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Duration Matters: Anticonvulsant Therapy Linked to Bone Loss in Interim Cross-Sectional Study

Длительность терапии антиконвульсантами как фактор риска потери костной ткани: промежуточные результаты наблюдательного кросс-секционного исследования

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Original research

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ABSTRACT

BACKGROUND: Anticonvulsants are widely used in treating patients with mental and neurological disorders. Their long-term use increases the risk of a decrease in bone mineral density (BMD) and low-energy fractures. Despite the growing number of studies of drug-induced osteoporosis, the effect of anticonvulsants on bone microarchitecture remains poorly studied.

AIM: To study the effect of treatment duration with different generations of anticonvulsants on bone mineral density and fracture risk.

METHODS: We examined 100 adult patients with epilepsy who had been on anticonvulsants for more than 12 months and 58 healthy subjects who had never taken anticonvulsants. All the participants underwent a general clinical and neuropsychological assessment, as well as bone densitometry using quantitative computed tomography in three regions of interest (lumbar vertebrae L1, L2 and femoral neck).

RESULTS: BMD reductions were observed in 47 patients (47%) taking anticonvulsants and 29 (50%) subjects in the control group. The mean duration of anticonvulsant therapy was 8.7 years (SD=8.05) in patients with normal BMD, 10.7 years (SD=7.07) in patients with osteopenia, and 9.5 years (SD=5.24) in patients with osteoporosis. Age was found to significantly affect BMD, while the duration of anticonvulsant therapy affected it to a lesser extent. Patients taking first-generation anticonvulsants had lower BMD ($p=0.018$). ROC analysis confirmed the existence of a relationship between the duration of anticonvulsant therapy and the risk of fractures ($p<0.001$). The “duration of anticonvulsant therapy” threshold at the cut-off point corresponding to the highest Youden index value was 10 years.

CONCLUSION: Long-term treatment with conventional anticonvulsants adversely affects BMD and can lead to pathological bone resorption, increasing the risk of fractures in patients. New-generation anticonvulsants did not show any significant negative impact on BMD. The results of this study indicate the need for further research to better understand the effects of anticonvulsants on bone tissue.

АННОТАЦИЯ

ВВЕДЕНИЕ: Антиконвульсанты широко применяются для лечения пациентов с неврологическими заболеваниями и психическими расстройствами. Их длительный приём повышает риск снижения минеральной плотности костной ткани (МПКТ) и низкоэнергетических переломов. Несмотря на рост исследований лекарственно-индуцированного остеопороза, влияние антиконвульсантов на микроархитектонику костной ткани изучено недостаточно.

ЦЕЛЬ: Изучить влияние длительности приема антиконвульсантов различных поколений на МПКТ и риск развития переломов.

МЕТОДЫ: Обследовали 100 взрослых пациентов с эпилепсией, принимающих антиконвульсанты более 12 месяцев, и 58 здоровых участников, которые никогда не принимали антиконвульсанты. Все участники прошли общеклиническое, психиатрическое и неврологическое обследование, а также денситометрическое исследование с помощью количественной компьютерной томографии в трех точках (поясничные позвонки L1, L2 и шейка бедра).

РЕЗУЛЬТАТЫ: У 47 (47%) пациентов, принимающих антиконвульсанты, выявили снижение МПКТ, в контрольной группе — у 29 (50%). Средняя длительность приёма антиконвульсантов у пациентов с нормальной МПКТ составила 8,7 года (SD=8,05), с остеопенией — 10,7 года (SD=7,07), с остеопорозом — 9,5 года (SD=5,24). Установлено, что возраст значительно влияет на показатели МПКТ, а длительность приёма антиконвульсантов — в меньшей степени. Пациенты, принимающие антиконвульсанты первого поколения, имели более низкие показатели МПКТ ($p=0,018$). ROC-анализ подтвердил связь между длительностью приёма антиконвульсантов и риском переломов ($p<0,001$). Пороговое значение показателя «длительность приема антиконвульсантов» в точке cut-off, которой соответствовало наивысшее значение индекса Юдена, — 10 лет.

ЗАКЛЮЧЕНИЕ: Длительная терапия традиционными антиконвульсантами негативно влияет на МПКТ и может приводить к патологической остеорезорбции, увеличивая риск переломов у пациентов. Антиконвульсанты нового поколения не показали выраженного негативного воздействия на МПКТ. Результаты исследования указывают на необходимость дальнейших исследований для более точного понимания влияния антиконвульсантов на костную ткань.

Keywords: *epilepsy; bone mineral density; osteoporosis; osteopenia; densitometry; anticonvulsants*

Ключевые слова: *эпилепсия; минеральная плотность костной ткани; остеопороз; остеопения; денситометрия; антиконвульсанты*

INTRODUCTION

Anticonvulsants are commonly used in clinical practice to treat various mental and neurological disorders. However, the use of anticonvulsants in neurology and anticonvulsants with mood-stabilizing properties in psychiatry is significantly complicated by the adverse effects of drugs that affect the quality of life and the effectiveness of therapy in patients suffering from epilepsy and mental disorders. One of the negative consequences of long-term anticonvulsant therapy in neurological and psychiatric clinics is the metabolic effect it has on the bone system, leading to the development of osteopenia and osteoporosis, which can eventually result in low-energy fractures. Studies have demonstrated a decrease in bone mineral density (BMD) and an increased

risk of fractures in patients with mental disorders receiving long-term treatment with psychotropic drugs, including anticonvulsants [1, 2].

The prevailing context for the use of anticonvulsant drugs is epilepsy, a neuropsychiatric disorder affecting more than 50 million people worldwide [3]. Patients with epilepsy are a heterogeneous group characterized by variable durations and severities of the disease, as well as, in most cases, the presence of concomitant mental disorders. Today, epilepsy and its consequences represent a serious medical problem with an added socio-economic component. Most patients with epilepsy need lifelong anticonvulsant therapy for the symptomatic treatment of epileptic seizures and psychopathological disorders [4, 5].

The main goal of pharmacotherapy in epilepsy is to achieve complete remission of seizures with the lowest risk of adverse effects associated with drug therapy. Currently, about 30 anticonvulsants are in daily use worldwide. Factors usually taken into account for the choice of antiepileptic therapy include the type of seizures, the form of epilepsy, the age and sex of the patient, as well as concomitant diseases and the characteristics of the anticonvulsants, including efficacy, safety, tolerability, the pharmacological profile and availability of the drug for the patient. It is important to remember that monotherapy with an anticonvulsant cannot provide control of the patient's condition in most cases, not only in neurological practice, but also when it is used as a mood stabilizer in psychiatry. As a result, psychiatric and neurological patients usually receive multiple-drug therapy. Unlike patients with mental disorders, for whom anticonvulsants are usually combined with psychotropic drugs of other classes, the drug combination for epileptic patients can often include several anticonvulsants of different generations. This increases the cumulative adverse effects of medicinal products and, at the same time, complicates the management of adverse events through the discontinuation of antiepileptic therapy.

One of the insufficiently studied adverse effects of anticonvulsants is their negative impact on mineral and bone metabolism. On the one hand, many researchers have reported the negative effect of inducers of microsomal liver enzymes (cytochrome P450) on BMD [6]. Antiepileptic drugs increase the activity of the enzyme 25-hydroxyvitamin D₃ 24-hydroxylase (CYP24), which catalyzes the conversion of 25(OH)D to its inactive metabolite, 24,25-dihydroxycholecalciferol (24,25-(OH)₂D₃). Deficiency of the active metabolite of vitamin D, 1,25(OH)₂D₃, leads to decreased calcium absorption, which, in turn, increases the proliferation of parathyroid cells and parathyroid hormone secretion [6]. Such secondary hyperparathyroidism stimulates bone resorption, impairing bone remodeling and mineralization, reducing bone density, altering the bone microarchitecture, and increasing the risk of low-energy fractures [6, 7]. On the other hand, there is evidence that long-term use of anticonvulsants (inducing and non-inducing enzymes) can cause secondary osteoporosis [8]. Findings from a recent study identified drug type, dosage, treatment duration, and polytherapy as predictors of osteoporosis induced by anticonvulsant medications. The use of carbamazepine and valproic acid has been shown to be an independent factor in the development of

osteoporosis, but nevertheless, these drugs are still the most widely used agents in psychiatric and neurological clinical practice [9]. Anticonvulsants with minimal enzyme-inducing activity, such as lamotrigine, are considered to be safer than conventional anticonvulsants [10]. However, despite the increasing application of new-generation anticonvulsants, data on their effect on BMD are lacking and the mechanisms of their effect on bone metabolism remain unknown [11]. Calcitonin deficiency, hyperhomocysteinemia (associated with changes in the bone microarchitecture and increased bone fragility), vitamin K and carnitine deficiency, decreased sex hormone levels, and direct effects on osteoclasts are among the hypotheses that exist to explain bone loss during anticonvulsant therapy. Anticonvulsants also have a direct effect on chondrocyte growth, especially in children, and on vitamin D and calcium levels [7]. In this regard, control of vitamin D levels in patients with mental and neurological disorders on long-term anticonvulsant therapy seems to be a rational osteoporosis prevention measure.

However, there are quite contradictory data in this area. A study conducted in India showed a significant decrease in BMD of the femoral neck in patients taking anticonvulsants, in contrast to the control group [12]. By contrast, a more recent study, also in India, did not find significant differences in BMD of the lumbar spine or femoral neck between compared groups. Computed tomography (CT) densitometry in patients with epilepsy demonstrated a negative correlation between cumulative exposure and the T-score. In patients on long-term treatment with anticonvulsants, bone tissue microarchitecture significantly changes, as evidenced by biochemical parameters and a decrease in BMD [13]. Since patients need to take anticonvulsants for a long time, often combining drugs of different generations and receiving multiple drugs simultaneously for maximum control of their condition, some researchers believe that the use of anticonvulsant therapy for ≥2 years (carbamazepine, phenobarbital, phenytoin, valproic acid) is a risk factor of increased incidence of vertebral fractures [14].

Bone loss associated with anticonvulsant therapy is usually asymptomatic and inconspicuous. Osteoporosis is usually detected only after a fracture. Vertebral compression fractures are the most common type of osteoporotic fractures and are associated with an increased risk of hip and wrist fractures. Vertebral compression fractures are often diagnosed untimely in the general population [15]. At that stage, the impairment of bone microarchitecture is already so pronounced that bone damage can occur

with minimal injury or even without it. Such fractures are called pathological or low-energy fractures.

Patients with epilepsy have a six-fold increased risk of falling compared with the general population, which can increase the likelihood of injury. In addition, the incidence of osteoporosis in this group of patients is 1.7-fold higher [6]. Patients with primary mental disorders are also at an increased risk of falling compared with the general population. Their risk factors include an acute psychotic episode, bipolar affective disorder and the risky behavior associated with it, and the adverse effects of psychotropic therapy (sedation, orthostatic hypotension) [16]. Decreased BMD generally complicates the treatment of injuries in patients. Any planned surgery, whether it is the replacement of a deformed joint or osteosynthesis of a broken vertebra with metal implants, is associated with an increased risk due to bone fragility and the risk of implant migration. The combination of these factors adversely affects the quality of life of patients with mental and neurological disorders; for example, by decreasing motor activity through prolonged hospitalization and immobilization, which, in turn, exacerbates vitamin D deficiency and worsens the condition of the bone tissue [17]. It should be noted that the risk group for the development of low-energy fractures includes, in addition to elderly and very old patients, young and middle age individuals; that is, active working people, which worsens the burden of the disease.

Despite the available data describing the relationship between changes in bone and mineral metabolism in patients on long-term anticonvulsant therapy, there has been a limited number of studies in Russia that considered this aspect. The poorly understood mechanisms of the effects of anticonvulsants on bone metabolism emphasize the need for studies that evaluate the risk factors of anticonvulsant-induced osteoporosis in the Russian population.

Based on the abovesaid, the basic hypothesis of our study was as follows: long-term use of anticonvulsants adversely affects mineral metabolism, which leads to a decrease in BMD. A number of additional hypotheses were formulated: 1) last-generation anticonvulsants affect bone tissue in the same way as older products of this class, leading to pathological bone resorption; 2) long-term use of anticonvulsants increases the likelihood of fractures in patients with epilepsy, as they experience the highest exposure to regular anticonvulsant therapy.

The study aims to study the effect of treatment duration with different generations of anticonvulsants on bone

mineral density and fracture risk. To achieve this aim, the following objectives were defined:

1. To study BMD using CT densitometry in epilepsy patients meeting neuropsychiatric criteria with >12 months of anticonvulsant therapy, and in relatively healthy volunteers who had not received anticonvulsant therapy.
2. To determine the frequency and severity of BMD loss in two compared groups (AC and NAC).
3. To compare the differential impact of traditional (AC1: carbamazepine, valproic acid, benzobarbital, phenobarbital) and last-generation agents (AC2: levetiracetam, lacosamide, lamotrigine, oxcarbazepine) on BMD.
4. To analyze the effect of anticonvulsant therapy duration on the bone tissue condition, and to identify the relationship between the duration of anticonvulsant therapy and a decrease in BMD with the construction of a prognostic risk model for BMD changes during long-term antiepileptic therapy.
5. To assess the effect of the duration of anticonvulsant therapy on the probability of fracture with the construction of a prognostic risk model for BMD changes during long-term antiepileptic therapy.

METHODS

Study design

An observational cross-sectional study was conducted in the two compared groups: patients with epilepsy who had received anticonvulsants for more than 12 months and healthy volunteers who had never undergone antiepileptic drugs.

Setting

The study was conducted at the V.M. Bekhterev National Medical Research Centre for Psychiatry and Neurology. Inclusion criteria for the group of patients with epilepsy:

1. Male and female participants aged between 21 and 60 years inclusive.
2. In- and outpatients.
3. A confirmed diagnosis of "epilepsy" (G40 according to ICD-10).
4. Disease duration of no less than 12 months.
5. Anticonvulsant therapy duration of no less than 12 months (AC1: carbamazepine, valproic acid, benzobarbital, phenobarbital; AC2: levetiracetam, lacosamide, lamotrigine, oxcarbazepine).

6. Ability to read, understand, and sign the informed consent form for inclusion in the study.
7. Ability and willingness to comply with all study procedures in accordance with the protocol.
8. Signed voluntary informed consent of the patient to participation in the study, collection of demographic and medical data, imaging studies, collection and examination of biomaterial (venous blood), as well as the processing of anonymized personal demographic and medical data.
9. For women of childbearing age: a negative pregnancy test.

7. For women of childbearing age: a positive pregnancy test.

Exclusion criteria for all study participants:

1. Refusal to undergo protocol-specified procedures, withdrawal of consent.
2. Pregnancy detected during the study.
3. Initiation of medical use of antidepressants, antipsychotics, glucocorticoids, heparin, hormone replacement therapy.
4. Uncontrolled somatic diseases that interfere with participation in the study.

Inclusion criteria for the group of healthy volunteers:

1. Male and female participants aged between 21 and 60 years inclusive.
2. No current or previous anticonvulsant therapy.
3. Ability to read, understand, and sign the informed consent form for inclusion in the study.
4. Ability and willingness to comply with all study procedures in accordance with the protocol.
5. Signed voluntary informed consent of the patient to participation in the study, collection of demographic and medical data, imaging studies, collection and examination of biomaterial (venous blood), as well as the processing of anonymized personal, demographic, and medical data.
6. For women of childbearing age: a negative pregnancy test.

Assessment tools

All study participants underwent a clinical examination with an assessment of their somatic, neurological, and psychiatric status, detailed drug history, and the collection of information on their lifestyle, social activities, and factors likely to affect bone metabolism. A case report form was developed for the study, which included anonymized data on the subjects' age, diagnosis, treatment, and previous injuries.

BMD was assessed by bone densitometry using quantitative computed tomography performed with a Canon Aquilion One 640 multidetector computed tomography system, in three regions of interest (lumbar vertebrae L1, L2 and femoral neck). CT bone densitometry data were evaluated based on the T- and Z-scores, according to the World Health Organization (WHO) classification.

Non-inclusion criteria for all study participants:

1. Age less than 21 years or more than 60 years.
2. Refusal of the patient or his/her legal guardian to participate in the study.
3. Presence of clinically significant, uncontrolled somatic diseases, endocrine diseases, cancer, or other progressive diseases.
4. Present or past use of hormone replacement therapy, glucocorticoids, heparin, antidepressants, antipsychotics.
5. Suicidal thoughts or aggressive behavior that require immediate medical intervention, as revealed during the assessment interview.
6. Severe cognitive impairment, manifested by the participant's inability to read and understand the essence of the informed consent form for participation in the study.

Statistical analysis

The study data were encoded, organized into tables, and analyzed statistically using the StatTech software, version 3.1.10. Quantitative variables were tested for distribution normality using the Shapiro–Wilk test. If the data were normally distributed, they were described by the mean (M) and standard deviations (SD), as well as the limits of the 95% confidence interval (95% CI). Non-normally distributed quantitative data were represented by the median (Me) and the lower and upper quartiles (Q1–Q3). Categorical data were expressed in absolute values and percentages. Comparison of two groups in terms of a quantitative parameter with normal distribution and equal variance was performed using the Student's t-test. For data with non-standard distribution, the Mann–Whitney U-test was used. Univariate analysis of variance was used to compare three or more groups with normal distribution,

and the Kruskal–Wallis test was used for data with non-standard distribution. Comparison of two groups in terms of a binary attribute was performed by calculating the odds ratio. Percentages were compared using Pearson's chi-square test and Fisher's exact test when analyzing four-way contingency tables. The relationship between a binary dependent variable and one or more independent variables was assessed by multivariate logistic regression. The correlation was assessed using the Spearman's rank correlation coefficient. The linear regression method was used to develop a prognostic model, and the diagnostic significance of quantitative attributes was analyzed using the ROC curve method. The ROC curve was plotted by comparing the sensitivity and specificity of the test at different cut-off points. The Youden index was used to select the optimal point on the ROC curve. Significance levels (*p*-values) were considered as follows: *p*<0.05 were significant, *p*<0.01 were highly significant, and *p*≥0.05 were non-significant.

Ethical approval

All participants were provided full information about the study, and they gave their written consent to participate in it. The study protocol, the informed consent form, and the case report form, as well as the conduct of the study, were reviewed and approved at a meeting of the Ethics Committee of the V.M. Bekhterev National Medical Research Centre

for Psychiatry and Neurology (Minutes No. 3K-I-1/23 dated January 26, 2023).

RESULTS

The study included 100 adult patients with epilepsy aged 21–60 years (Me=29.0; interquartile range (IQR): 25.0; 43.3) who were on long-term (more than 12 months) anticonvulsant therapy (AC group), receiving outpatient or inpatient treatment at the V.M. Bekhterev National Medical Research Centre for Psychiatry and Neurology. Of these, 53 (53%) were women and 47 (47%) were men. The median duration of anticonvulsant therapy was 7 (IQR: 3; 14) years, with a minimum duration of 1 year and a maximum duration of 25 years. The control group included 58 somatically healthy volunteers aged 22–60 years (Me=29; IQR: 25; 43) who were not on anticonvulsants (NAC group) or other medications that could have affected BMD. Of these, 42 (72%) were women and 16 (28%) were men. The characteristics of the AC and NAC groups are presented in Table 1.

The distribution of study participants by age and sex in the AC and NAC groups was heterogeneous (*H*=4.008; *p*=0.045 and $\chi^2=4.990$; *p*=0.026, respectively). Although the median age and interquartile range in the AC and NAC groups were within the same age category according to WHO criteria, the distribution of participants by age was significantly different: participants aged about 40 years

Table 1. General characteristics of study participants

Parameter	Group		All participants (n=158)	Values	
	AC (n=100)	NAC (n=58)			
Age, Me (IQR)	36.0 (29.0; 43.0)	29.0 (25.0; 43.3)	34.5 (26.0; 43.0)	<i>H</i> =4.008, <i>p</i> =0.045, ϵ^2 =0.026	
T-score, L1/L2, M (SD)	-0.864 (1.224)	-0.724 (1.500)	-0.812 (1.329)	<i>F</i> =0.402, <i>p</i> =0.527, <i>d</i> =0.102	
Z-score, L1/L2, M (SD)	-0.550 (1.183)	-0.512 (1.129)	-0.536 (1.160)	<i>F</i> =0.040, <i>p</i> =0.842, <i>d</i> =0.033	
BMDmean, L1, M (SD)	145.850 (34.189)	142.500 (39.528)	144.620 (36.152)	<i>F</i> =0.314, <i>p</i> =0.576, <i>d</i> =0.091	
BMDmean, L2, M (SD)	145.080 (34.436)	142.138 (39.185)	144.000 (36.156)	<i>F</i> =0.242, <i>p</i> =0.624, <i>d</i> =0.080	
Sex, n (%)	Women	53 (53.00%)	42 (72.41%)	95 (60.13%) $\chi^2=4.990$, <i>p</i> =0.026, <i>V</i> =0.178	
	Men	47 (47.00%)	16 (27.59%)		63 (39.87%)
BMD changes on CT, n (%)	Normal	53 (53.00%)	29 (50.00%)	82 (51.90%) $\chi^2=0.294$, <i>p</i> =0.863, <i>V</i> =0.043	
	Osteopenia	32 (32.00%)	21 (36.21%)		53 (33.54%)
	Osteoporosis	15 (15.00%)	8 (13.79%)		23 (14.56%)

Note: AC — group of patients taking anticonvulsants; NAC — group of healthy volunteers not taking anticonvulsants; BMD — bone mineral density; BMDmean — mean bone mineral density; CT — computed tomography; *d* (Cohen's *d*) — effect size; ϵ^2 — effect size for the Kruskal–Wallis test; *F* — Fisher's exact test; *H* — Kruskal–Wallis test; IQR — interquartile range; L1 — first lumbar vertebra; L2 — second lumbar vertebra; M — mean value; Me — median value; n — number of subjects; SD — standard deviation; *V* (Cramér's *V*) — effect size for contingency tables; χ^2 — Pearson's chi-squared test.

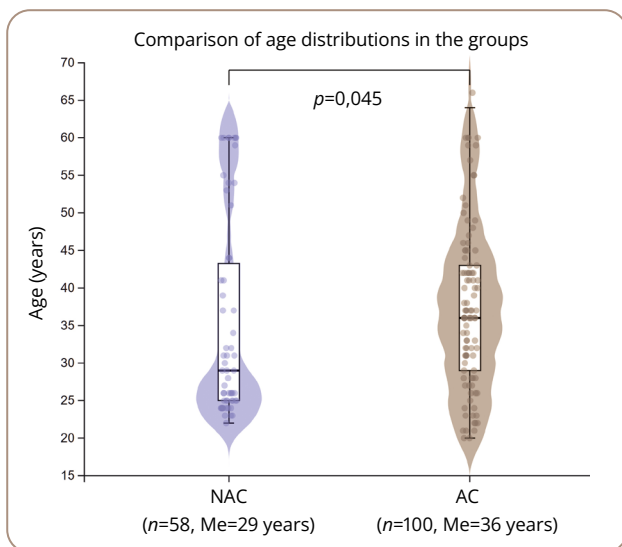


Figure 1. Age distribution in the group of patients with epilepsy taking anticonvulsants and in the group of healthy volunteers not taking anticonvulsants.

Note: AC — group of patients taking anticonvulsants; Me — median value; NAC — group of healthy volunteers not taking anticonvulsants; *n* — number of participants; *p* — level of statistical significance (or $p < 0.05$ indicates the statistical significance of the effect).

Source: Sivakova et al., 2025.

prevailed in the AC group, whereas the NAC group had 2 peaks at approximately 25 and 60 years (Figure 1).

The identified differences are important for the analysis of the results and interpretation of the study data, given that osteoporotic disorders are age- and sex-dependent. Therefore, an additional analysis was carried out in two groups selected from the total study sample, which were comparable in terms of sex ($\chi^2=0.000$, $p=1.000$) and age ($H=0.006$, $p=0.941$). The first group included subjects treated with anticonvulsants (ACa) and consisted of 46 patients with a median age of 33 years (IQR: 26.3; 47.3), while the second group included adjusted samples of healthy subjects (NACa) and consisted of 46 subjects with a median age of 31 years (IQR: 25.3; 49.3). It should be noted that comparability of study groups in terms of key demographic characteristics minimizes the impact of potential biases and increases the integrity of the study results. Thus, NACa and ACa groups were established. Further analysis of these age- and sex-matched groups will enable a more precise assessment of the impact of anticonvulsant treatment duration on osteoporotic changes (Table 2).

Table 2. General characteristics of the adjusted groups

Parameter	Group		All participants (n=92)	Values
	ACa (n=46)	NACa (n=46)		
Age, Me (IQR)	33.0 (26.3; 47.3)	31.0 (25.3; 49.3)	32.0 (26.0; 49.5)	$H=0.006$, $p=0.941$, $\epsilon^2=0.000$
T-score, L1/L2, M (SD)	-0.797 (1.250)	-0.884 (1.496)	-0.840 (1.371)	$F=0.091$, $p=0.763$, $d=0.063$
Z-score, L1/L2, M (SD)	-0.617 (1.231)	-0.601 (1.193)	-0.609 (1.206)	$F=0.004$, $p=0.949$, $d=0.013$
BMDmean, L1, M (SD)	146.804 (39.395)	136.413 (38.211)	141.609 (38.946)	$F=1.649$, $p=0.202$, $d=0.268$
BMDmean, L2, M (SD)	144.783 (39.360)	137.587 (39.189)	141.185 (39.225)	$F=0.772$, $p=0.382$, $d=0.183$
T-score, FN, Me (IQR)	-0.2 (-1.4; 0.8)	0.0 (-0.9; 1.1)	0.0 (-1.0; 0.8)	$H=0.679$, $p=0.410$, $\epsilon^2=0.007$
Z-score, FN, M (SD)	-0.171 (1.100)	0.179 (1.068)	0.004 (1.093)	$F=2.394$, $p=0.125$, $d=0.323$
BMDmean FN, Me (IQR)	0.8 (0.7; 0.9)	0.8 (0.7; 0.9)	0.8 (0.7; 0.9)	$H=0.085$, $p=0.771$, $\epsilon^2=0.001$
Sex, <i>n</i> (%)	Women	30 (65.22%)	30 (65.22%)	$\chi^2=0.000$, $p=1.000$, $V=0.000$
	Men	16 (34.78%)	16 (34.78%)	
BMD changes on CT, <i>n</i> (%)	Normal	26 (56.52%)	20 (43.48%)	$\chi^2=2.430$, $p=0.297$, $V=0.163$
	Osteopenia	12 (26.09%)	19 (41.30%)	
	Osteoporosis	8 (17.39%)	7 (15.22%)	

Note: ACa — adjusted group of patients taking anticonvulsants; NACa — adjusted group of healthy volunteers not taking anticonvulsants; BMD — bone mineral density; BMDmean — mean bone mineral density; CT — computed tomography; F — Fisher's exact test; FN — femoral neck; H — Kruskal-Wallis test; IQR — interquartile range; L1 — first lumbar vertebra; L2 — second lumbar vertebra; Me — median value; SD — standard deviation; V (Cramér's V) — effect size for contingency tables; d (Cohen's d) — effect size; ϵ^2 — effect size for the Kruskal-Wallis test; M — mean value; *n* — number of subjects; *p* — level of statistical significance (or $p < 0.05$ indicates the statistical significance of the effect); χ^2 — Pearson's chi-squared test.

Patients in the AC group were divided into two subgroups depending on the generation of the anticonvulsant taken: AC1 — patients taking conventional anticonvulsants (carbamazepine, valproic acid, benzobarbital, phenobarbital); AC2 — patients taking latest generation anticonvulsants (levetiracetam, lacosamide, lamotrigine, oxcarbazepine). The AC1 subgroup included 40 patients, of whom 21 (52.5%) were male and 19 (47.5%) were female. The median age was 36 (IQR: 29.8; 42.0) years. The AC2 subgroup included 59 individuals, of whom 25 (42.4%) were men and 34 (57.6%) women. The median age was 37 (IQR: 28.5; 43.5) years. The AC1 and AC2 subgroups were comparable in terms of sex ($\chi^2=0.618, p=0.432, V=0.079$) and age ($H=0.572, p=0.449, \epsilon^2=0.006$). The differences between the subgroups are not related to demographic factors such as sex and age, which allows to focus on the assessment of the impact of the different generations of anticonvulsants on the studied parameters. The general characteristics of the studied subgroups AC1 and AC2 are presented in Table 3.

Changes in bone mineral density

Changes in BMD were assessed based on the degree of its regression: normal→decreased→osteopenia→osteoporosis. BMD measurements using CT densitometry showed that 47 (47%) patients from the AC group had decreased BMD, including 32 (32.0%) patients with CT signs of osteopenia and 15 (15%) patients with CT signs of osteoporosis. In the NAC group, BMD changes were detected in 29 (50.0%) subjects and were distributed as follows: CT osteopenia was observed in 21 (36.21%) subjects; CT osteoporosis, in 8 (13.79%) subjects. The comparative analysis of the frequency of detection and the degree of BMD changes on CT between the NAC and AC groups did not reveal statistically significant differences ($\chi^2=0.294, p=0.863, V=0.043$) (see Table 1). The analysis of the frequency and degree of BMD changes on CT in the age- and sex- adjusted samples ACa and NACa also demonstrated no significant differences between the compared groups ($\chi^2=2.430, p=0.297, V=0.163$) (see Table 2).

Table 3. General characteristics of patients taking conventional anticonvulsants and new-generation anticonvulsants

Parameter	Subgroup		All participant (n=99)	Values	
	AC1 (n=40)	AC2 (n=59)			
Age, Me (IQR)	36.0 (29.8, 42.0)	37.0 (28.5, 43.5)	36.0 (29.0, 43.0)	$H=0.572, p=0.449, \epsilon^2=0.006$	
Duration of AC therapy, years, M (SD)	11.850 (9.542)	7.814 (4.950)	9.444 (7.396)	$F=7.577, p=0.007, d=0.531$	
T-score, L1/L2, M (SD)	-1.126 (1.193)	-0.662 (1.216)	-0.850 (1.222)	$F=3.518, p=0.064, d=0.385$	
Z-score, L1/L2, M (SD)	-0.860 (1.310)	-0.317 (1.040)	-0.536 (1.181)	$F=5.247, p=0.024, d=0.459$	
BMDmean, L1, M (SD)	137.675 (32.734)	151.932 (34.256)	146.172 (34.211)	$F=4.279, p=0.041, d=0.426$	
BMDmean, L2, M (SD)	136.425 (33.012)	151.441 (34.409)	145.374 (34.486)	$F=4.690, p=0.033, d=0.445$	
T-score, FN, M (SD)	-0.478 (1.469)	-0.010 (1.424)	-0.196 (1.453)	$F=2.477, p=0.119, d=0.324$	
Z-score, FN, M (SD)	-0.083 (1.140)	0.116 (1.104)	0.037 (1.117)	$F=0.743, p=0.391, d=0.177$	
BMDmean, FN, M (SD)	0.769 (0.156)	0.825 (0.210)	0.802 (0.191)	$F=2.027, p=0.158, d=0.303$	
Sex, n (%)	Women	19 (47.50%)	34 (57.63%)	$\chi^2=0.618, p=0.432, V=0.079$	
	Men	21 (52.50%)	25 (42.37%)		46 (46.46%)
BMD changes on CT, n (%)	Normal	19 (47.50%)	34 (57.63%)	$\chi^2=1.048, p=0.592, V=0.103$	
	Osteopenia	15 (37.50%)	17 (28.81%)		32 (32.32%)
	Osteoporosis	6 (15.00%)	8 (13.56%)		14 (14.14%)

Note: AC — anticonvulsants; AC1 — subgroup of patients taking conventional anticonvulsants; AC2 — subgroup of patients taking new-generation anticonvulsants; BMD — bone mineral density; BMDmean — mean bone mineral density; CT — computed tomography; d (Cohen's d) — effect size; ϵ^2 — effect size for the Kruskal-Wallis test; F — Fisher's exact test; FN — femoral neck; H — Kruskal-Wallis test; IQR — interquartile range; L1 — first lumbar vertebra; L2 — second lumbar vertebra; M — mean value; Me — median value; n — number of subjects; p — level of statistical significance (or $p<0.05$ indicates the statistical significance of the effect); SD — standard deviation; V (Cramér's V) — effect size for contingency tables; χ^2 — Pearson's chi-squared test.

In the quantitative BMD analysis conducted in the AC and NAC groups, the mean T-score of the L1/L2 vertebrae was -0.864 (SD=1.224) in the AC group and -0.724 (SD=1.500) in the NAC group ($F=0.402$, $p=0.527$, $d=0.102$). The mean Z-score of the L1/L2 vertebrae was -0.550 (SD=1.183) in the AC group and -0.512 (SD=1.129) in the NAC group ($F=0.040$, $p=0.842$, $d=0.033$). The mean BMD of the L1 vertebra was 145.850 (SD=34.189) in the AC group and 142.500 (SD=39.528) in the NAC group ($F=0.314$, $p=0.576$, $d=0.091$). The mean BMD of the L2 vertebra was 145.080 (SD=34.436) in the AC group and 142.138 (SD=39.185) in the NAC group ($F=0.242$, $p=0.624$, $d=0.080$). Thus, no statistically significant differences were demonstrated between the AC and NAC groups in terms of BMD values. The mean T-scores of the L1/L2 vertebrae, Z-scores of the L1/L2 vertebrae, and BMD values (for the L1 and L2 vertebrae) in the two groups were in comparable ranges, which is confirmed by the absence of significant differences in the F-test ($p>0.05$) and small effect size values ($d<0.2$) (see Table 1).

In the adjusted samples comparable in terms of age and sex (ACa and NACa), the following results were obtained in the analysis of BMD values. The mean T-score of the L1/L2 vertebrae was -0.797 (SD=1.250) in the ACa group and -0.884 (SD=1.496) in the NACa group ($F=0.091$, $p=0.763$, $d=0.063$). The mean Z-score of the L1/L2 vertebrae was -0.617 (SD=1.231) in the ACa group and -0.601 (SD=1.193) in the NACa group ($F=0.004$, $p=0.949$, $d=0.013$). The mean BMD of the L1 vertebra was 146.804 (SD=39.395) in the ACa group and 136.413 (SD=38.211) in the NACa group ($F=1.649$, $p=0.202$, $d=0.268$). For the L2 vertebra, the mean values were

144.783 (SD=39.360) and 137.587 (SD=39.189), respectively ($F=0.772$, $p=0.382$, $d=0.183$). The median T-score of the femoral neck was -0.2 (IQR: -1.4 ; 0.8) in the ACa group and 0.00001 (IQR: -0.9 ; 1.1) in the NACa group ($H=0.679$, $p=0.410$, $\epsilon^2=0.007$). The mean Z-score of the femoral neck was -0.171 (SD=1.100) in the ACa group and 0.179 (SD=1.068) in the NACa group ($F=2.394$, $p=0.125$, $d=0.323$). The median BMD of the femoral neck was 0.8 (IQR: 0.7 ; 0.9) in both groups ($H=0.085$, $p=0.771$, $\epsilon^2=0.001$). Thus, the analysis of BMD values in the adjusted ACa and NACa groups also did not reveal significant differences in the T-score, Z-score or mean BMD values for the lumbar spine (L1 vertebra, L2 vertebra) or the femoral neck (see Table 2).

Effect of the generations of anticonvulsants on bone mineral density

The mean number of years of anticonvulsant therapy was 11.850 (SD=9.542) in the AC1 subgroup and 7.814 (SD=4.950) in the AC2 subgroup, which is significantly longer treatment with conventional anticonvulsants ($F=7.577$, $p=0.007$, $d=0.531$).

When assessing the categorical parameters of BMD changes in the AC1 subgroup, normal bone density values were revealed in 19 (47.5%) patients, decreases to the level of osteopenia in 15 (37.5%) patients, and reductions to the level of osteoporosis in 6 (15%) patients. In the AC2 subgroup, bone density values within the normal range were revealed in 34 (57.63%) subjects, decreases to the level of osteopenia in 17 (28.21%) patients, and reductions to the level of osteoporosis in 8 (13.56%) subjects. The analysis of

Table 4. Comparison of bone mineral density data in patients taking conventional anticonvulsants and patients treated with new-generation anticonvulsants, as well as in healthy subjects

Subgroup	T-score, L1/L2 (LS means [95% CI])	Z-score, L1/L2 (LS means [95% CI])	BMDmean, L1 (LS means [95% CI])	BMDmean, L2 (LS means [95% CI])	T-score (LS means [95% CI])	FN Z-score, FN (LS means [95% CI])	BMDmean, FN (LS means [95% CI])
AC2	-0.539 [-1.062 , -0.016]	-0.198 [-0.643 , 0.248]	152.481 [137.675 , 167.288]	151.296 [136.345 , 166.247]	-0.043 [-0.555 , 0.470]	0.030 [-0.381 , 0.442]	0.784 [0.711 , 0.858]
Control	-0.884 [-1.285 , -0.483]	-0.601 [-0.942 , -0.259]	136.413 [125.069 , 147.757]	137.587 [126.133 , 149.041]	-0.119 [-0.512 , 0.274]	0.179 [-0.137 , 0.494]	0.773 [0.716 , 0.829]
AC1	-1.163 [-1.787 , -0.539]	-1.212 [-1.743 , -0.681]	138.737 [121.086 , 156.387]	135.526 [117.704 , 153.349]	-0.837 [-1.449 , -0.226]	-0.457 [-0.948 , 0.034]	0.720 [0.632 , 0.808]
Pr>F (Model)	0.304	0.018	0.222	0.279	0.1	0.101	0.503
Significant	No	Yes	No	No	No	No	No

Note: a, b — statistically homogeneous groups identified through pairwise comparisons; AC1 — subgroup of patients taking conventional anticonvulsants; AC2 — subgroup of patients taking new-generation anticonvulsants; BMDmean — mean bone mineral density; FN — femoral neck; L1 vertebra — first lumbar vertebra; L2 vertebra — second lumbar vertebra; NAC — group of healthy volunteers not taking anticonvulsants; Pr>F (Model) — significance level (p), indicates a statistically significant effect at $p<0.05$.

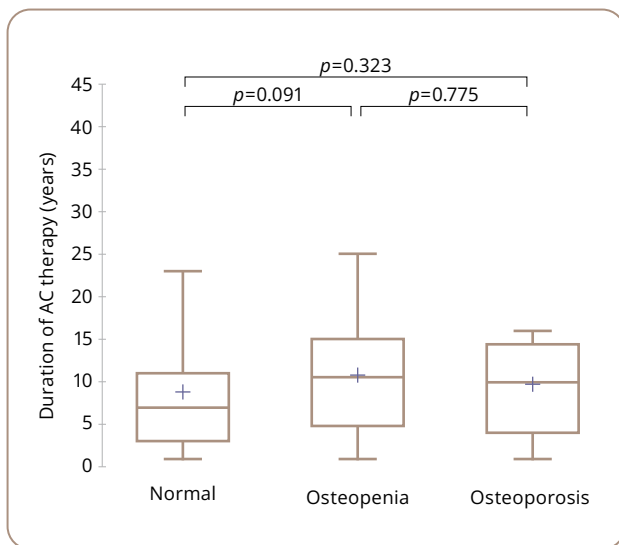


Figure 2. Changes in bone mineral density depending on the duration of the anticonvulsant therapy.

Note: AC — anticonvulsants.

Source: Sivakova et al., 2025.

the frequency and degree of changes in BMD with respect to the generation of anticonvulsants did not reveal statistically significant differences in the compared subgroups AC1 and AC2 ($\chi^2=1.048$, $p=0.592$, $V=0.103$) (see Table 3).

In the analysis of BMD values obtained by CT densitometry, statistically significant differences were found between the AC1 and AC2 subgroups in the following parameters: the Z-score of the L1/L2 vertebrae ($F=5.247$, $p=0.024$, $d=0.459$), the BMDmean of the L1 vertebra ($F=4.279$, $p=0.041$, $d=0.426$), and the BMDmean of the L2 vertebra ($F=4.690$, $p=0.033$, $d=0.445$), which may indicate a lower level of bone mineralization in patients taking conventional anticonvulsants. However, no statistically significant differences were found in the other CT parameters: the T-score of the L1/L2 vertebrae ($F=3.518$, $p=0.064$, $d=0.385$), as well as the T-score of the femoral neck ($F=2.477$, $p=0.119$, $d=0.324$), the Z-score of the femoral neck ($F=0.743$, $p=0.391$, $d=0.177$), and the BMDmean of the femoral neck ($F=2.027$, $p=0.158$, $d=0.303$) (see Table 3).

Comparison of CT densitometry results in the AC1 and AC2 subgroups with the group of healthy subjects (NAC) demonstrated a more pronounced decrease in BMD in the subgroup of patients receiving conventional anticonvulsants (AC1) (Table 4).

The analysis of BMD data obtained by CT allowed a conclusion that the difference in the Z-score of the L1/L2 vertebrae was statistically significant ($p=0.018$). The rest of

the parameters, including the T-scores and BMDmean, did not show statistically significant differences between the groups ($p>0.05$). The results indicate a significant decrease in BMD in the subgroup of patients taking conventional anticonvulsants (AC1), as compared with AC2 and NAC. The obtained data may indicate a potentially more negative effect of conventional anticonvulsants on bone density. At the same time, no negative effect of the new-generation anticonvulsants on BMD was observed; on the contrary, they demonstrated higher mineralization compared with the control group.

Effect of the duration of anticonvulsant therapy on bone mineral density

The analysis of BMD changes depending on the duration of anticonvulsant therapy revealed the following: the average duration of anticonvulsant therapy was 8.7 years in patients with normal bone density, 10.7 years in patients with BMD values decreased to the level of osteopenia, and 8.5 years in patients with BMD values decreased to the level of osteoporosis. No statistically significant differences in the duration of anticonvulsant therapy were found between patients with different levels of bone density ($p_{\text{normal}}-p_{\text{osteopenia}}=0.091$; $p_{\text{normal}}-p_{\text{osteoporosis}}=0.323$; $p_{\text{osteopenia}}-p_{\text{osteoporosis}}=0.775$) (Figure 2).

An analysis of multiple linear regression was performed in order to assess the relationship between the duration of the anticonvulsant therapy and BMD, using the “sex” and “age” of participants as covariates (Table 5). For the T-score of the L1/L2 vertebrae, duration of anticonvulsant therapy had no statistically significant effect ($p=0.171$), while age had a significant impact ($p=0.001$). This suggests that age is the main factor affecting the T-score of the L1/L2 vertebrae, and that the duration of the anticonvulsant therapy does not play a significant role; the model explains 14% of the variation ($R^2=0.14$). A statistically significant negative relationship with the duration of the anticonvulsant therapy was shown for the Z-score of the L1/L2 vertebrae ($p=0.005$), while age had no significant impact ($p=0.682$). The obtained data may indicate that the duration of the anticonvulsant therapy decreases the Z-score of the L1/L2 vertebrae, while the model explains 8.7% of the variation ($R^2=0.087$). For the mean BMD of the L1 vertebra, the duration of the anticonvulsant therapy showed a tendency towards significance ($p=0.053$); at the same time, age had a significant impact ($p<0.001$). This demonstrates that age is a key factor and the duration of the anticonvulsant

Table 5. Regression analysis of the relationship between the duration of anticonvulsant therapy and bone mineral density assessed using computed tomography densitometry, with “sex” and “age” covariates

Parameter	R ²	Duration of therapy (p-value)	Age (p-value)	Gender (p-value)	Conclusion
Z-score, L1/L2	0.14	0.171 (non-significant)	0.001 (significant)	0.270 (non-significant)	Duration has no effect, age has an effect
Z-score, L1/L2	0.087	0.005 (significant)	0.682 (non-significant)	0.583 (non-significant)	Duration has a significant effect (negative relationship)
BMDmean, L1	0.286	0.053 (on the edge of significance)	<0.001 (significant)	0.129 (non-significant)	Duration is weakly correlated, age is a key factor
BMDmean, L2	0.224	0.132 (non-significant)	<0.001 (significant)	0.278 (non-significant)	Duration has no effect, age has an effect
T-score, FN	0.083	0.146 (non-significant)	0.026 (significant)	0.406 (non-significant)	Duration has no effect, age has an effect
Z-score, FN	0.028	0.119 (non-significant)	0.921 (non-significant)	0.752 (non-significant)	No relationship with duration and age
BMDmean, FN	0.088	0.083 (non-significant)	0.035 (significant)	0.872 (non-significant)	No relationship with duration, age is significant

Note: BMDmean — mean bone mineral density; FN — femoral neck; L1 — first lumbar vertebra; L2 — second lumbar vertebra; p-value — significance level, indicates a statistically significant effect at $p < 0.05$; R² — determination coefficient.

therapy is weakly associated; the model explains 28.6% of the variation ($R^2=0.286$). The mean BMD of the L2 vertebra was associated with the duration of therapy without a statistical significance ($p=0.132$), and the age was significant, again ($p < 0.001$), and remains an important factor; the explanatory power of the model stood at 22.4% ($R^2=0.224$). For the T-score of the femoral neck, the model explains 8.3% of the variation ($R^2=0.083$), while duration has no effect ($p=0.146$), and the age remains significant ($p=0.026$). When analyzing the Z-score of the femoral neck, the model showed very low explanatory power ($R^2=0.028$) and none of the factors showed a significant impact. Duration of anticonvulsant therapy was not significant for the mean BMD of the femoral neck ($p=0.083$), while age showed a significant impact ($p=0.035$). This indicates a weak relationship with the duration of anticonvulsant use, while age continues to be a significant factor; the model explains 8.8% of the variation ($R^2=0.088$).

Effect of the duration of anticonvulsant therapy on the risk of fracture

An analysis of the relationship between the duration of anticonvulsant therapy and the history of fractures in the AC group was performed, with 2 subgroups of patients used. Subgroup 1 included 36 people with a history of fractures, subgroup 2 consisted of 64 people without a history of fractures. In the subgroup of patients with a history of fractures, the duration of anticonvulsant therapy was 14

(8–15) years, which is statistically longer ($U=50.5$, $p < 0.001$) compared with patients without fractures, 5 (3–8) years (Figure 3).

In the control group (NAC), 16 (27.6%) individuals had a history of fractures, while 42 (72.4%) subjects had had no fractures. All healthy subjects had a history of a traumatic injury leading to a fracture. Nevertheless, the NAC and AC groups had no statistically significant differences in the fracture rate ($\chi^2=0.205$, $p=0.651$).

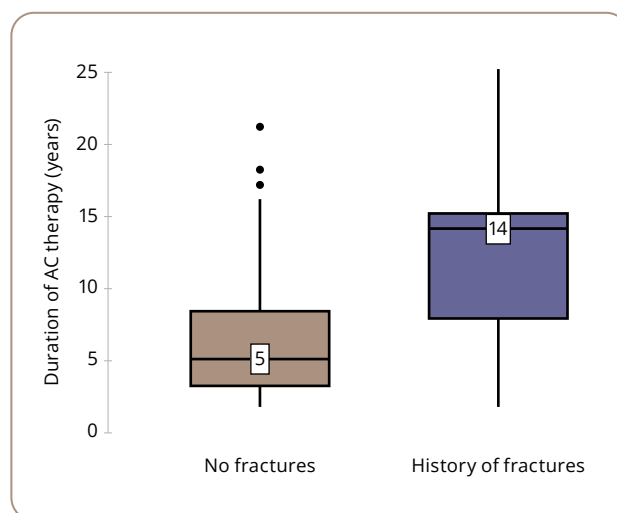


Figure 3. Relationship between the duration of anticonvulsant therapy and the history of fractures.

Note: AC — anticonvulsants.

Source: Sivakova et al., 2025.

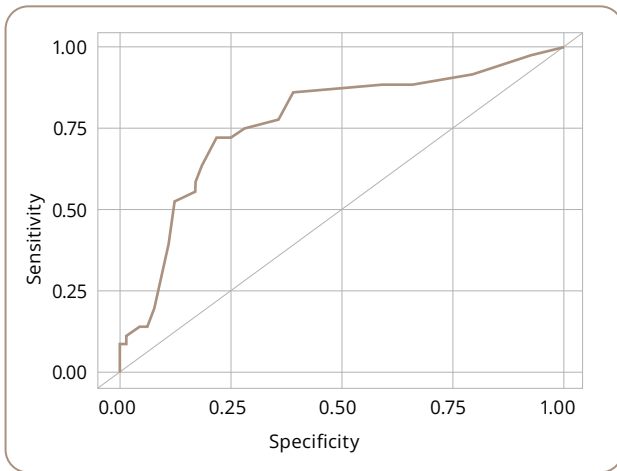


Figure 4. ROC curve relating the probability of fracture and the duration of anticonvulsant therapy.

Source: Sivakova et al., 2025.

A multivariate logistic regression performed to assess the impact of the duration of AC therapy on the development of fractures, with adjustments for sex and age, revealed that the R-squared was 0.103; therefore, the resulting model can explain only 10% of the identified cases of previous fractures. The obtained model also demonstrated the absence of a statistically significant relationship between the sex, age of the participants and the history of fractures ($B=-0.86, p=0.381$ and $B=0.16, p=0.871$, respectively), but it confirmed a statistically significant relationship between the duration of anticonvulsant therapy and the development of fractures ($B=0.295, p=0.03$).

To more accurately determine the relationship between the probability of fractures and the duration of anticonvulsant therapy, a ROC analysis was performed (Figure 4).

The area under the ROC curve was 0.769 ± 0.052 with a 95% CI of 0.667–0.870 (Figure 4). The obtained model demonstrates a statistically significant relationship between the probability of fracture and the duration of anticonvulsant therapy ($p < 0.001$).

The analysis of the specificity and sensitivity of the model demonstrated that the “duration of anticonvulsant therapy” threshold at the cut-off point corresponding to the highest Youden index value was 10 years (Figure 5, Table 6). This allows one to predict the probability of fracture in patients with epilepsy who have received anticonvulsant therapy for 10 years or longer. The sensitivity and specificity of the final model were used to select the cut-off line: the highest values for both characteristics were 72.2 and 78.1%, respectively (Table 6).

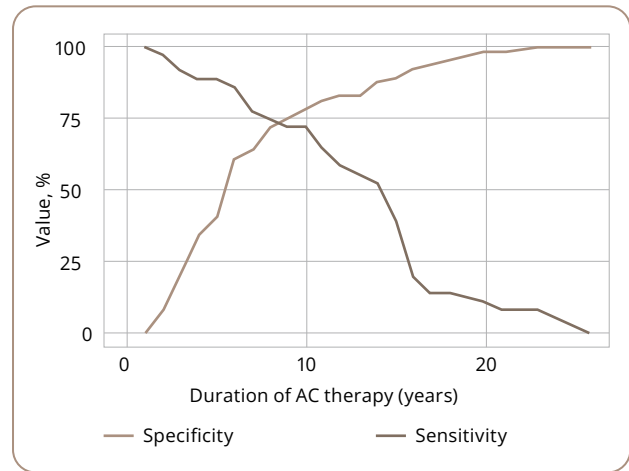


Figure 5. Analysis of the sensitivity and specificity of the ROC model depending on the threshold values of the duration of anticonvulsant therapy in the group of patients with epilepsy.

Note: AC — anticonvulsants.

Source: Sivakova et al., 2025.

Table 6. Threshold values of the duration of anticonvulsant therapy and the probability of fracture according to the ROC model, taking into account the sensitivity and specificity

Threshold	Sensitivity (%)	Specificity (%)	PPV	NPV
14	52.8	87.5	70.4	76.7
13	55.6	82.8	64.5	76.8
12	58.3	82.8	65.6	77.9
11	63.9	81.2	65.7	80.0
10	72.2	78.1	65.0	83.3
9	72.2	75.0	61.9	82.8
8	75.0	71.9	60.0	83.6
7	77.8	64.1	54.9	83.7
6	86.1	60.9	55.4	88.6

Note: NPV — negative predictive value; PPV — positive predictive value. The highest values for both characteristics (sensitivity and specificity) at the same time are shown in bold.

The results of the ROC analysis indicate a significant impact of the duration of anticonvulsant therapy on the risk of fracture in the patients. It was established that with increasing duration of anticonvulsant therapy, the probability of fractures significantly increases. The obtained results emphasize the importance of considering the duration of antiepileptic therapy, along with its efficacy, when assessing potential risks and adverse effects.

DISCUSSION

Osteoporosis represents a major public health challenge with far-reaching implications for both population health and economic systems [8, 18]. Despite expectations, the results of this study did not reveal statistically significant differences ($\chi^2=0.294$, $p=0.863$, $V=0.043$) in the BMD decrease between patients receiving long-term anticonvulsant therapy and healthy subjects not taking anticonvulsants. The analysis of BMD values obtained using CT revealed that the mean T-scores and Z-scores of the L1/L2 vertebrae, as well as the mean BMD values (for the L1 and L2 vertebrae) in the two groups were in comparable ranges, which is confirmed by the absence of significant differences in the F-test ($p>0.05$) and small effect size values ($d<0.2$). Thus, the study results demonstrate that there were no significant differences in BMD changes between the AC and NAC groups. This contradicts the results of many epidemiological studies suggesting a negative effect of anticonvulsants on BMD [19]. Taking into account that the AC and NAC groups were heterogeneous in terms of sex and sex composition, we formed adjusted groups matched for sex and age. It is important to emphasize that comparability of study groups in terms of key demographic characteristics minimizes the impact of potential biases and increases the reliability of the study results. Thus, an additional analysis was performed in adjusted samples of healthy subjects (NACa) and subjects taking anticonvulsants (ACa) for a more accurate assessment of the effect of the duration of anticonvulsant therapy on changes in BMD. However, the analysis of BMD values in the adjusted ACa and NACa groups also did not reveal significant differences in the T-score, Z-score, or mean BMD values for the lumbar spine (L1 vertebra, L2 vertebra) or the femoral neck ($p>0.05$, $d<0.2$). The obtained results demonstrate that the duration of anticonvulsant therapy does not have a significant effect on BMD, which contributes to the ongoing discussion about the safety profile of these drugs in relation to bone health. Further studies with large samples and diverse demographics are needed to better understand the relationship between anticonvulsant therapy and BMD, especially taking into account individual risk factors and the pathogenic mechanisms of action of the drugs. It should be noted that these results are interim and the enrollment of study subjects is ongoing. Upon completion of data collection, we plan to conduct an in-depth analysis that will provide more informative data.

The analysis of changes in BMD depending on the generation of the anticonvulsant used revealed significant

differences in CT parameters: the Z-score of the L1/L2 vertebrae ($F=5.247$, $p=0.024$, $d=0.459$), the BMDmean of the L1 vertebra ($F=4.279$, $p=0.041$, $d=0.426$), and the BMDmean of the L2 vertebra ($F=4.690$, $p=0.033$, $d=0.445$). These data may indicate that anticonvulsants of different generations have a heterogeneous effect on bone density, which is probably due to different mechanisms of action. In particular, there is a tendency to lower bone density in patients taking conventional anticonvulsants. This may indicate a potentially more unfavorable effect on bone tissue and the development of pathological bone resorption. At the same time, no negative effect of new-generation anticonvulsants on BMD was observed; on the contrary, they demonstrated higher mineralization compared with the control group. However, a comparative analysis of the frequency and degree of changes in BMD showed no statistically significant differences between groups of patients taking conventional anticonvulsants (AC1) or latest generation drugs (AC2) ($\chi^2=1.048$, $p=0.592$, $V=0.103$). These results are consistent with the results in the study by Hamed (2016), which demonstrated no significant differences in BMD changes depending on the generation of the anticonvulsant either [8]. Given the heterogeneous results obtained, it makes sense to analyze the effect of specific groups of anticonvulsants on BMD in future studies, taking into account their different pathogenic mechanisms of action. Such studies will provide a deeper understanding of the relationship between the use of various anticonvulsants and the condition of bone tissue, which may be important for optimizing therapeutic approaches and improving the quality of life of patients.

In addition to the generation and different pathogenic mechanisms of action of anticonvulsants, the duration of their use may be a significant factor affecting bone density. A study by Fahmy et al. (2018) demonstrated a significant increase in the risk of decreased BMD with increasing duration of antiepileptic therapy, regardless of the generation of the drug used [19]. Multiple regression models were constructed to assess the relationship between decreased bone density and the duration of antiepileptic therapy. The results of a multiple linear regression analysis, which evaluated the relationship between the duration of anticonvulsant therapy and BMD using the covariates "sex" and "age" showed a significant negative relationship between the duration of anticonvulsant therapy and the BMD decrease assessed by the Z-score of the L1/L2 vertebrae ($p=0.005$, $R^2=0.087$). However, age and sex

did not have any significant effect on the Z-score of the L1/L2 vertebrae ($p=0.682$, $p=0.583$, respectively), which can be explained by the age and sex dependence of this parameter. The Z-score is based on the average age-specific values and serves for comparison with standardized population values. This approach provides greater sensitivity in detecting the influence of external factors — such as duration of medication use — on bone tissue status, taking into account the individual age characteristics of each respondent. The study also demonstrated a weak relationship between the changes in the mean BMD values of the L1 vertebra and FN and the duration of anticonvulsant therapy ($p=0.053$ and $p=0.083$). However, age had a greater effect on these parameters ($p<0.001$ and $p=0.035$). The duration of anticonvulsant therapy had no significant association with changes in BMD according to the T-score of the L1/L2 vertebrae and femoral neck, with age showing a pronounced effect on these parameters. The T-score compares the bone density with the peak bone mass of young, healthy individuals, and this makes it more sensitive to age-related changes and decreases its sensitivity to changes caused by long-term anticonvulsant therapy. We believe that the more significant relationship between the duration of anticonvulsant therapy and the Z-score, as compared with the T-score, can be explained by the fact that the Z-score is a better reflection of the impact of external factors on bone tissue, including the duration of anticonvulsant therapy, and takes into account the age-related changes by default for each respondent.

The obtained interim results emphasize the need for a more in-depth study of the effect of long-term anticonvulsant therapy on changes in BMD, taking into account both age and sex, as well as therapeutic factors in patients with psychiatric and neurological diseases, in whom long-term use of anticonvulsants for different indications may be one of the factors. In addition, understanding the relationship between anticonvulsant therapy and the condition of bone tissue may contribute to the development of preventive strategies aimed at maintaining bone health in long-term users of these drugs. This, in turn, can improve the quality of patients' life, reducing the fractures risk and related complications. Thus, this study has significant potential to improve the conduct of studies aimed at evaluating the effect of anticonvulsants on BMD and the development of pathological bone resorption.

According to the recommendations of the National Osteoporosis Foundation (NOF), individuals with a history

of fractures are at an increased risk of osteoporosis [20]. However, we have not seen any studies that examined the relationship between the duration of anticonvulsant therapy and fractures. Our study provided data on the association between the duration of anticonvulsant therapy and the history of fractures in patients with epilepsy. In the subgroup of patients with a history of fractures, the duration of anticonvulsant therapy was 14 (8–15) years, which was significantly longer ($p(U)<0.001$) than in the subgroup of patients with no history of fractures (64 people), 5 (3–8) years. These results indicate that the duration of anticonvulsant therapy is a potential risk factor for the development of fractures in patients with epilepsy and other neuropsychological disorders requiring the use of anticonvulsants. The absence of such assessments in prior research underscores a critical gap, necessitating further investigation into how the duration of antiepileptic therapy affects BMD and fracture risk. Studies with a subsequent development of management strategies for patients taking anticonvulsants will help lower the risks of osteoporotic fractures and improve the quality of life of patients.

Limitations

The presented data are an interim result of the research project “The effect of anticonvulsants on the development of osteoporosis in patients with epilepsy”. The age and sex distributions are significantly different in the groups, which may be important in analyzing the results and interpreting the study data. However, the final sample of the study will include participants in groups of relatively equal sex and age distributions, and each group will include equal proportions of female and male subjects in two age categories (young age of 21–40 years and middle age of 41–60 years, according to the WHO classification). Anticonvulsants represent a heterogeneous group of medications, and the findings described in this article will be further specified for individual agents as the ongoing study progresses.

CONCLUSION

The results of the study demonstrated that patients with epilepsy have no statistically significant differences in the BMD decrease compared with healthy subjects, which is not consistent with previous research into the effect of anticonvulsants on BMD. The study also yielded conflicting data on the effect of the duration of anticonvulsant therapy on changes in BMD. However, long-term anticonvulsant

therapy was found to be associated with an increased fractures risk. The results of the study highlight the importance of further studying the impact of antiepileptic therapy on bone health and the need to develop strategies to minimize the fractures risk. The development of a set of measures to prevent anticonvulsant-induced osteoporosis is an important undertaking, since the main goals of healthcare remain the prevention and prophylaxis of diseases, and the preservation of the life quality and working ability of the population.

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The Neurophysiological Features of Anticipation in Schizophrenia: A Cross-Sectional Study of Event-Related Potentials

Нейрофизиологические особенности антиципации при шизофрении: исследование потенциалов мозга, связанных с событиями

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Original research

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ABSTRACT

BACKGROUND: It is known that disorders of mental activity in schizophrenia patients may be caused by an impairment in the actualization of past experience during anticipation (prediction), which leads to impairment in constructing predictions, comparing incoming sensory information with the predictions, and updating the predictions. Previous studies have shown that the probability of an expected event affects the components of event-related potentials in mentally healthy individuals. However, it has not yet been studied how changes in the probability of an expected stimulus influence the behavior of individuals with schizophrenia and their event-related potential measures.

AIM: To compare the influence of event probability on the characteristics of brain potentials in patients with schizophrenia and healthy individuals.

METHODS: The study included mentally healthy individuals and male schizophrenia patients. Electroencephalograms were recorded while participants performed a saccadic task within the Central Cue Posner's Paradigm under conditions of varying probability (50% and 80%) of target stimulus presentation. Pre-stimulus (Contingent Negative Variation) and post-stimulus (Mismatch Negativity and P3) components of event-related potentials were analyzed upon the presentation of two types of target stimuli: standard (presented on the same side as the cue stimulus) and deviant (presented on the opposite side), under conditions of 50% and 80% stimulus congruence probability.

RESULTS: The study involved 20 mentally healthy individuals and 18 schizophrenia patients. In healthy subjects, the amplitude of the contingent negative variation increased with high stimulus congruence probability, while the amplitude of the Mismatch Negativity (MMN) and P3 component was higher for deviant stimuli under conditions of high (80%) probability. In schizophrenia patients, changes in probability demonstrated no impact on the amplitude of the contingent negative wave, MMN, or P3.

CONCLUSION: The characteristics of event-related potentials in patients with schizophrenia indicate impaired anticipation processes.

АННОТАЦИЯ

ВВЕДЕНИЕ: Известно, что расстройства психической деятельности у больных шизофренией могут быть обусловлены нарушениями актуализации прошлого опыта в процессе антиципации (прогнозирования), которые приводят к нарушениям построения прогноза, сопоставления поступающей сенсорной информации с прогнозом и коррекции прогноза. Ранее было показано, что у здоровых людей вероятность ожидаемого события влияет на компоненты вызванных потенциалов головного мозга. Однако до сих пор не изучено, как изменение вероятности ожидаемого стимула влияет на поведение и мозговые ответы у лиц с шизофренией.

ЦЕЛЬ: Сравнить влияние вероятности событий на характеристики мозговых потенциалов у пациентов с шизофренией и здоровых людей.

МЕТОДЫ: В исследование были включены психически здоровые лица и больные шизофренией мужского пола. При выполнении участниками саккадической задачи в парадигме пространственной сигнализации в условиях разновеероятностного (50 и 80%) предъявления целевого стимула регистрировались электроэнцефалограммы. Проанализированы достимульные (условная негативная волна) и постстимульные (негативность рассогласования и P3) компоненты связанных с событиями потенциалов мозга при предъявлении двух типов целевых стимулов: стандартные (предъявляемые с той же стороны, что и сигнальный стимул) и девиантные (предъявляемые с противоположной стороны) в условиях 50 и 80% вероятности совпадения стимулов.

РЕЗУЛЬТАТЫ: В исследовании приняли участие 20 психически здоровых лиц и 18 больных шизофренией. У психически здоровых лиц амплитуда условной негативной волны увеличивалась при высокой вероятности совпадения стимулов, амплитуда негативности рассогласования и компонента P3 была выше при девиантных стимулах в условиях высокой (80%) вероятности. У пациентов с шизофренией изменение вероятности не оказывало влияния на амплитуду условной негативной волны, негативности рассогласования и P3.

ЗАКЛЮЧЕНИЕ: Характеристики связанных с событиями потенциалов мозга у больных шизофренией указывают на наличие у них нарушений процессов антиципации.

Keywords: *schizophrenia; anticipation; predictive coding; event-related potentials*

Ключевые слова: *шизофрения; антиципация; прогностическое кодирование; связанные с событиями потенциалы мозга*

INTRODUCTION

Theoretical and experimental studies have shown that psychiatric disorders in schizophrenia patients are, in part, underpinned by a disruption in the actualization of previous experience [1, 2]. Reliance on experience is one of the fundamental requirements for anticipation, which is the process of foreseeing or predicting events. Therefore, the study of anticipation processes is essential for understanding the mechanisms underlying psychopathological symptoms in schizophrenia patients. In recent years, the theory of predictive coding has frequently been used to explain the mechanisms of anticipation and the symptoms of schizophrenia [3, 4]. According to this theory, the brain is a hierarchically organized system that performs probabilistic (Bayesian) inferences about future events by

comparing incoming sensory information with preceding predictions, with the aim of minimizing prediction errors — discrepancies between predictions and sensory data [5, 6]. In schizophrenia patients, abnormalities in the brain regions involved in predictive coding have been demonstrated to result in sensory, motor, and cognitive disorders, as well as to disorders in the systems responsible for salience attribution and reward expectation. The development of psychopathological symptoms in patients with schizophrenia may be attributable to these abnormalities [4, 7, 8].

The predictive coding theory has explained some neurophysiological phenomena, particularly event-related potentials (ERP). Thus, mismatch negativity (MMN) is considered one of the key indicators of prediction error generation. In the classical methodology [9], MMN

is recorded in the auditory modality during passive (unattended) listening to auditory stimuli in an oddball paradigm. It appears as a negative peak in the amplitude of the difference wave (obtained by subtracting the event-related potential to standard stimuli from the ERP to deviant stimuli) approximately 100–250 ms following stimulus presentation. The appearance of MMN indicates that a pattern in the stimulus sequence has been identified, and that deviations from this pattern have been detected. This phenomenon is widely regarded as a signal of prediction error [10]. Reduced MMN amplitude is one of the most consistent electrophysiological signs of schizophrenia [11] and a primary indicator of impaired predictive coding mechanisms [8, 12]. It is known that in individuals without mental illnesses, MMN in the passive oddball paradigm does not differ from that in the active variant, when the subject's attention is directed towards the stimuli [13–15]. This confirms the assumption that the MMN reflects pre-attentive processes involved in discriminating sensory stimuli and automatically detecting changes in their parameters [16, 17]. Thus, the MMN can be associated with a prediction error that is generated due to deviations in local regularities related to stimulus characteristics [18]. Visual MMN is more pronounced in the occipital and parietotemporal regions [19] and is also reduced in patients with schizophrenia [20].

In addition to the MMN, the P3 component of the ERP is recorded in the active oddball paradigm. This positive component occurs between 250 and 500 ms after the presentation of a deviant stimulus. The P3 amplitude in schizophrenia patients is lower than that in individuals without mental disorders [21]. MMN and P3 are considered to index different stages of discrepancies detection between predictions and sensory data [22]. Whereas MMN reflects the detection of local deviations tied to specific details of incoming information that fail to match predictions (e.g., pitch, brightness, motion trajectory), P3 reflects the processing of generalized information related to stimulus selection and/or evaluation, incorporating global deviations associated with complex patterns (e.g., differences between sequences comprising a specific number of stimuli) [18].

Anticipation (prediction) processes are also reflected by such a neurophysiological phenomenon known as the contingent negative variation (CNV). The CNV is characterized by a gradual buildup of negative potential in frontal-central brain regions occurring between two interrelated stimuli: a cue/warning stimulus (S1) and a trigger/target stimulus (S2) [23]. CNV is thought to represent preparatory

processes related to the pre-tuning and optimization of the brain systems involved in a particular task [24, 25]. The amplitude of the CNV could reflect the processes of anticipation of stimulus S2, which are triggered by the presentation of stimulus S1 [26]. During the anticipation of the subsequent stimulus, the amplitude would increase if the target stimulus corresponded to the cue, and decrease if the target stimulus violated the established rules [27]. In patients with schizophrenia, the amplitude of CNV is lower in comparison to in individuals without mental disorders. Furthermore, a disruption of the CNV topography has also been observed in these patients [28–30]. Based on the predictive coding theory, a reduced CNV amplitude may be indicative of an insufficiency in expectations and predictions concerning upcoming events, as well as an impaired ability to utilize contextual information in making predictions [31].

Studies of predictive coding processes using the Central Cue Posner Paradigm (CCPP) have shown that prior direction of attention improves reaction speed and visual perception of target objects. According to the CCPP, spatial cue stimuli activate hypotheses about the characteristics of subsequent events, prepare motor responses, and adjust predictions in case of mismatch [32]. In addition, the influence of the probability of target stimuli matching the cue on event-related potential characteristics was revealed in the visual-auditory version of CCPP for mentally healthy individuals (50, 64/68 and 86/88% valid trials [matches between cue and target stimulus] were used) [27, 33, 34]. However, the effects of the probabilistic organization of stimulus material on predictive coding processes in individuals with schizophrenia remain unexplored.

The study aimed at evaluating the effects of the probability of the events on event-related potentials in schizophrenia patients compared to healthy individuals.

METHODS

We published the preliminary results of this study in [35]. The article, which covers the results of a pilot study on this topic, provides an analysis of existing methods, describes the development and testing of a technique (stimulation, analysis algorithm, and ERP component selection). The results of the pilot study were employed in this research.

Study design

A cross-sectional comparative study was conducted.

Setting

The study was conducted at V. Serbsky National Medical Research Centre of Psychiatry and Narcology of the Ministry of Health of the Russian Federation (V. Serbsky National Medical Research Centre) (Moscow, Russia). The main group consisted of patients with schizophrenia who underwent forensic psychiatric evaluation at V. Serbsky National Medical Research Centre from November 2022 to March 2023. The control group included employees of V. Serbsky National Medical Research Centre and acquaintances of the investigators.

Participants

Inclusion criteria: The main group included male patients with normal or corrected vision, without signs of acute psychotic state (to ensure quality recording of electroencephalogram [EEG]), who had not received pharmacotherapy (for at least 7 days before inclusion in the study), without a history of neuroinfectious diseases and concomitant mental disorders (according to medical documentation and examination findings at the time of assessment). All patients underwent forensic psychiatric evaluation at V. Serbsky National Medical Research Centre and were diagnosed with schizophrenia by their attending physicians (F20 according to the International Classification of Diseases, 10th Revision).

The control group consisted of male individuals without neurological or psychiatric disorders (according to self-reported data). This group was selected by frequency matching, so that the age distribution would be similar to that of the main group.

Non-inclusion criteria: Individuals were not included in the study if they were unable to follow the study protocol (severe cognitive impairment that made it difficult to understand the instructions for conducting the electrophysiological study), if they had been diagnosed with alcohol or drug dependence (the presence of the disease was established by the attending physician at V. Serbsky National Medical Research Centre), or were left-handed. The dominant hand was determined just before the neurophysiological study based on the results of a questionnaire (which hand the patient uses for writing, drawing, holding a toothbrush, scissors, a match when lighting it, a spoon when stirring liquids) and motor tests for the dominant hand (applause, interlocked fingers).

Exclusion criteria: Participants with unsatisfactory EEG quality were excluded from further analysis.

Electroencephalography

Registration

The recording of the brain's electrical activity was performed using a Neuroscan Synamps System (Compumedics, USA) from 19 channels according to the standard 10–20 system. Reference electrodes were placed on the earlobes, and a ground electrode was located at the Fpz position. The EEG signal was recorded with a sampling rate of 1000 Hz and a bandwidth of 0–500 Hz.

The study was conducted in a darkened and electrically shielded room. During the investigation, which lasted approximately 30 minutes, the participants were seated in a chair with soft upholstery, a high headrest, and armrests, which allowed them to maintain a stable posture and minimized discomfort.

The recordings were carried out by the study authors, who had over 15 years of experience in EEG recording.

Study protocol

To study the features of anticipation, a visual stimulation paradigm based on CCPP was applied, according to which two probability conditions were proposed [32]. The choice of visual stimulation is attributable to the fact that predictive coding processes have been most thoroughly studied in the visual modality. The STIM2 stimulator (Compumedics Neuroscan, USA) was used for presenting visual stimuli. The stimuli were displayed on a monitor (19" diagonal, screen resolution 1280x1024), with the center of the screen adjusted vertically to align with the participants' eye level and positioned at a distance of approximately 60 cm from their eyes. The presentation protocol had been previously tested [35]. All participants were given the same instructions and were asked to perform a saccadic task — shifting their gaze to the target stimulus [32].

Before the main session, participants had completed a brief training session to become familiar with the study procedure. In case of incorrect task performance, participants were re-instructed. The quality of instruction comprehension and the process of performing the study protocol were monitored using electrooculography with Ag/AgCl skin electrodes placed at the lateral corners of both eyes by monitoring correct eye movements in response to the stimuli. In addition, the electrooculography channels were used to determine the characteristics of behavioral responses (saccades): the latency period of correct saccades was identified using a peak detection algorithm that exceeded a predefined threshold for random fluctuations.

Based on the direction of the saccades, the percentage of correct and incorrect task performances was calculated.

The study consisted of five consecutive blocks, each containing 45 trials, with a one-minute break between blocks. Each trial consisted of four sequentially presented stimulus types: (1) green or yellow preparatory stimulus appeared in the center of the screen for 200 ms; (2) white central fixation stimulus appeared 600–800 ms after the disappearance of the preparatory stimulus, at the same location, and remained for 900–1100 ms; (3) white cue stimulus appeared immediately after the disappearance of the central fixation stimulus, positioned 5 cm to the left or right of it, and displayed for 150 ms; (4) green target stimulus appeared 1300–1500 ms after the disappearance of the cue stimulus, located 3 cm from the edge of the monitor, and shown for 1000 ms (Figure 1). Each trial began with the participant pressing a button, which initiated the sequence of four stimuli. Participants were instructed to maintain their gaze fixed at the center of the screen during the presentation of the first three stimuli. They were also instructed to shift their gaze to the target stimulus as quickly as possible once it appeared. After each trial,

participants were required to return their gaze to the center of the screen.

The number of trials was chosen so that each type of stimulus was presented the necessary and sufficient number of times to average the ERP, taking into account possible artifacts [36]. Breaks between blocks were included to minimize fatigue.

Two experimental schemes were used in the study. In the first scheme, the preparatory stimulus was green and indicated to the participants (according to the instructions) that the target stimulus would appear on the same side as the cue stimulus with an 80% probability. In the second scheme, the preparatory stimulus was yellow and indicated that the probability of the cue and target stimuli had a 50% probability of appearing on the same side. A target stimulus presented on the same side as the cue stimulus will hereafter be referred to as a standard stimulus, while one presented on the opposite side will be referred to as a deviant stimulus. Thus, the target stimulus was presented under four conditions: 1) match with the cue stimulus at 80% probability (standard stimulus in the 80% condition) — 91 trials; 2) mismatch with the cue stimulus at

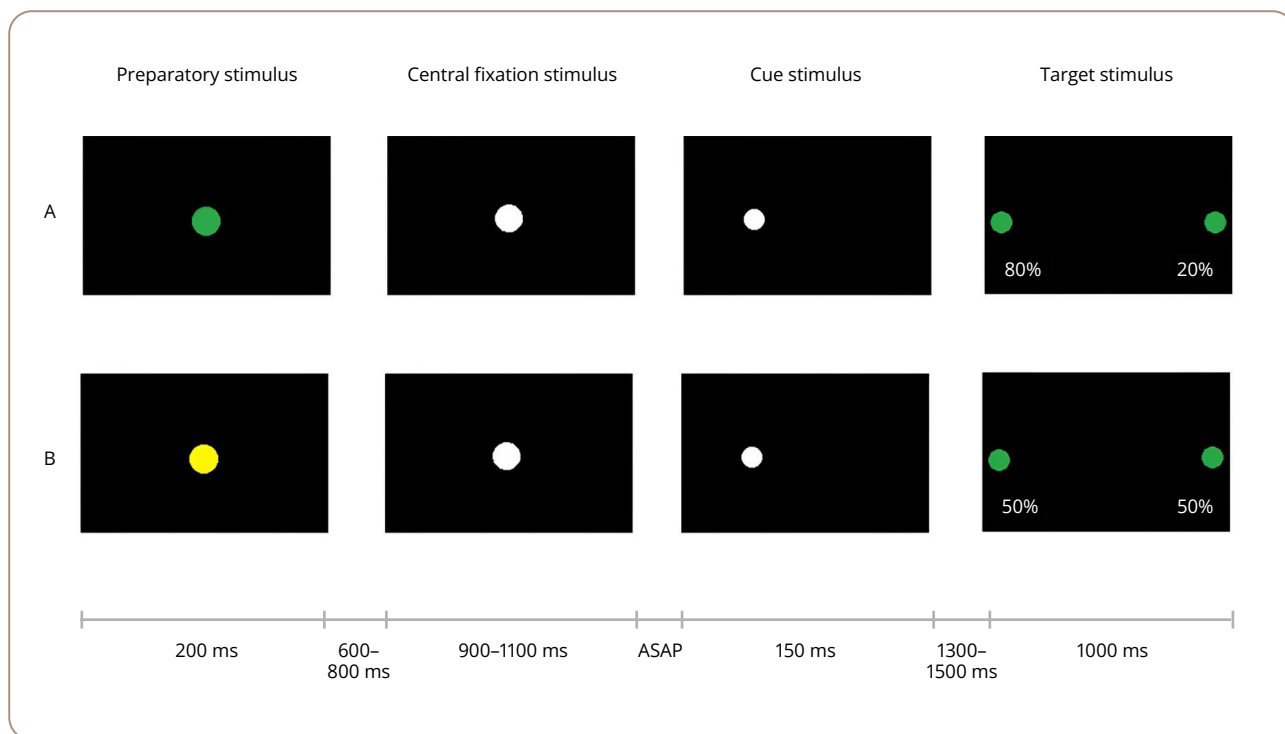


Figure 1. Visual stimuli presentation scheme.

Note: ASAP — as soon as possible; A — the target stimulus appears on the same side as the cue stimulus in 80% of the cases; B — the target stimulus appears on the same side as the cue stimulus in 50% of the cases.

Source: Adapted from [35]. © Psychology. Psychophysiology, 2024. Published with permission of the copyright holder.

80% probability (deviant stimulus in the 80% condition) — 25 trials; 3) match with the cue stimulus at 50% probability (standard stimulus in the 50% condition) — 54 trials; and 4) mismatch with the cue stimulus at 50% probability (deviant stimulus in the 50% condition) — 55 trials.

The sequence of trials was predetermined and consistent for all participants. To avoid sequence effects, the order was randomized prior to the initiation of the study. The randomization was achieved by employing a sequence of random numbers generated using the Python programming language, in accordance with the specified stimulus probabilities. Given that the stimuli were generated probabilistically, the final distribution of stimuli was approximate and might not have exactly matched the predefined probabilities.

Record preprocessing

The EEG recordings were filtered within the range of 0 to 30 Hz. Oculomotor artifacts were removed using independent component analysis. After that, the records were visually inspected for the presence of artifacts. The CNV was isolated by epoching EEG data from -1 to 0 seconds, relative to the onset of regular saccades (latency >120 ms). A baseline was defined from -1 to -0.9 seconds, and the epochs were then averaged for each participant. Then, the EEG recordings were converted to a time constant of 5 seconds to obtain slow potentials. The transformation procedure is based on the fact that the cutoff frequency of analogue filters corresponds to a transmission coefficient drop of only -3 dB, meaning that only a portion of the slow activity passes through the filter. However, the part of the activity that did not pass through the filter's stopband can be restored, except for the direct current component [37]. The CNV analysis was conducted in the early (900 – 600 ms before the target stimulus) and late (300 – 0 ms before the target stimulus) intervals, for which average amplitude values were obtained.

For post-stimulus ERP, the records were segmented in the range from -0.2 to 0.7 seconds relative to the target stimulus, with a baseline correction applied in the range from -0.2 to 0 seconds, and then averaged for each study participant. For the ERP components extraction, filtering was performed in the 1 – 7 Hz range to eliminate slow-wave artifacts and alpha rhythm interference. For the purpose of further analysis and to minimize data redundancy, 9 key channels were selected. These channels cover the regions responsible for the generation of the analyzed

potentials and are least susceptible to oculographic and myographic artifacts (F3, F4, Fz, C3, C4, Cz, P3, P4, Pz). The P3 component was identified on these channels as the maximum positive peak within the 220 – 400 ms interval (for latency analysis, see Table S1 in the Supplementary). The P3 amplitude was evaluated as the peak-to-peak amplitude from the preceding negative peak within the 100 – 300 ms interval, which was identified visually (see Figure 2). For the MMN analysis, the mean amplitude was extracted within a ± 50 ms window centered on the peak negative amplitude in the 100 – 250 ms time range after subtracting the ERP elicited by the standard stimulus from that elicited by the deviant stimulus. Data were preprocessed by one of the authors of the study (Rabinovich EI).

Statistical analysis

Data analysis was performed in the software environment for the Python programming language (EEG processing, multiple-comparison correction) and with the Jamovi statistical software package, version 2.3.31 (normality testing, ANOVA, and t-tests). The visualization of ERP and the construction of topographic maps were carried out using the MNE library for the Python programming language [38]. The Shapiro–Wilk test was applied to assess

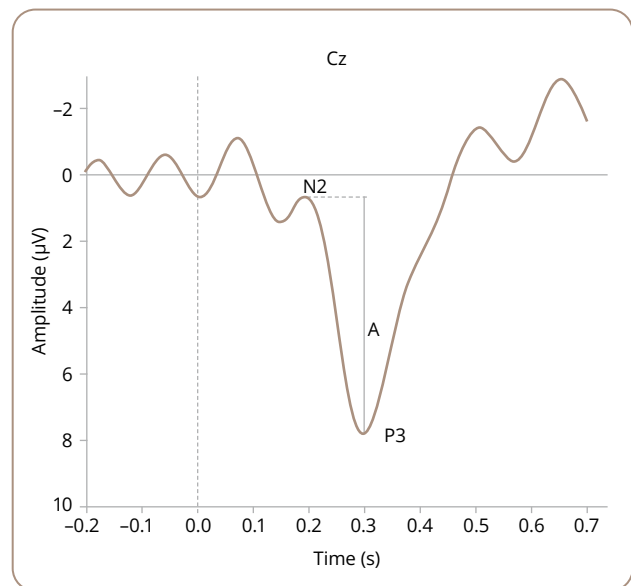


Figure 2. The event-related potential waveform recorded on the Cz electrode.

Note: The method for measuring the amplitude (A) of the P3 component is indicated. N2 — the preceding negative peak. Vertical dashed line — the time of stimulus presentation.

Source: Rabinovich, Telesheva, 2025.

the distribution of the quantitative variables (there were no deviations from the normal distribution, $p > 0.05$ in all cases). In this connection, the quantitative variables were described using the arithmetic mean (standard deviation).

The amplitudes of ERP components were compared using repeated measures analysis of variance with the between-subjects factor "group" ($n=2$, schizophrenia and control groups). In the analysis of CNV, P3, and MMN, the following within-subject factors were taken into account: the probability of the cue and target stimuli matching ($n=2$: 50% and 80%) and electrode location ($n=3$: frontal, central, and parietal). Additionally, when analyzing the CNV, the analysis interval was taken into account ($n=2$: early [900–600 ms before the peripheral stimulus] and late [300–0 ms before the peripheral stimulus]), while for the P3 analysis, the match between the cue and target stimuli was taken into account ($n=2$: standard and deviant stimuli). The selection of the listed factors is based on theoretical premises and the methodology employed in the study of anticipation.

Post hoc analysis was conducted using paired Student's *t*-tests and independent Student's *t*-tests. Multiple-comparison correction was performed by calculating the False Discovery Rate (FDR).

Ethical approval

The study was approved by the Ethics Committee of V. Serbsky National Medical Research Centre (Minutes No. 3 6/3 dated December 6, 2021). All participants signed an informed consent form for participation in the study.

RESULTS

Participants

During the study period, 20 patients with schizophrenia undergoing a forensic psychiatric evaluation at V. Serbsky National Medical Research Centre met the inclusion criteria. All patients were invited to participate in the study, of whom two declined to participate; 18 patients were included in the study and completed the protocol in full. The data from one patient was excluded from the CNV analysis due to poor EEG quality (a large number of slow-wave artifacts).

Twenty-two mentally healthy individuals were invited to join the control group; all of them were included in the study and completed the protocol in full. However, one EEG record was completely excluded from the analysis due to the participant's functional state (drowsiness), and another was excluded due to a large number of artifacts. The control group comprised 20 people.

Characteristics of the study groups

The mean age of the subjects in the control group and the patient group was 30.4 (6.5) years and 33.3 (6.3) years, respectively ($p=0.121$). Sixteen patients were diagnosed with paranoid schizophrenia (F20.0), one with hebephrenic schizophrenia (F20.1), and one with another form of schizophrenia (F20.8). The duration of the disease exceeded 5 years in 15 patients and was less than 5 years in the rest of the patients. In the main group, Positive and Negative Syndrome Scale (PANSS) scores averaged 16.3 (5.8) for positive symptoms, 18.4 (6.1) for negative symptoms, and 34.4 (8.3) for general psychopathological symptoms.

Main results

The performance results were analyzed using saccade characteristics under different stimulus presentation conditions. Table 1 shows the latencies of regular saccades (latency ≥ 120 ms) toward the target stimulus, the percentage of anticipatory saccades (latency < 0 ms) and express saccades (latency ≥ 0 ms, < 120 ms), and the percentage of error saccades, defined as gaze shifts to the direction opposite to the cue stimulus. The latent periods of regular saccades in the study groups were comparable. The percentage of errors when responding to the standard stimuli was higher in schizophrenia patients. Schizophrenia patients also showed a higher overall percentage of anticipatory and express saccades compared to the control group under conditions of 50% stimulus matching probability, although the differences did not reach the level of statistical significance (see Table 1). Within-group analysis revealed that, in the control group, saccade latency to the standard stimulus in the 80% condition was shorter than that to the deviant stimulus ($t=-3.94$, $p=0.002$). No differences were revealed in the latencies of saccades to the standard and deviant stimuli in the 50% condition ($t=-0.53$, $p=0.599$). The highest number of saccadic errors was observed in response to deviant stimuli under the 80% condition, compared to other conditions ($p < 0.01$ in all cases). At the same time, the 80% matching condition produced the highest number of anticipatory and express saccades. In schizophrenia patients, no statistically significant differences were found across conditions in saccade latency, the percentage of error saccades, or the percentage of anticipatory and express saccades. A repeated-measures ANOVA in the control group revealed a significant probability and matching interaction affecting latency ($F=12.74$, $p=0.002$, partial $\eta^2=0.401$) and

Table 1. Parameters of saccadic eye movements in control group and schizophrenia patients

Parameters	Control group (n=20)	Schizophrenia patients (n=18)	t	p
Latency of regular saccadic eye movements (ms)				
Standard 50%	263.1 (43.3)	273.7 (51.7)	-0.67	0.603
Deviant 50%	264.1 (40.3)	280.1 (61.0)	-0.92	0.479
Standard 80%	247.8 (40.1)	266.4 (55.2)	-1.17	0.376
Deviant 80%	270.7 (43.6)	281.5 (64.0)	-0.60	0.603
Errors in saccadic eye movements (%)				
Standard 50%	2.2 (3.6)	10.1 (11.3)	-2.99	0.031
Deviant 50%	4.1 (8.2)	7.7 (8.3)	-1.31	0.376
Standard 80%	1.5 (1.3)	7.4 (8.2)	-3.17	0.031
Deviant 80%	10.3 (7.2)	5.5 (5.9)	2.01	0.156
Anticipatory and express saccades (%)				
Standard 50%	3.7 (6.2)	10.8 (10.5)	-2.56	0.060
Deviant 50%	4.5 (6.5)	8.9 (8.5)	-1.78	0.202
Standard 80%	7.1 (8.0)	10.7 (9.6)	-1.21	0.376
Deviant 80%	8.3 (7.5)	7.6 (6.8)	0.25	0.803

Note: The quantitative variables were described using the arithmetic mean (standard deviation).

error rate ($F=12.58$, $p=0.002$, partial $\eta^2=0.398$); a significant main effect of probability on the proportion of anticipatory and express saccades ($F=11.40$, $p=0.003$, partial $\eta^2=0.375$). The schizophrenia group demonstrated a link between the matching factor and the regular saccade latency ($F=5.70$, $p=0.030$, partial $\eta^2=0.276$).

Subsequent to the comparison of CNV values between groups using analysis of variance, no significant differences were identified. The control group demonstrated a statistically significant influence of the probability factor ($F=9.26$, $p=0.009$, partial $\eta^2=0.398$), as well as a significant interaction of the probability and interval factors ($F=7.60$, $p=0.015$, partial $\eta^2=0.352$). *Post hoc* analysis revealed no statistically significant differences in the early CNV interval between the 50% and 80% probability conditions ($t=1.70$, $p=0.111$). Significant differences were observed in the control group during the late CNV interval in two conditions ($t=3.32$, $p=0.006$). The mean amplitude at 50% probability was $-6.35 \mu\text{V}$; at 80% probability was $-8.46 \mu\text{V}$.

The analysis of MMN showed the significant effect of the intergroup factor ($F=5.53$, $p=0.025$, partial $\eta^2=0.144$). In the control group, differences between the conditions of 50% and 80% stimulus matching probabilities were identified in the parietal ($t=3.521$, $p=0.022$) and central ($t=2.627$, $p=0.045$) regions. The mean amplitude of MMN for all analyzed leads

in the 50% and 80% conditions was $-0.17 \mu\text{V}$ and $-1.58 \mu\text{V}$, respectively ($t=3.09$, $p=0.007$). The schizophrenia group demonstrated no differences between the 50% and 80% probability conditions. A decrease in the MMN was more pronounced in the frontal and parietal regions (when compared to the control group in the 80% probability condition [$p=0.038$ and $p=0.019$, respectively]). The mean MMN amplitudes in the 80% condition in the schizophrenia group on the frontal and parietal electrodes were $0.12 \mu\text{V}$ and $0.43 \mu\text{V}$, respectively.

The analysis of P3 amplitudes revealed differences between the groups in the interaction between probability and matching factors ($F=4.39$, $p=0.044$, partial $\eta^2=0.117$).

The analysis of P3 amplitudes in the control group demonstrated that the most pronounced differences between the amplitudes to the standard and deviant stimuli were observed in the frontal ($t=-4.93$, $p<0.001$) and central ($t=-5.13$, $p<0.001$) regions. Moreover, in the control group the amplitude to deviant stimuli was significantly higher than that to standard stimuli under both the 50% ($t=-3.02$, $p=0.009$) and 80% ($t=-5.44$, $p<0.001$) probability of stimulus side matching. In the schizophrenia group, no increase in amplitude to deviant stimuli relative to standard stimuli was observed in the 80% probability of stimulus side congruence. In the 50% condition, the amplitude

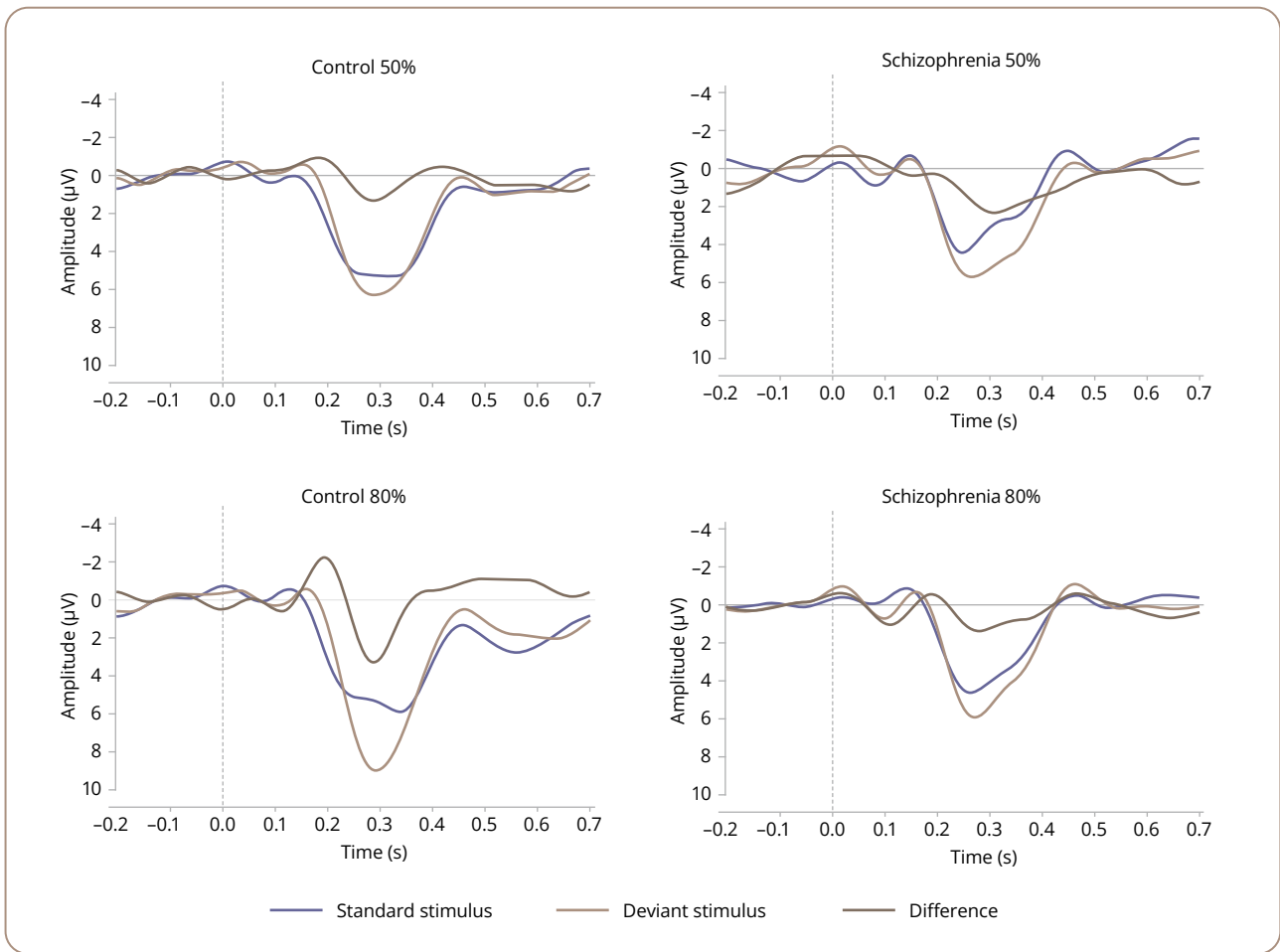


Figure 3. Event-related potentials (grand averaged for the groups) to the target stimuli on the Cz electrode.

Note: The dashed line marks the moment of stimulus presentation.

Source: Rabinovich, Telesheva, 2025.

to the deviant stimulus was higher than in the standard stimulus ($t=-2.32$, $p=0.034$). The averaged ERPs for the two groups at the Cz electrode are presented in Figure 3.

Additional results of the study

Analysis of the ERPs in individuals with schizophrenia showed variations in CNV amplitudes across the two conditions in contrast to the control group, where such variations were not observed. Accordingly, two patient subgroups were identified: the first subgroup included 10 patients (59%) whose CNV amplitude was higher in the 50% condition than in the 80% condition, or showed no difference between the two conditions; the second subgroup included 7 patients (41%) whose CNV amplitude was higher in the 80% condition. Thus, among patients in the first subgroup there was no effect (or a distorted effect) of probability on the CNV amplitude, whereas in

the second subgroup a higher event probability produced a larger CNV amplitude. All subjects in the control group satisfied the criterion of the second subgroup (the CNV amplitude was higher in the 80% condition versus the 50% condition).

A subsequent comparison of the first subgroup with the control group revealed a significant differences between the groups in the interaction between probability and interval factors ($F=5.10$, $p=0.034$, partial $\eta^2=0.182$). Significant differences between these groups were observed in the late interval under the 80% condition ($t=2.83$, $p=0.019$). Within the first subgroup, no factors were found to influence CNV amplitude. There were no differences between the probabilities in either early ($t=0.093$, $p=0.928$) or late ($t=-0.40$, $p=0.834$) intervals. The results of the second subgroup did not show any significant differences from the control group. In the second subgroup there were

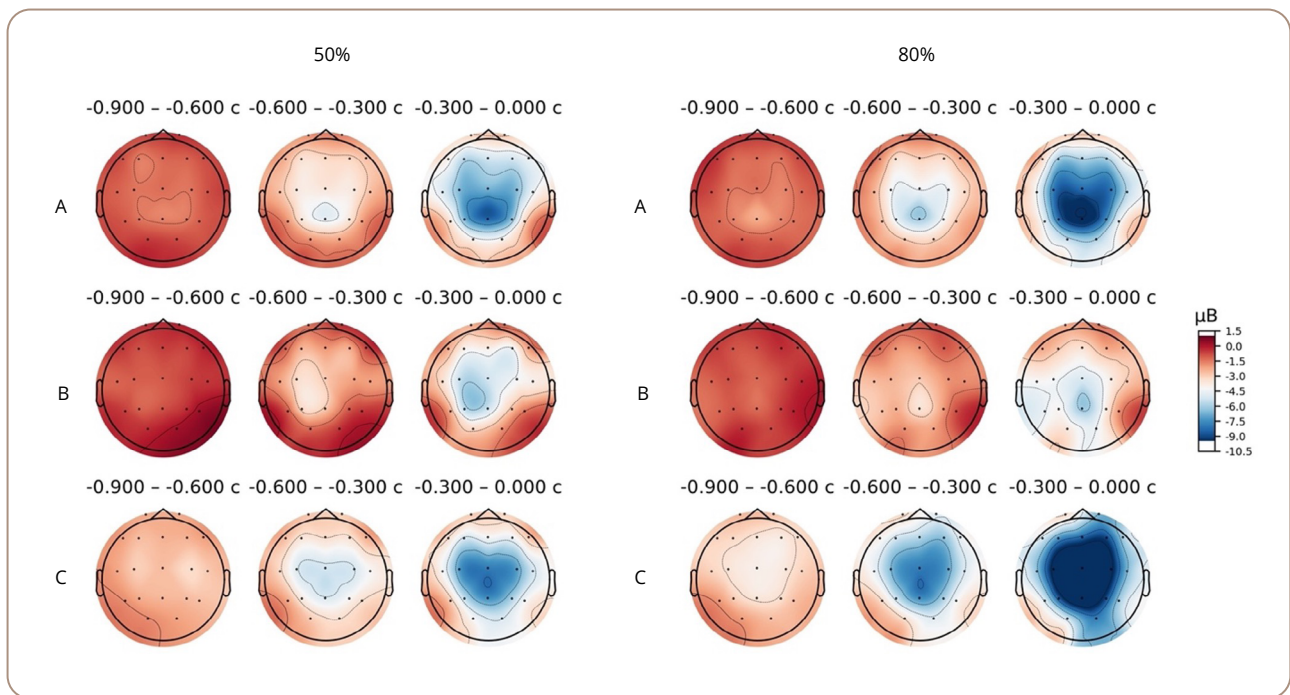


Figure 4. Topographic maps of the contingent negative variation.

Note: The left column represents the 50% probability condition, and the right column represents the 80% probability condition. Averaged amplitudes for the specified time intervals are shown. A — control group; B — first schizophrenia subgroup (CNV amplitude was higher in the 50% condition than in the 80% condition, or showed no difference between the two conditions); C — second schizophrenia subgroup (CNV amplitude was higher in the 80% condition versus the 50% condition).

Source: Rabinovich, Telesheva, 2025.

significant differences between probabilities in the late interval: the mean amplitude in the 50% and 80% conditions was $-5.35 \mu\text{V}$ and $-9.88 \mu\text{V}$, respectively ($t=3.34, p=0.024$).

There were no significant differences in the MMN and P3 amplitudes between the first and second subgroups.

Topographic maps of the CNV for the control group, the first subgroup, and the second subgroup of individuals with schizophrenia are shown in Figure 4.

DISCUSSION

Key results

The study demonstrated neurophysiological features of anticipation in schizophrenia patients: the patients showed a higher error rate in response to standard stimuli and a greater proportion of anticipatory and express saccades in the 50% matching probability condition compared to mentally healthy individuals. There were no significant differences in the CNV characteristics between the groups. However, schizophrenia patients showed differences in MMN and P3 component amplitudes from the control group. Specifically, no substantial differences in

the MMN amplitude were detected between the 50% and 80% stimulus congruence probability conditions within the schizophrenia group. In contrast, these differences were found to be statistically significant in the control group. Under the 80% stimulus congruence probability condition, the schizophrenia group lacked the characteristic increase in P3 amplitude in response to deviant stimuli that was observed in the control group. Both behavioral and neurophysiological responses in mentally healthy individuals depended on the probability and stimulus type. At an 80% probability, saccade latency was found to be shorter, the number of anticipatory and express saccades (and the deviant stimulus error rate) increased, and the late CNV phase, MMN amplitude, and P3 amplitude all differed between the 50% and 80% conditions, with the largest amplitude appearing for the deviant stimulus in the 80% condition. Schizophrenia patients showed no differentiation of behavioral or neurophysiological responses depending on the conditions. The saccade latency did not vary when the probability changes, and the overall number of saccade errors (anticipatory and

express saccades) was higher than in mentally healthy individuals. There were no changes in the CNV, MMN, and P3 amplitudes between the conditions.

Interpretation

The study showed that there is an absence of influence of the probability in predictive processing in schizophrenia patients. Analysis of saccade characteristics revealed impairment in assessing stimulus probability. In the control group, presenting the standard stimulus under the 80% matching probability condition led to an the expectation of its occurrence in a specific location. This expectation resulted in a reduction in the latency of regular saccades and an increase in the number of anticipatory and express saccades. With deviant stimulus presentation in the 80% probability range, the error response rate increased. This reflects the ability of the patient to form robust predictions based on probabilistic information. The latent period of regular saccades in schizophrenia patients did not differ from that in mentally healthy individuals, consistent with earlier published studies [39]. However, no differences between conditions were observed in patients, which may indicate an inability to form reliable predictions regarding the appearance of stimuli under different probabilities. At the same time, patients with schizophrenia generally exhibit a higher number of errors, which may be linked to an increased incidence of express saccades due to the dysfunction of the prefrontal cortex and impaired inhibitory control, consistent with findings from other studies [30, 40].

In healthy individuals, changes in predictive processes are associated with a preliminary activation of neuronal structures and are reflected in CNV characteristics [26]. Mentally healthy individuals showed an increase in the CNV amplitude under the 80% stimulus matching probability compared to the 50% probability. This is consistent with the literature indicating that an informative signal stimulus elicits a higher CNV amplitude compared to a neutral stimulus [41]. Thus, top-down probabilistic predictions facilitate the optimization of stimulus processing and motor response preparation [41, 42]. In mentally healthy participants, the maximum CNV amplitude shifted over time from parietal sites in the early phase to central-parietal and frontal regions in the late phase. The gradual increase in the CNV amplitude in these regions may reflect anticipatory processes linked to visuospatial attention that facilitate the selection of relevant stimuli for subsequent processing [43].

Additional analysis of the CNV in patients with schizophrenia revealed divergent changes across the two conditions. Particularly, half of patients demonstrated an increase in the CNV amplitude when the stimulus matching probability increased. The other half did not show such a trend. Accordingly, two principal patterns of predictive impairment can be distinguished in schizophrenia patients: one subgroup relies more on prior predictions than on sensory data, while the other relies more on sensory information than on top-down influences [44, 45]. Overall, our results demonstrate the heterogeneity of disorders in predictive processes in schizophrenia patients [46].

Many studies have considered the MMN and the P3 component to reflect the response to expectation violations [12, 23, 47]. Our study showed that, in mentally healthy individuals, the MMN amplitude is higher under the 80% probability condition compared to the 50% condition. This may which may reflect a higher generation of prediction errors when deviations occur in a context of high stimulus-congruence probability. The MMN amplitude in schizophrenia patients was lower than in the control group, which is consistent with the results of studies demonstrating a MMN decrease in schizophrenia patients [8, 12, 48]. Our data showed that schizophrenia patients had the lowest MMN amplitude in the frontal and parietal leads. This is supported by research findings indicating that the automatic response to a visual deviant stimulus is modulated by the fronto-occipital network, and that the lowest amplitude of visual MMN in schizophrenia patients is observed in the frontal and occipitoparietal regions [49, 50].

Based on the results obtained with mentally healthy individuals, it can be concluded that a higher probability of stimulus appearance increases the contribution of predictive and top-down processes to perception and motor-response preparation [4]. A stimulus that does not match the prediction leads to a prediction error and serves as an informative signal that updates further predictions [8, 12]. It is proposed that the reduced MMN amplitude in schizophrenia patients is associated with impaired predictive processes and probability assessment, such that each stimulus fails to conform to the learned sequence and triggers a prediction error [4]. The greatest reduction in amplitude in the frontal and parietal regions may indicate a dysfunctional integration of brain networks, which manifests as in impaired descending modulation of the parietal-occipital regions by the prefrontal cortex [51].

The analysis of the P3 component in mentally healthy individuals showed an increased amplitude to the deviant stimuli under the 80% matching condition. Schizophrenia patients showed an increase in the amplitude to the deviant stimuli in the 50% probability condition and a decrease in the amplitude to the deviant stimuli in the 80% condition, which reflects the aberrant probability assessment [52, 53]. This supports the hypothesis that prediction errors in schizophrenia patients are generated in response to stimuli that are less significant for predictive processes (e.g., a stimulus with a 50% probability) and are linked to an impaired ability to identify significant stimuli (aberrant salience) [49, 54]. The paradigm employing deviant stimuli with equal probability to standard stimuli may represent a novel approach for evaluating impairment in probabilistic prediction and anticipation in schizophrenia patients.

Limitations

These study results cannot be extrapolated to all cases of schizophrenia, since the patients included in this study were not experiencing an acute psychotic episode and displayed minimal manifestations of positive symptoms.

Another limitation is the small sample size, which increases the risk of type II errors and limits the ability to account for within-group heterogeneity.

Non-standard frequency ranges were used for filtering when extracting ERP peaks, which impedes comparison of the results with other investigations. This was due to an attempt to identify clear peaks not affected by noises from the alpha rhythms (without any significant amplitude distortions). Moreover, it appeared that the various filters had not significantly distorted the P3 component [55].

Our study did not aim to evaluate the connection between the neurophysiological parameters of anticipation and clinical manifestations of schizophrenia, or the effects of the latter on the key findings of this study.

CONCLUSION

The results of our investigation indicate that there are significant differences in ERP reflecting anticipation and information processing between mentally healthy individuals and patients with schizophrenia. These results align with existing theories about disturbances in prediction and error detection processes in schizophrenia. In mentally healthy individuals, the probability was associated with the CNV amplitude, MMN, and P3 characteristics. This suggests an

effective use of probabilistic information in the prediction and preparation of the motor response and is confirmed in the saccade characteristics. The lack of a definite influence of the probability factor on the CNV, MMN, and P3 amplitudes in patients with schizophrenia confirms the impairment of predictive processes in these individuals.

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Supplementary data

Supplementary material to this article can be found in the online version:

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Russian Version of the Inventory of Motivations for Suicide Attempts: Validation in a Clinical Sample of Adolescents

Русскоязычная адаптация «Опросника мотивов суицидальных попыток» на клинической выборке подростков

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Original research

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ABSTRACT

BACKGROUND: Understanding the motives for suicide attempts is a necessary condition of suicide risk assessment in adolescents. However, there is a lack of measures in Russian that assess these motives, particularly, in adolescent populations. The Inventory of Motivations for Suicide Attempts (IMSA) measures a variety of theoretically grounded intrapersonal and interpersonal motives and can be used in adolescent samples.

AIM: To validate the Russian version of the IMSA in a clinical sample of adolescents with suicidal behavior.

METHODS: The Russian-language adaptation of the IMSA was conducted on a clinical sample of 522 inpatient adolescents 12–17 years old ($M=14.51\pm 1.52$), including 425 girls and 97 boys. All the adolescents were hospitalized in a psychiatric hospital due to a suicide attempt, suicidal intentions, or a history of suicide attempts. To test the convergent and discriminative validity of the Russian version of the IMSA, the Interpersonal Needs Questionnaire, Interpersonal Sensitivity Measure and Self-Concept Clarity Scale were used.

RESULTS: Confirmatory factor analysis showed that the original 10-factor structure did not have a good fit. After modifications and removal of 12 items an 8-factor structure emerged, which had the following scales: Hopelessness, Psychache, Escape, Burdensomeness, Low belongingness, Fearlessness, Problem-solving, Interpersonal motivations. A generalizing Intrapersonal motivations scale was also defined. The fit measures for the final model were as follows: $\chi^2(df)=1,757.23(808)$; CFI=0.911; RMSEA=0.053 ($p=0.087$); SRMR=0.058. All the scales in the Russian version of the IMSA displayed satisfactory internal (above 0.8 except for Problem-solving) and retest reliability (above 0.6 except for Interpersonal motivations) and statistically significant positive correlations with scales from the Interpersonal Needs Questionnaire and Interpersonal Sensitivity Measure and negative correlations with Self-Concept Clarity Scale.

CONCLUSION: The IMSA displayed satisfactory psychometric properties in a Russian adolescent inpatient sample and can be used to differentiate between the motives for suicide attempts in adolescents.

АННОТАЦИЯ

ВВЕДЕНИЕ: Понимание мотивов суицидальных попыток является необходимым условием оценки суицидального риска у подростков. Однако, русскоязычных опросников, предназначенных для изучения суицидальной мотивации, недостаточно, особенно — разработанных для подросткового возраста. Опросник мотивов суицидальных попыток (The Inventory of Motivations for Suicide Attempts, IMSA) предназначен для измерения внутриличностных и межличностных мотивов суицидальных попыток и может быть использован в исследованиях с участием подростков.

ЦЕЛЬ: Провести психометрическую проверку русскоязычной версии «Опросника мотивов суицидальных попыток» на клинической выборке подростков с суицидальным поведением.

МЕТОДЫ: Русскоязычная адаптация «Опросника мотивов суицидальных попыток» была выполнена на клинической выборке, состоящей из 522 подростков (425 девочек и 97 мальчиков) в возрасте 12–17 лет ($M=14,51\pm 1,52$). Все подростки были госпитализированы в психиатрический стационар в связи с совершенной суицидальной попыткой, суицидальным намерением или имели суицидальные попытки в анамнезе. Для проверки конвергентной и дискриминантной валидности использовались русскоязычные версии «Опросника межличностных потребностей», «Опросника межличностной чувствительности» и «Шкалы ясности Я-концепции».

РЕЗУЛЬТАТЫ: Конфирматорный факторный анализ показал, что оригинальная 10-факторная модель не соответствовала эмпирическим данным. В результате модификаций и удаления 12 пунктов была выделена 8-факторная модель со шкалами «Безнадежность», «Душевная боль», «Бегство», «Восприятие себя как обузы», «Чувство брошенности», «Бесстрашие», «Решение проблем», «Межличностные мотивы». Также была выделена обобщающая шкала — «Внутриличностные мотивы». Индексы пригодности модели: $\chi^2(df)=1757,23(808)$; CFI=0,911; RMSEA=0,053 ($p=0,087$); SRMR=0,058. Все шкалы русскоязычной версии опросника продемонстрировали приемлемые показатели внутренней (выше 0,8, кроме шкалы «Решение проблем») и ретестовой (выше 0,6, кроме шкалы «Межличностные мотивы») надежности, а также статистически значимые положительные связи со шкалами «Опросника межличностных потребностей», «Опросника межличностной чувствительности» и отрицательные — со «Шкалой ясности Я-концепции».

ЗАКЛЮЧЕНИЕ: «Опросник мотивов суицидальных попыток» продемонстрировал приемлемые психометрические характеристики на клинической выборке российских подростков и может использоваться для дифференцированной оценки мотивов суицидальных попыток в подростковом возрасте.

Keywords: *suicidal behavior; adolescents; The Inventory of Motivations for Suicide Attempts; validity*

Ключевые слова: *суицидальное поведение; подростки; «Опросник мотивов суицидальных попыток»; адаптация опросника*

INTRODUCTION

Suicide is one of the most common causes of death in many countries, and the risk of suicidal ideation increases dramatically in adolescents and young adults [1], with a higher probability of suicide at 15–19 years than at 10–14 years [2]. In most cases, a suicide attempt is the result of a rather long suicidal process, and intervention

at any stage can prevent suicide [3, 4]. Therefore, it is important to understand and be able to identify the causes of suicidal behavior, which may include the high intensity of psychological pain [5, 6] and hopelessness [7], impaired sense of belonging [8], feelings of defeat and entrapment [9].

A number of measures aimed at assessing the causes of suicidal behavior have gained wide acceptance and have been adapted into Russian. These include the Psychache Scale by Holden R., which allows for the assessment of the intensity of psychological pain [10]; the Beck Hopelessness Scale by Beck A., which reveals the magnitude of a person's negative expectations in relation to his/her life and self [10]. Data obtained through these scales can be used to gauge suicidal risk: the higher the intensity of psychological pain or hopelessness, the higher the risk [10]. The Interpersonal Needs Questionnaire designed to assess the risk factors of suicide, such as thwarted belongingness and perceived burdensomeness [11], and the Reasons for Living Inventory by Linehan M., which measures the factors that prevent a suicide attempt [12], have also been adapted into Russian. However, these measures are focused on adults, in some cases including 16–17-year-old adolescents in the sample [10], which raises questions about their applicability in early and middle adolescence. It should also be taken into account that the wording of some of the items included in the suicide risk questionnaires refers to the life experience of an adult, psychologically mature person, but not a child. We could not find any Russian-language measures developed for adolescents and focused on identifying the motivational factors of suicidal behavior, with the exception of scales assessing specific emotional states (for example, a pediatric version of the Hopelessness scale [13]).

Therefore, the Inventory of Motivations for Suicide Attempts (IMSA), which was validated in both adult and adolescent samples, is of scientific and practical interest. This measure was developed in 2013 by May A.M. and Klonsky E.D. in an attempt to synthesize theoretical concepts about the causes of suicidal behavior [8, 14, 15], that were later generalized by the authors in the three-step theory of suicide [16, 17]. According to this theory: 1) suicidal thoughts arise from a combination of psychological pain and hopelessness; 2) impaired communication with other people contributes to increased suicidal thoughts; 3) the transition from suicidal ideation to suicide attempts occurs due to an acquired capacity for suicide, which is predicated on the availability of suicide means and individual features [17].

The IMSA is a self-report measure with a choice of responses on the Likert scale: from 0 ("not at all important") to 4 ("most important"). The questionnaire was initially validated on an adult sample [18]. Based on previous studies and theories of suicidal behavior, the authors proposed 10 scales of suicidal motivation: Hopelessness, Psychache,

Escape, Burdensomeness, Fearlessness (lack of fear of death), Low belongingness, Help-seeking, Interpersonal influence, Problem-solving, and Impulsivity. Each of those scales combined 5 items characterizing one of the possible motivations behind suicide. In addition, the authors kept 4 items that were not included in any of the scales but were still considered clinically important. These items related to the desire to die, feeling humiliated, experiencing the severity of circumstances, and loneliness. Thus, the original version of the IMSA consists of 54 items and includes 10 substantive scales [18]. Although the authors of the original inventory did not verify this factorial structure, they performed a factor analysis on 10 first-order scales and identified two higher order factors, intrapersonal and interpersonal motivations behind suicide attempts [18, 19]. In later versions, the authors switched to the terms internal and communication motivations [19, 20].

Psychometric testing of the IMSA in a clinical sample of adolescents who attempted suicide was published in 2016 [19]. The adult and adolescent versions of the inventory were identical. A suicide attempt was defined as a "self-inflicted, potentially injurious behavior with a nonfatal outcome for which there is evidence (either explicit or implicit) of intent to die" [21]. The sample included 52 adolescents (85% female) aged between 12 and 17 years. Most of them reported only one suicide attempt (67%). In this case, the authors excluded the Problem-solving scale from the analysis due to its low internal reliability (Cronbach's $\alpha=0.65$). Exploratory factor analysis also helped identify a two-factor structure equivalent to the structure obtained in the adult sample. The intrapersonal factor combined the scales of Hopelessness, Psychache, Escape, Burdensomeness, Low belongingness, and Fearlessness. The communication/interpersonal factor included the scales Interpersonal influence and Help-seeking. The Impulsivity scale was not included in any of the factors and was retained as an independent scale [19]. Psychological pain, hopelessness, and escape were key motivations behind suicide attempts in adolescents [19].

In both adult and adolescent samples, correlations were found between the intent to die and intrapersonal motivations for suicide attempt, whereas interpersonal motivations showed weaker correlation with the intent to die and a stronger correlation with rescue probability [18, 19].

We have found only one adaptation of this measure, the Persian version of the IMSA, which consists of 43 items and 9 scales (Hopelessness, Psychache, Escape,

Burdensomeness, Low belongingness, Fearlessness, Help-seeking, Interpersonal influence and Impulsivity) [22]. The IMSA has not been adapted into Russian.

The aim of this study was to validate the Russian version of the Inventory of Motivations for Suicide Attempts (IMSA) in a clinical sample of adolescents with suicidal behavior.

METHODS

Procedure and sample

The members of the research group who are proficient in English professional vocabulary performed a translation of the questionnaire into Russian. The reverse translation into English was performed by a clinical psychologist with an additional philological degree. The final text of the questionnaire was agreed upon during a discussion by all members of the research group, who took into account the linguistic accuracy, psychological clarity, and cultural appropriateness of the wording of the items.

Permission for Russian adaptation of the IMSA was obtained from one of its authors, Dr. Klonsky.

The study was conducted at the Crisis Department of the Scientific and Practical Center for Mental Health of Children and Adolescents named after G.E. Sukhareva (Moscow, Russia) from November 2023 to April 2024. All patients meeting the inclusion criteria were included in the sample.

Inclusion criteria: Adolescents aged 12–17 years who were hospitalized due to a suicide attempt with clinically confirmed suicidal intent or who were hospitalized for other reasons, but had a history of suicide attempt; without intellectual disability; without impairment of critical and purposeful thinking.

Non-inclusion criteria: Impairment of critical and purposeful thinking; intellectual disability; only non-suicidal self-injury without suicidal intent or suicide attempts.

Exclusion criteria: Incomplete or incorrect completion of the IMSA — the participant listed an inaccurate (only the year or month was indicated) or distant (before 2023) date of the suicide attempt when indicating the date of his/her most recent attempt, a negative answer to all items about the motivation behind this attempt.

The study was conducted individually or in small groups of 2–3 people. Each adolescent received a set of 4 measures, which he/she completed on his/her own in the presence of a resident physician. It took the subjects an average of 30 minutes to complete the procedure.

Statistical power analysis was performed using the semPower package [23]. A sufficient sample size was calculated to correctly determine the statistical significance of the root mean square error of approximation (RMSEA) ≤ 0.05 (effect size 0.80). The following models were tested: a model with 10 factors measuring motivations and 1 factor including the 4 clinically-relevant items; a model with 10 factors without the clinically-relevant items; a model with 2 higher-order factors (intra- and interpersonal motivations) [18, 19]. All factors within each model were assumed to be correlated to each other. The number of degrees of freedom was calculated using the following formula:

$$\frac{1}{2} (p \times (p+1)) - k$$

where p is the number of observed variables (items in the IMSA), and k is the number of measured parameters in the model (free parameters) consisting of the number of factor loadings for the observed variables minus the number of latent variables (since the first factor loading in each factor was assumed to be equal to 1 and was not measured), residuals for the observed variables (error variances), variances for the latent variables and covariances between them [24].

The analysis showed that 42 observations were sufficient to reject the model with 11 factors (1,322 degrees of freedom); 19 observations were sufficient for the model with 10 factors (1,130 degrees of freedom); and 23 observations were sufficient for the model with 2 factors (739 degrees of freedom). However, this number is significantly smaller compared to the recommended sample size for structural modeling, especially for complex models with more than 7 constructs (the recommended size is 500) [24], and for applying estimators that account for deviations from the normal distribution (the recommended size is >250 for maximum likelihood with a robust estimates (MLM), 200–500 for diagonally weighted least squares (DWLS)) [25]. Thus, when forming a sample, we aimed to enroll more than 500 respondents.

A total of 615 adolescents (500 girls, 115 boys) aged 12–17 years, hospitalized due to a recent suicide attempt or due to an intention to commit suicide, as well as adolescents hospitalized for other reasons, but with a history of suicide attempt, participated in the study. To measure the test-retest reliability of the inventory, respondents who continued inpatient treatment completed the IMSA again 10–15 days after participating in the initial testing ($n=131$).

During data processing we excluded the answers of 87 respondents who had not specified the date of their suicide attempt, which had been a necessary condition for filling out the questionnaire, as well as those that gave an incomplete date (for example, only a year) or a date earlier than 2023 (this was done in order to reduce recollection errors). Six respondents who had chosen only one answer for all IMSA items (“not at all important”) were also excluded. The final analysis included 522 respondents.

Measures

The Inventory of Motivations for Suicide Attempts is a self-report measure that includes 54 items and assesses intrapersonal and interpersonal motivations for suicide attempts [18, 19]. The inventory was preceded by a detailed instruction (see Appendix 1 in the Supplementary). For each item, the adolescent chose the answer that best matched the phrase “I attempted suicide because I...”. The individual significance of each cause was determined according to the following scale: 0 — “not important at all”; 1 — “somewhat important”; 2 — “important”; 3 — “very important”; 4 — “most important”.

Three measures were used to test the convergent and discriminant validity of the IMSA.

The Interpersonal Needs Questionnaire consists of 12 items and is grouped into two scales associated with the risk of suicide in Joiner’s interpersonal theory of suicidal behavior, perceived burdensomeness ($\alpha=0.94^1$) and thwarted belongingness ($\alpha=0.85$) [11].

The Interpersonal Sensitivity Measure is a Russian version of the questionnaire proposed by Boyce P. and Parker G. [26]. The questionnaire includes 22 items and consists of 3 scales: “Fear of Rejection” ($\alpha=0.83$), “Interpersonal Worry” ($\alpha=0.79$), and “Dependence on the Appraisal by Others” ($\alpha=0.88$). The total score for interpersonal sensitivity can also be calculated by summing up the scores of the three scales ($\alpha=0.92$) [27]. Interpersonal sensitivity is a predictor of depression, non-suicidal self-injury, and suicidal behavior [26, 28].

The Self-Concept Clarity Scale [29] includes 12 items and is univariate ($\alpha=0.78$). Self-concept clarity reflects the integrity and clarity of a person’s self-image and is associated with psychological well-being and mental health, whereas weakness in internal consistency and chronological stability of the self-concept is associated with the risks of suicide and psychopathology [29, 30].

Statistical analysis

Data analysis was conducted using the R language (4.2.3)², with the psych 2.4.3³, lavaan 0.6–17 [31], and semTools 0.5–6 packages⁴. The following types of analyses were performed: distribution normality tests, confirmatory factor analysis, correlation analysis, and group comparisons using nonparametric tests.

Distribution normality tests were performed for responses to the items of the IMSA. The Kolmogorov-Smirnov test and the Jarque-Bera test were used to check the skewness and kurtosis (with a normal distribution, the skewness is considered close to 0 and the kurtosis is approximately 3) [32]. Mardia’s test [32] was used to check multivariate normality, which is required for confirmatory factor analysis [33]. Statistical significance of these tests (at $\alpha<0.05$) indicates deviations of the responses to the inventory item from its normal distribution.

Confirmatory factor analysis (CFA) was performed to determine the structure of the IMSA. Maximum likelihood with robust estimates (MLM estimator) was used. The choice of this method was dictated by a non-normal distribution of responses [31, 33].

Three models that could be derived from the original key were used as a starting point for the CFA: one with 54 items and 11 factors (10 scales measuring motivations and a scale with 4 additional items), one with 50 items and 10 factors, and one with 40 items and 2 factors [18, 19]. We retained the Problem-solving factor, in contrast to the creators of the original measure, who excluded it in an attempt to assess the factor structure as was proposed by May A.M. and Klonsky E.D. based

¹ Here and below, internal consistency coefficients (Cronbach’s alphas) in the current sample are shown.

² R Core Team. R: A language and environment for statistical computing [Internet]. Vienna: R Foundation for Statistical Computing; 2023 [cited 2024 Dec 28]. Available from: <https://www.R-project.org>

³ Revelle W. Procedures for Psychological, Psychometric, and Personality Research [Internet]. R package version 2.4.6. Evanston: Northwestern University; 2024 [cited 2024 Sept 1]. Available from: <https://CRAN.R-project.org/package=psych>

⁴ Jorgensen TD, Pornprasertmanit S, Schoemann AM, et al. semTools: Useful tools for structural equation modeling [Internet]. R package version 0.5-6. 2022 [cited 2024 Sept 1]. Available from: <https://CRAN.R-project.org/package=semTools>

on the theoretical concepts of the motivations of suicide attempts [18].

The following indicators of satisfactory (good in parentheses) correspondence between the model and empirical data were used: $\chi^2/df < 3$ (2); comparative fit index (CFI) > 0.90 (0.95); RMSEA < 0.08 (0.05) and $p_{close} > 0.05$; standardized root mean square residual (SRMR) < 0.08 . Information criteria (Akaike information criterion, AIC; Bayesian information criterion, BIC) were also calculated, as a decrease in their values indicates an improvement in the correspondence between the model and the data⁵ [34].

To further improve the models, the following was done: 1) items with factor loadings of less than 0.4 were excluded [24]; 2) suggestions of the modIndices function, which calculates possible ways to improve the chi-square of structural models, were used [31]. In the latter case, the model was changed in the following ways. Items were moved to other factors they better aligned with. Covariances were also introduced between the residual terms (unexplained variance) of items with conceptually similar wording. The suggested improvements were incorporated only if they could be meaningfully analyzed in the context of the model.

Internal consistency of the IMSA scales modified as a result of the CFA was tested with the help of Cronbach's alpha and McDonald's omega and was considered satisfactory at values higher than 0.7 [24, 35]. The use of the second parameter becomes important in the context of factor structures that do not meet the condition of τ -equivalence, when the factor loadings of the items on the scale are different from each other, as well as in cases where the scale contains other scales (the factor structure is hierarchical). For first-order scales that include questionnaire items, the omega total is calculated; for hierarchical scales, or second-order scales, the omega hierarchical coefficient is obtained [35].

The Spearman correlation coefficient was used to assess the test-retest reliability (the consistency of the scales in different measurement conditions), convergent and discriminant validity (the former reflecting the presence of relationships with theoretically close constructs, and the latter showing the absence of relationships when measuring theoretically independent constructs). This coefficient was also used to establish correlations between the IMSA scales and age.

Nonparametric criteria (Mann-Whitney and Kruskal-Wallis tests) were used to determine the specific motivations behind suicide attempts based on the IMSA, depending on the gender, diagnosis, and type of suicidal behavior. The following group variables were determined: gender (2 groups: male or female), type of suicidal behavior (2 groups: attempt or intention), and type of diagnostic category (3 groups: depressive episode; mixed disorders of conduct and emotions; reaction to severe stress, and adjustment disorders), according to the International Classification of Diseases, 10th revision (ICD-10). The Mann-Whitney test for independent samples was used when comparing two groups, and the Kruskal-Wallis test was used when comparing three groups (in the case of statistical significance of the test, the Dunn test was used for pairwise comparisons of the groups).

The Wilcoxon test for paired samples was used in order to identify preferences for a particular suicide motivation. The purpose of this analysis was to determine the hierarchy of motivations in the overall sample.

Holm-Bonferroni corrections for multiple hypothesis testing were applied in the correlation analysis and all types of group comparisons (both for independent groups and paired groups). The alpha level for all types of analysis was 0.05.

Ethical approval

The study was approved at the meeting of the Local Ethics Committee of the Scientific and Practical Center for Mental Health of Children and Adolescents named after G.E. Sukhareva (Minutes No. 3/2022 dated 20 Oct. 2022). Participation in the study was contingent upon providing informed consent: written consent from legal representatives or the adolescent himself/herself if over 15 years of age and oral consent obtained from the adolescent immediately before engaging the questionnaires. All data obtained during the study were used in an anonymous form.

RESULTS

Sample characteristics

The psychometric characteristics of the IMSA were tested in 522 adolescents (425 girls and 97 boys) aged 12–17 years ($M = 14.51 \pm 1.52$). All of them live in the Russian Federation, with 516 (98.9%) residing in Moscow. Most adolescents (511, 97.9%) identified as Russian, 11 indicated other nationalities,

⁵ Kenny DA. Measuring Model Fit [Internet]. 2024 [cited 2024 Sept 1]. Available from: <https://davidakenny.net/cm/fit.htm>

while they cited Russian as their language of communication and instruction. The majority (476 subjects, 91.1%) were in secondary school, 29 (5.6%) of the adolescents were in college, 4 (0.8%) were homeschooled, 2 (0.4%) were university students, and 11 (2.1%) of the adolescents were not enrolled in classes at the time of hospitalization. Almost all the adolescents (507 people, 97.1%) lived with their parents, 4 (0.8%) indicated that they lived with other relatives, while 11 (2.1%) indicated that they lived apart from their family.

The clinical characteristics of the sample are presented in Table 1.

As Table 1 suggests, the majority of the adolescents were diagnosed with affective disorders, including depressive episode, mixed disorders of conduct and emotions, reaction

to severe stress, and adjustment disorders. In all the cases, depression remained the leading syndrome. For the majority of the sample ($n=406$), the reason for hospitalization was rooted in the current suicide attempt. The most common methods used to attempt suicide were poisoning, including drug overdose; cuts (including stabbing the body with a knife) which were inflicted with suicidal intent; falling from a height and throwing oneself in front of a train or car.

Distribution of responses to the items in the Inventory of Motivations for Suicide Attempts

The responses to the items of the IMSA showed a non-normal distribution and a multivariate non-normal distribution (Kolmogorov-Smirnov test and Jarque-Bera test for all variables: $p<0.001$; Mardia's test: 44,140.43,

Table 1. Clinical characteristics of the sample

Parameter	n	%
Hospitalization		
Primary*	430	82.4
Re-hospitalization	92	17.6
Diagnosis		
Moderate depressive episode (F32.1)	230	44.1
Mixed disorders of conduct and emotions (F92)	149	28.5
Reaction to severe stress, and adjustment disorders (F43)	115	22
Other anxiety disorders (F41)	11	2.1
Bipolar affective disorder (F31)	7	1.3
Recurrent depressive disorder (F33)	3	0.6
Obsessive-compulsive disorder (F42)	1	0.2
Other disorders** (F98)	6	1.2
Type of suicidal behavior leading to the current hospitalization		
Suicidal intent	70	13.4
Suicide attempts	406	77.8
Current suicidal ideation (a history of suicide attempts)	46	8.8
Method of suicide attempt		
Poisoning	189	46.6
Cuts and stabs	100	24.6
Falling from a height, throwing oneself under a train or a car	86	21.2
Strangulation	16	3.9
Drowning	4	1
Combination of several methods	11	2.7

Note: n — number of patients. *Adolescents hospitalized for the first time. **Other behavioral and emotional disorders with onset usually occurring in childhood and adolescence.

$p < 0.001$; kurtosis: 68.89, $p < 0.001$). For most of the items, the skewness was positive (the distribution was left-skewed); a negative skewness was observed for items "2", "6", "7", "9", "12", "13", "16", "21", "35", "37", "40", "45–47".

An analysis of the frequency of the different responses made by respondents showed that negative responses ("not at all important") prevailed for several items. More than 50% of respondents answered negatively to the following items: "3" — from the Fearlessness scale in the original version of the questionnaire; "10", "19" — Burdensomeness; "11", "15", "36", "39", "53" — all items on the Interpersonal influence scale; "43" — Help-seeking, "42", "33" — Impulsivity; "20" — Problem-solving; "23" and "25" — additional items.

Factor structure of the Inventory of Motivations for Suicide Attempts

Model fit indices are presented in Table 2. Models 1–3, which corresponded to the authors' key, were found to be unsatisfactory.

The interpersonal factors from the original version of the IMSA (Help-seeking and Interpersonal influence) were found to have a very high correlation ($r = 0.92$), which led to the decision to combine these scales into one (Model No. 4). In the resulting model, several items turned out to have low factor loadings ("19", "20", and "43"); therefore, they were removed. Further modifications to the model included moving item "8" ("...wanted to know if someone really cared about me") from the Interpersonal motivations

scale (this item was initially included in the Help-seeking scale) to the Low belongingness scale, and item "40" ("...my thoughts were too much to bear") from the Escape scale to the Psychache scale. Covariates were introduced between the residuals of items "8" ("...wanted to know if someone really cared about me") and "31" ("...thought nobody loved me"), "4" ("...wanted to make my family better off") and "41" ("...thought it could fix some important practical problems for my family/friends"), which may be explained by the similar wording of these items. The resulting model (Model No. 5) had a satisfactory fit. However, after the introduction of the hierarchical latent variable Intrapersonal motivations, which combined the Hopelessness, Psychache, Escape, Burdensomeness, Low belongingness, Fearlessness, and Problem-solving scales (Model No. 6), the CFI dropped below the cut-off value for satisfactory model fit.

Further, it was decided to exclude the Impulsivity scale from the model, since it demonstrated the lowest internal consistency (Cronbach's $\alpha = 0.71$) and the correlations with all IMSA scales, except for the Interpersonal motivations scale, scored lower than 0.2. In addition, the items included in this scale showed low factor loadings (the average factor loading for all five items was 0.58, and one item had a loading < 0.5). The 8-factor model before the modifications is presented as Model No. 7. To improve it, the same modifications were made as in Model No. 5, and a covariance was added between the residuals of items "17" ("...had thought about it for a while and finally acted on my plan") and "32" ("...had been working myself

Table 2. Model fit indices (confirmatory factor analysis)

No.	Model description	χ^2 (df)	CFI	RMSEA (p _{close})	SRMR	AIC	BIC
1	Original factor structure — 2 higher-order factors	3,094.39 (739)	0.762	0.087 ($p < 0.001$)	0.086	66,917	67,262
2	Original factor structure — 10 factors and 4 additional items	3,254.33 (1,322)	0.850	0.058 ($p < 0.001$)	0.072	89,446	90,140
3	Original factor structure — 10 factors without the additional items	2,731 (1,130)	0.866	0.057 ($p < 0.001$)	0.071	82,526	83,144
4	9-factor structure	2,816.51 (1,139)	0.860	0.058 ($p < 0.001$)	0.077	82,600	83,179
5	9-factor structure with modifications	2,136.57 (996)	0.902	0.051 ($p = 0.207$)	0.063	77,020	77,582
6	9-factor structure with the hierarchical factor Intrapersonal motivations	2,257.01 (1,022)	0.894	0.053 ($p = 0.054$)	0.068	77,113	77,564
7	8-factor structure (without the Impulsivity scale)	2,328.87 (917)	0.873	0.060 ($p < 0.001$)	0.073	73,866	74,368
8	8-factor structure with modifications	1,656 (788)	0.919	0.051 ($p = 0.295$)	0.051	68,253	68,743
9	8-factor structure with the hierarchical factor Intrapersonal motivations	1,757.23 (808)	0.911	0.053 ($p = 0.087$)	0.058	68,338	68,742

Note: AIC — Akaike information criterion; BIC — Bayesian information criterion; CFI — comparative fit index; RMSEA — root mean square error of approximation; SRMR — standardized root mean square residual.

Table 3. Factor loadings of the items in the Inventory of Motivations for Suicide Attempts (8-factor model with the hierarchical factor “Intrapersonal motivations” — Model No. 9)

Factors with included items	Factor loading
Hopelessness	
“2” ...was feeling hopeless	0.712
“6” ...lost all hope that things could get better in the future	0.814
“37” ...my future seemed dark	0.833
“44” ...didn’t think things would get better, no matter what I did	0.765
“45” ...was the most hopeless I’d ever been	0.778
Psychache	
“7” ...couldn’t stand all the emotions in my head anymore	0.736
“9” ...my state of mind was too unbearable	0.759
“21” ...my emotions were too overwhelming to handle	0.757
“35” ...needed to stop my mental pain	0.782
“40” ...my thoughts were too much to bear	0.813
“46” ...could no longer tolerate my emotional pain	0.882
Escape	
“1” ...was so flawed I had to escape from myself	0.639
“16” ...couldn’t stand being aware of my failings anymore	0.749
“18” ...hated myself so much	0.815
“47” ...thought so poorly of myself, dying seemed like a relief	0.853
Burdensomeness	
“4” ...wanted to make my family better off	0.657
“14” ...was only dragging down those around me by staying alive	0.826
“30” ...was causing too much trouble for those around me	0.846
“34” ...needed to stop being a burden to others	0.775
“50” ...was a drain on my loved ones	0.700
Low belongingness	
“8” ...wanted to know if someone really cared about me	0.597
“10” ...didn’t belong to any community	0.556
“31” ...thought nobody loved me	0.603
“38” ...didn’t fit in anywhere	0.813
“51” ...felt disconnected from everyone in my life	0.820
Fearlessness	
“3” ...had almost attempted in the days or weeks beforehand, but this time it didn’t seem as scary	0.622
“17” ...had thought about it for a while and finally acted on my plan	0.704
“29” ...was no longer afraid to try attempting suicide	0.714
“32” ...had been working myself up and this time I followed through	0.719
“52” ...was less afraid of the physical pain than I used to be	0.653

Problem-solving	
"13" ...needed to get out of an impossible situation	0.569
"22" ...seemed like the best way to deal with my problems (e.g., personal, financial)	0.776
"41" ...thought it could fix some important practical problems for my family/friends	0.644
"48" ...felt it would help solve some specific problems	0.738
Interpersonal motivations	
"5" ...wanted to get help from someone	0.490
"11" ...wanted to make people sorry for the way they treated me	0.683
"15" ...needed to persuade someone to change his or her mind	0.531
"28" ...needed to make other people understand how distressed I was	0.725
"36" ...wanted to make others afraid	0.629
"39" ...wanted to make other people feel guilty for not helping me	0.784
"53" ...hoped to influence the actions of people around me	0.752
"54" ...wanted others to recognize how much I was hurting	0.817
Intrapersonal motivations (general scale)	
Hopelessness	0.889
Psychache	0.823
Escape	0.936
Burdensomeness	0.833
Low belongingness	0.848
Fearlessness	0.776
Problem-solving	0.887
Correlations	
Intrapersonal motivations and Interpersonal motivations	0.433
Covariances between residuals	
Item "4" and item "41"	0.356
Item "8" and item "31"	0.407
Item "17" and item "32"	0.357

Note: For all factor loadings and covariances, $p < 0.001$.

Table 4. Internal consistency and test-retest reliability of the Inventory of Motivations for Suicide Attempts

IMSA scales	Internal consistency		Test-retest reliability
	Cronbach's α	McDonald's ω	Spearman's r_s
Hopelessness	0.89	0.89	0.63
Psychache	0.91	0.91	0.69
Escape	0.85	0.85	0.64
Burdensomeness	0.88	0.86	0.72
Low belongingness	0.82	0.82	0.64
Fearlessness	0.82	0.83	0.65
Interpersonal motivations	0.87	0.88	0.58
Problem-solving	0.78	0.78	0.62
Intrapersonal motivations (general scale)	0.91	0.91	0.66

Note: All Spearman correlation coefficients are significant with $p < 0.001$. IMSA — Inventory of Motivations for Suicide Attempts.

up and this time I followed through”), which had similar wordings. Model No. 8 had a satisfactory correspondence to the data, which was maintained when the hierarchical factor of intrapersonal motivations was introduced (Model No. 9). For further analysis, Model No. 9 served as the final model (Table 3).

Reliability of the scales of the Inventory of Motivations for Suicide Attempts

The IMSA scales showed satisfactory indicators of internal consistency and test-retest reliability (Table 4).

Convergent and discriminant validity of the Inventory of Motivations for Suicide Attempts

The Intrapersonal motivations scale from IMSA (and its sub-scales) demonstrated the strongest correlations with the scales of the Interpersonal Sensitivity Measure and the Interpersonal Needs Questionnaire, whereas the correlations with the Self-Concept Clarity Scale were weak. The Interpersonal motivations scale had either weak correlations (with the Burdensomeness scale from the Interpersonal Needs Questionnaire and all scales of the Interpersonal Sensitivity Measure) or no statistically significant correlation (with the Low belongingness scale from the Interpersonal Needs Questionnaire and the Self-Concept Clarity Scale) (Table 5).

Hierarchy of motivations for suicide attempts

Following in the path of the authors of the original version of the IMSA [18], we performed an analysis of the raw responses of the participants to determine the percentages of “very important” and “most important” responses on each scale. Such responses made up 48% of all responses to items in the Hopelessness scale, 49% in the Psychache scale, 40% in the Escape scale, 32% in the Burdensomeness scale, 30% in the Low belongingness scale, 27% in the Fearlessness scale, 38% in the Problem-solving scale, and 20% in the Interpersonal motivations scale.

Afterwards, these scales were ranked using the Wilcoxon test with the Holm–Bonferroni correction for multiple comparisons: significant differences indicate a difference in the magnitude of the motivations for suicide attempts in the sample, whereas the absence of significant differences indicates that the compared scales are at the same level (Table 6).

The Hopelessness and Psychache scales scored significantly higher than the other scales, indicating that the adolescents were more likely to confirm the suicidal motivations included in these scales. Escape, Problem-solving, and Intrapersonal motivations ranked second (there were no significant differences between these scales). The Burdensomeness, Low belongingness, and Fearlessness scales were in third place. The reasons

Table 5. Correlations of the scales of the Inventory of Motivations for Suicide Attempts with the scales of the Interpersonal Needs Questionnaire, Interpersonal Sensitivity Measure, Self-Concept Clarity Scale and age

Scales	Inventory of Motivations for Suicide Attempts								
	1	2	3	4	5	6	7	8	9
Interpersonal Needs Questionnaire									
Perceived burdensomeness	0.50***	0.40***	0.56***	0.67***	0.60***	0.52***	0.25***	0.49***	0.65***
Thwarted belongingness	0.24***	0.20***	0.30***	0.21***	0.41***	0.27***	0.07	0.17**	0.30***
Interpersonal Sensitivity Measure									
Dependence on the appraisal by others	0.53***	0.46***	0.57***	0.47***	0.51***	0.45***	0.32***	0.48***	0.59***
Fear of rejection	0.53***	0.52***	0.61***	0.56***	0.61***	0.55***	0.25***	0.48***	0.66***
Interpersonal worry	0.43***	0.40***	0.45***	0.42***	0.41***	0.36***	0.27***	0.41***	0.50***
Interpersonal sensitivity	0.58***	0.53***	0.63***	0.55***	0.58***	0.52***	0.32***	0.53***	0.67***
Self-Concept Clarity Scale									
Self-concept clarity	-0.45***	-0.41***	-0.41***	-0.32**	-0.34**	-0.27*	-0.10	-0.24	-0.41***
Age									
Age	0.15*	0.14*	0.11	0.05	0.02	0.04	-0.05	0.06	-0.02

Note: The Inventory of Motivations for Suicide Attempts scales: 1 — Hopelessness; 2 — Psychache; 3 — Escape; 4 — Burdensomeness; 5 — Low belongingness; 6 — Fearlessness; 7 — Interpersonal motivations; 8 — Problem-solving; 9 — Intrapersonal motivations. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Table 6. Descriptive statistics for the scales of the Inventory of Motivations for Suicide Attempts and their comparison in the overall sample (Wilcoxon test for paired samples)

Scale	Min	Q1	Med	Q3	Max	Significant differences
Hopelessness (A)	0	1.25	2.4	3.2	4	AC**, AD***, AE***, AF***, AG***, AH***, AI***
Psychache (B)	0	1.17	2.42	3.33	4	BD***, BE***, BF***, BG***, BH***, BI***
Escape (C)	0	0.75	2	3	4	CD**, CE***, CF***, CG***
Burdensomeness (D)	0	0.4	1.6	2.6	4	DF*, DG***, DI*
Low belongingness (E)	0	0.4	1.4	2.4	4	EG***, EH***, EI***
Fearlessness (F)	0	0.2	1.2	2.2	4	FH***, FI***
Interpersonal motivations (G)	0	0.25	0.75	1.88	4	GH***, GI***
Problem-solving (H)	0	0.75	1.75	2.75	4	—
Intrapersonal motivations (I)	0	1.06	1.89	2.57	3.89	—

Note: Max — maximum; Med — median; Min — minimum; Q1 — first quartile (25th percentile); Q3 — third quartile (75th percentile). * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ (p -values after the Holm-Bonferroni correction are given).

included in the Interpersonal motivations scale were the least frequently cited.

The relationships between motivations for suicide attempts with the demographic and clinical characteristics of respondents

The correlations of the IMSA scales with age were insignificant, except for weak correlations with the Hopelessness ($r_s = 0.15$, $p < 0.05$) and Psychache ($r_s = 0.14$, $p < 0.05$) scales (see Table 5).

When comparing IMSA scores across genders, significant differences were encountered for the Burdensomeness ($p = 0.013$) and Intrapersonal motivations ($p = 0.036$) scales, with higher values observed in girls (see Table S1 in the Supplementary).

No significant differences in IMSA scores between groups with specific types of suicidal behavior were detected, when adolescents with suicide attempt and adolescents with suicidal intent were compared (see Table S2 in the Supplementary).

We also compared the 3 largest groups of ICD-10 diagnostic categories: 1) depressive episode; 2) mixed disorders of conduct and emotions; and 3) reaction to severe stress, and adjustment disorders. Significant differences were found on the Hopelessness and Fearlessness scales (see Table S3 in the Supplementary). According to the Dunn test, the scores on both scales in the group diagnosed with a depressive episode were significantly higher than in the other two groups. The mean values of the Hopelessness and Fearlessness scales were, respectively, 2.41 ± 1.14 and 1.50 ± 1.11 for depressive episode; 1.99 ± 1.33 and 1.20 ± 1.22 for

mixed disorders of conduct and emotions; and 1.96 ± 1.40 and 1.18 ± 1.12 for reaction to severe stress, and adjustment disorders.

DISCUSSION

The Russian version of the Inventory of Motivations for Suicide Attempts, tested in a clinical sample of adolescents with suicidal behavior, showed satisfactory psychometric characteristics. The Russian version differs from the original version of the IMSA in the number of items (42 questions in the Russian version instead of 54 in the original one) and the questionnaire structure. The Russian version of the IMSA includes 8 scales that characterize suicidal motivations: Hopelessness, Psychache, Escape, Burdensomeness, Low belongingness, Fearlessness, Problem-solving and Interpersonal motivations. A generalizing scale (Intrapersonal motivations) may also be used. At the same time, the Impulsivity scale present in the original version was excluded from the factor structure because of relatively low indicators of internal reliability and the absence of significant correlations with other motivations [18, 19], and the scales of Help-seeking and Interpersonal influence were combined into the Interpersonal motivations scale.

The identified factor structure corresponds to the theoretically justified components of suicide, such as unbearable psychological pain and hopelessness, the idea of death as the only way to solve one's problems [5, 14], the perception of self as a burden, thwarted belongingness [8], and fearlessness (lack of fear of death) [8, 16].

All the scales of the IMSA demonstrated acceptable internal consistency (Cronbach's alpha 0.78–0.91) and

test-retest ($r_s=0.58-0.72$) reliability, which confirms the interrelations between the items in the scales and their relative ability to withstand changes in test conditions.

Intrapersonal motivations for suicide attempts showed significant ($r_s>0.5$) correlations with different features of psychological vulnerability to suicide (interpersonal sensitivity, suicidal motivations identified in Joiner's theory), whereas the correlations of the interpersonal motivations for suicide attempts with these same parameters were either weaker ($r_s=0.25-0.32$) or absent. As for the self-concept clarity, which characterizes a psychologically integral, healthy person, its correlations with the intrapersonal motivations were mostly negative and weak, while its correlations with the interpersonal motivations were non-significant. The obtained data confirm the convergent and discriminant validity of the Russian version of the IMSA.

The discrepancy between the Russian version and the factor structure of the original inventory is due to the following factors: the original measure was not tested using confirmatory factor analysis, and its factor structure was based on the synthesis of theoretical concepts of the nature of suicide. The exploratory factor analysis, which was used to identify intra- and interpersonal motivations in different samples, was conducted on scale scores [18, 19] rather than on raw data (responses to the items of the inventory). Thus, the factor structure of the Russian version of the IMSA may have changed due to the use of a different analytical method. This change could also be due to the cultural differences between Russian and American adolescents.

The most powerful motivations for suicide attempts/intentions in Russian adolescents were hopelessness and psychache, followed by the motivations of escape and problem-solving. These results are close, although not identical, to the results obtained by the authors of the original version of the inventory [18, 19]. Interestingly, the authors of the original version excluded the Problem-solving scale from the inventory as unreliable after testing it in a sample of adolescents [19], whereas in the Russian version, this scale showed satisfactory reliability and, moreover, was the second most frequent choice of the adolescents. Like the authors of the original inventory [18, 19], we discovered that the items relating to interpersonal motivations for suicide attempts were rarely endorsed.

Although intrapersonal suicidal motivations dominate interpersonal ones, we believe that the Interpersonal motivations scale contained in the inventory requires

a separate interpretation, as it affects the social aspects of suicidal behavior, when a suicide attempt is both a cry for help and a way to influence the behavior of other people. Interpersonal suicidal motivations come into play when other ways to communicate life's difficulties and painful experiences are unavailable or ineffective. The IMSA provides an opportunity for future studies to focus on assessing both individual suicidal motivations and their correlations over time in the follow-up of adolescents with suicidal behavior.

We found that hopelessness and psychache scores tend to increase with age, which improves our understanding of the causes of the increase in suicides among older adolescents compared with younger ones [4]. Burdensomeness scores were significantly higher in girls (this is of interest in the sociocultural perspective of parenting practices for girls and boys).

No differences on IMSA scales were detected depending on the type of suicidal behavior (attempt or intention). This confirms that factors other than motivation can also increase the risk of a suicide attempt when combined. In addition, this may be due to the combination of individual features with the availability of means of suicide, which is defined as the third step to a suicide attempt in Klonsky's three-step theory. Thus, the decision to commit suicide is determined not only by the motivation, but also by the availability of the means to carry it out [17].

Adolescents with a depressive episode scored the highest on the scales of Hopelessness and Fearlessness, which is consistent with the clinical presentation of depression and studies performed in clinical samples of adolescents. Thus, hopelessness is associated with worsening symptoms of depression [36] and fearlessness is viewed as a predictor of future suicide attempts [37].

Limitations

The Inventory of Motivations for Suicide Attempts uses recollections of a suicide attempt, which does not completely rule out errors in recollection, deliberately incorrect answers to painful questions, or avoiding answers to suicidal topics. Another limitation is that the sample was not gender-matched, but the predominance of girls in this sample corresponds to the gender pattern observed by researchers among adolescents with suicidal behavior [4].

Generalization of the study results is limited to the clinical population of adolescents with a history of suicide attempts. The inventory allows one to garner a rather

wide profile of the motivations behind suicidal behavior. However, an additional test of its applicability for diagnostic purposes in comparison with other measures (for example, the assessment of the intention to die during a clinical interview) is necessary. To extrapolate the results to the entire population of adolescents with suicidal behavior, the sample should be expanded in subsequent studies to include adolescents with suicide attempts who are not in hospital (for example, adolescents undergoing outpatient treatment). The study of motivations in the context of the development of suicidal behavior will help assess the diagnostic validity of this measure.

CONCLUSION

The Russian version of the Inventory of Motivations for Suicide Attempts (IMSA) adapted in a clinical sample of adolescents allows for a differentiated assessment of the motivations for suicidal behavior in adolescents. The inventory consists of 9 scales characterizing intrapersonal and interpersonal motivations for suicide attempts. The Intrapersonal motivations scale combines Hopelessness, Psychache, Escape, Burdensomeness, Low belongingness, Fearlessness, and Problem-solving. Interpersonal motivations for suicide attempts are measured by one scale.

The inventory demonstrated satisfactory reliability and validity. The intrapersonal suicidal motivations (hopelessness, psychache, escape, and problem-solving) were the most endorsed ones in the clinical sample of Russian adolescents. The highest hopelessness and fearlessness scores were found in adolescents diagnosed with a depressive episode. The motivations of hopelessness and psychological pain seemingly increase with age, but the causes of this increase require a separate study. Girls had higher scores on the Burdensomeness scale and the general scale of intrapersonal suicidal motivations.

The structure of the inventory is consistent with the theoretical concepts of suicidal behavior, and it also improves our understanding of the reasons behind suicide, which in the future may provide an opportunity for a more accurate assessment of the sources of suicidal motivations and how they develop.

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Supplementary data

Supplementary material to this article can be found in the online version:

Appendix 1: 10.17816/CP15597-145614

Table S1: 10.17816/CP15597-145615

Table S2: 10.17816/CP15597-145616

Table S3: 10.17816/CP15597-145617

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Association of Polygenic Risk Scores for Schizophrenia with Psychosis-Proneness Indicators in the General Population: A Narrative Review

Связь оценок полигенного риска шизофрении с показателями предрасположенности к психозу в общей популяции: нарративный обзор литературы

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Review

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ABSTRACT

BACKGROUND: Schizotypy (ST) and psychotic-like experiences and negative symptoms (PENS) are commonly used phenotypes in high-risk and early intervention research for schizophrenia and other non-affective psychoses. However, the origin of these phenotypes in the general population is poorly understood and their association with the genetic predisposition to psychoses has not yet been proven.

AIM: The aim of this study is to answer the question of whether data on the relations of ST and PENS with polygenic risk scores for schizophrenia (SZ-PRS) support the hypothesis that these phenotypes are subclinical manifestations of genetic liability for schizophrenia.

METHODS: Literature describing these relations in the general population was analyzed. The literature search was performed in the PubMed database using the following keywords in English: (“schizotyp*” OR “psychotic-like experiences” OR “psychosis proneness” OR “psychotic experiences”) AND (“polygenic risk” OR “genetic liability” OR “polygenic score”); the search in eLIBRARY.RU was conducted using the Russian words for “schizotypy”, “schizotypal features”, “psychotic experiences”, “psychotic experience”, “psychotic symptoms”, and “polygenic risk”, covering publications from 2009 to 2024.

RESULTS: Of the identified records, 45 publications were found eligible. No expected positive correlations of SZ-PRS with common ST measures have been observed. For PENS, the results are inconsistent. Overall, SZ-PRS correlate more often with the PENS general factor and negative symptoms than with psychotic experiences *per se*.

CONCLUSION: The literature does not provide convincing evidence of the association between SZ-PRS and ST/PENS. The search for the substantive psychological meaning of polygenic vulnerability to psychosis captured by SZ-PRS should be expanded to other personality processes and traits.

АННОТАЦИЯ

ВВЕДЕНИЕ: Шизотипия (ШТ), а также переживания, сходные с психотическими и негативными симптомами (ППНС), — это фенотипы, широко используемые в исследованиях высокого риска и ранних вмешательств при шизофрении и других неаффективных психозах. Однако происхождение этих фенотипов в общей популяции остается недостаточно изученным, а их связь с генетической предрасположенностью к психозам пока не доказана.

ЦЕЛЬ: Рассмотреть достоверность гипотезы о том, что ШТ и/или ППНС являются субклиническими проявлениями генетической предрасположенности к шизофрении, на основе анализа данных литературы о взаимосвязи психометрической ШТ и ППНС с оценками полигенного риска шизофрении в общей популяции.

МЕТОДЫ: Был проведен анализ литературных источников, в которых описаны эти взаимосвязи в общей популяции. Поиск литературы осуществлялся в базах данных PubMed и eLIBRARY.RU с использованием следующего поискового запроса: ((«schizotyp*» OR «psychotic-like experiences» OR «psychosis proneness» OR «psychotic experiences») AND («polygenic risk» OR «genetic liability» OR «polygenic score»)); а также соответствующих русскоязычных терминов «шизотипия», «шизотипические черты», «психотические переживания», «психотический опыт», «психотические симптомы» и «оценка полигенного риска». Поиск охватывал публикации за период с 2009 по 2024 год.

РЕЗУЛЬТАТЫ: Из записей, выявленных в ходе поиска, было отобрано 45 публикаций, соответствующих критериям включения. Ожидаемые положительные корреляции между оценкой полигенного риска шизофрении и распространенными показателями ШТ установлены не были. Результаты оценки ППНС неоднозначны. В целом оценка полигенного риска шизофрении чаще коррелирует с общим фактором ППНС и негативными симптомами, чем с психотическими переживаниями как таковыми.

ЗАКЛЮЧЕНИЕ: Литературные данные не предоставляют убедительных доказательств связи между оценкой полигенного риска шизофрении и ШТ/ППНС. Чтобы лучше понять основное психологическое содержание полигенной предрасположенности к психозу, отражаемой оценкой полигенного риска шизофрении, следует расширить поиск и учитывать другие личностные процессы и характеристики помимо ШТ и ППНС.

Keywords: *schizophrenia; schizotypy; psychotic-like experiences; PLEs; PENS; polygenic risk scores*

Ключевые слова: *шизофрения; шизотипия; психотические переживания; PLEs; PENS; оценка полигенного риска*

INTRODUCTION

Schizophrenia is a chronic disabling disorder in which polygenic predisposition plays an important role [1]. Early intervention is assumed to reduce the risk of psychosis in individuals with genetic vulnerability to the disease. Approaches to identifying vulnerable individuals in non-clinical samples are based on the idea of a psychoses-proneness continuum, with psychotic patients at one end and individuals from the general population with schizophrenia-like traits or experiences at the other [2–4].

Schizotypy (ST) is an early concept of the “schizophrenic genotype” subclinical expression [3]. ST represents a constellation of personality traits resembling positive, negative, and disorganized symptoms of schizophrenia. These traits can manifest as several personality disorders or as normal personality variants [5]. In the latter case, they

are measured mainly with questionnaires for schizotypal personality and are called psychometric ST. Psychotic-like experiences (PLEs) are another conceptualization of schizophrenia liability [4]. PLEs are defined as subclinical psychotic symptoms (delusions and hallucinations) in the absence of illness/in a non-clinical population/in individuals who do not seek psychiatric help [4]. The prevalence of PLEs in the population is about 8%, with the highest frequency in childhood (up to 17%) [4]. Recently, it has been proposed to supplement the PLEs with cognitive disorganization and negative dimensions, this wider concept being referred to as psychotic experiences and negative symptoms (PENS) [6].

The development of molecular genetic technologies in the last decades has made it possible to directly assess the relationship between genetic liability to schizophrenia and psychosis-proneness indicators [7–11].

The methodologies include calculating genetic correlations between schizophrenia and ST/PENS based on genome-wide association studies (GWAS) of these traits and assessing associations of ST/PENS with polygenic risk scores for schizophrenia (SZ-PRS). SZ-PRS is the sum of schizophrenia risk alleles in an individual genome, weighted by the strength of the association of each allele with the disease [7]. The weights are effect sizes derived from GWAS conducted by the Psychiatric Genomics Consortium (PGC) [7–10].

A systematic review, considering the comprehensive genome-wide data on PENS obtained by 2018, concluded that PENS in the general population are genetically associated with schizophrenia and that the negative dimension in addition shares genetic influences with major depression [6]. Regarding the relations of PENS with SZ-PRS, the review's authors found 10 relevant studies, and four of them reported significant associations, though the proportion of variance in PENS explained by SZ-PRS did not exceed 1%. The results obtained for different age groups and with different instruments were more consistent for the negative dimension than for PLEs. Notably, only one of the reviewed papers concerned ST [6]. Since then, new large-scale studies of both ST and PENS, some of which used SZ-PRS based on the summary statistics of the latest and most powerful schizophrenia GWAS (PGC3 GWAS [10]), have been conducted but not reviewed.

The aim of this study was to answer the question of whether data on the relations of ST and PENS with polygenic risk scores for schizophrenia support the hypothesis that these phenotypes are subclinical manifestations of genetic liability for schizophrenia. Developing an accurate picture of the relationship between genetic liability to schizophrenia and ST/PENS is of importance for the conceptualization of psychosis-proneness and might help to advance the prevention of psychotic disorders.

METHODS

Eligibility criteria

Inclusion criteria:

The review included articles, containing the empirical research on the relationship in the general population of psychometric Schizotypy and psychotic-like experiences and negative symptoms with SZ-PRS.

Information sources

The literature search was performed in the PubMed and eLIBRARY.RU databases.

Search strategy

The search in PubMed was conducted using the following keywords: (“schizotyp*” OR “psychotic-like experiences” OR “psychosis proneness” OR “psychotic experiences”) AND (“polygenic risk” OR “genetic liability” OR “polygenic score”) published from 01 Jan. 2009 to 30 Dec. 2024. The lower time threshold was chosen because the GWAS-based PRS concept in 2009 [7]. The search in eLIBRARY.RU was conducted using the Russian words for “schizotypy”, “schizotypal features”, “psychotic experiences”, “psychotic experience”, “psychotic symptoms”, and “polygenic risk”. Reference of the identified papers were manually examined to find additional relevant articles.

Selection process

The primary screening of potentially relevant articles was conducted by reviewing their titles and abstracts and performing a preliminary assessment if they meet the eligibility criteria. The selected articles were listed for further review of their full texts and selection of relevant studies that met all the planned inclusion and exclusion criteria. Exclusion criteria were as follows: 1) clinical samples or samples of psychotic patients' relatives; 2) the use of basic personality traits (e.g., openness to experience) as a proxy of ST/PENS; 3) the use of SZ-PRS as a modifying factor without presenting data on the direct effects of SZ-PRS on ST/PENS; 4) conference proceedings, dissertation thesis, or preprints. No restrictions were imposed on the language of publication or the age of the subjects. Works with overlapping or even almost identical samples from the same projects were not excluded to demonstrate the level of in/consistency of the results and since different publications of the same project could report on different aspects of ST/PENS.

The resulting publications were then selected for analysis based on the following inclusion criteria: 1) research articles; 2) articles contained data on the association of SZ-PRS with ST or PENS measured in individuals from the general population using questionnaires or diagnostic interviews; 3) SZ-PRS based on GWAS conducted in 2009 or later; 4) articles published in peer-reviewed scientific journals.

Data analysis

From the publications selected for consideration, the author extracted information on: 1) available demographic characteristics of the sample (age, sex, ethnicity, relatedness between subjects); 2) the way of measuring ST/PENS;

3) GWAS to build SZ-PRS; 4) the presence of a statistically significant relationship between ST/PENS and SZ-PRS; 5) associations between ST/PENS and PRS for other mental illnesses or psychological traits.

RESULTS

Characteristics of articles

The search in PubMed returned 87 articles, of which 35 met the criteria, and one relevant publication (our own [12]) was found in the eLIBRARY.RU database. The investigation of the references lists yielded another 9 articles. Thus, 45 publications were selected for analysis, of which 9 investigated the associations of SZ-PRS with ST, 4 — ST and PENS, and 32 — with PENS (Table S1 in the Supplementary).

Of the eligible studies [12–56], most were carried out within a several large longitudinal projects, which had the genome-wide data for their participants. They mainly included individuals of European ethnicity, used PGC2 GWAS [8] for SZ-PRS calculation and were balanced by sex of participants. Of the instruments assessing ST, the most popular (5 out of 13 publications) was the Schizotypal Personality Questionnaire (SPQ, or its short form SPQ-B) measuring cognitive-perceptual (positive), interpersonal (negative), and disorganized dimensions of ST. PENS were primarily evaluated with project-specific interviews and questionnaires exploring selected items from common clinical diagnostic instruments [26–39]. The exception was the Community Assessment of Psychic Experience (CAPE) questionnaire consisting of positive, negative, and depressive scales, which is a widely used international instrument for assessing PENS [13, 20–23, 31–33, 42–46, 48, 49]. The main difference between the instruments measuring ST and PENS was that the former addressed stable characteristics (personality traits), and the later evaluated states (whether there were PENS, how often, and whether this experience was distressing). In addition, the PENS items were formulated more psychopathologically, i.e. they concerned symptoms. However, there was no clear boundary between the PENS and ST indices either in terms of the temporal stability of characteristics or in terms of their content. In particular, the CAPE has been created using items from clinical scales (the Present State Examination, Scale for the Assessment of Negative Symptoms, Subjective Experience of Negative Symptoms, and Calgary Depression Scale) but also assesses stable characteristics of a person (e.g., magical thinking), and its

positive and negative scales significantly correlate with similar scales from the Structured Interview for Schizotypy, Revised (SIS-R) [13].

Association of polygenic risk scores for schizophrenia with schizotypy

The first study of self-reported ST using the GWAS-based SZ-PRS was performed on two samples of Greek conscripts [14]. The first sample completed SPQ and the Perceptual Aberrations Scale (PAS). Instead of the expected positive correlations of the SZ-PRS with ST indicators, the authors found negative ones that reached the level of significance for the positive and disorganized ST [14]. When retesting 121 people from the original cohort of 875 conscripts in 18 months, these relationships disappeared, which the authors explained by a decrease in distress in the conscripts. In the second sample, the Schizotypal Personality Scale (STA) was applied to assess paranoid and magical thinking and unusual experiences; in addition, trait anxiety was measured with the State-Trait Anxiety Inventory (STAI). SZ-PRS did not correlate with ST indicators but associated with anxiety [14].

Subsequent studies also failed to find positive correlations of SZ-PRS with standard measures of the SPQ or other ST questionnaires [12, 15–20]. A recent publication [21] has reported an association of SZ-PRS with the positive dimension of the Multidimensional Schizotypy Scale (MSS) in men. However, there were no associations of SZ-PRS with either the MSS positive dimension in women and in the combined group, or with the MSS negative dimension in either group.

Some of the above-mentioned studies attempted to develop non-standard ST indicators with which the SZ-PRS could correlate [16, 18, 19]. Nenadić et al. [18] explored an uncorrelated 4-factor model of the SPQ-B to avoid the influence of neuroticism on the responses and did not reveal a relationship between the ST factors and SZ-PRS. Docherty et al. [16] conducted a factor analysis of the SPQ-B in the entire sample of more than 9,000 participants and in groups of men and women and found that in men the first factor was associated with SZ-PRS. This factor included four items reflecting difficulties in social interaction. The first factor extracted in female group consisted of items from various SPQ-B scales and did not correlate with SZ-PRS. Tiegó et al. [19] used factor analysis and the Item Response Theory to construct a bifactor model of ST based on 12 different scales. The model consisted of 9 specific factors

(delusions, hallucinations, etc.) and three higher-order factors (general, positive and negative ones). SZ-PRS correlated positively with the delusions factor and the decreased social interest and involvement factor, without sex differences. These correlations were not mediated by the higher-order factors.

Two projects — European Network of National Networks studying Gene-Environment Interactions in Schizophrenia (EU-GEI) and Genetic Risk and Outcome for Psychosis (GROUP) — applied the interview (SIS-R) to assess ST. The first study was on participants from the GROUP cohort and found positive correlations of SZ-PRS with the SIS-R positive factor [13]. However, in a replication study of GROUP and EU-GEI data, the correlations of SZ-PRS with all analyzed SIS-R indicators (total score, positive and negative factors) turned out to be negative, and in the larger sample (EU-GEI) they reached the level of significance for the total score and the positive scale [22]. Of importance, in unaffected relatives of psychotic patients from the same projects, SIS-R scores positively correlated with SZ-PRS [13, 22]. Later, for the EU-GEI sample a bifactor model was developed that included a general factor and three specific factors (cognitive-perceptual, paranoid and negative), and the expected positive correlation of SZ-PRS with the general factor was observed; the associations with specific factors were not assessed in this work [23].

Also worth mentioning is the study of Schaefer et al. [24] carried out on samples of twins at the age of 24 and 34 years using the Personality Inventory for DSM-5 Psychoticism scale (the total score of psychoticism and subscales: unusual beliefs and experiences, eccentricity, perceptual dysregulation). The authors found correlations between SZ-PRS and all indicators of psychoticism, even when the cannabis use during adolescence was controlled for. Of note, the items of this instrument were formulated in a more psychopathological manner than those of ST personality questionnaires.

To summarize, despite some positive results, the pooled data indicate the absence of significant, reproducible relationships between the psychometric ST and SZ-PRS in the general population. At the same time, some studies [12, 14, 16, 18] have found positive correlations of standard and non-standard ST indicators with PRS of emotional dysregulation (neuroticism, anxiety, depression), which might suggest the influence of genetically determined negative affectivity on the self-reported ST.

Association of polygenic risk scores for schizophrenia with psychotic experiences and negative symptoms

Childhood and youth

Of significant interest is the relation of genetic predisposition to schizophrenia with PENS in youth, i.e., in individuals who are approaching or at the age of maximum risk for developing psychosis. This relation has been examined in several research projects [25–46].

Two USA longitudinal studies evaluated PLEs in youth using diagnostic interviews. In the Adolescent Brain Cognitive Development (ABCD) middle childhood (9–10 years) cohort, SZ-PRS correlated with the presence of distressing PLEs but not with the total number of PLEs, while the total number of PLEs correlated positively with cross-disorder (psychiatric) PRS and negatively with education PRS [25]. These findings were taken to suggest that among the PLEs, only the most severe psychotic experiences might reflect genetic liability to schizophrenia. However, Hernandez et al. [26] revealed no difference in SZ-PRS between children (aged 9–12) from the ABCD project who had and had no severe and/or distressing PLEs. Then Ku et al. [27], having assessed not only the severity but also the recurrence of PLEs over 4 years after the first examination, found in this cohort a positive correlation of SZ-PRS with the presence of distressing recurring PLEs, but not with transient ones, which was partly consistent with the initial hypothesis of Karcher et al. [25]. In the Philadelphia Neurodevelopmental Cohort (PNC), no association was found between the presence of PLEs and SZ-PRS or PRS for emotional traits in youth (8–22 years) of either European or African American descent; at the same time, the presence of PLEs, especially in children under 12 years of age, was associated with PRS for attention deficit hyperactivity disorder (ADHD) [28, 29].

In the UK Avon Longitudinal Study of Parents and Children (ALSPAC), PLEs (delusions, hallucinations, thought interference) were assessed using the Psychosis-Like Symptoms interview (PLIKSi) or a corresponding questionnaire (PLIKS-Q), and negative symptoms were measured with the CAPE negative scale [30–34]. No association was found between SZ-PRS and PLEs measured at 12, 18, and 20 years [30–32]. SZ-PRS correlated with negative symptoms, as well as with anxiety disorders at age 16 [31]. Later, the data of 16-year-old participants were examined applying two models of PENS: a model of four correlated factors (positive, negative, depressive and anxious) and a bifactor model with a general factor and four specific ones [33]. In the

correlated model, SZ-PRS were significantly positively associated with all factors. In the bifactor model, there were positive correlations of SZ-PRS with the general and negative factors. In addition, the general factor was associated with PRS for neuroticism. It was also shown that individuals with different severity and age trajectories of PENS did not differ in SZ-PRS [34]. Of interest, the latter study showed a high comorbidity of PENS with generalized anxiety disorder and depressive episode, reaching 80% in the group with multiple recurring PENS [34].

Another UK project, the Twins Early Development Study (TEDS), assessed 16-year-old twins using the Specific Psychotic Experiences Questionnaire (SPEQ: paranoia, hallucinations, cognitive disorganization, grandiosity, and anhedonia) and parental assessment of negative symptoms [35–38]. No positive correlations were found between SZ-PRS and the presence, severity or age dynamics of PENS components [35–38]. However, associations were observed between PENS and PRS for other mental illnesses and traits, mainly depression PRS and education PRS [37, 38]. Similarly, in the sample of the UK Environmental Risk (E-Risk) Longitudinal Twin Study, the number of PENS at 12–18 years was significantly associated with depression PRS, and only at the trend level — with SZ-PRS [39]. In contrast, in the Child and Adolescent Twin Study in Sweden (CATSS), there were positive correlations between PLEs and SZ-PRS [40]. Notably, the authors did not screen the sample for schizophrenia due to the young age (18 years) of the subjects. In a meta-analysis of data from the three mentioned projects (TEDS, ALSPAC and CATSS) published by 2019, Pain et al. [41] obtained significant associations of SZ-PRS with cognitive disorganization, anhedonia and negative symptoms. Associations of SZ-PRS with hallucinations and delusions were significant only in the subgroup of adolescents who had these PLEs: the higher the SZ-PRS, the more pronounced delusions and hallucinations were. Anhedonia and negative symptoms, in addition, correlated positively with depression PRS, while delusions and hallucinations were negatively associated with PRS for bipolar disorder (BD) [41].

The CAPE-based results are also mixed. In Brazilian children and adolescents, no association was found between SZ-PRS and the scores of this questionnaire, which was slightly modified in the context of this study [42]. In adolescents and young adults from the European projects IMAGEN and Dutch Utrecht Cannabis Cohort (UCC), different authors obtained correlations of SZ-PRS

with different CAPE indicators. Marchi et al. [43] found positive associations of SZ-PRS with CAPE total scores in the UCC sample, which included a significant number of individuals who used cannabis (the latter is a risk factor for PLEs), but failed to replicate this association in the IMAGEN sample. Elkrief et al. [44] found positive associations of SZ-PRS with CAPE total scores in both samples. Regarding the CAPE scales, however, it turned out that in the IMAGEN sample SZ-PRS correlated with the positive and depressive scales, while in the UCC sample — with the negative and depressive ones. Previously, Velthorst et al. [45] found a positive correlation of the CAPE positive symptoms scale with the SZ-PRS in a subsample of UCC, but the authors did not report on the use of the other CAPE scales. In the IMAGEN subsample aged 21–22 years, SZ-PRS predicted the higher versus low CAPE total scores both directly (a significant direct effect in a mediation analysis) and indirectly, through age-related dynamics of personality traits and victimization (significant indirect effects); however, in a large replication sample of adolescents from another project, only the indirect effects were confirmed [46].

In sum, studies of children and young people have not yielded convincing evidence in favor of a relationship between SZ-PRS and delusional and hallucinatory experiences. In some cases, associations of SZ-PRS with the PENS general factor and negative symptoms have been observed.

Broad age groups of adults

A significant portion of the PENS studies was conducted on broad age groups of predominantly adult individuals (16–65 years). The research of Derks et al. [47] included 148 people of 18–50 years (the initial stage of the GROUP sample recruitment) and did not find correlations of SZ-PRS with PENS. Mas-Bermejo et al. [20, 21] observed no significant correlations between SZ-PRS and the CAPE indicators in Spanish students aged 18–62. Of the GROUP and EU-GEI studies mentioned in the ST section, the first study of the GROUP cohort reported no significant correlations of SZ-PRS with the CAPE measures [13], while the replication study of both cohorts found negative correlations [22]. However, subsequent EU-GEI publications reported positive correlations of SZ-PRS with the CAPE positive scale [48] and with the positive, negative, depressive [49] and general factors of the CAPE bifactor model [23, 49].

Some studies considered the relationship of PENS with the context in which they occurred. Thus, Johnson et al. [50]

assessed cannabis-related PENS in individuals of European and African descent who were ascertained for addictive disorders. The authors found positive associations of SZ-PRS with all symptoms measured by the Semi-Structured Assessment for the Genetics of Alcoholism interview (paranoia, depression-anhedonia, decreased social contacts, and cognitive difficulties), except for hallucinations. In a replication sample consisting predominantly of individuals with opioid dependence, the associations did not reach significance.

In the longitudinal Dutch project NEMESIS-2, Hasmi et al. [51] tested the hypothesis that PLEs occurring outside the context of non-psychotic mental disorders (mood, anxiety and drug use disorders) might not be of interest for predicting the development of psychosis. Using a clinical interview, they assessed the occurrence of 20 delusional and hallucinatory symptoms in people from the general population during a 9-year follow-up period, then dividing the symptoms into isolated ones and those observed in the context of non-psychotic disorders. The authors compared individuals with the isolated PLEs and with PLEs in the context of non-psychotic disorders to controls without PLEs on the frequency of high SZ-PRS (from the upper quartile of the SZ-PRS distribution). In accordance with the hypothesis, only the group with non-psychotic disorders differed from the controls.

Pries et al. [52] examined suspiciousness, fear of losing control, racing and pervasive thoughts, and difficulties to express thoughts in a Belgian sample of 593 people aged 15–35 using the ecological momentary assessment. The authors also assessed everyday stress. The symptoms studied correlated with childhood trauma and everyday stress, but not with SZ-PRS. The authors found only a weak positive effect of the interaction of SZ-PRS and childhood trauma on psychotic symptoms. At the same time, SZ-PRS correlated positively with positive emotions and were not associated with negative affect or stress reactivity.

Several publications presented the relationships between SZ-PRS and PLEs in an UK BioBank cohort, which included people over 40 years old, i.e., those who had already passed the age of risk [53–56]. Of the almost half a million biobank sample, 157,387 people completed the UKB online Mental Health Questionnaire (MHQ). The MHQ included one question each on the presence and frequency of visual and auditory hallucinations, persecutory delusions, and delusions of reference [53]. Additionally, the distress associated with each symptom was assessed. The findings

regarding correlations between PLEs and SZ-PRS in the entire group, which included not only healthy individuals but also individuals who had previously sought psychiatric help, were mixed [53, 54]. When studying only healthy unrelated individuals of British or Irish decent, Legge et al. [55] observed positive correlations of SZ-PRS with the presence of each symptom, with the strongest associations being found for distressing experiences and persecutory delusions. Similar data were obtained by the authors using PRS for BD, depression, ADHD, and autism, which suggest a nosologically non-specific relationship between PLEs and genetic liability to mental disorders. Later, Barbu et al. [56] confirmed the association of PLEs with SZ-PRS for this sample, based on the latest and more powerful GWAS of schizophrenia (PGC3 GWAS).

In summary, there is inconsistency of data regarding the association of SZ-PRS with PENS in adults from the general population. It is important to note the discrepancy between the results obtained by using different factor models of the same instruments in practically the same or overlapping samples.

DISCUSSION

Since the introduction of PRS, numerous studies have been conducted on the contribution of SZ-PRS to the phenotypic manifestations of psychosis-proneness in the form of ST or PENS. Their results do not provide convincing evidence of the association between SZ-PRS and the studied phenotypes. No expected positive correlations of SZ-PRS with common ST measures have been observed. The findings regarding PENS are more complicated. Among the few positive results, there are more correlations of SZ-PRS with the general factor of PENS and negative symptoms than with positive ones. An exception is the findings for individuals over 40 years old, for whom a significant relationship between SZ-PRS and PLEs is shown [55]. However, these results have been obtained within one biobank and may be subject to population stratification bias. Of note, in the absence of the reproducible relation with SZ-PRS, the psychosis-proneness indicators correlate with PRS for other disorders and traits, particularly PRS for major depressive disorder and neuroticism. As discussed earlier [12, 16], this is partly expected given the high prevalence of symptoms of depression and anxiety in the population, their potential to bias self-reports, and twin studies linking schizotypy and neuroticism. However, further research that takes into account sex differences is needed to provide

a mechanistic understanding of the relationship between neuroticism and susceptibility to psychosis. In addition, the PRS-based findings overlap with other types of genetic data (genetic correlations, Mendelian randomization) from some projects described above. According to the latter: 1) ST does not show significant genetic commonality with schizophrenia, but is genetically associated with depression; 2) genetic correlations of PENS with major depressive disorder are higher than with schizophrenia; 3) PENS in adolescence are not genetically associated with PENS and ST in adulthood; and 4) genetic associations of PENS with schizophrenia and depression are higher in adulthood than in adolescence [57].

The lack of associations between SZ-PRS and the psychosis-proneness indicators might be partly explained by the studies' methodologies. Most investigations used data collected within multi-center longitudinal projects aimed at answering different research questions. Due to this, the studies have shortcomings associated with sample compositions. In particular, cohorts of some projects included related individuals (siblings/twins), which was not always controlled for. The UK Biobank research applied minimal phenotyping. A significant number of studies included heavily overlapping samples. Finally, some studies included individuals across a broad age range. Age might be critical for the phenotypic expression of genetic susceptibility to psychosis. However, the broad age range hardly fully explains the lack of correlations between PENS and SZ-PRS, since such correlations have not been observed in the majority of studies with strict age cutoffs.

Also this review has some limitations, including the analysis of only two databases and the lack of co-authors to discuss the process and results of the literature search. Future quantitative assessment based on meta-analysis should provide more rigorous evidence of the presence or absence of correlations between SZ-PRS and PENS than the qualitative one and could clarify the reasons for the heterogeneity of the results related to the sample composition and measurement instruments used.

CONCLUSION

The available results allow to draw preliminary conclusions about the relationship between SZ-PRS and behavioral indicators of predisposition to psychosis, refute previously stated hypotheses and provide grounds for new ones that should be tested in future studies. First, they do not confirm

that the current ST assessment is adequate for identifying individuals at risk for psychosis and necessitate a revision of existing ST measurement instruments. Second, it has been previously suggested that psychosis vulnerability scores may be an expression of both a specific psychotic factor and a general (transdiagnostic) psychopathological factor p [2, 58]. The combined data, and especially the data obtained using the bifactor models of ST and PENS, support the idea of a transdiagnostic genetic nature of ST/PENS and the hypothesis that the p factor may to some extent be a consequence of genetically determined negative emotionality/affective dysregulation. At the same time, they do not confirm the association of a specific psychotic factor with SZ-PRS. Next, only the most severe, recurring and distressing psychotic experiences appear to reflect genetic liability to schizophrenia, which calls into question the idea of a genetic continuum of ST and psychotic experiences in non-clinical and clinical populations. Further, given the discrepancy between the data obtained for youth and late adulthood, it can be assumed that the nature of ST and PENS in different age groups is different. Finally, the lack of correlations between SZ-PRS and ST/PENS echoes the lack of correlations between SZ-PRS and specific clinical characteristics of schizophrenia [59]. Thus, the search for the substantive psychological meaning of polygenic vulnerability to psychosis captured by SZ-PRS should be expanded to personality processes and characteristics other than ST and PENS.

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Supplementary data

Supplementary material to this article can be found in the online version:

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The Role of the 5-HTTLPR Gene Variation of the SLC6A4 Serotonergic System in the Development of Addictive Disorders: A Narrative Review

Роль вариации 5-HTTLPR гена SLC6A4 серотонинергической системы в формировании аддиктивных расстройств: нарративный обзор литературы

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Review

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ABSTRACT

BACKGROUND: Addictive disorders remain a global problem, affecting health, society and the economy. The etiopathogenesis of addictions, which have a multifactorial nature, is poorly understood, making it difficult to develop personalized treatment approaches. Of particular interest is the *SLC6A4* gene, which regulates serotonergic transmission. The 5-HTTLPR variation of this gene is associated with the risk of addictions, but the data are contradictory due to the heterogeneity of clinical manifestations and pleiotropic effects of the gene. Integration of genetic, environmental and neurobiological factors into multidimensional models is becoming relevant.

AIM: The aim of this study is to assess the role of 5-HTTLPR variations in the *SLC6A4* gene of the serotonergic system in the development of addictive disorders.

METHODS: The manuscripts were searched in the MEDLINE and eLIBRARY.RU databases using the keywords in Russian and English: “SLC6A4”, “5-HTTLPR”, “addictive disorders”, “pharmacogenetics”, “serotonin”, “antidepressants”, “ethnic differences”. After eliminating duplicates and a two-stage screening (by titles/annotations and full-text analysis) of the 1,561 discovered papers, the final review included 41 publications that meet the stated inclusion criteria.

RESULTS: The S-allele of 5-HTTLPR is associated with an increased risk of addictions and comorbid affective disorders, but its role is ambiguous due to the heterogeneity of symptoms. Ethnic differences have been identified: the S-allele predominates (70.6–80.9%) in Asian populations, the L-allele in Europeans (38.5–66.7%). Unique neurobiological markers for S-allele carriers have not been established, and the pleiotropic effects of *SLC6A4* are also observed in other mental disorders, which reduces its specificity for addictions.

CONCLUSION: The inconsistency of the data on 5-HTTLPR highlights the need to take into account ethnic specificity and develop multivariate models that integrate genetic, environmental and clinical factors. This will improve risk prediction (development of addictions), personalization of therapy and the effectiveness of pharmacogenetic approaches, reducing the likelihood of adverse reactions.

АННОТАЦИЯ

ВВЕДЕНИЕ: Аддиктивные расстройства остаются глобальной проблемой здравоохранения, комплексно влияя на здоровье, социум и экономику. Этиопатогенез зависимостей, имеющих мультифакториальную природу, изучен недостаточно, что затрудняет разработку персонализированных подходов к лечению пациентов. Особый интерес представляет ген *SLC6A4*, регулирующий серотонинергическую передачу. Вариация 5-HTTLPR этого гена ассоциирована с риском развития зависимостей, однако данные противоречивы из-за гетерогенности клинических проявлений и плейотропных эффектов гена. Актуальной становится интеграция генетических, средовых и нейробиологических факторов в многомерные модели.

ЦЕЛЬ: Оценить роль изменения 5-HTTLPR гена *SLC6A4* серотонинергической системы в формировании аддиктивных расстройств.

МЕТОДЫ: Поиск публикаций производили в базах MEDLINE и eLIBRARY.RU с использованием ключевых слов «SLC6A4», «5-HTTLPR», «аддиктивные расстройства», «фармакогенетика», «серотонин», «антидепрессанты», «этнические различия», «addictive disorders», «pharmacogenetics», «serotonin», «antidepressants», «ethnic differences». После исключения дубликатов и двухэтапного скрининга (по названиям/аннотациям и полнотекстовому анализу) из 1561 обнаруженной работы в финальный обзор вошла 41 публикация, соответствующая заявленным критериям включения.

РЕЗУЛЬТАТЫ: S-аллель 5-HTTLPR ассоциирован с повышенным риском развития зависимостей и коморбидных аффективных нарушений, однако его роль неоднозначна из-за гетерогенности симптомов. Выявлены следующие этнические различия: S-аллель преобладает (70,6–80,9%) в азиатских популяциях, L-аллель — у европейцев (38,5–66,7%). Уникальные нейробиологические маркеры для носителей S-аллеля не установлены, а плейотропные эффекты *SLC6A4* наблюдаются и при других психических расстройствах, что снижает его специфичность для аддикций.

ЗАКЛЮЧЕНИЕ: Противоречивость данных о 5-HTTLPR подчеркивает необходимость учета этнической специфики и разработки многомерных моделей, объединяющих генетические, средовые и клинические факторы. Это позволит улучшить прогнозирование рисков возникновения аддикций, персонализацию терапии и эффективность фармакогенетических подходов, снижая вероятность развития нежелательных реакций.

Keywords: *5-HTTLPR variant in the SLC6A4 gene; psychogenetics; serotonin; addictive behavior*

Ключевые слова: *изменение 5-HTTLPR гена SLC6A4; психогенетика; серотонин; аддиктивное поведение*

INTRODUCTION

The number of people who are dependent on psychoactive substances is rapidly increasing worldwide, including in Russia [1, 2]. According to the World Health Organization (WHO), alcohol and drug abuse, as well as the use of other psychoactive substances, has become an epidemic in this early 21st century [3, 4]. It should also be noted that the number of affected families by addiction and requiring professional and timely assistance is also on the increase [5]. Differences amongst individuals in the propensity for addictive behavior, including nicotine dependence, are partially mediated by genetic factors [6]. Current estimates

of heritability for all major addictive disorders range from 40% to 80% [7].

Addictive behavior is one form of deviant behavior that arises from the desire to escape reality [8]. The presence of addictive behavior indicates impaired ability to adapt to altered environmental conditions [9]. Addictive behavior traditionally includes alcohol abuse, toxicomania, drug addiction, tobacco smoking (chemical dependencies), as well as computer addiction, gambling, love addictions, sexual addictions, workaholism, and food addiction (overeating, fasting) [10]. Disorders related to psychoactive substance use represent the most common and severe forms of

addiction, classified under the International Classification of Diseases, 10th Revision (ICD-10), code F1: “Mental and behavioral disorders due to psychoactive substance use” [11].

Such functions as mood, emotions, cognition, motor abilities, and circadian and neuroendocrine rhythms — including appetite, sleep, and reproductive activity — are regulated by the serotonin system in the midbrain [12]. Fluctuations in serotonin levels is one of the effects of addictive behavior, underscoring the importance of the genes that encode serotonergic receptors and the transporters in the pathogenesis of dependence [13]. One of the candidate genes that affect the development of dependences is the *SLC6A4* serotonin transporter gene [10]. Recent studies have demonstrated that the 5-HTTLPR (serotonin transporter-linked polymorphic region) variant in this gene is associated with smoking behavior; however, the level of its implication remains inconclusive due to insufficient research [10, 14].

Studies of the 5-HTTLPR pathological allele in the *SLC6A4* gene indicate that there is a connection between various mental disorders and the transcriptional activity levels of the S and L-alleles [15]. For example, reduced activity of the S-allele has been associated with anxiety, depression, suicide attempts, and bipolar disorder, whereas enhanced activity of the L-allele is considered protective against depression, but has also been linked to suicidal behavior, nicotine dependence, and attention-deficit/hyperactivity disorder [15–17]. The aforementioned alleles may also influence treatment efficacy; for example, serotonin reuptake inhibitors may prove more effective in patients with depression and posttraumatic stress disorder who carry the L-alleles [18]. In particular, S-allele carriage is associated with an increased risk of adverse outcomes as relates to alcohol use, mediated by reduced sensitivity to ethanol [19].

The aim of this study is to assess the role of 5-HTTLPR variations in the *SLC6A4* gene of the serotonergic system in the development of addictive disorders.

METHODS

Eligibility criteria

Inclusion criteria:

- original research and meta-analyses regarding the role of the 5-HTTLPR variant in the *SLC6A4* gene in the development of addictive disorders, including interaction of genetic and environmental factors;
- publications analyzing the pharmacogenetic aspects of the use of antidepressants (selective

serotonin reuptake inhibitors, SSRIs) in carriers of different 5-HTTLPR polymorphisms;

- studies related to ethnic differences in the S and L-alleles distribution and their association with clinical outcomes.

Exclusion criteria:

- case reports and case series without the use of control groups;
- publications related solely to therapy for addictive disorders without the analysis of genetic factors;
- publications in languages other than Russian or English.

Information sources

The search was conducted in the electronic databases MEDLINE and eLIBRARY.RU. The search was carried out in December 2024.

The search period covered ran from January 2003 to December 2024. The search was limited to 2003 because that year marked the publication of the first fundamental studies on the role of 5-HTTLPR [20], which laid the foundation for the study of the interaction between this polymorphism and mental disorders, as well as addictive behavior.

Search strategy

The following combination of keywords in Russian and English were used to search for publications: “*SLC6A4*”, “5-HTTLPR”, “addictive disorders”, “pharmacogenetics”, “serotonin”, “antidepressants”, “ethnic differences”. The search for publications was performed in stages. The search sequence is shown in Figure 1.

Selection process

Each publication was identified by a manual search. Several specialists from the group of authors of this article conducted the search and selection of publications (see Authors' contributions section). Some publications selected at the screening stage were excluded from further analysis once it became clear that they did not meet the eligibility criteria (Figure 1).

Analysis of the results

The authors analyzed each publication and summarized information from the selected sources. The results of the summarization are presented in the structured text and figures.

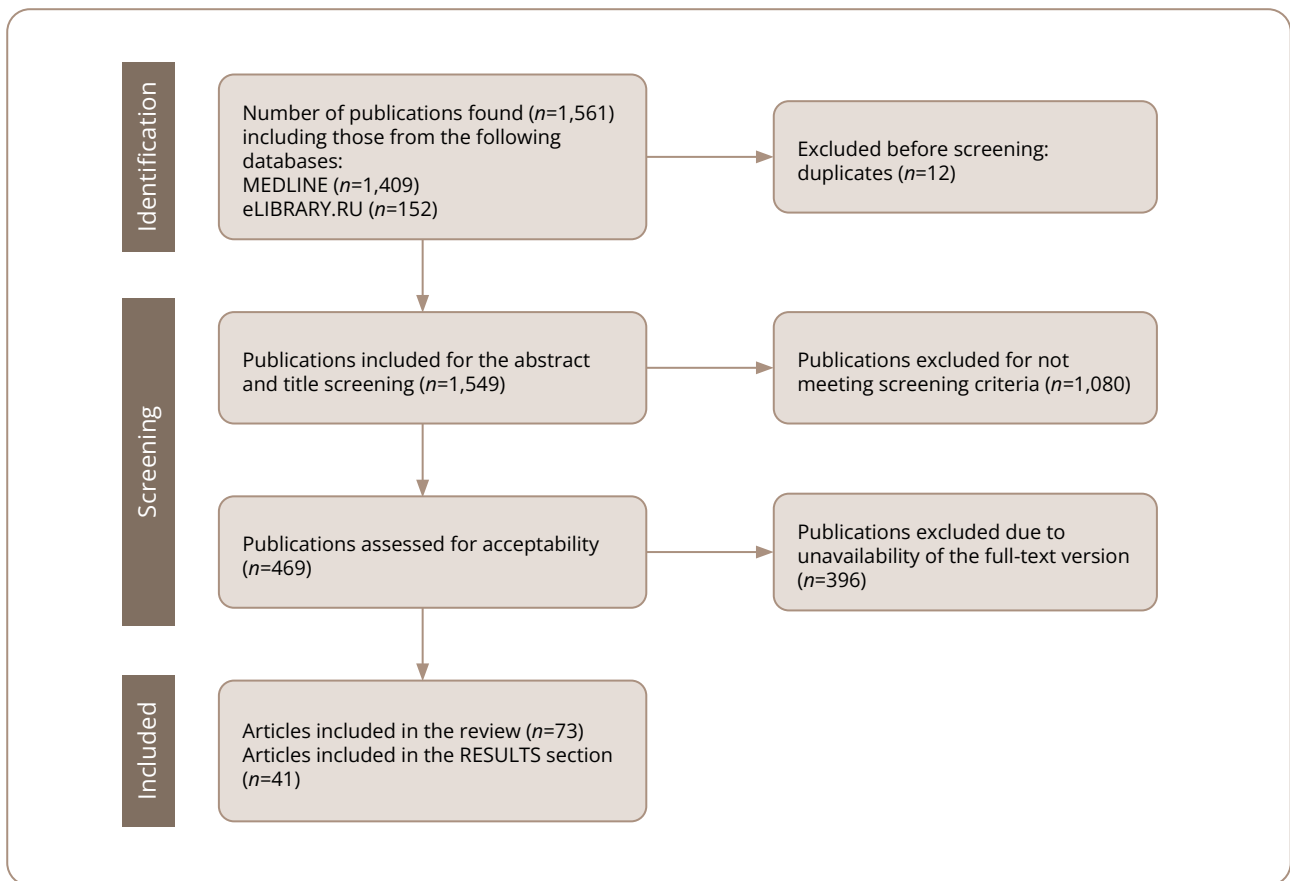


Figure 1. Flow chart demonstrating the selection process.

Source: Krylov et al., 2025.

RESULTS

The *SLC6A4* gene and its relation to psychiatric peculiarities

The 5-HTTLPR (rs4795541) polymorphic region is a functional insertion/deletion polymorphism of 44 base pairs in the promoter region of the *SLC6A4* serotonin transporter gene (Figure 2) [21]. 5-HTTLPR is one of the variants that has most extensively been studied in patients with mental disorders [22–24]. It has also been widely investigated in the context of intermediate phenotypes, such as neuroimaging modalities and gene-environment interactions, with the latter typically examined in relation to affective and anxiety phenotypes [21, 25, 26].

However, it should be noted that addictive disorder is a complicated process whose development depends on a number of factors, including those associated with family history, as well as factors associated with neurobiology, the social context, and experience [14]. This is why the contribution of the pathological allele of the *SLC6A4* gene to mental characteristics may be

only one of many factors influencing this psychological trait [27].

In a study comparing the frequency of pathogenic variations in 5-HTTLPR and rs25531 A<G of the *SLC6A4* gene among the Yakuts and other population samples, a high frequency of the S-allele was identified, which was similar to that observed in Chinese and Japanese populations [14, 25]. According to the study by Nardi et al., the S-allele (deletion) is associated with a lower expression of the serotonin transporter gene [28]. Moreover, carriers of the S-allele demonstrate increased sensitivity to environmental stimuli [28], which likely contributes to the accumulation of this allele among the Yakuts [14].

Some mental disorders with a comprehensive mechanism of pathogenesis (such as schizophrenia) are associated with a disruption of the serotonin system, which affects the development and differentiation of neurons [29]. Moreover, its transporter, encoded by the *SLC6A4* gene, plays a key role in the regulation of the activity level of the serotonergic system [30].

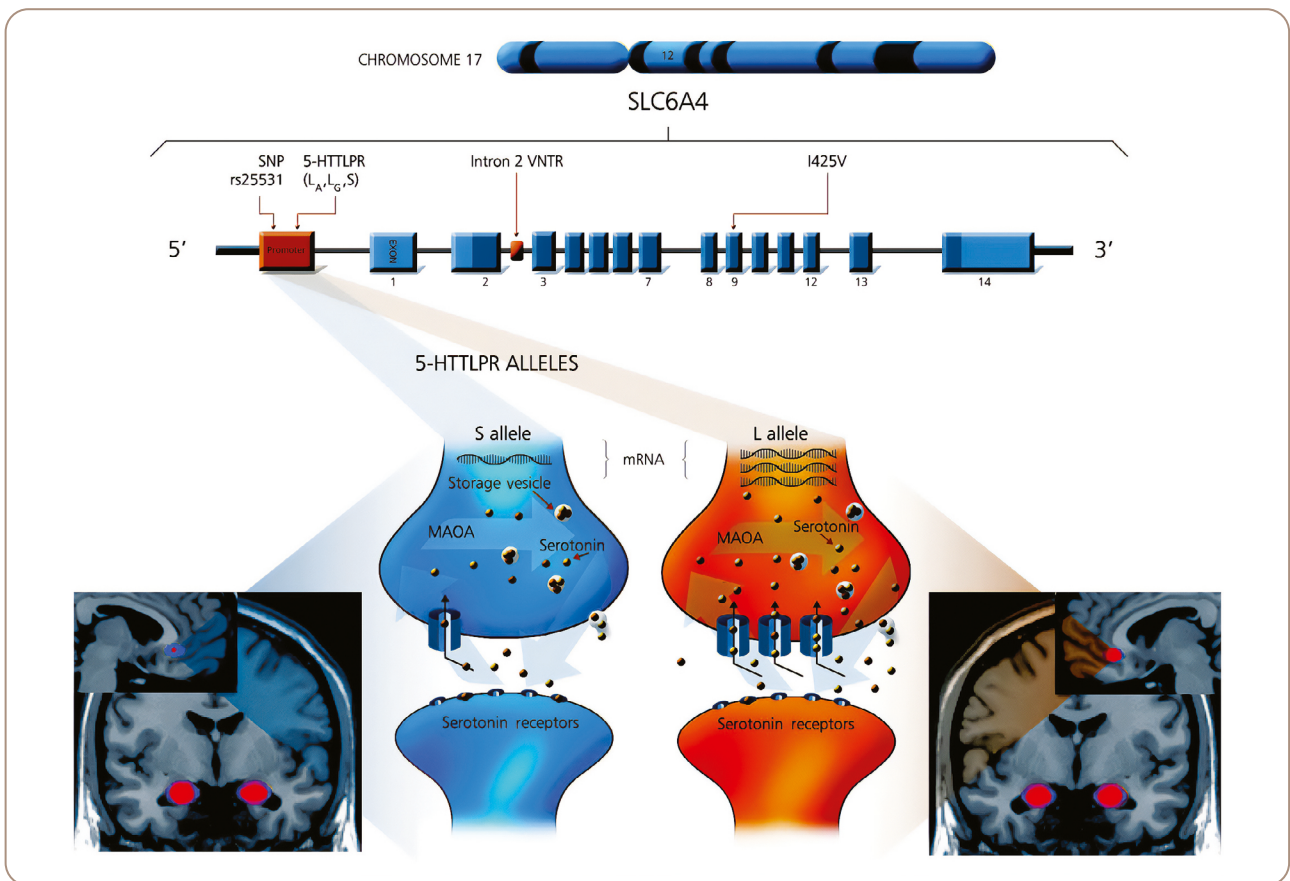


Figure 2. Mapped illustration of the 5-HTTLPR variant in the SLC6A4 gene with allele variants.

Note: 5-HTTLPR — serotonin transporter-linked polymorphic region; CHROMOSOME 17 — the 17th human chromosome, which contains the SLC6A4 gene; Intron 2 VNTR — variable number tandem repeat; MAOA — monoamine oxidase A; mRNA — messenger RNA; rs25531 — is the identifier for a single nucleotide polymorphism (SNP) in the SLC6A4 gene, which affects the expression of the transporter; SNP — single nucleotide polymorphism.

Source: Gerretsen et al., 2009 [21].

It has been reported that there is a link between altered DNA methylation of the gene encoding the serotonin transporter SLC6A4 and mood disorders, anxiety, as well as amygdala responsiveness [31]. Furthermore, some studies have evaluated the epigenetic changes in the SLC6A4 gene in schizophrenia patients [32–34]. CpG sites (DNA regions consisting of cytosine and guanine separated by a phosphate) of the SLC6A4 gene are known to exhibit changes in methylation levels in patients with bipolar disorder [35]. Male patients with schizophrenia also demonstrated similar results [36].

The impact of the 5-HTTLPR variant of the SLC6A4 gene in the development of addictions

Scientific studies in psychogenetics over the past decade have demonstrated that a significant number of mental disorders have a genetic origin [37]. It should be noted

that alcohol abuse is the leading cause of disability and mortality amongst people [38]. The lack of awareness about the harmful effects of alcohol and commitment in society to the ritual of merrymaking, where alcohol is a key element in bringing young people together, can lead to the emergence of behavioral patterns of alcohol consumption [39].

There are two types of addictive disorders:

- chemical addictions (alcohol abuse, drug addiction, toxicomania, etc.);
- non-chemical addictions (pathological gambling, computer addiction, Internet addiction, etc.).

In combination, they can lead to organic disruptions in the higher nervous functions, which can ultimately result in the development of mental disorders [40, 41]. Data suggest that there may be differential genetic vulnerability to alcohol abuse and opiate dependence in serotonergic genes [42].

There is also evidence that the serotonin system plays a role in the pathogenesis of multiple neuropsychiatric disorders and may be involved in addictions such as smoking, since nicotine increases serotonin production in the brain [43–45]. It is assumed that nicotine and other components of tobacco smoke may contain serotonin and thereby contribute to the development of homeostatic resistance [46]. According to some researchers, the genetic variants of different nations lead to different patterns. For example, among residents of Texas (USA) with the LL genotype, smoking was more common than among carriers of the S-allele [47], whereas the 5-HTTLPR variant of the serotonin transporter gene and any association with smoking have not been documented among the Polish population [48].

It is well known that the genetic basis of alcohol abuse lies in the mechanism of ethanol metabolism and the reward system (the neurobiological system associated with dopamine production and the development of addiction) [49]. The scientific community has shown a greater interest in the association between changes in the promoter region of the serotonin transporter gene *SLC6A4* and alcoholism [50]. The S-allele is associated with alcohol consumption, while the L-allele is associated with a positive pharmacological response during the resolution of the withdrawal syndrome [51, 52].

The effects of the 5-HTTLPR variant of the *SLC6A4* gene on the outcomes of therapy with antidepressants in various ethnic groups

SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine) and serotonin modulators with SSRI-like properties are the main pharmacological options for treating major depressive and anxiety disorders [53–55]. The updated guidelines of the Clinical Pharmacogenetics Implementation Consortium (CPIC) emphasize the import of genotyping *CYP* (*CYP2D6*, *CYP2C19*, *CYP2B6*) genes for dosage optimization; however, our knowledge on the pharmacodynamic *SLC6A4* gene remains insufficient for clinical application [56, 57]. Antidepressants constitute the main therapeutic option for patients with depression; however, about 50% of patients fail to achieve an adequate response to them [58]. The site of action of SSRIs is the serotonin transporter, which means that the concentration of this protein can affect its efficacy both directly and through adaptive changes in the serotonergic function [59, 60]. Due to the differences in the transcriptional activity of 5-HTTLPR,

the dose of SSRIs may inhibit a greater proportion of serotonin in individuals carrying the S-allele, leading to a rapid accumulation of synaptic serotonin and increasing the risk of adverse reactions [20]. The Biallelic (5-HTTLPR) and triallelic (5-HTTLPR/rs25531) patterns in the *SLC6A4* gene are frequently studied, but any idea of association with the antidepressant response remains tenuous [61]. Researchers note differences in the response to SSRIs depending on ethnic variations in 5-HTTLPR: the S-allele is associated with a better antidepressant response in Koreans and Japanese, while the L-allele is associated with a better response in Europeans. However, it is unclear whether the 5-HTTLPR variant and its high expression variant rs25531 have any association with the response to antidepressants [62].

DISCUSSION

Brief interpretation of the results

The 5-HTTLPR variant of the *SLC6A4* gene may interact with the environment and affect the development of addictive disorders [59, 60]. Such stressful events as losses or unfavorable household conditions may have a greater effect on patients with the S-allele, making them predisposed to addictive behavior [63]. It has also been shown that the presence of the S-allele may lead to a reduction in serotonin concentration in synapses, which, in turn, is associated with an increased predisposition to the development of mental disorders and addictive behavior [63, 64]. At a physiological level, this may manifest as emotional instability and increased sensitivity to stress [15, 65]. This emphasizes the importance of considering both genetic and environmental factors when assessing the risk of developing dependences [61, 66]. As can be seen in Table 1, the distribution of genotypes (LL, SL, SS) and alleles (L/S) of the 5-HTTLPR variant of the *SLC6A4* gene varies greatly across different ethnic groups. For instance, in Asian populations (Japanese, Chinese, Yakut), the S-allele predominates (70.6%–80.9%), whereas in European populations (Russian, Ukrainian, Belarusian), the L-allele is more frequently encountered (38.5%–66.7%) [26]. These differences indicate the need to consider population specificity when analyzing genetic risks [26]. Fundamental studies have not identified any unique neurobiological markers (e.g., features of neuroimaging or immune parameters) that would clearly distinguish carriers of the S-allele from patients with other genetic profiles [20].

Table 1. The frequencies of the genotypes and alleles of the 5-HTTLPR variant in the SLC6A4 gene in various populations [26]

Population	n	Frequency of genotypes, % (n)			Frequency of alleles (%)		Reference
		LL	SL	SS	L	S	
Russian (St. Petersburg)	908	38.10 (346)	46.69 (424)	15.19 (138)	61.5	38.5	[67]
Ukrainian	60	21.21 (14)	37.87 (25)	40.90 (27)	61.5	38.5	
Belarusian	39	46.15 (18)	41.02 (16)	12.82 (5)	66.7	33.3	
Chuvash	372	24.46 (91)	51.61 (192)	23.92 (89)	50.3	49.7	
Kabardian	289	26.64 (77)	44.63 (129)	28.71 (83)	49.0	51.0	
Tatar	142	26.05 (37)	51.40 (73)	22.53 (32)	51.8	48.2	
Yakut	158	5.7 (9)	32.3 (51)	62.0 (98)	21.8	78.2	[26]
Chinese (Beijing)	558	6.09 (34)	36.02 (201)	57.88 (323)	24.1	75.9	[44]
Thai	187	9.09 (17)	36.89 (69)	54.01 (101)	27.5	72.5	[20]
Taiwanese	192	10.93 (21)	36.97 (71)	52.08 (100)	29.4	70.6	[68]
Japanese	101	3.7 (4)	31.4 (31)	65.7 (66)	19.3	80.7	[69]
Japanese (Tottori)	501	3.19 (16)	31.73 (159)	65.06 (326)	19.1	80.9	[70]
Chines (Shanghai)	587	6.30 (37)	41.39 (243)	52.29 (307)	27.0	73.0	[71]

Note: The specified samples (Russian — St. Petersburg, Chinese — Beijing, Japanese — Tottori, Chinese — Shanghai) are consistent with the data of original studies (see the references in the table) and reflect local rather than general national samples.

Table 2. Studies of 5-HTTLPR variations of the SLC6A4 gene

Category	Brief description	References
Human studies		
Mental disorders	Relation to schizophrenia, depression, and anxiety in various populations.	[6], [14], [27], [20], [32], [33], [35], [37]
Smoking/nicotine	Association with nicotine dependence and behavioral patterns.	[10], [43–47]
Alcohol	The role of 5-HTTLPR in the development of alcohol abuse.	[19], [51]
Anxiety/stress	Association with panic attacks and stress reactivity.	[17], [21–23], [61], [69], [70]
Pharmacokinetics	Effects on the efficacy of antidepressants (SSRIs).	[53], [63], [67]
Personality/neurodegeneration	Role in personality traits and neurodegenerative processes.	[28], [29], [71]
Population differences	Ethnic variability of alleles and risks.	[25], [42]
Epigenetics	Promotor hypermethylation and its clinical correlates.	[30], [35], [36]
Animal studies		
Epigenetics/environment	The effect of environmental enrichment on SLC6A4 expression and demethylation in mice.	[34]

Discussion of the results

Recently, in the study by Bousman et al., the authors excluded the SLC6A4 gene from clinical recommendations due to conflicting data and insufficient evidence for its clinical implementation [56]. However, in their systematic review and meta-analysis, Stein et al. showed that the pathological variant of 5-HTTLPR can serve as a marker for antidepressant treatment outcomes in patients with

mental disorders and may be particularly relevant for the use of SSRIs in individuals of European descent [68]. Laje et al. [69] and Rahikainen et al. [70] demonstrated that male patients with a low-functioning genotype SS 5-HTTLPR/rs25531, who were on SSRIs (citalopram), were at increased risk of violent suicide (bringing to suicide). At the same time, studies conducted in Korean patients with severe depression by Jang et al. showed that carriers of the

SS 5-HTTLPR genotypes had significantly better treatment outcomes, while the genotype containing the G (AG+GG) rs25531 variant was associated with remission only [71]. Despite the fact that this pathological allele is involved in the development of addictive disorders, it cannot serve as a clinical marker due to a lack of evidence. Moreover, at the current stage of research, many investigators associate this genetic variant with other mental disorders, such as depression and anxiety (Table 2) [72, 73].

Limitations

Although the coverage of scientific publications based on the keywords used in MEDLINE and eLIBRARY.RU could be considered comprehensive, the descriptive nature of some publications prevented us from including them in the study. The limitation of the search by the specified search engines and keywords led to the heterogeneity of the study material in the meta-analyses, as well as to the retrospective nature of the meta-analyses themselves and the insufficient comprehensiveness of the studies initially selected for them. In this review, only one gene *SLC6A4* and its two variants (5-HTTLPR and rs25531 A<G) were considered. Furthermore, since the pleiotropic effects of the *SLC6A4* gene are associated with depression and anxiety, this limits the possibility of isolated interpretation of its role in the development of addictive disorders. The authors acknowledge the limitations of the information presented and recognize that, even with the most thorough possible approach, the study cannot encompass all aspects of the topic being considered.

CONCLUSION

This review attempted to systematize the data on the role of the 5-HTTLPR variant of the *SLC6A4* gene in the development of addictive disorders, highlighting its ambiguous nature and pleiotropic effects. In contrast to previous studies, the emphasis here is centered on the need for a multidimensional approach to risk assessment that takes into account genetic, environmental, and ethnic factors. Further studies with an in-depth analysis of the molecular mechanisms of the interaction between the 5-HTTLPR variant of the *SLC6A4* gene and the serotonergic system are needed. Future research should also include the development of personalized prevention and treatment strategies, which can potentially improve the efficacy of addiction treatment and reduce the frequency of adverse reactions.

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Modern Concept of Depression Pathogenesis: The Contribution of I.P. Lapin's Research Team

Вклад работ коллектива И.П. Лапина в становление современной модели патогенеза депрессивных расстройств

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Information

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ABSTRACT

BACKGROUND: The advent of neuroleptics and antidepressant therapy marked a significant step forward in clinical psychiatry. Numerous experiments worldwide had been dedicated to a search for the potential neurobiological mechanisms underlying the potency of new psychopharmacological drugs. The first laboratory of psychopharmacology in the USSR was established in 1960 at the Leningrad Psychoneurological Institute. It was headed by Professor Izyaslav Petrovich Lapin. The foundational article by Lapin I.P. and Oksenkrug G.F. (The Lancet, 1969) continues to be cited 55 years after its publication, which determines the interest in the role of this research team in shaping temporal concepts of the pathogenesis of depression and the development of psychopharmacology.

AIM: To analyze the contribution of Lapin I.P. and his research team to the development of experimental approaches for studying the mechanisms of depression.

METHODS: We analyzed the articles and monographs authored by Professor Lapin I.P., both individually and in co-authorship, available in PubMed, Google Scholar, eLIBRARY.RU, and in the bibliographic collection of the V.M. Bekhterev National Medical Research Centre for Psychiatry and Neurology.

RESULTS: This analysis highlights the significance of Lapin I.P. and his scientific team's work in advancing our understanding of serotonin role in the mechanisms of depression and in the development of animal depression models. The scientific contribution of this team is an important milestone towards future research into the neurobiological mechanisms underlying depression, as well as the development of therapeutic approaches.

CONCLUSION: Lapin's scientific publications and the work of his team in the field of psychopharmacology have had a significant impact on the development of neuroscience and continue to be of unquestionable importance in advancing scientific practice more than 50 years later.

АННОТАЦИЯ

ВВЕДЕНИЕ: Появление нейролептиков и антидепрессивной терапии стало существенным шагом вперед в развитии клинической психиатрии. Поиску возможных нейробиологических механизмов, лежащих в основе действия новых психофармакологических препаратов, были посвящены многочисленные эксперименты во всем мире. В 1960 г. в Ленинградском психоневрологическом институте была создана первая в СССР лаборатория психофармакологии, которую возглавил профессор Изяслав Петрович Лапин. Фундаментальную статью И.П. Лапина и Г.Ф. Оксенкруга (*The Lancet*, 1969) продолжают цитировать спустя 55 лет после публикации, что определяет интерес к роли этого научного коллектива в формировании временных представлений о патогенезе депрессии и развитии психофармакологии.

ЦЕЛЬ: Проанализировать вклад И.П. Лапина и его научного коллектива в разработку экспериментальных подходов к исследованию механизмов развития депрессии.

МЕТОДЫ: Авторы проанализировали статьи и монографии, написанные профессором И.П. Лапиным как индивидуально, так и в соавторстве, доступные в базах данных PubMed, Google Scholar, eLIBRARY.RU и в библиографическом фонде ФГБУ «Национальный медицинский исследовательский центр психиатрии и неврологии им. В.М. Бехтерева» Минздрава России.

РЕЗУЛЬТАТЫ: Проведенный анализ подчеркивает значимость работы И.П. Лапина и его коллег в углублении понимания роли серотонина в механизмах депрессии и в разработке моделей депрессии на животных. Научное наследие этого коллектива является важной вехой на пути к будущим исследованиям нейробиологических механизмов, лежащих в основе депрессии, а также разработке терапевтических подходов.

ЗАКЛЮЧЕНИЕ: Научные публикации И.П. Лапина и работа его коллектива в области психофармакологии оказали существенное влияние на развитие нейронауки и сохраняют свою значимость для передовых научных исследований уже более 50 лет.

Keywords: *psychopharmacology; affective disorder; neuroscience; history of medicine; history of psychiatry*

Ключевые слова: *психофармакология; аффективное расстройство; нейронаука; история медицины; история психиатрии*

INTRODUCTION

Psychopharmacology, as a branch of clinical pharmacology, underwent intensive development in the middle of the 20th century. However, the deliberate use of pharmacological agents for their psychotropic properties in medicine had begun as early as the 9th century [1]. However, the treatment of pain and insomnia, as well as the psychostimulant effects of certain medicinal products, primarily centered on symptomatic relief and only rarely relied on the understanding of the etiology and pathogenesis of the disorders that held sway at the time [2].

The emergence of psychopharmacotherapy, with effects not only at the symptomatic but also at the syndromal level, enabling the control of psychoses and depressive syndromes, marked a new era in clinical psychiatry. Since the confirmation of the specific psychotropic effects of

chlorpromazine, iproniazid, and imipramine, antipsychotics (neuroleptics) and antidepressants (thymoleptics) have been the subject of ongoing research [3, 4]. Neurobiological hypotheses that proposed mechanisms that explained the observed effects of medicinal products and received empirical confirmation subsequently became the basis for the development of new psychotropic drugs [2, 4].

As early as 1960, just 8 years after the publication of the first data on chlorpromazine's efficacy, the first psychopharmacology laboratory in the Soviet Union was established at Leningrad Psychoneurological Institute (currently known as V.M. Bekhterev National Medical Research Centre for Psychiatry and Neurology). The novelty of the scientific field and the prompt establishment of this new unit ensured the pioneering nature of the work conducted by the laboratory staff.

In the 1960s, the concept of the leading role of norepinephrine in the development of depression was widely accepted [5]. Studies that allowed for the formulation of the catecholamine hypothesis of mood disorders were largely based on testing the serendipitously discovered psychotropic effects of various pharmacological agents in animal models of depression [6]. One of the first thymoleptics (trazodone), developed in the early 1970s with a predetermined spectrum of neurobiochemical activity, was supposed to lower the pain threshold in depression by acting on α -adrenergic receptors, according to the original hypothesis [7]. However, in 1981, by the time of the drug's approval by the Food and Drug Administration (FDA), its antidepressant effect had become associated with the mechanism of serotonin reuptake. In 1971, another group of researchers was developing a selective serotonin reuptake inhibitor, which was authorized by the FDA in 1988 as fluoxetine [8]. Thus, in the early 1970s, the consensus on the mechanisms of depression development had shifted from the noradrenergic theory to the serotonergic theory. This opened the next stage in the development of psychopharmacology — the targeted synthesis of drugs with the desired properties. Selective serotonin reuptake inhibitors (SSRIs), antidepressants of the currently most common group, appeared. This paradigm shift in the development of psychopharmacology was, to some degree, facilitated by the original research performed by a team at the Psychopharmacology Laboratory of the Leningrad Psychoneurological Institute [9]. It was also supported by their analysis of similar studies by international colleagues (including joint projects with the University of Tartu), focusing on the mechanisms of action of psychotropic agents.

A significant milestone in the field of psychopharmacology was the publication of an article by Soviet scientists Lapin I.P. and Oksenkrug G.F. in the "Hypothesis" section of *The Lancet* journal in 1969 [10]. Given its scientific importance and high citation count in international scientific literature, Oksenkrug's commentary on the writing of the 1969 landmark article was published in 1987 in the "This Week's Citation Classic" section of "Current Contents" [11, 12]. Lapin I.P. and Oksenkrug G.F. summarized their experience and data from their colleagues' research and were among the first to provide consistent evidence of the involvement of serotonergic mechanisms in the development of depression [10]. The studies by Professor Lapin I.P. made a significant contribution to the improvement of our understanding of the pathogenesis of depression; in this context, determining

their role in the formation of modern concepts of the pathogenesis of depression and the development of psychopharmacology is of particular interest.

This study aims to analyze the contribution of Lapin I.P. and his research team to the development of experimental approaches for studying the mechanisms of depression.

METHODS

Articles and monographs written by the professor personally or in co-authorship, available in PubMed, Google Scholar, eLIBRARY.RU databases, as well as in the bibliographic collection of the V.M. Bekhterev National Medical Research Centre for Psychiatry and Neurology, were analyzed. The studies included in the review were systematized by the authors on the basis of the three main aspects of the professor's scientific research into the pathogenesis of depression: location of abnormalities; improvement of experimental methods; and systematic analysis of the information known in the 1960s about the pathogenesis of depression. The landmark publication by Lapin I.P. and Oksenkrug G.F. "Intensification of the central serotonergic processes as a possible determinant of the thymoleptic effect" [10], which appeared as a result of scientific work within the framework of the latter direction, was analyzed for semantic groups of scientific papers citing it according to the Semantic Scholar scientometric database in 2022.

RESULTS

Research into the role of brain structures in the pathogenesis of depression in animal models

Professor Lapin I.P. in collaboration with Allikmets L.H. (an Honored Scientist of the Estonian SSR, physician-researcher in the field of the clinical pharmacology of antidepressants and neuroleptics), tested the hypothesis of the possible involvement of the hypothalamus and the amygdala complex in the etiology of depression and the effects of antidepressants. While studying the behavior of amygdala-lesioned rats and their responses to thymoleptics, the authors concluded that these compounds exert their action outside the amygdala [13], in particular by affecting self-stimulation of the lateral hypothalamic regions. When analyzing the results of the chemical stimulation of limbic structures and the hypothalamus in cats [14], the research team hypothesized that the final common pathway of depression, regardless of its etiology, involves decreased activity of the hypothalamus and the dorsomedial amygdala, and increased activity of the basolateral amygdala.

During experiments with the chemical stimulation of the hypothalamus, septum, and amygdala [15] of cats using a serotonin solution combined with intramuscular administration of imipramine, a sharp intensification of autonomic symptoms was noted, which opened the way to suggest the existence of synergism between the action of tricyclic antidepressants and serotonin [16]. A study of rat behavioral patterns following the destruction of specific regions of limbic structures [17] led to the conclusion that the hippocampus is involved in the regulation of emotional behavior.

Use of animal models in studies of the pathogenesis of depression

In the early 1980s, the Professor Lapin I.P. and his colleagues investigated the role of serotonin in the pathogenesis of depression, an effort that led to the development of a model in which experimental animals were subjected to a diet devoid of tryptophan, the amino acid precursor of serotonin [10, 18]. The model of tryptophan depletion has become a widely used animal model of depression [19–21], as it reliably induces a transient drop in serotonin levels and depression-like behavior seen in humans, such as reduced activity and increased immobility.

Formulation of the serotonergic theory of the pathogenesis of depression

The enhancement of serotonin's autonomic effects and the potentiation of reserpine's sedative action observed in imipramine studies prompted Lapin I.P. and Oksenkrug G.F. to further investigate the role of serotonin in the development of depression. This led to the important publication of their joint paper, "Intensification of the central serotonergic processes as a possible determinant of the thymoleptic effect", in *The Lancet* journal [10]. Over the years since the publication of the article, it has been cited numerous times and, thus, has influenced research in the fields of neuropharmacology and psychiatry. Research based on the serotonergic hypothesis outlined in the article has covered a wide range of issues from studying molecular mechanisms to clinical research aimed at optimizing the treatment of depression.

Based only on the data from Semantic Scholar, we were able to identify about 500 studies that had cited this article by 2022 (Appendix S1 in the Supplementary). Those publications can be divided into several groups:

1. *Studies related to the etiology and pathogenesis of psychiatric disorders.* This group included works on the pathogenesis of affective disorders and neurotransmitter metabolism, as well as studies on animal models of the serotonin model of depression — also applied to human research — and critical articles (Figure 1).

2. *Clinical publications on psychiatry, neurology, and addiction medicine.* Figure 2 illustrates the popularity of the article by Lapin I.P. and Oksenkrug G.F. within this field of research publications.

3. *Studies of the pharmacodynamics and therapeutic effects of medicinal products, as well as those describing the action and efficacy of newly developed drugs, primarily in relation to affective disorders.* Figure 3 shows the activity of respective citations.

4. *General medical issues.* This group included theoretical studies from anesthesiology, medical genetics, cardiology, gynecology, allergology, endocrinology, oncology, and gastroenterology. The publications explored and described models of the pathogenesis of mental (predominantly affective) disorders and the evolution of these concepts, fundamental or deontological topics, as well as materials where the subject of research extended beyond neuroscience but, nevertheless, touched upon the serotonergic hypothesis (Figure 4).

DISCUSSION

Based on the results of this review, it appears legitimate to conclude that the work of Lapin I.P. and his team was key in deepening our scientific understanding of serotonin's role in the mechanism of depression and in the development of experimental animal models. The contribution of the scientist and his colleagues has become a landmark in the path toward further research into the neurobiological mechanisms underlying depression and the development of new methods for its treatment, as evidenced by the persisting demand for their publication in the international scientific literature for over more than five decades.

The hypothesis proposed by Professor Lapin as regards the importance of reducing hypothalamic activity is echoed in modern concepts of the involvement of the hypothalamic-pituitary-adrenal axis and glucocorticoid receptors in the formation of not only physiological, but also behavioral responses [22]. This significantly outpaced the widespread dissemination of the results obtained in modern neuroimaging studies. Recent studies [23] have validated Professor Lapin's experimental findings

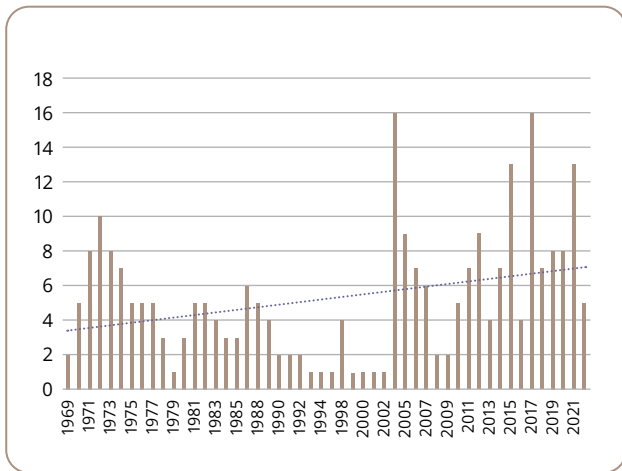


Figure 1. Citations of the paper by Lapin I.P. and Oksenkrug G.F. (1969) over time in articles related to etiology and pathogenesis of psychiatric disorders.

Source: Neznanov et al., 2025.

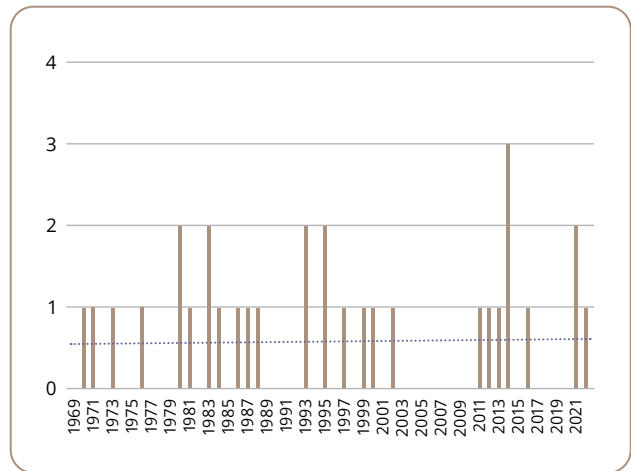


Figure 2. Citations of the paper by Lapin I.P. and Oksenkrug G.F. (1969) over time in articles related to clinical neuroscience.

Source: Neznanov et al., 2025.

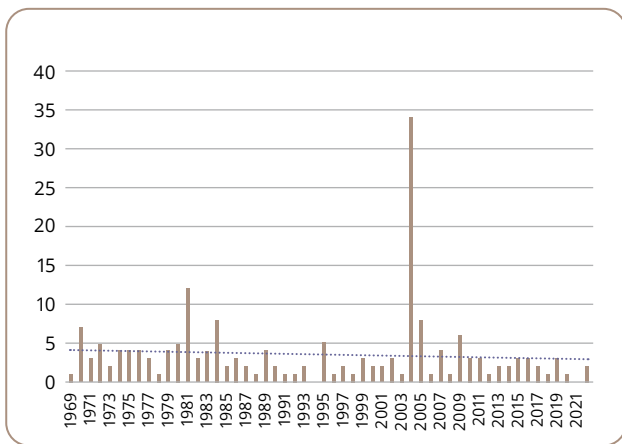


Figure 3. Citations of the paper by Lapin I.P. and Oksenkrug G.F. (1969) over time in articles related to psychopharmacology.

Source: Neznanov et al., 2025.

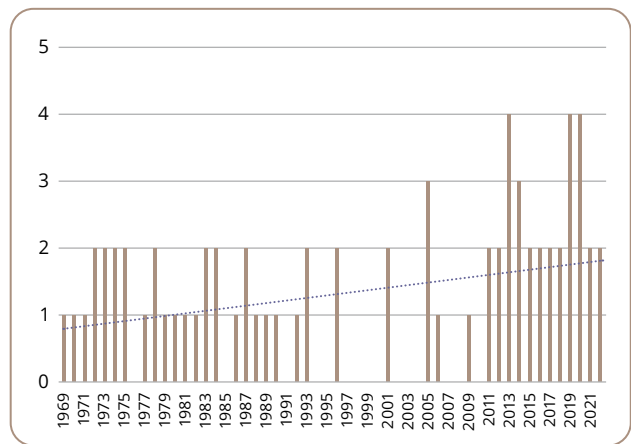


Figure 4. Citations of the paper by Lapin I.P. and Oksenkrug G.F. (1969) over time in broad-subject publications beyond neuroscience.

Source: Neznanov et al., 2025.

regarding the decrease in activity in the dorsomedial part of the amygdaloid complex, which supports mood, alongside an increase in the activity of the basolateral part, which regulates anxiety, stress, and tension. This can explain the existence of several depression subtypes. Specifically, a large neuroimaging project by the ENIGMA Consortium [24] demonstrated a significant decrease in the hippocampal volume in patients with depression compared to the control group. This result aligns with the findings of Lapin I.P. and Allikmets L.H. [17], who showed that the destruction of specific limbic brain structures affects rat behavior, specifically emphasizing the pivotal role the hippocampus plays in the regulation of emotional

behavior. The results of the professor's studies also found confirmation in the brain-derived neurotrophic factor (BDNF) theory of depression, which identifies the BDNF as the molecule mostly responsible for the abnormalities that lead to depressive symptoms. What is more, several researchers have suggested that the BDNF plays an important role in the induction of depression in mice: a decrease in hippocampal volume caused by chronic mild stress leads to reduced synaptic transmission and lower BDNF concentration [25].

Since the discovery of antidepressants in the 1950s, their mechanism of action has been the subject of study. One of the main issues for the investigators was a lack

of the corresponding tests and models in experimental pharmacology required for the assessment of the effects of thymoleptics in laboratory animals. This limitation made it difficult to grasp the pharmacodynamics of the drugs and to further work on them. Professor Lapin and colleagues played a significant role in the creation and refinement of animal models of depression during the 1970s and 1980s. Their work was used to investigate the neurobiological mechanisms underlying the disorder and to assess the efficacy of antidepressants. The experimental studies conducted by his team were focused on the use of pharmacological agents such as reserpine [26, 27] to induce depression-like conditions in animals. These were characterized by behavioral changes manifesting as reduced locomotor activity and increased immobility in the forced swimming test. These studies not only helped establish the validity and reliability of animal models of depression, but they also paved the way for the development of new ones: learned helplessness and chronic mild stress, which are widely used in research today [28]. The professor also became known for his contribution to the development of the tryptophan depletion model. Despite technological advances, animal models of depression remain an important tool for studying the pathophysiology of the disorder [29–31], as well as for conducting clinical trials.

According to current scholarship, depression is a complex disorder associated with changes in neurotransmitter systems, signaling pathways in the central nervous system, hormonal dysregulation, epigenetic factors, systemic inflammatory responses, and reduced neuroplasticity [32–34]. The neurogenic theory of depression [35, 36] describes a decrease in the formation of new neurons in the hippocampus. One of the potential pathways that could lead to reduced neurogenesis in the hippocampus and affect catecholamine levels involves the impact on the hypothalamic-pituitary-adrenal axis [35]. Lapin's research into the role of this axis and its connection to reduced catecholamine levels in the brain was an important contribution to our understanding of the mechanism of depression [37].

The analysis and summary of earlier studies, supported by a diverse range of his own research, allowed the professor and his colleagues to lay the foundation for the development of the serotonin theory of depression, which has become a cornerstone in the practical implementation of the most frequently used class of antidepressants today, SSRIs [38].

CONCLUSION

The clinical presentation, etiology, and pathogenesis of depressive disorders have remained the subject of scientific research throughout the history of psychiatry. The steps taken by Lapin I.P. and his team in the 1960s–1980s in their study of the mechanisms of depression development, as well as the research hypotheses they put forth shaped the path of modern research and represent a significant contribution of the Soviet psychopharmacologist to the development of neuroscience. Lapin's work was recognized with numerous awards, including the prestigious Order of Lenin in 1985. The professor's scientific legacy remains of significant importance in the development of scientific practice, even after his death in 2010.

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Supplementary data

Supplementary material to this article can be found in the online version:

Appendix S1: 10.17816/CP15601-145609

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Erratum to “Comparative Analysis of Corpus Callosum Lipidome and Transcriptome in Schizophrenia and Healthy Brain” (Consortium PSYCHIATRICUM, 2025, Volume 6, Issue 1, doi: 10.17816/CP15491)

Ошибки в статье «Сравнительный анализ липидома и транскриптома мозолистого тела головного мозга при шизофрении и в здоровом состоянии» (Consortium PSYCHIATRICUM, 2025, Т. 6, № 1, doi: 10.17816/CP15491)

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Erratum | Сообщение об ошибке

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In the article by M.S. Osetrova et al. titled "Comparative Analysis of Corpus Callosum Lipidome and Transcriptome in Schizophrenia and Healthy Brain", published in the Consortium PSYCHIATRICUM journal (Volume 6, Issue 1), the editorial team made some technical errors. Without any malicious intent, the quantitative indicators in Figure 1 "Experiment design" were incorrectly stated: 1,254 genes instead of 14,254 in the RNAseq section and 385 peaks instead of 384 in the LC-MS section.

The technical errors in Figure 1 have been corrected, and updated PDF and HTML versions of the article have been uploaded on the journal's website. The editorial team of the journal hopes that the mistakes could not significantly affect the perception and interpretation of the published work by readers, and should not become the reason for retraction. The editorial team apologizes to the authors and readers for the mistakes made.

В статье М.С. Осетровой и соавт. «Сравнительный анализ липидома и транскриптома мозолистого тела головного мозга при шизофрении и в здоровом состоянии», опубликованной в журнале Consortium PSYCHIATRICUM (Т. 6, № 1), редакционным коллективом были допущены технические ошибки. Без какого-либо злого умысла в рисунке 1 «Дизайн эксперимента» были некорректно указаны количественные показатели: 1,254 гена вместо 14,254 в блоке RNAseq и 385 пиков вместо 384 в блоке LC-MS.

Технические ошибки в рисунке 1 были устранены, обновленные PDF- и HTML-версии статьи размещены на сайте журнала. Редакция надеется, что допущенные ошибки не оказали существенного влияния на восприятие и интерпретацию опубликованной работы и не являются основанием для ретракции статьи. Редакция журнала приносит свои извинения авторскому коллективу и читателям за допущенные ошибки.

Keywords: *erratum; schizophrenia; lipidomics; transcriptomics; mass spectrometry; corpus callosum*

Ключевые слова: *ошибки; шизофрения; липидом; транскриптом; масс-спектрометрия; мозолистое тело*

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