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Brief article

## Predictive saccade behavior is enhanced in schizophrenia<sup>1</sup>

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### Abstract

In this study, we investigated the ability of schizophrenic patients to produce predictive saccades in response to a visual target moving with predictable timing and location. The performance of visually guided saccades and predictive saccades (gain and latency) were analyzed in a group of 12 schizophrenic patients as compared with a group of ten control subjects. Our main finding was an enhancement of the predictive tracking ability in schizophrenics. In particular, the predictive tracking built-up and became installed as a steady pattern of highly anticipatory saccades (in terms of percentage of negative latency saccades) much faster in the schizophrenic group than in the control group. These data are discussed in terms of an involvement of the fronto-striatal system in this specific enhancement of predictive saccade behavior in schizophrenia. © 1998 Elsevier Science B.V. All rights reserved

*Keywords:* Predictive saccades; Fronto-striatal system; Schizophrenia

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### 1. Introduction

Schizophrenic patients demonstrate abnormal voluntary saccade movements in a variety of behavioral conditions. For example, in an antisaccade task, they have difficulty in suppressing reflexive saccades and in producing voluntary saccades to the opposite direction of a visual target (Thaker et al., 1989; Fukushima et al., 1994; Karoumi et al., 1998) Furthermore, when performing saccades to remembered locations, they show saccadic disorders including increased latency and reduced gain (Park and Holzman, 1992; Karoumi et al., 1998) These abnormalities in the gen-

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eration of voluntary saccades observed in schizophrenia have been attributed to a frontal lobe dysfunction.

Another type of internally generated saccadic eye movements are the predictive saccades elicited when a subject has to move the eyes in time with a target. Interestingly, the production of predictive saccades can be perturbed in individuals who have damage involving the fronto-striatal system as in frontal lobe lesions, in Parkinson's disease and in Huntington's disease (MacAvoy and Bruce, 1989; Tian et al., 1991; Ventre et al., 1992). Very few studies report on the predictive behavior and the ability in producing anticipatory movements in schizophrenia. Excessive anticipatory saccades have been sparsely described in smooth pursuit tracking (Hommer and Radant, 1989; Matsue et al., 1994) and in predictive gap saccades (Hommer et al., 1991) but the pathophysiological mechanism subserving this behavior is not understood. Whether or not schizophrenics are able to produce adaptive predictive tracking, which implies the integrity of fronto-striatal function, remains a question to be explored.

To address this issue, we investigated the ability of schizophrenic patients to produce predictive saccades in response to a visual target moving with predictable timing and location. We also studied the possible correlation between saccadic performance and neuropsychological (WCST, Stroop test) and psychopathological (brief psychiatric rating scale (BPRS), positive and negative symptoms scale (PANSS)) evaluations.

## 2. Materials and methods

### 2.1. Materials

Predictive saccades were studied in 12 patients with schizophrenia, six males and six females; mean age:  $32 \pm 5.5$  years. Seven of them were classified as disorganized type, four as paranoid type and one as residual type, according to the DSM III R criteria (American Psychiatric Association, 1987). Six of the patients were hospitalized (CHS 'Le Vinatier') and six were outpatients. The mean educational score of the schizophrenic group was  $13.2 \pm 2.4$  years. The clinical symptoms were assessed by the PANSS (Kay et al., 1987) (mean positive score =  $25.3 \pm 6.1$ ; mean negative score =  $26 \pm 8.2$ ). The symptoms severity was assessed by the BPRS (Overall and Gorham, 1962) (mean BPRS score =  $57.5 \pm 14$ ) and the mean duration of illness was  $5.7 \pm 4.5$  years.

All patients but two received a stable dosology of neuroleptic medication, expressed in chlorpromazine (CPZ) equivalents (mean CPZ dose =  $274 \pm 186$  mg). Anticholinergic medication was administered to seven patients (with Simpson Angus Scale score < 6).

The patient group was compared with a group of ten control subjects (seven males and three females). The mean age of the control group was  $33 \pm 6.8$  years and the mean educational score was  $14.7 \pm 3.4$  years. Control subjects were screened for no psychiatric history. Subjects who met DSM-III-R criteria for past or present sub-

stance abuse or dependence or with low intelligence were excluded. Patient and control subjects had no history of neurological and ophthalmological disease and they did not receive benzodiazepine or lithium medication, for at least 1 month.

Neuropsychological performance was measured in both schizophrenic and control groups with the Wisconsin card sorting test (WCST) according to Nelson's method (Nelson, 1976) and the Stroop test.

All subjects gave informed consent to the study which was approved by the local ethic committee.

## 2.2. *Methods*

### 2.2.1. *Apparatus and procedure*

The subject was seated, in darkness, in front of a panel (radius 114 cm), supporting light emitting diodes located at the center and at 10, 20 and 30° right and left from the center. Eye movements were recorded by direct current electro-oculography (EOG). Cutaneous electrodes were placed on the outer canthi and on the upper and the lower ridges of the right eye, respectively, for horizontal and vertical eye movement recordings. Vertical eye movements were registered only for blink monitoring. Head movements were prevented by a frontal strap attached to the head support of the chair. EOG signals were amplified and filtered with a low-pass analogue filter (40 Hz) and digitized (sample rate of 250 Hz) and saved on computer for off-line analysis.

### 2.2.2. *Paradigms*

Saccades were tested in two behavioral paradigms: (1) visually guided saccades paradigm – the session started with the fixation of a center point (fixation point). At a random time (1400–2400 ms), the fixation point was extinguished and simultaneously the peripheral target was illuminated, at a random location (10, 20, 30°), on the right or on the left. The subject had to make saccade to the target as quickly as possible; (2) predictive saccades paradigm – the visual target was alternating between two fixed locations (10° right and left), in a predictable sequence (frequency, 0.5 Hz) The subjects were instructed to move their eyes in synchrony with the target.

A total of 60 trials were run for this paradigm.

## 2.3. *Data analysis*

Saccades were analyzed with an interactive software program. The EOG calibration was performed by measuring the EOG voltage at the final fixation of the visually guided saccade and then by a linear voltage to degrees transformation. For each paradigm, the oculomotor performance was quantified by measuring the latency and the amplitude (measured from the starting position of the eyes) of the first saccade of each correct trial. The gain was calculated by the ratio of the saccade amplitude to the target eccentricity.

For the predictive saccade paradigm, all the saccades initiated within 100 ms (minimal time for integration of a visual stimulus, Becker, 1989; Wenban-Smith

and Findlay, 1991) of, or prior to the target jump, were classified as anticipatory. A negative latency indicated that the saccade was initiated before the target jumped. The responses were divided into two subgroups: (1) the anticipatory saccades (latency less than 100 ms), and (2) the non-anticipatory saccades. Latency and gain were analyzed independently in each group of saccades and the percentage of anticipatory saccades was calculated.

Data were analyzed by a two-way multifactor analysis of variance (ANOVA). The between-group factor was the group (control and schizophrenic) and the within group factor was the direction (left and right). The inter-group differences in predictive tracking were also analyzed by a *t*-test comparison of the mean saccade latencies for the independent samples (schizophrenic group and control group).

Multivariate analysis of variance (MANOVA) was performed to assess the group differences in neuropsychological performance (WCST and Stroop). A possible correlation between saccadic abnormalities and clinical evaluation (score of BPRS and PANSS), CPZ dose and neuropsychological performance (WCST and Stroop) was established with a Spearman's rank correlation analysis.

### 3. Results

#### 3.1. Neuropsychological performance

With the WCST test, schizophrenic patients showed a significantly worse performance than control subjects on the total errors and the preservation. Likewise, the patients were slow in executing the Stroop test (Table 1).

#### 3.2. Visually guided saccades

The latency of visually guided saccades (VGS) was slightly, but not significantly increased in the schizophrenic group as compared with control group (Main group effect:  $F(1,122) = 2.11$ ;  $P = 0.14$ ). Mean latency was  $240 \pm 36$  ms in the control group and  $252 \pm 51$  ms in schizophrenic group. The VGS gain was not significantly

Table 1

Neuropsychological performance (WCST and STROOP test) obtained in the schizophrenic group and in the control group

	Schizophrenic group, mean (SD)	Control group, mean (SD)	
<i>WCST</i>			
Categories	5.16 (1.3)	5.80 (0.4)	NS
% Preservative errors	25.40 (21.7)	3.92 (8.6)	$P < 0.009$
Total errors	5.25 (3.3)	2.30 (3.02)	$P < 0.05$
<i>Stroop</i>			
Time (s)	117 (24)	92.3 (16)	$P < 0.02$
Errors	3.6 (3.6)	1.7 (1.4)	NS

NS, not significant.

different between the normal ( $0.91 \pm 0.04$ ) and the schizophrenic group ( $0.93 \pm 0.06$ ). Main group effects:  $F(1,22) = 0.63$ ;  $P = 0.42$ .

### 3.3. Predictive saccades

As shown in the predictive saccade latency histogram of Fig. 1, we observed a clear bias of the predictive saccade latencies towards anticipatory values in the schizophrenic group as compared with the control group. In each group we dissociated the anticipatory saccades (AS) with latencies less than 100 ms from the non-anticipatory saccades (NAS) with latencies more than 100 ms.

Non-anticipatory saccades (NAS): as for the VGS, the NAS latency in the schizophrenic group ( $182 \pm 42$  ms) was slightly, but not significantly increased with respect to the control group ( $160 \pm 30$  ms). Main group effect:  $F(1,44) = 3.52$ ,  $P = 0.06$  (Fig. 2). The NAS gain in the schizophrenic group ( $0.90 \pm 0.09$ ) was normal as compared with the control group ( $0.88 \pm 0.12$ ). Main group effect:  $F(1,44) = 0.20$ ,  $P = 0.65$

Anticipatory saccades (AS): as shown in Fig. 3, the mean percentage of AS in the schizophrenic group ( $80 \pm 11\%$ ) was significantly higher than in the control group ( $61 \pm 22\%$ ). Main group effect:  $F(1,44) = 13.77$ ,  $P < 0.001$ ). Saccades were more anticipatory as mean latencies became more negative in the schizophrenic group ( $-140 \pm 84$  ms) as compared with the control group ( $-53 \pm 110$  ms). Main group effect:  $F(1,44) = 8.75$ ,  $P = 0.005$ . The AS gain was decreased in the schizophrenic group ( $0.83 \pm 0.11$ ) as compared with the control group ( $0.90 \pm 1.4$ ). Main group effect:  $F(1,44) = 4.89$ ,  $P = 0.03$ .

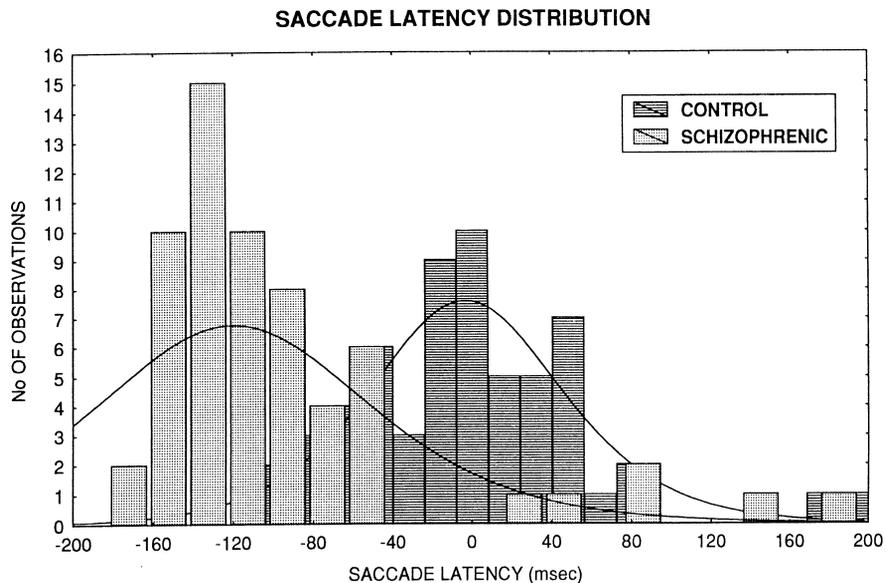


Fig. 1. Saccade latency distribution during the predictive tracking in the schizophrenic group and in the control group.

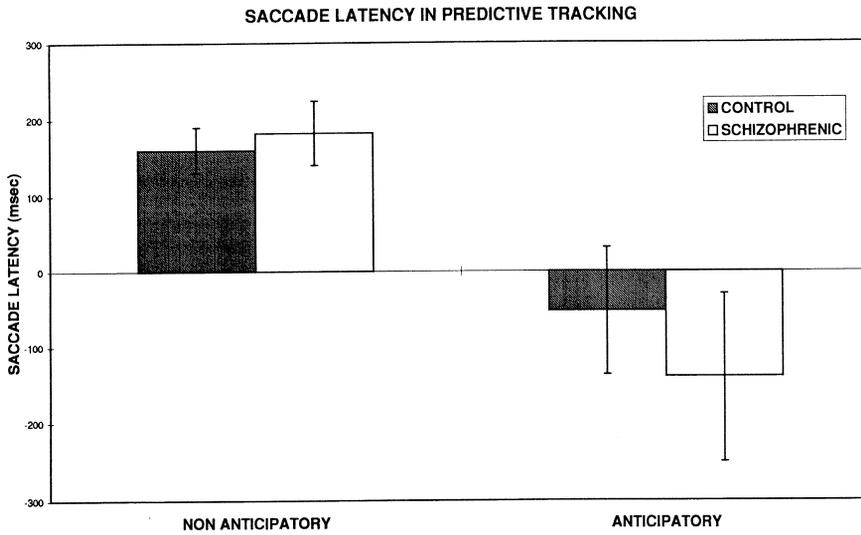


Fig. 2. Mean latency of non-anticipatory saccades (NAS) and of anticipatory saccades (AS), in the control group and in the schizophrenic group. Standard deviation are represented by the bars.

3.3.1. Pattern of predictive tracking

For each subject, we plotted the latency, at each point in time, and we evaluated the variability of this tracking by measuring the within subject standard deviation

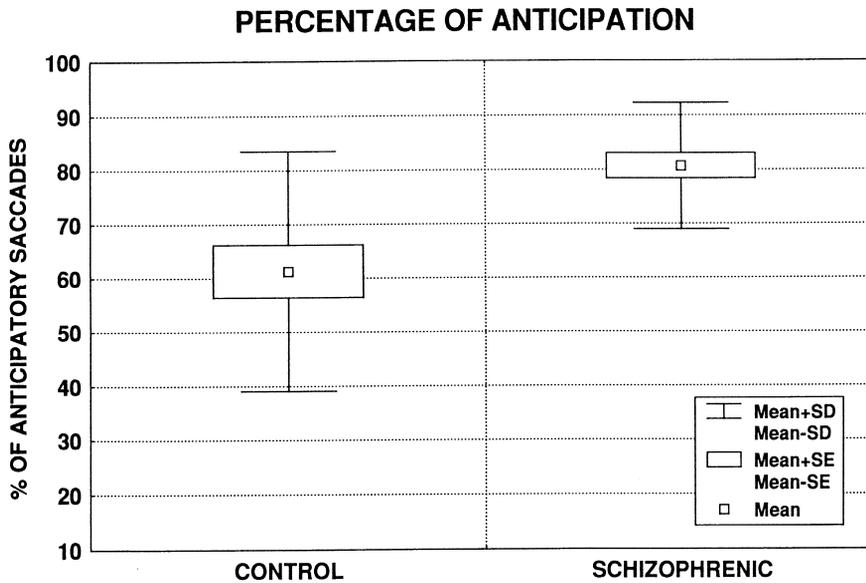


Fig. 3. Mean percentage of anticipatory saccades during predictive tracking in the control group and in the schizophrenic group.

### PREDICTIVE TRACKING OVER TIME

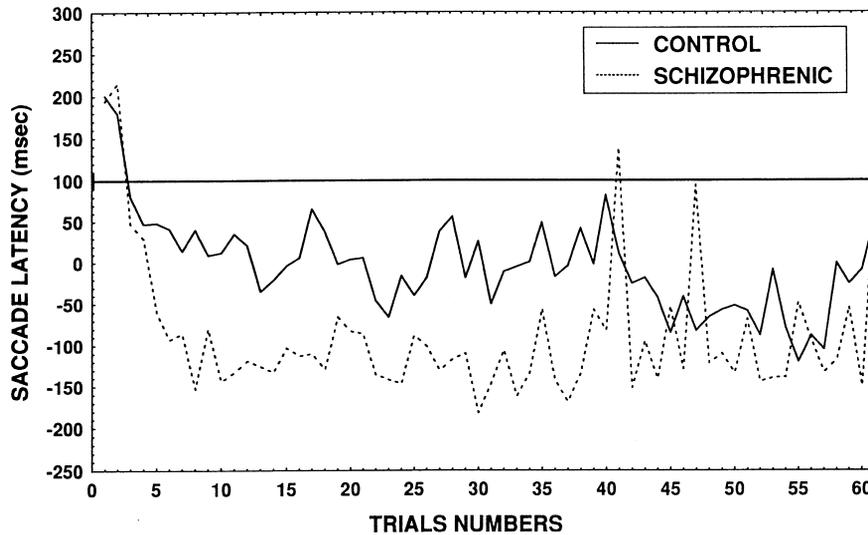


Fig. 4. Pattern of predictive tracking in the control group and in the schizophrenic group. Mean latency of predictive saccades is plotted at each point of time (trial numbers).

(SD) of saccadic latency. We found that the saccadic latency variability was slightly increased in schizophrenics (within subject  $SD = 142 \pm 44$ ) as compared with the controls (within subject  $SD = 118 \pm 45$ ).

For each group, mean latency was plotted at each point in time, during the entire periode of predictive tracking. This pattern of predictive tracking in the schizophrenic group and in the control group is illustrated in Fig. 4. The mean latency of predictive saccades (including anticipatory and non-anticipatory saccades) was less in the schizophrenic group (mean,  $-89$ ;  $SD$ , 82 ms) than in the control group (mean,  $-3$ ;  $SD$ , 58 ms). As for the within subjects variability, the within-group latency variability over time increased in the schizophrenic group (within-group  $SD$ , 82 ms) mainly in the last trials as compared with the control group (within-group  $SD$ , 58 ms). The pattern of predictive tracking over time was significantly different between the schizophrenic and the control groups ( $t$ -test for independent samples:  $t$ -value = 6.6,  $p < 0.0001$ ). As shown in Fig. 4, the main characteristics of predictive tracking in the schizophrenic group with respect to the control group can be outlined as a fast build-up (in five trials) to a high anticipatory and relatively steady pattern.

#### 3.4. Correlation between predictive tracking abnormalities and clinical and neuropsychological ratings

Oculomotor abnormalities were correlated with some of the neuropsychological deficits and clinical rating. As main data, we found (1) a significant positive correla-

tion between the anticipatory saccade latency and WCST categories, ( $r = 0.77$ ,  $P = 0.002$ ), and (2) a positive correlation between the percentage of anticipation and the negative score of the PANSS ( $r = 0.59$ ,  $P = 0.04$ ).

No significant correlation was found (1) either between anticipatory latency and the CPZ dose ( $r = 0.03$ ,  $P = 0.91$ ), the duration of illness ( $r = 0.40$ ,  $P = 0.18$ ) and the clinical severity ( $r = -0.49$ ,  $P = 0.09$ ) (2) either the percentage of anticipation and the CPZ dose ( $r = -0.40$ ,  $P = 0.19$ ), the duration of illness ( $r = 0.39$ ,  $P = 0.20$ ) and the clinical severity ( $r = 0.20$ ,  $P = 0.51$ ).

In the control group, no significant correlation was found between saccadic parameters and neuropsychological performance.

## 4. Discussion

### 4.1. Predictive tracking in schizophrenic patients

The main finding of this study is that schizophrenic patients show an enhancement of their predictive tracking of a visual target jumping with predictable timing and location. In particular, the predictive saccadic tracking built-up and became installed as a steady pattern of highly anticipatory saccades, much faster in the schizophrenic group than in the control group.

A predictive tracking requires that the temporal and spatial components of the target motion are correctly stored in an internal representation (Bloxham et al., 1984). Anticipation requires the ability to use this internal representation to predict the direction and the timing of the next target. During the predictive tracking, the saccades made within 100 ms of the target jump, (referred to as anticipatory saccades) have no immediate visual information available to assist in saccade programming (Becker, 1989; Wenban-Smith and Findlay, 1991) and thus are internally generated. The analysis of the predictive tracking pattern shows that schizophrenic patients began to anticipate in the first trials, and produced more anticipatory saccades than did the controls. At the end of the session, their saccadic latency was more variable over time, particularly in the last trials, which might result from an effect of fatigue on the motor performance. To our knowledge, this study provides the first data describing an enhanced performance in the ability of prediction in visuo-motor behavior in schizophrenics. This behavior could functionally be paralleled to usual stereotyped behavior often described in schizophrenia (Pedro et al., 1994) and might be related to modified gating of the sensorimotor information coming from the mental representation of target motion.

### 4.2. Pathophysiology of predictive abnormalities in schizophrenics

The pathophysiological mechanisms subserving the predictive tracking behavior in schizophrenic patients are not known. However, the difficulty in inhibiting inappropriate saccades observed in our patients is compatible with the idea of a fronto-striatal implication in predictive tracking (MacAvoy and Bruce, 1989; Tian et al.,

1991; Ventre et al., 1992). The excessive production of anticipatory saccades demonstrated by schizophrenic patients might be related to the difficulty of these patients to inhibit the generation of inappropriate saccades, triggered on the basis of an internal representation. Some behavioral studies have shown that schizophrenics made more maladaptive anticipatory saccades than controls during smooth pursuit tracking (Hommer and Radant, 1989; Matsue et al., 1994), and also more reflexive saccades in antisaccade tasks (Thaker et al., 1989; Fukushima et al., 1994; Karoumi et al., 1998). These saccadic abnormalities have been attributed to a failure of the frontal lobe to inhibit subcortical structures involved in the oculomotor control, particularly the superior colliculus (Thaker et al., 1989). In agreement with this hypothesis, we observed a significant positive correlation between the anticipatory saccade latency and impaired performance on the WCST, presumed sensitive to frontal lobe dysfunction (Weinberger et al., 1986).

Another possible explanation could arise from the role of basal ganglia in the control of saccadic eye movement. The superior colliculus (SC) is the midbrain structure involved in the generation of all types of saccades. The basal ganglia, through the substantia nigra pars reticulata (SNPR), may gate the activity in the SC, to suppress unwanted saccades and to facilitate volitional saccades in the context of learned or memorized behavior (Hikosaka and Wurtz, 1989). Consequently, a dysfunction at any level of the cortico-striatal circuit could lead to a failure in gating information into SC and thus, induce abnormal saccades. Interestingly, the comparison between the predictive performance of Parkinson patients and schizophrenic patients may help to clarify the physiopathological mechanisms underlying predictive behavior in these two pathologies involving the same nervous structures. In contrast to the schizophrenic patients, Parkinson's patients are characterized by an impairment in generating anticipatory saccades in a predictive tracking task (Bloxham et al., 1984; Crawford et al., 1989; Ventre et al., 1992), and this defect has been attributed to a dopaminergic deficiency in the nigrostriatal system (Bronstein and Kennard, 1985). This paradoxical difference in Parkinson and schizophrenic behavior could be explained by different specific perturbations of dopaminergic activity in the fronto-striatal system in schizophrenia and in Parkinson's disease. Interestingly, such a behavioral dichotomy has been recently observed in sequence learning tasks in Parkinson disease and in schizophrenia (Dominey and Georgieff, 1997; Dominey et al., 1997).

Several studies have demonstrated that the anatomo-functional dysfunction of the fronto-striatal system is implicated in cognitive and clinical disturbances of schizophrenia (Buchsbaum et al., 1992; Wolking et al., 1992; Buchanan et al., 1993; Dominey and Georgieff, 1997), such as negative symptoms, stereotyped behavior and cognitive eye movement disorders (Buchanan et al., 1993; Pedro et al., 1994; Ross et al., 1995). It is of interest to note that in our patients, we observed a positive correlation between anticipatory saccade rate and negative symptoms score. This suggests that the fronto-striatal system functionality and likely dopaminergic dysregulation, might be involved in the predictive saccade enhancement found in schizophrenic patients. As no correlation has been found between neither the illness severity and duration, nor the neuroleptic medication, similar to previous observa-

tions (Hommer et al., 1991), the predictive saccade enhancement observed in our study reflects a specific fronto-striatal system dysfunction.

The fronto-striatal system and its disorders remain a complex topic of research. Further studies using similar protocols in these two pathological models, schizophrenia and parkinsonism will help to provide a better understanding of fronto-striatal system regulation.

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