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Characteristics of Saccadic Responses in an Experimental "Go/No Go" Scheme in Healthy Subjects and Those at Ultra High Risk of Developing Schizophrenia

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Studies using presentation of visual stimuli in a "go/no go" scheme revealed differences in saccadic responses in healthy subjects and patients at ultra high risk of developing schizophrenia. Patients showed a greater number of erroneous responses to inhibitory stimuli and shorter latent periods (LP) for correct and erroneous saccades. Opposite asymmetries were demonstrated for the LP of saccadic responses in healthy subjects and patients: the LP of saccades to the right was shorter than to the left in healthy subjects, while the LP of saccades to the right was longer than to the left in patients. These data showed that impairments to the mechanisms controlling voluntary behavior occur at the pre-manifest stage of the course of schizophrenia when there is a ultra high risk of developing this condition. The results obtained here suggest that patients at ultra high risk of developing schizophrenia have impairments to the processes of voluntary and involuntary attention, as well as to the processes of inhibitory control, which may be due to dysfunction of the right prefrontal cortex and weakening of top down influences in the attention and inhibitory control systems.

Keywords: saccade, latent period, attention, inhibition, "go/no go," ultra high risk of developing schizophrenia.

Cognitive control of adaptive behavior in humans is a relevant challenge in contemporary neuro- and psychophysiology. A suitable approach to addressing this challenge is provided by studies of the behavioral and EEG correlates of the preparation of saccadic responses in different conditions of presentation of visual information. Saccadic eye movements as an unavoidable component of vision are involved in selecting the visual targets determining behavior in humans. Clinical and neurophysiological data provide evidence of a tight interaction between the programming of saccades and the processes underlying attention and decision-taking and of the functional and anatomical overlapping of the structures controlling these processes at different levels of the brain [Slavutskaya et al., 2008; Eimer et al., 2007; Gaymard et al., 1998; Kable and Glimcher, 2009].

Clinical conditions provide an additional opportunity for studying the cognitive control of saccadic movements. Weakening of attention processes, decision-taking, and inhibition in schizophrenia are accompanied by impairments to oculomotor functions [Benson et al., 2012; Broerse et al., 2001; Camchong et al., 2008].

The development of schizophrenia is preceded by a prodromal phase of "ultra high risk" (UHR) of developing the disease [Yung et al., 2007]. The following inclusion criteria apply to patients in the UHR group: 1) repetitive weak, subthreshold symptoms (subpsychotic symptoms: referential ideas, magical thinking, impaired perception, paranoid ideas, unusual thoughts and speech); 2) transient psychotic symptoms (brief, time-limited intermittent psychotic symptoms); 3) inherited burden, i.e., the existence of first-degree relatives with psychotic illness or schizotypic disorder, as

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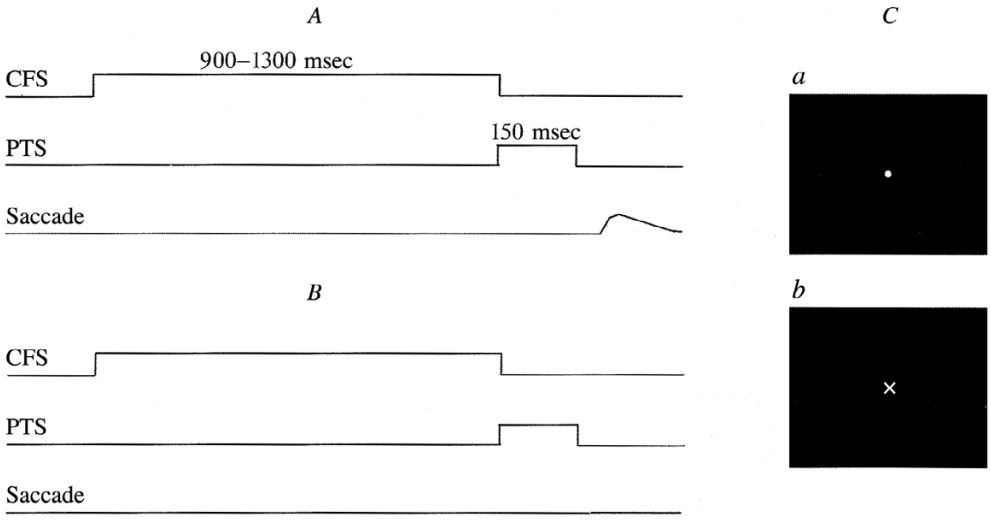

Fig. 1. Diagram showing presentation of "go/no go" visual stimuli. *A*) The "go" condition; *B*) the "no go" condition; *C*) *a* and *b* are the "go" and "no go" stimuli, respectively (the presentation probabilities in different subjects was 50%).

well as schizotypic disorder in the patient him- or herself with significant deterioration of premorbid functioning for at leas one month (but not more than five years); 4) the presence of "basal" symptoms – subjectively identified impairments in the domains of perception, thinking, speech, and attention, with a structure not corresponding to classical psychotic disorders (difficulty in focusing attention, impairments to expressive speech and the perception of speech, disordered abstract thinking, absentmindedness with bewilderment, broken thoughts, blocked thoughts, perseveration, unstable referential ideas, signs of derealization, elementary perceptual abnormalities) [Omel'chenko et al., 2016].

The mechanisms of the transfer from the prodromal phase to schizophrenia have received little study. There are only a few reports analyzing impairments to eye movements in the UHR group [Nieman et al., 2007; van Tricht, 2010], which makes studies of this type very relevant.

One methodological approach to studying the cognitive control of saccadic behavior is provided by the experimental "go/no go" paradigm [Lisberger, 1975; Becker and Jurgens, 1979]. In this scheme, two peripheral visual stimuli are presented in random order, one being a target for saccades, the other being an inhibitory stimulus to which the subject has to refrain from responding but must maintain gaze fixation.

The aim of the present work was to study the nature of saccadic responses in an experimental "go/no go" scheme in healthy people and patients at ultra high risk of developing schizophrenia as correlates of the cognitive control of programming saccadic responses.

Analysis of the behavioral characteristics of saccadic responses and their latent periods (LP) depending on visual control and saccade direction provide for assessment of the recruitment of attention and voluntary inhibition processes in the programming of saccades in healthy subjects and patients at ultra high risk of developing schizophrenia. This type of study also has applied value for developing neurobiological markers for impaired cognitive functions in this disease and for selecting appropriate treatments and prognosticating the course of illness.

Methods. The study included a total of 17 patients aged 17–23 (mean 19 ± 3) years with nonpsychotic forms of mental disorders who at the stage of primary hospitalization met the following criteria: presence of psychopathological symptomatology at a nonpsychotic level, individual symptoms on the psychotic spectrum, and absence of concomitant mentally clinically significant somatic or neurological pathology (history of psychotic episodes, organic mental disorders, alcoholism, drug addiction, mental retardation).

The control group consisted of 15 healthy male subjects aged 18–22 (mean 20 ± 2) years.

All subjects had normal or corrected vision and were right-handed. All subjects gave written informed consent to take part in the study, which was approved by the Ethics Committee of the Faculty of Biology, Lomonosov Moscow State University, and the Ethics Committee of the Scientific Center for Mental Health. The study complied with the code of ethics of the World Medical Association (Helsinki Declaration) for studies in humans.

Horizontal eye movements were recorded using a bipolar electrooculogram (EOG) method with a time constant of 0.5 sec. Non-polarized cup electrodes 10 mm in diameter were positioned around the margins of the right and left eye sockets. The electroencephalogram (EEG) was recorded in all subjects using 24 leads distributed according to the 10–20 system for subsequent analysis. The signal digitization frequency was 512 Hz; the upper frequency filter was set to 80 Hz and the time constant for EEG recording was 1 sec. EEG analysis results are not presented here.

TABLE 1. Numbers of Saccades and Mean LP for Correct and Erroneous Saccades in the Go/No Go Experimental Scheme in Healthy Subjects and in Patients at Ultra High Risk of Developing Schizophrenia

Group	Correct saccades to target stimulus (N/M; Qt)		Erroneous saccades to the inhibitory stimulus (N/M; Qt)	
	saccades to the left	saccades to the right	saccades to the left	saccades to the right
Healthy	926/260; 197, 310	997/250; 197, 296	359/174; 142, 233	277/194; 154, 233
Patients	773/180; 130, 266	936/204; 156, 272	604/151; 126, 192	524/150; 126, 192

N is the number of saccades; M is the median; Qt is the quartile.

During the experiments, subjects were in a dark room, sitting in a chair with a head support. Visual stimuli consisting of white circles or crosses (0.2° in diameter) were presented on a black monitor screen positioned 60 cm from the subject's eyes (Fig. 1, *C*). Three visual stimuli were used – a central fixation stimulus (CFS) at the center of the screen and two peripheral target stimuli (PTS) positioned 7° to the left and right of the central stimulus along a horizontal line. The signal value of the PTS ("go" or "no go") was distributed with equal probabilities in different subjects.

Subjects were given the instruction: "Fix your gaze on the central stimulus. When the peripheral stimulus, a circle (or cross), is presented, divert your gaze to it as quickly as you can. Then return your gaze to the center of the screen and maintain gaze there. Do not move your gaze when the stimulus is a cross (or circle)."

The experimental scheme is shown in Fig. 1. The duration of presentation of the central stimulus was 900–1300 msec, while that of the peripheral stimulus was 150 msec. Peripheral visual stimuli were presented in the left and right visual hemifields at equal probabilities. This modification of the "go/no go" paradigm minimizes the possibility of forming a defined mindset in relation to performing saccades or inhibiting saccades depending on the probability of target or inhibitory stimulus presentation. The interval between sequential stimulus presentations was 900–1300 msec.

Each healthy subject or patient was presented with 200–250 visual stimuli during the study. Stimuli were presented in blocks of 50 stimuli. Behavioral characteristics of responses were monitored in terms of the numbers of erroneous saccades per inhibitory stimulus and the number of missed target stimuli, as well as the latent periods (LP) of correct and erroneous saccades in relation to their directions.

Planning and control of the experiment and collection and preliminary analysis of the results were run on the CONAN-m electrophysiological laboratory system. Monitoring of saccades and calculation of LP values were performed automatically using the original Saccade Search computer program. Only those saccades whose LP were in the range 85–500 msec were included in the analysis.

The influences of three main factors with two gradations were analyzed separately: the type of saccade (correct or erroneous), laterality (saccades to left and right), and group (healthy subjects or patients). This was performed by two-factor analysis of variance (ANOVA for a model of fixed factor effects) with repeat measures (9–114 saccades recorded in individual subjects); the second accessory factor was "subjects." This scheme allowed the effects of each main factor to be refined by removing interindividual variation.

Significant differences between mean numbers of erroneous responses were identified using the nonparametric Wilcoxon test (*W*). Differences in event frequencies were identified using the *Z* goodness-of-fit test for frequencies [Urbakh, 1965].

Results. Significant between-group differences were found in the numbers of erroneous saccadic responses and in their latent periods depending on the spatial distribution of the signal stimuli in the "go/no go" scheme (Table 1, Fig. 2).

Erroneous responses in the form of saccades in response to inhibitory stimuli ("no go," "false anxiety" errors) were encountered in all patients and 14 of the 15 healthy subjects. Patients made significantly more errors than healthy subjects: 38 ± 7% errors in patients and 24.3 ± 4% errors in healthy subjects ($W(34, 28) = 1375$, $p < 0.0001$). There were no significant differences in either group in the proportions of errors depending on saccade direction ($p > 0.05$).

Analysis of variance (ANOVA) showed that the "type of saccade" × "group" and the "direction" × "group" factors influenced the latent periods of saccadic reactions.

Patients showed a shorter mean LP for correct saccades in response to "go" stimuli than seen in healthy subjects (Fig. 2, *A*): 180 msec vs. 260 msec for saccades to the left ($F(1,1550) = 38.4$; $p < 0.0001$) and 204 msec vs. 250 msec for saccades to the right ($F(1,1803) = 34.6$; $p < 0.0001$). An analogous situation was also seen in relation to the LP of erroneous saccades (Fig. 2, *B*): 151 msec in patients vs. 174 msec in healthy subjects for saccades to the left ($F(1,615) = 50.9$; $p < 0.0001$) and 150 msec vs. 194 msec for saccades to the right ($F(1,650) = 15.7$; $p < 0.0001$).

Most subjects of both groups (13 of the 15 healthy subjects, $Z = 4.38$; $p < 0.0001$, and in 15 of the 17 patients, $Z = 4.8$; $p < 0.0001$) showed shorter LP for erroneous saccades in response to "no go" stimuli as compared with correct saccades in response to "go" stimuli (Table 1; Fig. 2): 174 msec vs. 260 msec for saccades to the left ($F(1,1275) = 42.1$; $p < 0.0001$) and 194 msec vs. 250 msec for saccades

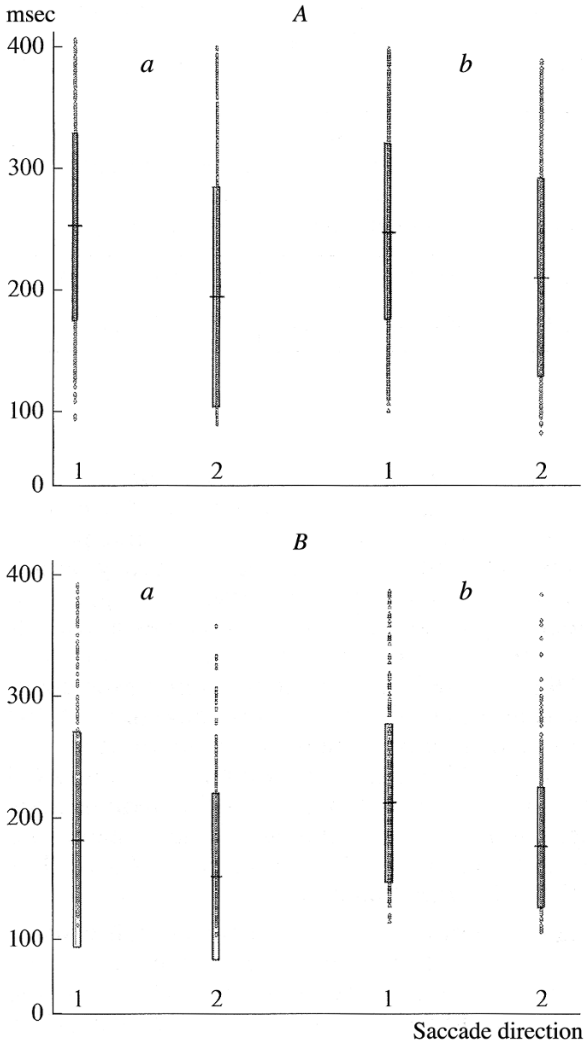

Fig. 2. Box and whisker plots of distributions of LP of saccades. *A*) Saccades to "go" stimuli in the healthy (*a*) and patients (*b*) groups; *B*) erroneous saccades in response to "no go" stimuli; 1) saccades to the left; 2) saccades to the right. Vertical rectangles show standard deviations. Horizontal bars at the centers of rectangles show arithmetic means.

to the right ($F(1,1423) = 13.54$; $p < 0.0001$) in healthy subjects; 151 msec vs. 180 msec for saccades to the left ($F(1,1428) = 32.7$; $p < 0.0001$) and 150 msec vs. 250 msec for saccades to the right ($F(1,1464) = 37.5$; $p < 0.0001$) in patients.

Correct saccades in response to "go" stimuli showed an opposite group relationship between LP and saccade laterality. Most healthy subjects (11 of 15, $Z = 2.92$; $p = 0.003$) showed shorter LP for saccades to the right than to the left (by 10 ± 8 msec, $F(1,2202) = 37.2$; $p < 0.0001$). Most patients (13 of 17, $Z = 3.43$; $p = 0.0006$) showed the opposite relationship – shorter LP for saccades to the left than to the right (by 12.4 ± 3 msec, $F(1,1539) = 42.9$; $p < 0.0001$).

Analysis of variance (ANOVA) identified a significant interaction between the "laterality" × "group" factors, lateral differences in the LP of saccadic responses in healthy subjects and schizophrenia patients being in the opposite directions. Most healthy subjects (11 of 15, $Z = 2.92$ $p =$ $= 0.003$) showed shorter mean LP for correct saccades in response to "go" stimuli to the right than for saccades to the left (by 10 ± 8 msec, $F(1,2202) = 37.2$; $p = 0.0001$). Patients (13 of 17, $Z = 3.43$; $p = 0.0006$) showed shorter LP for correct saccades to the left than for saccades to the right (by 12.4 ± 3 msec; $F(1,1539) = 42.9$; $p < 0.0001$).

A different relationship in the spatial asymmetry of LP values was seen in the patients and normal groups for erroneous saccades in response to the inhibitory stimulus. Most patients (11 of 17, $Z = 2.4$; $p < 0.0001$) lacked lateral differences in the LP for correct and erroneous saccades ($p > 0.05$). In healthy subjects (11 of 15, $Z = 2.92$; $p = 0.003$), LP for erroneous saccades to the left were shorter than LP for saccades to the right, by 16 ± 6 msec ($F(1,669) = 33.5$; $p < 0.0001$), i.e., spatial asymmetry in LP was in the opposite directions for correct and erroneous saccades in healthy subjects.

Discussion. Thus, these studies using the "go/no go" paradigm identified significant differences between healthy subjects and patients with diagnoses of ultra high risk of developing schizophrenia in terms of the number of erroneous responses, the durations of their latent periods, and the nature of lateralization.

The greater number of erroneous saccades seen here in patients at ultra high risk of developing schizophrenia than in healthy subjects has been reported previously in schizophrenia in different experimental conditions [Klein, 1996]. The cause of the greater number of errors in schizophrenia has been suggested to consist of frontal cortex dysfunction which, according to extensive clinical, electrophysiological, and fMRI studies, is a leading factor in executive functions [Goldman-Rakic, 1988; Everling and Fischer, 1998].

This increase in the number of errors in the "go/no go" paradigm in patients at ultra high risk of developing schizophrenia may be evidence of impairment to spatial attention and weakening of inhibitory control, which have been demonstrated previously in schizophrenia [Thakkar et al., 2011]. On the basis of neurophysiological studies in primates, the authors suggested that the main mechanism of these impairments in schizophrenia lies in specific changes in the reciprocal connections of saccadic and fixation neurons in the oculomotor zones of the frontal cortex and superior colliculi.

Our studies identified differences in the latent periods of correct and erroneous responses in healthy subjects and patients at ultra high risk of developing schizophrenia. In the group of patients, LP for both correct and erroneous saccades were shorter than in healthy subjects. This phenomenon has been demonstrated previously in schizophrenia. It has been suggested that acceleration of sensorimotor integration processes is reflected in the latent period of saccades and may be due to the cognitive dysfunctions specific to schizophrenia: impairments to the processes of "sensory filtration" [Lijffijt et

al., 2009], a decrease in the sensory processing time [Strelets et al., 2012], along with impairment to involuntary attention [Nestor et al., 1992; Spencer, 2011]. However, other studies have demonstrated slowing of responses in schizophrenia [Hughes et al., 2011]. It may be that these contradictions result from differences in experimental paradigms, in terms of different cognitive loadings on the functions of executive control. Our previous studies using the "double step" scheme demonstrated that schizophrenia patients show reductions in the LP of saccades to the first stimulus and increases in the LP of saccades to the second stimulus as compared with healthy subjects [Shul'govskii, 2015].

In this paradigm, two short stimuli are sequentially presented in opposite visual hemifields. Our suggestion is that the cause of this increase in the latent period of the second saccade in schizophrenia may be impairment to the processes of the reorientation of attention from one visual hemifield to the other [Maruff and Hay, 1995] and weakening of the extraretinal efferent copy signal ("corollary discharge") required for programming the second saccade [Thakkar et al., 2015].

In the present study, both healthy subjects and patients showed decreases in the LP of erroneous saccades as compared with saccades to the target stimulus. This has been demonstrated in many studies and reflects the nature of erroneous saccades as a correlate of exogenous automatic attention [Ptak et al., 2011], increases in which in schizophrenia may also be related to weakening of the process of fixation [Reuter et al., 2011].

Interesting data were obtained by comparing lateral differences in the latent periods of saccadic responses in healthy subjects and patients at ultra high risk of developing schizophrenia. Healthy subjects showed shorter LP for correct saccades to the right than for saccades to the left. This asymmetry in LP values reflects dominance of the leading left hemisphere in the processes organizing saccades to the right in healthy subjects [Bragina and Dobrokhotova, 1988]. Furthermore, it may be the consequence of the lack of targeted spatial attention in the modification of the "go/no go" paradigm used here, due to the equal probabilities of presentation of target and inhibitory stimuli. We have previously demonstrated this asymmetry in LP using equal probabilities of the use of individual visual stimuli (the "step" paradigm), while use of other experimental schemes (the "antisaccadic," "focused attention," "cost-benefit," and "saccades by memory" schemes) produced the opposite type of lateralization – shorter LP for saccades to the left [Slavutskaya et al., 2001; Slavutskaya and Shulgovskiy, 2007]. All these paradigms share the features of strengthening of spatial attention controlled by the right hemisphere mechanism responsible for saccades to the left [Bragina and Dobrokhotova, 1988; Coull, 1998; Posner, 1980].

In the present study, healthy subjects showed the opposite asymmetry in LP values for correct and erroneous saccades: erroneous saccades to the left had a shorter LP than saccades to the right. These data confirmed the suggestion that erroneous saccades are a correlate of involuntary attention, which is controlled by the right hemisphere [Ptak et al., 2011].

In patients at ultra high risk of developing schizophrenia, there were no differences in the LP of erroneous saccades in relation to direction, which may also reflect impairment to the attention system in this disorder. The process of "disengagement of attention" in the right visual hemifield, which is required for saccades to be generated to the left, is known to be weakened in schizophrenia [Maruff and Hay, 1995; Moran and Thaker, 1996].

Comparison of our data from the present study with previous results obtained using the "double step" paradigm and published data demonstrated similarities in the specific features of saccadic responses in patients at ultra high risk of developing schizophrenia and in schizophrenia. This suggests that neurophysiological impairments to the mechanisms controlling voluntary behavior operate at the premanifest stage of the development of schizophrenia.

Conclusions. Studies using the experimental "go/no go" scheme demonstrated differences in saccadic responses in healthy subjects and patients at ultra high risk of developing schizophrenia. Patients showed increases in the numbers of erroneous responses to inhibitory stimuli and decreases in the latent periods (LP) of correct and erroneous saccades. Opposite asymmetries in the LP of saccadic responses were demonstrated in healthy subjects as compared with the group of patients: LP for saccades to the right was smaller in healthy subjects, while LP for saccades to the right was greater in patients, than LP for saccades to the left. These data suggest that neurophysiological impairments to the mechanisms of cognitive control of voluntary behavior are manifest in patients at ultra high risk of developing schizophrenia.

The results of this study suggest that patients at ultra high risk of developing schizophrenia have impairments to the processes of voluntary and involuntary attention and inhibitory control, possibly due to dysfunction of the right prefrontal cortex and weakening of top-down influences in the attention and inhibitory control system.

Further analysis of the parameters and topography of EEG potentials linked with activation of stimuli or the beginning of a saccadic response will yield a more complete understanding of the neurophysiological nature of cognitive control of saccade programming in health and in patients at ultra high risk of developing schizophrenia.

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