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ORIGINAL PAPER

Antisaccade and prosaccade eye movements in individuals clinically at risk for psychosis: comparison with first-episode schizophrenia and prediction of conversion

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Abstract

Saccadic eye movements are well-described markers of cerebral function and have been widely studied in schizophrenia spectrum populations. However, less is known about saccades in individuals clinically at risk for schizophrenia. Therefore, we studied individuals in an at-risk mental state (ARMS) ($N=160$), patients in their first episode of schizophrenia ($N=32$) and healthy controls ($N=75$). $N=88$ ARMS participants showed an early at-risk mental state (E-ARMS), defined by cognitive-perceptive basic symptoms (COPER) or a combination of risk and loss of function, whereas $N=72$ were in a late at-risk mental state (L-ARMS), defined by attenuated psychotic symptoms or brief limited intermittent psychotic symptoms. We examined prosaccades, reflecting overt attentional shifts, and antisaccades, measuring inhibitory control, as well as their relationship as an indicator of the interplay of bottom–up and top–down influences. L-ARMS but not E-ARMS participants had increased antisaccade latencies compared to controls. First-episode patients had higher antisaccade error rates compared to E-ARMS participants and controls, and increased latencies compared to all other groups. Prosaccade latencies did not differ between groups. We observed the expected negative correlation between prosaccade latency and antisaccade error rate, indicating that individuals with shorter prosaccade latencies made more antisaccade errors. The magnitude of the association did not differ between groups. No saccadic measure predicted conversion to psychosis within 2 years. These findings confirm the existence of antisaccade impairments in patients with schizophrenia and provide evidence that volitional response generation in the antisaccade task may be affected even before onset of clinically overt psychosis.

Keywords Antisaccade · Prosaccade · Clinical high risk · Prognostic biomarkers

Introduction

The pathogenesis of schizophrenia is still poorly understood. In recent years, there has been intense clinical and research focus on the early phase of the disease with a view to optimising early recognition and treatment of individuals in an

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at-risk mental state of psychosis (ARMS) [1]. Longitudinal studies of individuals in an ARMS have yielded transition rates of 9.6% after 6 months and 29.1% after 3 years, if ultra-high-risk (UHR) criteria are considered for study entry or 13.9% and 50.0%, if basic symptom criteria are used [2]. Whilst bolstering the importance of early recognition, these figures also indicate that a large number of individuals in an ARMS as defined by currently available methods do not develop the disorder, at least in the investigated study periods. Therefore, reliable and valid prognostic markers are desperately needed to improve prediction of transition to psychosis. Cognitive, neuroimaging, and psychophysiological biomarkers and endophenotypes have begun to play a prominent role in this context. Specifically, promising findings have been obtained for verbal cognition, processing speed, structural and functional magnetic resonance imaging (MRI) parameters, and auditory electrophysiology [3–5].

Antisaccade performance is a well-validated endophenotype of schizophrenia. An antisaccade is a rapid eye movement away from a sudden-onset, peripheral visual stimulus. The rate of direction errors (glances towards the target) represents a highly reliable, translational measure of inhibitory control [6, 7]. Patients with schizophrenia show increased rates of direction errors and longer latencies of correct antisaccades [6, 8]. Antisaccade impairments are also observed in clinically unaffected relatives of schizophrenia patients [9] and individuals with high levels of schizotypy [10–12]. In contrast, performance on prosaccades, a sensorimotor control condition indexing overt attentional shifts, is by and large unimpaired in schizophrenia spectrum populations [8].

Despite this substantial body of evidence in support of antisaccade performance as a schizophrenia spectrum endophenotype, only two previous studies have applied the task to ARMS individuals [13, 14]. Nieman et al. [13] observed that ARMS individuals had higher error rates than healthy controls, but lower error rates than recent-onset schizophrenia patients. In contrast, Caldani et al. [14] found increased error rates in schizophrenia patients, but not in UHR individuals. A follow-up was reported only by Nieman et al. [13] in a small sample of ARMS individuals, showing a trend towards increased error rate in those who transitioned to psychosis compared to those who did not ($p = 0.09$). Generally, whilst several endophenotypes of schizophrenia have been found to be altered in ARMS and to have predictive value [3–5], the evidence for antisaccade measures is still scant and inconclusive. Therefore, we studied antisaccade performance in a large sample of clinical high-risk individuals as well as first-episode schizophrenia patients and healthy controls. This is the largest study to date of antisaccade performance in clinical high-risk individuals ($N = 160$).

In addition, we included a prosaccade control task to confirm whether impairments, should they be observed, are specific to this top–down oculomotor task or whether impairments occur more generally even in a simple task requiring highly automatic saccadic eye movements [8]. Inclusion of the prosaccade task also allowed us to investigate relationships between prosaccade latency and antisaccade direction errors, which is indicative of the competition between the speed of an automatic response to the target and the top–down generated response away from it [15]. There is evidence that this negative correlation typically observed in healthy samples is lost in schizophrenia, suggestive of executive disturbances rather than deficits due to altered attentional shifting capacity [16].

Given the known heterogeneity of high-risk groups [17], we also examined oculomotor performance in two at-risk subgroups differing in clinical symptoms which, based on prior work [18], were considered to be in an early or late prodromal stage, respectively. Previous research has suggested that subjects in an early at-risk state (E-ARMS) have milder cognitive [19] and electrophysiological deviations than subjects in a late at-risk state (L-ARMS) [20, 21], although not all studies have observed this pattern [22].

We hypothesised that increased risk for psychosis would be accompanied by increased impairment in antisaccade but not prosaccade performance. Finally, a large proportion of at-risk subjects of this study was followed up clinically, allowing an evaluation of whether antisaccade performance may be able to predict transition to psychosis, with a view to validating the task as a prognostic biomarker.

Method

Participants

A total of 160 individuals in an ARMS, 32 patients with a first episode of schizophrenia and 75 healthy controls took part in this study.

ARMS participants were recruited at the Early Recognition and Intervention Centres of the Departments of Psychiatry at the University of Bonn, Cologne and Düsseldorf as part of the German Research Network on Schizophrenia (GRNS). Details of recruitment, evaluation and treatment have been described elsewhere [18, 19]. Briefly, a two-step approach was employed. A screening instrument was used for help-seeking people who approached general practitioners or mental health professionals, followed by a detailed assessment at our local centres using the Structured Clinical Interview for DSM-IV (SCID-I) [23] and the Early Recognition Inventory for the Retrospective Assessment of the Onset of Schizophrenia (ERIraos) [24]. ARMS participants were included according to the two-stage risk concept of the GRNS: (1) E-ARMS, defined by cognitive-perceptive basic symptoms (COPER), and/or a combination of a first-degree relative with a lifetime diagnosis of schizophrenia

or a schizophrenia spectrum disorder or pre- or perinatal complications with a Global Assessment of Function (GAF) reduction [25] of at least 30 points within the last year; (2) L-ARMS, defined by attenuated positive symptoms (APS) or brief limited intermittent psychotic symptoms (BLIPS) and not fulfilling exclusion criteria [18]. Seventy-two subjects met L-ARMS criteria, 88 E-ARMS criteria.

The group of schizophrenia patients included 32 inpatients with a first episode of schizophrenia according to DSM-IV criteria. Patients were recruited from the in-patient departments of the study centres where they had received their diagnosis of first-episode schizophrenia. Shortly thereafter, patients were included in a clinical trial comparing the effect of risperidone and haloperidol whose results are reported elsewhere [26]. In the present sample, 17 patients received risperidone, 15 patients were treated with haloperidol at the time of testing.

Healthy controls ($N=75$) were recruited from the same geographical region by local advertisements. None had past or present psychiatric or neurological disorders, or a family history of psychiatric disorders and were not using psychotropic medication or illicit drugs. Moreover, none of the controls fulfilled inclusion criteria for E-ARMS or L-ARMS.

Written informed consent was obtained from all participants. The study was approved by the Institutional Review Boards of all participating universities.

Clinical and cognitive assessment at baseline

The Global Assessment of Function (GAF) score was employed to provide an index of overall psychological, social, and occupational functioning [25]. The Positive and Negative Syndrome Scale (PANSS) was applied to evaluate severity of positive, negative, and general psychopathology of schizophrenia [27]. The Montgomery-Åsberg Depression Rating Scale (MADRS) was used to assess affective, cognitive, and vegetative dimensions of depression [28] in ARMS patients and the Calgary Depression Scale for Schizophrenia (CDSS) was used to assess depressive symptoms in first-episode patients [29]. Verbal intelligence was assessed with the Mehrfachwahl-Wortschatz-Intelligenztest (MWT-B), a German word recognition test [30].

Interventions and clinical assessment at follow-up

Out of 160 ARMS participants, 130 participants (81%) were available for follow-up assessment with an average follow-up period of 14.47 (SD = 9.59) months. Conversion to psychosis was diagnosed at follow-up according to SCID-I. We dated the onset of psychosis using the anchor point method [31], which makes use of memorable biographical events to determine the onset of psychosis. The date of onset was set for the month in which the first positive symptom persisted for more than 1 week according to participant report.

Subsequent to baseline assessment including the oculomotor task, E-ARMS and L-ARMS participants received different treatments [18]. E-ARMS received cognitive behavioural therapy or clinical management within a randomised controlled trial [31]; L-ARMS patients were treated with amisulpride plus a needs-focused intervention (NFI) or NFI alone. In this sample, 39 of 68 (57.4%) E-ARMS and 36 of 62 (58.1%) L-ARMS patients obtained an active treatment, the remaining 55 patients received no specific intervention.

Eye movement tasks

Stimuli were generated using ERTS® (Berisoft Cooperation) and presented using a 15-inch monitor with a distance of 41 cm from participants' nasion. Head movements were reduced using a chinrest. Testing took place in a quiet, dimly lit room. There were two blocks each of prosaccades and antisaccades in a fixed order (prosaccades, antisaccades, prosaccades, antisaccades), with each block comprising 5 practice and 25 experimental trials (see Fig. 1).

The prosaccade task used overlap (200 ms) trials. A trial began with a white fixation cross (1° high, 1° wide) in the centre of the black screen, with a pseudo-randomised duration of 1500 ms, 2000 ms, 2500 ms or 3000 ms. The target (identical to the fixation cross, but rotated by 45°) appeared at ± 16° from the central position, where it remained for 1000 ms. Participants were instructed to focus on the cross

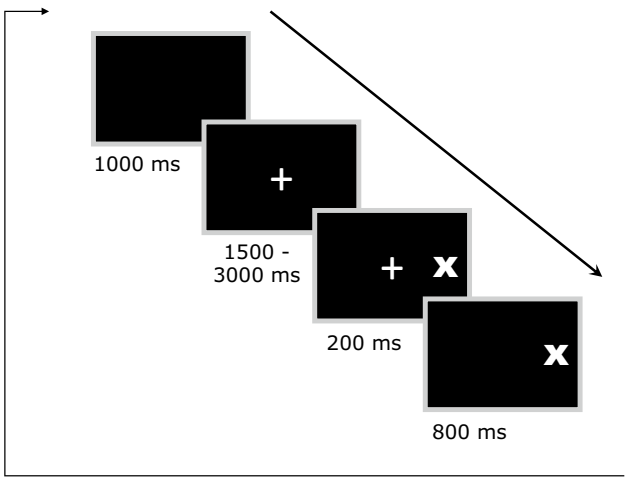

Fig. 1 Schematic presentation of the eye movement task. In the prosaccade task, participants were instructed to focus on the cross in the centre and quickly direct their gaze to the target as soon as it appeared and then to look back to the centre of the screen. In the antisaccade task, they were instructed to look at the fixation cross at the central location and to redirect their gaze to the exact mirror image location of the target as soon as it appeared in the periphery and then to look back to the centre of the screen. Stimuli are larger than shown on screen

in the centre and quickly direct their gaze to the target as soon as it appeared and then to look back to the centre of the screen.

The antisaccade task was identical to the prosaccade task except for instructions. Here, participants were instructed to look at the fixation cross at the central location and to redirect their gaze to the exact mirror image location of the target as soon as it appeared in the periphery and then to look back to the centre of the screen.

Eye movement recording and analysis

Saccades were recorded by direct horizontal electro-oculography derived from the outer canthi (F9, F10). Vertical electro-oculography was recorded from two electrodes positioned above and below the right eye. Recordings were carried out using Neuroscan Labs™ with a Synamps® 5083 amplifier controlled by Acquire® software package (Neurosoft Inc.). It was registered with a bandwidth from 0.1 to 50 Hz using non-polarisable Ag-AgCl electrodes with the electrolyte Abralyte® 2000 as conducting agent. The impedance was kept below 5 kΩ at all electrode locations and checked at the beginning of each recording procedure. Data were digitized at a rate of 250 Hz with a 450Mhz microprocessor PC (CPU Intel Pentium® III) and stored on hard disk for later analysis.

Eye movement recordings were edited using Brain Vision Analyzer® (Brain Products GmbH, Munich, Germany) in an interactive procedure. Data were filtered off-line with a band-pass of 0.1–30 Hz and with a 50 Hz notch filter and then segmented in intervals of 1200 ms with a prestimulus interval of 200 ms. These epochs were baseline-corrected by subtracting the average amplitude of the prestimulus interval.

Saccades were automatically detected on the basis of a minimum amplitude criterion. A horizontal saccade was marked if the signal exceeded the mean amplitude of the baseline period ± 3SD. The onset of the saccade was determined where a sign change in the first derivate (second derivative peak) occurred. This point is the true foot point of the HEOG peak. All segments were inspected and rated blinded to group. Trials with blinks and/or head movements were excluded based on a rating of amplitude, velocity, and duration of eye movement, i.e. the characteristic shape of the wave.

Saccade latency was defined as the time (ms) from target presentation to saccade initiation. Prosaccade latency was computed from prosaccade trials where a primary saccade was performed in the direction of the target within 80–500 ms of target onset. Antisaccade latency was computed from antisaccade trials when a primary saccade was performed in the direction opposite to the peripheral target after 80 ms of target onset. An antisaccade error was counted when a saccade towards the peripheral target occurred in an antisaccade trial. A correction was counted when an antisaccade error was followed by a saccade in the opposite direction. The percentage of direction errors in the antisaccade task was calculated by dividing the number of errors by the number of valid antisaccade trials (excluding, e.g. blink trials).

Statistical analysis

Statistical analyses were conducted in SPSS 22 (IBM, USA). Two-sided p-values < 0.05 were regarded as significant. Chi square tests were used for categorical variables. We performed ANOVAs to assess the effect of 'Group' (control, E-ARMS, L-ARMS, first-episode) on dependent variables. In case of violations of homoscedasticity (as indicated by Levene test), we used Welch variance-weighted ANOVA. Normality of dependent variables was checked using Q–Q-plots. If necessary, we applied square-root transformation to reduce skewness. We performed Dunnet-T3 post-hoc tests that are robust against violations of homoscedasticity [32]. We also performed a 2×4 repeated measurement ANOVA of pro- and antisaccade latencies to analyse potential task-specific differences between groups. To exclude possible confounding of differences in oculomotor parameters by significant differences in demographic variables (see Table 1), we additionally conducted ANCOVA adjusting for age and verbal intelligence score. Furthermore, we sought to exclude the confounding influence of psychoactive medication. To this end, we repeated the analyses excluding patients taking one of the drug class noted in Table 1 each time. When excluding patients with antipsychotic medication, first-episode patients were not excluded because all of them were treated with this substance. Accordingly, we additionally excluded all ARMS patients taking any psychoactive drug. In an exploratory analysis using all ARMS and first-episode patients, we correlated transformed antisaccade performance measures and clinical variables (i.e. GAF and PANSS scores).

Next, we performed Pearson correlations between prosaccade latency and antisaccade error rate, first across all participants and then separately for each group. Correlation coefficients were compared between groups using Fisher r-to-z transformation.

Finally, Cox proportional hazard models adjusting for age, gender, use of psychoactive medication at testing and intervention (i.e. non-specific intervention vs. cognitive behavioural therapy or amisulpride) were conducted to evaluate the predictive utility of oculomotor parameter concerning conversion to psychosis. Because our cross-sectional results suggested that oculomotor deficits were specific to the antisaccade task (see results), we also computed the difference in latencies between the pro- and antisaccade to

Table 1 Demographic and clinical data by group

	Controls ($N=75$)		*N*	E-ARMS ($N=88$)		*N*	L-ARMS ($N=72$)		*N*	First Episode ($N=32$)		*N*	Comparison	
	Mean	SD		Mean	SD		Mean	SD		Mean	SD		Test statistic	*p*
Age	27.41	8.20	74	26.32	7.11	87	25.03	6.05	72	32.41	10.70	32	$F(3,106.1)=5.05^{a,c}$	0.003
Verbal IQ	105.38	12.41	33	108.30	11.82	84	105.59	13.00	70	113.55	15.19	31	$F(3,213)=3.11^{b,c}$	0.03
MADRS	–	–	–	19.06	7.15	81	18.12	7.68	69	–	–	–	$F(1,148)=0.66^{b}$	0.42
CDSS	–	–	–	–	–	–	–	–	–	1.92	2.48	25	–	–
GAF	–	–	–	58.53	9.45	76	58.21	1.43	68	69.60	8.78	25	$F(2,166)=12.48^{b}$	< 0.001
PANSS positive	–	–	–	8.75	1.82	85	12.51	3.83	69	9.50	3.08	32	$F(2,73.4)=33.63^{a,c}$	< 0.001
PANSS negative	–	–	–	10.84	3.74	85	14.94	5.13	69	14.38	5.91	32	$F(2,108.8)=16.51^{a,c}$	< 0.001
PANSS general psychopathology	–	–	–	28.29	6.21	85	33.00	7.63	69	23.84	8.09	31	$F(2,182)=20.84^{b,c}$	< 0.001
	N	%		*N*	%		*N*	%		*N*	%		Test statistic	*p*
Gender (% male)	38	50.0		63	71.6		45	62.6		22	68.8		$Chi^2(3)=7.57$	0.06
Use of any psychoactive medication	–	–		10	11.4		12	16.7		32	100.0		$Chi^2(2)=0.94^{d}$	0.333
Use of antipsychotic medication	–	–		2	2.3		3	4.2		32	100.0		$0.469^{d,e}$	0.658
Use of antidepressive medication	–	–		9	10.2		8	11.1		2	6.3		0.95^{e}	0.812
Use of sedative or sleep-inducing medication	–	–		1	1.1		1	1.4		3	9.4		5.08^{e}	0.055

MADRS Montgomery-Åsberg Depression Rating Scale, *CDSS* Calgary Depression Scale for Schizophrenia, *GAF* Global Assessment of Functioning, *PANSS* Positive and Negative Syndrome Scale

[a]Welch variance-weighted ANOVA

[b]ANOVA

[c]Test statistic based on square-root transformed data

[d]First-episode patients were excluded during calculation, test refers to differences between E-ARMS and L-ARMS patients only

[e]Fisher's exact test. Verbal IQ was measured using the MWT-B

obtain a measure indexing the cognitive demands specific to the antisaccade task.

Results

Descriptive statistics of demographic and clinical variables are given in Table 1. Skewness of age, verbal intelligence test score and PANSS scores were reduced by square-root transformation. Groups differed regarding age and verbal intelligence levels. Post-hoc showed that first-episode patients were significantly older than E-ARMS ($p = 0.02$) and L-ARMS ($p = 0.003$) participants but not controls ($p = 0.11$). E-ARMS and L-ARMS participants did not differ from each other or from controls (all $p > 0.18$). There were no significant results in post-hoc tests of verbal intelligence scores (all $p > 0.08$). L-ARMS participants had higher PANSS scores than E-ARMS participants.

Group differences in eye movements

Descriptive statistics of eye movement variables are in Table 2. On average, 48.37 prosaccade trials (SD = 3.14, range: 26–50; 96.7%, range: 52–100%) and 48.82 antisaccade trials (SD = 2.39, range = 31–50; 97.6%, range: 62–100%) per participant were usable. Antisaccade error rate and latency showed significant deviations from normality and were, therefore, adjusted by square-root transformation. ANOVA revealed effects of 'Group' on antisaccade but not prosaccade performance. Regarding antisaccade error rate, post-hoc tests showed significant differences between first-episode patients and controls ($p = 0.02$, $d = 0.70$) and E-ARMS subjects ($p = 0.04$, $d = 0.64$). Antisaccade error correction rates did not differ between groups. In antisaccade latency, first-episode patients differed from all other groups in (controls: $p < 0.001$, $d = 1.11$; E-ARMS participants: $p = 0.01$, $d = 0.71$; L-ARMS participants: $p = 0.049$, $d = 0.62$) and L-ARMS participants differed from controls ($p = 0.01$, $d = 0.52$).

A 2 × 4 repeated measures ANOVA showed a significant effect of 'Task' (antisaccade, prosaccade) ($F(1,263) = 788.35$, $p < 0.001$, $\text{eta}^2 = 0.750$) and 'Group' ($F(3,263) = 5.93$, $p = 0.001$, $\text{eta}^2 = 0.063$) as well as a significant 'Task x Group' interaction ($F(3,263) = 7.37$, $p < 0.001$, $\text{eta}^2 = 0.078$), confirming that the increase in latency across groups was observed for antisaccades but not for prosaccades (see Table 2 for descriptive statistics).

Group differences in antisaccade error rate ($F(3,211) = 4.60$, $p = 0.004$, $\text{eta}^2 = 0.061$) and latency ($F(3,211) = 5.26$, $p = 0.002$, $\text{eta}^2 = 0.070$) remained significant in an ANCOVA controlling for age and verbal intelligence score. Exclusion of all participants using antidepressants or sedative drugs as well as the exclusion of ARMS patients using antipsychotic drugs or any other psychoactive medication did not substantially alter the results (see supplementary material 1).

There were no significant correlations of transformed antisaccade error rate and latency with clinical measures (i.e. GAF, PANSS) in the pooled sample of ARMS and first-episode patients. Only in E-ARMS participants, there was a significant association between antisaccade latency and PANSS global score ($r = -0.26$, $p = 0.016$) which did not withstand Bonferroni-Holm correction for multiple testing.

Correlations between prosaccade latency and antisaccade error rate

There were significant correlations between prosaccade latency and antisaccade error rate across all participants ($r = -0.24$, $p < 0.001$) and in controls ($r = -0.42$, $p < 0.001$), E-ARMS ($r = -0.24$, $p = 0.02$) and first-episode patients ($r = -0.46$, $p = 0.008$). The correlation in L-ARMS participants was not significant ($r = -0.08$, $p = 0.49$); however, inspection of the scatterplot indicated an outlying score (Fig. 2). The correlation became significant following exclusion of this subject ($r = -0.24$, $p = 0.047$). All reported correlations remained significant after Bonferroni-Holm correction. There were no significant pairwise differences in correlation coefficients between any groups (all $p > 0.20$).

Table 2 Eye movement data by group

	Controls ($N = 75$)		E-ARMS ($N = 88$)		L-ARMS ($N = 72$)		First-episode patients ($N = 32$)		Welch variance-weighted ANOVA	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Test statistic	p
PS latency (ms)	213	29	214	39	221	41	225	56	$F(3,105.0) = 0.98$	0.404
AS latency (ms)	283	37	300	66	308	56	351	80	$F(3,105.2) = 9.25$[a]	< 0.001
AS error rate (%)	16.49	11.84	17.40	15.92	20.77	17.87	31.06	24.79	$F(3,107.0) = 3.66$[a]	0.015
AS correction rate (%)	97.17	7.23	95.60	12.38	95.55	10.17	96.01	10.67	$F(3,108.2) = 0.56$	0.644

E-ARMS early at-risk mental state, *L-ARMS* late at-risk mental state, *PS* prosaccade, *AS* antisaccade

[a]Test statistic is based on square-root transformed data

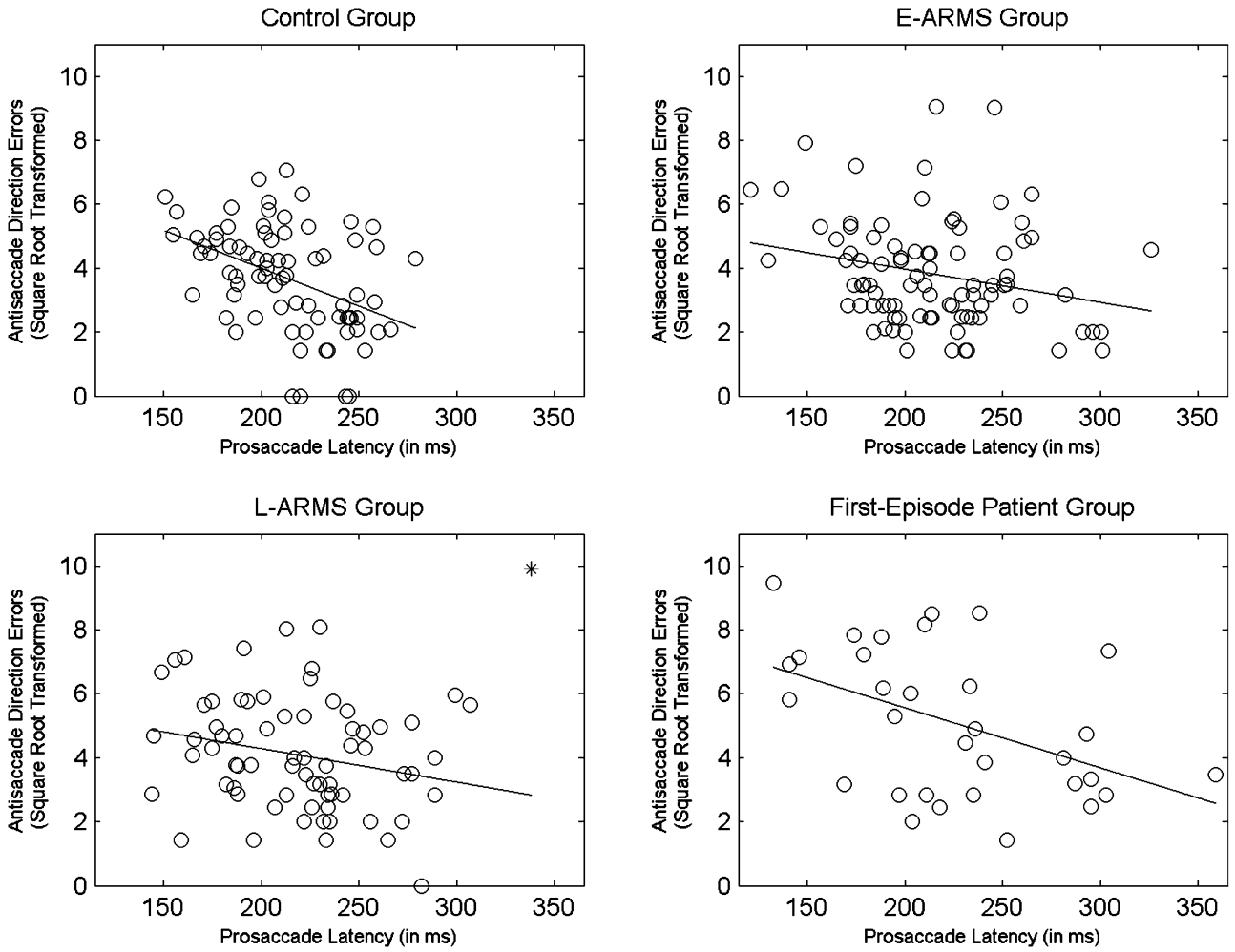

Fig. 2 Scatterplot of Relationship between Antisaccade Errors and Prosaccade Latency. *E-ARMS* early at-risk mental state, *L-ARMS* late at-risk mental state. Prosaccade latency is given in milliseconds. Antisaccade direction error rate (%) has been square-root transformed to reduce skew. The data point marked as asterisk was considered as outlier (see "Results" section) and was excluded when computing the correlation

Prediction of conversion

ARMS participants who were followed up did not differ from those who were not followed up regarding demographic variables, proportion of L-ARMS individuals and most clinical, cognitive and oculomotor measures. The only differences were found in the PANSS global scale [$t(152) = 2.59$, $p = 0.011$] and antisaccade latency [$t(158) = -2.70$, $p = 0.008$] with followed subjects showing longer latency but lower PANSS scores. At follow-up, 23 participants showed a conversion to psychosis [17.7%, 7 E-ARMS (10.3%) and 16 L-ARMS patients (25.8%)] within an average of 8.74 month [SD = 7.65; E-ARMS participants: 9.71 (9.79); L-ARMS participants: 8.31 (6.84)]. Mean follow-up time for non-converters was 16.25 months [SD = 9.46; E-ARMS participants: 18.65 (8.84); L-ARMS participants: 12.57 (9.31)]. No saccadic variable significantly predicted conversion to psychosis in the Cox proportional hazard model (Table 3). There were no significant interactions between any oculomotor parameter and intervention (i.e. non-specific intervention vs. cognitive behavioural therapy or amisulpride), ARMS groups (i.e. E-ARMS and L-ARMS patients) and use of any psychoactive medication indicating the absence of significant effects in either of these subgroups.

Discussion

In this study, we investigated antisaccade and prosaccade task performance in patients in their first episode of schizophrenia, individuals in an at-risk mental state, and healthy controls. We first replicated the observation of antisaccade impairments in first-episode patients. The impairment consisted of an increased rate of direction errors and

Table 3 Prediction of conversion to psychosis by eye movement parameters

	Converters ($n=23$)		Non-converters ($n=107$)		HR	CI−	CI+	p
	M	SD	*M*	SD				
Prosaccade latency	219	39	222	37	1.001	0.991	1.012	0.803
Antisaccade latency	310	66	307	51	1.002	0.995	1.009	0.639
Difference in pro- and antisaccade latency	91	58	85	46	1.001	0.993	1.010	0.739
Antisaccade error rate	18.97	17.89	17.94	13.52	1.001	0.975	1.027	0.947

The hazard ratio describes the increase (HR > 1) or decrease (HR < 1) of the probability of an event (i.e. conversion to psychosis) in the observed time interval associated with a unit increase in the predictor

HR hazard ratio of the Cox-regression model, *CI* confidence interval, *M* mean, *SD* standard deviation

an increased latency of directionally correct antisaccades, as reported in first-episode psychosis patients before [13, 33–35]. We also detected a selective deficit in antisaccade latency in L-ARMS participants, suggesting this measure may be sensitive to disease severity along the continuum of psychosis [1]. The antisaccade latency deficit showed selectivity across measures and groups, as there were no impairments in E-ARMS and no antisaccade error rate or prosaccade latency impairments in L-ARMS.

We also observed negative correlations between prosaccade latency and antisaccade error rate [15, 16]. This correlation indicates that faster prosaccades, indexing overt attentional shifts, are associated with greater difficulty inhibiting unwanted saccades to the target in antisaccade trials. This pattern is consistent with models explaining antisaccade performance in terms of competition between top–down and bottom–up signals [6, 15, 36]. Whilst previous evidence points to a loss of this relationship in schizophrenia patients [16], here we observe correlations of comparable magnitude in both first-episode patients and controls. Specific task features (see paragraph below) or clinical characteristics may explain these differences across studies. Whereas both E- and L-ARMS participants tended to show lower correlations than controls or first-episode patients, there were no significant differences in the magnitude of correlations between groups, suggesting that the basic interplay of top–down and bottom–up processes and its inter-individual variation in strength may be unaltered, at least with the current experimental task design.

Unexpectedly, no saccadic measure predicted conversion to psychosis. The only previous study on this issue observed a non-significant trend towards higher antisaccade error rates in participants who later transitioned ($N=10$) compared to those who did not [13]. With a larger number of transitioning individuals in our study ($N=23$) and conversion rates that are consistent with the literature [37, 38], we did not find any evidence of prediction, despite the increased antisaccade latency in L-ARMS individuals. Our findings may clarify the ambiguous finding by Nieman and colleagues [13]. However, differences in experimental methods between our studies may also have contributed to the discrepancy in results. Specifically, overlap tasks and large target eccentricities, as in our study, are known to produce lower error rates than step tasks (i.e. fixation cross and target are not simultaneously displayed) and smaller target eccentricities (i.e. smaller amplitude from the centre to the peripheral target position) [39, 40], as in the study by Nieman and colleagues [13]. Additionally, the mean interval to transition in our study (8.74 months) was somewhat shorter than in the study by Nieman et al. [13] (10.8 months).

It should also be noted that ARMS participants who were not available for follow-up had lower antisaccade latencies than those who were followed up. It remains speculative whether this range restriction may have masked a putative predictive effect of the antisaccade latency measure. Moreover, the inclusion of ARMS participants in a subsequent clinical trial might have influenced our ability to detect predictive factors of transition to psychosis. We did, however, control for possible effects of interventions (i.e. non-specific intervention vs. cognitive behavioural therapy or amisulpride) and found no modifications of the predictive utility.

The failure of antisaccade performance to predict transitions would fit with evidence from neuropsychological investigations of ARMS participants in showing that executive functions, while clearly impaired in these subjects [19], are less predictive of disease progression than other cognitive functions, like declarative memory [41] or emotion recognition [42]. The finding may also be integrated with previous evidence of the substantial temporal stability of antisaccade performance in schizophrenia spectrum samples [43–45] as well as healthy controls [46, 47]. Impairments in antisaccade performance and executive functions in general thus might be a sensitive marker for susceptibility to schizophrenia, without indicating an imminent conversion.

A limitation of our study is that ARMS participants were not followed up with an eye movement assessment. Such an extension of our study would have been informative in allowing to examine whether those individuals who converted to

psychosis differed in eye movement variables at follow-up from those who did not convert. We also acknowledge that the differences between the E-ARMS and L-ARMS group do not necessarily arise from differences in temporal proximity to psychosis onset but might also represent distinct clinical subgroups.

In conclusion, we confirm previous evidence of antisaccade impairments in patients with schizophrenia. The latency of correct antisaccades, which measure volitional response generation, is also impaired in L-ARMS, suggesting an association of this measure with symptom severity. However, oculomotor parameters did not predict transition to psychosis in at-risk subjects, indicating that these impairments reflect vulnerability rather than imminent psychosis. The interaction between antisaccade impairments and other risk factors for psychosis should be further investigated.

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Compliance with ethical standards

Conflict of interest All authors report no biomedical financial interests or potential conflicts of interest.

References

1. Nieman DH, McGorry PD (2015) Detection and treatment of at-risk mental state for developing a first psychosis: making up the balance. Lancet Psychiatry 2:825–834. https://doi.org/10.1016/S2215-0366(15)00221-7
2. Schultze-Lutter F, Michel C, Schmidt SJ et al (2015) EPA guidance on the early detection of clinical high risk states of psychoses. Eur Psychiatry 30:405–416. https://doi.org/10.1016/j.eurpsy.2015.01.010
3. de Paula ALD, Hallak JEC, Maia-de-Oliveira JP et al (2015) Cognition in at-risk mental states for psychosis. Neurosci Biobehav Rev 57:199–208. https://doi.org/10.1016/j.neubiorev.2015.09.006
4. Bodatsch M, Brockhaus-Dumke A, Klosterkötter J, Ruhrmann S (2015) Forecasting psychosis by event-related potentials-systematic review and specific meta-analysis. Biol Psychiatry 77:951–958. https://doi.org/10.1016/j.biopsych.2014.09.025
5. Wood SJ, Reniers RLEP, Heinze K (2013) Neuroimaging findings in the at-risk mental state: a review of recent literature. Can J Psychiatry 58:13–18. https://doi.org/10.1177/070674371305800104
6. Hutton SB, Ettinger U (2006) The antisaccade task as a research tool in psychopathology: a critical review. Psychophysiology 43:302–313. https://doi.org/10.1111/j.1469-8986.2006.00403.x
7. Munoz DP, Everling S (2004) Look away: the anti-saccade task and the voluntary control of eye movement. Nat Rev Neurosci 5:218–228. https://doi.org/10.1038/nrn1345
8. Gooding DC, Basso MA (2008) The tell-tale tasks: a review of saccadic research in psychiatric patient populations. Brain Cogn 68:371–390. https://doi.org/10.1016/j.bandc.2008.08.024
9. Calkins ME, Iacono WG, Ones DS (2008) Eye movement dysfunction in first-degree relatives of patients with schizophrenia: a meta-analytic evaluation of candidate endophenotypes. Brain Cogn 68:436–461. https://doi.org/10.1016/j.bandc.2008.09.001
10. Ettinger U, Meyhöfer I, Steffens M et al (2014) Genetics, cognition, and neurobiology of schizotypal personality: A review of the overlap with schizophrenia. Frontiers Media SA
11. Gooding DC (1999) Antisaccade task performance in questionnaire-identified schizotypes. Schizophrenia Res 35:157–166
12. O'Driscoll GA, Lenzenweger MF, Holzman PS (1998) Antisaccades and smooth pursuit eye tracking and schizotypy. Arch Gen Psychiatry 55:837–843
13. Nieman D, Becker H, van de Fliert R et al (2007) Antisaccade task performance in patients at ultra high risk for developing psychosis. Schizophr Res 95:54–60. https://doi.org/10.1016/j.schres.2007.06.022
14. Caldani S, Bucci MP, Lamy J-C et al (2017) Saccadic eye movements as markers of schizophrenia spectrum: exploration in at-risk mental states. Schizophrenia Res 181:30–37. https://doi.org/10.1016/j.schres.2016.09.003
15. Talanow T, Kasparbauer A-M, Steffens M et al (2016) Facing competition: neural mechanisms underlying parallel programming of antisaccades and prosaccades. Brain Cognit 107:37–47. https://doi.org/10.1016/j.bandc.2016.05.006
16. Reilly JL, Frankovich K, Hill S et al (2014) Elevated antisaccade error rate as an intermediate phenotype for psychosis across diagnostic categories. Schizophr Bull 40:1011–1021. https://doi.org/10.1093/schbul/sbt132
17. Fusar-Poli P, Cappucciati M, Borgwardt S et al (2016) Heterogeneity of psychosis risk within individuals at clinical high risk: a meta-analytical stratification. JAMA Psychiatry 73:113–120. https://doi.org/10.1001/jamapsychiatry.2015.2324
18. Häfner H, Maurer K, Ruhrmann S et al (2004) Early detection and secondary prevention of psychosis: facts and visions. Eur Arch Psychiatry Clin Neurosci 254:117–128. https://doi.org/10.1007/s00406-004-0508-z
19. Frommann I, Pukrop R, Brinkmeyer J et al (2011) Neuropsychological profiles in different at-risk states of psychosis: executive control impairment in the early—and additional memory dysfunction in the late—prodromal state. Schizophr Bull 37:861–873. https://doi.org/10.1093/schbul/sbp155
20. Quednow BB, Frommann I, Berning J et al (2008) Impaired sensorimotor gating of the acoustic startle response in the prodrome of schizophrenia. Biol Psychiat 64:766–773. https://doi.org/10.1016/j.biopsych.2008.04.019
21. Frommann I, Brinkmeyer J, Ruhrmann S et al (2008) Auditory P300 in individuals clinically at risk for psychosis. Int J Psychophysiol 70:192–205. https://doi.org/10.1016/j.ijpsycho.2008.07.003
22. Wölwer W, Brinkmeyer J, Stroth S et al (2012) Neurophysiological correlates of impaired facial affect recognition in individuals at risk for schizophrenia. Schizophr Bull 38:1021–1029. https://doi.org/10.1093/schbul/sbr013

23. First MB, Spitzer RL, Gibbon M, Williams JBW (1997) Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV)
24. Maurer K, Hörrmann F, Trendler G et al (2006) Früherkennung des Psychoserisikos mit dem Early Recognition Inventory (ERIraos) Beschreibung des Verfahrens und erste Ergebnisse zur Reliabilität und Validität der Checkliste. Nervenheilkunde 25:11–16
25. American Psychiatric Association (2000) DSM-IV
26. Möller HJ, Riedel M, Jäger M et al (2008) Short-term treatment with risperidone or haloperidol in first-episode schizophrenia: 8-week results of a randomized controlled trial within the German research network on Schizophrenia. Int J Neuropsychopharmacol 11(7):985–997. https://doi.org/10.1017/S1461145708008791
27. Kay SR, Fiszbein A, Opler LA (1987) The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophrenia Bull 13:261–276
28. Montgomery SA, Asberg M (1979) A new depression scale designed to be sensitive to chnage. Br J Psychiatry 134:382–389
29. Addington D, Addington J, Maticka-Tyndale E (1993) Assessing depression in schizophrenia: the Calgary depression scale. Br J Psychiatry 163(S22):39–44
30. Lehrl S, Triebig G, Fischer B (1995) Multiple choice vocabulary test MWT as a valid and short test to estimate premorbid intelligence. Acta Neurol Scand 91:335–345
31. Maurer K, Häfner H (1995) Methodological aspects of onset assessment in schizophrenia. Schizophr Res 15:265–276. https://doi.org/10.1016/0920-9964(94)00051-9
32. Stoline MR (1981) The status of multiple comparisons: simultaneous estimation of all pairwise comparisons in one-way ANOVA designs. Am Stat 35:134–141. https://doi.org/10.2307/2683979
33. Harris MSH, Reilly JL, Thase ME et al (2009) Response suppression deficits in treatment-naïve first-episode patients with schizophrenia, psychotic bipolar disorder and psychotic major depression. Psychiatry Res 170:150–156. https://doi.org/10.1016/j.psychres.2008.10.031
34. Hutton SB, Crawford TJ, Puri BK et al (1998) Smooth pursuit and saccadic abnormalities in first-episode schizophrenia. Psychol Med 28:685–692
35. Ettinger U, Kumari V, Chitnis XA et al (2004) Volumetric neural correlates of antisaccade eye movements in first-episode psychosis. Am J Psychiatry 161:1918–1921. https://doi.org/10.1176/ajp.161.10.1918
36. Massen C (2004) Parallel programming of exogenous and endogenous components in the antisaccade task. The quarterly journal of experimental psychology A. Hum Exp Psychol 57:475–498. https://doi.org/10.1080/02724980343000341
37. Bechdolf A, Wagner M, Ruhrmann S et al (2012) Preventing progression to first-episode psychosis in early initial prodromal states. Br J Psychiatry 200:22–29. https://doi.org/10.1192/bjp.bp.109.066357
38. Fusar-Poli P, Bonoldi I, Yung AR et al (2012) Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. Arch Gen Psychiatry 69(3):220–229. https://doi.org/10.1001/archgenpsychiatry.2011.1472
39. Fischer B, Weber H (1997) Effects of stimulus conditions on the performance of antisaccades in man. Exp Brain Res 116:191–200. https://doi.org/10.1007/PL00005749
40. McDowell JE, Myles-Worsley M, Coon H et al (1999) Measuring liability for schizophrenia using optimized antisaccade stimulus parameters. Psychophysiology 36:138–141. https://doi.org/10.1017/S0048577299980836
41. Seidman LJ, Shapiro DI, Stone WS et al (2016) Association of neurocognition with transition to psychosis. JAMA Psychiatry 73:1239. https://doi.org/10.1001/jamapsychiatry.2016.2479
42. Allott KA, Schäfer MR, Thompson A et al (2014) Emotion recognition as a predictor of transition to a psychotic disorder in ultra-high risk participants. Schizophr Res 153:25–31. https://doi.org/10.1016/j.schres.2014.01.037
43. Calkins ME, Iacono WG, Curtis CE (2003) Smooth pursuit and antisaccade performance evidence trait stability in schizophrenia patients and their relatives. Int J Psychophysiol 49:139–146
44. Gooding DC, Shea HB, Matts CW (2005) Saccadic performance in questionnaire-identified schizotypes over time. Psychiatry Res 133:173–186. https://doi.org/10.1016/j.psychres.2003.12.029
45. Gooding DC, Mohapatra L, Shea HB (2004) Temporal stability of saccadic task performance in schizophrenia and bipolar patients. Psychol Med 34:921–932
46. Ettinger U, Kumari V, Crawford TJ et al (2003) Reliability of smooth pursuit, fixation, and saccadic eye movements. Psychophysiology 40:620–628
47. Meyhöfer I, Bertsch K, Esser M, Ettinger U (2016) Variance in saccadic eye movements reflects stable traits. Psychophysiology 53:566–578. https://doi.org/10.1111/psyp.12592