Neurology, Psychiatry and Brain Research 33 (2019) 48–55

Contents lists available at ScienceDirect

Neurology, Psychiatry and Brain Research

journal homepage: www.elsevier.com/locate/npbr

Cognitive impairment in patients with treatment resistant schizophrenia: Associations with *DRD2*, *DRD3*, *HTR2A*, *BDNF* and *CYP2D6* genetic polymorphisms

Dmitriy Sosin[a,*], Dmitriy Ivashchenko[b], Zhannet Sozaeva[c], Kristina Ryzhikova[d], Veronika Fadeeva[e], Veronika Chomskaya[f], Roman Sheidakov[g], Maria Yanushko[a], Andrey Otmakhov[g], Elena Grishina[d], Dmitriy Sychev[c], Mikhail Ivanov[a]

[a] *Department of Biological Psychiatry, V. M. Bekhterev National Research Medical Center for Psychiatry and Neurology, Saint–Petersburg, Russia*
[b] *Department of Personalized Medicine, Research Institute of Molecular and Personalized Medicine, Russian Medical Academy of Continuous Professional Education, Moscow, Russia*
[c] *Department of Clinical Pharmacology and Therapeutics, Russian Medical Academy of Continuous Professional Education, Moscow, Russia*
[d] *Department of Molecular Medicine, Research Institute of Molecular and Personalized Medicine, Russian Medical Academy of Continuous Professional Education, Moscow, Russia*
[e] *Department of medical rehabilitation, Saint – Petersburg state budgetary institution of public health services psycho-neurological dispensary, Saint–Petersburg, Russia*
[f] *Department of outpatient, Saint – Petersburg psychoneurological dispensary of Petrogradskiy district, Saint–Petersburg, Russia*
[g] *Kashcenko Mental Hospital No1, Saint–Petersburg, Russia*

ARTICLE INFO

Keywords:
Treatment-resistant schizophrenia
Genetics
Polymorphisms
Antipsychotics
Cognitive impairment
Psychotic symptoms
Pharmacotherapy

ABSTRACT

Introduction: According to various data, 25–50% of all patients with schizophrenia suffer from treatment resistance. It is believed that patients with treatment-resistant schizophrenia (TRS) have reduced cognitive skills, compared to the patients with a more favourable type of schizophrenia. However, according to some authors, there is limited evidence-based research on this topic at present.

Materials and methods: The total number of patients included 130 patients with a diagnosis of schizophrenia (F20 according to ICD 10). All patients were examined according to the following scales: Positive and Negative Syndrome Scale (PANSS), Global Assessment of Functioning (GAF), Brief Assessment of Cognition in Schizophrenia (BACS).

Results: Our results showed that patients with TRS as a whole had worse cognitive functions than nTRS patients ($p = 0.357$). In the group of patients with TRS, polymorphism *CYP2D6*4* showed an effect on executive functions. Carriers of the heterozygous GA genotype had higher values of executive functions ($p = 0.043$). No association between the studied gene polymorphic variants and TRS was found in this research.

Conclusion: The polymorphic variant *CYP2D6*4* showed an effect on cognitive function in the TRS group, regardless of their mental state and the effect of pharmacotherapy. In the future, it will be necessary to conduct larger prospective studies with a greater number of patients and a greater number of polymorphic variants of genes. Further identification of genetic predictors of cognitive impairment will improve researchers' understanding of their causes and possibly move closer to more targeted therapy for schizophrenia.

1. Introduction

In modern psychiatry, treatment-resistant schizophrenia (TRS) remains one of the most challenging problems. Treatment resistance is understood as the lack of response to antipsychotic therapy (Iasevoli et al., 2018). According to various data, 25–50% of all patients with schizophrenia suffer from TRS (Lally & MacCabe, 2015), which, leads to a high frequency of disability and results in a poor prognosis (Iasevoli et al., 2016). TRS leads to significant financial expenses; however, any partial solution to the problem can be considerably beneficial

* Corresponding author.
E-mail addresses: sosin.dmitriy@gmail.com (D. Sosin), dvi1991@yandex.ru (D. Ivashchenko), zhannet.sozaeva@gmail.com (Z. Sozaeva), kriistinkaa@mail.ru (K. Ryzhikova), veronysha@bk.ru (V. Fadeeva), nicuha@gmail.com (V. Chomskaya), romsheid@ya.ru (R. Sheidakov), yanushko@list.ru (M. Yanushko), otmakhov@kaschenko-spb.ru (A. Otmakhov), gelana2010@yandex.ru (E. Grishina), dmitry.alex.sychev@gmail.com (D. Sychev), profmikhailivanov@gmail.com (M. Ivanov).

https://doi.org/10.1016/j.npbr.2019.06.003
Received 3 April 2019; Received in revised form 25 June 2019; Accepted 26 June 2019
Available online 01 July 2019
0941-9500/

(Kennedy, Altar, Taylor, Degtiar, & Hornberger, 2014). The definition of treatment resistance itself, or rather absence of generally accepted criteria for this form of schizophrenia, creates additional complexities (Howes et al., 2017; Mazo & Gorobets, 2017).

One of the main clinical characteristics of schizophrenia is represented by cognitive impairment (Yanushko, Ivanov, & Sorokina, 2014), which is observed in more than 80% of patients with schizophrenia (Keefe & Fenton, 2007). TRS patients are believed to have reduced cognitive skills, compared to the patients with a more favourable type of schizophrenia. However, according to some authors, there is limited evidence-based research on this topic at present (Woodward & Meltzer, 2010). Today, there are few many studies confirming that TRS patients have lower scores when performing cognitive tests (Anderson, McIlwain, Kydd, & Russell, 2015). The causes of this fact also require attention. The most likely risk factors are as follows: explicit positive and negative symptoms of schizophrenia, intensive pharmacotherapy and individual biomarkers – primarily genetic (Albert et al., 2018).

There is evidence that the first-generation antipsychotics impair cognitive function significantly (Medalia, Gold, & Merriam, 1998), while the second-generation drugs have a positive effect on them (Clissold & Crowe, 2018). However, according to the results obtained by Kontis et al. (2010), polypharmacy does not affect cognitive functions of patients with schizophrenia (Kontis et al., 2010). There is also evidence that refusal to receive antipsychotic therapy in the future leads to a significant improvement in the cognitive sphere (Albert et al., 2018).

Considering the fact that cognitive abilities are a feature with a high degree of heritability (Blokland et al., 2017), the study of the regulation of these processes by genetic mechanisms is a promising area of research (Yanushko, Sosin, Shamanina, & Ivanov, 2018). The International Consortium for Psychiatric Genetics has confirmed the presence of at least 108 loci, which act as significant risk factors for schizophrenia. Thus, since cognitive impairment is determined in a significant portion of patients with schizophrenia, each of these genes can affect cognitive functions (Schizophrenia Working Group of the Psychiatric Genomics Consortium Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014)).

Today, several genome-wide association studies (GWAS) have been conducted in which the authors have attempted to explore the relationship between schizophrenia, cognitive functions, and various SNPs. Bansal et al. (2018) found a similar association (Bansal et al., 2018). A total of 21 SNPs have been shown to have an impact on schizophrenia and higher educational attainment. Other authors have investigated domains of reaction time and verbal-numerical reasoning as cognitive functions. They also found a relationship between 21 single-nucleotide polymorphisms (SNPs, which differed from the previous study) and these cognitive domains and schizophrenia (Smeland et al., 2017). Smeland et al. (2019) have already installed 75 SNPs affecting intelligence and schizophrenia (Smeland et al., 2019). They studied patients with bipolar disorder and compared 37 SNPs common to schizophrenia, intelligence and bipolar disorder.

According to various pharmacological and neuroimaging studies, the dopamine system has a significant impact on schizophrenia in general (Howes, McCutcheon, & Stone, 2015) as well as on cognitive functions (Woodward, Jayathilake, & Meltzer, 2007). Based on these findings, data on the effects of catechol-O-methyltransferase (COMT) (Matsuzaka et al., 2017) and dopamine type 1 receptor gene (DRD1) (Tsang et al., 2015) on cognition performance were obtained.

In addition to the dysfunctionality dopamine system, disorders in the serotonin metabolism system play an important role in the pathogenesis of schizophrenia, and serotonin receptors (5-HTR) are known to be a target in the implementation of the therapeutic effect of second-generation antipsychotic drugs (Goldberg & Weinberger, 1994; Lee, Thompson, & Meltzer, 1994; Meltzer, Alphs, Bastani, Ramirez, & Kwon, 1991). Moreover, the serotonin system plays a role in synaptic plasticity disorders (Stephan, Friston, & Frith, 2009). Chen et al. (2001) showed a significant association of the polymorphic variant of the HTR2A gene (5-Hydroxytryptamine Receptor 2A) T102C with cognitive impairment in schizophrenia (Chen et al., 2001). Other researchers have shown that T-allele carriers of this polymorphism spent more time performing the tests (Alfimova, Golimbet et al., 2008; Alfimova, Lezheĭko et al., 2008) and had a lower "continuous performance task" (Polesskaya & Sokolov, 2002; Uçok, Alpsan, Cakir, & Saruhan-Direskeneli, 2007), while homozygous T-allele carriers performed worse in verbal fluency, both in the patient group and in the healthy control group (Alfimova, Golimbet, & Mitiushina, 2003).

The role of glutamate system disorders in schizophrenia is widely known. Several authors have reported that patients with TRS have higher concentrations of glutamate from the anterior cingulate cortex. This fact suggests the feasibility of studying the role of this neurotransmitter in TRS (Gillespie, Samanaite, Mill, Egerton, & MacCabe, 2017; Nucifora, Woznica, Lee, Cascella, & Sawa, 2018).

The brain-derived neurotrophic factor (BDNF) is associated with the neuroplasticity of the hippocampus, which in turn participates in the cognitive processing of incoming information (Gorski, Zeiler, Tamowski, & Jones, 2003; Nieto, Kukuljan, & Silva, 2013).

Schizophrenia causes changes in the development of the nervous system, which leads to changes in the neuroplasticity of the hippocampus mediated by BDNF, which is, according to researchers, one of the causes of cognitive impairment. In this regard, a large number of researchers have tried to find a relationship between the BDNF gene and cognitive functions. Thus, different authors have found that the polymorphic variant of the Val66Met BDNF gene is significantly associated with the cognitive impairment as a whole (Chung, Chung, Jung, Chang, & Hong, 2010; Ho, Andreasen, Dawson, & Wassink, 2007; Rybakowski et al., 2006). Carriers of one or two Met alleles had lower values when performing learning tasks, attention (Egan, Weinberger, & Lu, 2003) and verbal memory (Ho et al., 2006). Carriers of the Val/Val allele, on the contrary, had better results when performing tasks for attention (Alfimova, Golimbet et al., 2008; Alfimova, Lezheĭko et al., 2008), as well as visual and spatial orientation (Zhang et al., 2012).

In 2014, Kroken et al. proposed to prioritise the improvement of cognitive functions in the treatment of schizophrenia (Kroken et al., 2014). Thus, the allocation of cognitive impairment characteristics in patients with TRS seems the most relevant, which should certainly facilitate the comprehension of the problem.

2. Aim of research

To identify the roles of *DRD2*, *DRD3*, *HTR2A*, *BDNF* and *CYP2D6* genetic polymorphisms in the presence of cognitive impairment in patients with schizophrenia, depending on the presence or absence of treatment resistance.

3. Materials and methods

The study included patients receiving treatment in the V. M. Bekhterev National Research Medical Centre for Psychiatry and Neurology, Kashcenko Mental Hospital №1, Saint – Petersburg Psychoneurological Dispensary of Petrogradskiy District, Saint Petersburg State Budgetary Institution of Public Health Services Psycho-neurological Dispensary №2.

The duration of each patient's mental disorder at the time of inclusion in the study was at least 24 months. The study was approved by the local ethics committee at V. M. Bekhterev National Research Medical Centre for Psychiatry and Neurology. The study was approved by the local ethics committee at V. M. Bekhterev National Research Medical Centre for Psychiatry and Neurology. According to the rules of International Conference on Harmonisation-Good Clinical Practice (ICH-GCP), the patients were included in the study after having provided voluntary informed consent. The study excluded patients whose mental condition did not allow the assessment of their cognitive

functions, as well as patients with comorbid mental disorders and/or somatic and infectious diseases in the stage of decompensation.

The total number of patients included 130 patients with diagnosis of schizophrenia (F20 according to International Statistical Classification of Diseases Tenth Revision (ICD 10), of which 85 (65.4%) were men and 45 (34.6%) were women.

The patients were divided into 2 groups: 1) with TRS and 2) nTRS (not treatment-resistant). The selection of patients with TRS was carried out according to the following criteria (Stahl et al., 2013):

2 courses of antipsychotic therapy (one of which done by the second generation antipsychotic) in an adequate dose, lasting 4–6 weeks without a proper response, especially while maintaining psychotic symptoms; persistent psychotic symptoms affecting the patient's behaviour and functioning; suicidal tendencies, violent acts or comorbid abuse of surfactants.

The mental condition of patients was assessed by means of the Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein, & Opler, 1987). The values on these scales stay in positive correlation with the severity of psychotic state. The assessment of the social and professional functioning quality was carried out using the Global Assessment of Functioning (GAF) scale (Endicott, Spitzer, Fleiss, & Cohen, 1976). The assessment of cognitive functions was carried out using a battery of Brief Assessment of Cognition in Schizophrenia (BACS) tests (Keefe et al., 2014). Composite scores were calculated by averaging all z and T scores for the six subcomponents (verbal memory, working memory, motor speed, verbal fluency, attention and speed of information processing and executive functions (Sarkisian, Gurovich, & Keefe, 2010). Score values in the tests correlate positively with cognitive functions, i.e., the higher the score, the better the cognitive function.

Information on current pharmacotherapy, as well as on the previous two courses of treatment was obtained retrospectively for each patient. The rationality of antipsychotic therapy (using a standardized tool, the Medical Appropriateness Index (MAI), the version adapted to the Russian language) (Sychev, Sosnovsky, & Otdelenov, 2016) and drug interactions (medium and high-risk interactions using the Drug Interactions Checker Tool – www.drugs.com) were evaluated.

The laboratory portion of study was carried out in the Research Institute of Molecular and Personalised Medicine of the Russian Medical Academy of Continuous Professional Education (Moscow). The DNA from the blood samples was isolated by the sorption method using "Ampliprime" kits (produced by Synthol Ltd.). Genotyping was performed using the real-time polymerase chain reaction (real-time PCR) on a BioRad CFX-96 amplifier. For amplification of polymorphic variants: *DRD2* Taq1A, *DRD3* Ser9Gly and *BDNF* rs6265, HTR2A T102C commercial kits were used (produced by Synthol Ltd.).

Our sample includes patients on clozapine therapy (as the main drug); all included patients had a response to the therapy with this drug.

4. Statistical analysis

Statistical processing of the results was carried out in the program SPSS Statistics 21.0. Quantitative variables were compared using the Mann-Whitney and Kruskal-Wallis methods due to the abnormal distribution of values in the sample (Shapiro-Wilk test, $p < 0.05$). Pearson's chi-squared test was used to compare categorical variables, and the Bonferroni correction was introduced for multiple comparisons.

A linear regression analysis was carried out. Linear regression included a quantitative dependent variable and covariates, which were selected on the basis of pairwise comparisons using non-parametric statistics. The plausibility of the model was calculated by means of single-factor dispersion analysis (F), while a significance of $p < 0.05$ in the model was considered plausible (i.e., it predicted the value of the dependent variable using the included covariates). The method of selection of covariates into the equation was inverse stepwise, with consecutive exclusion of insignificant covariates from the regression equation.

Table 1
Comparison of clinical and medical history parameters of patients with TRS and Ntrs.

Characteristics	TRS/ nTRS	N	Mean	SD	p
Age (years)	TRS	51	36,84	11,95	0,357
	nTRS	79	34,81	11,58	
Trials of antypsychotics therapy[a] (number)	TRS	31	11,06	7,32	0,0001
	nTRS	52	5,12	3,69	
Effective trials of antypsychotics [b] (number)	TRS	31	3,32	3,99	0,053
	nTRS	52	4,17	3,49	
Uneffective trials of antypsychotics [c] (number)	TRS	31	7,68	5,79	0,0001
	nTRS	49	0,92	1,04	
Duration of last remission (months)	TRS	45	2,64	8,7	0,0001
	nTRS	73	15,78	23,58	
Average duration of remission (months)	TRS	45	5,22	12,2	0,0001
	nTRS	73	22,67	29,74	
"Major" drug-drug interactions during trial 1[d] (number)	TRS	28	0,36	0,69	0,06
	nTRS	44	0,11	0,32	
MAI course 1 [e] (score)	TRS	29	1,14	1,3	0,019
	nTRS	44	0,55	1,02	

[a] The total number of antipsychotic therapy trials throughout life.
[b] The total number of effective antipsychotic therapy trials throughout life.
[c] The total number of uneffective antipsychotic therapy trials throughout life.
[d] The total number of drug-drug interactions of the relevant category during any course of therapy. All groups of drugs used at the same time were taken into account.
[e] The total score scale MAI during any course of therapy.

5. Results

5.1. Comparison of patients with TRS and nTRS groups

5.1.1. Clinical and anamnestic parameters of patients

There was no statistically significant age difference between the patients with TRS and nTRS ($p = 0.357$). It was proven that patients in the TRS subgroup had a less favourable disease course, which was reflected by the shorter remission period, worse response to therapy and ratio of effective antipsychotic therapy courses to their total number (see Table 1).

5.1.2. Assessment of cognitive functions and severity of mental condition

Cognitive function was assessed in each subgroups using by the BACS and mental state severity was evaluated by the PANSS.

When comparing the TRS and nTRS groups, there were no reliable differences in the performance of several BACS battery tests. However, when comparing composite values, patients with TRS had lower values of z ($p = 0.002$) and T ($p = 0.002$). In assessing the mental state using the PANSS, patients with TRS had more pronounced positive and negative symptoms of schizophrenia. The additional assessment of the level of adaptation in society or in everyday life on the GAF scale proved that the TRS subgroup is less safe ($p = 0.0001$) (see Table 2).

5.2. Associations of genetic polymorphisms DRD2, DRD3, HTR2A, BDNF and CYP2D6 with cognitive functions

5.2.1. General sample of patients

No statistically significant differences between the carriers of different genotypes of the studied polymorphisms and cognitive functions were obtained in the general group of patients ($p > 0.05$).

5.2.2. TRS group

The association of the GA genotype carrying of the polymorphic variant *CYP2D6*4* with higher values during the "Tower of London" test was found in the group of patients with TRS according to both z

Table 2
Comparison of cognitive functions between TRS and nTRS subgroups according to the BACS, PANSS, GAF.

Characteristics	TRS/nTRS	N	Mean	SD	p
BACS duration	TRS	48	29,17	7,03	0,813
	nTRS	75	28,36	5,43	
z Verbal memory	TRS	51	−9,08	1,44	0,649
	nTRS	79	−9,24	1,26	
T Verbal memory	TRS	51	−40,38	14,24	0,526
	nTRS	79	−42,37	12,63	
z Digit sequencing task	TRS	51	−9,02	1,23	0,526
	nTRS	79	−9,2	1,05	
T Digit sequencing task	TRS	51	−40,14	12,12	0,581
	nTRS	79	−40,82	14,15	
z Test with Tokens	TRS	51	−8,97	1,3	0,921
	nTRS	79	−9,1	1,15	
T Test with Tokens	TRS	51	−39,66	13,02	0,927
	nTRS	79	−40,92	11,49	
z Semantic or category fluency	TRS	51	−9,51	1,45	0,996
	nTRS	79	−9,59	1,16	
T Semantic or category fluency	TRS	51	−45,08	14,47	0,992
	nTRS	79	−45,87	11,58	
z Symbol coding	TRS	51	−9,27	1,34	0,908
	nTRS	79	−9,3	1,12	
T Symbol coding	TRS	51	−42,31	14,05	0,91
	nTRS	79	−42,97	11,19	
z Tower of London	TRS	51	−8,59	1,21	0,31
	nTRS	79	−8,39	1,17	
T Tower of London	TRS	51	−34,65	15,4	0,293
	nTRS	79	−32,19	15,93	
z Composite	TRS	51	−2,99	1,7	0,002
	nTRS	79	−1,98	1,33	
T Composite	TRS	51	20,16	17,07	0,002
	nTRS	79	30,22	13,34	
PANSS P common (score)	TRS	51	13,55	2,54	0,0001
	nTRS	79	10,82	2,78	
PANSS N common (score)	TRS	51	24,24	5,18	0,0001
	nTRS	79	18,86	5,51	
PANSS O common (score)	TRS	51	33,29	5,44	0,0001
	nTRS	79	27,9	5,32	
PANSS common (score)	TRS	51	70,98	10,12	0,0001
	nTRS	79	57,81	10,57	
GAF (score)	TRS	46	40,87	8,6	0,0001
	nTRS	72	59,96	13,9	

Table 3
Associations of the *CYP2D6* gene polymorphism with cognitive impairment in the TRS subgroup.

Gene	Characteristics	Genotype	N	Mean	SD	p
*CYP2D6*4*	z Tower of London	GG	30	−8,87	1,25	0,043
		GA	21	−8,21	1,05	
	T Tower of London	GG	30	−38,76	12,43	0,043
		GA	21	−28,94	17,56	

(p = 0.043) and T (p = 0.043) values (see Table 3).

5.2.3. nTRS group

The association of polymorphic variant rs6265 of the *BDNF* gene with the "Tower of London" test was found in the nTRS group. Carriers of the GG genotype had higher z-values in the London Tower test (p = 0.036). In the same group of patients, an association of general parameters with the polymorphism of T102C of the *HTR2A* gene was found. CC genotype carriers had higher values for both z (p = 0.042) and T (p = 0.042) (see Table 4).

5.3. Associations of the DRD2, DRD3, HTR2A and BDNF gene polymorphisms with the severity of mental state

To exclude the influence of mental status on cognitive functions, the association of the studied genes polymorphisms carrier with the severity of mental state was analysed.

Table 4
Associations of the *BDNF* and *HTR2A* gene polymorphisms with cognitive impairment in the nTRS subgroup.

Gene	Characteristics	Genotype	N	Mean	SD	p
BDNF (rs6265)	z Tower of London	GG	60	−8,25	1,2	0,036
		AG + AA	19	−8,82	0,97	
HTR2A (T102C)	z Composite	CC	21	−1,44	1,15	0,042
		CT	42	−2,23	1,29	
		TT	16	−2,02	1,53	
	T Composite	CC	20	35,62	11,56	0,042
		CT	42	27,67	12,85	
		TT	16	29,81	15,36	

5.3.1. The total sample of patients

Mental state measured at the moment of inclusion of patients in the study in the general group of patients showed the relationship with the polymorphism of *DRD2*, *DRD3*, *HTR2A* and *CYP2D6*4* genes. In particular, the association of carrying Taq1A *DRD2* with a higher score on the points of the PANSS scale "Stereotyped of Thinking", the sum of points on the subscale "Negative Symptomatic", "Mannerisms & posturing" and "Unusual thought content" was revealed. The T102C *HTR2A* polymorphism was associated with a higher degree of "Emotional withdrawal", "Passive/apathetic social withdrawal", "Lack of spontaneity & flow of conversation", "Poor rapport" and "Disorientation". The polymorphic variant of Ser9Gly *DRD3* was associated with the subscale of "Positive symptoms" of PANSS scale. In addition, differences were obtained in the item "Somatic concern" between the carriers of different polymorphism genotypes *CYP2D6*4* (p = 0.042). Carrying polymorphic variants of rs6265 *BDNF* and *CYP2D6*10* did not show any effect on the mental state in this group of patients (p > 0.05) (see Table 5).

Table 5
Associations of the *DRD2*, *HTR2A, DRD3* and *CYP2D6* gene polymorphisms with the severity of mental state on the PANSS in the general sample of patients.

Gene	PANSS scale [a]	Genotype	N	Mean	SD	p
DRD2 (Taq1A)	Stereotyped of Thinking	CC	88	2,25	1,18	0,05
		CT; TT	42	2,67	1,22	
	Negative Symptomatic (total score)	CC	88	20,39	6,11	0,05
		CT; TT	42	22,19	5,55	
	Mannerisms & posturing	CC	88	2,3	1,12	0,05
		CT; TT	42	2,69	1,02	
	Unusual thought content	CC	88	2,22	1,01	0,023
		CT; TT	42	2,64	0,88	
HTR2A (T102C)	Emotional withdrawal	CC	42	3,1	1,3	0,017
		CT	65	3,55	1,03	
		TT	23	2,83	1,27	
	Passive/apathetic social withdrawal	CC	42	2	1,17	0,022
		CT	65	2,57	1,17	
		TT	23	2	1,21	
	Lack of spontaneity & flow of conversation	CC	42	3,17	1,27	0,027
		CT	65	3,52	1,06	
		TT	23	2,78	1,28	
	Poor rapport	CC	42	2,52	1,27	0,016
		CT	65	2,85	1,18	
		TT	23	1,96	1,26	
	Disorientation	CC	42	1,1	0,43	0,032
		CT	65	1,48	0,89	
		TT	23	1,22	0,6	
DRD3 (Ser9Gly)	Positive symptoms (total score)	TT	64	12,67	3,33	0,014
		TC	42	10,88	2,41	
		CC	24	11,58	2,43	
*CYP2D6*4*	Somatic concern	GG	85	1,65	1,03	0,042
		GA	45	1,27	0,65	

[a] Relevant items of the PANSS scale.

Table 6
Associations of the *DRD2*, *HTR2A, DRD3* and *CYP2D6* gene polymorphisms with the severity of mental state according to the PANSS in the TRS subgroup.

Gene	PANSS scale[a]	Genotype	N	Mean	SD	p
DRD2 (Taq1A)	Delusions	CC	31	2,71	1,13	0,05
		CT; TT	20	3,35	1,23	
HTR2A (T102C)	Disorientation	CC	21	1,19	0,6	0,012
		CT	23	2	1,09	
		TT	7	1,29	0,76	
DRD3 (Ser9Gly)	Motor retardation	TT	29	2,24	1,09	0,029
		TC	12	2	1,04	
		CC	10	3,2	1,32	
*CYP2D6*10*	Guilt feelings	CC	26	1,58	0,95	0,037
		CT	25	1,12	0,44	

[a] Relevant items of the PANSS scale.

5.3.2. TRS group

In the group of patients with TRS, an association was found between mental state severity and the polymorphic variants of *DRD2*, *HTR2A, DRD3* and *CYP2D6* genes under study, in particular, the polymorphic variant *DRD2* Taq1A with the item "Delusions", the polymorphic variant T102C *HTR2A* with the item "Disorientation", and the polymorphic variant Ser9Gly *DRD3* with the item "Motor retardation", *CYP2D6*10* with the item "Guilt feelings", as well as the general score of the scale PANSS. Polymorphisms of rs6265 of *BDNF* and *CYP2D6*4* gene did not show any effect on mental state ($p > 0.05$) (see Table 6).

5.3.3. nTRS group

The association of polymorphic variants of *DRD2*, *DRD3* and *HTR2A* genes was shown in this group of patients. The polymorphic variant of Taq1A *DRD2* was associated with the item "Unusual thought content", Ser9Gly *DRD3* with the item "Excitement", "Somatic concern", "Disturbance of volition", T102C *HTR2A* with "Poor rapport" and *CYP2D6*10* with "Delusions" and "Suspiciousness/persecution" of the PANSS scale. Polymorphic variants of rs6265 *BDNF* and *CYP2D6*4* also showed no effect on the mental state of this group of patients. ($p < 0.05$) (see Table 7).

5.4. Analysis of the medical appropriateness among the carriers of polymorphic variants of the studied genes

The analysis of pharmacotherapy and drug interactions rationality was carried out to assess the impact of this exogenous factor on cognitive impairment. It was necessary to determine the level of aggravation of the pharmacological anamnesis in the carriers of polymorphic variants of the studied genes. In addition, ineffective antipsychotic therapy courses were compared (see Tables 8–10).

Table 7
Association of the *DRD2, DRD3, HTR2A and CYP2D6* gene polymorphisms with the severity of the mental state according to the PANSS in the nTRS subgroup.

Gene	PANSS scale[a]	Genotype	N	Mean	SD	p
DRD2 (Taq1A)	Unusual thought content	CC	57	1,86	1,03	0,022
		CT, TT	22	2,45	0,96	
DRD3 (Ser9Gly)	Excitement	TT	35	1,54	0,89	0,031
		TC	30	1,07	0,37	
		CC	14	1,5	1,02	
	Somatic concern	TT	35	1,31	0,72	0,043
		TC	30	1,4	0,77	
		CC	14	2	1,11	
	Disturbance of volition	TT	35	3,31	1,02	0,029
		TC	30	2,77	1,07	
		CC	14	2,57	1,16	
HTR2A (T102C)	Poor rapport	CC	21	1,62	1,07	0,05
		CT	42	2,38	1,17	
		TT	16	2,06	1,29	
*CYP2D6*4*	Delusions	CC	47	1,87	1,03	0,012
		CT	32	1,31	0,74	
	Suspiciousness / persecution	CC	47	1,45	0,85	0,047
		CT	32	1,13	0,55	

[a] Relevant items of the PANSS scale.

Table 8
Analysis of the previous therapy depending on the *DRD2*, *HTR2A*, *DRD3* and gene polymorphisms carriers in the general group of patients.

Gene	Characteristics	Genotype	N	Mean	SD	p
DRD2 (Taq1A)	Uneffective trials of antypsychotics (number)	CC	51	2,47	4,13	0,048
		CT	18	5,39	6,31	
		TT	7	5,43	4,61	
HTR2A (T102C)	Number of hospitalization (number)	CC	37	3,62	3,03	0,038
		CT	59	6,25	6,15	
		TT	19	6,16	6,62	
	Duration of last remission (months)	CC	37	10,68	22,73	0,053
		CT	59	7,47	12,68	
		TT	19	22,26	30,6	
	MAI course 1 (score)	CC	24	1,25	1,33	0,04
		CT	34	0,62	1,02	
		TT	13	0,46	1,13	
DRD3 (Ser9Gly)	Uneffective trials of antypsychotics (number)	TT	37	3,7	4,74	0,059
		TC	25	2,88	5,49	
		CC	15	4,27	4,8	

Table 9
Analysis of the previous therapy depending on the *BDNF*, *HTR2A*, *DRD3* gene polymorphisms carrier in patients with TRS.

Gene	Characteristics	Genotype	N	Mean	SD	p
BDNF (rs6265)	"Major" drug-drug interactions during current trial (number)	GG	31	0,26	0,68	0,045
		AG;AA	10	0,6	0,7	
HTR2A (T102C)	"Moderate" drug-drug interactions during trial 2 (number)	CC	12	2,17	2,33	0,044
		CT	16	0,81	1,22	
		TT	3	2,33	0,58	
DRD3 (Ser9Gly)	"Major" drug-drug interactions during current trial (number)	TT	24	0,54	0,83	0,059
		TC	8	0	0	
		CC	9	0,11	0,33	
	MAI current trial (number)	TT	24	1,46	1,32	0,03
		TC	8	0,38	0,52	
		CC	9	0,44	1,01	

Table 10
Analysis of the previous therapy depending on the *HTR2A*, *DRD3* genes polymorphisms carrier in patients with nTRS.

Gene	Characteristics	Genotype	N	Mean	SD	p
HTR2A (T102C)	Number of hospitalization (number)	CC	19	2,63	1,71	0,059
		CT	38	6,18	6,16	
		TT	15	4,13	2,33	
	"Major" drug-drug interactions during trial 1 (number)	CC	13	0,31	0,48	0,036
		CT	20	0,05	0,22	
		TT	10	0	0	
	MAI trial 1 (number)	CC	13	1,31	1,38	0,009
		CT	20	0,35	0,76	
		TT	10	0	0	
DRD3 (Ser9Gly)	Average duration of remission (month)	TT	31	27,65	30,17	0,024
		TC	27	14,56	27,58	
		CC	13	27,31	33,82	
	Duration of last remission (month)	TT	31	22,03	31,44	0,022
		TC	27	6,89	8,98	
		CC	13	16,23	15,7	

5.5. Linear regression for the "Tower of London" test z-value of the BACS test battery in the TRS group

The total PANSS score, disease duration and polymorphism carriers rs6265 *BDNF*, Taq1A *DRD2*, Ser9Gly *DRD3*, T102C *HTR2A* and *CYP2D6*4* were used as covariates. This model is reliable and can

reliably predict the z-value of the London Tower Battery BACS test in the TRS group ($F = 25.02$, $p = 0.0001$, $R^2 = 0.375$). This model was created by reverse step-by-step inclusion of covariates.

As a result of the model construction, all covariates except for the duration of the disease were excluded. Predictive significance was in the middle range (beta = 0.625, $p = 0.0001$) and indicated a direct correlation with z-value of the "London Tower" test of the BACS battery in the TRS group. Of the excluded covariates, the greatest influence on this parameter was caused by the presence of T102C *HTR2A* polymorphism (beta = −0.23, $p = 0.08$).

5.6. Linear regression for the "Tower of London" test T-value of the BACS test battery in the group TRS

The covariates were chosen by analogy with the last model. This model is able to reliably predict changes in the dependent variable ($F = 14.45$, $p = 0.0001$, $R^2 = 0.25$). The model was created by the reverse step-by-step inclusion of covariates.

As a result of the model construction, all covariates except for the duration of the disease were excluded. Predictive significance was in the middle range (beta = 0.52, $p = 0.0001$) and indicated a direct correlation with the T-value of the "Tower of London" test of the BACS test battery in the group of TRS. Of the excluded covariates, this dependent variable was influenced by the carriage of *CYP2D6*4* polymorphism (beta = 0.24, $p = 0.09$).

6. Discussion

Traditionally, it is believed that patients with TRS are worse at coping with cognitive tests, and also have more pronounced psychotic symptoms (de Bartolomeis et al., 2013). The reasons for parameter deterioration can be a more "malignant" course of the mental disorder itself and some indirect factors of both external and internal character. Genetic features, in particular, the carrier of polymorphic variants of certain genes, are first among the internal causes (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Yanushko et al., 2018). In addition to more pronounced positive and negative symptoms, pharmacotherapy is a related external cause. Concerning the absence of antipsychotic therapy effect, most practicing psychiatrists will do augmentation, which means a combination of several psychotropic drugs. As is widely known, polypharmacy leads to various drug interactions, which in turn increases the risk of adverse drug reactions that can affect cognitive functioning and mental condition, reduce compliance, lead to a change of therapy and eventually exacerbate therapeutic resistance (Cheng et al., 2018).

In our study, we obtained associations of several polymorphic gene variants with cognitive functions.

The T102C *HTR2A* polymorphism has been shown to have an effect on cognitive functions in the nTRS group. Carrying the CC genotype was associated with higher cognitive functions, according to the general z- and T-indicators of the BACS. In the analysis of current and past pharmacotherapy courses, carriers of the homozygous genotype according to allele C had a significantly higher number of drug interactions of the category "Major", as well as a higher index of rationality of pharmacotherapy during the course of therapy 1. Since CC genotype carriers had a greater number of drug interactions and a higher index of rationality, and these differences were obtained for the therapy in the history, we can only discuss the indirect influence of this therapy on cognitive functions. In this case, we can exclude the effect of the therapy on cognitive function. When analysing the differences in the psychotic state of the carriers of different genotypes of this polymorphism, the carriers of the CC genotype had a more pronounced negative symptomatology (according to the item "Emotional withdrawal" of the PANSS scale) at the moment of inclusion in the study. This fact does not allow us to draw a conclusion about the influence of the studied polymorphism on cognitive functions in this group of patients, since these differences may depend on the severity of negative disorders.

In the group of patients with TRS polymorphism *CYP2D6*4* showed the effect on the executive functions. Carriers of the heterozygous GA genotype had higher indices during the "Tower of London" test. When analyzing pharmacotherapy in patients with TRS, it was obtained that the carriers of this genotype had a higher index of rationality of pharmacotherapy during the current course of therapy. Taking into account a higher index of rationality in patients of this genotype, it can be concluded that there is no effect of pharmacotherapy on cognitive functions in this group of patients. There were no statistically significant differences in the mental state of the carriers of this polymorphism. Thus, in the group of patients with TRS, this polymorphism showed the influence on the executive functions outside of the psychotic state severity and psychopharmacotherapy performed. No association between the studied gene polymorphic variants and TRS was found in this research.

According to the data obtained by constructing linear regression models, the duration of the disease significantly affected the executive functions in the TRS group. At the same time, the correlation was directly related: the longer the duration of the disease, the better the indicators of executive functions. However, at the level of the tendency to reliability, we can say about the influence of *CYP2D6*4* polymorphism on the executive functions. Carriers of the GA genotype had higher indices of executive functions.

At the trend level, the T102C polymorphism of the *HTR2A* gene showed its influence on the executive functions in patients in the TRS group. Carriers of the CC genotype had higher indices of executive functions.

At the trend level, the effect of the Taq1A polymorphism of the *DRD2* gene on cognitive function in the general patient group can be seen. Carriers of the TT genotype of this polymorphism had the lowest total z- and T- values, and carriers of the homozygous genotype by allele C were the highest.

In the nTRS group, we obtained data on the effect of the disease duration on the executive functions. This relationship is directly proportional, i.e., cognitive functions improve in patients with increased disease duration.

7. Limitations

We considered the most significant polymorphic variants of genes. The limited genetic panel does not allow the full assessment of the treatment resistance problem. Although it reduces time expenses, the cross-sectional design of our study leads to some restrictions. The assessment of mental condition at one point does not allow a detailed study of the efficiency or fully capture the parameters of safety of the antipsychotic therapy. We did not have the opportunity to replicate the results of our study to a larger cohort of patients with schizophrenia. In addition, we were unable to find similar studies of patients with TRS, and as a result, we were unable to compare our results with others. Additional difficulties come with collecting the information about past courses of therapy and the course of the mental disorder itself.

8. Conclusion

We examined the most significant pharmacodynamic genes associated with mental state and cognitive functions (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Additionally, pharmacokinetic genes also play an important role, affecting drug metabolism and therefore, effectiveness and safety of antipsychotic therapy. Further research on the role of these genes is also necessary. The absence of association between the carriers of the studied polymorphic variants and TRS may be explained by the fact that this problem is the most complex, and the mechanisms involved are quite diverse.

The polymorphic variant of the *CYP2D6*4* gene showed its influence on cognitive functions regardless of the mental state, pharmacotherapy used or the presence or absence of TRS. The association of this gene with cognitive impairment was also obtained in the study by Zeng et al. (2017); however, this work was carried out in patients with schizophrenia, without distinguishing a separate group of TRS (Zeng et al., 2017).

Considering the large number of difficulties encountered in the treatment of TRS, this topic seems the most interesting and promising for further research. Future studies should focus on expanding the panel of polymorphic gene variants and conducting larger prospective studies with a large number of patients, despite the high cost. Early prediction of TRS will enable the start of the anti-resistant therapy at an earlier stage, which can prevent social decline and disability. In turn, further identification of genetic predictors of cognitive impairment will help to understand their causes and possibly approach a more targeted therapy for schizophrenia.

CRediT authorship contribution statement

Dmitriy Sosin: Conceptualization, Formal analysis, Investigation, Methodology, Software, Visualization, Writing - original draft. **Dmitriy Ivashchenko:** Conceptualization, Data curation, Formal analysis, Methodology, Software, Visualization, Writing - original draft. **Zhannet Sozaeva:** Investigation, Validation. **Kristina Ryzhikova:** Investigation, Validation. **Veronika Fadeeva:** Investigation, Resources. **Veronika Chomskaya:** Investigation, Resources. **Roman Sheidakov:** Investigation, Resources. **Maria Yanushko:** Investigation. **Andrey Otmakhov:** Investigation, Resources. **Elena Grishina:** Investigation, Validation. **Dmitriy Sychev:** Conceptualization, Methodology, Project administration, Supervision, Validation, Writing - review & editing. **Mikhail Ivanov:** Conceptualization, Methodology, Project administration, Supervision, Writing - review & editing.

References

Albert, N., Randers, L., Allott, K., Jensen, H. D., Melau, M., Hjorthøj, C., & Nordentoft, M. (2018). Cognitive functioning following discontinuation of antipsychotic medication. A naturalistic sub-group analysis from the OPUS II trial. *Psychological Medicine, 30*, 1–10. https://doi.org/10.1017/S0033291718001836.

Alfimova, M. V., Golimbet, V. E., Korovaitseva, G. I., Lezheiko, T. V., Abramova, L. I., Kaleda, V. G., & Barkhatova, A. N. (2008). The modulatory influence of polymorphism of the serotonin transporter gene on characteristics of mental maladaptation in relatives of patients with endegenous psychoses. *Neuroscience and Behavioral Physiology, 38*(3), 253–258. https://doi.org/10.1007/s11055-008-0037-8.

Alfimova, M. V., Golimbet, V. E., & Mitiushina, N. G. (2003). Polymorphism of the serotonin receptor (5-HTR2A) gene and verbal fluency in normalcy and schizophrenia. *Mol Biol (Mosk). 37*(1), 68–73.

Alfimova, M. V., Lezheĭko, T. V., Golimbet, V. E., Korovaĭtseva, G. I., Lavrushkina, O. M., Kolesina, N. Iu, ... Kaleda, V. G. (2008). [Investigation of association of the brain-derived neurotrophic factor (BDNF) and a serotoninreceptor 2A (5-HTR2A) genes with voluntary and involuntary attention in schizophrenia]. *Zhurnal Nevrologii I Psikhiatrii Imeni SS Korsakova, 108*(4), 62–69.

Anderson, V. M., McIlwain, M. E., Kydd, R. R., & Russell, B. R. (2015). Does cognitive impairment in treatment-resistant and ultra-treatment-resistant schizophrenia differ from that in treatment responders? *Psychiatry Research, 230*(3), 811–818. https://doi.org/10.1016/j.psychres.2015.10.036.

Bansal, V., Mitjans, M., Burik, C. A. P., Linnér, R. K., Okbay, A., Rietveld, C. A., ... Koellinger, P. D. (2018). Genome-wide association study results for educational attainment aid in identifying genetic heterogeneity of schizophrenia. *Nature Communications, 9*(1), 3078. https://doi.org/10.1038/s41467-018-05510-z.

Blokland, G. A. M., Mesholam-Gately, R. I., Toulopoulou, T., Del Re, E. C., Lam, M·, DeLisi, L. E., ... Petryshen, T. L. (2017). Heritability of neuropsychological measures in schizophrenia and nonpsychiatric populations: A systematic review and meta-analysis. *Schizophrenia Bulletin, 43*(4), 788–800. https://doi.org/10.1093/schbul/sbw146.

Chen, R. Y., Sham, P., Chen, E. Y., Li, T., Cheung, E. F., Hui, T. C., ... Murray, R. (2001). No association between T102C polymorphism of serotonin-2A receptor gene and clinical phenotypes of Chinese schizophrenic patients. *Psychiatry Research, 105*(3), 175–185.

Cheng, C. M., Chang, W. H., Chiu, Y. C., Sun, Y., Lee, H. J., Tang, L. Y., ... Tsai, C. F. (2018). Association of polypharmacy with mild cognitive impairment and cognitive ability: A nationwide survey in Taiwan. *The Journal of Clinical Psychiatry, 25*(6), pii. https://doi.org/10.4088/JCP.17m12043 79 17m12043.

Chung, S., Chung, H. Y., Jung, J., Chang, J. K., & Hong, J. P. (2010). Association among aggressiveness, neurocognitive function and the Val66Met polymorphism of brain-derived neurotrophic factor gene in male schizophrenic patients. *Comprehensive Psychiatry, 51*(4), 367–372. https://doi.org/10.1016/j.comppsych.2009.10.003.

Clissold, M., & Crowe, S. F. (2018). Comparing the effect of the subcategories of atypical antipsychotic medications on cognition in schizophrenia using a meta-analytic approach. *Journal of Clinical and Experimental Neuropsychology, 20*, 1–17. https://doi.org/10.1080/13803395.2018.1488952.

de Bartolomeis, A., Balletta, R., Giordano, S., Buonaguro, E. F., Latte, G., & Iasevoli, F. (2013). Differential cognitive performances between schizophrenic responders and non-responders to antipsychotics: Correlation with course of the illness, psychopathology, attitude to the treatment and antipsychotics doses. *Psychiatry Research, 15*(2), 387–395. https://doi.org/10.1016/j.psychres.2013.06.042 210.

Egan, M. F., Weinberger, D. R., & Lu, B. (2003). Schizophrenia, III: Brain-derived neurotrophic factor and genetic risk. *The American Journal of Psychiatry, 160*(7), 1242.

Endicott, J., Spitzer, R. L., Fleiss, J. L., & Cohen, J. (1976). The global assessment scale: A procedure for measuring overall severity of psychiatric disturbance. *Archives of General Psychiatry, 33*(6), 766–771.

Gillespie, A. L., Samanaite, R., Mill, J., Egerton, A., & MacCabe, J. H. (2017). Is treatment-resistant schizophrenia categorically distinct from treatment-responsive schizophrenia? A systematic review. *BMC Psychiatry, 17*(1), 12. https://doi.org/10.1186/s12888-016-1177-y.

Goldberg, T. E., & Weinberger, D. R. (1994). The effects of clozapine on neurocognition: An overview. *The Journal of Clinical Psychiatry, 55*(Suppl. B), 88–90.

Gorski, J. A., Zeiler, S. R., Tamowski, S., & Jones, K. R. (2003). Brain-derived neurotrophic factor is required for the maintenance of cortical dendrites. *The Journal of Neuroscience: the Official Journal of the Society for Neuroscience, 23*(17), 6856–6865.

Ho, B. C., Andreasen, N. C., Dawson, J. D., & Wassink, T. H. (2007). Association between brain-derived neurotrophic factor Val66Met gene polymorphism and progressive brain volume changes in schizophrenia. *The American Journal of Psychiatry, 164*(12), 1890–1899.

Ho, B. C., Milev, P., O'Leary, D. S., Librant, A., Andreasen, N. C., & Wassink, T. H. (2006). Cognitive and magnetic resonance imaging brain morphometric correlates of brain-derived neurotrophic factor Val66Met gene polymorphism in patient with schizophrenia and healthy volunteers. *Archives of General Psychiatry, 63*(July (7)), 731–740 2006.

Howes, O., McCutcheon, R., & Stone, J. (2015). Glutamate and dopamine in schizophrenia: An update for the 21st century. *Journal of Psychopharmacology (Oxford, England), 29*(2), 97–115. https://doi.org/10.1177/0269881114563634.

Howes, O., McCutcheon, R., Agid, O., de Bartolomeis, A., van Beveren, N. J., Birnbaum, M. L., ... Correll, C. U. (2017). Treatment-resistant schizophrenia: Treatment response and resistance in psychosis (TRRIP) working group consensus guidelines on diagnosis and terminology. *The American Journal of Psychiatry, 174*(3), 216–229. https://doi.org/10.1176/appi.ajp.2016.16050503.

Iasevoli, F., Avagliano, C., Altavilla, B., Barone, A., Ciccarelli, M., D'Ambrosio, L., ... de Bartolomeis, A. (2018). Evaluation of a few discrete clinical markers may predict categorization of actively symptomatic non-acute schizophrenia patients as treatment resistant or responders: A study by ROC curve analysis and multivariate analyses. *Psychiatry Research, 269*, 481–493. https://doi.org/10.1016/j.psychres.2018.08.109.

Iasevoli, F., Giordano, S., Balletta, R., Latte, G., Formato, M. V., Prinzivalli, E., ... de Bartolomeis, A. (2016). Treatment resistant schizophrenia is associated with the worst community functioning among severely-ill highly-disabling psychiatric conditions and is the most relevant predictor of poorer achievements in functional milestones. *Progress in Neuro-psychopharmacology & Biological Psychiatry, 65*, 34–48. https://doi.org/10.1016/j.pnpbp.2015.08.010.

Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin, 13*(2), 261–276.

Keefe, R. S., & Fenton, W. S. (2007). How should DSM-V criteria for schizophrenia include cognitive impairment? *Schizophrenia Bulletin, 33*(4), 912–920.

Keefe, R. S., Fox, K. H., Davis, V. G., Kennel, C., Walker, T. M., Burdick, K. E., & Harvey, P. D. (2014). The Brief Assessment of Cognition in Affective Disorders (BAC-A): Performance of patients with bipolar depression and healthy controls. *Journal of Affective Disorders, 166*, 86–92. https://doi.org/10.1016/j.jad.2014.05.002.

Kennedy, J. L., Altar, C. A., Taylor, D. L., Degtiar, I., & Hornberger, J. C. (2014). The social and economic burden of treatment-resistant schizophrenia: A systematic literature review. *International Clinical Psychopharmacology, 29*(2), 63–76.

Kontis, D., Theochari, E., Kleisas, S., Kalogerakou, S., Andreopoulou, A., Psaras, R., ... Tsaltas, E. (2010). Doubtful association of antipsychotic polypharmacy and high dosage with cognition in chronic schizophrenia. *Progress in Neuro-psychopharmacology & Biological Psychiatry, 34*(7), 1333–1341. https://doi.org/10.1016/j.pnpbp.2010.07.029.

Kroken, R. A., Loberg, E. M., Dronen, T., Gruner, R., Hugdahl, K., Kompus, K., ... Johnsen, E. (2014). A critical review of pro-cognitive drug targets in psychosis: Convergence on myelination and inflammation. *Frontiers in Psychiatry, 4*(5), 11. https://doi.org/10.3389/fpsyt.2014.00011.

Lally, J., & MacCabe, J. H. (2015). Antipsychotic medication in schizophrenia: A review. *British Medical Bulletin, 114*(1), 169–179. https://doi.org/10.1093/bmb/ldv017.

Lee, M. A., Thompson, P. A., & Meltzer, H. Y. (1994). Effects of clozapine on cognitive function in schizophrenia. *The Journal of Clinical Psychiatry, 55*(Suppl. B), 82–87.

Matsuzaka, C. T., Christofolini, D., Ota, V. K., Gadelha, A., Berberian, A. A., Noto, C., ... Bressan, R. A. (2017). Catechol-O-methyltransferase (COMT) polymorphisms modulate working memory in individuals with schizophrenia and healthy controls. *Braz J Psychiatry, 39*(4), 302–308. https://doi.org/10.1590/1516-4446-2016-1987.

Mazo, G. A., & Gorobets, L. N. (2017). Replacement of antipsychotics as a method of preventing the formation of resistance in schizophrenia.OBozrenie psikhiatrii I meditsinskoi psikhologii im. *V.M. Bekhtereva, 3*, 74–80.

Medalia, A., Gold, J., & Merriam, A. (1998). The effects of neuroleptics on

neuropsychological test results of schizophrenia. *Archives of Clinical Neuropsychology: the Official Journal of the National Academy of Neuropsychologists, 3*(3), 249–271.
Meltzer, H. Y., Alphs, L. D., Bastani, B., Ramirez, L. F., & Kwon, K. (1991). Clinical efficacy of clozapine in the treatment of schizophrenia. *Pharmacopsychiatry. 24*(2), 44–45.
Nieto, R., Kukuljan, M., & Silva, H. (2013). BDNF and schizophrenia: From neurodevelopment to neuronal plasticity, learning, and memory. *Frontiers in Psychiatry, 4*, 45. https://doi.org/10.3389/fpsyt.2013.00045.
Nucifora, F. C., Jr, Woznica, E., Lee, B. J., Cascella, N., & Sawa, A. (2018). Treatment resistant schizophrenia: Clinical, biological, and therapeutic perspectives. *Neurobiology of Disease, 18*, 30494–30497. https://doi.org/10.1016/j.nbd.2018.08.016 pii: S0969-9961.
Polesskaya, O. O., & Sokolov, B. P. (2002). Differential expression of the "C" and "T" alleles of the 5-HT2A receptor gene in the temporal cortex of normal individuals and schizophrenics. *Journal of Neuroscience Research, 67*(6), 812–822.
Rybakowski, J. K., Borkowska, A., Skibinska, M., Szczepankiewicz, A., Kapelski, P., Leszczynska-Rodziewicz, A., ... Hauser, J. (2006). Prefrontal cognition in schizophrenia and bipolar illness in relation to Val66Met polymorphism of the brain-derived neurotrophic factor gene. *Psychiatry and Clinical Neurosciences, 60*(1), 70–76.
Sarkisian, G. R., Gurovich, I. I., & Keefe, R. S. E. (2010). [Нормативные данные для российской популяции и стандартизация шкалы «Кратка оценка когнитивных функций у пациентов с шизофренией (BACS)] Normative data for the Russian population and standardization of the scale Brief Assessment of Cognition in Schizophrenia (BACS). *Social and clinical psychiatry,* 13–19 Т. 20. № 3. С.
Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014). Biological insights from 108 schizophrenia-associated genetic loci. *Nature, 511*(7510), 421–427. https://doi.org/10.1038/nature13595.
Smeland, O. B., Frei, O., Kauppi, K., Hill, W. D., Li, W., Wang, Y., ... NeuroCHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology) Cognitive Working Group (2017). Identification of Genetic Loci Jointly Influencing Schizophrenia Risk and the Cognitive Traits of Verbal-Numerical Reasoning, Reaction Time, and General Cognitive Function. *JAMA Psychiatry, 1*(10), 1065–1075. https://doi.org/10.1001/jamapsychiatry.2017.1986 74.
Smeland, O. B., Bahrami, S., Frei, O., Shadrin, A., O'Connell, K., Savage, J., ... Andreassen, O. A. (2019). Genome-wide analysis reveals extensive genetic overlap between schizophrenia, bipolar disorder, and intelligence. *Molecular Psychiatry*. https://doi.org/10.1038/s41380-018-0332-x.
Stahl, S. M., Morrissette, D. A., Citrome, L., Saklad, S. R., Cummings, M. A., Meyer, J. M., ... Warburton, K. D. (2013). "Meta-guidelines" for the management of patients with schizophrenia. *CNS Spectrums, 18*(3), 150–162. https://doi.org/10.1017/S109285291300014X.
Sychev, D., Sosnovsky, E., & Otdelenov, V. (2016). Medical appropriateness index as a method for polypharmacy control. *Clinical Pharmacology and Therapeutics, 25*(3), 79–82.
Stephan, K. E., Friston, K. J., & Frith, C. D. (2009). Dysconnection in schizophrenia: From abnormal synaptic plasticity to failures of self-monitoring. *Schizophrenia Bulletin, 35*(May (3)), 509–527. https://doi.org/10.1093/schbul/sbn176.
Tsang, J., Fullard, J. F., Giakoumaki, S. G., Katsel, P., Katsel, P., Karagiorga, V. E., ... Roussos, P. (2015). The relationship between dopamine receptor D1 and cognitive performance. *NPJ Schizophrenia, 1*, 14002. https://doi.org/10.1038/npjschz.2014.2.
Uçok, A., Alpsan, H., Cakir, S., & Saruhan-Direskeneli, G. (2007). Association of a serotonin receptor 2A gene polymorphism with cognitive functions in patientswith schizophrenia. *American Journal of Medical Genetics Part B, Neuropsychiatric Genetics: the Official Publication of the International Society of Psychiatric Genetics, 144*(B(5)), 704–707.
Woodward, N. D., Jayathilake, K., & Meltzer, H. Y. (2007). COMT VAL108/158MET genotype, cognitive functions, and cognitive improvement with clozapine in schizophrenia. *Schizophrenia Research, 90*(1–3), 86–96.
Woodward, N., & Meltzer, H. (2010). Neuropsychologyoftreatment-resistantschizophrenia. In H. Elkis, & H. Meltzer (Eds.). *Therapy-resistant schizophrenia* (pp. 33–51). Basel (Switzerland): Karger.
Yanushko, M. G., Ivanov, M. V., & Sorokina, A. V. (2014). Когнитивные нарушения при эндогенных психозах: современные представления в свете дименсионального подхода [Cognitive impairment in endogenous psychosis: Modern views in the light of the dimensional approach]. *Socialnaya I klinicheskaya psikhiatriya, 24*(1), 90–95.
Yanushko, M. G., Sosin, D. N., Shamanina, M. V., & Ivanov, M. V. (2018). Генетические корреляты когнитивных нарушений при шизофрении (обзор литературы) [Genetic correlates of cognitive impairment in schizophrenia (review)]. *Sibirskii vestnik psichiatrii i narcologii, 2*(99), 98–103. https://doi.org/10.26617/1810-3111-2018-2 (99)-98-103.
Zeng, L., Kang, C., Yuan, J., Zhang, Y., Wei, Y., Xu, L., ... Yang, J. (2017). CYP2D6 polymorphisms are associated with effects of risperidone on neurocognitive performance in schizophrenia. *Schizophrenia Research, 188*, 50–51. https://doi.org/10.1016/j.schres.2017.01.030.
Zhang, X. Y., Chen, D. C., Xiu, M. H., Haile, C. N., Luo, X., Xu, K., ... Kosten, T. R. (2012). Cognitive and serum BDNF correlates of BDNF Val66Met gene polymorphism in patients with schizophrenia and normal controls. *Human Genetics, 131*(7), 1187–1195. https://doi.org/10.1007/s00439-012-1150-x.