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Neurocognitive Deficits in Schizophrenia and Polymorphic Variants of Protein Kinase Signaling Pathway Genes: Search for Associations

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ABSTRACT

Aim. To study the associations of polymorphic variants in the *BDNF, GSK3B, AKT1, MAPK,* and *CREB1* genes with neurocognitive deficits (NCD) in patients with schizophrenia.

Materials and methods. The study included 148 patients with schizophrenia, who underwent psychometric examination and genotyping. The Brief Assessment of Cognition in Schizophrenia (BACS) was used to assess neurocognitive functioning indicators. Ten polymorphic variants in the genes *BDNF*, *GSK3B*, *AKT1*, *MAPK*, and *CREB1* were genotyped. Statistical processing was carried out using the $\chi 2$ goodness-of-fit test, Fisher's exact test, cluster analysis, the Kruskal – Wallis test, and multivariate analysis of variance.

Results. The CT genotype of the *BDNF* rs6265 polymorphic variant was more common in the group of patients with severe NCD, while the CC genotype was more typical of patients with moderate and mild NCD. In patients with severe and moderate NCD, the AG *MAPK* rs8136867 genotype was predominant, while in patients with mild NCD, the GG genotype was predominant. A statistically significant effect of polymorphic variants of the *BDNF* gene on performance in the Token motor task (rs6265: $p = 0.025$ and rs11030104: $p = 0.027$) and the Tower of London subtests (rs6265: $p = 0.016$ and rs11030104: $p = 0.037$) was found. There was also a significant effect of *MAPK* gene polymorphisms on the performance in the Token motor task subtest (rs8136867: $p = 0.003$) and *CREB1* on the Tower of London test (rs6740584: $p = 0.022$).

Conclusion. For the first time, associations of *BDNF* rs6265 and *MAPK* rs8136867 polymorphisms with neurocognitive deficit in patients with schizophrenia, as well as *BDNF* rs6265, *BDNF* rs11030104, *MAPK* rs8136867, and *CREB1* rs6740584 polymorphisms with performance in the BACS battery subtests were found.

Keywords: schizophrenia, neurocognitive deficits, molecular genetics, protein kinases, BDNF, single nucleotide polymorphism

Conflict of interest. The authors declare no obvious or potential conflicts of interest related to the publication of this article.

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Conformity with the principles of ethics. All participants signed an informed voluntary consent to participate in the study. The study protocol was approved by the local Ethics Committee of the Mental Health Research Institute of Tomsk NRMC (Minutes No. 157 dated November 11, 2022).

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Нейрокогнитивный дефицит при шизофрении и полиморфные варианты генов протеинкиназных сигнальных путей: поиск ассоциаций

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РЕЗЮМЕ

Цель. Изучить ассоциации полиморфных вариантов в генах *BDNF*, *GSK3B*, *AKT1*, *MAPK* и *CREB1* с нейрокогнитивным дефицитом (НКД) у больных шизофренией.

Материалы и методы. В исследование включены 148 пациентов с шизофренией, у которых было проведено психометрическое обследование и генотипирование. Для оценки показателей нейрокогнитивного функционирования использовалась краткая шкала оценки когниции при шизофрении (BACS). Подвергнуты генотипированию 10 полиморфных вариантов в генах *BDNF*, *GSK3B*, *AKT1*, *MAPK* и *CREB1*. Статистическая обработка осуществлена с помощью критерия согласия $\chi 2$, точного критерия Фишера, кластерного анализа, критерия Краскела – Уоллиса и многофакторного дисперсионного анализа.

Результаты. Генотип CT полиморфного варианта *BDNF* rs6265 чаще встречался в группе пациентов с выраженным НКД, в то время как для пациентов с умеренным и легким НКД был более характерен генотип CC. У пациентов с выраженным и умеренным НКД преобладал генотип AG *MAPK* rs8136867, тогда как у пациентов с легким НКД – генотип GG. Обнаружено статистически значимое влияние полиморфных вариантов гена *BDNF* на результативность в субтестах «Двигательный тест с фишками» (rs6265: $p = 0{,}025$ и rs11030104: $p = 0{,}027$) и «Башня Лондона» (rs6265: $p = 0{,}016$ и rs11030104: $p = 0{,}037$). Также наблюдался значимый эффект полиморфных вариантов гена *MAPK* на показатели в субтесте «Двигательный тест с фишками» (rs8136867: $p = 0{,}003$) и *CREB1* – в субтесте «Башня Лондона» (rs6740584: $p = 0{,}022$).

Заключение. Впервые обнаружены ассоциации полиморфных вариантов *BDNF* rs6265 и *MAPK* rs8136867 с нейрокогнитивным дефицитом у больных шизофренией, а также полиморфных вариантов *BDNF* rs6265, *BDNF* rs11030104, *MAPK* rs8136867 и *CREB1* rs6740584 с результативностью в субтестах батареи BACS.

Ключевые слова: шизофрения, нейрокогнитивный дефицит, молекулярная генетика, протеинкиназы, BDNF, однонуклеотидный полиморфизм

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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Соответствие принципам этики. Все пациенты подписали информированное согласие на участие в исследовании. Исследование одобрено этическим комитетом НИИ психического здоровья Томского НИМЦ (протокол № 157 от 18.11.2022).

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INTRODUCTION

Despite the fact that antipsychotic therapy effectively relieves the main clinical symptoms of psychosis (hallucinations, psychomotor agitation, delusions, and mental health conditions), the problem of developing neurocognitive deficit (NCD) in patients with schizophrenia is still relevant in psychiatry. NCDs are often some of the causes of reduced social and work adaptation of patients, as well as disability [1]. Despite the fact that NCD does not belong to the fundamental criteria of schizophrenia in

modern diagnostic guidelines [2, 3], it is a persistent symptom complex that forms at the very beginning of the disease and makes a significant contribution to its clinical polymorphism [4].

It is believed that NCDs in schizophrenia are based on dopamine neurotransmission dysfunctions, as well as the psychotomimetic and cognitive-disruptive effects of N-methyl-d-aspartate (NMDAR) receptor antagonists [5]. In this regard, it is currently becoming relevant to search for opportunities not only for targeted drug therapy, but also for mechanisms to increase the neuroplasticity of people with schizophrenia.

The *BDNF* gene encodes a brain neurotrophic factor that supports brain development, survival of nerve cells [6], branching of their dendrites, and neuroplasticity in general [7]. BDNF is expressed in all areas of the brain, with its highest concentration in the hippocampus and the cerebral cortex [8]. When BDNF binds to its high-affinity TrkB receptor (tropomyosin-related kinase B), this leads to phosphorylation of the latter and activation of intracellular cascades, such as PI3K/AKT and MAPK/ERK signaling pathways [9].

The product of the *AKT1* gene, protein kinase type 1, regulates cell growth, proliferation, and metabolism, apoptosis, and angiogenesis [10, 11], and also plays an important role in the negative regulation of GSK-3ß (glycogen synthase 3ß kinase). By activating AKT, BDNF is able to block GSK-3ß, thereby increasing neuronal polarization, growth, and branching of neuronal axons.

The MAPK pathway is the main point of convergence in all protein kinase signaling pathways. It is responsible for regulating cell growth and differentiation and neuroplasticity [12]. The downstream target of the MAPK pathway is the transcription factor CREB, which regulates many cellular functions: neurotransmission, transcription, neuroplasticity, and metabolism. There is evidence confirming the contribution of CREB to the development of addictive disorders, subclinical and clinical manifestations of anxiety and depression [13].

The contribution of the genetic component to the development of schizophrenia has been repeatedly confirmed in research [14, 15]. A number of publications have demonstrated that BDNF, AKT, and GSK-3 can be considered as potential biomarkers of schizophrenia [16–18]. In this regard, we hypothesized that polymorphic variants in the *BDNF*, *GSK3B*, *AKT1*, *MAPK*, and *CREB1* genes may contribute to the formation of NCD as a component of the clinical pattern of schizophrenia.

The aim of the research was to study the associations of polymorphic variants in the *BDNF*, *GSK3B*, *AKT1*, *MAPK*, and *CREB1* genes with neurocognitive deficits in patients with schizophrenia.

MATERIALS AND METHODS

The study was conducted at the clinic of the Mental Health Research Institute of Tomsk National Research Medical Center of the Russian Academy of Sciences. The study included 148 patients born and living in the Siberian Federal District of the Russian Federation with an established diagnosis of schizophrenia (F20 in accordance with the criteria of the International Classification of Diseases, 10th Revision (ICD-10)). Inclusion criteria were as follows: age of patients from 18 to 55 years, belonging to the Slavic ethnic group, established diagnosis of schizophrenia according to the ICD-10 criteria, and consent to participate in the study. Exclusion criteria were the following: mental retardation, dementia, severe organic pathology or somatic-symptom somatic disorders in the stage of decompensation, and refusal to participate in the study.

All patients included in the sample received basic antipsychotic therapy with conventional or atypical antipsychotics. To unify the assessment of pharmacotherapy, the doses of the drugs were converted to the chlorpromazine equivalent (CRZeq, mg/day).

The Basic Map of Socio-demographic and Clinical-dynamic Characteristics for Patients with Schizophrenia [19], which had been previously tested in clinical trials, was filled out for all subjects. The severity of the patients' psychopathological symptoms was verified by the Positive and Negative Syndrome Scale (PANSS) [20] in the adapted Russian version (SCI-PANSS) [21].

The assessment of neurocognitive functioning indicators was carried out using the Brief Assessment of Cognition in Schizophrenia (BACS) in an adapted Russian-language version [22] using normative indicators for the Tomsk population [23]. The scale consists of six subtests: 1) List Learning (verbal memory); 2) Digit Sequencing Task (working memory); 3) Token Motor Task (motor functions); 4) Controlled Oral Word Association Test (semantic fluency); 5) Symbol Coding (attention); 6) Tower of London (executive functions).

Blood sampling for genotyping was performed on an empty stomach (after 12 hours of fasting, between 7.00 am and 9.00 am) through ulnar venipuncture into

BD Vacutainer tubes. Ten polymorphic variants of five genes were genotyped using polymerase chain reaction methods on a QuantStudio 3D Digital PCR System (Applied Biosystems, USA): *BDNF* (rs6265, r s11030104), *GSK3B* (rs13321783, rs6805251, rs334558), *AKT1* (rs1130233, rs3730358), *MAPK* (rs8136867, rs3810608), and *CREB1* (rs6740584).

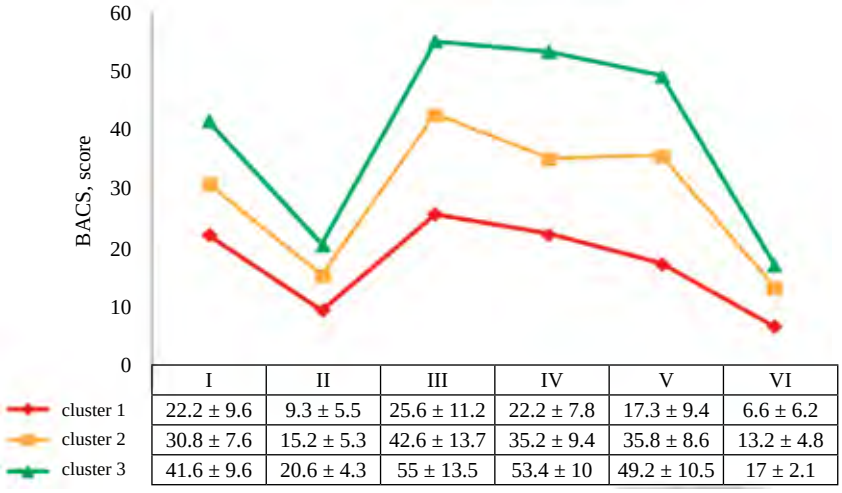
The statistical analysis was performed using the software Statistica 12.0 and R 4.4.3. The nature of the distribution of variables (agreement with the law of normal distribution) was assessed using the Shapiro–Wilk test. Data with a normal distribution were presented as the mean and standard deviation – $M \pm SD$, in the absence of a normal distribution – as the median of the interquartile range $Me\ [_{Q1;\ Q3}]$. Qualitative variables were represented as absolute (n) and relative (%) units.

The frequency analysis was carried out using the agreement $\chi 2$ test and the Fisher's exact test (in the case of frequencies less than 5). K-means clustering was used to identify the severity of NCD. The Kruskal–Wallis test was used to compare several independent samples. The genetic balance was calculated in the R program using the "genetics" package. Multifactorial analysis of variance (factorial ANOVA) was used to study the relationship between polymorphic variants and indicators of cognitive functioning. The value of $p < 0.05$ was considered statistically significant.

RESULTS

Based on the BACS, we identified three clusters of neurocognitive disorders registered across all subtests, which differed in clinical severity: cluster 1 (38 (25.7%) patients) with severe NCD, cluster 2 (67 (45.3%) patients) with moderate NCD, and cluster 3 (43 (29%) patients) with mild NCD ($p < 0.001$) (Fig. 1).

The socio-demographic and clinical indicators of the selected clusters of patients with schizophrenia are presented in Table 1.



	I	II	III	IV	V	VI
cluster 1	22.2 ± 9.6	9.3 ± 5.5	25.6 ± 11.2	22.2 ± 7.8	17.3 ± 9.4	6.6 ± 6.2
cluster 2	30.8 ± 7.6	15.2 ± 5.3	42.6 ± 13.7	35.2 ± 9.4	35.8 ± 8.6	13.2 ± 4.8
cluster 3	41.6 ± 9.6	20.6 ± 4.3	55 ± 13.5	53.4 ± 10	49.2 ± 10.5	17 ± 2.1

Fig. 1. The cognitive profile of the identified variants of the severity of neurocognitive deficits according to BACS in the group of patients with schizophrenia: I – List Learning, II – Digit Sequencing Task, III – Token Motor Task, IV – Controlled Oral Word Association Test, V – Symbol Coding, VI – Tower of London

Table 1

Socio-demographic and Clinical Parameters of Patients in the Identified Clusters according to BACS

Parameter		Cluster 1, $n = 38$	Cluster 2, $n = 67$	Cluster 3, $n = 43$	p
Sex (male/female), n		20/18	39/28	22/21	0.735
Age, $Me\ [Q_1; Q_3]$, years		38 [33; 47]	34 [30; 38]	35 [29; 40]	0.107
Age of symptom manifestation, $Me\ [Q_1; Q_3]$, years		23 [18; 28]	24 [20; 30]	23 [20; 29]	0.621
Duration of the disease, $Me\ [Q_1, Q_3]$, years		12 [4; 21]	7 [3; 16]	10 [5; 14]	0.124
PANSS, $Me\ [Q_1; Q_3]$	Positive symptoms	25 [20; 29]	26 [19; 30]	23 [18; 28]	0.104
	Negative symptoms	26 [24; 29]	26 [24; 29]	25 [21; 28]	0.161
	General psychopathological symptoms	57 [51; 62]	55 [50; 60]	53 [48; 60]	0.146
	Total score	111 [101; 119]	108 [97; 114]	100 [92; 107]	0.073
Duration of baseline therapy, $Me\ [Q_1, Q_3]$, years		4 [0.5; 17]	3 [0.5; 9]	3.5 [0.6; 8]	0.308
Type of antipsychotic, n (%)	Atypical	16 (42.1)	32 (47.8)	31 (72.1)	0.012
	Conventional	22 (57.9)	35 (52.2)	12 (27.9)	
CPZeq, $Me\ [Q_1; Q_3]$, mg / day		379 [225; 800]	400 [250; 599]	300 [125; 599]	0.105

The selected clusters were comparable in terms of sex, age, age of manifestation of the schizophrenic process, duration of the disease, and severity of psychopathological symptoms. The duration of the baseline therapy received by the patients, as well as the overall antipsychotic load, did not differ between the clusters, however, in patients with mild NCD, atypical antipsychotics were used as baseline therapy compared with the rest of the study participants (p = 0.012).

The frequencies of the studied polymorphic variants in the general sample of patients with schizophrenia followed the Hardy–Weinberg equilibrium (all p > 0.05). Analysis of the genotype frequency distribution revealed statistically significant differences between patient clusters for the polymorphic variant *BDNF* rs6265 and *MAPK* rs8136867 (Table 2).

The CT *BDNF* rs6265 genotype was more common in the group of patients with severe NCD, while the CC genotype was more typical of patients with moderate and mild NCD. However, in patients with severe and moderate NCD, the AG *MAPK* rs8136867 genotype prevailed, whereas in patients with mild NCD, the GG genotype prevailed.

Table 2

Genotype Frequencies in Patients with Schizophrenia Depending on the Severity of NCD, units

Polymorphism	Genotype	Cluster 1	Cluster 2	Cluster 3	$\chi 2$/F	p
BDNF rs6265	CT	13 (34.2)	11 (16.4)	9 (20.9)	8.546	0.045
	CC	23 (60.5)	56 (83.6)	33 (76.8)		
	TT	2 (5.3)	0 (0)	1 (2.3)		
MAPK rs8136867	AG	27 (71.1)	36 (53.7)	15 (34.9)	12.829	0.012
	GG	5 (13.2)	15 (22.4)	18 (41.9)		
	AA	6 (15.7)	16 (23.9)	10 (23.2)		

Next, the influence of the studied polymorphic variants on the indicators of neurocognitive functioning in patients with schizophrenia was analyzed using multifactorial analysis of variance (factorial ANOVA). A statistically significant effect of polymorphic variants of the *BDNF* gene on performance was found in the subtests: Token Motor Task (rs6265: p = 0.025 and rs11030104: p = 0.027) and Tower of London (rs6265: p = 0.016 and rs11030104: p = 0.037). There was also a significant effect of the polymorphic variant *MAPK* rs8136867 on the indicators in the Token Motor Task subtest (p = 0.003) and *CREB1* rs6740584 on the Tower of London subtest (p = 0.022) (Fig. 2).

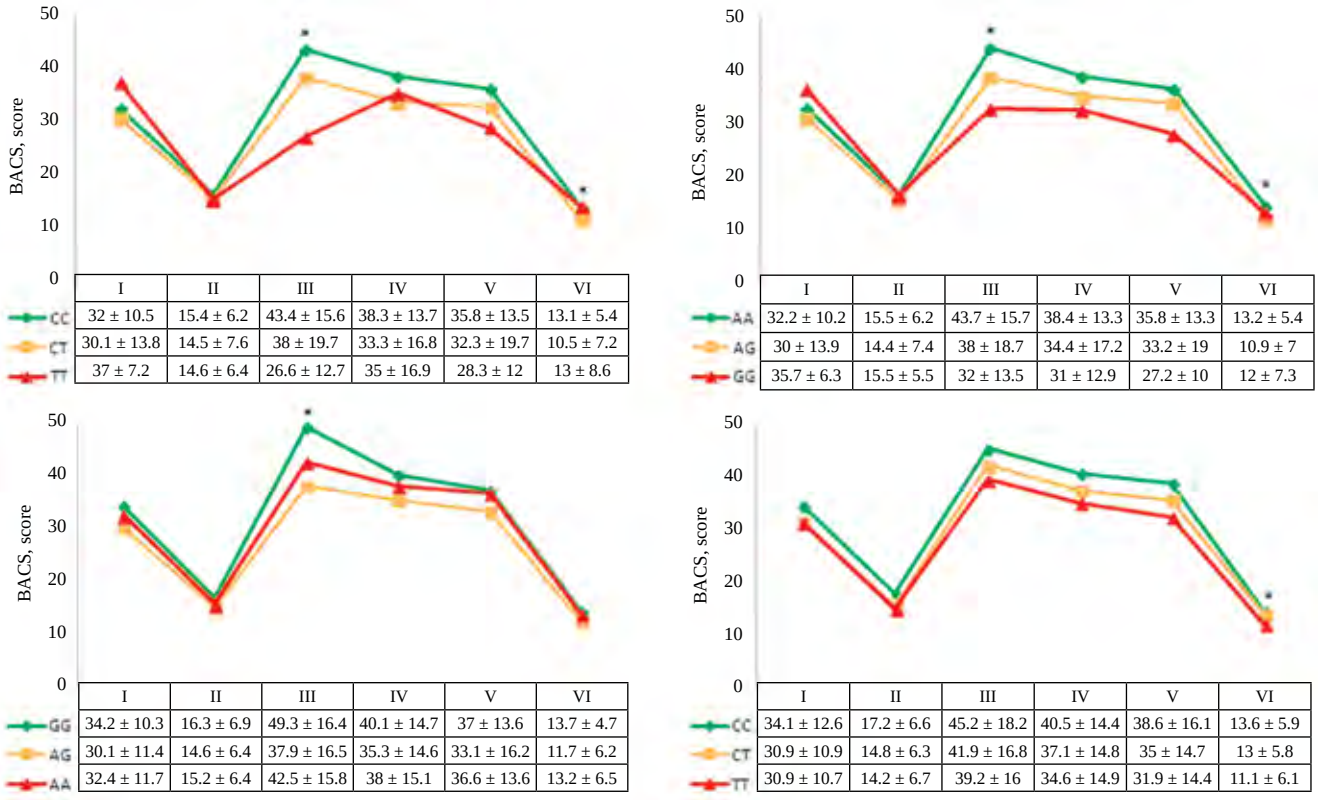


Fig. 2. Associations of polymorphic variants of the *BDNF*, *MAPK*, and *CREB1* genes with cognitive functioning in patients with schizophrenia: *a* – *BDNF* rs6265; *b* – *BDNF* rs11030104; *c* – *MAPK* rs8136867; *d* – *CREB1* rs6740584. * – the level of statistical significance

DISCUSSION

The problem of a genetic predisposition to NCD in schizophrenia is no less acute than a predisposition to the disease itself or the undesirable effects of its pharmacotherapy. Polymorphic variants of the studied genes have been repeatedly tested for associations with the clinical pattern of mental and addictive disorders. In addition to the above, our study raises the issue of neuroplasticity as a protective factor against neurocognitive disorders.

We found that the CT genotype of the polymorphic variant of *BDNF* rs6265 was more common in the group of patients with severe NCD. The C allele of the polymorphic variant of *BDNF* rs6265 encodes the amino acid valine, the T–methionine allele. The expression of the latter leads to a decrease in BDNF production [24]. RS6265 also contributes to the formation of the hippocampus and prefrontal cortex, two brain regions that have the highest expression of BDNF and are centers of learning and memory processes [25]. In 2005, E. Dempster et al. [26] showed the association of the T allele with lower values on the Wexler Memory Scale compared to the C allele. A study was also conducted where apparently healthy subjects with different *BDNF* rs6265 genotypes were presented with verbal recognition tasks similar to the Controlled Oral Word Association test [27]. Then it turned out that the best results are shown by carriers of the CC genotype. These data are partially consistent with ours.

NCD is the third domain of schizophrenia after positive and negative. Schizophrenia itself was described in the late 19th century. century as "early dementia." There is an interpretation that Emil Kraepelin introduced this phrase as the equivalent of dementia in Alzheimer's disease for young patients [4]. There is biological evidence for this interpretation, in particular, an association with Alzheimer's disease has been shown for the polymorphic variant of *BDNF* rs6265 [28]. In another study, no such association was found, but the authors were able to show an increased incidence of the heterozygous rs6265 genotype and the diplotype of three polymorphic *BDNF* variants (rs6265, rs11030104, rs2049045; H1-GTC/H2-ACG) in the subgroup without the carriage of apolipoprotein E4 (APOE 4), which increases the risk of developing Alzheimer's disease [29].

Attention deficit hyperactivity disorder (ADHD) is another clinical problem associated with cognitive impairment. There is an association of the polymorphic variant of *BDNF* rs6265 with both ADHD and general intellectual disabilities [30]. In both groups of patients, the G allele and GA genotype of this polymorphic variant were more common than in the control group, which is consistent with the results of our study. The association of rs6265 with ADHD is also confirmed by the fact that medications used to treat this disorder can increase BDNF levels in the central nervous system [31]. Based on this, it can be assumed that the decrease in indicators for individual subtests of the BACS is associated with attention instability, which is an important link in the pathogenesis of ADHD, especially the subtype predominantly with attention disorders [32].

Concentration of attention plays an important role in the performance in the BACS subtests, especially Towers of London and Symbol Coding, so we consider the hypothesis to be well-founded. It is worth clarifying that there are also opposite data [33, 34] indicating the absence of an association between ADHD and the polymorphic variant of *BDNF* rs6265, as well as the variant rs11030104 in the same gene [35]. In 2010, a meta-analysis was conducted [36], which showed that the contribution of the *BDNF* gene to the development of ADHD was not statistically significant when sex or comorbidity with mood disorders were taken into account.

The presented facts suggest that the involvement of this genetic mechanism is most likely not specific to schizophrenia, but is responsible for cognitive functioning in general. The transdiagnostic comparison of the results obtained in other mental disorders with the data obtained by us is an argument for supporters of the dimensional model of psychiatry over the categorical one.

In the course of this study, it was found that the AG *MAPK* rs8136867 genotype prevailed in patients with severe and moderate NCD. Previously, polymorphic variants of the *MAPK* gene were studied mainly in European populations in the context of affective disorders: major depressive and bipolar disorder. In one study, the MAPK1 variant rs8136867 showed an association with bipolar disorder [37]. In another [38], polymorphic variants *MAPK1* rs8136867 and *CREB1* rs6740584 demonstrated a contribution to resistance to antidepressant treatment in patients with major depressive disorder, and the heterozygous MAPK1 rs8136867 genotype also contributed to the duration and quality of remissions in both groups of patients.

Previously, this was explained by the relatively general thesis that changes in neuroplasticity are

necessary for a therapeutic response, and treatment of affective disorders is most often prolonged and depletes the plasticity potential in neurons [39, 40]. Later, information appeared that the MAPK pathway is the target of several antidepressants [41, 42]. So, G. Mercier et al. showed that fluoxetine itself rapidly activates MAPK cascades in rat astrocytes [40]. However, it was also shown that the MAPK signal prevented the inhibition of glutamate release by bupropion [43].

In modern psychiatry, the concept of overlapping symptoms of schizophrenia and bipolar disorder has been repeatedly confirmed [44, 45], which allowed us to hypothesize common pathogenetic pathways of these disorders. Like schizophrenia, depressive states are also accompanied by cognitive impairments associated with the death of neurons in the prefrontal cortex and hippocampus [46]. In light of this, it is reasonable to conclude that genes whose products are involved in protein kinase signaling pathways contribute to the pathogenesis of not only affective disorders, but also schizophrenia. This is demonstrated, among other things, by the results of our study showing the effect of polymorphic variants of the *MAPK* and *CREB1* genes on the performance in individual BACS subtests. This is the second transdiagnostic dimensional perspective, which is the result of comparing the data we have obtained with studies performed in other mental disorders.

Among the limitations of this study, a small sample size is worth mentioning, but it was, but sufficient for correct statistical processing reflecting objective clinical and neuropsychological data.

Our hypothesis was confirmed with respect to polymorphic variants in the *BDNF*, *MAPK*, and *CREB1* genes, which may contribute to the formation of NCD as a component of the clinical picture of schizophrenia. The results obtained suggest the specificity of the effect of the considered polymorphic variants on impaired neuropsychological development, which plays an important role in the etiology of schizophrenia and confirms the validity of identifying its cognitive phenotypes.

CONCLUSION

For the first time, we found associations of polymorphic variants *BDNF* rs6265 and *MAPK* rs8136867 with neurocognitive deficits in patients with schizophrenia, as well as polymorphic variants *BDNF* rs6265, *BDNF* rs11030104, *MAPK* rs8136867, and *CREB1* rs6740584 with performance in the BACS subtests. The data obtained once again prove the involvement of genetic factors in NCD in schizophrenia. Further research will reveal reliable genetic markers of schizophrenia and related disorders, which will prevent an unfavorable outcome of schizophrenia and complicate the social readaptation of patients.

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