: Non-corrective forward saccades (B), defined as saccades that take the eye ahead of the target (Some researchers have used the term anticipatory saccades for the latter group, because they precede future target direction, or are ahead of current target location (Levy et al., 2000)). Non-corrective backward saccade (D), defined as saccades moving in opposite direction of the target movement. As presented, two parts of SPEM were excluded from the SPEM analysis: 1) The first 150 ms before and after the turning point (for details see Section 3). 2) Square Wave Jerks, defined as pairs of small horizontal saccades, up to 4° of amplitude, that take the eye away from the target and then return to the target with an intersaccadic interval of less than 250 ms (Leigh & Zee, 2006; Levy et al., 2000 and Shaffer et al., 2003). Pairs of saccades with these characteristics were excluded from the calculation of either corrective or non-corrective saccades.
3.4. Psychiatric symptoms
All UHR patients were assessed with the Structured Interview for Prodromal Syndromes (SIPS; Miller et al., 2003), Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) and Scale for the Assessment of Basic Symptoms-Prediction List (BSABS-P; Klosterkötter et al., 2001). The SIPS is a comprehensive diagnostic tool designed specifically for the assessment of the whole spectrum of prodromal signs and symptoms. The scale is composed of 19 items (five positive, six negative, four disorganization, four general symptoms) each of which is given a score of zero to six according to defined criteria. A score between 3 and 5 on the positive symptoms indicates attenuated psychotic symptoms and a score of 6 indicates a psychotic state or BLIPS. The PANSS is composed of 30 items, each of which is given a score of one to seven according to defined criteria. Sub scores for positive, negative and disorganization symptoms can be calculated (Bryson et al. 1999; Lindenmayer et al., 1995). The BSABS-P assesses 17 selected self-perceived disturbances in cognition and perception that were found to be predictive for a transition to psychosis in the long term (Klosterkötter et al., 2001). Each basic symptom is given a score of zero to six according to frequency of occurrence.

All control subjects were also interviewed with the SIPS and BSABS-P. When their scores were in the UHR range, subjects were excluded from the study.

3.5. Procedure
In all participants, SPEM was assessed in a session of approximately 10 minutes. The psychiatric questionnaires were administered in 1.5–2 hours at inclusion. The SPEM task was administered within a week after inclusion. All participants were instructed not to smoke, use drugs or drink coffee or other caffeine holding drinks the day of the recording. Before administering the SPEM procedure participants were asked whether they complied with this instruction.

3.6. Statistical analysis
Differences between groups in education (highest level ever reached), and gender were analyzed with the Chi-square test. Two-tailed t-tests for independent samples were applied to evaluate group differences in SPEM parameters. Differences between the two groups in psychopathology, as assessed with the SIPS, PANSS, GAF and BSABS were assessed using Mann Whitney U tests. Correlations between SPEM parameters and psychiatric symptoms were examined with nonparametric correlation tests (Spearman’s Rho). Associations between SPEM parameters, medication use and inclusion criteria in the UHR group were assessed using both Kruskal Wallis and Spearman’s Rho. For all tests, p values of less than .05 were accepted as significant. The data were analyzed with a statistical computer program (SPSS 17.0).
4. RESULTS

4.1. Demographic and clinical characteristics

The groups did not significantly differ with respect to age or the highest level of education ever reached (Table 1). There were significantly more women in the control group compared to the UHR group (Chi-square = 4.73, \( p = .04 \)). Preliminary analyses revealed no gender differences in SPEM or saccades in any of the groups. Thus men and women performed equally well in both the UHR and the control group. In addition, no evidence of a gender–group interaction was found. Hence, gender was not included as a covariate in the following statistical analyses.

Table 1 Demographic and clinical characteristics of the UHR patients and control subjects.

<table>
<thead>
<tr>
<th></th>
<th>UHR patients</th>
<th>Control subjects</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD)</td>
<td>20.6 (3.8)</td>
<td>20.1 (3.3)</td>
<td>.52</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>36/10</td>
<td>15/13</td>
<td>.04</td>
</tr>
<tr>
<td>Highest education level (%)</td>
<td></td>
<td></td>
<td>.88</td>
</tr>
<tr>
<td>1</td>
<td>6 (13.0)</td>
<td>5 (18)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>14 (30.4)</td>
<td>7 (25)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>11 (23.9)</td>
<td>8 (28)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>15 (32.6)</td>
<td>8 (28)</td>
<td></td>
</tr>
<tr>
<td>Nicotine (% users)</td>
<td>16 (36)</td>
<td>4 (14)</td>
<td>.20</td>
</tr>
<tr>
<td>Inclusion symptoms n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attenuated symptoms</td>
<td>16 (34.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attenuated and BS</td>
<td>22 (47.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BLIPS(^1)</td>
<td>1 (2.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BLIPS and BS</td>
<td>2 (4.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BLIPS and AS</td>
<td>2 (4.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BLIPS, AS and BS</td>
<td>1 (2.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genetic risk, reduced functioning and BS</td>
<td>1 (2.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genetic risk, reduced functioning and AS</td>
<td>1 (2.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genetic risk, reduced functioning, AS and BS</td>
<td>0 (0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^1\)highest level of education ever reached on a scale of 1 to 4; 1. lower vocational training, 2. lower general secondary education/intermediate vocational training, 3. higher general secondary education/higher vocational training, 4. pre-university education/university. Abbreviations: UHR = Ultra High Risk; BS = basic symptoms; AS = attenuated symptoms; BLIPS = Brief limited intermittent psychotic symptoms.

4.2. SPEM task

The results of the SPEM task are presented in Table 2. There were no differences between the groups in the number of analyzed SPEM ramps. T-tests for independent samples showed a significantly higher saccadic rate during SPEM in the UHR group compared to healthy controls. Furthermore, both the rate of corrective as well as the rate of non-
corrective saccades was higher in the UHR group compared to the control group. As for the corrective saccade rate, the groups differed only in the rate of catch-up saccades. When comparing the non-corrective saccade rate between the two groups, differences were found only in the rate of backward saccades, thus saccades moving in opposite direction of the target movement. We found no significant differences in the rates of back-up saccades, non-corrective forward saccades, square wave jerks, nor in the pursuit gain between UHR patients and healthy controls. As expected, our correlation analyses revealed a negative correlation between the pursuit gain and the total number of saccades ($rho = -0.359$, $p = 0.013$). Thus, UHR patients with a lower gain tended to make more saccades. However, when investigating the relationship between the pursuit gain and the distinct saccadic rates, a modest correlation was only found with the rate of back-up saccades ($rho = -0.300$, $p = 0.04$). The pursuit gain was not associated with any of the other saccadic rates. We did find a significant correlation between the corrective and non-corrective saccadic rates ($rho = 0.403$, $p = 0.005$).

We found no significant correlations between SPEM parameters and education level, nicotine, alcohol, cannabis and medication usage. Furthermore, we investigated whether SPEM measures varied over the distinct inclusion groups, as presented in Table 1. These analyzes revealed no differences in any of the SPEM measures.

Table 2 SPEM parameters in UHR patients and control subjects

<table>
<thead>
<tr>
<th></th>
<th>UHR patients n = 46</th>
<th>Control subjects n = 28</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saccades (total)</td>
<td>1.84 (.9)</td>
<td>1.21 (.4)</td>
<td>$t=3.25$, $p=0.002$</td>
</tr>
<tr>
<td>Corrective saccades</td>
<td>1.33 (.9)</td>
<td>.87 (.4)</td>
<td>$t=2.62$, $p=0.011$</td>
</tr>
<tr>
<td>Catch-up saccades</td>
<td>1.11 (.6)</td>
<td>.76 (.2)</td>
<td>$t=2.99$, $p=0.004$</td>
</tr>
<tr>
<td>Back-up saccades</td>
<td>.21 (.4)</td>
<td>.10 (.1)</td>
<td>$t=1.31$, $p=0.194$</td>
</tr>
<tr>
<td>Non-corrective saccades</td>
<td>.55 (.2)</td>
<td>.33 (.2)</td>
<td>$t=2.19$, $p=0.023$</td>
</tr>
<tr>
<td>Forward</td>
<td>.35 (.2)</td>
<td>.26 (.2)</td>
<td>$t=0.82$, $p=0.517$</td>
</tr>
<tr>
<td>Backward</td>
<td>.20 (.2)</td>
<td>.06 (.1)</td>
<td>$t=5.24$, $p&lt;0.001$</td>
</tr>
<tr>
<td>Square wave jerks</td>
<td>.02 (.02)</td>
<td>.01 (.02)</td>
<td>$t=1.50$, $p=0.137$</td>
</tr>
<tr>
<td>Pursuit gain</td>
<td>.92 (.1)</td>
<td>.93 (.1)</td>
<td>$t=0.63$, $p=0.597$</td>
</tr>
<tr>
<td>Pursuit ramps</td>
<td>28.98 (.2)</td>
<td>28.96 (.19)</td>
<td>$t=0.57$, $p=0.692$</td>
</tr>
</tbody>
</table>

Values are mean (SD). UHR=Ultra High Risk. **Bold** indicates significant $p$ values

4.3. SPEM and psychiatric symptoms

The results of the psychiatric questionnaires are presented in Table 3. Using Spearman nonparametric correlation tests, we found that a higher rate of non-corrective saccades was related to a higher score on the positive scale of the SIPS ($rho = 0.412$, $p = 0.004$). Thus, UHR patients with a higher rate of non-corrective saccades tended to report more perceptual abnormalities. This effect was mainly due to the relation between the SIPS
Table 3 Psychiatric evaluation in UHR patients and control subjects

<table>
<thead>
<tr>
<th></th>
<th>UHR patients (n=46)</th>
<th>Control subjects (n=28)</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GAF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>48.8 (11.0)</td>
<td>85.2 (7.8)</td>
<td>U=21.0, p&lt;.001</td>
</tr>
<tr>
<td>Highest in past year</td>
<td>57.7 (11.9)</td>
<td>86.7 (7.0)</td>
<td>U=12.5, p&lt;.001</td>
</tr>
<tr>
<td><strong>PANSS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive symptoms</td>
<td>12.38 (2.3)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>11.98 (4.8)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>General pathology</td>
<td>25.36 (5.8)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>SIPS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive symptoms</td>
<td>11.2 (3.8)</td>
<td>1.5 (1.5)</td>
<td>U=20.0, p&lt;.001</td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>14.4 (7.3)</td>
<td>1.1 (1.4)</td>
<td>U=38.5, p&lt;.001</td>
</tr>
<tr>
<td>Disorganization</td>
<td>5.4 (2.9)</td>
<td>.7 (9)</td>
<td>U=45.5, p&lt;.001</td>
</tr>
<tr>
<td>General pathology</td>
<td>9.5 (4.1)</td>
<td>.9 (1.4)</td>
<td>U=21.0, p&lt;.001</td>
</tr>
<tr>
<td><strong>BSABS-P</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive thought disturbances</td>
<td>15.8 (9.6)</td>
<td>1.8 (2.4)</td>
<td>U=49.5, p&lt;.001</td>
</tr>
<tr>
<td>Cognitive perceptual disturbances</td>
<td>9.2 (8.2)</td>
<td>1.1 (1.8)</td>
<td>U=173.5, p&lt;.001</td>
</tr>
<tr>
<td>Cognitive motor disturbances</td>
<td>2.0 (2.8)</td>
<td>.1 (.3)</td>
<td>U=326.5, p&lt;.001</td>
</tr>
</tbody>
</table>

Values are mean (SD). Abbreviations: GAF = Global Assessment of Functioning; PANSS = Positive and Negative Syndrome Scale. SIPS = Structured Interview for Prodromal Syndromes; BSABS-P = Bonn Scale for the Assessment of Basic Symptoms; Prediction List

positive score and the rate of forward non-corrective saccades (\(\rho = .422, p = .003\)). We found no significant associations between the rate of backward non-corrective saccades and UHR symptoms, nor did we find significant correlations between the distinct saccadic rates and subscales of the BSABS or the PANSS.

5. DISCUSSION

Patients at Ultra High Risk for developing psychosis showed a higher rate of both corrective and non-corrective saccades during SPEM, compared to the healthy controls. More specifically, the rates of backward non-corrective saccades and catch-up saccades were increased in the UHR group. We found no differences in pursuit gain between the two groups. Thus, there seems to be a selective impairment: the saccadic rate is predominantly affected in UHR patients.

There are several explanations for our finding of the increased saccadic rate in combination with a normal smooth pursuit gain. One possibility is that the increased saccadic rate observed in our study is not the result of compensatory mechanism for pursuit deficits. Rather, it is a reflection of dysinhibition of saccades. Accordingly, the pursuit gain was associated only with the rate of back-up saccades, which did not differ between groups. No associations between the pursuit gain and other saccadic rates
were found. The increased rate of catch-up saccades observed in our study may be due to corrective mechanisms to control for the higher rate of non-corrective saccades. This view is supported by our correlation analyses, from which we found evidence for a relationship between non-corrective and corrective saccades. As has been suggested by Lencer and colleagues (2008), another possibility is that the higher rate of catch-up saccades is explained by an instability of the pursuit response, resulting in increased catch-up saccade rates due to brief periods of slow pursuit rather than consistently slowed pursuit maintenance velocity. Indeed, our findings are quite similar to the results of their study on SPEM in antipsychotic-naïve schizophrenia patients. The rate of non-corrective saccades was however not assessed in the study of Lencer and colleagues. The hypothesis that the increased rate of catch-up saccades is an effect of the higher rate of non-corrective saccades can therefore not yet be rejected.

As mentioned previously, the frontal eye fields are an important contributor to the saccadic system, by inhibiting the superior colliculus in non-purposive saccades (Shaffer et al., 2003). The saccadic dysinhibition observed in our study may be due to a failure of prefrontal areas and a frontostriatal network in inhibiting saccadic related structures (Raemaekers et al., 2002; Tregellas et al., 2004). In accordance, frontal lobe abnormality is the most consistent finding in neuro-imaging studies in UHR patients (Sun et al., 2009; Wood et al., 2008).

In our group of UHR patients, back-up saccades and square wave jerks only accounted for a very small portion of all saccadic intrusions during pursuit tracking. Furthermore, there were no differences with respect to these types of saccadic intrusions between the groups. This finding is in accordance with some studies on SPEM in schizophrenia patients, in which both the rates of back-up saccades and square wave jerks were similar in schizophrenia and controls (Litman et al., 1994; Ross et al., 1998). Others however suggest that saccadic dysinhibition can be viewed as mainly an effect of an increased rate of square wave jerks in schizophrenia patients (Levy et al., 2000).

The stimuli used in our experiment moved in a predictable fashion, moving back and forth with a constant velocity. Moreover, we excluded pursuit initiation, which is directly driven by visual motion areas (Lencer & Trillenberg, 2008). Thus, our subjects have probably generated an internal mode of future target location during the task, in which the oculomotor system uses prediction to anticipate the future target trajectory (Orban de Xivry & Lefèvre, 2007). Studies in schizophrenia patients suggest that the SPEM impairments may be caused by a deficit in the processing of internal representations of extra-retinal object motion (Hong et al., 2005). In addition, deficits in anticipation have been proposed as a presumed genetic risk for schizophrenia (Ross et al., 1998). Non-corrective saccades preceding target motion do however not necessarily have to be anticipatory saccades and may well be involuntary generated saccades as a result of decreased saccadic inhibition. By distinguishing between backward and forward non-corrective saccades, we were able to demonstrate differences only in the rate of backward non-corrective saccades. The rate of forward non-corrective saccades, i.e. saccades that take the eye ahead of the target, did not differ between groups. Thus, our results more likely reflect a dysinhibition of the saccadic system, rather than difficulties in stimulus anticipation.
As for SPEM and the psychiatric questionnaires, we found a relationship between the non-corrective saccadic rate and a measure of positive symptoms. Positive symptoms have been linked to (pre)frontal cortical abnormalities, as has SPEM (Liddle et al., 1992; Nakashima et al., 1994). On the other hand, neuropsychological, neuroimaging and EEG studies have also ascribed psychomotor poverty and disorganization syndromes to the frontal lobes (Lee et al., 2001). Accordingly, these authors found a strong association between SPEM parameters, and disorganization symptoms in schizophrenia patients. We did not find associations between SPEM and disorganization symptoms, nor with negative symptoms. This might be explained by a more modest symptom presentation in UHR patients as compared to schizophrenia patients.

Effects of medication, such as anticholinergic or antipsychotic drugs, on SPEM parameters have been reported frequently (e.g. Ettinger et al., 2003; Leigh & Zee, 2006). However, we found no evidence of a relationship between the use of medication, in particular antidepressants or antipsychotics, and any of the SPEM parameters in our study. The increased saccadic rate in our UHR sample is most likely not the result of medication use. Accordingly, SPEM impairments in medication naïve subjects have repeatedly been reported (e.g. Campion et al., 1992).

In another study of our group (Nieman et al., 2007), using a sample that partly overlaps with our UHR sample, abnormalities were also reported on the antisaccade test. The antisaccade error rate was higher in UHR patients compared to healthy controls. This finding has been interpreted as an inability of UHR patients to suppress reflexive processes. These and our finding suggest that eye movement abnormalities, in particular an inability to suppress unwanted saccades, are present before a first psychotic episode and may reflect a vulnerability to psychosis. The value of both antisaccade and SPEM task performance in predicting a first psychotic episode will be discussed in a subsequent paper.

We conclude that patients at UHR for developing psychosis showed disabilities in the smooth tracking of a moving object. The rate of both corrective and non-corrective saccades was increased, reflecting mainly a dysfunction in the inhibition of saccades. Our findings are indicative of the presence of oculomotor abnormalities in UHR patients, before a transition to psychosis. This suggests that saccadic dysinhibition may indeed be useful as a vulnerability marker of a first psychotic episode. Longitudinal studies are however needed to reveal whether these SPEM deficits are also helpful in predicting the transition to psychosis.
REFERENCE LIST


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SMOOTH PURSUIT EYE MOVEMENTS IN UHR SUBJECTS AND CONTROLS


SMOOTH PURSUIT EYE MOVEMENTS IN UHR SUBJECTS AND CONTROLS


Roitman, SE., Keefe RS, Harvey PD, & Siever LJ (1997). Attentional and eye tracking deficits correlate with negative symptoms in schizophrenia. Schizophr Res 26, 139-146.


I: Apparent motion evoked smooth pursuit eye movement reveals a hidden dysfunction in smooth pursuit eye movement in schizophrenia. Exp Brain Res 182, 399-413.


