Predictive saccades are impaired in biological nonpsychotic siblings of schizophrenia patients

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Objective: Although impairments in predictive saccades have been reported in patients with schizophrenia, this has never been explored in their biological relatives. We examined predictive saccades in age- and sex-matched siblings of patients with schizophrenia. **Method:** Thirty siblings of schizophrenia patients, 30 healthy matched control subjects and 30 patients with schizophrenia performed a predictive saccades paradigm. Nonanticipated and anticipated saccades were analyzed separately. **Results:** Compared with control subjects, primary saccades and final eye position were hypometric (they undershot the target) in siblings, as in patients. The proportion of anticipated saccades and latencies did not differ between the 3 groups. The maximum velocity was decreased only in patients. **Conclusion:** Alterations in predictive saccades observed in biological siblings are similar to those seen in patients, although they tend to be of a lesser degree. This finding supports predictive saccades as a valid endophenotypic marker. Further research is necessary to understand the physiopathological value of these disturbances and their link to a visuospatial representation deficit.

Objectif : Même si l'on a signalé des déficits des saccades prédictives chez les patients atteints de schizophrénie, on n'a jamais exploré le problème chez des membres leur fratrie biologique. Nous avons examiné des saccades prédictives de frères et sœurs de patients atteints de schizophrénie, jumelés en fonction de l'âge et du sexe. **Méthode :** Trente frères et sœurs de patients atteints de schizophrénie, 30 sujets témoins en bonne santé jumelés et 30 patients atteints de schizophrénie ont effectué un paradigme de saccades prédictives. On a analysé séparément les saccades imprévues et prévues. **Résultats :** Comparativement aux sujets témoins, les saccades primaires et la position finale de l'œil étaient hypométriques (n'ont pas atteint la cible) chez les frères et sœurs comme chez les patients. La proportion des saccades anticipées et des latences n'a pas différé entre les trois groupes. La vélocité maximale a diminué seulement chez les patients. **Conclusion :** Des altérations des saccades prédictives observées chez les membres de la fratrie biologique sont semblables à celles que l'on constate chez les patients, même si elles ont tendance à être moindres. Cette constatation appuie le rôle des saccades prédictives comme marqueur endophénotypique valide. D'autres recherches s'imposent pour comprendre la valeur pathophysiologique de ces troubles et leur lien avec un déficit de la représentation visuospatiale.

Introduction

Various ocular motor abnormalities have been reported in people with schizophrenia and their biological relatives. These include impaired smooth pursuit[1] (for a review, see Calkins and Iacono[2]) and abnormal performance on antisaccade tasks,[3,4] although data on the cofamiliality of the latter are inconsistent.[2,5] Predictive saccade tasks have been less extensively studied in schizophrenia. During this task, the visual target alternates with a constant frequency between 2 positions in the horizontal plane, eliciting anticipated saccades and allowing the analysis of externally elicited nonanticipated and internally elicited anticipated saccades[6] during the same task.

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In healthy subjects, Ross and Ross[7] reported a rapid decrease in predictive saccades reaction time over the very first trials until the saccades were based only on the internal anticipation of the target. Studies in subjects with schizophrenia gave conflicting results regarding predictive saccades latency, reporting no anticipation,[8] increased anticipation[9] or no difference in anticipation or latencies.[10–12]

Impaired predictive saccades accuracy has previously been reported in schizophrenia patients.[9,10,13,14] McDowell and Clementz[10] found that the reduction in saccadic amplitude was independent of reaction time in patients, suggesting that it does not reflect a simple lack of time for saccade preparation. In a previous study in recent-onset, untreated or drug-naive schizophrenia patients,[14] we found that predictive saccades accuracy was impaired specifically in anticipated saccades during a predictive saccades task, suggesting that this impairment could reflect an internally based motor planning disturbance. Comparing patients treated with antipsychotic medication and drug-naive, first-episode schizophrenia patients, Hutton and colleagues[13] found that hypometria did not depend on medication. Altogether these results suggest that hypometric saccades during a predictive saccades task are an intrinsic characteristic of the schizophrenia spectrum and could be an endophenotype. If so, a similar pattern of disturbances during predictive saccades should be present in untreated, nonpsychotic, first-degree relatives of schizophrenia patients. However, to the best of our knowledge, this has never been explored.

We hypothesized that full siblings, compared with control subjects, would display abnormalities in predictive saccades resembling those found in schizophrenia patients, in particular, hypometria. Because age could be a confounding factor, we chose to consider only unaffected full siblings of schizophrenia patients and to compare them with schizophrenia patients and with healthy control subjects matched for age, sex and educational level.

Method

All study procedures were approved by the local ethical committee (Comité Consultatif de Protection des Personnes se prêtant à une Recherche Biomedicale (CCPPRB) at the Pitié-Salpétriére Hospital, Paris).

Participants

We recruited 30 full biological siblings of patients suffering from schizophrenia: 15 men and 15 women with a mean age of 28.6 (standard deviation [SD] 8) years. These were compared with 30 healthy control subjects: 15 men and 15 women with a mean age of 28.7 (SD 8.1) years. They were also compared with 30 stabilized schizophrenia patients: 15 men and 15 women with a mean age of 28.4 (SD 7.6) years. Before subjects were enrolled, 15–30 minutes of the interview were devoted to describing all study procedures to ensure a fully informed written consent and to give subjects the opportunity to ask any questions. Written informed consent was obtained only after the study was explained to the potential participants and after they were questioned to ensure that they did understand what they were consenting to. Siblings and control subjects were given €30.

Exclusion criteria for all subjects included neurologic hard signs, a history of head trauma and substance abuse or dependence. All subjects were examined according to a standardized interview: for siblings and patients, the Diagnostic Interview for Genetic Studies[15] (DIGS 3.0) (translated into French by Krebs and colleagues[14]) was used; for control subjects, the Structured Clinical Interview for DSM-III-R, Non Patient[16] (SCID-NP) was used. Participants were all assessed for neurologic and cognitive functioning.

Full siblings were enrolled through family contacts established during the clinical follow-up of patients or from family support groups (the Union Nationale des Amis et Familles de Malades Psychiques and Schizo-Oui). Control subjects were recruited from our clinical research centre; we excluded members of the clinical department and subjects with a family history of psychiatric disorders up to the second degree. Both full siblings and control subjects were screened to exclude schizophrenia spectrum disorders. In addition, control subjects were excluded if they had a diagnosis of any DSM-IV axis I disorders. None of the full siblings or control subjects had ever received any antipsychotic medication. Except for a single depressive episode and nonspecific neurotic symptoms in 2 full siblings, the only difference between full siblings and the control subjects was that the former had a brother or sister diagnosed with schizophrenia. Seven siblings were siblings of patients also included in the study.

Patients with schizophrenia met DSM-IV criteria.[17] They were recruited from the Ambulatory Center, 15th arrondissement, and from the University Department of Psychiatry, Sainte-Anne Hospital, Paris, France. One-half (n = 15) of the schizophrenia patients were receiving antipsychotic medication at the time of the study (33% atypical, 66% typical; mean chlorpromazine equivalent 470 [SD 72] mg/d, and 450 [SD 350] mg/d, respectively[18]). Any other medications were excluded (specifically, lithium, anticonvulsivants or benzodiazepines). Among the 30 patients, 8 had participated in a previous study.[14]

Eye movement recordings

Testing procedures and ocular motor tasks were similar to those previously published.[14] Participants sat on a height-adjustable chair in a darkened, quiet room 150 cm in front of a light-emitting diode bar. Preprogrammed, pseudo-random visual sequences were administered and sampled with a frequency of 500 Hz with data acquisition software developed in our laboratory by J. Serran and D. Vital. Horizontal eye movements were recorded with an infrared oculography device (IRIS, Skalar, Cambridge Research Systems Ltd., Rochester, Kent, England) employing iris and sclera reflection (5 V, resolution of 1 m of an arc, linearity 0 ± 25°).[19] After initial calibration, at least 3 blocks were performed, consisting of 20 stimuli each and allowing a minimum of 60 saccades per participant to be analyzed.

Briefly, the predictive saccades task consisted of 2 targets

at +5° and –5° alternated with a frequency of 1.43 Hz. Each light was illuminated for 700 milliseconds; offset of the preceding light and onset of the following light occurred simultaneously (Fig. 1A). The subjects were not allowed to practise and were asked to direct their gaze toward the peripheral light as quickly and precisely as possible. Latency was defined as the time elapsed between target onset and reaction initiation. Accuracy was measured as primary gain (primary eye movement amplitude / target amplitude) and final gain (final eye movement amplitude / target amplitude). To be included, saccades had to have a primary and final gain between 0.2 and 3.0 and a primary maximum velocity between 60° and 800°/s. A conservative latency cut-off for saccades to be visually guided is 60 milliseconds.[6] We distinguished between anticipated saccades (latency of less than 60 ms) and nonanticipated saccades (latency of more than 60 ms) (Fig. 1B). Because we used only 1 target amplitude (10°), we took into account the absolute number of hypometric primary saccades and hypermetric primary saccades.

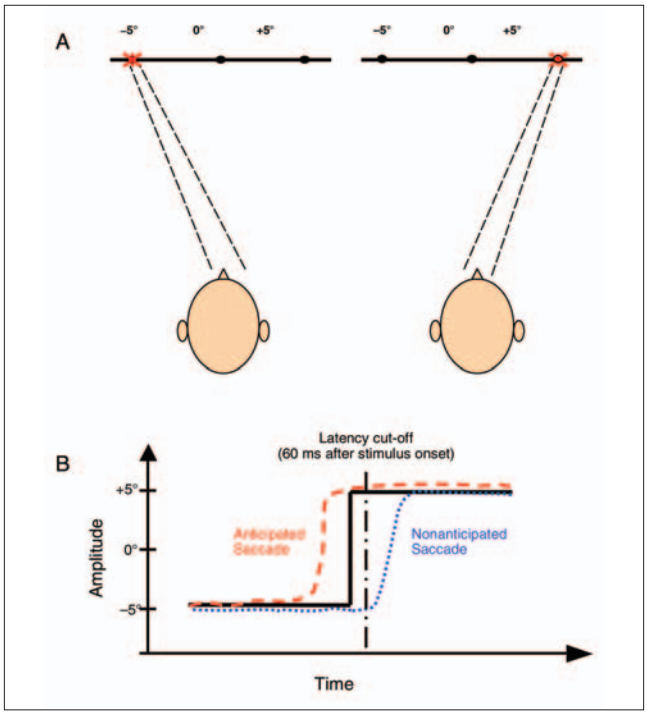

Fig. 1: The predictive saccades paradigm. (**A**) Targets alternate 5° left and right from the fixation point with a frequency of 1.43 Hz. (**B**) Two examples of predictive saccades illustrating the difference between nonanticipated saccades (eye movements occurring after target onset, dotted line) and anticipated saccades (eye movements occurring before target onset, dashed line).

Statistical analysis

The Statistical Package for the Social Sciences (SPSS), Version 12.0.1. (SPSS Inc., Chicago, Ill., 2004) was used. The Kolmogorov–Smirnov test was performed and did not show significant departure from a normal distribution in the 3 groups for any variable. We used a univariate 1-way analysis of variance (ANOVA) to test effect of group (full sibling, control and schizophrenia) on latency, maximum velocity, accuracy and relative amount of hypometric primary saccades. Separate analyses were carried out for anticipated and nonanticipated saccades. We used a post hoc Dunnett test to separately compare siblings with control subjects and with patients. To test for between-trials differences in the variables (anticipated and nonanticipated saccades), we conducted repeated-measures *t* tests separately for each group.

Because the sample of siblings belonging to the same family as the patients was small, we were not able to use intraclass correlations or use a model with a familial random effect to study familial transmission.

Results

Preliminary analyses

Full siblings, healthy control subjects and schizophrenia patients did not differ in age ($F_{2,87} = 0.014$, $p = 0.986$) , IQ ($F_{2,63} = 2.699$, $p = 0.075$) or educational level ($F_{2,87} = 2.27$, $p = 0.11$). We did not find an effect of sex for any of the variables (data not shown), and we therefore collapsed the data for subsequent analyses. Means, SDs and significance values for all trials and all variables are shown in Table 1. The percentage of anticipated saccades was 67% for schizophrenia patients, 72% for

Table 1: Means, SDs and significance values for all variables in the predictive saccades paradigms*

Group	Mean latency, ms (and SD)	Mean % primary gain (and SD)	Mean % final gain (and SD)	PM velocity, degrees/s (and SD)	Rate, %
Anticipated predictive saccades					
C (*n* =30)	–101.7 (59)	0.97 (13)	1.00 (14)	355.7 (91)‡	67 (23)
FS (*n* =30)	–99.9 (74)	0. 87 (20)†	0.92 (16)†‡	365.6 (88)‡	72 (19)
SZ (*n* =30)	–97.3 (75)	0.78 (14)†‡	0. 86 (13)†	292.6 (67)†‡	58 (27)
Nonanticipated predictive saccades					
C (*n* =30)	130.2 (20)	0.99 (14)	0.97 (12)	389.1 (105)‡	NA
FS (*n* =30)	129.5 (21)	0. 88 (19)‡	0. 87 (18)†‡	395.4 (84)‡	NA
SZ (*n* =30)	137.1 (41)	0.87 (14)†‡	0.85 (12)†	348.9 (78)‡	NA

SD = standard deviation; PM velocity = primary maximum velocity; C = control group; FS = full siblings; SZ = schizophrenia patients; NA = not applicable.
*Significance level in all cases is 5%. Values within a group were compared with univariate analysis of variance.
†Value differs from control group within the group.
‡Values vertically were compared separately for each group with repeated-measures *t* tests. These values show differences between anticipated saccades and nonanticipated saccades.

full siblings and 58% for control subjects; it did not differ between groups ($F_{2,87}$ = 2.532, p = 0.085).

Anticipated predictive saccades

We found a main effect of group in primary ($F_{2,87}$ = 10.46, p < 0.010) and final ($F_{2,87}$ = 7.39, p = 0.001) gain and in primary maximum velocity ($F_{2,87}$ = 6.94 p = 0.002). The post hoc Dunnett test showed that full siblings had a lower primary gain than control subjects (p = 0.033) and that they only tended to have a better primary gain than schizophrenia patients (p = 0.063). Full siblings also tended to have a lower final gain than control subjects (p = 0.06), and no difference was found between full siblings and schizophrenia patients (p = 0.18).

Primary maximum velocity did not differ (p = 0.86) between full siblings and control subjects and was higher in siblings than in schizophrenia patients (p = 0.002). Full siblings, schizophrenia patients and control subjects did not differ in latency of anticipated saccades ($F_{2,87}$ = 0.029, p = 0.97).

The ANOVA testing for differences in the relative amount of hypometric saccades between full siblings, schizophrenia patients and control subjects found a main effect of group ($F_{2,87}$ = 9.9, p < 0.010). The post hoc Dunnett test showed that, among anticipated primary saccades, the percentage of hypometric saccades was significantly higher in full siblings than in control subjects (siblings = 70% [3]; control subjects = 55% [3]; p = 0.02); again, there was no difference between full siblings and schizophrenia patients (siblings = 70% [3]; schizophrenia patients = 83% [1]; p = 0.1).

Nonanticipated saccades

We found a main effect of group on primary ($F_{2,87}$ = 5.64, p = 0.005) and final ($F_{2,87}$ = 5.46, p = 0.006) gain of nonanticipated saccades. The post hoc Dunnett test showed that full siblings had a lower primary and final gain than control subjects (p = 0.011 and p = 0.018, respectively), whereas siblings and schizophrenia patients did not differ (p = 0.99 and p = 0.90, respectively). Neither primary maximum velocity nor latency differed between groups ($F_{2,87}$ = 2.34, p = 0.1 and $F_{2,87}$ = 0.63, p = 0.53, respectively). The ANOVA testing for differences in the relative amount of hypometric nonanticipated saccades between full siblings, schizophrenia patients and control subjects was not significant ($F_{2,87}$ = 2.95, p = 0.06).

Nonanticipated versus anticipated saccades

Regarding within-group comparisons, the t tests for repeated measures showed that full siblings had lower final gain in the nonanticipated trials (87%), compared with the anticipated trials (92%) (t_{29} = 4.097, p < 0.001), whereas in control subjects, primary and final gain did not differ between the 2 types of saccades (t_{29} = 1.300, p = 0.204; and t_{29} = 1.516, p = 0.140, respectively). As previously reported,[14] schizophrenia patients displayed lower primary gain in the anticipated saccades (78%), compared with the nonanticipated saccades (87.0%) (t_{29} = 5.311, p < 0.001).

All 3 groups showed a higher primary maximum velocity in nonanticipated than in anticipated saccades (schizophrenia patients, t_{29} = 3.542, p = 0.001; full siblings, t_{29} = 8.982, p < 0.001; control subjects, t_{29} = 3.298, p = 0.003). To illustrate how accuracy impairment differed among the 3 groups, we superimposed the 3 Gaussian distributions of absolute primary amplitude for a total of more than 3300 anticipated saccades (Fig. 2).

Discussion

The main results of this study support our initial hypothesis that ocular motor abnormalities can be considered an endophenotype in schizophrenia. Indeed, full biological siblings of patients with schizophrenia showed impairments in the predictive saccades paradigm when compared with control subjects and did not differ from schizophrenia patients for most of the parameters. In particular, siblings demonstrated lower accuracy of the primary saccade than control subjects, whether they anticipated the target or not. They also showed lower final accuracy than control subjects when the target was not anticipated and, as a tendency, when the target was anticipated. In addition, siblings did not differ significantly from schizophrenia patients for primary and final gain in anticipated and nonanticipated predictive saccades. We also took into account a less conservative measure of accuracy by comparing the relative amount of hypometric and hypermetric saccades between groups. During anticipated saccades, siblings made more primary hypometric saccades than control subjects and did not differ from the patients; no

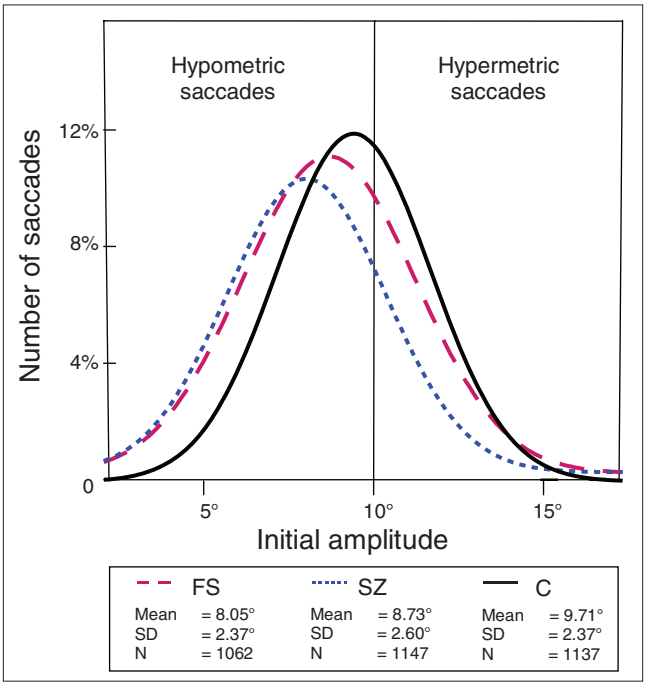

Fig. 2: Gaussian distributions for absolute primary amplitude of anticipated saccades in the predictive saccades task. FS = full siblings; SD = standard deviation; N = number of saccades; SZ = schizophrenia patients; C = healthy control subjects.

between-groups difference was found when the target was not anticipated. When we compared anticipated and nonanticipated saccades, full siblings displayed a more accurate final eye position in nonanticipated saccades (but no difference in primary accuracy), whereas in control subjects, accuracy of primary and final gain did not differ between the 2 types of predictive saccades. These results, therefore, highlight how abnormalities in ocular motor planning detectable in the siblings of schizophrenia patients are comparable for numerous points to those seen in schizophrenia patients.[20] Our results are in line with previous results regarding decreased accuracy of predictive saccades in patients.[9,10,13,14] In our own previous study,[14] untreated schizophrenia patients showed less accuracy in primary saccades when they anticipated a predictive target, but they did not show lowered accuracy in nonanticipated saccades. Here, we found only a tendency for final eye position to be less accurate in anticipated saccades, whereas we found lower accuracy during nonanticipated saccades. Possible explanations for these differences could include medication status (one-half of the patients in the present study were treated); clinical heterogeneity, although no obvious difference was found in the main clinical features of the 2 samples and inclusion criteria were similar except in regard to antipsychotic medication (data not shown); and a sample size that might have been too small to detect some of the differences observed in the earlier report. Because our primary goal was to study siblings, the patient group was only included as a positive comparison group; we did not conduct direct comparisons of treated patients and untreated patients. Heterogeneity in the received medication and size of the subsample would have hindered a reliable interpretation, and because Hutton and colleagues[13] found primary and final eye position to be impaired in schizophrenia patients regardless of their medication status, we considered treated and untreated patients together. Notably, when we considered the percentage of hypometric saccades, we found between-group differences in anticipated saccades but not in nonanticipated saccades, suggesting, in line with our previous report, that hypometria is a more marked characteristic in anticipated saccades.

Previous research suggests that performance in reflexive saccades is unimpaired in schizophrenia patients[21–25] and their full biological siblings.[5,9] Nonanticipated saccades recorded during a predictive saccades task resemble reflexive saccades[26] but may obey different control mechanisms. In contrast to reflexive saccades, nonanticipated predictive saccades are 1) rapid consecutive movements with interstimulus intervals of less than 1 second, 2) attempts to follow a rhythmic chain of targets with defined and predictable characteristics and 3) artificially extracted from a trial including a mixture of anticipated and nonanticipated saccades. These differences do not allow a direct comparison between nonanticipated predictive saccades and reflexive saccades. Our findings in this study support this view; accuracy in regard to a predictable target is impaired in full siblings, compared with control subjects, and is similar to that of schizophrenia patients. In our condition, the percentage of anticipated saccades was high and did not differ between groups. In contrast to some previous results,[8,9] but not all,[10–12] latency did not differ between the 3 groups. The characteristics of the paradigms could influence these parameters, in particular the use of a fixed target location and rather rapid alternate frequency, which might facilitate anticipation. The distinction between anticipated and nonanticipated saccades might also have artificially altered the latency distributions. In addition, the conservative cut-off point of 60 milliseconds may seem low because there is evidence that saccades as fast as 70 or 80 milliseconds after stimulus onset may not be visually guided.[6] Finally, Hutton and colleagues[13] suggest that drug-treated patients may show a steeper reduction in latency than drug-naive patients.

Siblings show primary peak velocity similar to that of control subjects and higher than that of patients. There are very few reports concerning change of peak velocity in predictive saccade paradigms, and most of the studies do not report any results on this variable. In our previous study, we had already found that schizophrenia patients had a significantly lower peak velocity in anticipated saccades,[14] which is consistent with reduced hypometric saccades. In schizophrenia patients, the conjunction of a lower primary gain, decreased maximum velocity of anticipated saccades and increased primary gain from anticipated and nonanticipated saccades indicates a more severe impairment than is found in their relatives.

Some limitations should be kept in mind when interpreting our results. First, only a small subsample of siblings came from the same families as patients. We were thus unable to use intrafamilial transmission analysis (e.g., intraclass correlations), which would more directly address the question of familial transmission of predictive saccades characteristics. However, this does not invalidate the observation that age- and sex-matched first-degree relatives present anomalies in predictive saccades when compared with healthy control subjects with no psychiatric family history. Second, in the patient group, the various antipsychotic medication statuses could have influenced performance. On the other hand, exclusion criteria in regard to concomitant medications, including neurologic side effects of treatment and substance abuse, were very stringent. Moreover, as already underlined, the group of schizophrenia patients was included in the analysis as a "positive" comparison group, and owing to the rather small subsample of patients, we did not directly compare treated and untreated patients.

Conclusion

The novelty of the present findings is that they describe for the first time impairment in a predictive saccades task in siblings of patients with schizophrenia who were compared with healthy control subjects matched for age, sex and level of education. In siblings, decreased accuracy in both anticipated and nonanticipated predictive saccades is similar to, although somewhat less than, that seen in the patients. Since the siblings in our study had never been treated with antipsychotic medications and were screened as not suffering from psychosis, the observed impairments cannot be explained as antipsychotic side effects or as the impact of disease.

These results support the view that predictive saccade anomalies are endophenotypic characteristics related to the genetic risk for developing schizophrenia. To fully establish these anomalies as endophenotypic markers, further research is needed that explores their specificity, their stability over time and disease course and their presence in at-risk subjects before disease onset. Paradigms testing schizophrenia patients and siblings in visual selective attention and internal representation tasks might yield further insight into the nature of the predictive saccades deficits. Because motor learning and motor anticipation processes are involved in the predictive paradigm, knowledge of the cerebellar contribution to the acquisition and integration of spatial target information might be useful for understanding the relation of this ocular motor impairment to the risk of developing schizophrenia.

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Contributors: Drs. Leonardi and Krebs designed the study. Drs. Amado, Leonardi, Krebs, and Mr. Landgraf acquired the data, which all authors analyzed. Drs Amado and Krebs and Mr. Landgraf wrote the article, and all authors revised it. All authors gave final approval for the article to be published.

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