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Original article

Are eye movement abnormalities indicators of genetic vulnerability to schizophrenia?

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Abstract

Fifty to eighty-five percent of schizophrenic patients are impaired on ocular pursuit paradigms. However, results regarding the relatives are more discordant. The aim of this study was to investigate whether eye movement disorders could be a vulnerability marker of schizophrenia.

Method. **–** Twenty-one schizophrenic patients (DSM-IV), 31 first-degree relatives of those patients without schizophrenic spectrum disorders, and two groups of healthy controls matched by age and sex were included. Three oculomotor tasks (smooth pursuit, reflexive saccades and antisaccades) were used.

Results. **–** Patients had a lower averaged gain ($P = 0.035$) during smooth pursuit than controls, made less correct visually guided saccades ($P < 0.001$) and more antisaccades errors ($P = 0.002$) than controls. In contrast, none of the comparison between the relatives and their controls was significant.

Conclusion. **–** Schizophrenic patients were impaired on smooth pursuit and antisaccade paradigms. None of these impairments was, however, observed in their first-degree relatives. Our results suggest that the eye movement parameters tested could not be considered as vulnerability markers for schizophrenia.

Keywords: Schizophrenia; Relatives; Smooth pursuit eye movements; Saccades; Antisaccades; Genetics; Age effect

1. Introduction

It was demonstrated by Diefendorf and Dodge [13], in 1908, that schizophrenic patients exhibit impaired smooth pursuit eye movements. In the last three decades, numerous studies have observed that 50–85% of probands are impaired on ocular paradigms such as smooth pursuit or antisaccades tasks [9,23,26,27,37,40,46]. Studying genetic vulnerability markers, eye-tracking was also tested in the relatives of schizophrenic patients. Some studies showed that nearly 45% of the relatives of schizophrenic patients had significantly poor performances on ocular pursuit. It has therefore been proposed that the eye-tracking impairments could be used as genetic vulnerability markers for this pathology.

Most of the studies testing differences between relatives of schizophrenics and healthy subjects observed impairments of the relative's performances [8,10,11,24,28,36]. They concluded that those eye movement deficits could be due to a potential genetic risk factor. But, some of the relatives included in those studies had present or passed psychiatric signs, or they were not matched by age to the control subjects. Moreover, psychiatric symptoms [21,35,47] and age [10,11,37] are known to affect eye movement performances. On the one hand, relatives with schizophrenia spectrum disorders are known to have more eye movement disorders than subjects with schizophrenia spectrum disorders but not related to schizophrenic patients, as it has been observed by Blackwood et al. [4]; Thaker et al. [57]. But, as it is well known

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that schizophrenic spectrum symptoms induce eye movement disorders (as it has been observed by O'Driscoll et al. [47]; Gooding [21]; Larrison et al. [35]), neither study [4,57] was able to distinguish which part of the impairments was due to schizophrenia and which part was due to the schizophrenic spectrum symptoms. It is then not clear if the eye movement impairments observed in those studies resulted from the genetic risk or to the psychiatric disorders themselves. On the other hand, if eye movement disorders are genetically linked, the impairments should be the same in patients with schizophrenia and their non-schizophrenic biological relatives, as it has been observed by Blackwood et al. [4]; Kathmann et al. [30]. Some of the previous studies [10,11,37], however, compared the relatives to controls without matching those subjects for age. Sharpe and Sylvester [53]; Munoz et al. [45]; Ross et al. [50] showed that smooth pursuit and saccades are impaired with age. It is then not clear if the eye movement impairments observed in those studies resulted from the genetic risk or the age factor.

In the present study, we reappraised the hypothesis that eye movement impairments may be genetic markers of liability to schizophrenia by testing both healthy relatives of schizophrenic patients and patients themselves. According to Kremen et al. [33], to be defined as risk indicators for schizophrenia, neuropsychological impairments have, first, to be relatively stable or trait-like in patients and must not appear to be simply a consequence of acute exacerbations of the illness. Second, the deficits have to be found in non-psychotic relatives and psychiatrically well relatives compared to control subjects. Consequently, to define the eye movement deficits as neurophysiological impairments, according to Kremen's definition, they have to be stable and not simply a consequence of acute exacerbations of the illness which has been showed previously [5,15], and have to be present in non-psychotic relatives and psychiatrically well relatives compared to control subjects, which we decided to address in this experiment. We studied both smooth pursuit and saccadic eye movement performances in schizophrenic patients and their healthy first-degree relatives without any past or present psychotic disorders, to ascertain that eye movement disorders are linked to a genetic risk of schizophrenia and not to psychotic symptoms. We also matched each patient and each relative to a healthy subject of the same age and gender, to avoid the effect of age.

2. Methods

2.1. Subjects

Twenty-one patients (16 men, five women) meeting DSM-IV criteria for schizophrenia [1] were recruited. They were 31.6 ±7.5 years (mean ± standard deviation (S.D.), between 21 and 50 years). Patients were required to be clinically stable for a minimum of two months, with no change in the neuroleptic dose at the time of their participation in the study. None of the patients had an ancestral history of schizophrenia. All patients were receiving neuroleptic treatment. Doses of antipsychotics were expressed in chlorpromazine (CPE) equivalent calculated according to Ban [3] and Foster's [16] estimated equivalent dose. For recent antipsychotics such as risperidone and olanzapine, we calculated the chlorpromazine equivalent using the estimated equivalent doses provided by their pharmaceutical laboratory. None was treated with drugs, such as lithium, benzodiazepines, antidepressants, barbiturates or chloral hydrate, which are all known to affect eye movements [17,22,25,34,41,54]. Schizophrenic patients were evaluated with the Positive And Negative Syndrome Scale (PANSS [31]) and with the Extrapyramidal Symptoms Rating Scale [7].

Thirty-one healthy first-degree relatives of these patients (16 mothers, nine fathers, three sisters, two brothers and one daughter) were also recruited. They were 53.4 ± 11.6 years (mean ± S.D., between 25 and 69 years). They were evaluated by the "Schedule for the Affective Disorder and Schizophrenia Life Time" (SADS-LA) [14] and the "International Personality Disorder Examination" (IPDE) [43]. None had present or past schizophrenia spectrum disorders (schizophrenia, schizoaffective disorders, personality disorders as paranoia, schizoid personality disorder or schizotypy).

Two groups of normal controls were recruited from the general population through newspaper announcements. They were matched by gender and age to the patients ($N = 21$: 16 men, five women) and the relatives ($N = 31$: 11 men, 20 women). The mean age was of 31.1 ± 7.0 (mean ± S.D., between 20 and 48 years) and 53.1 ± 11.5 (between 25 and 69 years) respectively. Healthy subjects were screened by Diagnostic Interview Schedule (DIS). They had no personal history of neurological or psychiatric disease and no family history of psychiatric illness.

Subjects with strabismus, nystagmus, neurological disease, mental retardation, and alcohol or substance abuse were excluded from the study. Visual acuity was normal, or corrected if necessary. They were asked to abstain from cigarette smoking for 1 h before beginning the study. All subjects gave written informed consent before participating in this study.

2.2. Oculomotor measures

Horizontal eye movements were recorded by an infrared photoelectric limbus eye-tracking device (Iris, Skalar, Delft, The Netherlands) in a quiet darkened room. A chin rest was used to minimize head movements. For calibration and saccadic paradigms, the target system consisted of an array of light emitting diodes (LED) placed horizontally on a flat screen placed 110 cm in front of the subject. For the pursuit paradigm, the target was a projected light from a mirror mounted on a galvanometer.

Eye and target movements were sampled on-line at 200 Hz using a 12 bit analog-to-digital converter. Eye velocity was calculated digitally using the two-point central difference

derivative algorithm with a step of 50 ms, which is the optimal size for smooth pursuit eye movements [2]: velocity at time t is equal to the difference between eye position at time (t + 50 ms) and eye position at time (t – 50 ms) divided by 0.1. Saccades were detected by an algorithm using velocity, acceleration and duration criteria, then systematically checked and corrected as required [12].

Each subject acquisition started and finished with a calibration accomplished by sequentially illuminating the LEDs (0°, ± 5°, ± 10°, ± 15°, ± 20° and ± 25°), each lasting 1 min. Subjects were tested in three tasks (smooth pursuit, reflexive saccades, and antisaccades) assigned in a pseudorandom order: half of each group of subjects had pursuit first and then saccadic tasks (always in the order saccades, antisaccades), the second half had saccadic tasks first and then smooth pursuit.

2.3. Smooth pursuit paradigm

Subjects were asked to track for one minute a projected laser spot, which moved in horizontal sinusoidal waveform at 0.4 Hz with an amplitude of ± 15° (30° peak to peak). After removing blinks and saccades, slow velocity was recalculated using the two-point central algorithm with a 50 ms step size. Amplitude of eye velocity modulation was calculated by least-square fitting a sinusoid on slow-phase velocity. The pursuit gain was computed as the ratio of the amplitude of eye velocity to the amplitude of target velocity. Corrective catch-up saccades (CUS) and compensatory back-up saccades (BUS) were defined as saccades occurring during pursuit, respectively, in the direction of target motion and in the opposite direction of target motion that took the eyes from a position behind the target (for CUS) or ahead of the target (for BUS) to one on or near the target, thereby reducing the position error. Anticipatory saccades (AS) were defined as saccades that took the eye ahead of the target, were larger than 5° in amplitude, and were followed by a post-saccadic velocity close to zero. Square-wave jerks (SWJ) were defined as pairs of small intrusive saccades in opposite directions, separated by more than 200 ms and less than 400 ms. For the five to ten better cycles of pursuit, we quantified the rate of total saccades, CUS, BUS, anticipatory saccades, and SWJ after subtracting blinks and artifacts.

2.4. Reflexive saccade paradigm

Subjects were instructed to fixate on a central LED and, after two to four seconds the fixation LED's was extinguished. Simultaneously to the fixation LED extinction, a peripheral target LED appeared 15° to the left or right. The subjects were asked to look as quickly and as accurately as possible to the peripheral target. The peripheral target was extinguished after 0.5 s. There was an inter-trial interval of two seconds before the next trial commenced. Sixty trials of reflexive saccade paradigm were administered. The peripheral target appeared randomly in either the right or the left side, but a 50:50 ratio of right and left trials was used. The percentage of reflexive saccades (correct saccades) was calculated by the number of reflexive saccades well executed (good direction and amplitude) divided by the number of target (60). The latency of the reflexive saccades was measured.

2.5. Antisaccade paradigm

The antisaccade paradigm was identical to the reflexive saccade paradigm, except that the subjects were instructed to make a saccade to the opposite location from the peripheral LED as soon as the central LED was extinguished. Sixty trials were administered, but the first ten trials were considered practice trials and were not taken into account. Saccades in the wrong direction, i.e. toward the peripheral target, were considered as errors and their percentage was calculated. The number of antisaccades and errors were measured for each subject. Then, the percentage of antisaccade errors was calculated for each subject as the number of errors divided by the sum of the number of antisaccades and errors. Both latencies of antisaccades and errors were also measured.

2.6. Statistical analyses

All data are expressed as mean ± S.D. All p values were two-tailed and considered significant when probabilities were less than 0.05.

The ages of the two youngest groups and of the two oldest groups were compared using t-tests.

We compared the performances of the patients and their matched controls on the one hand and of the relatives and their controls on the other hand using univariate analyses of covariance with the gender and age as cofactors.

3. Results

The t-tests showed no difference of age between the patients and their healthy subjects ($P = 0.815$) or between the relatives and their matched controls ($P = 0.922$).

3.1. Patients clinical data

The clinical characteristics of the probands are shown in Table 1.

All patients were receiving antipsychotics, of which eight under typical neuroleptics (two pipotiazine, two haloperidol, one flupentixol, one pimozide, one clopentixol and one under haloperidol, fluphenazine and cyamemazine), thirteen under atypical neuroleptics (six amisulpride, three olanzapine, two clozapine and two under risperidone). The mean ± S.D. doses of antipsychotics were 990.4 ± 1739.5 mg per day of chlorpromazine equivalent for the typical antipsychotics and 337.7 ± 238.3 mg per day for the atypical antipsychotics. Six patients received antiparkinsonian drugs (two trihexyphenidyle, one tropatepine, one biperidine, one trihexiphenidyle and one under biperidene and alpha-tocopherol).

Table 1
Clinical characteristics of the patients

	Minimum	Maximum	Mean	S.D.
Age (years)	21	50	31.62	7.47
Chouinard				
Parkinson	0	30	9.71	8.77
Dystonia	0	7	0.88	2.18
Dyskinesia	0	4	0.59	1.23
PANSS				
Positive	7	25	12.95	5.2
Negative	8	31	15.85	6.87
General	18	48	30.7	8.01

S.D.: standard deviation; PANSS: Positive and Negative Syndrome Scale.

3.2. Smooth pursuit paradigm

Results are given in Table 2.

The *t*-test comparisons showed that the patients had a gain significantly lower than controls ($P < 0.001$). None of the other comparisons was significant.

3.3. Reflexive saccade paradigm

Results are given in Table 3.

The *t*-test comparisons showed that the patients had a percentage of correct saccades significantly lower ($P < 0.001$) than their controls. None of the other comparisons was significant.

3.4. Antisaccade paradigm

Results are given in Table 3.

The *t*-test comparisons showed that the patients presented significantly more antisaccade errors than their matched subjects ($P = 0.002$). None of the other comparisons was significant.

4. Discussion

4.1. Smooth pursuit paradigm

Smooth pursuit paradigm impairments were characterized by significantly lower gain [26,28,38,39,40,42,49,51] and significantly higher saccadic rates in patient groups compared to healthy subjects [28,38,39,42,49]. Consistent with these studies, our patients' group had a significantly lower gain. Unlike most of the previous studies, our patients were not impaired for the saccadic intrusions.

This difference between our study and previous ones could be due to the small samples ($N = 21$ subjects in each group). Another explanation might be due to the definitions and the detection of saccades, which were not the same in all the studies. SWJ were defined in our study as pairs of small intrusive saccades in opposite directions, separated by more than 20 ms and less than 400 ms while Clementz et al. [8] used an intersaccadic interval of 150–450 ms. Our results also showed that the relatives were not impaired in smooth pursuit eye movements since no difference with the matched healthy subjects was found. These observations were consistent with those of Keefe et al. [32] who did not find any difference on quantitative parameters (gain and number of large saccades) between relatives of schizophrenic patients and healthy subjects. Litman et al. [42], likewise, compared the performances between schizophrenic patients and non-schizophrenic twins and observed that the non-affected twins had better results than the probands but did not differ from healthy subjects. Ross et al. [49] did not observe any difference between the less likely carrier relatives and healthy subjects. The criteria of the less likely carrier relatives were similar to those we used in our study to select the relatives, so the two groups were comparable.

Table 2
Smooth pursuit paradigm results

	Patients		Controls		Stat [1]	Relatives		Controls		Stat [2]
	Mean	S.D.	Mean	S.D.	*P*	Mean	S.D.	Mean	S.D.	*P*
Gain	0.766	0.173	0.863	0.08	***0.035***	0.781	0.166	0.797	0.141	0.705
f sac	2.046	0.600	1.985	0.533	0.716	1.982	0.646	1.845	0.504	0.374
f CUS	1.688	0.584	1.718	0.504	0.890	1.721	0.669	1.571	0.495	0.334
f BUS	0.132	0.108	0.127	0.097	0.881	0.058	0.065	0.082	0.071	0.175
f AS	0.061	0.113	0.014	0.036	0.081	0.085	0.162	0.071	0.126	0.702
f SWJ	0.164	0.122	0.127	0.082	0.267	0.118	0.081	0.121	0.094	0.894

f sac = frequency of all saccades; f CUS = frequency of catch-up saccades; f BUS = frequency of back-up saccades; f AS =frequency of anticipatory saccades; f SWJ = frequency of square-wave-jerks; Stat [1]: comparisons between patients and controls; Stat [2] : comparisons between relatives and controls.

Table 3
Reflexive saccade and antisaccade paradigms results

	Patient		Controls		Stat [1]	Relatives		Controls		Stat [2]
	Mean	S.D.	Mean	S.D.	*P*	Mean	S.D.	Mean	S.D.	*P*
% sac	89.33	11.91	98.65	2.33	***<0.001***	93.87	7.15	95.86	4.89	0.210
lat sac	227.20	39.74	216.97	32.70	0.392	241.34	40.67	248.02	27.63	0.367
% E AS	29.62	19.63	13.62	12.34	***0.002***	13.00	9.98	14.27	12.96	0.669
lat AS	319.27	74.19	287.38	54.65	0.128	344.40	57.46	347.16	67.09	0.840
lat EAS	246.06	58.68	224.02	45.9	0.213	272.37	73.83	262.2	38.54	0.435

% sac = percentage of correct saccades; lat sac = saccades latency (ms); % E AS = percentage of antisaccade errors; lat AS = antisaccades latency (ms); lat EAS = antisaccade errors latency (ms); Stat [1]: significance of the comparisons between patients and controls Stat [2] : comparisons between relatives and controls.

On the other hand, Ross et al. observed significant differences for the frequency of anticipatory saccades between the less likely carriers and the more likely carriers of the genetic vulnerability, resulting in favor of a link between genetic vulnerability and ocular pursuit disorders. Our results were discordant with those of Lencer et al. [38,39] who had observed rates of total saccades, of CUS and of AS significantly higher in relatives compared to controls. In these studies, some of the relatives had schizophrenic spectrum disorders (schizoaffective, schizotypy and paranoid personality disorders) and the differences observed between our study and these studies could be due to differences in healthy subjects, since such schizophrenic spectrum disorders are known to be associated with an impairment of the eye movement [56]. Karoumi et al. [28] observed both significant reduced gain and increased CUS rate in relatives compared to healthy volunteers, but no difference was found between the siblings and the probands. As in our study, the siblings did not have schizotypal personality disorder and their groups were matched for age. But, the relatives included by Karoumi et al. were all siblings, whereas most of the relatives of our study were parents of patients. When the similarity between the patients and their parents is only genetic, due to the potential sharing of similar genes, the similarity between the patients and their siblings is both genetic and environmental due to the fact that they both share identical genes and grew in the same environment. The difference between the Karoumi's study and ours could, therefore, be due to an environmental factor introduced in Karoumi's study.

4.2. Reflexive saccade paradigm

For the reflexive saccade paradigm, no statistical difference was observed for the latency of saccades between patients versus controls and between relatives and their controls, as in previous studies [10,19,20,26–28]. That expressed that the patients and the relatives had no difficulty in triggering saccades in response to the appearance of a visual target, showing that they had no impairment in producing reflexive saccades. There was, however, a statistical difference for the percentage of saccades between patients and their controls, which has not been tested in previous studies [10,19,20,26–28]. The explanation for this difference could be due to the definition we used to calculate the percentage of correct saccades. We, indeed, calculated the percentage as the number of reflexive saccades well executed by the subjects divided by the total number of trials. And it has been showed in previous studies [6,29,44] that the schizophrenic patients trigger significantly more eye blinks than healthy subjects, it explains that the patients had lower saccadic rate than their matched controls.

4.3. Antisaccade paradigm

A significant difference of the percentage of antisaccade errors between patients and their controls was observed. There was no significant difference between both groups either for the latency of succeed antisaccades or for the latency of antisaccade errors. This test supposes that the subjects inhibit the reflexive eye movements in response to the appearance of a visual target and trigger voluntary saccades in the opposite direction. Our results were in accordance with previous studies, which also observed a higher percentage of antisaccade errors in patients than in controls [8,10,11,19,20,26–28,48,52].

On the other hand, except for Fukushima et al. [18]; Clementz et al. [8]; Crawford et al. [10], the other studies observed a significant increase of the latency of successful antisaccades in patients compared to controls. The discordance between the results could be due to three main reasons: symptomatology, treatment and methodology. Patients in our study had similar severity of positive and negative symptoms, as the PANSS scores displayed. On the other hand, patients of Fukushima et al. studies had predominant negative symptoms, which could impair the eye movement tests. Thaker et al. [55], indeed, showed that the subjects with predominant negative symptoms had more antisaccade disorders than the subjects with predominant positive symptoms. Nkam et al. [46] also observed significant longer successful antisaccades latency in deficit patients compared to non-deficit patients and healthy subjects.

Second, the discrepancy between the studies could be due to the treatments. None of the subjects in our study received drugs such as lithium, barbiturates, chloral hydrate or antidepressants that are known to influence eye movement tests. In some other studies [11,20], some patients received lithium or antidepressants.

Third, all the antisaccade paradigms were not similar between studies. Some used 20 trials and others 60. The number of trials is a significant factor, because more antisaccade errors are due to an impairment of attention and concentration and to the tiredness of the subjects. Some studies used a fixed distance between the central fixation point and the peripheral targets whereas others used mixed of different distances [8,19]. More attention is needed when two different parameters (direction and amplitude) change simultaneously. Consequently, the more concentrated the subjects are, the more difficult it is to inhibit the reflexive response, so the subjects would take longer to trigger their antisaccades. Moreover, some studies [10,26] used a buzzer signal, which invited the subjects to trigger antisaccades. Finally, the definition of the latency parameter was not always the same through all the studies. In our study, the latency was defined as the time spent between the target appearance and the initiation of the saccadic eye movements, whereas others [52] defined the latency as the time spent between the stimulus appearance and the end of the saccadic eye movements. Thus, since controls generally trigger only one saccade while patients trigger several saccades to reach the final position, the latency in the controls can be shorter than the latency in patients.

4.4. Limitations of the study

The first limitation was the small size of the samples, which might have dismissed true differences between groups due to a type II error. The present results, due to a probable lack of power, should be considered as preliminary and need to be confirmed with larger samples. Nevertheless, the fact that reasonably large effects were observed for patients, demonstrated that the power and methodology of the study was sufficient to find large effects, and their absence in the relatives is therefore an important negative finding. That suggests that if there is any effect in relatives, it is likely to be very small compared to the effect in patients which would severely limit its potential as a useful endophenotypic marker, at least in ″non-familial″ schizophrenia. The second limitation was to select schizophrenic probands without an ancestral history of schizophrenia and to eliminate parents with personality disorders (paranoid, schizotypal, schizoid). Thus, the parents could be considered as ″low-risk″ to schizophrenia. The presence of negative findings does not exclude the possibility that inherited neurophysiological dysfunctions related to schizophrenia might be expressed only in 'high-risk' families for schizophrenia.

6. Conclusion

We observed impairments in the performance of the smooth pursuit, the saccades and the antisaccades in the schizophrenic patients. But none of these was present in the group of their relatives. Our results seem to indicate that the eye movement disturbances do not appear prominent in relatives without schizophrenia spectrum disorders and consequently that eye movement impairments could not be considered as vulnerability markers for schizophrenia. But since the number of subjects was small and the range of age was very spread in each group, and only healthy relatives were included, further experiments considering those aspects should be done to confirm our results.

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