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# Functional States of the Magnocellular and Parvocellular Neural Systems and Cognitive Impairments in Schizophrenia at Different Stages of the Disease

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### Abstract

**Introduction**. This paper discusses possibilities for using an integrated (psychophysiological and experimental psychological) approach to diagnosing cognitive processes to objectify disorders in patients with schizophrenia. This study represents the first attempt to apply psychophysiological methods to diagnose impairments in perception and thinking in schizophrenia. It is important to clarify the relationship between cognitive functioning and functional states of magnocellular and parvocellular neural visual networks and their dynamics during the development and progression of schizophrenia. The authors' intention is to provide convincing evidence that the imbalance between these neural systems leads to impairments in the integrity of visual perception and, subsequently, to impairments in selective thinking, which makes it difficult to assess and recognize meaningful, essential information when forming judgments, and impedes the construction of a full and adequate world picture.

**Methods**. The study used the methods of visocontrastometry; contrast sensitivity and immunity to interference were assessed. To diagnose cognitive functions, the study used an experimental psychological method combined with the following neuro- and pathopsychological diagnostic tools: Exclusion of the 4th Superfluous, Comparison of Concepts, Poppelreuter Test, and Incomplete Images.

**Results and Discussion**. The authors examined functional states of the magnocellular and parvocellular visual systems, characteristics of their interaction, and cognitive functions at different stages of the disease. Psychophysiological characteristics of perception are associated with the processes of perception, memory, attention, and thinking. The findings indicate that magnocellular system is associated with the characteristics of perception, working memory, and characteristics of attention. Hyperactivation of the magnocellular system is accompanied by impairments in selective attention. Magno- and parvocellular systems (mechanisms of global and local analysis) contribute to the realization of thinking processes. Hypoactivation of the parvocellular system leads to a decrease

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in selective thinking. Progression of schizophrenia is accompanied by a decrease in the activity of both neural systems.

## **Keywords**

visual perception, visual perception in schizophrenia, cognitive processes, cognitive impairments in schizophrenia, neural systems, magnocellular system, parvocellular system, contrast sensitivity, thinking, thinking disorders

## Highlights

In schizophrenia, there is an imbalance between the magnocellular and parvocellular neural systems, which provide the mechanisms of global and local analysis in perceiving information.
 The first episode of schizophrenia is accompanied by a hyperactivation of the magnocellular neural network and a decrease in the activity of the parvocellular neural network. However, long-term treatment with antipsychotic drugs leads to a decrease in the activity of both neural systems.
 Magnocellular and parvocellular systems are associated with thinking processes. The magnocellular system provides the processes of abstraction and categorization; the parvocellular system provides the processes of recognition and assessment of meaningful characteristics.

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## Introduction

Cognitive disorders in schizophrenia (disorders of attention, perception, thinking, and regulatory functions), described in the works by E. Kraepelin and E. Bleuler, constitute a separate cluster of pathological disorders along with positive and negative symptoms. These disorders are defined as components of a schizophrenic defect that lead to severe maladjustment of patients, deterioration of social functioning, and disability (Gurovich, Shmukler, & Magomedova, 2001; Ivanov & Neznanov, 2008; Neznanov, Shmukler, Kostyuk, & Sofronov, 2018; Mukhitova, 2013; Yanushko, Ivanov, & Sorokina, 2014; Lebedeva & Isaeva, 2017; Nuechterlein et al., 1992; Addington, Addington, & Gasbarre, 2001; Savla, Moore, & Palmer, 2008; Green & Harvey, 2014).

Current studies demonstrate a variety of cognitive impairments in schizophrenia, describing different components of the cognitive defect. Cognitive impairments in schizophrenia occur at all the levels, starting from direct sensory reflection of reality, affecting the processes of attention, memory, learning, and up to complex processes of thinking, planning, control and regulation of cognitive activity (Tkachenko & Bocharov, 1991; Zaitseva, Sarkisyan, Sarkisyan, & Storozhakova, 2011; Cherednikova, 2011; Mukhitova, 2013; Lebedeva, Isaeva, & Stepanova, 2013; Harvey & Keefe, 2009; Kalkstein, Hurford, & Gur, 2010; Schaub, Neubauer, Mueser, Engel, & Möller, 2013; Moustafa et al.,

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2016; Penadés, Franck, González-Vallespí, & Dekerle, 2019; Peskin, Koren, & Gabay, 2020); depending on drug therapy, form and duration of the disease (Gurovich et al., 2001; Mosolov & Kabanov, 2005; Lebedeva & Isaeva, 2017; Addington et al., 2001; Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009; Green & Harvey, 2014; Isaeva, Lebedeva, & Simon, 2018).

Studies of the perception process in patients with schizophrenic spectrum disorders are traditionally considered within the framework of emotional and social cognition (Rychkova, Fedorova, & Priimak, 2011; Addington et al., 2001; Green & Leitman, 2008; Kurylo, Pasternak, Silipo, Javitt, & Butler, 2007; Savla et al., 2008). Moreover, perception is studied within cognitive processes in patients with cognitive deficits (Bleikher, Kruk, & Bokov, 2002; Bologov, Kritskaya, & Meleshko, 2009; Zaitseva et al., 2011; Mukhitova, 2013; Shoshina & Shelepin, 2016; Shoshina et al., 2020). It is no coincidence that many authors consider schizophrenia as a 'cognitive-perceptual dysfunction' or a disorder with dysfunction of thinking and perception (Sartorius et al., 2014).

In current psychological studies perception is understood as a complex mental process that is associated with universal processes (memory, attention), and with thinking as well. The process of perception involves both underlying (physiological) and overlying (mental, cognitive) processes and associated with perceptual hypotheses and expectations (Arbib, 2004; Velichkovskii, 1999; Glezer, 1993; Falikman & Pechenkova, 2004). This study takes into account the interpenetration of the processes of processing cognitive information and attempts to describe associations between psychophysiological indicators of visual perception and the characteristics of 'through' processes (memory, attention) and thinking.

The studies combining traditional psychodiagnostic and psychophysical and psychophysiological methods of studying cognitive processes are the most promising today. Examining functional states of the magnocellular and parvocellular visual systems was proposed as the basis for the psychophysiological approach to the assessment of perception. Magnocellular and parvocellular neural systems differ in their sensitivity to the spatial frequency of the visual information. The magnocellular system is most sensitive to low spatial frequencies; the parvocellular system is most sensitive to high spatial frequencies. Recording the contrast sensitivity of the visual system in various spatial frequency ranges is a generally accepted method for assessing their condition (Shoshina, Shelepin, Vershinina, & Novikova, 2015).

Therefore, there is a need for complex studies of the mechanisms of impairments of visual perception and thinking in their association with functional states of the magnocellular and parvocellular neural systems in schizophrenic patients to objectify the data in identifying early signs of the disease and their dynamics during treatment.

This study *aims* to determine the mechanisms of sensory-cognitive impairments in schizophrenia and their relationship with changes in the functioning of the magnocellular and parvocellular neural systems at different stages of the disease.

## Methods

The study was carried out on the basis of the departments of the Psychiatric Hospital no. 1 named after P. P. Kashchenko, St. Petersburg. The study involved patients with paranoid schizophrenia (F20), established in accordance with the ICD-10 diagnostic criteria, without a pronounced intellectual decline. The patients participated in the study in the absence of a pronounced psychotic state, in a state of drug remission; all the patients received neuroleptic therapy as prescribed by the attending physician. The research conditions met the requirements of the Declaration of Helsinki

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of the World Medical Association and were approved by the Ethics Committee of Pavlov First Saint Petersburg State Medical University. The study sample comprised 68 patients (mean age  $34 \pm 12$  years, 51 (75%) males and 17 (25%) females). The sample was divided into 2 subgroups: (a) patients with the first psychotic episode (disease duration up to 1 year), n = 30; (b) patients with chronic schizophrenia (disease duration from 3 to 15 years), n = 38.

We used the method of visocontrastometry, based on the assessment of the contrast sensitivity of the visual system (Shelepin, Kolesnikova, & Levkovich, 1985), and the method for assessing immunity to interference of the visual system, based on recording the probability of a correct answer in distinguishing the location of gaps in Landolt rings presented under conditions of the imposition of noise of different amounts and qualities, which indicates the level of internal noise of the visual system. These methods helped us assess functional states of magno- and parvocellular neural networks that provide mechanisms for global and local analysis of information and its transmission within the dorsal and ventral streams to the frontal cerebral cortex for image building, decision-making, and action programming.

Visocontrastometry was performed using a computer program developed by S. V. Pronin, Pavlov Institute of Physiology of the Russian Academy of Sciences, which made it possible to form test images of any type without preliminary calibration. To transmit the brightness profile of the test images, it uses density variations of white dots randomly located on a black background. The adaptive staircase procedure was used to measure the threshold contrast. The stimuli were presented on a 15.4" TFT, WXGA screen, with an active matrix of increased brightness (Toshiba TruBrite), a resolution of 1024\*600 pixels, a refresh rate of 60 Hz. Gabor elements were displayed randomly to the left or right of the center of the screen (Fig. 1) with spatial frequencies of 0.4, 0.6, 0.8, 1.0, 4.0 and 10.0 c/deg. When analyzing the obtained data, spatial frequencies of 0.4, 0.6, 0.8 c/deg were attributed to low ones, spatial frequencies of 1.0 and 4.0 c/deg were attributed to average ones, and spatial frequencies of 10 c/deg were attributed to high ones.

The subject's task was to click on the right mouse button if he/she saw the image on the right, and the left button if the image was on the left.



Figure 1. Examples of images of Gabor elements presented in the study

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We asked to make a choice, even when the subject was not sure that there was a test image on the screen. Measurements were started with a contrast of 0.5 and decreased to a threshold level at which the tester made at least one error with a probability of 0.5, after which the contrast began to fluctuate around this level. The contrast change step was 20 %.

The number of repetitions for each spatial frequency was eight.

The monitor was located at 1.5 meters; the level of the subject's eyes corresponded to the middle of the screen. The position of the head was fixed using a frontal-chin support. The observation was carried out binocularly. In our experiment, the visual acuity of the subjects participating in the study had to correspond to the norm or be corrected to the norm using glasses. The measurements were carried out in the dark; the monitor screen was the only source of illumination.

The assessment of immunity to interference was carried out using a computer program developed by S. V. Pronin and Yu. E. Shelepin in the laboratory of physiology of vision, Pavlov Institute of Physiology, Russian Academy of Sciences (Shoshina, Shelepin, Vershinina, & Novikova, 2014; Shoshina et al., 2020). On a black background the monitor screen displayed white stylized images of Landolt rings of different sizes with ring gaps of 4, 8, 12, 16, 20, 28, 36, 60, and 100 pixels with and without noise (Fig. 2).



Figure 2. Stylized images of Landolt rings without (a) and (b) with noise

We used noise at which the size of the elementary interference was equal to 25% of the size of the ring gap. In each case the amount of noise was 30%. The subject's task was to distinguish the location of the ring gap (right, left, top or bottom). The probability of a correct answer was recorded (in portions of 1.0, when 1.0 was the maximum) for the images with and without noise. The number of repetitions of presentation of images of Landolt rings of different sizes was 5. The time for viewing the images was not limited. High probability of a correct answer was associated with high immunity to interference.

We also used the following experimental psychological diagnostic tools to examine cognitive processes: (a) Exclusion of the 4th Superfluous, Comparison of Concepts, and Similarities to diagnose the ability to carry out the operations of analysis and synthesis, generalization, abstraction, ability to distinguish the main, essential features of objects or concepts at the figurative level (Bleikher et al.,

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2002); (b) Stroop Color-Word Interference Test to assess the degree of flexibility/rigidity of cognitive control, selectivity of voluntary attention and selectivity of thinking (Zotov, 2012); (c) TMT (Trail Making Test), subtests A and B, to examine the characteristics of attention (concentration, switching, level of distribution) and the rate of mental activity (Mosolov & Kabanov, 2005); (d) Poppelreuter Test to evaluate visual gnosis, the ability to distinguish a figure from the background; and (e) the Underpainting Images technique to assess the constancy of perception, the preservation of the visual image of an object, and the presence of fragmented perception (Rubinstein, 2004). The calculation of mathematical and statistical data was carried out using the STATISTICA 10 software package combined the following methods of statistical data analysis: comparative analysis (the Mann-Whitney test), Spearman correlation analysis. Considering the small size and unevenness across the group size, which implies some heteroscedasticity of the data and the possibility of outliers, we chose nonparametric methods of statistical processing (comparative analysis using the Mann–Whitney test). The selected methods are robust and do not require data distribution. The correlation analysis was carried out using the Spearman's correlation coefficient calculation algorithm, which includes the stage of converting all the presented data into a single scale, where the calculation itself according to the coefficient formula occurs after the transformation and is impossible without it. Since this transformation was included in the calculation itself and was done automatically, we do not describe the algorithm itself in the article (it is standard for the statistical method that we used). In the correlation analysis the following physiological indicators were used: (a) contrast sensitivity in the range of low, medium and high spatial frequencies (c/deg) and (b) accuracy in identifying the location of the Landolt ring gap under conditions of external interference (immunity to interference, portion of 1.0).

### **Results and Discussion**

The results of a psychophysiological study of functional states of magnocellular and parvocellular neural networks indicate that patients have imbalance in the mechanisms of global and local information analysis, which substrate is mainly represented by these neural networks. Compared to mentally healthy subjects, patients with the first episode of schizophrenia who did not receive long-term antipsychotic treatment, showed an increase in the activity of the magnocellular neural system (mechanism of global analysis), while the activity of the parvocellular system (mechanism of local analysis) was reduced. Patients with long-term course of schizophrenia (chronic patients) who perceived long-term antipsychotic treatment showed a decrease in the sensitivity (activity) of both neural systems (p < 0.05).

Patients with the first episode of schizophrenia and chronically ill patients as well (p < 0.05) showed a decrease (compared to normal values) in contrast sensitivity in the range of medium spatial frequencies. As a result of recording the efficiency of distinguishing noisy images, a significant decrease in the number of correct answers about the location of the gap of the Landolt ring for noisy images was observed in chronic schizophrenic patients, compared to the patients with the first episode of schizophrenia. At the same time, patients with the first episode of schizophrenia (without long-term pharmacotherapy) demonstrated the same performance of recognizing noisy images in comparison with chronically ill patients receiving long-term therapy. The data obtained indicate an increase in the level of internal noise of the visual perception system as the disease progresses.

Schizophrenic patients with the first psychotic episode cope worse with figure/ground discrimination compared to chronically ill patients (Poppelreuter Test). Table 1 presents the results.

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Table 1Comparative analysis of perception in patients with different duration of the disease									
<u>Indicator</u>	<u>Chronic</u> patients	<u>First episode</u>	<u>U-criterion</u>	<u>Z-transformed</u>	<u>Significance</u> level, p				
Perception (Poppelreuter Test)									
Number of recognized images	9.44 ± 0.70	8.73 ± 0.93	332.00	2.07	0.04				

Deterioration in the performance of this technique in schizophrenic patients is associated with a decrease in contrast sensitivity in the range of low spatial frequencies to which the magnocellular system is specific. In the psychophysical experiment, the results of which are presented above, we found that during the first psychotic episode, the magnocellular neuronal system is hyperactivated. This fact explains impairments in figure/ground discrimination in persons with the first episode of schizophrenia, which is a consequence of a shift in the balance of concentration and distribution of attention towards distribution.

Table 2 presents psychological diagnostics of memory and attention characteristics.

Table 2 Comparative analysis of memory and attention indicators in patients with different duration of the disease									
Indicator	Chronic patients	<u>First episode</u>	<u>U-criterion</u>	<u>Z-transformed</u>	<u>Significance</u> level, p				
10 Words test									
Growth rate of memorization of words	0.55 ± 0.45	0.76 ± 0.30	96.00	-2.08	0.04				

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#### Table 2 Comparative analysis of memory and attention indicators in patients with different duration of the disease Chronic patients Indicator <u>First episode</u> U-criterion Z-transformed Significance <u>level, p</u> TMT (attention) Time sec., A 54.62 ± 25.47 50.39 ± 25.41 463.00 0.84

In patients in the early stages of the disease (first episode), the growth rate of memorization of words is significantly higher (with each presentation, patients reproduce more words) than in chronically ill patients. Figure 3 shows the averaged profile over five samples.

335.50

2.04

0.04

125.48 ± 70.29

Patients with a chronic form of the disease are characterized by unequal reproduction of memorized material. Compared to chronic schizophrenic patients, the process of attention switching and the speed of information processing (TMT, part B, execution time) is significantly higher in patients with the first episode.

Thus, the data obtained in this study indicate that patients with the first episode of schizophrenia demonstrate greater memorization performance, a higher speed of information processing and mobility of nervous processes (flexibility of cognitive control), and higher scores of attention switching and distribution, compared to chronic patients with schizophrenia. However, the patients of the first group gave more false identifications in the perception of visual images and false reproductions in the memorization of words. This indicates the severity of the mental state and can be explained by hyperactivation of the magnocellular neural system, changes in the characteristics of interaction between the magnocellular and parvocellular neural systems, and, accordingly, an imbalance in the interaction between the processes of concentration and distribution of attention.

Further, we carried out a correlation analysis of physiological indicators and psychological parameters of the processes of memory, perception, attention and thinking. Further, we constructed the correlation pleiades (Fig. 4–5).

We found that all the memory indicators (Fig. 4), including delayed reproduction, have a direct correlation with contrast sensitivity in the range of low spatial frequencies, to which the magnocellular neural system is specific, providing a global mechanism for analyzing the visual field (Shoshina et al., 2014; Shoshina & Shelepin, 2016). Processes of neurons in the magnocellular system form the dorsal pathway of information transmission from the caudal regions to the frontal cortex, which are responsible for control, decision-making, and programming of actions (Merigan & Maunsell, 1993).

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Time sec., B

163.58 ± 92.68

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Figure 3. Averaged profile for the 10 Words tests in patients with different duration of the disease



Figure 4. Correlation pleiad for physiological indicators and memory characteristics

Legend: 1) 1 presentation; 2) 4 presentation; 3) 5 presentation; 4) retention; 5) mean for memory tests; 13) contrast sensitivity in the range of low spatial frequencies; 14) contrast sensitivity in the range of medium spatial frequencies; 15) contrast sensitivity in the range of high spatial frequencies; 17) immunity to interference.

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Figure 5. Correlation pleiad for physiological indicators and characteristics of perception and attention

Legend: 6) rigidity coefficient (Stroop Test); 7) time, sec (TMT, attention); 8) number of errors (TMT, attention); 9) number of recognized images (Poppelreuter Test); 10) number of recognized images (Incomplete Images); 11) number of unrecognized images (Incomplete Images); 12) distortions in perception (Incomplete Images); 13) contrast sensitivity in the range of low spatial frequencies; 14) contrast sensitivity in the range of medium spatial frequencies; 15) contrast sensitivity in the range of high spatial frequencies; 17) immunity to interference.

The findings indicated that delayed reproduction correlates with contrast sensitivity in the range of high spatial frequencies, to which the parvocellular neural system is specific, which provides a local analysis of the visual field (Shoshina et al., 2014; Shoshina & Shelepin, 2016). Processes of neurons in the parvocellular system form the ventral pathway of information transmission from the caudal regions to the frontal cortex (Merigan & Maunsell, 1993). Thus, the data obtained in our study provide direct evidence that the magnocellular neural system is involved in memory processes and provides *procedural* memorization, because neurons of the magnocellular system are specific to the assessment of movements and, accordingly, are associated with motor learning. Procedural memorization is based on memorizing a sequence of actions without referring to the content and capturing the essence, and determines the automatization of actions that underlie the formation of habits and skills. The fact that the delayed reproduction indicator is associated with contrast sensitivity in the range of high spatial frequencies indicates the involvement of the parvocellular neural network in memory processes, probably due to the establishment of semantic connections. Thus, we demonstrated the characteristics of interaction between the magnocellular and parvocellular neural networks in the processes of memorization. The results of the regression analysis indicate a high coefficient of determination of memory indicators by contrast sensitivity in the range of low and high spatial frequencies and immunity to interference as well as (the efficiency of identifying the location of the Landolt ring gap under noise conditions).

Contrast sensitivity in the range of high spatial frequencies associated with the operation of the parvocellular system makes the greatest contribution to the efficiency of delayed reproduction.

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Let us examine associations of the parvo- and magno-systems and the characteristics of perception and attention (see Fig. 5). We found a direct correlation between contrast sensitivity in the range of low, medium and high spatial frequencies and the number of correctly completed images in the Incomplete Images test; accordingly, there was an inverse correlation with the number of incorrectly completed images. Moreover, we found a pronounced direct relationship between contrast sensitivity in the low spatial frequency range and the number of recognized images in the Poppelreuter Test.

Our findings indicate the role of the mechanisms of global and local analysis in figure/ground discrimination, the role of each of the neural systems, and their interaction in completing the image and ensuring holistic perception. Thus, the importance of interaction between magnocellular and parvocellular neural systems, and, respectively, the mechanisms of global and local analysis in providing perception regardless of the task has been demonstrated once again.

At the final stage, we examined the relationship between physiological indicators and the characteristics of thinking (Fig. 6).





Legend: 1) contrast sensitivity in the range of low spatial frequencies; 2) contrast sensitivity in the range of medium spatial frequencies; 3) contrast sensitivity in the range of high spatial frequencies; 4) immunity to interference; 5) level of generalization; 6) distortions in the generalization process.

The correlation analysis of the results of psychophysiological diagnostics and examination of thinking indicated that contrast sensitivity in the range of medium spatial frequencies had a positive correlation with the level of generalization (abstraction and categorization) and a negative one

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with the parameter of distortions in the generalization process (discrimination of essential, relevant features of objects and phenomena when forming judgments) the Exclusion of the 4th Superfluous test. Thus, both magno- and parvocellular systems (mechanisms of global and local analysis) contribute to thinking processes (abstraction and categorization, assessment and selection of essential information), which is fundamental for constructing a complete and realistic picture of the world, planning and regulating social behavior and choice of adequate strategies of behavior in social interaction.

### Findings

1. Patients with first-episode schizophrenia, not receiving long-term antipsychotic treatment, showed an increase in the activity of the magnocellular neural system and a decrease in the activity of the parvocellular system. Patients with long-term schizophrenia and long-term use of antipsychotic drugs showed a decrease in the activity of both neural systems. As the disease progressed, a decrease in the immunity to interference of the visual perception system was observed.

2. In comparison with chronically ill patients, those with the first psychotic episode cope worse with figure/ground discrimination, give more false identifications in the perception of visual images, which indicates the severity of their mental states and is determined by hyperactivation of the magnocellular neural system at the first stage of the disease.

3. Compared to chronic patients, those with first-episode schizophrenia have a higher speed of information processing and flexibility of cognitive control, higher levels of attention switching and distribution, and higher productivity of memorization, which is associated with a general decrease in the activity of the magno- and parvocellular neural systems as the disease progresses and the treatment lasts.

4. In thinking, the level of generalization (abstraction and categorization) is closely associated with the level of activity of the magnocellular system, and also with the consistency and balance in the interaction of both neural systems that provide the processes of global and local analysis of information.

5. The parameter of distortion of the generalization process, which reflects the process of analysis and recognition of essential (relevant) features when forming judgments, is mainly associated with the activity of parvocellular system (the mechanism of local analysis): a decrease in its activity and imbalance with the magnocellular system leads to an increase in the number of responses to 'latent' signs and deterioration in selective thinking.

### Conclusion

We obtained a pool of data for the development of a method for objective diagnostics of thinking and perception disorders in mental illness that may help monitor functional states of the brain in neuropsychiatric disorders, assessing the effectiveness of pharmacological therapy and its effect on sensory-cognitive functions, thereby ensuring the implementation of a personalized approach to the therapy of the mentally ill.

The combination of psychophysiological, psychophysical, and psychodiagnostic methods that we used in this study made it possible to examine the relationship between perception and thinking in schizophrenia. As a result of the implementation of this stage of our project, we obtained new data on the relationship between the mechanisms of global and local analysis of visual information and cognitive impairments in schizophrenic patients at different stages

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of illness. Our findings suggest that early sensory deficits are closely interrelated with the level and nature of functioning of higher-level cognitive processes (perception, attention, memory, and thinking).

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### **Author Contributions**

**E. R. Isaeva** carried out research planning and management, conducted experimental psychological research, analyzed and interpreted experimental data, and prepared and edited the manuscript.

**I. A. Tregubenko** carried out research planning and statistical processing of research data, analyzed and described mathematical and statistical data for the manuscript, worked with sources, and prepared the manuscript.

**Yu. V. Mukhitova** carried out research planning, conducted experimental psychological research, filled out research protocols, worked with sources, and prepared the manuscript.

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**I. I. Shoshina** carried out research planning, performed consulting work on the organization of the study, conducted psychophysical studies of visual functions using the method of visocontrastometry, assessed the immunity to interference in schizophrenic patients, and prepared the manuscript.

### The authors declare no conflicts of interest.