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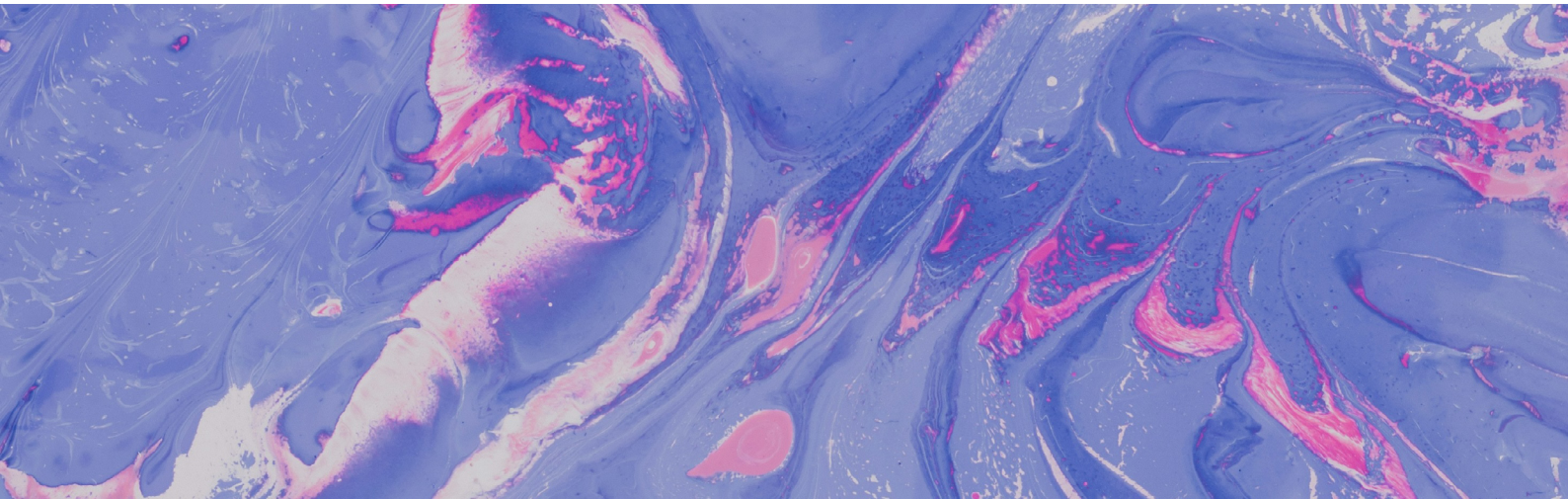
Genetic Associations of Anhedonia: Insights into Overlap of Mental and Somatic Disorders Page 5



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Genetic Associations of Anhedonia: Insights into Overlap of Mental and Somatic Disorders

Генетические ассоциации ангедонии: новые аспекты взаимосвязи психических и соматических расстройств

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Original research

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ABSTRACT

BACKGROUND: Anhedonia is characterized by a reduced ability to anticipate, experience, and/or learn about pleasure. This phenomenon has a transdiagnostic nature and is one of the key symptoms of mood disorders, schizophrenia, addictions, and somatic conditions.

AIM: To evaluate the genetic architecture of anhedonia and its overlap with other mental disorders and somatic conditions.

METHODS: We performed a genome-wide association study of anhedonia on a sample of 4,520 individuals from a Russian non-clinical population. Using the available summary statistics, we calculated polygenic risk scores (PRS) to investigate the genetic relationship between anhedonia and other psychiatric or somatic phenotypes.

RESULTS: No variants with a genome-wide significant association were identified. PRS for major depression, bipolar disorder, and schizophrenia were significantly associated with anhedonia. Conversely, no significant associations were found between PRS for anxiety and anhedonia, which aligns well with existing clinical evidence. None of the PRS for somatic phenotypes attained a significance level after correction for multiple comparisons. A nominal significance for the anhedonia association was determined for omega-3 fatty acids, type 2 diabetes mellitus, and Crohn's disease.

CONCLUSION: Anhedonia has a complex polygenic architecture, and its presence in somatic diseases or normal conditions may be due to a genetic predisposition to mood disorders or schizophrenia.

АННОТАЦИЯ

ВВЕДЕНИЕ: Ангедония характеризуется снижением способности предвосхищать, испытывать и/или усваивать удовольствие. Этот феномен имеет трансдиагностическую природу и является одним из ключевых симптомов расстройств настроения, шизофрении, аддикций и соматических состояний.

ЦЕЛЬ: Оценить генетическую архитектуру ангедонии и её перекрытие с другими психическими расстройствами и соматическими состояниями.

МЕТОДЫ: Проведено исследование полногеномного поиска ассоциаций ангедонии на выборке из 4 520 человек из российской неклинической популяции. Используя доступную сводную статистику, мы рассчитали шкалы полигенного риска (polygenic risk scores, PRS), чтобы исследовать генетическую связь между ангедонией и другими психиатрическими или соматическими фенотипами.

РЕЗУЛЬТАТЫ: Не было идентифицировано ни одного варианта, достигшего полногеномного уровня значимости. PRS для депрессии, биполярного расстройства и шизофрении были значимо ассоциированы с ангедонией. И наоборот, не обнаружено значимых ассоциаций между PRS для тревожных расстройств и ангедонии, что хорошо согласуется с существующими клиническими данными. Ни один из PRS для соматических фенотипов не достиг уровня значимости после коррекции на множественные сравнения. При номинальном уровне значимости ассоциация с ангедонией выявлена для PRS ω-3 жирных кислот, сахарного диабета 2-го типа и болезни Крона.

ЗАКЛЮЧЕНИЕ: Ангедония имеет сложную полигенную архитектуру, в связи с чем её присутствие при соматических заболеваниях или нормальных состояниях может быть обусловлено генетической предрасположенностью к расстройствам настроения или шизофрении.

Keywords: *anhedonia; depression; bipolar disorder; schizophrenia; polygenic risk scores*
Ключевые слова: *ангедония; депрессия; биполярное расстройство; шизофрения; показатели полигенного риска*

INTRODUCTION

Anhedonia is characterized by a decrease in or complete loss of the ability not only to consume positive emotions and interest in response to a stimulus (consummatory anhedonia), but also to anticipate potential rewards (anticipatory anhedonia), as well as the awareness of rewards [1]. This phenomenon is considered to be a symptom of regulatory disruptions in the brain reward system [2]. Anhedonia has a transdiagnostic nature and is one of the key symptoms of major depression, bipolar disorder (BD), schizophrenia, and addictions affecting the effectiveness of therapy and the clinical course [3, 4]. The role of anhedonia in the risk of suicidal behavior is highlighted, regardless of the severity of major depression [5].

According to the Research Domain Criteria (RDoC) approach, anhedonia can be considered as a dimensional trait, acting not only as a sign of psychopathology, but also as a characteristic of the reward system malfunctioning in individuals without mental disorders [6]. Consistently, healthy first-degree relatives of patients with major depression have a blunted reward sensitivity [7]. Therefore, the mechanisms associated with the development of anhedonia are often considered as candidates for the endophenotypes of major depression and other mental disorders [8, 9].

Dysfunction of the mesolimbic dopamine system and its interaction with the endogenous opioid system have been proposed as the central mechanism underlying anhedonia [10, 11]. Anhedonia is also associated with a decrease in volume and a change in functional activity in the medial frontal cortex and subcortical striatal areas (caudate nucleus and putamen) [12, 13]. There are studies

of anhedonia in patients with somatic diseases, but their number remains extremely small [14–17].

Despite advances in biochemistry and neuroimaging, the genetic nature of anhedonia remains not fully understood. A study of 759 patients with depression revealed 18 single nucleotide polymorphisms (SNPs) that are associated with anhedonia [18]. A mega-analysis of three studies of young people from the UK and Sweden with a total sample size of 6,579 revealed one locus that was associated with anhedonia in the test sample, but not in the replication sample [19]. In a Finnish study, genetic associations with physical and social anhedonia were studied in 3,820 people, but no significant loci that reached a genome-wide significance level were identified [20].

In the largest genome-wide association study (GWAS) of anhedonia in the UK Biobank cohort (*n*=375,275), 11 new loci associated with anhedonia were identified with an SNP-based heritability score of 5.6% [21]. Strong positive genetic correlations were found between anhedonia and major depression, schizophrenia, and BD, but not with obsessive-compulsive disorder or Parkinson's disease. Moreover, it was found that the genetic risk of anhedonia is associated with structures associated with the processing of reward and pleasure [21].

An important limitation of the GWAS studies is the use of phenotyping methods that evaluate anhedonia only at the current moment, and not during life (lifetime phenotype) [18–21]. This fact increases the risk of false negative responses and bias of the results, because a person with a certain genetic risk could have experienced anhedonia in the past, and not at the time of inclusion in the study. The authors however admit that people prone to anhedonia are more likely to report its manifestations at any given time, and that the "residual" phenotype of anhedonia will occur in people with a stronger genetic predisposition [21].

The aim of our study is to evaluate the genetic architecture of anhedonia and its overlap with other disorders.

Here, we present the first GWAS of the lifetime anhedonia phenotype in the Russian population, based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria for anhedonia within the framework of major depression. Additionally, we perform polygenic risk scoring with summary statistics from a published large-scale GWAS to investigate the possible associations of anhedonia with various somatic conditions and mental disorders.

METHODS

Study design

This cross-sectional study was conducted under the auspices of the Russian National Consortium for Psychiatric Genetics [22]. The study was approved by an independent ethical committee in V.M. Bekhterev National Medical Research Centre for Psychiatry and Neurology (protocol No. 7 from 22.06.2017) and by the Genotek Ltd. ethics committee (protocol No. 12 from 26.10.2019). All procedures were performed in accordance with the World Medical Association Declaration of Helsinki. All participants signed a consent to the processing of personal data before registration.

Setting

The participants were recruited continuously amongst the clients of the Russian private genetic company Genotek Ltd. Most clients contact the company to determine their genotype in order to clarify their ethnic origin, seek dietary recommendations, and enquire about predispositions to various talents or health conditions. All subjects participated voluntarily and provided their genetic information for the study. They also completed an online questionnaire with socio-demographic and medical information posted on the Genotek Ltd. website[1]. The data was collected during 2019–2020. The data analysis was performed in 2021–2022.

Participants

The study involved respondents over 18 years of age, both sexes, height from 140 to 220 cm and weight from 40 to 150 kg.

Individuals who did not meet the stated age criteria (under 18 years of age), having abnormal height and weight (beyond 140–220 cm and 40–150 kg, respectively), as well as individuals whose biological samples did not pass quality control, were excluded from the study. Of the remaining 5,795 participants, only 5,724 completed the online survey questionnaire. In addition, all pairs of close relatives (up to 3 degrees of kinship) were identified based on genetic data using PRIMUS 16 and were excluded from the study. Of the remaining 5,116 participants, 4,520 passed the GWAS quality control test (for details see Section Genotyping).

[1] Available from: http://www.genotek.ru

Procedures

Phenotyping

Phenotyping of the participants took place on the Internet using an original screening test based on DSM-5 diagnostic criteria for depressive and generalized anxiety disorders [23]. The phenotype of anhedonia was determined in the study participants using a question based on the DSM-5 criteria for anhedonia in the framework of major depressive disorder: "*Did you have a period (2 weeks or more) during which you received much less pleasure from what caused pleasure earlier?*" According to the results of the answers (yes or no), the participants were stratified by the presence or absence of the lifetime anhedonia phenotype, respectively.

Genotyping

The DNA sample was obtained from saliva, and genotyping was performed using the Illumina Infinium Global Screening Array (GSA). Genetic data was subjected to quality filtering. We eliminated samples with genetic and reported sex mismatches, low call rate (<0.98), and abnormal heterozygosity (>3 standard deviations, based on linkage disequilibrium [LD]-pruned variants). Only good-quality DNA variants were retained for the analysis using the Hardy-Weinberg equilibrium filter (pHWE >$1x10^{-5}$), call rate (>0.98), and minor allele frequency (MAF >0.01). Genotype imputation was performed using the Haplotype Reference Consortium (HRC) and 1000 Genomes reference panels using Beagle 5.1 [24–26]. Imputed variants with dosage R-squared DR^2 >0.7 were kept for the downstream analysis. Thus, the quality control was conducted according to modern criteria [27].

GWAS methodology

GWAS analysis was performed with PLINK 1.9 [28]. We employed a logistical regression model corrected for age, sex, and the first 10 principal components (Figure S1 in the Supplementary). The Manhattan and Q-Q plots were built using the library "qqman" in R.

Prior to the GWAS analysis, population stratification was assessed and outliers were eliminated. At the first step, the Multidimensional Scaling (MDS) algorithm was employed for the Russian cohort, combined with the East Asian (EAS), African (AFR), and European (EUR) subsamples of 1000 Genomes. Common SNPs were used for both datasets, after filtering for HWE and LD pruning with the parameters (window=50 SNPs, R^2 between SNPs <0.2). Based on the values of the first and second principal components, clustering was conducted using the Density-Based Spatial Clustering of Applications with the Noise algorithm [29]. Samples that did not fall within the clusters were excluded. After eliminating outliers, the MDS algorithm was re-applied (without combination with a subsample of 1000 Genomes). The first 15 components were later used as covariates to account for population stratification.

LD-blocks were defined based on SNPs with R^2 >0.7 using the "LDPair Tool", NIH, USA[2]. A single variant with minimal *p* was selected within each of these blocks, resulting in a total of 5 leading non-linked variants. The variants were annotated with SnpEff 4.3t [29], and additional information on each variant, including estimated allele frequencies (EAF), was obtained with the Database for Single Nucleotide Polymorphisms (NIH, USA[3]). Gene annotation was performed using GeneCards (Weizmann Institute of Science, Israel[4]). The methods are also described in our earlier article with the results of the Mendelian randomization analysis [30].

In addition, we used ENSEMBL POSTGAP[5] to annotate variants with *p* <$1x10^{-5}$ to the nearest genes. To find anatomical therapeutic chemical (ATC) categories enriched in the obtained gene list, we assembled a dataset of 1,716 gene-targets belonging to drugs from the 384 ATC categories present in DrugBank and performed a gene-set enrichment analysis using the package enrichR[6]. The package ABAEnrichment [31] was used to perform enrichment analysis across brain regions represented in the adult human brain transcriptome dataset from the Allen Brain Atlas database [32]. Counts of significant enrichments were visualized with the Coldcuts package (a subset of regions present in the Coldcuts segmentation was considered). The expression levels of each of the genes were obtained from the atlas for comparison. The pipeline of enrichment analyses used in the study is presented in Figure S2, A and B in the Supplementary.

[2] Available from: https://ldlink.nci.nih.gov/?tab=ldpair

[3] Available from: https://www.ncbi.nlm.nih.gov/snp/

[4] Available from: https://www.genecards.org/

[5] Available from: https://github.com/Ensembl/postgap

[6] Available from: https://cran.r-project.org/web/packages/enrichR/index.html

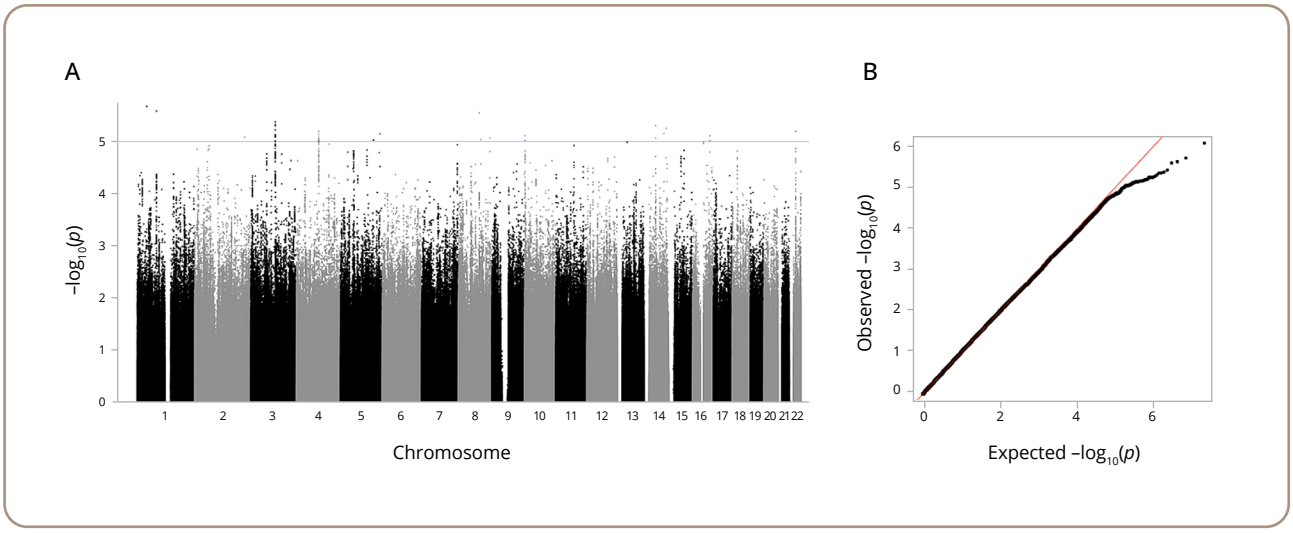

Figure 1. GWAS results of the lifetime anhedonia phenotype.

Note: (A) The Manhattan plot for the lifetime anhedonia phenotype. Association analysis *p* values for each SNP are plotted (as $-\log_{10}[p]$) vs the chromosomal position. The blue line indicates the significance level $p < 1 \times 10^{-5}$. (B) The QQ plot for the lifetime anhedonia phenotype. The QQ plot shows the observed vs expected *p*-value for every variant.

SNP-based heritability

SNP-based heritability (h^2_{snp}) was estimated as the proportion of phenotypic variance jointly accounted for by available SNPs in the GWAS studies. LDScore regression (v.1.0.1) (LDSC) was employed to estimate genetic heritability. European LD scores for SNPs were used from the 'eur_w_ld_chr/' files[7], and the estimates were based on 1,163,161 overlapping SNPs. We also present SNP heritability on the liability scale with a population prevalence of 0.3 for depression-related phenotypes [33].

Polygenic risk scoring

Polygenic risk scoring was used to dissect the genetic relationship between a lifetime anhedonia phenotype and the psychiatric disorders. We selected a range of large-scale GWAS with openly available summary statistics (SS) for psychiatric and somatic phenotypes from the Psychiatric Genomics Consortium (PGC) and UK Biobank (Table S1 in the Supplementary). The selection of psychiatric and somatic phenotypes for the analysis was dictated by the available scientific literature on the association of certain psychiatric disorders and somatic conditions with depression in clinical studies (Table S1 in the Supplementary). The variants with duplicated rsIDs and complementary alleles were discarded. The PRSice-2 software was used to generate the PRS [34]. PRS were investigated for association with a lifetime anhedonia phenotype in the dataset using a logistical regression model including five principal components. We employed the Bonferroni correction of the obtained *p*-values.

RESULTS

Sample characteristics

The study included 4,520 participants, of whom 50.4% (*n*=2,280) were female. The mean age of the participants was 36.8 (SD=9.8) years. An episode of anhedonia exceeding 2 weeks during their lifetime was reported by 57.6% (*n*=2,604) participants, of whom 53.3% (*n*=1,388) were female. At the time of the study, 11.5% (522) of participants had experienced anhedonia for two consequent weeks (current phenotype).

GWAS analysis

The GWAS on the lifetime anhedonia phenotype did not reveal variants with genome-wide significant association ($p < 10^{-8}$) (Figure 1). The leading five associated variants ($p < 10^{-5}$) are shown in Box S1 in the Supplementary. The most significant ($p = 9.71 \times 10^{-7}$) was the variant rs296009 (chr5:168513184). This SNP is in an intron of the *SLIT3* (slit guidance ligand 3) gene, and the risk allele (A) has a frequency of 0.08. The gene list obtained after linking the variants with $p < 10^{-5}$ with likely associated genes using

[7] Available from: https://data.broadinstitute.org/alkesgroup/LDSCORE

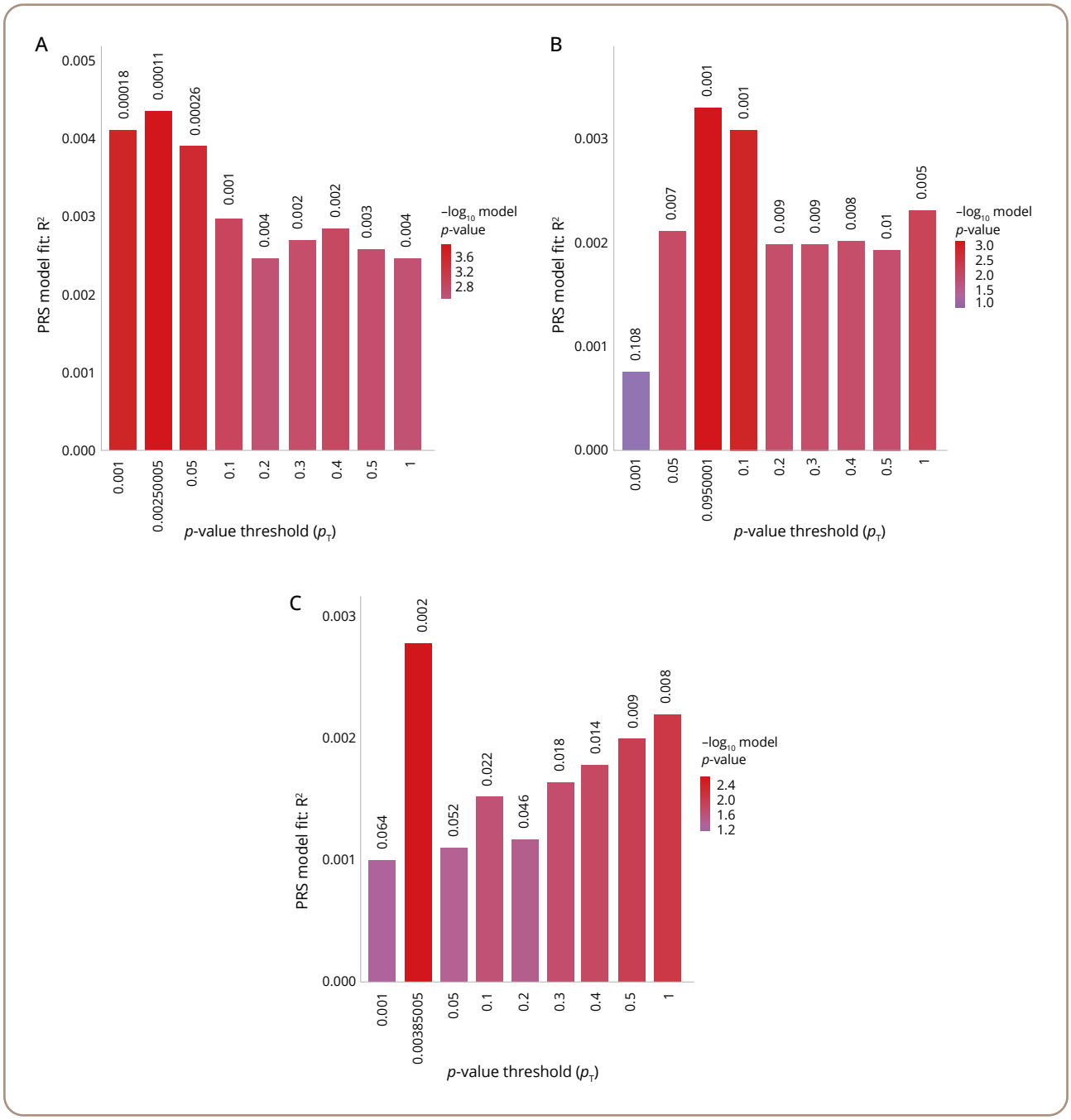

Figure 2. Polygenic risk scores for depression, bipolar disorder, and schizophrenia are significantly associated with the lifetime anhedonia phenotype.

Note: The x-axis shows the *p*-value threshold used to select SNPs from the discovery GWAS: (A) meta-analysis of depression from the PGC and UK Biobank; (B) bipolar disorder PGC; (C) schizophrenia PGC (2nd wave). The y-axis shows the percentage variance explained on the liability scale. *p*-values of the association between polygenic scores and the lifetime anhedonia phenotype are shown above each bar.

POSTGAP includes 51 genes (Box S1 in the Supplementary). Replication was not performed, because no results with a genome-wide significance level were obtained.

Enrichment analysis with targets of the ATC drug categories revealed a significant enrichment with B02B (vitamin K and other hemostatics) (*p*.adj.=0.048, Benjamini-Hochberg correction) and B02 (antihemorrhagics) (*p*.adj.=0.048, Benjamini-Hochberg correction) (Figure S2, C in the Supplementary). A single gene was driving the enrichment — *DUSP1*.

SNP-based heritability

SNP-based heritability for the lifetime anhedonia phenotype was h^2_{snp}=0.174 (SE=0.09). We also obtained liability-scale heritability considering phenotype prevalence in the population. We used approximated estimations of the prevalence of major depression during the lifetime — 0.3 [33]. Thus, for anhedonia h^2_{snp} the liability scale was 0.26 (SE=0.14). These results and their interpretation should be treated with caution due to the small sample size.

PRS analysis

Additional models with the usage of only covariates (age, sex, 15 Multidimensional scalings components for comparative assessment of genetic PRS.R^2) and other (Null.R^2) factors and complete models, considering both factor groups (Full.R^2), were built. The significance threshold with the Bonferroni correction for the psychiatric PRS analysis was 0.05/11=0.0045. As shown in Table S3 (in the Supplementary), PRS for major depression, BD, and schizophrenia were strongly associated with anhedonia, showing that the genetic liability of these disorders increases anhedonia risk. At the same time, PRS for neuroticism and anxiety were not significantly associated with anhedonia (p >0.0045). Nevertheless, nominal significance for neuroticism was noted.

The most significant models of PRSs regarding the prognosis of anhedonia among the three disorders were obtained with the meta-analysis GWAS summary statistics for depression from PGC and UK Biobank (PRS.R^2=0.00436498, Full.R^2=0.0295311, p=0.00011262), BD from PGC (PRS.R^2=0.00329757, Full.R^2=0.0284637, p=0.000785365), and schizophrenia from PGC, second wave (PRS.R^2=0.00276988, Full.R^2=0.02793, p=0.00208176). The quantitative characteristics of the most significant PRSs are shown in Figure 2.

As shown in Table S4 (in the Supplementary), none of the PRS for somatic phenotypes reached the significance level after correction for multiple comparisons (p >0.05/17=0.003). The nominal significance for the association of the lifetime anhedonia phenotype was determined for omega-3 fatty acids, type 2 diabetes mellitus, Crohn's disease, and ischemic stroke.

Enrichment analyses

Enrichment analysis with the ABA Enrichment package using the set of 51 genes associated with the variants with p <10^{-5} by POSTGAP shows the highest count of significant enrichments (n=4) in the posterior orbital gyrus (Table S5 in the Supplementary). The region with the smallest minimal family-wise error rate (FWER) with 3 significant enrichments was located in the retrosplenial part of the left cingulate gyrus. Comparison between the expression levels of the genes across the brain regions are shown in Figure S2 (D, E) in the Supplementary. The ATC drug category most significantly enriched in the gene set was B02B — vitamin K and other hemostatics (Table S6, Figure S2 (C) in the Supplementary).

DISCUSSION

This study is the first Russian GWAS of the lifetime anhedonia phenotype based on its DSM-5 criteria of major depression. According to the data of the RDoC transdiagnostic approach, we found that the polygenic component for major depression, BD, and schizophrenia had increased the risks of lifetime anhedonia phenotype. However, we did not find that PRS of somatic conditions could significantly predict the lifetime anhedonia phenotype.

PRS for major depression, BD, and schizophrenia, with the exception of neuroticism and anxiety disorders, were significantly associated with the lifetime anhedonia phenotype. Similar associations were revealed in the largest GWAS of anhedonia of UK Biobank participants [21]. The absence of a genetic link between anhedonia and anxiety disorders aligns well with existing clinical data, where anhedonia is considered a key symptom in the differential diagnosis of major depression and anxiety disorders [16, 35]. However, there is evidence that neuroticism can contribute to anxiety and anhedonia in patients with major depression [36]. The nominal significance for the association of the lifetime anhedonia phenotype was determined for omega-3 fatty acids, type 2 diabetes mellitus, Crohn's disease, and ischemic stroke, which had been previously confirmed in systematic reviews and meta-analysis of depression [37–40].

Despite the lack of genome-wide significant variants associations with the lifetime anhedonia phenotype in our study, some of the loci identified here include genes with known associations with mood disorders and metabolic phenotypes (Table S2 in the Supplementary). The rs296009 polymorphism of the *SLIT3* gene, the most significant SNP in our study, had not been previously reported in the published GWAS. However, other polymorphisms of this gene have been associated with BD (rs7720655) [41], treatment-resistant depression (rs7735612) [42], as well

as with cardiometabolic disorders during antidepressant therapy in patients with schizophrenia and BD (rs17665285) [43], leptin level (rs11954861 and rs11954861) [44], height (rs2974438), and body mass index (BMI) (rs76493495) [45, 46]. The rs577951495 polymorphism of the *NECAB1* gene had also not been previously detected in published GWAS studies. However, other polymorphisms of this gene were associated with the lifetime smoking index (rs2062882) [47], age of first sexual intercourse (rs3591843) [48], as well as the level of education and Alzheimer's disease (rs12675931) [49].

High estimates of SNP-based heritability of anhedonia, similar to ours, have been obtained in other studies: 69% [18], 20% [19], 20.4–26.6% [20]. Estimates of SNP-based heritability relate to the data of twin studies in which the heritability level of anhedonia amounted to 44% [50]. At the same time, the lowest SNP-based heritability level (5.6%) was observed in the UK Biobank study with the largest sample size [21]. Such differences can be explained by the characteristics of phenotyping; namely, the use of the lifetime anhedonia phenotype in our study. The bias in the calculation of SNP-based heritability results could also be affected by a small sample size (<5,000).

The set of 51 variants associated with anhedonia with a suggestive threshold (p <10^{-5}) with POSTGAP was significantly overrepresented in the ATC drug category B02B (p.adj.=0.048), which includes vitamin K and other hemostatics, due to *DUSP1* — one of the genes the expression of which is affected by vitamin K[8]. This vitamin has been implicated in the regulation of the sphingolipid metabolism and is protective against oxidative stress in the brain. It has been shown that higher dietary vitamin K intake was significantly associated with a lower level of depressive symptoms, including the fact that individuals with the highest dietary vitamin K intake had lower odds of depressive symptoms (OR=0.58; 95%CI: 0.43–0.80) [51]. Mice with deletion of *DUSP1*, in turn, are resilient to stress-induced depression [52]. Vitamin K3 decreases the expression of *DUSP1,* and overexpression of this gene significantly increases cellular susceptibility to oxidative damage [53]. Thus, the antidepressant and anti-oxidative effects of vitamin K could be partially associated with this gene interaction.

Enrichment analysis showed the highest degree of significant enrichment in the posterior orbital gyrus in our study. The posterior orbital gyrus receives inputs from the limbic regions (i.e., amygdala, hippocampus, olfactory cortex, and insula) and plays an important role in processing the olfactory and integration of emotions and memories associated with sensory experiences [54]. According to neuroimaging studies, parts of the orbital gyrus are associated with various manifestations of anhedonia and major depression [21, 55–57].

In summary, ours and other results indicate that anhedonia is a widespread phenomenon in the population, with a complex polygenic architecture that overlaps with a number of phenotypically similar mental disorders and somatic conditions. Moreover, the results of our anhedonia GWAS have significantly enriched our understanding of its biological mechanisms, which for a long time have been associated only with the dopaminergic reward system. Nevertheless, despite repeated attempts at genetically connecting anhedonia with mood disorders and schizophrenia, it remains premature to assert that the mechanisms triggering anhedonia are shared. To demonstrate such patterns, GWAS studies using deep phenotyping of anhedonia are required, considering its clinical characteristics, as well as a subsequent analysis of the biological risk of pathways enrichment. The study of the genetic overlapping of anhedonia and somatic diseases can help in understanding the relationship of these diseases with mental disorders.

Limitations

This study has a range of limitations. The main limitation is its small sample size, which is critical for identifying the variants with genome-wide significance. This could also be the reason for the lack of replication of our GWAS results in an independent sample. The second limitation is the heterogeneity of the anhedonia phenotype considered here: subtypes of anhedonia based on origin (physical/social, consummatory/anticipatory) were not considered. The study sample was assembled on the basis of the clients of a private genetic testing company, which could affect the socio-demographic characteristics of the participants as compared to the general population. Nevertheless, we believe that our results are relevant for a wide range of future studies, including replication analyses for GWAS on a wide range of psychiatric conditions, of which anhedonia is one.

[8] Available from: http://ctdbase.org/

CONCLUSION

Anhedonia has a complex polygenic architecture that overlaps with a number of other phenotypically similar psychiatric disorders and somatic conditions. This study demonstrates that genetic liability for schizophrenia, BD, and major depression increases the risk of a lifetime anhedonia phenotype. At the same time, we did not uncover common genetic factors between anxiety and anhedonia, which aligns well with existing clinical evidence. In addition, none of the PRS for somatic phenotypes reached the significance level after correction for multiple comparisons. Thus, the best predictive models were based on summary statistics of mental disorders. This fact may indicate that the appearance of anhedonia in somatic disorders or normal conditions may develop due to a genetic predisposition to mood disorders or schizophrenia. Further collaborative efforts to study the transdiagnostic nature of anhedonia would make it possible to identify reliable genetic associations and improve our understanding of the etiology of anhedonia.

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Supplementary data

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Data Availability Statement

The user agreement[9] states that disclosure of individual-level genetic information and/or self-reported Information to third parties for research purposes will not occur without explicit consent. Due to the user agreement the individual level cannot be made directly available to scientific community but have to be accessed indirectly via Genotek Ltd.

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Individual Burden of Illness Index in Bipolar Disorder Remission: A Cross-Sectional Study

Индекс индивидуального бремени болезни при ремиссии биполярного аффективного расстройства: результаты кросс-секционного исследования

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Original research

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ABSTRACT

BACKGROUND: A population-based method for estimating disease burden is commonly used. Nevertheless, these measurements do not entirely capture the comprehensive burden of illness on an individual patient. To address the problem, the Individual Burden of Illness Index (IBI index) Index was created and validated, specifically for major depressive disorder. The IBI represents the overall influence of the condition, encompassing distress from symptom intensity, functional impairment, and the patient's quality of life.

AIM: The aim of the study was to approve and validate the IBI index for the integral assessment of disease burden in patients with bipolar disorder (BD) in remission.

METHODS: The cross-sectional study was conducted in the outpatient psychiatric services in Saint Petersburg, Russia, from April through October 2020. Eighty-five patients aged 18 to 45 (mean age 36.6±5.7 years) with BD (type I — 75%, *n*=64; type II — 25%, *n*=21) in remission were examined. The study procedure included a structured clinical interview and the use of clinical scales: the World Health Organization's Quality of Life Questionnaire, Hamilton Rating Scale for Depression (HDRS), Young Mania Rating Scale (YMRS), and Personal and the Social Performance Scale.

RESULTS: The principal component analysis in accordance with the adjusted one showed that the burden of illness in patients with BD in remission is directly related to the severity of residual depressive symptoms, reflected in the HDRS

score: as the HDRS score increases (0.27, p <0.001), residual mania (-0.14, p <0.001), social functioning (-0.06, p <0.001), and quality of life (-0.04, p <0.001) decrease. In contrast, when there are remaining residual mania symptoms, as indicated by the YMRS score, the result tends to be a lower burden, better social functioning, and enhanced quality of life.

CONCLUSION: The study has demonstrated through statistical means a successful adaptation and validation of the previously calculated IBI index for patients with BD in remission. Residual affective symptoms were shown to have different impacts on the social functioning of patients with BD in remission, indicating the need for a timely assessment and targeted therapy of these symptoms in such patients.

АННОТАЦИЯ

ВВЕДЕНИЕ: С целью оценки бремени болезни обычно используют популяционный метод, однако такой подход не может в полной мере отразить индивидуальное бремя болезни (ИББ) для конкретного пациента. Для решения этой проблемы у пациентов с большим депрессивным расстройством был создан и валидирован индекс ИББ. Индекс ИББ отражает общее влияние заболевания, охватывая дистресс от интенсивности симптомов, функциональные нарушения и качество жизни пациента.

ЦЕЛЬ: Целью исследования было апробировать и валидировать индекс ИББ для интегральной оценки бремени болезни у пациентов с биполярным аффективным расстройством (БАР) в ремиссии.

МЕТОДЫ: Одномоментное исследование проводили на базе амбулаторной психиатрической службы г. Санкт-Петербурга в период с апреля по октябрь 2020 года. Обследовано 85 пациентов в возрасте от 18 до 45 лет (средний возраст 36,6±5,7 года) с БАР (I тип — 75%, n=64; II тип — 25%, n=21) в ремиссии. Процедура исследования включала структурированное клиническое интервью и использование таких клинических шкал, как Опросник качества жизни Всемирной организации здравоохранения, Шкала Гамильтона для оценки депрессии (Hamilton Depression Rating Scale, HDRS), Шкала мании Янга (Young Mania Rating Scale, YMRS), Шкала личностного и социального функционирования.

РЕЗУЛЬТАТЫ: Анализ главных компонент в соответствии с корректировкой показал, что бремя болезни у пациентов с БАР в ремиссии напрямую связано с выраженностью резидуальных депрессивных симптомов, отражённых в баллах HDRS: при увеличении балла HDRS (0,27, p <0,001) снижаются остаточные проявления мании (-0,14, p <0,001), снижаются показатели социального функционирования (-0,06, p <0,001) и качества жизни (-0,04, p <0,001). Напротив, при наличии резидуальных симптомов мании по шкале YMRS, как правило, снижается индивидуальное бремя болезни, улучшается социальное функционирование и повышается качество жизни.

ЗАКЛЮЧЕНИЕ: В ходе исследования при помощи статистических методов была продемонстрирована успешная адаптация и валидация ранее рассчитанного индекса ИББ для пациентов с БАР в ремиссии. Резидуальные аффективные симптомы оказывают различное влияние на функционирование пациентов с БАР в ремиссии, что свидетельствует о необходимости своевременной оценки и целенаправленной терапии этих симптомов у таких пациентов.

Keywords: *residual symptoms; quality of life; burden of disease; bipolar disorder*
Ключевые слова: *резидуальные симптомы; качество жизни; бремя болезни; биполярное аффективное расстройство*

INTRODUCTION

Bipolar disorder (BD) is a mental disorder that causes impairments in the functionality of daily life, resulting in substantial burdens upon affected individuals, their caregivers, and society at large [1, 2]. Despite the therapeutic advances achieved to date, BD remains one of the mental

disorders with the severest burden around the world [3]. People with BD often experience difficulties in psychosocial and occupational functioning, as well as cognitive impairment, and they are characterized by a reduced quality of life [4, 5]. Disfunction in psychosocial functioning have been demonstrated in 30–60% of adults with BD [6] and in 10–15% of patients with BD in remission [7]. Functioning impairments affect various spheres of the lives of patients with BD, such as work, communication, family relationships, recreation, as well as other social activities [8, 9]. Some data indicate that even with complete clinical remission, in 30–50% of patients with BD the premorbid level of psychosocial functioning is not restored, which leads to a reduced ability to assume a normal workload [10]. According to MacQueen et al., 30–60% of patients with BD experience social and occupational difficulties [11]. There is some indication that social adaptation proceeds better in patients with a higher level of education who enjoy the presence of a family or are in a civil marriage, with a shorter duration of the disease [12]. Mood fluctuations and shattered self-esteem are present in patients with BD in remission [13]. Residual symptoms and impairments in social cognition negatively affect the psychosocial functioning of patients with BD [5]. Clinically euthymic patients with BD continue to show impaired Quality of Life (QOL) [14], which is attributed to residual depressive and cognitive symptoms [15].

The concept of burden of illness (BOI) is used to assess the impact of health-related problems at the individual and social levels [16]. Researchers distinguish between the epidemiological (encompassing both the years of life lost due to the disease as well as the morbidity) and economic (direct and indirect costs as well as health care resource utilization) burden of the illness [17]. A population-based approach to estimating the burden of the disease using measurements such as Quality of Life Adjusted Years (QALY) [18] and Disability Adjusted Years (DALY) [19] is widely used; however, these measurements are not fully applicable to an individual patient's experience of the full burden of illness [20]. In this regard, the development of an individualized means of assessment of the burden of illness appears relevant.

The concept of the Individual Burden of Illness Index (IBI index) was first proposed by Ishak et al. [20]. The IBI index was specifically designed and validated for major depressive disorder [20], and its constituent parts have undergone initial validity testing and are recommended for assessing the functional remission status of patients with recurrent depression in Russia [21]. The use of the index in patients with BD would allow one to objectify their functional state on the basis of an integral assessment.

The aim of this study was to approve and validate the IBI index for the integral assessment of disease burden in patients with BD in remission (IBI-BD index).

METHODS

Study design

A cross-sectional study was conducted.

Setting

The study was conducted in the outpatient psychiatric services of Psychiatric Hospital No. 1 named after P.P. Kaschenko in Saint Petersburg, Russia. The patients in the study were recruited from April through October 2020. The patients were examined during the follow-up period in a community treatment setting to prevent disease relapse.

Participants

General information

Although only a small number (5%) of patients in the original study by Ishak et al. [20] were in remission, since there are no other studies concerned with validation of the IBI index in patients with BD, in the current research, the authors chose to concentrate on patients with BD in remission. This decision was dictated by the widespread interest in evaluating the functioning of individuals with BD during remission, as well as the impact of lingering residual mood symptoms on their overall functioning [22].

Eligibility criteria

The inclusion criteria were

- compliance of the patient's mental state with BD remission according to International Classification of Diseases-10 (ICD-10);
- symptom severity less than 7 points on the Hamilton Depression Rating Scale (HDRS) [23];
- symptom severity less than 12 points on the Young Mania Rating Scale (YMRS) [24].

The non-inclusion criteria were

- the presence of a comorbid psychiatric disorder;
- the presence of an actual somatic disease or exacerbation of a chronic disease.

The exclusion criteria were

- patients' refusal to participate in the study at any stage;
- identification of signs of a comorbid mental and/or substance use disorder during the clinical interview.

The criteria for remission assessment were based on the clinical guidelines for the treatment of BD approved in Russia[1].

Selection of participants in groups

Eighty-five patients with BD type I (75%; *n*=64) and BD type II (25%; *n*=21) in remission were examined.

Variables

The outcome is the calculation of an IBI-BD index, which can take any positive or negative value (for more information see Table S1 in the Supplementary).

Data sources/measurement

General information

The invitation to participate in the study was extended to patients with a confirmed diagnosis of BD by the psychiatrists who provided supportive treatment in the community. After securing patient consent to participate in the study, a face-to-face meeting between the patient and the psychiatrist-researcher (who was not involved in the treatment of the patient) was arranged at the outpatient psychiatric center. Participation in the study involved a one-time clinical interview with a psychiatrist-researcher with a structured interview and the use of clinical scales. The structured interview included the collection of socio-demographic characteristics (sex, age), as well as age of onset, and duration of the disease. During the clinical interview, a psychiatrist-researcher had to confirm that the patient met the criteria for a diagnosis of BD. Since there is no differentiation between BD types I and II in ICD-10 but their diagnosis is determined by an important stage of treatment planning according to clinical recommendations in Russia[1], the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM, 5th Edition) criteria were used to confirm the type of BD. The study was conducted in Russian.

Individual Burden of Illness Index adaptation

The process of IBI-BD index adaptation preceded the patient recruitment phase of the study and the validation of the index. Although other methodologies were used in Ishak's original study [20] (Quick Inventory of Depressive Symptomatology-Self Report, QIDS-SR, for depressive symptom severity; the Work and Social Adjustment Scale, WSAS, for functioning; and the Quality of Life Enjoyment and Satisfaction Questionnaire — Short Form, Q-LES-Q, for quality of life), the authors of the present study elected to replace them, because the methodologies from the original study, to the best of the authors' knowledge, had not been previously translated and validated for use in the Russian-speaking population. The methodologies chosen by the authors of this study on the contrary are widely used in the practice of psychiatry in Russia [25–29], not least because they are covered by clinical guidelines[1], meaning that their use in clinical practice will not require additional time resources.

The World Health Organization (WHO) describes QOL as how people perceive their existence in light of the cultural and value norms surrounding them, considering their aspirations, expectations, standards, and worries[2]. This concept encompasses various aspects, such as physical well-being, emotional state, individual beliefs, personal autonomy, social connections, and the living conditions they experience [30]. The WHO's Quality of Life Questionnaire, (WHOQOL)[2] was used to assess the QOL. The WHOQOL-100 is an extensive version of the WHOQOL assessment tool designed to provide a detailed and comprehensive understanding of an individual's QOL within their specific cultural, social, and personal contexts. The WHOQOL-100 consists of 100 questions. Specifically, the scale generates six domain scores, 24 specific facet scores, and a single overall score that assesses general health and quality of life. The six domain scores capture an individual's self-reported quality of life across six key areas: physical, psychological, level of independence, social relationships, environment, and spirituality. Each domain and facet scores are scaled in a positive direction, with higher scores indicating a higher quality of life.

[1] Ministry of Health of the Russian Federation. Bipolar affective disorder; 2021 [cited 10 November 2023]. Available from: https://cr.minzdrav.gov.ru/schema/675_1. Russian.

[2] World Health Organization. (1998). Programme on mental health: WHOQOL user manual, 2012 revision. World Health Organization, editor. [cited 10 November 2023]. Available from: https://iris.who.int/handle/10665/77932

The severity of affective symptoms was assessed using the HDRS and the YMRS as reflected in the clinical guidelines for the diagnosis and treatment of BD[1]. The HDRS is a widely used clinician-administered scale for assessing the severity of depressive symptoms in individuals with major depressive disorder or other mood disorders. The HDRS consists of 21 items that evaluate various aspects of depression, such as mood, cognitive symptoms, somatic symptoms, and suicidal ideation. The scale ranges from 0 to 53, with higher scores indicating more severe depressive symptoms. The YMRS is an 11-item clinician-rated scale specifically designed to assess the severity of manic or hypomanic symptoms in individuals with BD or other mood disorders. The YMRS evaluates various aspects of mania, such as mood elevation, irritability, and behavioral disturbances. The scale ranges from 0 to 60, with higher scores indicating more severe manic symptoms. The HDRS and YMRS are useful tools for monitoring the progress of patients in treatment and evaluating the efficacy of interventions.

To assess social functioning, the Personal and Social Performance Scale (PSP) was used [31]. PSP is an instrument designed to assess the functional outcomes and social adjustment of individuals with severe mental disorders assessed over the past 7 days in 4 main areas of social functioning: socially useful activities, relationships with relatives and other social relationships, self-care, and disturbing and aggressive behavior. Scores are given on a scale from 1 to 100, divided into 10 equal intervals, where each interval corresponds to a certain degree of difficulty in social functioning. Higher scores indicate higher levels of functioning.

Bias

No factors were used to stratify the sample. Remission boundaries were chosen according to the recommended cut-off points[1]. Since it was assumed that any level of quality of life and social functioning could be in remission, no cut-off points or groupings were used for these characteristics.

Statistical analysis

Study size

Since no similar studies have been conducted for patients with BD, it was not possible to perform the target sample size calculations. Therefore, we opted for empirical rules of thumb to determine the sample size. We defined a threshold of at least 80 observations, which is double the minimum sample size value [32].

Statistical methods

Statistical analysis was performed using the R v.3.6.1. (R Core Team, 2020). The mathematical and statistical analysis was performed by a bio-medical statistician who was not involved in data collection and only had access to numerical measures. Absolute values and fractions of the whole, *n* (%), were used to describe categorical variables. Variables with continuous distribution were described by mean (Mean) and standard deviation (SD); discrete variables and ordered data — by median, 1–3 quartiles (Md [Q1; Q3]). The normality of sample distribution was evaluated using the Shapiro–Wilk test and considered when choosing a method. Data were normally distributed, except where specified otherwise. We used Chi Square (χ^2) tests for categorical variables. The Mann–Whitney test was used to compare quantitative data. Correction for multiple hypothesis testing was performed using the Benjamini–Hochberg correction (false discovery rate).

The Kaiser–Meyer–Olkin criterion and Bartlett's sphericity criterion were used to measure sampling adequacy. The index was calculated using principal component analysis (PCA). The aim of PCA is to extract important information from the observed variables and represent it as a set of new orthogonal variables called principal components. In contrast to describing the variables separately, the data reduction technique provides a composite description of the observed pattern of values. Since scale scores by their nature belong to the ordered scale [33], a nonlinear version of PCA [34], which is implemented in the Gifi package[3], was used. A linear transformation of the original data was performed to extract the two components. The resulting eigenvalue was used to estimate the explained variance, and loadings showed the contribution of each variable to the extracted components. The validity of component extraction was also verified. For this purpose, a null distribution was generated from the original data by sequentially shuffling the data in each column independently (the so-called permutation of a single variable strategy) [35]. A total of 999 iterations were performed (separately for each variable), and the starting value of the random number generator (set. seed)

[3] Mair P, De Leeuw J. Gifi: Multivariate Analysis with Optimal Scaling; 2019. Version: 0.3-9. [cited 10 November 2023]. Available from: https://CRAN.R-project.org/package=Gifi

Table 1. Socio-demographic and clinical and scale characteristics of patients with BD types I and II

Parameter	BD type I (*n*=64)	BD type II (*n*=21)	Statistical test
Age (Mean [SD])	37.3 [6.5]	34.5 [6.8]	t=842, df=84, *p*=0.195
Age of the BD onset (Mean [SD])	27.4 [4.6]	27.1 [5.5]	t=692, df=84, *p*=0.982
Duration of the disorder (Mean [SD])	9.9 [5.0]	7.3 [4.3]	t=885.5, df=84, *p*=0.171
Sex, *n* (%)			
Male	24 (37.5%)	5 (23.8%)	χ^2=0.8, df=1, *p*=0.377
Female	40 (62.5%)	16 (76.2%)	χ^2=0.8, df=1, *p*=0.377
HDRS (Md [Q1; Q3])	3.0 [2.0; 4.0]	2.0 [2.0; 4.0]	U=776.5, *p*=0.394
YMRS (Md [Q1; Q3])	2.0 [1.75; 3.0]	2.0 [2.0; 3.0]	U=670.5, *p*=0.992
WHOQOL (Md [Q1; Q3])	63.5 [59.4; 68.4]	66.8 [60.3; 69.8]	U=560.5, *p*=0.394
PSP (Md [Q1; Q3])	75.5 [73.0; 79.0]	79.0 [75.0; 81.0]	U=479.0, *p*=0.171

Note: BD — bipolar disorder; HDRS — Hamilton Depression Rating Scale; YMRS — Young Mania Rating Scale; WHOQOL — World Health Organization's Quality of Life Questionnaire; PSP — Personal and Social Performance Scale. Benjamini–Hochberg multiple comparison correction was used in the calculations.

was 4,321. The observed eigenvalue was compared with the obtained null distribution. In this case, the one-tailed hypothesis about the superiority of the observed value over the center of the null distribution is tested [36]. Usually, the *p*-value is calculated as (q+1)/(i+1), where "q" is the number of values from the null distribution that are greater than or equal to the observed value, and "i" is the number of iterations performed [37]. Since the one-tailed backward hypothesis can be tested, a two-tailed *p*-value was calculated to ensure a more reliable result. Only those components that were significantly greater than the null distribution were selected for further analysis. "1" was added to the numerator and denominator, because the *p*-value during the Monte Carlo permutation cannot be equal to zero [38].

Linear regression was used for simple conversion of initial scores into the final index. It was tested for the conformity of the residuals to the normal distribution (Shapiro–Wilk test) and homoscedasticity (Breush–Pagan test) [39]. To assess the influence of the BD type and clinical and functional characteristics, separate logistic regressions (proportional odds logistic regressions) without interaction between independent variables were used. The rationale for using this model instead of the classical linear model is based on two considerations. Since the IBI-BD for these patients is calculated for the first time, the assumptions of normality of distribution and homoscedasticity are both strong and optional. The robustness of the model is due to the use of only guaranteed ordering information, which is invariant to any monotonic transformation [40]. The model with predictors was compared with the model without predictors using the log-likelihood test. Regression coefficients and their standard error (b(se)) are presented as the logarithm of the odds ratio [log(odd)]. Null hypotheses were rejected at $p < 0.05$, with additional attention paid to results where null hypotheses were rejected at $p < 0.005$.[4]

Ethical approval

Patients were included in the study after signing an informed voluntary consent form. The study protocol was approved by the Ethical Committee of Saint Petersburg State University (Protocol No. 02-195; March 16, 2020).

RESULTS

Participants

Eighty-five patients with BD type I (75%; *n*=64) and BD type II (25%; *n*=21) in remission were examined. The study sample consisted of 29 males and 56 females, aged from 18 to 45 (mean age 36.6±5.7 years).

Descriptive data

The main sociodemographic characteristics of the sample and the results of the scale score are summarized in Table 1. These data are in fact descriptive statistics of the

[4] R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2020. Version: 3.6.1. [cited 10 November 2023]. Available from: https://www.r-project.org/

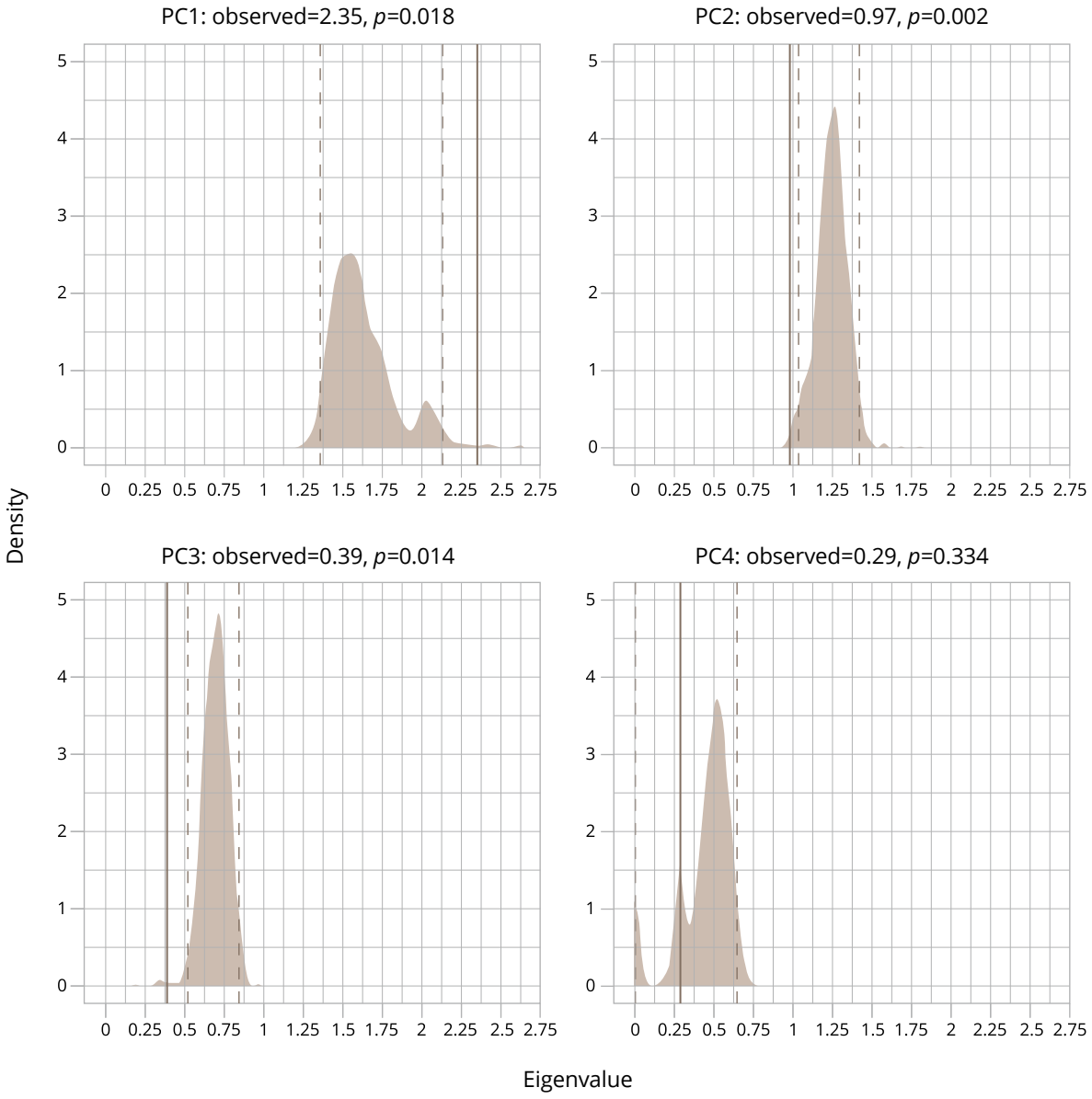

Figure 1. A graphical representation of the eigenvalue comparison with the null distribution by the bootstrap method in the sample.

Note: PC — principal component; *p* — *p*-value; shade area — null distribution; solid line — observed eigenvalue; dashed line — 95% confidence interval under null distribution.

IBI-BD index. Patients' age, age of onset, disease duration, sex distribution, and mean values of the scale scores did not differ between the comparison groups; so, further analysis was performed on the entire sample without taking into account the BD type. The mean value of social functioning on the PSP scale in the sample corresponded to the presence of mild difficulties in one or more of the areas of social functioning.

Main results

Factors contributing to the burden of illness in bipolar disorder

At baseline, the Kaiser–Meyer–Olkin criterion: overall MSA=0.66; YMRS — 0.61; HDRS — 0.63; WHOQOL — 0.77; PSP — 0.64 (all values exceed the mediocre level); and Bartlett's sphericity criterion — 98.67 (6), p <0.001. The mean scores of the HDRS, YMRS, PSP, and WHOQOL-100

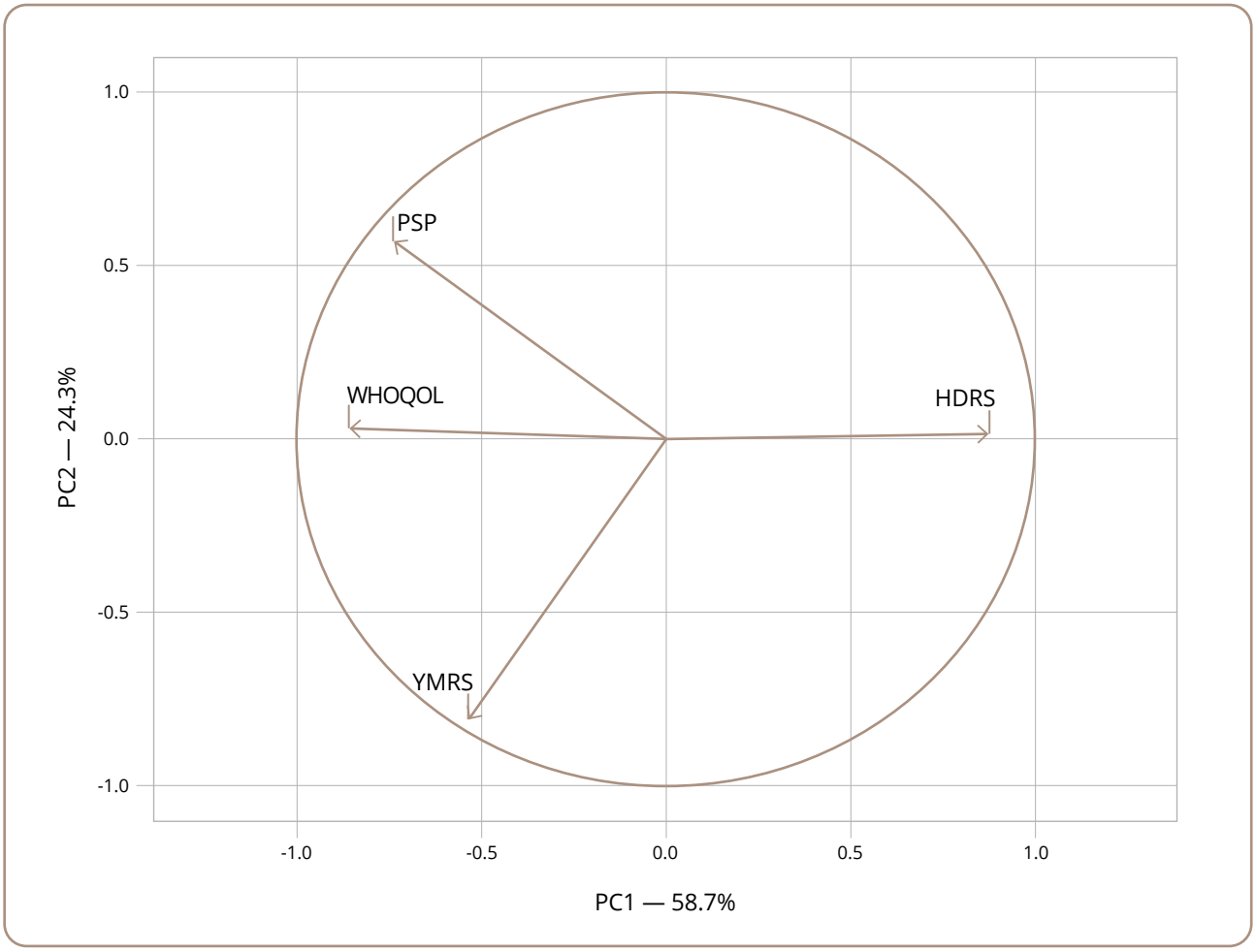

Figure 2. The loading plot of the burden of illness in patients with BD in remission.

Note: HDRS — Hamilton Depression Rating Scale; YMRS — Young Mania Rating Scale; WHOQOL — World Health Organization's Quality of Life Questionnaire; PSP — Personal and Social Performance Scale; PC – principal component.

were included in the analysis of the factors contributing to the burden of illness in BD in remission. A graphical representation of the eigenvalue comparison with the null distribution by the bootstrap method is presented in Figure 1. According to the data obtained during the enumeration, the eigenvalue of the principal component 1 (PC1) exceeds the upper limit of the 95% confidence interval of the null distribution. The observed values for the other components either do not exceed the boundaries of the null distribution or are on its lower boundary. Since the values exceeding the "noise data" are the ones of interest, only PC1 values were used in further analysis.

Principal component analysis in accordance with the adjusted variables is presented in Figure 2. The loading plot in Figure 2 shows that the burden of illness in remission is directly related to the severity of residual depressive symptoms (as the HDRS score increases, social functioning and quality of life decrease). Conversely, the presence of residual mania symptoms (YMRS score) is associated with a lower burden and higher level of social functioning and quality of life. The burden index explains 58.7% of the variance in the data (X-axis).

To calculate the IBI-BD index directly, we can use the equation from Table 2. The table shows the linear regression coefficients by which the scale scores should be multiplied. The obtained values are added up, and a constant is added. Thus, the equation for calculating the IBI-BD index looks as follows:

$$\text{IBI-BD index} = 6.64 + (-0.14 \times \text{YMRS}) + (0.27 \times \text{HDRS}) + (-0.04 \times \text{QOL}) + (-0.06 \times \text{PSP})$$

Table 2. Equation for calculating the IBI index for patients with BD in remission

Variable	Statistic	*p*-value
(Intercept)	6.64 (0.69)	p <0.001
YMRS	-0.14 (0.03)	p <0.001
HDRS	0.27 (0.03)	p <0.001
WHOQOL	-0.04 (0.00)	p <0.001
PSP	-0.06 (0.01)	p <0.001
Shapiro–Wilk test	W=0.98	p=0.193
Breusch–Pagan test	χ^2=7.8 (df=4)	p=0.101
Fisher test	F=207.5 (4; 80)	p <0.001
The coefficient of determination (adj.)	R^2=0.91	-

Note: IBI — Individual Burden of Illness; BD — bipolar disorder; HDRS — Hamilton Depression Rating Scale; YMRS — Young Mania Rating Scale; WHOQOL — World Health Organization's Quality of Life Questionnaire; PSP — Personal and Social Performance Scale.

Table 3. Assessment of the impact of the estimated characteristics on the IBI-BD index

Variable	Model test	BD type I vs BD type II; log(odd)(se), *p*	Key — log(odd)(se), *p*
Sex	χ^2=4.9 (df=72), p=0.084	-	-
Age	χ^2=18.2 (df=72), p <0.001	-0.77 (0.48), p=0.109	0.11 (0.03), p <0.001
Age of BD onset	χ^2=5.3 (df=72), p=0.079	-	-
Duration of the disorder	χ^2=22.5 (df=72), p <0.001	-0.49 (0.49), p=0.316	0.18 (0.04), p <0.001
YMRS	χ^2=31.0 (df=72), p <0.001	-0.90 (0.47), p=0.057	-0.88 (0.18), p <0.001
PSP	χ^2=63.0 (df=72), p <0.001	-0.23 (0.46), p=0.619	-0.39 (0.06), p <0.001
HDRS	χ^2=94.6 (df=72), p <0.001	-0.67 (0.48), p=0.162	1.49 (0.18), p <0.001
WHOQOL	χ^2=51.0 (df=72), p <0.001	-0.65 (0.48), p=0.174	-0.19 (0.03), p <0.001

Note: IBI — Individual Burden of Illness; BD — bipolar disorder; HDRS — Hamilton Depression Rating Scale; YMRS — Young Mania Rating Scale; WHOQOL — World Health Organization's Quality of Life Questionnaire; PSP — Personal and Social Performance Scale; Benjamini–Hochberg multiple comparison correction was used in the calculations.

This model satisfies the theoretical premises of linear regression (according to insignificant Shapiro–Wilk and Breusch–Pagan tests). Also, the linear model relates well the initial values with the final indicator (coefficient of determination >0.9). This equation allows for a quick calculation of the IBI-BD index value in case of lack of access to baseline data or inability to perform PCA. Because the IBI-BD index is based on a z-score, it is easy to calculate a patient's burden of illness relative to other patients with BD in remission. An IBI-BD index with a negative value indicates that the patient has a lower disease burden compared to the average patient seeking treatment, whereas an index with a positive value indicates that the patient's disease burden is higher.

The assessment of the influence of the evaluated characteristics on the IBI-BD index is presented in Table 3. The search for the dependence of the IBI-BD index on the main clinical and demographic characteristics was performed using proportional odd logistic regression, taking into account the diagnostic group. According to the obtained data, the sex and age of disease onset could not be associated with IBI-BD, as no superiority of the analyzed models over the models without predictors was revealed. The other indicators were statistically significantly associated with IBI-BD. In each model, the regression coefficient describing the intergroup difference is not different from zero (p >0.05). This implies that no significant intergroup difference in IBI between BD type I and BD type II diagnoses can be inferred. Patients' age [log(odd)=0.11(0.03)], as well as disease duration [log(odd)=0.18(0.04)], was directly related to the IBI-BD index value. The directions of association of the last four indicators do not differ from those in linear regression modeling (see Table 2).

DISCUSSION

Key results

The present study focuses on the approval and validation of the IBI index in patients with BD in remission, which was previously developed and validated for major depressive disorder. To the best of the authors' knowledge, this is the first time such work has been done. The IBI-BD index is a simple multidimensional metric based on patient-reported outcomes used to describe the complexity of affective disorder as an illness, including the burden it imposes on the individual by incorporating symptoms' severity, functioning, and QOL impairments [41]. The research yielded important findings for clinical practice, most notably the fact that residual depressive and manic symptoms differentially affect functioning and quality of life in individuals with BD in remission. Moreover, the BD type does not make an additional contribution to this state of affairs. And the validated IBI-BD index could be applied in clinical practice for a more personalized assessment of the BD in remission individual disease burden.

Strengths and limitations

A key strength of this study is that to the best of our knowledge it is the first study to address the individual burden of illness for patients with BD in remission. Another advantage is that the study included patients with both types of BD. We recognize, however, that the study has a number of potential limitations. The cross-sectional design of the study is among the limitations. The authors are aware that the sample size is rather small. However, the analysis showed statistically reliable results and the ability to draw conclusions even with such a sample. The research was conducted on patients in remission, which means the results cannot be directly applied to all individuals with BD.

The set of scales used in the present study differs from the original study [20], but the authors believe this discrepancy probably did not compromise the integrity of the findings. The instruments for calculating the IBI replacement are justified for the following theoretical reasons: undoubtedly, the concept of the IBI itself is theoretical and the options for its computation may not be limited to baseline scales or baseline diseases. The essential point is to link disease symptoms, quality of life, and social functioning into a consolidated assessment system that is not reduced to a one-dimensional comparison of individual parameters. Scales and questionnaires in their original form do not have the property of equidistance (i.e., the difference in scores does not indicate the true distance between 2 dimensions), but they do have the property of ranking. The ranking property is the unobserved metric of "depression", "quality of life", etc. When performing data reduction, we discard the original units of measurement and reach for some normalized values. Assuming the scales measure the same thing, we should obtain roughly comparable results (at the least, the same if the units differed by a constant, e.g., instead of kg–pounds, degrees Kelvin–Celsius, etc.). For scales, the number of categories claimed and self/external scoring can potentially influence the result. In our case, self-questionnaires were replaced by clinical scales recommended by clinical guideline[5], potentially affecting the adaptation results. However, the high statistical significance of our results demonstrates the feasibility of this approach.

We also did not take into account the influence of the pharmacotherapy received by the patients due to the considerable individual differences between the patients. Other clinical variables that potentially affect the burden of BD (presence of comorbid disorders, number of episodes, number of hospitalizations, etc.) were not assessed in relation to the IBI-BD index, because they were not included in the original study. Assessing the influence of these variables on the IBI-BD index could be one of the future directions of research. It is known that cognition, when objectively measured, is severely impaired in BD [42] and has also been associated with occupational outcomes. This suggests that cognitive functioning may also potentially contribute to the individual disease burden. However, since this aspect was not considered in the initial index, it was also disregarded in our study.

Interpretation

According to Ishak et al. [20], the concept of individual burden of illness represents the overall impact of a disease, which includes the suffering caused by symptom intensity, frequency, and duration; limitations in occupational, social, and leisure activities; and the patient's overall satisfaction with health, work, social life, and recreational pursuits. To quantify this concept, Ishak et al. [20] developed the IBI index through a principal component analysis of patient-reported data on symptom severity, functioning, and

[5] Ministry of Health of the Russian Federation. Bipolar affective disorder; 2021

quality of life, using it as a mathematical abstraction based on other psychometric scales.

The main goal of a doctor in clinical practice is to minimize symptoms, improve social functioning, and select a treatment adequate to the patient's condition. The relevance of this work is that the burden of disease at the individual level was calculated in patients with BD in remission. Given the new data on the frequency of residual [41] and subthreshold [22, 43, 44] symptoms in patients with BD in remission, the very notion of the limits of remission in BD is widely debated in the scientific literature. A growing body of evidence indicates that during remission, patients with BD often present subsyndromal mood symptoms, which are associated with poor psychosocial functioning, cognitive impairment, and reduced quality of life [45–48]. The validated IBI-BD index helps to assess the burden of negative factors on remission.

When compared with the original study of the application of the IBI index for patients with major depressive disorder [20], a limited explanation of data variance can be observed in our study. Possible reasons for this are as follows: mixing external ratings with self-reported questionnaires, and extreme heterogeneity of the parameters assessed. Since only the PC1 is greater than the zero distribution, its use for the IBI-BD index is consistent with an earlier study [20].

Depressive symptoms, including subsyndromal ones, are responsible for most of the burden that is associated with BD in terms of functioning, QOL, economic loss, and suicide [3]. The previous study suggested that personal recovery among patients with BD is affected by stigma, level of functioning, residual depressive symptoms, and employment status [49]. Functional impairment is an important driver of disability in patients with BD and can persist even when symptomatic remission has been achieved [50]. In our study, it was found that social functioning and quality of life decreased as the total score on the HDRS increased. At the same time, the presence of residual symptoms of hypomania (e.g., increased daytime activity and sexual interest) is subjectively evaluated by patients as positive phenomena, and it is also considered by patients as desirable and contrasted with residual depressive symptoms. Our data support the need for management of subsyndromal depressive symptoms in patients with BD even in the inter-episodic period [51]. The results of our study further contribute to the understanding of how residual affective symptomatology affects the functioning of patients with BD in remission, and it demonstrates the need to develop more targeted guidelines for the assessment and treatment of residual (subthreshold) symptoms.

When working with patients with BD, we need to bear in mind that BD is a complex psychiatric condition with a high heterogeneity in its manifestation, and that the BD II subtype may lead to similar health (and social) consequences as the BD I subtype [52]. In our study, this was confirmed, as patients with both types of BD showed no differences in functioning and no intergroup differences in the IBI-BD index.

The authors of the study consider the clinical significance of the validated IBI-BD index to reside in providing physicians with an additional technique for assessing patients' condition and grading its severity even when the remission criteria are formally met. Since the HDRS and YMRS scales are already included in the recommended scales for the assessment of patients with BD in clinical practice, the additional application of easy-to-use methods (WHOQOL, PSP) in the opinion of the researchers will not significantly increase the clinician's workload. Introducing the use of the IBI-BD index into clinical practice will allow additional interventions to be justified from the perspective of the patient's personal burden of illness and will allow interventions to be more personalized in the context of the lack of algorithms for the treatment of residual affective symptomatology in the remission of BD.

The use of the IBI index is not limited to assessing burden of illness and has already been tested in assessing the effectiveness of therapy [53] and predicting relapse in major depressive disorder [54]. Further work for researchers after the approval and validation of the index for patients with BD is seen in expanding opportunities for the scientific and practical use of the index, including the introduction of methods for its calculation in routine clinical practice. The practical application of the presented study is seen in the utilization of the IBI-BD index in clinical practice in order to objectify the functional status of patients with BD in remission.

Generalizability

The results of this study can be applied to comparable patients with BD for the following reasons: first, the validated tools were used to assess residual symptoms, quality of life, and social functioning. Second, we proposed a simple linear equation linking the disease burden index to its components; so, it can be used if methods are

available. Third, the methodology for obtaining the IBI-BD was described, making it possible to obtain a similar index on a different set of techniques independently. Despite the differences between the scales and questionnaires, they measure the same latent construct (different for each method); so, there should be no significant differences between the main components in the case of alternative IBI calculation. Fourth, there were no artificial conditions for the study — patients of both sexes with differences in age and disease history participated; that is, the sample was a cross-section of real patients that any physician or researcher may encounter.

CONCLUSION

To the best of authors' knowledge, this is the first study introducing and validating a composite calculation of the Individual Burden of Illness index in BD in remission. We have demonstrated by statistical means that it is possible to successfully approve and validate the previously calculated IBI index in major depressive disorder for patients with BD in remission. The proposed index assesses both the severity of symptoms and the functioning and QOL in patients with BD, resulting in a single weighted composite score that adequately reflects the disease burden. The study has shown that residual affective symptoms have a differing impact on the functioning of patients with BD in remission, reflecting the need for timely assessment and targeted therapy of these symptoms in such patients. It was found that social functioning and quality of life decrease in the presence of residual depressive symptoms, while residual symptoms of hypomania have the opposite effect. The results obtained may help to more objectively assess the functional status of patients with BD in remission using a statistical model.

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Supplementary data

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Potential Neurophysiological Markers of Combat-Related Post-Traumatic Stress Disorder: A Cross-Sectional Diagnostic Study

Потенциальные нейрофизиологические маркеры посттравматического стрессового расстройства у участников боевых действий: кросс-секционное диагностическое исследование

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Original research

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ABSTRACT

BACKGROUND: Studies suggest that the components of brain-evoked potentials (EPs) may serve as biomarkers of the post-traumatic stress disorder (PTSD) caused by participation in combat operations; however, to date, research remains fragmented, with no studies that have attempted to combine different paradigms. In addition, the mismatch negativity component has not been studied in a Russian sample of veterans with PTSD.

AIM: To identify objective neurophysiological markers of combat-related PTSD using the method of auditory-evoked potentials in active and passive listening paradigms.

METHODS: The study included a recording of auditory EPs in an oddball paradigm in three settings: 1) directed attention to auditory stimuli, 2) passive listening while viewing a neutral video sequence, and 3) viewing a video sequence associated with a traumatic event. Combatants diagnosed with PTSD (18 people) were compared with mentally healthy civilian volunteers (22 people).

RESULTS: An increase in the latency period of the early components of auditory EP (N100 and P200), an increase in the amplitude of the P200 component to a deviant stimulus, and a decrease to a standard one in the active listening

paradigm were established in the PTSD group. There were no significant differences in the parameters of the P300 component. The characteristics of mismatch negativity in the passive paradigm were revealed: an increase in the phenomenon amplitude, both when shown a video sequence associated with a traumatic event and when shown a neutral video sequence. A binary logistic regression model constructed using the selected parameters showed that the identified characteristics can potentially be considered as diagnostic markers of PTSD in combatants, as the classification accuracy stood at 87% (sensitivity — 81%, specificity — 91%).

CONCLUSION: Potential neurophysiological markers of PTSD are the following: the amplitude and latency of early components of auditory EPs in the paradigm of directed attention to stimuli and the amplitude of mismatch negativity during passive attention.

АННОТАЦИЯ

ВВЕДЕНИЕ: Исследования показывают, что компоненты вызванных потенциалов головного мозга (ВП) могут являться биомаркерами посттравматического стрессового расстройства (ПТСР) вследствие участия в боевых действиях, однако на сегодняшний день исследования фрагментарны, не представлены исследования, сочетающие различные парадигмы. На русской выборке ветеранов с ПТСР не изучался компонент негативности рассогласования.

ЦЕЛЬ: Выявление объективных нейрофизиологических маркеров ПТСР вследствие участия в боевых действиях методом слуховых вызванных потенциалов в парадигмах активного и пассивного слушания.

МЕТОДЫ: Исследование включало регистрацию слуховых ВП в парадигме вероятностного предъявления (oddball) в трех состояниях: 1) направленное внимание на слуховые стимулы; 2) пассивное слушание при просмотре нейтрального видеоряда; 3) при просмотре видеоряда, связанного с травматическим событием. Обследованы комбатанты с диагнозом ПТСР (18 человек) в сравнении с психически здоровыми гражданскими добровольцами (22 человека).

РЕЗУЛЬТАТЫ: В группе лиц с ПТСР обнаружено увеличение латентного периода ранних компонентов слухового ВП (N100 и P200), увеличение амплитуды компонента P200 на девиантный стимул и снижение на стандартный в парадигме активного слушания. Не выявлено значимых различий в показателях компонента P300. Выявлены особенности негативности рассогласования в пассивной парадигме: увеличение амплитуды феномена как при предъявлении видеоряда, связанного с травматическим событием, так и при предъявлении нейтрального видеоряда. Построенная с использованием выделенных показателей модель бинарной логистической регрессии показала, что выявленные особенности потенциально можно рассматривать как диагностические маркеры ПТСР у комбатантов — точность классификации составила 87% (чувствительность — 81%, специфичность — 91%).

ЗАКЛЮЧЕНИЕ: Потенциальными нейрофизиологическими маркерами ПТСР являются амплитуда и латентный период ранних компонентов слуховых ВП в парадигме направленного внимания на стимулы, а также амплитуда негативности рассогласования при пассивном внимании.

Keywords: *post-traumatic stress disorder; auditory evoked potentials; N100; P200; P300; mismatch negativity; combatants*
Ключевые слова: *посттравматическое стрессовое расстройство; слуховые вызванные потенциалы; N100; P200; P300; негативность рассогласования; комбатанты*

INTRODUCTION

As researchers stress, identifying a specific diagnostic biomarker for post-traumatic stress disorder (PTSD) is a challenging undertaking, because PTSD symptoms overlap with those of generalized anxiety, depressive disorder, and panic disorder (negative affect, anhedonia,

problems with sleep and concentration, irritability, overexcitement) [1]. PTSD encompasses those same psychopathological manifestations, but it is separated by a fairly typical clinical presentation [2]. In combat veterans, PTSD has unique features: the symptoms of PTSD are detected in more than a third of combatants within the first few days after the trauma, and they are accompanied by acute psychotic, affective, anxiety, dissociative, and other disorders [3, 4]. The diagnosis and treatment are further complicated by the fact that, among combatants, symptoms range in a continuum from the psychological to the psychopathological state [5].

The development of PTSD is triggered by changes in the subcortical reactivity to trauma-related memories and emotions, the impairment of inhibitory control and frontal regulation [6, 7], and a deficit in the downregulation of hyperreactivity in the amygdala [8, 9]. All this occurrences culminate in an inability to judiciously apportion attention when responding to threatening and emotional stimuli [10].

Cognitively evoked potentials are a method for recording the electrical potentials of the brain arising in response to the presentation of a significant sensory stimulus (deviant, different) in a series of insignificant (standard) ones [10, 11]. Early components of evoked potentials are associated with attention and the processing of incoming signals [12]. An increase in the amplitude of the early components of the evoked potentials N100 and P200 in response to an auditory stimulus indicates a modulation of the functioning of the amygdala and lateral prefrontal cortex [13], which is associated with hypervigilance in the event of a threat [14]. The amplitude of the N100 component increases both in individuals with PTSD and in individuals exposed to trauma but without PTSD symptoms [15], and it positively correlates with the assessment of hyperarousal [16]. In addition, individuals with PTSD exhibit a significant increase in the amplitude of the N1-P2 complex (the amplitude of the potential from the N100 peak to the P200 peak), which positively correlates with the severity of the symptoms of the disorder [16]. In this case, maladaptive avoidance is associated with a decrease in the amplitude of early components, while obsessive re-experiencing is associated with an increase in the amplitude of the P200 component [17]. An increase in the N100 amplitude was also found in other conditions associated with high levels of anxiety [18, 19].

The P300 component of evoked potentials is used to assess the severity of cognitive impairment, psychomotor functions, and the ability to plan and control goal-directed behavior at the decision-making stage [20]. In individuals with PTSD, there is an increase in the latency of the P300 component [21, 22], as well as a decrease in the amplitude of this component [22, 23], which respectively indicate a longer time for stimulus assessment (neural activity speed) and reduced cognitive processing efficiency [20]. It is also known that the P300 parameters (amplitude and latency) can be used to quantify the post-trauma state dynamics [22] and, in addition, to differentiate PTSD (due to various types of trauma, but not participation in combat) and depressive disorder [24].

The phenomenon of mismatch negativity (MMN) is assessed as the largest amplitude of the difference between the reaction to deviant and standard stimuli in the absence of directed attention [25]. The MMN amplitude reflects the processes of searching for discrepancies in short-term and sensory memory [26, 27], as well as cortical processing of the stimulus at the pre-attention stage, which does not depend on the direction of the attention [27]. In PTSD, a larger MMN amplitude was noted both in comparison with individuals who had no trauma and individuals with a history of traumatic events, but without PTSD [27, 28], which is regarded as a sign of increased sensitivity of these patients to deviant stimuli and reflects their hypervigilance, with a high MMN amplitude being associated with a high level of anxiety [29].

The development and progression of PTSD are complex mechanisms, due to symptoms that can manifest long after the trauma (within six months) and the lack of a correlation between acute reactions and long-term mental states [2, 30]. The similarity of PTSD symptoms with those of depressive, anxiety, and panic disorders [1], adaptation disorders, social and specific phobias further complicates its clinical diagnosis. The challenge is exacerbated by the wide range of symptom clusters, a low diagnostic threshold, and high comorbidity.[1] Therefore, objective diagnostic tools are crucial. Methods such as magnetic resonance imaging, positron emission tomography, computed tomography, and magnetic resonance spectroscopy are

[1] Russian Society of Psychiatris; Ministry of Health of the Russian Federation. Post-traumatic stress disorder. Clinical guidance; 2023–2024–2025. Available from: https://cr.minzdrav.gov.ru/schema/753_1. Russian.

used to diagnose PTSD, but they are expensive and labor-intensive [31]. Diagnostic models are being developed based on language characteristics (area under the curve 0.72) [32]. An attempt was made to create a diagnostic model based on physiological parameters; however, of all the parameters studied (heart rate, heart rate variability, respiratory recursion, galvanic skin response), differences at $p \leq 0.05$ were found only in the amplitude of the systolic wave in terms of stimulation options [33]. Electroencephalography (EEG) is an inexpensive, accessible and fairly flexible tool that can serve as an auxiliary method to improve the accuracy of PTSD diagnosis. However, a model using background EEG parameters (more than 25,000 characteristics, including spectral power, temporal and functional connectivity, frequency of microstate changes) showed an accuracy of 62.9%, indicating the limited efficiency of using background EEG parameters, with the recording process being labor-intensive [34]. The use of EPs can expand EEG diagnostic capabilities. To date, no comprehensive neurophysiological model of auditory-evoked potential testing has been proposed for combatants with PTSD. Studies of the MMN phenomenon have not previously been conducted in a Russian sample of PTSD patients. The combination of different paradigms (active and passive listening, with neutral and trauma-related videos) in one diagnostic model can significantly improve the quality of the neurophysiological diagnosis of the disorder.

The aim of this study was to search for quantitative neurophysiological markers of PTSD in combat participants.

METHODS

Study design

A cross-sectional diagnostic study was carried out.

Study conditions

The main group included persons who had undergone examination and treatment in general psychiatric department No. 11 of Mental-health clinic No. 1 named after N.A. Alexeev (Moscow), in the period from October to November 2023. The control group was selected among volunteers.

Participants

The main group included male combatants with PTSD. The diagnosis was made by the attending physician, in accordance with the ICD-10 diagnostic criteria. Individuals with a history of acute psychotic symptoms, other mental illness, traumatic brain injuries, or a neuroinfection (according to self-report data) were not enrolled. Enrollment was conducted within 2 weeks from the moment of hospitalization.

The control group included individuals without a history of mental illness, traumatic brain injuries or a neuroinfection (based on self-reported data), who did not participate in combat operations, and who did not report traumatic events in their past, from among colleagues and acquaintances of the investigators.

Both groups included only right-handed men.

All participants were assessed for functional interhemispheric asymmetry, having to do with the influence of the dominant hand on cognitive EP parameters [20]. The profile of the lateral organization was assessed based on the results of a questionnaire (with which hand the patient writes, draws, holds a toothbrush when brushing their teeth, uses scissors, a hammer, holds a match when lighting a fire, a spoon when stirring liquids) and motor tests on the dominant hand (applause, intertwined fingers).

Determination of the dominant hand was done immediately before the neurophysiological examination.

Variables

Evoked potentials for standard (100–120 realizations after artifact removal) and deviant stimuli (20–30 realizations after artifact removal) were averaged, and the averaged potentials were filtered in the frequency band of 0.3–20 Hz [31].

Data sources/measurement

EEG recording was performed in a separate darkened room, in the morning hours (09:00–13:00), and in a state of quiet wakefulness in a sitting position (in a chair). The Neuro-KM encephalograph (Statokin, Russia) was used, with the Brainsys analysis software package (developed by A.A. Mitrofanov, Russia) from 19 leads located according to the international 10–20 scheme, with reference electrodes on the earlobes. The sampling frequency of the EEG signal was 1000 Hz, and the bandwidth of the frequency filters when recording the signal was 0.3–70 Hz (the choice was determined by the characteristics of the amplifier).

Neurophysiological testing included 3 series of auditory stimulation with an oddball paradigm presentation: a standard stimulus of 1000 Hz with an 80% probability of presentation (120 stimuli), and a deviant stimulus of

2000 Hz with a 20% probability of presentation (30 stimuli). The duration of the sound stimuli was 10 ms, the intensity was 85 dB, and the interstimulus interval was 1 second [31]. Stimuli were presented binaurally through headphones randomly. The generation of stimuli and their presentation order were managed using the Brainsys software. In the first session, the subject sits with his eyes closed and receives instructions to press a button at the moment the deviant stimulus sounds. In the second and third sessions, the subject received instructions not to pay attention to sounds and to look at the laptop screen (diagonal 17.3 inches or 43.94 cm, resolution 1920x1080 pixels), located at a distance of 60 cm from the subject's eyes. The screen displayed a sequence of nature images (30 landscape images of bodies of water, mountains, steppes, forests, hereinafter referred to as "neutral video sequence"), then a video sequence with images associated with the traumatic event (25 photographs of military operations, destroyed buildings, military equipment, hereinafter referred to as "negative video sequence"). All the photographs were obtained from open sources. The images were presented at a frequency of 1 frame every 2 seconds, and the video sequences were looped and repeated until the total video length was 3 minutes. There were 1- to 2-minute breaks between each EEG recording session.

Visual analysis of all native EEG recordings involved the removal of artifacts and noisy channels. Data from the 9 channels (F3, F4, Fz, C3, C4, Cz, P3, P4, Pz) least susceptible to oculogram and myogram artifacts but characterized by sufficient information content regarding lateralization were selected for analysis [32].

EEG was recorded by a research assistant and a senior researcher at Mental-health clinic No. 1 named after N.A. Alexeev, in a specially equipped separate room. The EEG was analyzed by an employee of the laboratory of clinical neurophysiology of the V. Serbsky National Medical Research Centre of Psychiatry and Narcology of the Ministry of Health of the Russian Federation, with technical support from the software developer. All the researchers were aware of the diagnosis of the subjects.

Quantitative variables

In the first session (active listening — pressing a button at the moment the sound of a deviant stimulus is heard), the components of the auditory-evoked potential for standard and deviant stimuli (N100, P200, P300) were isolated and the amplitude and latent period of the components were analyzed. In sessions with visual stimulation (passive listening), the averaged EP files for the standard stimulus were subtracted from the potentials for the deviant stimulus to obtain the values of the MMN component and the amplitude and latent period of the negativity peak in the interval 150–250 ms were also analyzed.

Statistical methods

The study results were analyzed using the statistical software package SPSS, version 11.5 (SPSS Inc., USA) — distribution analysis, data description, comparison of the means, and binary logistic regression. The distribution of the values of quantitative characteristics was checked using the Shapiro-Wilk test. In all cases, the distribution deviated from normal. In this regard, quantitative parameters were described with the indication of the median, first and third quartiles (Q1; Q3), and the assessment of the differences was done using the Mann-Whitney test. Repeated measures analysis of variance (rmANOVA) with the Greenhouse–Geisser correction (accounting for the inequality of variances) with an inter-subject factor of "group" (nominal variable, n=2: control and PTSD) was used to assess the influence of the factors of stimulus frequency, stimulation content, laterality, and location, intra-subject factors of "stimulus" (n=2, quantitative parameters of evoked potentials to standard and deviant stimuli — for the analysis of the components of evoked potentials); "content of video sequence" (n=2, quantitative parameters of evoked potentials upon presentation of "neutral" and "negative" video sequences — for the analysis of the MMN phenomenon); "distribution" (n=3, quantitative parameters of evoked potentials by electrodes): frontal (F), central (C), and parietal (P); "lateralization" (n=3, quantitative parameters of evoked potentials on the electrodes of the left [F3, C3, P3], right hemisphere [F4, C4, P4], and central electrodes [Fz, Cz, Pz]).

Binary logistic regression models were used to identify independent predictors of PTSD from the evoked potentials and to determine the potential diagnostic value of auditory-evoked potentials for PTSD. Variables were selected using the method of direct, step-by-step inclusion into the equation of predictors with the greatest impact on the dependent variable (Forward: Wald), 8 steps were completed, and the step-by-step procedure was discontinued if there was no change in the previously fitted model when the variables were included.

Ethical approval

The study protocol was approved by the local ethics committee at Mental-health clinic No. 1 named after N.A. Alexeev (Meeting minutes No. 6 of August 11, 2023). A mandatory condition for inclusion in the study was signing the informed voluntary consent to participate in the study and the processing of personal data. Information included explaining to potential participants the purpose, methods, and protocol of the study, with the opportunity to ask clarifying questions.

RESULTS

Participants

During the study period, a diagnosis of PTSD was established for 20 patients and they were asked to participate in the study; 18 agreed and underwent neurophysiological examination. The main group included 18 people with experience of military combat diagnosed with PTSD. They were examined. The control group included 22 people.

Descriptive data

The median age of the PTSD patients and participants in the control group was 34.5 years (29; 41) and 27.5 years (25; 39), respectively (p=0.195). The median duration of the stay in combat conditions for the PTSD patients was 210 (130; 270) days, and the duration from the end of participation in military operations to the time of examination was 50 (38; 120) days.

Main results

Repeated measures analysis of variance was performed to assess the differences in evoked-potential components between the groups. The inter-subject factor of "group" (n=2: control and PTSD), the intra-subject factors of "stimulus" (n=2: standard and deviant), "distribution" (n=3: frontal, central, parietal), and "lateralization" (n=3: left hemisphere, right, central location) were selected.

Amplitude analysis of the N100 component revealed intergroup differences under the influence of the factors of "distribution" (F=14.45, p <0.001), "lateralization" (F=3.20, p=0.048), as well as the interaction of the factors of "stimulus–distribution" (F=9.48, p=0.002) and "distribution–lateralization" (F=10.83, p <0.001). When analyzing the latent period of the N100 component, a significant influence of the "lateralization" factor (F=5.64, p=0.006) and interaction of the "distribution" and "lateralization" factors (F=2.82, p=0.028) was revealed. For the amplitude of the P200 component, differences were revealed under the influence of the interaction of the "stimulus" and "group" factors (F=8.14, p=0.011), the factor "lateralization" (F=10.22, p=0.005), for latency — the influence of the "stimulus" factor (F=9.15, p=0.007), and interaction between the "stimulus" and "group" factors (F=4.92, p=0.040).

For the amplitude of the P300 component, intergroup differences were revealed under the influence of the factors of "stimulus" (F=82.23, p=0.0001), "lateralization" (F=11.97, p=0.0001), interaction of the "stimulus" and "lateralization" factors (F=6.78, p=0.002), and for latency, also the influence of the factors of "stimulus" (F=21.69, p=0.0001), "distribution" (F=3.72, p=0.031), interaction of the "stimulus" and "lateralization" factors (F=8.45, p=0.001). Comparison of the groups using the Mann-Whitney test revealed statistically significant differences in the early components of the evoked potentials, mainly for the deviant stimulus (Tables 1 and 2). The N100 component in individuals with PTSD is characterized by a long latency period to a deviant stimulus in the parietal-central regions, the P200 component has an increased amplitude and an increased latent period to a deviant stimulus in the frontal and central leads, and a reduced amplitude to a standard stimulus in the frontal leads. There were no significant differences between the compared groups *vis-a-vis* the parameters of the P300 component.

In the experimental design using video sequences, repeated measures analysis of the variance was also performed. Significant differences were found under the influence of the "zone" factor (F=18.77, p=0.0001), the "location" factor (F=6.25, p=0.005), and the combination of the "location" and "group" factors (F=3.43, p=0.043). The visual stimulation content factor did not have a significant effect on the MMN scores (F=0.143, p=0.709).

Further comparison of the mean values using the Mann-Whitney test revealed that in individuals with PTSD, the MMN latency period when presented with a negative video sequence, and the MMN amplitude when presented with a neutral video sequence, was higher than in participants in the control group (Table 3).

From among the studied EEG parameters, eight variables, independent predictors of PTSD, were selected: the latent period of the N100 component, the amplitude and latent period of the P200 component to a deviant stimulus, and the amplitude and latent period of the MMN upon presentation of a neutral and negative video sequence in different leads (Table 4).

Table 1. Parameters of evoked potentials to a deviant stimulus in individuals with PTSD compared with values in the control group [median (lower quartile; upper quartile) (number of people)]

Component	Lead	PTSD	Control	Z	*p*
Latent period (ms)					
N100	P3	134 (112; 138) (*n*=17)	108 (102; 116) (*n*=22)	2.549	0.011
	P4	124 (112; 137) (*n*=16)	108 (100; 116) (*n*=22)	2.453	0.014
	Pz	127 (104; 158) (*n*=16)	109 (98; 118) (*n*=22)	1.774	0.076
	C3	132 (117; 140) (*n*=17)	112 (110; 118) (*n*=21)	2.361	0.018
	C4	125 (116; 132) (*n*=16)	112 (106; 122) (*n*=22)	2.407	0.016
	Cz	128 (118; 136) (*n*=17)	110 (104; 116) (*n*=21)	2.143	0.032
	F3	132 (116; 142) (*n*=17)	116 (112; 124) (*n*=22)	1.644	0.100
	F4	130 (118; 134) (*n*=17)	113 (108; 126) (*n*=22)	1.784	0.074
	Fz	131 (115; 140) (*n*=18)	116 (110; 126) (*n*=22)	1.463	0.143
P200	P3	184 (162; 202) (*n*=17)	163 (152; 184) (*n*=22)	1.246	0.213
	P4	184 (152; 189) (*n*=16)	162 (152; 176) (*n*=22)	1.012	0.312
	Pz	187 (163; 197) (*n*=16)	163 (148; 180) (*n*=22)	1.567	0.117
	C3	193 (173; 202) (*n*=17)	166 (156; 184) (*n*=21)	2.883	0.004
	C4	183 (171; 189) (*n*=16)	166 (158; 180) (*n*=22)	1.839	0.066
	Cz	178 (167; 189) (*n*=17)	156 (148; 172) (*n*=21)	2.820	0.005
	F3	190 (176; 200) (*n*=17)	176 (160; 190) (*n*=22)	1.673	0.094
	F4	182 (172; 200) (*n*=17)	177 (160; 200) (*n*=22)	0.821	0.411
	Fz	193 (178; 204) (*n*=18)	172 (156; 188) (*n*=22)	2.484	0.013
P300	P3	334 (310; 366) (*n*=17)	340 (320; 354) (*n*=22)	-0.088	0.930
	P4	348 (313; 363) (*n*=16)	334 (326; 376) (*n*=22)	0.169	0.866
	Pz	340 (311; 362) (*n*=16)	330 (322; 346) (*n*=22)	0.981	0.327
	C3	332 (310; 360) (*n*=17)	334 (316; 342) (*n*=21)	0.107	0.915
	C4	336 (320; 359) (*n*=16)	330 (312; 354) (*n*=22)	0.322	0.748
	Cz	338 (320; 362) (*n*=17)	330 (308; 342) (*n*=21)	0.881	0.378
	F3	330 (320; 354) (*n*=17)	336 (322; 350) (*n*=22)	0.147	0.883
	F4	338 (320; 356) (*n*=17)	330 (314; 344) (*n*=22)	0.935	0.350
	Fz	349 (322; 361) (*n*=18)	335 (318; 342) (*n*=22)	1.390	0.165
Amplitude (μV)					
N100	P3	5.04 (3.61; 6.82) (*n*=17)	3.60 (1.59; 6.26) (*n*=22)	1.742	0.082
	P4	5.12 (2.08; 6.18) (*n*=16)	4.54 (2.50; 5.93) (*n*=22)	0.169	0.866
	Pz	5.12 (2.58; 6.16) (*n*=16)	2.87 (1.30; 5.30) (*n*=22)	1.478	0.139
	C3	4.73 (2.81; 6.82) (*n*=17)	5.50 (3.26; 6.93) (*n*=21)	-0.628	0.530
	C4	6.15 (2.43; 7.74) (*n*=16)	5.93 (3.27; 7.47) (*n*=22)	-0.337	0.736
	Cz	6.99 (2.60; 9.12) (*n*=17)	6.16 (4.45; 7.60) (*n*=21)	0.123	0.902
	F3	3.70 (2.89; 6.99) (*n*=17)	5.22 (3.79; 6.46) (*n*=22)	-0.587	0.557
	F4	5.00 (3.21; 7.79) (*n*=17)	6.42 (3.89; 7.79) (*n*=22)	-0.666	0.506
	Fz	5.15 (3.40; 7.09) (*n*=18)	5.54 (2.87; 8.230(*n*=22)	-0.414	0.679
P200	P3	2.73 (2.20; 3.44) (*n*=17)	1.63 (0.87; 3.56) (*n*=22)	1.303	0.193
	P4	2.49 (0.84; 3.22) (*n*=16)	1.89 (0.67; 2.70) (*n*=22)	0.567	0.571
	Pz	2.44 (1.45; 3.51) (*n*=16)	1.82 (0.84; 3.36) (*n*=22)	0.902	0.367
	C3	2.38 (1.59; 4.29) (*n*=17)	1.70 (0.40; 2.90) (*n*=21)	1.390	0.165
	C4	3.20 (1.68; 4.21) (*n*=16)	1.48 (0.91; 2.60) (*n*=22)	2.728	0.006
	Cz	3.24 (2.19; 5.89) (*n*=17)	2.57 (1.65; 3.68) (*n*=21)	1.502	0.133
	F3	2.66 (1.84; 4.61) (*n*=17)	1.53 (0.66; 3.93) (*n*=22)	1.894	0.058
	F4	3.72 (2.02; 4.73) (*n*=17)	2.13 (0.87; 3.27) (*n*=22)	1.898	0.058
	Fz	4.14 (2.88; 5.17) (*n*=18)	1.63 (0.65; 3.92) (*n*=22)	2.927	0.003
P300	P3	7.21 (5.88; 8.87) (*n*=17)	7.98 (4.99; 10.07) (*n*=22)	-0.878	0.380
	P4	6.82 (4.88; 8.76) (*n*=16)	7.40 (5.53; 11.46) (*n*=22)	-0.674	0.500
	Pz	7.41 (5.98; 9.41) (*n*=16)	8.40 (5.81; 11.82) (*n*=22)	-0.887	0.375
	C3	7.55 (5.03; 9.20) (*n*=17)	6.31 (4.78; 10.35) (*n*=21)	-0.207	0.836
	C4	7.15 (4.80; 9.51) (*n*=16)	7.01 (5.06; 9.34) (*n*=22)	-0.092	0.927
	Cz	8.39 (6.33; 11.14) (*n*=17)	7.43 (5.22; 10.84) (*n*=21)	0.602	0.547
	F3	6.34 (4.52; 8.44) (*n*=17)	6.09 (4.69; 8.89) (*n*=22)	-0.198	0.843
	F4	6.57 (3.87; 8.50) (*n*=17)	6.90 (4.54; 8.880) (*n*=22)	-0.227	0.821
	Fz	8.46 (5.86; 9.87) (*n*=18)	7.94 (6.18; 10.83) (*n*=22)	-0.237	0.813

Note: The description is made with the indication of the median (Q1; Q3). P, C, F — parietal, central and frontal location of electrodes; (F3, C3, P3) — quantitative parameters of evoked potentials on the electrodes of the left hemisphere; (F4, C4, P4) — on the right hemisphere; (Fz, Cz, Pz) — on the central electrodes.

Table 2. Parameters of evoked potentials to standard stimulus in individuals with PTSD versus the values in the control group

Component	Lead	PTSD	Control	Z	*p*
Latent period (ms)					
N100	P3	120 (108; 128) (*n*=17)	116 (110; 122) (*n*=22)	0.609	0.543
	P4	120 (102; 124) (*n*=16)	114 (102; 120) (*n*=22)	0.939	0.347
	Pz	122 (103; 127) (*n*=16)	115 (108; 122) (*n*=22)	0.828	0.408
	C3	119 (111; 129) (*n*=17)	116 (112; 124) (*n*=21)	0.429	0.668
	C4	120 (112; 124) (*n*=16)	116 (110; 120) (*n*=22)	0.828	0.408
	Cz	122 (112; 126) (*n*=17)	116 (110; 120) (*n*=21)	1.218	0.223
	F3	120 (112; 128) (*n*=17)	116 (112; 122) (*n*=22)	0.680	0.497
	F4	118 (114; 124) (*n*=17)	116 (108; 124) (*n*=22)	0.722	0.470
	Fz	122 (114; 126) (*n*=18)	118 (114; 124) (*n*=22)	0.665	0.506
P200	P3	188 (182; 206) (*n*=17)	192 (180; 204) (*n*=22)	-0.949	0.343
	P4	186 (172; 192) (*n*=16)	182 (168; 216) (*n*=22)	-0.381	0.703
	Pz	186 (181; 204) (*n*=16)	192 (180; 222) (*n*=21)	-0.889	0.374
	C3	185 (178; 194) (*n*=17)	187 (180; 204) (*n*=21)	-0.695	0.487
	C4	187 (171; 199) (*n*=16)	183 (176; 194) (*n*=22)	-0.191	0.849
	Cz	186 (176; 198) (*n*=17)	184 (176; 194) (*n*=21)	-0.042	0.966
	F3	184 (176; 192) (*n*=17)	182 (174; 204) (*n*=22)	-0.269	0.788
	F4	174 (168; 198) (*n*=17)	174 (170; 192) (*n*=22)	-0.368	0.713
	Fz	180 (172; 192) (*n*=18)	177 (170; 196) (*n*=22)	0.429	0.668
P300	P3	282 (270; 296) (*n*=17)	277 (264; 294) (*n*=22)	0.326	0.745
	P4	282 (264; 288) (*n*=16)	280 (262; 300) (*n*=22)	-0.558	0.577
	Pz	284 (267; 298) (*n*=16)	284 (264; 308) (*n*=22)	-0.177	0.859
	C3	285 (269; 303) (*n*=17)	287 (270; 310) (*n*=21)	0.015	0.988
	C4	286 (270; 299) (*n*=16)	278 (266; 294) (*n*=22)	0.506	0.613
	Cz	290 (274; 304) (*n*=17)	277 (268; 294) (*n*=21)	0.552	0.581
	F3	298 (280; 326) (*n*=17)	282 (274; 308) (*n*=22)	0.763	0.445
	F4	292 (268; 310) (*n*=17)	286 (270; 320) (*n*=22)	-0.227	0.821
	Fz	298 (285; 327) (*n*=18)	288 (272; 314) (*n*=22)	0.990	0.322
Amplitude (μV)					
N100	P3	3.85 (2.42; 4.72) (*n*=17)	4.34(3.10; 5.49) (*n*=22)	-1.147	0.251
	P4	3.40 (1.95; 4.71) (*n*=16)	3.97(3.02; 4.90) (*n*=22)	-1.453	0.146
	Pz	3.41 (1.73; 6.10) (*n*=16)	4.40(3.24; 5.30) (*n*=22)	-1.123	0.261
	C3	4.08 (2.72; 6.37) (*n*=17)	5.14(4.46; 7.73) (*n*=21)	-1.360	0.174
	C4	4.26 (3.08; 6.98) (*n*=16)	5.49(4.35; 6.82) (*n*=22)	-1.410	0.158
	Cz	5.29 (3.36; 7.55) (*n*=17)	5.51(4.04; 7.44) (*n*=21)	-0.765	0.444
	F3	3.65 (2.34; 5.51) (*n*=17)	5.13 (4.10; 7.17) (*n*=22)	-1.855	0.064
	F4	3.60 (2.32; 8.35) (*n*=17)	5.93 (4.11; 7.42) (*n*=22)	-1.301	0.193
	Fz	3.85 (2.42; 4.72) (*n*=18)	4.34 (3.10; 5.49) (*n*=22)	-1.147	0.251
P200	P3	1.26 (0.77; 1.99) (*n*=17)	1.99 (0.93; 3.15) (*n*=22)	-1.473	0.141
	P4	1.68 (0.86; 2.28) (*n*=16)	1.52 (0.62; 2.66) (*n*=22)	-0.061	0.951
	Pz	1.55 (0.91; 2.26) (*n*=16)	2.01 (0.96; 3.06) (*n*=22)	-0.659	0.510
	C3	1.17 (0.50; 1.94) (*n*=17)	1.90 (0.49; 3.41) (*n*=21)	-1.138	0.255
	C4	1.28 (0.77; 2.05) (*n*=16)	2.00 (1.10; 2.98) (*n*=22)	-1.544	0.123
	Cz	1.65 (1.00; 2.73) (*n*=17)	2.42 (0.65; 3.86) (*n*=21)	-0.991	0.322
	F3	1.30 (0.64; 2.10) (*n*=17)	1.55 (0.96; 3.31) (*n*=22)	-1.416	0.157
	F4	1.21 (0.88; 1.91) (*n*=17)	2.09 (1.34; 2.85) (*n*=22)	-2.068	0.039
	Fz	1.27 (0.61; 2.34) (*n*=18)	2.22 (0.99; 3.24) (*n*=22)	-1.744	0.081
P300	P3	3.02 (1.54; 3.56) (*n*=17)	2.63 (1.90; 4.34) (*n*=22)	-0.156	0.876
	P4	2.72 (1.80; 3.60) (*n*=16)	2.50 (1.83; 3.25) (*n*=22)	0.382	0.703
	Pz	2.77 (1.95; 4.22) (*n*=16)	2.69 (1.94; 4.83) (*n*=22)	-0.325	0.745
	C3	2.67 (1.74; 3.94) (*n*=17)	2.93 (1.91; 4.43) (*n*=21)	-0.443	0.657
	C4	2.38 (1.58; 3.90) (*n*=16)	3.07 (2.00; 3.81) (*n*=22)	-0.353	0.724
	Cz	2.27 (1.50; 4.78) (*n*=17)	3.09 (2.05; 4.04) (*n*=21)	-0.496	0.620
	F3	2.04 (1.57; 3.25) (*n*=17)	2.76 (1.87; 4.08) (*n*=22)	-0.705	0.481
	F4	1.94 (1.31; 2.76) (*n*=17)	2.62 (1.59; 3.53) (*n*=22)	-0.595	0.552
	Fz	2.02 (1.61; 3.56) (*n*=18)	2.99 (1.76; 4.57) (*n*=22)	-1.404	0.160

Note: The description is made with the indication of the median (Q1; Q3). P, C, F — parietal, central and frontal location of electrodes; (F3, C3, P3) — quantitative parameters of evoked potentials on the electrodes of the left hemisphere; (F4, C4, P4) — on the right hemisphere; (Fz, Cz, Pz) — on the central electrodes.

Table 3. Parameters of mismatch negativity in individuals with PTSD versus the values in the control group

Component	Lead	PTSD	Control	Z	*p*
Latent period (ms)					
Neutral video sequence	P3	189 (157; 220) (*n*=16)	169 (158; 211) (*n*=20)	0.446	0.656
	P4	189 (171; 209) (*n*=16)	174 (158; 212) (*n*=21)	0.644	0.520
	Pz	187 (165; 215) (*n*=16)	173 (160; 230) (*n*=20)	0.350	0.726
	C3	178 (160; 212) (*n*=16)	176 (162; 248) (*n*=19)	-0.116	0.908
	C4	181 (162; 199) (*n*=16)	168 (150; 178) (*n*=22)	1.176	0.240
	Cz	186 (169; 192) (*n*=16)	172 (160; 238) (*n*=20)	0.927	0.354
	F3	204 (171; 227) (*n*=16)	163 (158; 184) (*n*=20)	1.719	0.086
	F4	192 (165; 226) (*n*=16)	169 (157; 212) (*n*=22)	0.939	0.348
	Fz	176 (155; 229) (*n*=16)	174 (160; 244) (*n*=19)	-0.497	0.619
Negative video sequence	P3	188 (174; 236) (*n*=15)	170 (154; 183) (*n*=20)	2.136	0.033
	P4	184 (174; 240) (*n*=15)	169 (154; 201) (*n*=21)	1.718	0.086
	Pz	178 (160; 186) (*n*=15)	174 (158; 186) (*n*=22)	0.274	0.784
	C3	178 (158; 220) (*n*=15)	171 (159; 180) (*n*=19)	1.212	0.225
	C4	178 (162; 186) (*n*=16)	164 (154; 181) (*n*=22)	1.140	0.254
	Cz	178 (168; 184) (*n*=16)	168 (159; 183) (*n*=21)	1.126	0.260
	F3	178 (162; 182) (*n*=15)	172 (163; 180) (*n*=22)	0.505	0.613
	F4	176 (162; 182) (*n*=15)	168 (157; 176) (*n*=22)	0.852	0.394
	Fz	176 (164; 182) (*n*=16)	169 (162; 185) (*n*=20)	0.548	0.583
Amplitude (μV)					
Neutral video sequence	P3	2.64 (1.47; 5.36) (*n*=16)	2.64 (1.10; 3.54) (*n*=20)	0.891	0.373
	P4	3.32 (2.17; 4.63) (*n*=16)	2.13 (1.61; 2.64) (*n*=21)	1.931	0.053
	Pz	3.48 (2.17; 5.17) (*n*=16)	2.61 (0.70; 3.40) (*n*=20)	1.608	0.108
	C3	4.30 (2.55; 5.72) (*n*=16)	2.35 (0.91; 4.69) (*n*=19)	1.490	0.136
	C4	3.63 (2.36; 4.83) (*n*=16)	2.99 (1.60; 4.39) (*n*=22)	1.043	0.297
	Cz	3.75 (2.18; 5.15) (*n*=16)	4.13 (2.25; 5.21) (*n*=20)	0.099	0.921
	F3	4.69 (3.45; 6.50) (*n*=16)	3.56 (1.23; 5.05) (*n*=20)	2.006	0.045
	F4	3.74 (2.38; 6.22) (*n*=16)	3.40 (1.60; 4.82) (*n*=22)	1.114	0.265
	Fz	5.86 (3.92; 7.99) (*n*=16)	3.26 (1.31; 5.43) (*n*=19)	2.980	0.003
Negative video sequence	P3	1.38 (0.60; 3.15) (*n*=15)	2.07 (0.58; 3.33) (*n*=20)	-0.202	0.840
	P4	2.12 (1.10; 3.45) (*n*=15)	1.97 (0.78; 2.74) (*n*=21)	0.058	0.954
	Pz	2.84 (1.72; 4.35) (*n*=15)	2.21 (1.27; 3.20) (*n*=22)	1.472	0.141
	C3	3.05 (1.92; 6.10) (*n*=15)	2.53 (1.24; 3.81) (*n*=19)	1.184	0.237
	C4	2.85 (0.54; 4.16) (*n*=16)	1.59 (0.82; 3.21) (*n*=22)	0.606	0.544
	Cz	2.38 (1.72; 4.70) (*n*=16)	2.42 (1.13; 4.38) (*n*=21)	0.419	0.676
	F3	4.10 (1.54; 7.02) (*n*=15)	2.56 (1.85; 4.77) (*n*=22)	1.328	0.184
	F4	2.93 (1.88; 4.80) (*n*=15)	2.72 (1.49; 4.80) (*n*=22)	0.318	0.751
	Fz	4.57 (1.80; 5.63) (*n*=16)	3.29 (1.86; 5.02) (*n*=20)	0.346	0.729

Note: The description is made with the indication of the median (Q1; Q3). P, C, F — parietal, central, and frontal location of the electrodes; (F3, C3, P3) — quantitative parameters of evoked potentials on the electrodes of the left hemisphere; (F4, C4, P4) — on the right hemisphere; and (Fz, Cz, Pz) — on the central electrodes. Neutral video sequence — images of nature, negative video sequence — photographs of military operations.

Table 4. Independent PTSD predictors: binary logistic regression model

Parameter	Lead	B	Standard error	Wald test	*p*
Latent period N100	P3	0.027	0.036	0.569	0.451
Latent period N100	P4	-0.033	0.073	0.203	0.653
Latent period P200	P3	-0.037	0.025	2.126	0.145
Latent period N100	C3	0.058	0.074	0.625	0.429
Amplitude P200	P4	-0.185	0.318	0.340	0.560
Amplitude P200	Fz	0.492	0.306	2.586	0.108
Latent period MMN, negative video sequence	C4	0.175	0.140	1.555	0.212
Amplitude MMN, neutral video sequence	Fz	-0.081	0.100	0.663	0.415
Constant	-	-12.348	5.561	4.930	0.026

Note: Statistical characteristics of the model: log likelihood value of the regression model 32.580, Nagelkerke R2— 72.5%.

Predicted conditions were classified using a multifactorial model on the data of 16 people in the PTSD group and 21 in the control group, for whom the data of all independent predictors included in the model were known (data for some parameters were missing for 2 people in the PTSD group and 1 in the control group due to the removal of artifact channels). The classification accuracy was 86% (32 conditions out of 37 observations were correctly classified). The classification results are shown in Table 5.

The high percentage of correct matches proves that the chosen study design allows one to identify the information processing characteristics in individuals with PTSD. This experimental design with the specified predictors can be used as the basis for a diagnostic model.

Table 5. Classification table of the binary logistic regression model for the diagnosis of PTSD

Observed condition	Predicted condition		Correct classification, %
	Control	PTSD	
Control, abs.	19	2	91
PTSD, abs.	3	13	81

Note: Statistical characteristics of the discriminant model: chi-square 18.036, p=0.021.

DISCUSSION

Key results

The study that included different paradigms for recording auditory-evoked potentials revealed the characteristics of individuals with PTSD in the active paradigm: the most pronounced changes were found in the parameters of the N100 component; i.e., in PTSD patients, the amplitude was reduced and the latent period for the deviant stimulus was shortened versus the standard one. The P200 component in PTSD patients is characterized by an increased amplitude and latency period for a deviant stimulus, and a reduced amplitude for the standard stimulus. There were no significant differences in the parameters of the P300 component. In the passive paradigm, it was found that in the PTSD group, the latent period of MMN when presented with a negative video sequence, and the amplitude when presented with a neutral video sequence, was higher than in the control group

Limitations

A key limitation of the study is its small sample size. In this regard, it can be noted that the lack of statistically significant differences between the compared groups in certain parameters, particularly the P300 component, is indicative of a low information content. In addition, it is known that in small samples random factors have a greater influence on the identification of differences/associations than in studies with larger sample sizes. The use of mentally healthy individuals as controls is also an important limitation of the study, but this type of study constitutes a significant portion of the research on combat-related PTSD [1, 9, 35].

Another important limitation of the present study is the lack of comparison groups (persons with depression, generalized anxiety disorder), which could help assess the sensitivity of the proposed experimental design. Moreover, it seems relevant to test the diagnostic model on individuals who participated in combat but do not exhibit clinical symptoms of PTSD.

Validation of the model in such groups is a prerequisite for its clinical application.

The use of ANOVA for EEG data analysis assumes a normal distribution of the parameters, given the nature of the signal. However, applying parametric statistical methods to data with a skewed distribution is a limitation, as the discriminant function in this case reflects the properties of a specific sample rather than the general population [36].

Interpretation of the main study results

Differences have been identified that indicate impairment of the early components of auditory-evoked potentials in individuals with PTSD. The extended latency of the N100 component in response to a deviant stimulus is linked to the severity of the cognitive impairment in PTSD patients [37; 38; 39], the risk of psychotic symptoms [35], and the number of subconcussive impacts on the brain [40], potentially resulting from combat participation. The increased amplitude of the P200 component observed in PTSD patients is similar to that seen in attention deficit hyperactivity disorder and reflects insufficient inhibitory mechanisms [41], and the extended latent period of P200 suggests impaired stimulus recognition [42]. However, no differences were found in the P300 component parameters, which relate to attention efficiency, psychomotor functions, and the ability to plan and control goal-directed behavior [24]. The absence of differences in the P300 component may be associated with disease progression: PTSD symptoms may worsen after the end of combat participation, with reduced amplitude and increased latency correlating with symptom deterioration, and vice versa [22]. The study group had an average of 50 days from the end of combat participation, and changes in the later stages of evoked potentials may occur over a longer period. When developing a diagnostic model based on these parameters, it is necessary to consider the length of time after the trauma.

The limited number of significant differences in the parameters when presenting trauma-related videos is noteworthy. A recent meta-analysis comparing studies using affective and neutral paradigms showed that individuals with PTSD allocate more resources when faced with threatening stimuli (evidenced by an increased amplitude of early components), but they exhibit impairments in working memory updating (shown by extended latency and a decreased P300 amplitude) when exposed to non-affective information. However, this review included various types of PTSD while the affective stimuli in most studies were images (such as facial emotions) not specifically associated with trauma [35]. This limited number of differences may necessitate adjustments in the study design.

The differences in the components of auditory-evoked potentials identified in the pilot study when used as predictors in the classification model show high accuracy (87%: sensitivity — 81%, specificity — 91%). The use of the parameters obtained in three different stimulus presentation paradigms (active, passive with the presentation of video sequences: with content related to the traumatic event and not related) allows one to expand the diagnostic capabilities of the auditory-evoked potential method.

Generalizability

The evoked-potential performance is highly influenced by the amplifier characteristics, software, and examination settings. To use EP parameters as biomarkers, it is necessary to recruit a control group using the same amplifier, the same conditions, and identical settings and stimulus characteristics.

This pilot study identified potential targets for the diagnostic model, but it does not have sufficient bandwidth to be used as an off-the-shelf diagnostic tool due to these limitations.

CONCLUSION

Potential neurophysiological markers of combat-related PTSD within up to 120 days after the end of combat participation are the amplitude and latency of the early components of auditory-evoked potentials (N100 and P200) and the amplitude of the MMN phenomenon. A diagnostic model using a set of parameters in various stimulus presentation paradigms can be instrumental in diagnosing PTSD.

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Inflammatory Hematological Ratios in Adolescents with Mental Disorders: A Scoping Review

Гематологические коэффициенты воспаления при психических расстройствах в подростковом возрасте: обзор предметного поля

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Review

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ABSTRACT

BACKGOUND: Inflammatory hematological ratios (IHRs), such as neutrophil to lymphocyte, monocyte to lymphocyte, and platelet to lymphocyte ratios, are associated with mental disorders, symptoms severity, and the disease phase. Evidence from the studies in adult patients has been summarized in systematic reviews and meta-analyses. The results of the studies in adolescents remain poorly systematized.

AIM: To summarize the findings from the studies that investigated the relationship of IHRs with mental disorders in adolescent patients.

METHODS: This scoping review included studies of IHRs in patients aged 10–19 years with mental disorders (other than anorexia nervosa), published in English by December 31, 2023. The search for relevant papers was performed in MEDLINE. The studies were categorized into two groups: studies with external controls (healthy adolescents) and studies with internal controls (patients in different phases of mental disorder, with or without self-harm/suicidal behaviors).

RESULTS: A total of 11 studies were included in the review (all cross-sectional ones). The results of these studies demonstrate that 1) adolescents with mental disorders (major depressive disorder, psychotic disorders, obsessive-compulsive disorder, attention deficit hyperactivity disorder, substance use disorders) have higher IHR values than individuals of the same age without corresponding disorders (5 studies); 2) IHR values are positively correlated with the severity of psychopathological symptoms (1 study); 3) higher IHR values are associated with the phase of the mental disorder — manic episode in bipolar disorder (1 study) and exacerbation of psychosis in psychotic disorders (1 study); and 4) higher IHR values are associated with self-harm/suicidal behaviors — suicide attempts (1 study) and non-suicidal self-injury (1 study).

CONCLUSION: IHRs are associated with mental disorders in adolescents, and higher IHR values are associated with a more severe/acute clinical presentation (severity of symptoms, mania, acute psychosis, self-harm/suicidal behaviors). Further studies of higher methodological quality are needed to evaluate the diagnostic and prognostic value of IHRs as biomarkers of mental disorders in adolescence.

АННОТАЦИЯ

ВВЕДЕНИЕ: Гематологические коэффициенты воспаления (ГКВ), такие как нейтрофильно-лимфоцитарное, моноцитарно-лимфоцитарное, тромбоцитарно-лимфоцитарное отношение, ассоциированы с психическими расстройствами, их тяжестью, фазой заболевания. Данные, полученные у взрослых пациентов, обобщены в систематических обзорах и метаанализах. Результаты подобных исследований у подростков не систематизированы.

ЦЕЛЬ: Обобщить результаты исследований, в которых изучали связь ГКВ с психическими расстройствами у пациентов подросткового возраста.

МЕТОДЫ: В обзор предметного поля включали исследования ГКВ у пациентов в возрасте 10–19 лет с психическими расстройствами (кроме нервной анорексии), результаты которых опубликованы на английском языке до 31 декабря 2023 года. Поиск потенциально релевантных работ проводили в базе данных MEDLINE. Отобранные работы анализировали, разделив их на 2 группы: исследования с внешним контролем (здоровые подростки) и исследования с внутренним контролем (пациенты с разной фазой психического расстройства, наличием/отсутствием аутоагрессивного поведения).

РЕЗУЛЬТАТЫ: В обзор включены результаты 11 кросс-секционных исследований. Анализ их результатов показал: 1) у подростков с психическими расстройствами (депрессия, психотические расстройства, обсессивно-компульсивное расстройство, синдром дефицита внимания и гиперактивности, расстройства, связанные с употреблением психоактивных веществ) значения ГКВ выше, чем у их сверстников без соответствующих расстройств (5 исследований); 2) значения ГКВ положительно коррелируют с выраженностью психопатологических симптомов (1 исследование); 3) высокие значения ГКВ связаны с фазой психического расстройства — манией при биполярном аффективном расстройстве (1 исследование) и обострением психоза при психотических расстройствах (1 исследование); 4) высокие значения ГКВ связаны с аутоагрессивным поведением — суицидными попытками (1 исследование) и несуицидальными самоповреждениями (1 исследование).

ЗАКЛЮЧЕНИЕ: ГКВ связаны с психическими расстройствами у подростков, их тяжестью/остротой (выраженностью симптомов, фазой заболевания, наличием аутоагрессии). Для оценки диагностической и прогностической ценности ГКВ в качестве биомаркеров психических расстройств в подростковом возрасте необходимы дальнейшие исследования более высокого методологического качества.

Keywords: *inflammatory hematological ratios; systemic inflammation; mental disorders; adolescents; biomarkers*
Ключевые слова: *гематологические коэффициенты воспаления; системное воспаление; психические расстройства; подростки; биомаркеры*

INTRODUCTION

Low-grade systemic inflammation is a persistent condition characterized by subclinical activation of systemic immunoinflammatory processes [1, 2]. It is known that systemic inflammation is involved in the pathophysiology of cardiovascular [3], endocrine [4], dermatological [5], oncological [6], and neurological diseases [7]. There is also evidence of activation of immune and inflammatory mechanisms in mental disorders such as depression [8–10], schizophrenia [8, 11, 12], and anxiety disorders [13]. Genetic predisposition, early life adversity, acute or chronic stress, unhealthy diet, and changes in the microbiome all contribute to this activation [1, 9, 14]. Systemic inflammation might influence the course of mental disorders, their clinical features, and severity of psychopathological symptoms [15–17]. An association between systemic inflammation and treatment therapeutic resistance has been established [18, 19]. In addition, systemic inflammation may be one of the common pathogenetic links between mental disorders and the metabolic syndrome, contributing to their frequent comorbidity [20, 21].

Peripheral blood levels of pro- and anti-inflammatory cytokines are usually considered as biomarkers of systemic inflammation in various mental disorders [22, 23].

Inflammatory hematological ratios (IHRs), such as the neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR), platelet to lymphocyte ratio (PLR) can serve as inexpensive and readily available biomarkers [24, 25]. The above listed ratios, which characterize both innate and acquired immunity [26], have been studied as risk factors and/or predictors of the severity of COVID-19 [27], oncological [28], endocrine [29], and cardiovascular disorders [30, 31].

The rationale for studying IHRs in the context of mental disorders stems from the involvement of certain immune cells in the pathological processes associated with inflammation. One of the reasons for a decrease in the number of lymphocytes relative to other cells, in particular neutrophils, may be an increase in catecholamines, as well as in the blood prolactin and cortisol levels, which is observed, for example, under stress. There is evidence that monocytes can enter the central nervous system (CNS) and increase neuroinflammation, which, combined with a potential decrease in the lymphocyte count, justifies interest in the ratio of these cells. Platelets contain pro-inflammatory factors (metalloproteinases, chemokines, cytokines, etc.) and can be involved in an increase in the permeability of the blood-brain barrier and the regulation of inflammation in the CNS, which suggests that it is important to study their number relative to other cells; in particular, lymphocytes [32]. Elevated IHRs have been observed in patients with schizophrenia [33–35] and affective disorders [36, 37]. Research into the relationship between IHRs and schizophrenia is summarized in the scoping review that includes the results of 13 studies, predominantly in adult patients [38]. Given that many chronic and recurring mental disorders manifest themselves in adolescence [39, 40], systematizing IHRs studies in this age group is important. Moreover, many mental disorders in adolescence are "transdiagnostic" [41], posing challenges for their diagnosis and prognosis [42–44].

The aim of this scoping review was to summarize the findings from the studies that investigated the relationship of IHRs with mental disorders in adolescent patients. The following study questions were addressed in this review: 1) In what mental disorders in adolescents is there a difference in IHRs compared with healthy individuals of the same age? Have IHRs been examined as diagnostic biomarkers of mental disorders in adolescence (with cut-off values, sensitivity, and specificity calculations)? 2) Is there an association between IHRs and clinical features reflecting more severe/acute manifestations of mental disorders (severity of symptoms, acute phase of the disorder, presence of self-harm/suicidal behaviors), as well as the treatment response and the components of the metabolic syndrome? Have IHRs been examined as prognostic biomarkers for these variables (with cut-off values, sensitivity, and specificity calculations)?

METHODS

Protocol and registration

The aim of this scoping review, eligibility criteria, and methods for this review were defined in a protocol which is available upon request addressed to the corresponding author. The protocol was not registered in a public database. No changes were made to the protocol during the study (search, data extraction, and analysis). No deviations from the protocol were identified.

Eligibility criteria

The review included original studies that:

1. Were conducted in adolescents (aged 10 to 19 years inclusive) with mental disorders;
2. Assessed ihrs as a studied parameter (study factor);
3. Were published in english; and
4. Were published before December 31, 2023.

The following studies were not included:

1. Those with mixed-age samples (younger children and adolescents, adolescents and adults); and
2. Those that assessed IHRs in anorexia nervosa (criterion is justified by the likely influence of undernutrition on the activity of immune inflammation [45]).

Information sources

The search for information sources was carried out in the electronic database MEDLINE (access via PubMed[1]). The final search was conducted on January 16, 2024.

Search

To identify potentially relevant sources, a search query was used, which was generated through the following steps:

1. Identifying 3 primary concepts consistent with the aim of the review: IHRs, adolescence, mental disorders;

[1] Available from: https://pubmed.ncbi.nlm.nih.gov

2. Expanding these concepts with relevant synonyms;
3. Combining keywords using boolean operators;
4. Finalizing the search query based on the result of a discussion and consensus amongst all authors after a pilot search in the MEDLINE electronic database: (blood count parameters) OR (inflammatory ratios) OR (lymphocyte monocyte ratio) OR (platelet lymphocyte ratio) OR (systemic immune inflammation index) OR (monocyte-to-high-density lipoprotein ratio) AND (adolescents) AND (mental disorders) OR (depression) OR (suicide) OR (schizophrenia) OR (bipolar disorder).

The search was conducted by one of the authors (OL).

Selection of sources of evidence

The selection of publications from the identified sources was carried out in 3 stages:

1. Screening by titles and abstracts to exclude obviously irrelevant sources of information (e.g. *In vitro* studies, studies on laboratory animals, studies that included only adults);
2. Full texts retrieval; and
3. Analysis of the retrieved full-text sources using the eligibility criteria indicated above.

If the inclusion criteria were met and no exclusion criteria were met, studies were selected for inclusion in the review regardless of their design. Sources were selected independently by two authors (MP and OL). Discrepancies identified during comparison were corrected through discussion and consensus-building amongst all authors.

Data charting process

Data were extracted from the selected publications according to a pre-designed data collection form. Data were charted by one of the authors (OL) and subsequently cross-checked by another author (MP). Inconsistencies were discussed by all authors. All identified discrepancies were of a technical nature. There were no major discrepancies.

Data items

The following data were extracted: authors, country, year of publication, study design, diagnoses and diagnostic criteria, age, sample size, sex distribution of participants, presence/absence of treatment, study setting (inpatient or outpatient), IHR values (any parameters were extracted – all ratios calculated by the authors of the original papers based on hematology data), and the statistical significance of the differences compared with the control group. If there were healthy controls in the study, data from both the patients and the healthy participants were extracted.

Additionally, we extracted the findings regarding relationship between IHRs and the severity of symptoms, the disease phase, the presence of self-harm/suicidal behaviors, the treatment response, the components of the metabolic syndrome (body mass index, waist circumference, blood pressure, plasma glucose and glycated hemoglobin levels, lipid profile), as well as the results of the Receiver Operator Characteristic (ROC) curve analysis with IHRs cut-off values, sensitivity, and specificity (if the source contained these data).

Critical appraisal of individual sources of evidence

Not performed.

Synthesis of results

All relevant publications were analyzed after being assigned to one of the two groups. The first group included studies that compared IHR values between adolescents with a mental disorder and healthy individuals of the same age (healthy controls). The second group included studies that examined the relationship between IHRs and clinical variables (such as the phase of the disease, the presence of self-harm/suicidal behaviors). Data extracted from publications within each group were tabulated. Statistical methods were not used to analyze the data.

RESULTS

Selection of sources of evidence

The search query identified 490 publications. After reviewing the titles of the articles and their abstracts, 465 publications were excluded as not relevant to the scope of the review (the reasons for the exclusion of each source were not recorded at this stage). Of the remaining publications, 1 was excluded from the review due to the unavailability of the full text. After reviewing the full texts of 24 articles, we included 11 publications in the review [46–56]. The main reason for exclusion from analysis was that the studies were ineligible due to the age of the participants (Figure 1).

Characteristics of sources of evidence

The articles selected for the review were published between 2018 and 2023. All the publications included original studies. Geographically, 6 studies were conducted in Turkey

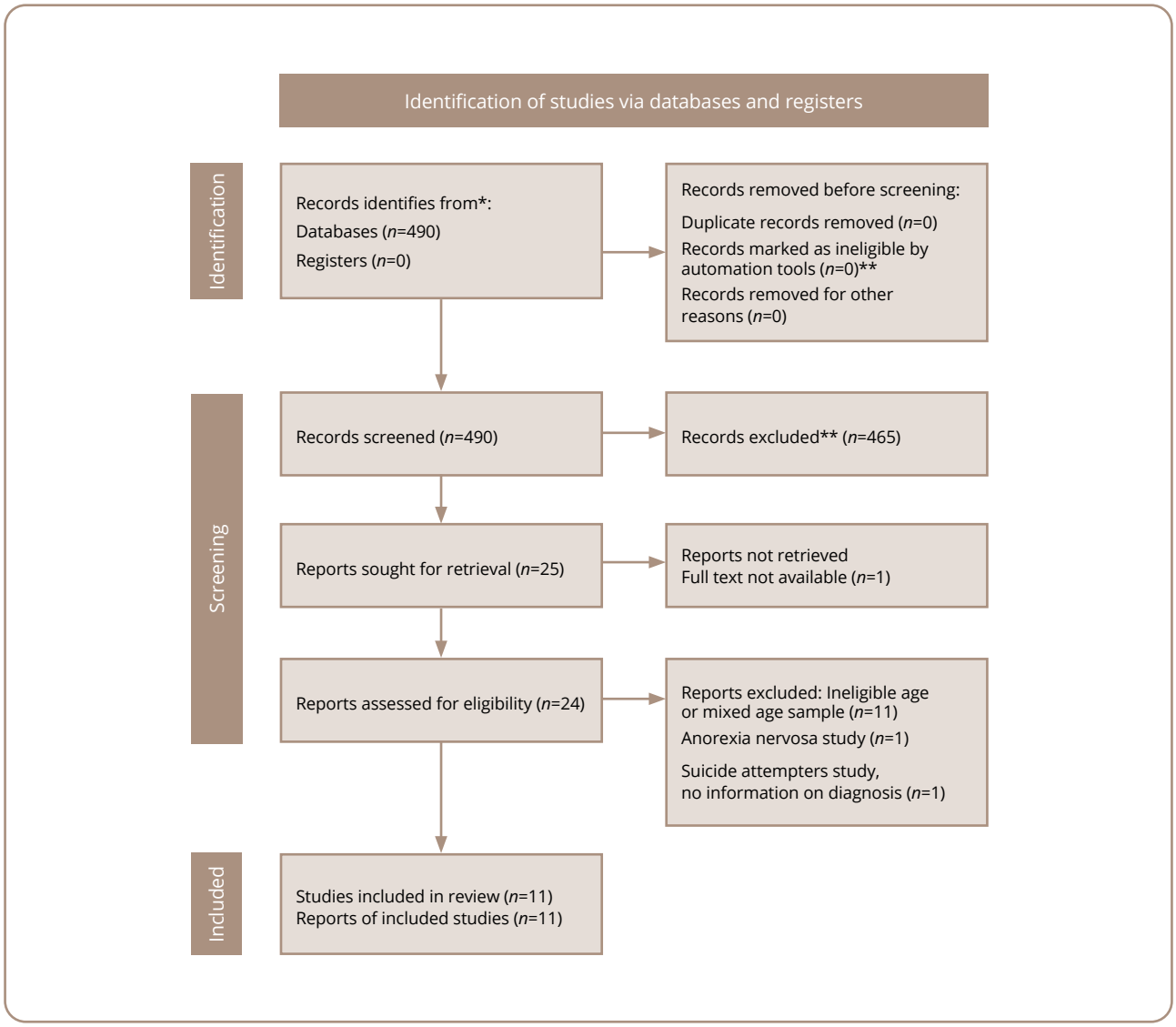

Figure 1. PRISMA flow diagram [57] of the literature search and the selection process.

Note: *All records were identified from MEDLINE database search (accessed via PubMed). **Automation tools were not used in this study. Records were excluded by a human.

[47–52], 2 in China [53, 54], 2 in Israel [55, 56], and 1 in Slovakia [46]. Six studies examined data from adolescents with affective disorders: 2 studies included patients with bipolar disorder (BD) [50, 52], 2 studies included patients with major depressive disorder (MDD) [51, 53], 1 study included patients with affective episodes of BD/MDD [55], and 1 study included patients with various types of affective disorders [54]. One study included adolescents with psychotic disorders [56]; 1 — obsessive-compulsive disorder (OCD) [49]; 1 — attention-deficit hyperactivity disorder (ADHD) [47]; and 1 — substance use disorders (SUD) [48]. Another study examined 2 groups of adolescents with autism spectrum disorders (ASD) and with ADHD [46]. All included studies were cross-sectional. The characteristics of the studies included in the review, as well as their main results, are presented in Tables 1 and 2. The description of the study designs in the Tables is indicated as per original sources.

Results of individual sources of evidence

Comparison of adolescents with mental disorders with healthy controls

IHR values in adolescents with mental disorders and healthy adolescents were compared in 7 [46–52] out of the 11 studies (see Table 1). In these studies, higher NLR and PLR values were found in adolescents with ADHD [47],

Table 1. Comparison of inflammatory hematological ratios in adolescents with psychiatric disorders vs healthy controls

Reference	Country	Type of study	Diagnosis/ diagnostic criteria	Eligible age, range	Patients					Healthy controls				*p*-value
					n	Average age*	Gender (M/F)	Treatment/ setting	IHR*	*n*	Average age*	Gender (M/F)	IHR*	
Ferencova, et al., 2023 [46]	Slovakia	Cross-sectional	ASD/ DSM-5	10–19	20	12.4 (1.9)	15/5	Naive/ inpatient	NLR 1.15 (1.02–1.43) MLR 0.20 (0.15, 0.28) PLR 113.0 (99.7–119.0) LMR 4.92 (3.64–6.52) PMR 409 (370–590)	20	13.2 (1.9)	15/5	NLR 0.97 (0.80-1.37) MLR0.19 (0.16-0.22) PLR 103.0 (85.4-113.0) LMR 5.23 (4.56-6.45) PMR 531 (466-688)	>0.05 (all variables)
			ADHD/ DSM-5	10–19	20	13.4 (1.8)	15/5	Naive/ inpatient	NLR 1.21 (0.91-1.73) MLR 0.19 (0.14–0.24) PLR 102.0 (72.1–125.0) LMR 5.22 (4.17–7.05) PMR 583 (415–700)					
Önder, et al., 2021 [47]	Turkey	Retrospective cross-sectional	ADHD/ DSM-5	12–17	24	NR	NR	Mixed (both naive and treated)/ outpatient	NLR 1.95 (0.81) PLR 132.50 (42.35)	29	NR	NR	NLR 1.16 (0.38) PLR 97.57 (18.37)	<0.001 (NLR) 0.001 (PLR)
Karatoprak, et al., 2021 [48]	Turkey	Retrospective cross-sectional	SUD/ DSM-5	12–18	55	17 (16–17)	55/0	Naive/ outpatient	NLR 1.65 (1.17–2.18) PLR 111.05 (86.11–130.62)	61	17 (16–17)	61/0	NLR 1.44 (1.10–1.68) PLR 92.39 (83.75–107.28)	0.006 (NLR) 0.007 (PLR)
Özyurt, et al., 2019 [49]	Turkey	Cross-sectional	OCD/ DSM-5	12–18	60	14.61 (1.81)	17/43	Naive/ outpatient	NLR 190.91 (148.00) PLR 118.02 (49.96)	128	14.37 (1.80)	27/101	NLR 148.81 (0.73) PLR 104.61 (44.66)	0.003 (NLR) 0.004 (PLR)
Ceylan, et al., 2019 [50]	Turkey	Cross-sectional	BD-type I (remission)/ DSM-5	14–17	38	16.3 (0.9)	10/28	NR/ outpatient	LMR 4.71 (1.7) NLR 1.84 (0.8)	37	16.8 (0.6)	10/27	LMR 5.57 (1.5) NLR 1.80 (0.6)	0.54 (LMR) 0.75 (PLR)
Özyurt, et al., 2018 [51]	Turkey	Cross-sectional	MDD/ DSM-5	12–18	67	14.47 (1.85)	20/47	Naive/ outpatient	NLR 2.1 (1.1) PLR 127.14 (35.26)	121	14.46 (1.77)	26/95	NLR 1.59 (0.57) PLR 113.3 (36.86)	<0.001 (NLR) 0.005 (PLR)
Binici, et al., 2018 [52]	Turkey	Cross-sectional	BD-type I (remission)/ DSM-IV-TR	NR	36	16.42 (1.29)	15/21	Treated/ outpatient	NLR 1.9 (0.78) PLR 107.03 (32.04)	30	16.3 (1.19)	16/14	NLR 1.72 (0.77) PLR 122.35 (32.04)	0.38 (NLR) 0.05 (PLR)

Note: ADHD — attention deficit/hyperactivity disorder; ASD — autism spectrum disorders; BD-type I — bipolar disorder, type I; DSM-IV-TR — Diagnostic and Statistical Manual of mental disorders, fourth edition, text revision; DSM-5 — Diagnostic and Statistical Manual of mental disorders, fifth edition; IHR — inflammatory hematological ratios; LMR — lymphocyte to monocyte ratio; MDD — major depressive disorder; MLR — monocyte to lymphocyte ratio; NLR — neutrophil to lymphocyte ratio; NR — not reported; OCD — obsessive-compulsive disorder; PLR — platelet to lymphocyte ratio; PMR— platelet to monocyte ratio; SUD — substance use disorders. *Data is presented in the following way: mean (standard deviation), if one value in parentheses; median (interquartile range), if two values in parentheses separated by a dash.

Table 2. Comparison of inflammatory hematological ratios in adolescents with psychiatric disorders with regard to clinical features

Reference	Country	Type of study	Diagnosis/ diagnostic criteria	Eligible age, range	Treatment/ setting	Patients					Controls (comparison group of patients)					*p*-value
						Clinical feature under study	*n*	Average age*	Gender (M/F)	IHR*	Clinical feature under study	*n*	Average age*	Gender (M/F)	IHR*	
Cui, et al, 2023 [53]	China	Retrospective cross-sectional	MDD/ ICD-10	10–18	Naive/ inpatient	Suicide attempt	38	14.87 (1.89)	9/29	SII index 537.49 (261.62)	No suicide attempt	225	14.75 (1.78)	76/149	SII index 396,92 (200.68)	0.002
Zheng, et al., 2022 [54]	China	Cross-sectional	Mood or emotional disorders/ ICD-10	13–18	Treated/ inpatient	NSSI, DSM-5	106	15 (median)	17/89	NLR 1.46 (0.33) MLR 0.19 (0.01) PLR 115.66 (3.4)	No NSSI, DSM-5	95	15 (median)	21/74	NLR 1.34 (0.53) MLR 0.16 (0.04) PLR 107.85 (17.52)	0.091 (NLR) 0.001 (MLR) 0.007 (PLR)
Drapisz, et al., 2022 [55]	Israel	Retrospective cross-sectional	Major affective episodes/ DSM-5	10–19	Treated/ inpatient	Manic episode	63	15.9 (1.6)	38/25	NLR 2.36 (1.7)	Depressive episode	242	15.1 (1.8)	147/95	NLR 1.87 (1.00)	0.001
						Manic episode	13	14.9 (mean)	6/7	NLR 2.00 (0.8)	Remission	13 **	15.6 (mean)	6/7	NLR 1.50 (0.5)	0.001
Bustan, et al., 2018 [56]	Israel	Retrospective cross-sectional	Patients hospitalized in the acute ward without evidence of affective episodes (depressive, manic, hypomanic or mixed episodes)/ DSM-5	10–19	Treated/ inpatient	Psychotic	81	15.9 (1.6)	47/34	NLR 2.51 (1.8)	Non psychotic	285	14.7 (1.8)	147/138	NLR 1.91 (1.0)	0.001
						Acute psychosis	20	15.9 (mean)	NR	NLR 2.65 (2.0)	Remission	20 **	16.3 (mean)	NR	NLR 1.74 (0.8)	0.048

Note: DSM-5 — Diagnostic and Statistical Manual of mental disorders, fifth edition; ICD-10 — International Classification of Diseases, 10th revision; IHR — inflammatory hematological ratios; MDD — major depressive disorder; MLR — monocyte to lymphocyte ratio; NLR — neutrophil to lymphocyte ratio; NR — not reported; NSSI — non-suicidal self-injury; PLR — platelet to lymphocyte ratio; SII — systemic immune-inflammation.
*Data is presented in the following way, unless otherwise stated: mean (standard deviation). ** Same patients as in the Patients group.

substance use disorders [48], MDD [51], and OCD [49]. In the latter study, the NLR values were many times higher (approximately 100 times) than in other studies, which may be the result of a technical error on the part of the authors of the original article (for more details, see below, section "Limitations"). No statistically significant differences in IHRs between patients and healthy individuals were found in the studies of adolescents with BD [50, 52], as well as in the study that included 2 samples — adolescents with ASD and ADHD [46].

Diagnostic value of IHRs

None of the 7 studies listed above assessed the diagnostic value of IHRs (cut-off values, sensitivity, and specificity were not reported).

Association between IHRs and the severity of symptoms of mental disorders

The association between IHRs and the severity of psychopathological symptoms was examined in 2 studies [47, 51]. In adolescents with ADHD, no association was found between IHRs and the symptoms severity [47]. In adolescents with MDD, NLR values were positively correlated with the Beck's Depression Inventory score and the disease duration [51]. It is worth noting that in adolescents with BD, neither NLR nor PLR were correlated with the duration of the disorder or age of its onset [52]. Adolescents with OCD and comorbid anxiety disorders (which indirectly suggests a greater severity of the disorder) had higher NLR compared with OCD without comorbidity [49].

Association between IHRs and other clinical features of mental disorders

Four studies [53–56] investigated the association between IHRs and certain clinical features of a mental disorder (see Table 2). One study demonstrated a statistically significant increase in the systemic immune-inflammation index (SII, the product of platelet and neutrophil counts divided by the lymphocyte count) in adolescents with MDD who had attempted suicide compared with patients with MDD without a history of suicide attempts [53]. Another study found a significant increase in MLR and PLR in adolescents with non-suicidal self-injuries in affective disorders compared with similar patients without self-injuries [54]. In the third study, higher NLR values were observed in adolescents in a manic episode of BD than in a depressive episode [55]. Additionally, a significant decrease in NLR in remission was observed compared with a manic episode (mean interval between blood tests was 264 days) [55]. Finally, the fourth study demonstrated that the mean value of NLR in adolescents with psychotic disorders (mainly schizophrenia spectrum) was higher than in non-psychotic patients (with conduct disorders, adjustment disorder, ADHD) [56]. The same study showed a decrease in NLR after patients had achieved clinical remission compared with an acute psychotic state (mean interval between blood tests was 157 days) [56].

Prognostic value of IHRs

Although a ROC analysis was conducted in two studies that included adolescents with self-harm/suicidal behaviors to determine the IHR cut-off values, their sensitivity and specificity [53, 54], the results did not allow us to assess the prognostic value of IHRs. In the study that included adolescents with MDD — with or without a history of suicide attempts [53] — the area under the curve for the SII index was 0.661 (95% confidence interval, CI, 0.550–0.772; p=0.002), the optimal cut-off value for the SII index (based on the maximum value of Youden's index) was 548.15, with a sensitivity of 63% and specificity of 83%. Based on this cut-off value, patients were divided into high and low SII groups and a binary logistic regression analysis was performed. After adjusting for sex, age, body mass index, illness duration, and Hamilton Depression Rating Scale score, the odds of a suicide attempt within the last 7 days in the group of adolescents with high SII index were almost 14 times higher compared with the group of patients with SII index below the cut-off (odds ratio, OR=13.92; 95% CI 5.60–34.69; p <0.001). At the same time, a high SII index was not associated with a suicide attempt more than 7 days prior (OR=0.55; 95% CI 0.06–4.84; p=0.587) [53]. For non-suicidal self-injury in patients with affective disorders [54], the area under the curve was 0.638 (95% CI 0.561–0.715; p <0.001) for MLR and 0.611 (95% CI 0.533–0.689; p <0.001) for PLR. The cut-off values calculated by the authors of the original study were 0.135 for MLR (sensitivity 91%, specificity 34%) and 127.5 for PLR (sensitivity 40%, specificity 81%) [54]. It should be emphasized that although the authors of these studies indicate the association between increased "risk" of self-harm/suicidal behaviors and higher IHR values, this conclusion is based on data from retrospective cross-sectional studies, which completely excludes the possibility of assessing the prognostic value of IHRs (for more details, see below, section "Limitations").

Association between IHRs and metabolic disturbances

The relationship between IHRs and the metabolic syndrome was not examined in the studies included in this review. In one study, which included adolescents with BD, no correlations between NLR or PLR and body mass index were found [52].

Association between IHRs and the treatment response

None of the studies included in this review examined the association between IHRs and the treatment response in mental disorders. One study revealed no differences in NLR or PLR in adolescents with ADHD who did and did not receive pharmacological treatment for their disorder, as well as no correlation of either NLR or PLR with the duration of atomoxetine and/or methylphenidate use [47].

DISCUSSION

Summary of evidence

Our search strategy did not identify any narrative reviews, scoping reviews, systematic reviews, or meta-analyses that systematized studies on the relationship between IHRs and mental disorders in adolescents. Having summarized the findings from 11 original studies selected for this scoping review, we can state the following. First, adolescents with mental disorders (depression, psychotic disorders, OCD, ADHD, substance use disorders) have higher IHRs compared with adolescents without these disorders. Second, IHRs are higher in adolescents with more severe/acute manifestations of the mental disorder (severity of symptoms, mania, exacerbation of psychosis, self-harm/suicidal behaviors). Third, the study results do not allow for the assessment of the diagnostic or prognostic value of IHRs in adolescents with mental disorders.

Limitations

The studies included in our review demonstrated heterogeneity (demographic and clinical characteristics of participants, different diagnoses, study settings, presence/absence of treatment, sample sizes). Although we did not assess the quality of the selected studies, several evident shortcomings are notable. In particular, most of the studies lack information on the procedures of blood collection and hematological analysis. In one study [49], the NLR values in both the patient and control groups were approximately 100 times higher than in other studies. The authors of the original article do not explain this in any way. Additionally, the existing discrepancy between the mean NLR value and its standard deviation in the control group (a difference of approximately two decimal orders, see Table 1) indicates a possible technical error (typo). However, such errors, combined with the above-mentioned heterogeneity of the studies, limit the comparability and generalizability of the results.

All the studies included in the review, according to their authors, were cross-sectional, which makes it impossible to establish causal relationships. Only 2 of these studies included a longitudinal (retrospective) part [55, 56], allowing to track the changes in the variables under study across time in some patients. About half of the studies were retrospective, raising concerns about the quality of the data that the study authors extracted from medical records not initially intended for study purposes. Both of the studies that performed an ROC analysis to calculate IHR cut-off values, sensitivity, and specificity were retrospective cross-sectional [53, 54]. Although the authors of these studies related high IHR values to the "risks" of self-harm/suicidal behaviors (suicide attempts and non-suicidal self-injury), those "risks" corresponds solely to past behaviors, precluding an assessment of the prognostic value of the suggested statistical models.

This review did not consider any other markers of inflammation, which prevents one from drawing conclusions about whether IHRs are independent indicators of systemic inflammation or are related to other immune inflammatory changes associated with mental disorders. This limitation precludes the possibility of assessing the influence of age on the associations of IHRs with other immune inflammatory markers.

Finally, some relevant studies may have been missed for the following reasons. First, the search for sources was limited to one database. Second, the search query used may not have been sensitive enough. Third, auxiliary search methods were not used, in particular, in searching through reference lists in the relevant sources and other work published on the topic that used a systematic literature search methodology. For example, a published retrospective study of IHRs in 32 adolescents with early-onset schizophrenia was identified after the completion of the selection of information sources [58]. The reason for the omission was that the publication was not indexed in the MEDLINE database in which the search was conducted. The omitted study showed higher NLR in adolescents with

schizophrenia compared with healthy controls of the same age, which is consistent with the results of the study included in our review demonstrating elevated NLR in adolescents with psychotic disorders (including schizophrenia) compared with non-psychotic adolescents [56].

Discussion of the main results in comparison with the results of IHR studies in adults and younger children

Association between IHRs and mental disorders

Several systematic reviews and meta-analyses have been published summarizing data on IHRs in mental disorders across various age groups, including children [25, 59], adults [33, 36, 37, 60, 61], and mixed-age samples [38]. The majority of these studies focus on affective disorders in adult patients.

A meta-analysis of the results of 7 studies on IHRs in BD in adults (1,334 participants) demonstrated that patients had higher NLR and PLR than healthy individuals: standardized mean difference, SMD=0.672; 95% CI 0.516–0.828; p <0.001 and SMD=0.425; 95% CI 0.004–0.846; and p=0.048, respectively [36], reflecting a moderate effect size. The results of 2 studies of BD in adolescents included in our review did not show differences in IHRs compared with the healthy controls [50, 52]. However, both adolescent studies included patients in remission, and, given this, their results are entirely consistent with the adult studies on BD which also included patients in remission and similarly revealed no differences from healthy controls [36].

A meta-analysis of the results of 4 studies on IHRs in MDD (553 participants) demonstrated higher NLR in adult patients compared with healthy controls (SMD=0.670; 95% CI 0.072–1.268; p=0.028) [36]. A meta-analysis of the results of studies examining any relationship between IHRs and depression (2,580 adult patients with depression and 2,664 healthy participants) allowed us to draw similar conclusions: higher NLR in depressive patients than in healthy controls (SMD=0.33; 95% CI 0.15–0.45; p <0.001) and no differences in PLR or MLR [60]. Another meta-analysis (18 studies, 2,264 adults with depression and 2,415 healthy participants) confirmed the increase in NLR (SMD=0.33; 95% CI 0.15–0.52; p <0.001) and PLR (SMD=0.24; 95% CI 0.02–0.46; p <0.05) in depression compared with healthy individuals [37]. All these results are consistent with the results of the study included in our review [51], which found higher NLR and PLR in adolescents with MDD compared with healthy individuals of the same age.

A meta-analysis of studies on IHRs in psychotic disorders in adults (8 studies, 3 of which included patients with the first psychosis episode and 5 with schizophrenia; a total of 683 patients and 551 healthy participants) demonstrated that patients with non-affective psychosis had higher NLR and MLR than healthy controls (SMD=0.715; 95% CI 0.525–0.905; p <0.001 and SMD=0.417; 95% CI 0.147–0.686; p=0.002, respectively) [33]. A study in adolescents with acute psychotic disorders included in our review also found an increase in NLR compared with healthy adolescents (MLR was not assessed in that study) [56]. The increase in NLR in adolescents with psychotic disorders compared with non-psychotic adolescents is also confirmed by a meta-analysis of the results of 3 studies in this age group including 557 participants [25].

A meta-analysis of the results of 8 studies on IHRs in younger children with ADHD (mean age of participants of these studies varied from 8.3±1.7 to 10.33±3.15 years) demonstrated that they had higher NLR and PLR than healthy children (939 patients and 652 healthy children; SMD=0.49; 95% CI 0.15–0.82; p=0.004 and SMD=0.31; 95% CI 0.03–0.59, respectively), while no difference in MLR was observed [59]. The results of the studies in adolescents included in our review were inconsistent: one study demonstrated increased NLR and PLR in adolescents aged 12–17 years with ADHD [47], while another found no differences compared with healthy controls [46].

As for other mental disorders (which have been studied in adolescents), elevated IHRs compared with healthy controls were demonstrated in adult patients with OCD [62, 63] and SUD [64, 65], and in children with ASD [66–68]. It should be noted that the number of such studies is limited and their results are somewhat contradictory, which makes comparisons extremely difficult, especially regarding the age-specificity.

Overall, a comparison of studies on IHRs in mental disorders between adolescents and adults indicates that the most reproducible abnormalities compared with healthy individuals in both age groups are NLR and (to a lesser extent) PLR increase in affective disorders [36, 37, 51, 60], as well as NLR increase in schizophrenia spectrum disorders (first psychotic episode and schizophrenia) [25, 33, 56]. Comparison of studies of IHRs in ADHD between adolescents [46, 47] and younger children [59] demonstrates an increase in NLR compared with healthy controls (although not in all studies) in both age groups. Thus, for those indications which were studied across various age groups

(younger children, adolescents, adults), we did not find any age-related differences in the association between IHRs and mental disorder.

Association between IHRs and the clinical features of mental disorders

Relationships between IHRs and the severity of psychopathological symptoms have been investigated in a few studies. One of the studies included in our review demonstrated a correlation between NLR and the severity of depressive symptoms in adolescents with MDD [51]. In adults, the severity of depression correlated for stronger with PLR than NLR [69, 70], which may indicate age-related differences in the relationship between IHRs and the severity of depressive symptoms. A correlation between NLR and symptom severity has been observed in adult patients with schizophrenia [71]. In ADHD, no correlations between IHRs and symptom severity have been found in either adolescents [47] or younger children [72]. Given the limited number of studies, it is difficult to determine the age-specific differences in the relationship between IHRs and the severity of psychopathological symptoms. Therefore, further studies are needed to confirm the reproducibility of the relevant findings.

In the studies investigating the relationship between IHRs and the illness phase, higher NLR values were observed in adolescents in a manic episode of BD than in a depressive episode or remission [55], as well as in adolescents with an acute psychosis compared with remission [56], which is fully consistent with the results of the studies in adults with BD [36, 73, 74] and psychotic disorders, including schizophrenia [33, 75]. These data confirm that higher IHR values are associated with more acute manifestations (mania, exacerbation of psychosis). However, no conclusions about the age-specificity in the relationship between IHRs and the disease phase can be drawn.

One of the important "indicators" of the acuity/severity in psychiatry is self-harm/suicidal behaviors. A study included in our review demonstrated an increase in the SII index in adolescents with MDD who attempted suicide compared with adolescents with MDD without suicide attempts [53]. Another study (193 adolescents aged 11–18 years with a history of suicide attempts and 109 non-suicidal participants of the same age), excluded from our review due to the lack of information regarding psychiatric diagnoses of study participants, demonstrated the association between suicidality and higher NLR, MLR, and PLR values [76]. In a sample of young adults (137 patients with MDD aged 18 to 24 years and 56 healthy controls of the same age), suicidality was associated with higher MLR values [77]. In adults, a systematic review of 11 studies (819 patients with MDD and suicidal behavior, 494 patients with MDD without suicidal behavior, and 388 healthy participants) revealed that suicidal behavior was associated with increased NLR, but not MLR or PLR [61]. This finding was supported by the results of the study of adult patients with depression who had survived a suicide attempt, and in whom NLR was also higher compared with controls [78]. The association between suicidal behavior in adults and high NLR values has been demonstrated not only in depression, but also in BD [26]. All these findings suggest age-related differences in the associations between IHRs and suicidal behavior in adolescents (increased NLR, MLR, and PLR [76]), young adults (only MLR increased [77]), and adult patients (only NLR increased [26, 61, 78]). It is noteworthy that non-suicidal self-injury in adolescents was associated with elevated MLR and PLR, but not NLR [54]. The differences between age groups in the correlation between certain IHRs with self-harm/suicidal behaviors may reflect age-related differences (to date unproven) in the biological mechanisms of such behaviors.

In our opinion, the associations between IHRs and certain clinical features of mental disorders (severity of symptoms, phase of the disease, presence of self-harm/suicidal behaviors) might hypothetically indicate a higher degree of activation of systemic inflammation in more severe/acute cases. One can assume that patients with higher IHR values (i.e. with more pronounced systemic inflammation) may represent a specific subtype of psychiatric disorders, likely differing in course and prognosis [16, 17]. However, the studies included in our review do not allow one to speculate on a causal relationship between IHRs and the severity of mental disorders. Elevated IHRs in various mental disorders may indicate common etiopathogenetic pathways, specifically common predisposing genetic factors [79–81]. Conversely, an increase in IHRs may be a consequence of a mental disorder, reflecting concomitant nonspecific physiological stress [17, 82]. It is quite likely that there is a bidirectional relationship between systemic inflammation and mental disorders, with each exerting a negative influence on the other [83]. Additionally, high intra- and inter-individual variability of inflammatory biomarkers is obvious, depending on a large number of factors (hereditary and environmental), which

largely accounts for the low reproducibility and frequent inconsistency of study results [84].

Association between IHRs and the treatment response

The hypothetical influence of systemic inflammation on the development of treatment resistance [18, 19, 85] provides a rationale to study the relationship between IHRs and the response to treatment. We were unable to find studies that examined this relationship in adolescents with mental disorders. Studies in other age groups (young adults, adults) demonstrate conflicting results. On the one hand, higher values of the SII index and SIRI (systemic inflammatory response index) have been demonstrated in non-responders compared with responders in bipolar depression [86, 87]. On the other hand, elevated IHRs have been shown to be associated with higher treatment efficacy in psychotic depression [88, 89] and schizophrenia [90, 91].

Association between IHRs and metabolic disturbances

Our search strategy did not identify studies specifically aimed at assessing the relationship between IHRs and the metabolic syndrome or its components in adolescents with mental disorders. In most of the selected studies, excess weight or obesity was an exclusion criterium, which likely explains the lack of association between the body mass index and IHRs in the only study that assessed their relationship [52]. This assumption is supported by the results of the study in a sample of young adults (18–24 years) demonstrating higher NLR in MDD comorbid with obesity than in MDD without obesity, as well as a weak positive correlation between NLR and the body mass index [92].

Diagnostic and prognostic value of IHRs in adolescents with mental disorders

The findings from the studies showing higher IHRs in adolescents with mental disorders compared with controls [47–49, 51, 56] are promising in regards of using IHRs as diagnostic biomarkers. However, there is no consistent data on differences in IHRs in various diseases, which could have objectified and significantly facilitated the differential diagnosis, which poses particular difficulties in adolescents due to the transdiagnostic clinical presentations [42–44]. The results of IHR comparisons between various mental disorders in adults have low reproducibility. As an example, one study demonstrated that adults with exacerbation of schizophrenia had higher NLR than patients with BD in a manic episode [93], while the other study showed the opposite results [94]. In another study differences in IHRs between adult patients with bipolar and unipolar depression were observed [95], however in the large-scale cross-sectional study (13,888 participants) no significant differences in IHRs either between BD and MDD, or between BD and schizophrenia, were found [82].

Although the results of 2 studies included in our review indicate an association between IHRs and self-harm/suicidal behaviors [53, 54], the retrospective cross-sectional design of both studies excludes the possibility of using calculated cut-off values to predict the risk of future suicide attempts or non-suicidal self-injury. In the absence of studies linking IHRs to treatment response and metabolic syndrome, one can speculate on a possible use of IHRs for predicting the treatment response or assessing metabolic risks in adolescents solely on the grounds of the studies conducted in young adults and adults [88–92].

Perspectives for future research

One of the potential directions for future research would appear to be clarifying the role of systemic inflammation in the etiopathogenesis of mental disorders at different stages of their development, which requires a comprehensive assessment of not only IHRs, but also other immune inflammatory markers in conjunction with neurobiological, genetic, socio-demographic, and clinical variables across various age groups (younger children, adolescents, young adults, adults) at different stages of development/manifestation of a mental disorder.

Another direction is examining the diagnostic utility of IHRs, taking into account the transdiagnostic nature of clinical presentation in adolescence and complicated differential diagnosis. This area requires large-scale comparative studies, including samples of adolescents with various psychiatric diagnoses.

Evaluating IHRs as prognostic biomarkers also seems to be a promising direction. Models predicting the risks of suicide attempts and non-suicidal self-injury could assist in identifying adolescents at increased risk of self-harm/suicide and developing personalized preventive programs. Research on the prognostic value of IHRs in predicting treatment response and the risk of treatment resistance is essential for the development of adolescent-specific interventions aimed at the management of treatment resistance. Finally, there is an obvious research gap in the

study of the relationship between IHRs and the metabolic syndrome, which are more prevalent in individuals with mental disorders than in the general population [96, 97]. The metabolic syndrome increases the risk of cardiovascular diseases [98, 99], leading to excessive early mortality and significant reduction in life expectancy for patients with mental disorders [100, 101]. That is why identifying adolescents with a high metabolic risk is, in our opinion, of great importance due to the potential reversibility of metabolic disturbances in the early stages. For the development of prognostic models predicting treatment response, the risk of self-harm/suicidal behaviors, and the risk of developing the metabolic syndrome, prospective studies are required.

CONCLUSION

The results of this scoping review support the hypothesis of systemic inflammatory mechanisms activation in mental disorders and demonstrate that IHRs can be used as indicators of immune inflammation in adolescent patients. Elevated IHRs have been observed across a wide range of mental disorders in adolescents (depression, psychotic disorders, OCD, ADHD, substance use disorders); however, the cut-off values for any of these disorders have not been calculated, which makes it impossible to assess IHRs diagnostic value. Also, there is no evidence to suggest that the association between IHRs and these disorders depend on age: similar patterns are observed in adolescents and adults. In both adolescents and adults, higher IHRs correspond to more severe/acute manifestations of mental disorders. Additionally, there is some evidence of age-specificity in the relationship of IHRs with both the severity of psychopathological symptoms and self-harm/suicidal behavior. At the same time, the limitations of the studies included in our review do not allow neither the assessment of the utility of IHRs as prognostic biomarkers for self-harm/suicidal behaviors in adolescents nor age-related comparisons. Assessment of the clinical value of IHRs as diagnostic and prognostic biomarkers requires confirmation of the reproducibility and specificity of their changes in various mental disorders in studies of higher methodological quality.

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Using the Strategy of Genome-Wide Association Studies to Identify Genetic Markers of Suicidal Behavior: A Narrative Review

Использование стратегии полногеномного поиска ассоциаций (GWAS) для идентификации генетических маркеров суицидального поведения: описательный обзор литературы

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Review

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ABSTRACT

BACKGROUND: Several studies involving various suicidal phenotypes based on the strategy of the search of genome-wide associations with single nucleotide polymorphisms have been performed recently. These studies need to be generalized.

AIM: To systematize the findings of a number of genome-wide association studies (GWAS) for suicidal phenotypes, annotate the identified markers, analyze their functionality, and possibly substantiate the hypothesis holding that these phenotypes reflect a nonspecific set of gene variants that are relevant as relates to stress-vulnerability as a key endophenotype of suicidal behavior (SB).

METHODS: A search on the PubMed and related resources using the combinations "suicide AND GWAS" and "suicidal behavior AND GWAS" was performed. It yielded a total of 34 independent studies and meta-analyses.

RESULTS: For the 10 years since such studies emerged, they have undergone significant progress. Estimates of the SNP heritability of SB in some cases are comparable with estimates of heritability based on the twin method. Many studies show a high genetic correlation with the genomic markers of the most common mental disorders (depression, bipolar disorder, schizophrenia, post-traumatic stress disorder). At the same time, a genomic architecture specific to SB is also encountered. Studies utilizing the GWAS strategy have not revealed any associations of SB with candidate genes that had been previously studied in detail (different neurotransmitters, stress response system, polyamines, etc.). Frequently reported findings from various studies belong in three main groups: 1) genes involved in cell interactions, neurogenesis, the development of brain structures, inflammation, and the immune responses; 2) genes encoding receptors for neurotrophins and various components of the intracellular signaling systems involved in synaptic plasticity, embryonic development, and carcinogenesis; and 3) genes encoding various neuro-specific proteins and regulators.

CONCLUSION: In general, GWAS in the field of suicidology mainly serve the purpose of a deeper understanding of the pathophysiology of suicidal behavior. However, they also demonstrate growing capability in terms of predicting and preventing suicide, especially when calculating the polygenic risk score among certain populations (psychiatric patients) and in combination with tests of different modalities. From our point of view, there exists a set of markers revealed by the GWAS strategy that seems to point to a leading role played by stress vulnerability, an endophenotype that is formed during early development and which subsequently comes to play the role of key pathogenetic mechanism in SB.

АННОТАЦИЯ

ВВЕДЕНИЕ: В последние годы накапливаются данные, полученные с использованием стратегии поиска ассоциаций различных суицидальных фенотипов с однонуклеотидными полиморфизмами, которые нуждаются в обобщении.

ЦЕЛЬ: Систематизировать находки полногеномного поиска ассоциаций (GWAS) по суицидальным фенотипам, аннотировать выявленные маркеры, проанализировать их функциональность и найти возможные подтверждения гипотезы о том, что они отражают неспецифический набор генных вариантов, имеющих отношение к стресс-уязвимости как к ключевому эндофенотипу суицидального поведения.

МЕТОДЫ: Поиск материала осуществляли в базе данных PubMed по ключевым словосочетаниям «suicide AND GWAS», «suicidal behavior AND GWAS» с использованием взаимосвязанных источников, что позволило выявить 34 независимых исследования и метаанализа.

РЕЗУЛЬТАТЫ: За 10 лет с момента своего появления исследования этого типа продемонстрировали значительный прогресс. Оценки SNP-наследуемости суицидального поведения (СП) в ряде случаев приближаются к оценкам наследуемости близнецовым методом. Во многих исследованиях выявляется высокая генетическая корреляция с геномными маркерами наиболее распространённых психических расстройств (депрессия, биполярное расстройство, шизофрения, посттравматическое стрессовое расстройство), но в то же время обнаруживается и специфическая для СП геномная архитектура. Исследования в рамках стратегии GWAS не выявляют ассоциаций СП с наиболее детально исследованными ранее генами-кандидатами (медиаторные системы мозга, система стресс-реагирования, полиамины и др.). Повторяющиеся геномные находки относятся к трем основным группам: 1) гены, вовлечённые в межклеточные взаимодействия, формирование структур мозга, нейрогенез, воспаление и иммунные реакции; 2) гены, кодирующие рецепторы к нейротрофинам и различные компоненты внутриклеточных сигнальных систем, участвующих в синаптической пластичности, эмбриональном развитии и канцерогенезе; 3) гены, кодирующие различные нейроспецифические белки и регуляторы.

ЗАКЛЮЧЕНИЕ: Стратегия GWAS в сфере суицидологии в основном служит целям более глубокого понимания патофизиологии СП, но при этом демонстрирует растущий потенциал в плане предикции и превенции суицидов, особенно при расчёте полигенного риска, среди определённых контингентов (психиатрические пациенты) и в сочетании с тестами других модальностей. Выявляемый средствами GWAS набор наиболее часто повторяющихся маркеров, с нашей точки зрения, отражает ведущую роль в генезе СП феномена стресс-уязвимости — формируемого в процессе раннего развития эндофенотипа, который впоследствии играет роль ключевого патогенетического механизма суицида.

Keywords: *suicidal behavior; genome-wide associative studies; genomic markers; stress vulnerability*
Ключевые слова: *суицидальное поведение; полногеномные ассоциативные исследования; геномные маркеры; стресс-уязвимость*

INTRODUCTION

The research on the genetics of suicide has a long history. The tendency for suicide to run in families has been recognized for a considerable time, and this understanding has consistently served as a basis for acknowledging the role of heredity in this vexing phenomenon, as supported by dedicated studies [1]. Behavioral genetics (psychogenetics) seeks to tackle the challenge of determining the relative contributions of genes and the environment to specific behaviors, psychological traits, or mental disorders [1, 2]. During the pre-genomic era, research on the genetics of suicide used family and twin studies, as well as studies involving adopted children. Those types of studies estimated the heritability of suicidal behavior (SB) to be between 43% and 55%, attributing the remaining influence to environmental factors in their broadest sense (family, upbringing, peers, life stress, social factors, etc.) [3, 4].

In the subsequent phase of the investigation of heredity contributors to SB following the sequencing of the human genome and the advent of cost-effective methods for identifying gene variants, such as the polymerase chain reaction, the genetics of suicide has developed for a long time along the candidate-gene approach [2]. From the perspective of pathophysiology and psychobiology, crucial brain systems such as the serotonergic system, the catecholamine system, the GABAergic system, the excitatory amino acid system, and the stress response system, along with other neurobiological mechanisms, play a central role in SB. These systems influence the diathesis–stress and the associated predisposing traits and behavior patterns that can lead to impulsive or deliberate self-harming actions [5]. Despite hundreds of studies conducted in this area, only a few identified associations, such as those with the genes for tryptophan hydroxylase 2 (*TPH2*), serotonin transporter (*5-HTT*), and the brain-derived neurotrophic factor (*BDNF*), have been confirmed in independent studies [6]. Factors contributing to the frequent discrepancies in the results include small and not-always-monoethnic samples and the heterogeneity of phenotypes [6]. SB accompanies various psychopathologies; some suicides are committed in the context of depression, bipolar disorder, alcohol or drug addiction, and schizophrenia (SCZ) [7]. This is particularly significant for Russian psychiatry, as preventing suicides in clinical populations remains a challenge and has been the focus of targeted studies funded by the state. Notably, only a small proportion of patients with these disorders commit suicide, indicating that the inheritance of SB can be differentiated from the inheritance of mental disorders. This necessitates an in-depth study of the genetic markers of suicide as they compare with markers of the aforementioned psychopathologies and some personality traits, such as aggressiveness or impulsivity [7].

In recent years, the focus of research has shifted from the candidate gene strategy to genome-wide association studies (GWAS) [8]. Unlike the candidate gene approach, GWAS involve a hypothesis-unencumbered search for associations between specific traits, pathologies, or behaviors and a broad array of polymorphisms across the human genome [8]. Central to this approach are single nucleotide polymorphisms (SNPs), the most common genetic variations in the human genome, their proximity to known coding regions, their potential functional significance, and their overall contribution to the heritability of particular pathologies or behaviors. The "Common Disease-Common Variants" hypothesis underlies the GWAS strategy, suggesting that familial pathologies with heritability around 40% can be attributed to the very weak effects of hundreds or thousands of polymorphisms, each with allele frequencies of approximately 40% in the population [8]. Many other considerations from population genetics, the identification of direct and indirect effects, and accounting for linkage disequilibrium and correlations between polymorphisms have led to the understanding that analysis from 500,000 to 1 million SNPs simultaneously, given a sufficiently large monoethnic sample, should result in successful identification of the relevant markers [8]. The tools employed in these studies, such as diagnostic arrays, are commercially available from companies like Illumina, Inc. and Affymetrix, Inc.

The design of studies within this strategy typically involves case-control studies, where populations that either exhibit or do not exhibit a particular behavior or trait (categorical variant) or show a continuum of a trait or behavior (dimensional variant) are compared across a large number of markers. Factors such as phenotype homogeneity and statistical data processing methods, which rely on non-trivial approaches and specialized software when p-values $<7.2\times10^{-8}$ are set as a significance criterion for the entire genome, play a crucial role [9]. Additionally, the GWAS approach employs special techniques such as the multilocus analysis, and analysis from the perspective of protein-protein interactions or probable biochemical pathways, where a set of SNPs is identified based on their potential relation to metabolic processes [8]. From

the identified independent risk markers associated with a particular disorder (ranging from several dozen to several hundreds), a polygenic risk score (PRS) is calculated based on data from the largest or most informative GWAS to date [10]. The importance of the PRS lies in its potential predictive value for certain individuals under particular conditions. Thus, the effectiveness of GWAS significantly depends on data accumulation, sample pooling, comparison with existing databases (repositories of biomedical knowledge), and the statistical analysis methods used. Another important task is to calculate the heritability of the pathology considering all identified markers: known as SNP heritability (h^2_{snp}). Overall, the GWAS strategy enables the exploration of the "genomic architecture" of any complex trait, behavior, or disorder.

Despite the limitations, assumptions, and uncertainties inherent in the method and data processing, GWAS have demonstrated their effectiveness in revealing the genomic architecture of various diseases, such as macular degeneration. They have also led to advances in pharmacogenetics, particularly in psychiatry and addiction medicine [11]. In suicidology, GWAS have also gained wide acceptance despite a significant limitation: a completed suicide (CS) is a relatively rare event globally, occurring in just 0.014% of the population [12], which makes it difficult to classify the occurrence as common. However, it should be borne in mind that the prevalence of suicide attempts (SA) is tens of times higher, and that suicidal ideation (SI), according to various data, can occur in 20-30% of people depending on the sample [13]. These forms of suicidality are not linearly related; while SI and SA can predict future SI and SA to some extent, they have little correlation with future CS [14, 15]. This underscores the need to study genetic markers for each type of SB separately, complicating the task of generalizing GWAS results in suicidology. In response to this, the organization of the Suicide Working Group and the International Suicide Genetics Consortium (ISGC) within the international Psychiatric Genomics Consortium (PGC) appears entirely justified. These groups comprise researchers who collect and curate accumulating data, exchange information, conduct individual GWAS, refine phenotypes, and perform meta-analyses.[1]

Given the challenges associated with the phenomenon of suicide, various approaches are employed in the genetics of suicidality research. Recently, there has been increased attention to both widespread and rare genomic variations, including probable *de novo* mutations, utilizing methodologies like whole exome sequencing (WES) [16]. This approach involves sampling a relatively small number of extended families exhibiting SB across multiple generations [17]. Another interesting combined approach is "convergent functional genomics", which identifies genetic markers through RNA in the blood. This method uses reverse transcription and predicts suicide risk based on several independent lines of evidence, including genetic data, psychological questionnaires, functional tests (such as dexamethasone supression test), and biomarkers profile [18]. Despite these advances, "classical" GWAS remain the strategies most used for studying the genetic architecture of SB.

The results of GWAS projects related to suicidal phenotypes have been summarized multiple times. For instance, in 2014, a group led by M. Sokolowski analyzed 8 studies published at the time. They found no consistent patterns and noted that genome-wide findings were rarely replicated in independent studies [19]. Nevertheless, the potential of such studies was highlighted, especially when it comes to identifying polygenic effects and calculating PRS. Additionally, considerable attention was drawn to a significant predominance of the genes involved in neurogenesis among the findings [19]. In 2020, we conducted a comprehensive review of 15 individual studies on this subject, meticulously annotating all the mentioned genes and scrutinizing the observed associations through the lens of the pathogenetic model of stress vulnerability, which serves as the foundation for understanding SB [20]. Our analysis yielded a significant conclusion: GWAS in the field of SB fail to uncover associations with neurotransmitter systems or the stress response system as pathophysiologically predicted: however, they allow one to identify numerous associations with the genes implicated in the processes of nervous system development and formation, neuroplasticity, intercellular interactions, cell adhesion and proliferation, intracellular signaling systems, and immune responses. We speculated that this validates the diathesis–stress models (vulnerability–stress model), which offer the most logical explanations for SB [4, 21]. According to these models, vulnerability stems

[1] Psychiatric Genomics Consortium (PGC): Suicide Working Group [cited November 2023]. Available from: https://pgc.unc.edu/for-researchers/working-groups/suicide-working-group/

from adverse factors during early development (such as severe stress, multiple adversities and traumatic events), with suicide seen as a consequence of later-life stressors impacting the already "set stage" [21, 22]. Central to these concepts are the interactions between genetic factors and environmental ones, as well as the timing and sensitive periods of development during which these influences occur [20].

Given that stress exerts a pervasive influence affecting various bodily systems, it is unsurprising to uncover associations with a broad spectrum of genetic markers linked to diverse bodily functions, each potentially contributing to vulnerability. This may encompass disruptions in cellular mechanisms during brain structure formation, as well as dysfunctions in other systems such as the neurohumoral regulation system, metabolic functions, and immune responses [20]. We suggested that an unusual set of genetic markers, often inexplicable from the perspective of SB pathophysiology, reflects a degree of susceptibility to early traumatic stress, leading to deviations from normal neural development, cellular imbalances in brain regions, disturbances in synaptogenesis and neuroplasticity, and subsequent structural abnormalities detectable through neuroimaging techniques [20].

Indeed, recent evidence suggests that individuals in various age groups with histories of SI and SA may display deviations from normal cortical and subcortical maturation. Common findings include reduced volumes of the ventral and dorsal regions of the prefrontal cortex, decreased surface areas in the right frontal cortex, and disruptions in the connections between the inferior frontal gyrus and temporal lobes and other brain regions [23–25]. Despite inconclusive findings and remaining challenges in distinguishing between groups displaying SB and those exhibiting depression or bipolar disorder, mounting evidence indicates that SB may indeed stem from the abnormalities of specific brain structures responsible for self-control, risk-taking, impulsivity, affective symptoms, and decision-making errors [23, 24]. These observations underscore the growing interest in further exploration to attempt to identify the genetic markers associated with suicidality, including through GWAS.

It is worth noting that since the publication of our review [20], several new GWAS results focusing on SB and utilizing increasingly larger sample sizes have emerged, alongside new overarching analytical studies. A recent comprehensive review specifically addressed the genetics and epigenetics of SB in all its forms (including non-suicidal self-injury, SI, SA, and CS), encompassing various genetic methodologies [26]. The authors analyzed data from 31 classical GWAS; 7 genome-wide studies employing copy number variation (CNV) as markers; 4 whole-exome studies identifying rare markers; 39 studies assessing PRS; 4 linkage studies (analyzing linked inheritance); 438 studies using the candidate gene strategy, of which 53 assessed gene-environment interaction (GxE); 7 studies that utilized Mendelian randomization; 16 whole-epigenomic association studies (EWAS); 36 studies aimed at identifying DNA methylation of candidate genes; 13 studies on non-coding RNAs; and 6 studies on identifying histone modifications [26]. In this comprehensive review, the authors primarily focused on listing the diverse cellular and neurometabolic pathways identified among the signals from GWAS, paying less attention to their functionality and implications for understanding the pathophysiology of SB.

This review aims to systematize the findings of GWAS on suicidal phenotypes, annotate the identified markers, analyze their functionality, and potentially confirm the previous hypothesis that they reflect a nonspecific set of gene variants associated with stress vulnerability as a key endophenotype of suicidal behavior. Additionally, the review aims to achieve a higher level of generalization and pathogenetic explanation of SB beyond merely listing the technical processes or genes involved in the associations presented [26]. Given the continuous influx of new research in this field, one of the goals was to encompass as many publications as possible in existence by the end of 2023, primarily focusing on original GWAS and meta-analyses. Such a review could serve as a valuable information resource for similar studies conducted in Russia.

METHODS

Sources of information, search strategy and selection criteria

The research represents the result of a monitoring of all recent original studies and reviews regarding the use and efficacy of GWAS in the field of suicidology since 2014. Conducted from January to December 2023, this work involved directly annotating all markers and constructing an informative table of sources. We conducted searches on the PubMed platform using the keywords "suicide AND GWAS" and "suicidal behavior AND GWAS". Additionally, we considered interrelated sources, including references from original studies, previously published reviews (including

our own), and analytical articles by leading experts in the field. The analysis encompassed all sources identified as of December 2023, totaling 34 original papers. We included studies on all suicidal phenotypes, irrespective of the definitions of SB, SA, and SI. Our focus was solely on "classical" GWAS, primarily aimed at conducting GWAS using SNPs as markers. This review is not a systematic one and does not purport to be. According to its design and stated objective, it aims to validate previously put forth hypotheses regarding the association of suicidal phenotypes with genomic markers that may sometimes be challenging to elucidate.

Analysis of the results

The publications identified and selected for analysis were studied in full text, including additional information posted on the journal's websites. The necessary information was copied and tabulated. The obtained data were considered from the following angles:

1. Increased attention to the sample, its characteristics, methods for accounting for SB and ideation;
2. Accounting exclusively for genome-wide markers (some GWAS projects used the candidate gene strategy on the same sample as an additional measure, which led to an excessive number of genes mentioned);
3. A broad approach to marker analysis, i.e. inclusion of polymorphisms in the list not only exclusively at a significance level of $p < 7 \times 10^{-8}$, but also nominal (presumptive), i.e. at values of the order of $p < N \times 10^{-7\text{-}6}$;
4. Special attention paid to the SNP inheritance indicator;
5. Mandatory annotation of the closest genes and comparative analysis of their reproducibility on the entire data set.

The sources of the information on the functional role of the mentioned genes were the resources Gene Cards[2], National Library of Medicine[3], and UniProt[4]. All 34 analyzed publications [27–60] are summarized in Table S1 in the Supplementary.

RESULTS

Evolution of methodology and performance of GWAS on suicidal phenotypes

While initial studies of this type were primarily incidental ramifications of pharmacogenetic projects, where certain patients exhibited increased suicidal tendencies during treatment, subsequent projects have deliberately focused on exploring SB or SI [27–29]. Thus, while in the studies [27–29] the suicidal phenotype emerged as a series of responses to single queries regarding SI from widely used questionnaires on depressive symptoms, in latter works [30–32], direct inquiries about SB from structured diagnostic interviews were employed. In the studies reviewed, SI was characterized as a phenotype in 15 (45.5%) works; SA — in 25 (75.8%); and CS — in 9 (27.3%). Notably, a significant portion of the studies (n=14) accounted for both SI and SA simultaneously, sometimes including CS as well, resulting in a cumulative percentage exceeding 100%.

Various tools were utilized by authors to identify and delineate these phenotypes, ranging from individual questions extracted from diverse depression scales to comprehensive assessment instruments like the Columbia Suicide Severity Rating Scale, the Beck Scale for Suicide Ideation, the Beck Suicide Intent Scale, and sections dedicated to suicidal tendencies in psychiatric diagnostic tools such as SCAN, CIDI 2.1, SCID, and MINI (refer to Table S1 in the Supplementary). In recent years, some authors have developed proprietary methodologies based on gradations of suicidality, as demonstrated in the work by Zai et al. [53]. These approaches, employing ordinal scales ranging from 0 to 4–5 based on the presence and severity of SI and SB, contribute to the construction of the concept of ordinal suicidality [26]. Furthermore, several studies draw on medical databases (national or regional mortality registries, mental health records, and data from frontline health assessments or alcohol consumption among large cohorts), while in certain instances online surveys meant to gauge participants' psychological well-being or specialized surveys targeting military personnel or war veterans are utilized (refer to Table S1 in the Supplementary).

Hence, a wide variety of phenotypes is used in GWAS studies on suicidality, extending beyond the primary indicators of SI, SA, and CS. This undoubtedly impacts the findings of GWAS and their reproducibility. Consequently, specialists from the Suicide Working Group of the PGC have taken to developing a protocol to standardize these phenotypes. Given that some GWAS also incorporate the notions of non-suicidal self-harm, it is imperative to

[2] Available from: https://www.genecards.org/
[3] Available from: https://www.ncbi.nlm.nih.gov/gene/
[4] Available from: https://www.uniprot.org

distinctly delineate suicidal tendencies from other forms of self-injury and establish uniform definitions.

Upon considering factors such as sample size and characteristics, the following conclusion seems appropriate. In initial studies focusing on patients with depression and bipolar disorder (BD), sample size was dictated by the design of the pharmacogenetic objectives, ranging from 400 to 2,000 individuals, with 10–25% exhibiting increased SI during treatment. Subsequent studies tailored to specific populations (e.g., patients with SCZ, depression, or familial cohorts) included sample sizes ranging from several dozen to several thousand participants. Nearly all studies, especially those that yielded negative results, seemed to suggest that enhanced success could be attained through larger sample sizes. A logical development was the combination of cohorts based on disorder presence and suicidal manifestations, with the use of large databases of genotyped individuals (for example, UK BioBank) proving to be pivotal. In the most recent meta-analysis, the sample size exceeded 40,000 individuals (collected from 22 cohorts) with varied manifestations of suicidality, alongside over 900,000 controls [60] (refer to Table S1 in the Supplementary). Genotyping was conducted using different variants of arrays manufactured by Illumina, Inc. and Affymetrix, Inc.

The focus of our analysis lies on the performance of GWAS, as characterized by the identification of associations with specific markers, their reproducibility, and their functional genomics significance. While early studies spanning 2015–2019 typically failed to detect significant genome-wide associations, and the identified markers were considered putative (nominal), a breakthrough occurred with the study by Strawbridge et al. [42]. Leveraging large cohorts and biobank data, the identification of markers became more frequent, with the set significance criteria (p <5–7x10^{-8}). Across experiments, the likelihood of detecting such markers increased with larger numbers of cases and controls (refer to Table S1 in the Supplementary). Notably, meta-analyses conducted by Mullins et al. [56], Kimbrel et al. [59], and Docherty et al. [60] proved the most efficient in this regard.

Concurrently, all studies confirmed these previously observed patterns, as documented in prior review papers [19, 20, 26]. Specifically, this means that GWAS in the field of SB have failed to confirm any associations with the anticipated (canonical) genes related to monoamine and other neurotransmitter systems, the stress response system, the neurotrophin system, and other systems previously investigated within the candidate gene strategy. At the same time, numerous associations with genes whose products initially appeared challenging to correlate with the pathophysiology of SB have been revealed. This complexity can be understood through the analysis of metabolic pathways, an enrichment analysis based on functional attributes, and protein-protein interactions. Such a generalization is presented, for example, in the work by Galfalvy et al., which identified broad clusters such as the "cell assembly and organization", "development and function of the nervous system", "cell death and survival", "immune diseases", "infectious diseases", and "inflammatory response" [40].

Polygenic risk scores calculation and GWAS reproducibility

PRS calculation is a widely used technique that was employed in many of the studies reviewed. Sokolowski et al. in their work, since no marker achieved genome-wide significance in GWAS, used a combined approach, where PRS were calculated for a set of genes "ontologically related to neurological functions, developmental processes, and synaptic processes" [35]. On that basis, a set of 590 polygenes associated with SA was presented. They revealed associations with processes such as cell adhesion and migration, as well as intracellular signaling systems, particularly those associated with small GTPases and receptor tyrosine kinases. All these systems are somehow related to the death and survival of neurocytes and synaptic plasticity; that is, the development and formation of the central nervous system, including under various external (stressful) influences [35]. The same work presented a list of 16 genes associated with SA which were previously recognized as markers of SB namely: *BDNF, CDH10, CDH12, CDH13, CDH9, CREB1, DLK1, DLK2, EFEMP1, FOXN3, IL2, LSAMP, NCAM1, NGF, NTRK2,* and *TBC1D1*. Among these markers are genes encoding known nerve growth factors, their receptors, cadherin proteins (the main factors responsible for cell adhesion), transcription factors, as well as other factors of cell growth and differentiation.

In this context, it appears interesting to analyze Table S1 in the Supplementary in terms of the reproducibility of the results of different GWAS. Our review of the first 15 GWAS on suicidal phenotypes from 2009 to 2015 identified 4 genes as recurrent across different independent studies (*NTRK2, FOXN3, LSAMP,* and *CTNNA3*) [20]. To date, based on the analysis of 34 studies, we have identified

27 repeating genes, including 8 genes involved in cell-cell interactions, neurogenesis, and immune responses: namely, *LSAMP* (a cell adhesion protein involved in axon targeting during central nervous system development), *CDH13* (cadherin 13, a member of the major Ca-dependent cell-cell adhesion regulators family that inhibits axon growth during differentiation), *CNTN5* (contactin, a member of the immunoglobulin superfamily that is involved in cell interactions), *NCAM1* (a cell adhesion protein, which is a member of the immunoglobulin superfamily), *DCC* (netrin receptor 1, an adhesion molecule and axon growth directing factor), *SEMA3A* (semaphorin 3A, which is secreted immunoglobulin that can act as a neurorepellent or neuroattractant and is necessary for the normal development of neurons), *NLGN1* (neuroligin, a neuronal surface protein and synaptic plasticity factor), and *CTNNA3* (a vinculin/alpha-catenin family protein involved in intercellular interactions). Additionally, 2 genes have been identified whose products are associated with the state of the intercellular matrix: *HS3ST1* (heparan sulfate sulfotransferase, an enzyme synthesizing the heparan anticoagulant) and *ABI3BP* (a heparin and glycosaminoglycan binding protein). Hence, most of the genes (*n*=10) are in some manner linked to intercellular interactions, which are crucial in the early development of nervous tissue and the maintenance of its condition throughout an individual's life.

The second most numerous group (*n*=8) included genes encoding neurotrophin receptors and constituents of intracellular signaling systems, which are also involved in synaptic plasticity, neurogenesis, embryonic development, and carcinogenesis: namely, *GFRA1* (a receptor for neurotrophins GDNF and NTN), *NTRK2* (a membrane tyrosine kinase and receptor for neurotrophin BDNF), *RHEB* (a universal GTP-binding protein involved in the regulation of the cell cycle and carcinogenesis in humans), *STK3* (a serine/threonine protein kinase involved in the regulation of apoptosis and that inhibits proliferation and tumor growth), *SOX5* (a transcription factor related to the SRY gene and key factor determining the male sex that is involved in embryonic development), *PDE4B* (phosphodiesterase 4B, an intracellular signaling factor), *RGS18* (a regulator of the G protein-dependent signaling system), and *ZNF406* (the zinc finger of ZFAT that is involved in the regulation of transcription and the immune response).

The third group consists of 9 genes which are primarily linked by the fact that their products are neurospecific proteins or are associated with nervous tissue functions. They are genes such as *BRINP3/FAM5C* (a retinoic acid-induced neurospecific protein), *LRRTM4* (a leucine repeat-rich transmembrane protein of the nervous tissue), *LINC01392* (non-coding RNA of unknown function), *MHC* (a major histocompatibility complex), *SLC6A9* (a glycine transporter), *FURIN* (a subtilisin-like protein convertase), *CACNG2* (a subunit of the calcium voltage-dependent channel), *FOXN3* (a forkhead/winged helix transcription factor presumably involved in the elimination of transcription errors), and *LUZP2* (a leucine zipper protein presumably involved in the pathogenesis of Alzheimer's disease).

Over the past decade, there has been significant progress achieved in the reproducibility of GWAS results in suicidology. Growing evidence suggests that the identified markers are linked not to neurochemical processes and the main neurotransmitter systems, but to mechanisms involving the formation of cellular components in the nervous tissue, neuroplasticity, the maintenance of neuronal and glial cell interactions, neurocyte survival and death, signaling systems, and immune responses. These mechanisms are likely connected to structural impairments in the developing brain during early stress exposure, contributing to vulnerability-stress, which is a key transdiagnostic endophenotype that may underlie both SB and various mental disorders, many of which are associated with stress [61].

Gene-environment interactions according to GWAS

In the genetics of SB, gene-environment interactions are crucial, since the trait itself is not what is inherited but the vulnerability to environmental factors. This constatation is supported by several of the GWAS that have assessed such interactions. For example, Wendt et al. identified several genome-wide markers that were different between men and women, demonstrating the interaction of suicidality with various environmental psychotraumatic factors, the levels of social support, and one's socioeconomic status [54]. Significant gene-environment (GxE) associations were uncovered with neuroimaging data between these markers, particularly with the volume of the hippocampus, amygdala, and the structural features of the white matter bundles integrating the brain structures involved in goal-setting behavior. One polymorphism, including association with the *CHST14* gene (carbohydrate sulfotransferase involved in the synthesis of mucopolysaccharides), was shown to interact with physical and sexual abuse experienced

in childhood and later life. The authors concluded that these identified relationships and interactions highlight the relevance of synaptic plasticity as a potential target for addressing suicidality and post-traumatic conditions [54].

Several recent studies have used GWAS to identify genetic markers and associations of suicidality with various physiological and psychobiological characteristics. For instance, Levey et al. utilized data from a study on suicide risks among U.S. Army servicemen, employing an approach that allowed them to assess the severity of suicidal thoughts and actions (ordinal suicidality) [45]. They found associations with the *LDHB* gene (lactate dehydrogenase, anaerobic metabolism), the *FAH* gene (tyrosine catabolism), and the *ARNTL2* gene (regulation of circadian rhythm) [45]. Brick et al. discovered an association with the *SEMA3A* gene, which encodes the semaphorin 3A protein, a secreted immunoglobulin necessary for normal neuronal development [46]. This gene is also linked to comorbid alcohol dependence, depression, inflammatory processes, and asthma. Notably, a significant genetic correlation with neurocognitive functions, specifically facial expression identification tasks, was observed [46]. Russel et al. used Mendelian randomization to identify an association between components of the immune system (interleukin 6 and the C-reactive protein) and various forms of self-harm (non-suicidal and suicidal), highlighting the relationship between these behaviors [50]. Campos' study produced similar results, showing a genetic correlation between suicidal thoughts and non-suicidal self-harm [51]. Polimanti et al. identified a link between suicidal thoughts and various addictions mediated by markers on chromosome 16 [52].

Our analysis bolsters previously posited hypotheses about the role of identified genetic markers in the formation of the cellular and regulatory mechanisms of vulnerability–stress. It also highlights the relationship between suicidal phenotypes and various pathogenetically based phenomena, such as the immune reactions found in multiple mental disorders, self-harming behavior, and addictions. This underscores the importance of examining the overlaps amongst various mental illnesses, which are significant risk factors for suicide.

Genetic correlation with mental disorders according to GWAS

The question of which common polygenes carry the risk of fostering the development of depression (or other mental disorders) and SB simultaneously, and whether it is possible to differentiate polygenic influences that increase the risk of suicide within mental disorders from those actually associated with the disorders themselves, is crucial. This question is addressed in numerous studies [35, 36, 38–40, 43, 47, 48, 52, 53, 55, 56, 58, 60]. Almost all studies of this type have identified common genotypes for SI, SA, CS, and clinical phenotypes. For instance, Sokolowski et al. as early as in 2016 [35] identified 750 genes associated with the development of nervous tissue that are more specific to SA than to psychiatric diagnoses. They also showed, using the PGC databases for SCZ, BD, and depression, that PGC-SCZ polygenes are associated with SA in both diagnosed and undiagnosed patients, and characterized the overlap markers between PGC-SCZ and patients with SA without diagnoses. These 590 markers were believed to be primarily associated with neuronal development genes, emphasizing the importance of common vulnerability genes for SA and mental disorders, particularly SCZ, even in the absence of a formal diagnosis [35].

Mullins et al., using data from several clinical cohorts (including those with depression, BD, and SCZ), calculated the PRS for SA in each condition and conducted a meta-analysis [43]. They found that a genetic predisposition to major depression increases the risk of SA in patients with depression, BD, and SCZ. The authors suggest that the genetic etiology of SA may be both unique and partly shared with major depression. In other words, individuals who commit SA carry a burden of depression risk alleles, rather than merely a higher genetic load that is responsible for the mental disorder they are diagnosed with.

The predictive value of PRS in psychiatry remains low; previous studies have shown that PRS for severe depression explains only about 2% of the differences in patient statuses [62]. However, based on the work of Mullins et al., PRS appears to be a promising indicator for assessing suicide risk among psychiatric patients, especially as the volume of international databases grows and more genetic material from various ethnic groups is collected [43].

The studies by Docherty et al. [49] and Li et al. [58] are particularly illustrative in this context. Docherty et al., using data from 3,413 cases of CS in Utah, U.S., and over 14,000 controls of European origin, identified several highly significant genome-wide markers (see Table S1 in the Supplementary). They also established genetic correlations with various psychiatric and psychological traits and variables, including (in order of increasing effect size)

alcohol consumption, autism spectrum disorders, childhood IQ, loneliness, depressive symptoms, impaired self-control (disinhibition), and diagnoses of depression and SCZ [49]. Li et al., using the same dataset and conducting a meta-analysis with 8,315 cases and over 2.45 million controls of European origin, found positive genetic correlations between CS and depression, anxiety, stress, sleep disorders, SCZ, and pain syndrome, as well as negative correlations with smoking and education/intelligence levels [58]. Additionally, in the same study, when analyzing further cohorts, positive genetic correlations were found between CS and BD, post-traumatic stress disorder, generalized anxiety disorder, autism spectrum disorders, attention deficit hyperactivity disorder (ADHD), chemical dependencies, neuroticism, serum triglyceride and cholesterol levels, and negative correlations with subjective well-being, intracranial volume, and cognitive functions [58].Thus, based on GWAS, PRS are increasingly demonstrating a degree of predictive power logically explained by our understanding of risk factors and the pathogenesis of SB.

SNP heritability indices according to GWAS data

It should be noted that as the sample size increases and large cohorts from various databases are included in the analysis, SNP heritability indices are also refined (see Table S1 in the Supplementary). They fluctuate within fairly significant boundaries: from 1–2% [33, 57] to 24–48% [44, 45, 49] (the latter already approaches the estimates obtained by the twin method [3]). At the same time, most studies provide estimates of about 5–10% [42, 43, 48, 51, 56, 58, 60]. Moreover, if the h^2_{snp} values for SA often remain within the 5–7% range, then for CS they already reach 24.5% [49], which can be regarded as a consequence of greater certainty of the phenotype. This bridges the gap between heritability estimates from behavioral genetics and molecular genetics, which is characteristic of mental disorders [63], and which has called into question the value of SNP heritability assessment in general [64]. This phenomenon, known as "missing heritability problem", has several potential explanations [65]. In particular, it has been suggested that many common variants with negligible effects remain undiscovered, that rare variants with large effects undetectable by standard GWAS genotyping are too influential, and that behavioral genetic approaches may overestimate heritability in general [65]. Interestingly, the highest h^2_{snp} estimates (around 35–48%) were obtained from monoethnic samples (Japan) [44], while meta-analyses of multiethnic cohorts yield average values [56, 58, 60].

Meta-analyses of GWAS results

The results of recent meta-analyses are of the greatest interest. Thus, in the work by Mullins et al. [56], there were 29,782 SA cases and 519,961 controls, all from the ISGC database. The analysis methods used allowed the researchers to exclude the genetic influences on SA mediated by mental disorders. Two loci achieved genomic significance for SA: the major histocompatibility complex (MHC) and an intergenic locus on chromosome 7. The latter remained associated with SA even after excluding the influence of mental disorders and was replicated in an independent cohort. This locus was also linked to risky behavior, smoking, and sleep disorders [56]. This meta-analysis identified six genes previously mentioned in earlier studies (see Table S1 in the Supplementary). In the meta-analysis by Li et al. [58], there were 10 such genes. The authors highlighted the *NLGN1* gene, which encodes neuroligin, a postsynaptic neuronal protein. Proteins from this family act as ligands for the presynaptic agents β-neurexins and are involved in the formation and remodeling of synapses in the central nervous system [58]. Additionally, the *ROBO2* gene, variants of which are associated with morning chronotype, smoking, and mathematical abilities, was of interest. Noteworthy in this regard is also the *ARNTL2* gene from the study by Levey et al. [45], which is also associated with circadian rhythms [58].

Kimbrel et al. conducted a large-scale meta-analysis as part of the Million Veterans Program, which was initiated to address the sharp rise in suicides among U.S. veterans of wars and military conflicts [59]. The analysis included data from 633,778 genotyped veterans, 19% of whom had some form of SB, with cohorts from the ISGC collection used as a replication sample. A notable feature of this meta-analysis was the clear division by ancestry (European, African, Asian, and Latin American groups), allowing for the identification of markers common to all groups, as well as those specific to each group. The meta-analysis identified over 200 highly significant individual markers, including new ones such as *ESR1* (the estrogen receptor), *TRAF3* (the tumor necrosis factor receptor), *METTL15* (mitochondrial methyltransferase), and *MKNK1* (the protein kinase involved in the stress response) [59]. Functional enrichment analysis using the FUMA GWAS catalog identified markers that are universal across all ethnic groups, are expressed in the

brain and pituitary gland, and are associated with synaptic mechanisms, axonal interactions, ubiquitination, parathyroid hormone synthesis, the dopaminergic, glutamatergic, and oxytocin synapses in the brain, intracellular cAMP-dependent pathways, and cell adhesion. The highest genetic correlation (r >0.75) was observed between SB and depression, as well as post-traumatic stress disorder, while the correlation with SCZ and BD was significantly lower (r=0.36–0.29).

The most comprehensive meta-analysis to date was performed by Docherty et al., in which the phenotype was SA [60]. The ISGC sample included data on 43,871 SA cases from 22 cohorts with the number of controls approaching a million, taking into account ancestry, with a significant proportion of the controls being clinically assessed for mental disorders. As a result, 12 loci were identified at p <5×10^{-8}. The closest genes to these loci included *DRD2* (dopamine receptor type 2), *SLC6A9* (the glycine transporter), *FURIN* (subtilisin-like protein convertase), *NLGN1* (neuroligin), *SOX5* (the transcription factor), *PDE4B* (phosphodiesterase B), and *CACNG2* (the calcium voltage-gated channel subunit). These markers were consistent with those previously identified in other studies (see Table S1 in the Supplementary). The authors found common genetic variability between SA with ADHD, smoking, and risk tolerance, even after accounting for the influence of comorbid BD and post-traumatic stress disorder. Additionally, multiple analyses identified 519 significant gene sets affecting areas such as epigenetic mechanisms, genome regulation and transcription, cellular stress response mechanisms, DNA repair, and immune responses [60]. The study also revealed a significant genetic overlap with the genes associated with various mental and somatic conditions, particularly smoking, ADHD, risk tolerance (linked to impulsivity and risk-taking behavior), and pulmonary pathology. The authors stressed that many findings in the meta-analysis regarding the involvement of genes associated with epigenetic regulation, as well as the overlap with mental disorders, support the concept of diathesis–stress as the leading pathogenetic mechanism of suicide [60].

DISCUSSION

Interpretating the data

Based on the analysis of 34 original studies and meta-analyses, we have identified and annotated 27 recurring genomic markers associated with various suicidal phenotypes. When considering each of these markers individually, their direct involvement in SB remains challenging to explain. However, as genes and their products increasingly appear across multiple studies, we believe they can be fitted into a certain pathogenetic framework. This framework is most logically linked to the impact of stress and the concept of vulnerability–stress, often regarded as the primary endophenotype of SB [5, 20, 21]. The presence of associations with the genes involved in neural tissue formation, neuroplasticity, synaptogenesis, cellular interactions, and immune responses, coupled with accumulating epigenetic and neuroimaging evidence, provides a logical explanation of suicide as a consequence of early traumatic experiences and subsequent interactions with existing stressors [20]. Equally logical within this framework is the role of mental disorders, whose genetic architecture partially overlaps with that of SB and is similarly influenced by vulnerability–stress and gene-environment interactions [61]. While this framework is not exhaustive or universally applicable, it offers a means to analyze future GWAS findings in terms of their alignment with this concept, thereby facilitating the interpretation of the diverse data generated in such studies.

Suicide represents a profoundly complex and multifaceted polyetiological behavioral phenomenon stemming from a combination of neurobiological, psychiatric, psychological, and social factors. A contentious, unresolved issue revolves around whether SA constitutes an independent, evolutionarily formed behavior or a complication of mental disorders such as depression, borderline personality disorder, or SCZ. Large-scale meta-analyses conducted within the ISGC underscore the existence of a distinct genomic architecture unique to SA [66]. Conversely, studies of extensive cohorts employing traditional psychogenetic methods assert that parental mental illness explains nearly half of the genetic transmission of the habit of suicide attempts, albeit without impacting transmission through upbringing [67]. Moreover, while suicide itself is partially inherited, the genetic overlap between SA and CS underscores the presence of two distinct groups: those that attempt suicide and those that commit it [67].

Therefore, elucidating the genomic architecture of SB as a transdiagnostic phenotype across major psychopathologies, including depression and other disorders, alongside the psychological constructs underpinning SA, offers insight into SB mechanisms, especially given the fact that vulnerability–stress can be an endophenotype of both SB and mental

disorders. As research into the genetics of suicide employing GWAS strategies progresses and evolves, with advancements in analysis methods, accumulation of genomic data, and the integration of multi-omics data (epigenomics, proteomics, metabolomics, microbiomics) [68], the issue of summarizing these findings within the context of suicide pathogenesis remains paramount.

Limitations

This review primarily adopts a descriptive approach, and the search strategy utilized is limited, potentially impacting the scope of the analyzed data. This, alongside the exclusive focus on SNPs while disregarding other markers, constitutes the primary limitation of the review.

Practical utility of GWAS for suicide

Currently, anticipating the predictive efficacy of genetic markers in the general population remains challenging. However, this prospect appears to be more feasible in high-risk cohorts, such as patients of psychiatric clinics. Particularly, PRS assessments offer increasingly robust predictive capacities, potentially extending to the individual level, contingent upon the identification of specific marker sets and their comparison with continuously expanding genetic databases. Despite various uncertainties and diverse analytical approaches, GWAS findings in suicidology progressively, as sample sizes grow and ethnic diversity is considered, alongside the augmentation of international genetic databases, allow one not only to confirm some pathogenetic hypotheses, but also provide hope for practical implementation (when combined with diverse test modalities) to predict and prevent suicides, which constitutes the ultimate objective of research in this field.

Prospects for further research

Based on the results of our review, we can opine that the enhanced effectiveness of suicide studies using the GWAS approach points toward several directions. First of all, they are the standardization of phenotypes based on more accurate definitions of all manifestations of SB; the use of the most clinically proven suicide risk scales, an increase in sample sizes and their standardization in terms of ethnicity and origin; the homogeneity of clinical samples and their detailed psychiatric verification; the stratification of samples by age with a focus on adolescents and young adults, men and women; the integration of genetic data with psychological constructs of suicide; and the widespread use of international databases of genetic information.

CONCLUSION

In our opinion, the set of most frequently recurring markers identified by GWAS reflects the leading role in the genesis of SB of the vulnerability–stress phenomenon — an endophenotype formed in early development, which subsequently plays the role of key pathogenetic mechanism of suicide.

The GWAS strategy in suicidology primarily serves the purpose of better understanding the pathophysiology of SD, but it also shows the growing potential of suicide prediction and prevention, especially when calculating PRS, among certain populations (psychiatric patients) and in combination with other test modalities.

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Supplementary data

Supplementary material to this article can be found in the online version:
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Clinical Characteristics and Treatment Responses of Patients in Delirious Mania: A Case Series

Клинические характеристики и лечение пациентов с делириозной манией: серия клинических случаев

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Case report

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ABSTRACT

BACKGROUND: Delirious mania (DM) is a severe psychiatric condition having rapid onset of delirium, mania, and psychosis. It is an emergency condition as it has acute onset and is characterized by extreme hyperactivity. Catatonic signs may also be present. Very few cases have been reported from India, hence making it imperative to study its clinical characteristics and possible treatment, which can help in providing care to such patients in emergency settings.

CLINICAL CASES DESCRIPTION: This paper describes four cases with a diagnosis of DM — demography, clinical features, investigations, treatment. All the patients had an acute onset and rapid progression of symptoms, with clinical symptoms of talkativeness, increased psychomotor activity, decreased need for sleep, aggressive and violent behavior, increased libido, increased appetite with delusion of grandiosity, disorientation to time/place/person, impaired memory of recent events, impaired attention with fluctuating course, negativism, echolalia, and echopraxia.

CONCLUSION: There is a high likelihood of misdiagnosing DM in the absence of diagnostic guidelines. There should be an active search for the underlying aetiology in all cases of DM. Atypical antipsychotics and mood stabilizers may be used to treat less severe forms of DM. Modified electric convulsive treatment and intravenous benzodiazepines elicit a good response.

АННОТАЦИЯ

ВВЕДЕНИЕ: Делириозная мания (ДМ) — это тяжелое психическое нарушение, характеризующееся быстрым возникновением и сочетанием делирия, мании и психоза, также возможны симптомы кататонии. Такое состояние является неотложным ввиду характерных для него острого начала и крайнего возбуждения. В Индии зарегистрировано очень мало случаев этого расстройства, поэтому важно изучать его клинические характеристики и приемлемые методы лечения, чтобы иметь возможность обеспечить таким пациентам адекватную неотложную помощь.

ОПИСАНИЕ КЛИНИЧЕСКИХ СЛУЧАЕВ: В статье описано 4 случая пациентов с диагнозом ДМ — их демографические характеристики, клинические особенности, лабораторные и инструментальные данные, лечение. У всех пациентов отмечали острое начало и быстрое прогрессирование клинических симптомов. Частыми проявлениями были многоречивость, повышенная и психомоторная активность, сниженная потребность во сне, агрессивное и буйное поведение, усиление либидо, повышенный аппетит, бред величия, дезориентация во времени/пространстве/

личности, нарушение памяти на недавние события, нарушение внимания по типу неустойчивости, негативизм, эхолалия, эхопраксия.

ЗАКЛЮЧЕНИЕ: В связи с отсутствием специфических диагностических рекомендаций для делириозной мании высока вероятность допущения диагностической ошибки. Во всех подобных случаях необходимо активно искать этиологические факторы, лежащие в основе ДМ. Для лечения менее тяжёлых форм ДМ могут применяться атипичные антипсихотические препараты и нормотимики. Хороший терапевтический эффект дают модифицированная электросудорожная терапия и внутривенное введение бензодиазепинов.

Keywords: *mania; delirious mania; delirium; electroconvulsive therapy; case report*
Ключевые слова: *мания; делириозная мания; делирий; электросудорожная терапия; клинический случай*

INTRODUCTION

Delirious mania (DM) was previously known as Bell's mania. Delirium, mania, and psychosis constitute the main clinical features of this condition. It is a severe psychiatric syndrome in which the clinical features have a rapid onset. It can morph into an emergency situation, as it may lead to the sudden onset of severe agitation. It can be described as "a syndrome of the acute onset of hyperactivity, emotional lability, grandiosity and insomnia characteristic of mania, and the disorientation and altered consciousness characteristic of delirium" [1]. Catatonic signs and autonomic dysfunction may accompany the condition. Catatonic signs and symptoms may include mutism, grimacing, stereotypy, mannerisms, rigidity, negativism, automatic obedience, and echopraxia/echolalia (i.e., mimicking of the examiner's movements/speech) [2]. Kraepelin used the term DM; however, Calmeil described these cases extensively. He identified high morbidity and mortality in cases of DM [3, 4]. This was also found by Bell in 1849, who reported a 75% mortality rate in admitted patients with DM [5]. Carlson and Goodwin published a case series wherein 6 out of 20 patients with a diagnosis of mania were not oriented to time and place [6]. Ritchie et al. have found that the incidence of delirium in hospitalized patients with bipolar disorder is 35.5% [7]. In the absence of a consensus on the diagnostic criteria of DM, the incidence of DM varies across studies. There are no standardized diagnostic guidelines or clinical assessment measures. Very few cases have been reported from India, hence making it imperative to study its clinical characteristics and possible treatment, which can help in providing care to such patients in emergency settings. The profound hyperactivity encountered in this condition is distressing to both the caregivers and clinicians providing treatment. Unfortunately, the information gathered so far has remained limited to case reports, which provide a similar picture. We hope this work will be of help to clinicians in successfully diagnosing and treating patients with DM.

Our aim was to examine the clinical profile and treatment responses of patients presenting with delirium and mania at a government psychiatric inpatient unit.

Informed consents for publication in a medical journal were signed on 26.06.2019, 11.07.2020, 28.01.2021 and 01.11.2021 for Cases 1, 2, 3 and 4 respectively.

CLINICAL CASES

Case 1

Patient information

Mr. N., a 40-year-old married male, educated to class 8th, unemployed, belonging to a Muslim nuclear family of lower socio-economic status. He presented with complaints of over-talkativeness, increased goal directed activity, decreased need for sleep, violent behavior, increased libido, increased appetite, and decreased self-care since 3 days. He had a past history of manic episode 9 years prior, which resulted in 20 days of treatment and was taken off treatment after remission. He had a nil significant family and personal history.

Clinical findings

At the time of admission, the patient was conscious but had no orientation to time or place. He showed increased psychomotor activity, talked excessively, was extremely irritable, and sometimes exhibited disinhibited behavior of disrobing in front of others. He talked very highly of himself. He had impaired attention span and poor memory of recent events. He refused to follow commands like putting out his tongue or extending his hands in front of him for examination. He would repeat words spoken to him and sometimes mimic his examiner's behavior.

Diagnostic assessment

Diagnostic testing: Upon investigation there was increased Total Leucocyte Count (TLC) — 15,940/mm^3 (normal — 4,000–11,000/mm^3), increased Absolute Neutrophil Count (ANC) — 14,940/mm^3 (normal — 2,500–6,000/mm^3), increased Serum Glutamic Oxaloacetic Transaminase (SGOT) — 223 U/L (normal — 8–45 U/L), increased Serum Glutamic Pyruvic Transaminase (SGPT) — 142 U/L (normal — 7–56 U/L). All routine haematological investigations other than these were within normal range. Non-Contrast Computed Tomography of the head did not show any anomaly.

Diagnostic challenges: As the testing was done in a government-funded health institution, the patient did not face any financial burden related to bearing the diagnostic cost.

Diagnosis: A provisional diagnosis of DM with a differential diagnosis of bipolar disorder and current episode of mania with psychotic symptoms. Encephalitis was also considered.

Therapeutic intervention

The patient was administered several doses of injections. Haloperidol 5 mg intramuscularly with injections. Promethazine 25 mg intramuscularly, but the patient responded poorly to it, after which he was started on injections. Lorazepam 2 mg intravenously repeated doses (maximum — 8 mg/d) to which his response was good. He was also started on Lithium, which was optimized to 900 mg/d and Thioridazine optimized to 500 mg/d.

Follow-up and outcomes

By day 6 of admission, there was a 50% reduction in symptoms (reduction in Young Mania Rating Scale, YMRS, — from 36 to 20). The patient was febrile on day 7 and exhibited shortness of breath. He was referred for this and was diagnosed with pulmonary tuberculosis, with pleural effusion. He was discharged on medical grounds.

Case 2

Patient information

Mrs. S., a 22-year-old married female, uneducated, a homemaker belonging to a Hindu nuclear family of lower socio-economic status. She presented with complaints of hyperactivity, abusive and agitated behaviour, excessive talkativeness, hypersexuality-sexual gestures, disrobing, sleep disturbance since 4 days and no significant family and personal history. She is a known case of bipolar affective disorder.

Clinical findings

At the time of admission, the patient was conscious but was not oriented to time and place. She suffered from impaired attention span and poor memory of recent events. She was extremely restless and would get up from her bed purposelessly. She talked rapidly, and sometimes it was difficult to make sense of what she was saying. She displayed a labile affect and would go from crying to bursting into laughter in an instant. She displayed delusion of grandiosity, flight of ideas, poor insight, and impaired judgement. She often repeated the words spoken to her and sometimes mimicked her examiner's behavior. All routine haematological investigations like complete blood count, liver function test, renal function test, thyroid function test, and blood sugar were within normal range except.

Creatine phosphokinase (CPK) — 202 mcg/L (normal — 10–120 mcg/L). The neuroimaging finding was non-significant.

Therapeutic intervention

Upon treatment the patient showed no response to intravenous Lorazepam up to 12 mg/d in divided doses: hence, she was started on a Modified Electric Convulsive Treatment (MECT), to which she showed a good response. She went through 6 sessions of MECT, which resulted in a reduction in the YMRS score from 48 to 8. Delirium resolved by the 2nd day of MECT. She was discharged on Lithium 900 mg/d, Risperidone 8 mg/d, and Trihexyphenidyl (THP) 2 mg/d in divided doses.

Follow-up and outcomes

The patient was discharged with significant improvement.

Case 3

Patient information

Mr. K., a 35-year-old married male, educated to class 5th, unemployed, belonging to a Muslim nuclear family of lower socio-economic status, with a past history of pulmonary tuberculosis (treated) and no significant personal or family history. He had undergone an episode of DM 6 years prior. Currently, he displays over-talkativeness, increased goal-directed activity-overspending, increased libido, aggressive behavior, grandiosity, and a decreased need for sleep for 10 days.

Clinical findings

On examination, the patient was not oriented to time, place, or person. He had impaired attention span and poor memory of recent events. No medical cause was identified for his delirium. He often repeated the words spoken to him and sometimes mimicked his examiner's behavior. All routine haematological investigations and neuroimaging findings were within normal range.

Therapeutic intervention

The patient was started on intravenous Lorazepam optimized up to 6 mg/d in divided doses and showed improvement in delirium within the next 3 days. Later, he was treated with Sodium Valproate optimized up to 1,500 mg/d, Lithium optimized up to 900 mg/d, Risperidone optimized up to 8 mg/d, and was discharged 25 days after admission with a change in YMRS from 32 to 6.

Follow-up and outcomes

This patient was discharged with significant improvement.

Case 4

Patient information

Mr. A., a 38-year-old male, educated to class 12th, working as a factory helper, belonging to an Hindu nuclear family of lower socio-economic status with a history suggestive of multiple manic episodes dating back 15 years, with current presentation from 7 days with abrupt onset of aggression, over religiosity, always ready to engage in some activity, decreased need for sleep, grandiosity, poor personal hygiene, and decreased appetite.

Clinical findings

He was not oriented to time during admission. He had impaired attention span and poor memory of recent events. He had no significant personal or family history. He talked rapidly and often repeated the words spoken to him. He would be extremely restless during interviews and mimic his examiner's behavior. He displayed a labile affect and claimed to have supernatural powers. All routine haematological investigations were within normal range.

Therapeutic intervention

The patient was started on Lithium optimized up to 900 mg/d and Thioridazine optimized up to 600 mg/d and showed minimal improvement; hence, MECT was started and a total of 8 sessions were administered, to which he showed a good response, with a reduction in the YMRS score from 44 to 11. Later, Lurasidone was started, which was optimized up to 160 mg/d; and Sodium Valproate, optimized up to 1,000 mg/d.

Follow-up and outcomes

The patient was discharged with significant improvement.

Cases summary

The cases presented in this study are summarized in Table 1.

DISCUSSION

This case report adds to the available medical literature on the clinical features, risk factors, investigations to be ordered, and treatment of DM. This information will be of help to clinicians in improving their knowledge and modifying their treatment methods in order to achieve a faster response. This is extremely important as patients with DM present extreme hyperactivity and might pose an imminent threat of harm to themselves or others. However, this study is a case series and the documentation of such case reports dates back to the 19th century. There exist no diagnostic guidelines for this condition and no higher level of evidence available for this condition. This saps interest among researchers who want to analyze such cases. However, every mental health institution providing treatment to a large number of patients often faces challenges in the identification and adequate treatment of this condition: hence, such studies should continue in order to help upgrade clinicians' knowledge and skills, with a view to alleviating the distress of patients and their caregivers. The onset of DM usually happens in early adulthood. It is characterized by disorientation, extreme psychomotor activity, emotional lability, delusions, and hallucinations [8, 9]. After recovery, patients are unable to recall the events that occurred during their episode of illness. The clinical picture might indicate an exploration of the differentials of drug toxicity, metabolic disorders, and central nervous system infections. Electroconvulsive therapy and high-dose benzodiazepines provide effective management of DM [10, 11]. Putative aetiologies of DM include the following:

- Klerman described DM as a variant of classical bipolar disorder [12];
- Mann et al. defined Delirious mania to have resulted from underlying medical and neuropsychiatric aetiologies [13];

Table 1. Summary of clinical cases

Parameter	Case 1	Case 2	Case 3	Case 4
Patient age	40	22	35	38
Patient gender	M	F	M	M
Family history of bipolar disorder	-	-	-	-
Past history of manic episode	+	+	+	+
Onset of symptoms	Acute	Acute	Acute	Acute
Progress of symptoms	Rapid	Rapid	Rapid	Rapid
Manic symptoms	↑Talk, ↑PMA, ↓need for sleep, ↑libido, ↑appetite, ↓self-care. Aggressive and violent behavior. Del. of grandiosity.	Hyperactivity, flight of ideas. Abusive and agitated behavior. Hypersexuality-disrobing self-sexual gestures disrobing. Sleep disruption. Emotional lability.	↑Talk, ↑PMA, ↓need for sleep, ↑libido, ↑appetite, ↓self-care. Aggressive and violent behavior. ↑Goal directed activity (overspending). Del. of grandiosity.	↑Talk, ↓need for sleep, ↓self-care, ↑PMA. Aggression, over religiosity, disrobing self. Del. of grandiosity. Emotional lability.
Delirium signs	Disoriented to time and place. Impaired memory of recent events. Impaired attention span with fluctuating course.	Disoriented to time and place. Impaired memory of recent events. Impaired attention span. Floccillation with fluctuating course.	Disoriented to time, place and person. Impaired memory of recent events. Impaired attention span with fluctuating course.	Disoriented to time, impaired memory of recent events. Impaired attention span, floccillation with fluctuating course.
Catatonic signs	Negativism Echolalia Echopraxia	Echolalia Echopraxia Negativism	Echolalia Echopraxia	Echolalia Echopraxia
Treatment given	No response to intramuscular antipsychotics. Thioridazine 500 mg/d. Lithium 900 mg/d. LZM 8 mg/d intravenously till Day 6 of admission with 50% remission.	No response to intravenous Lorazepam 12 mg/d. Good response with MECT-6 sessions, delirium resolved by 2nd MECT. D/C on Lithium 900 mg/d. Risperidone 8 mg/d. THP 2 mg/d.	Good response to intravenous Lorazepam 6 mg/d. D/C on Valproate 1,500 mg/d. Lithium 900 mg/d. Risperidone 8 mg/d.	No response to intramuscular antipsychotics and Lithium 900 mg/d. Thioridazine 600 mg/d. Good response with MECT-8 sessions. D/C on Lurasidone 160 mg/d. Valproate 1,000 mg/d.
Haematological findings	↑TLC, ↑ANC, ↑SGOT, ↑SGPT with fever	Haematological, Neuroimaging-WNL	Haematological, Neuroimaging-WNL	Haematological, Neuroimaging-WNL
YMRS score	36 to 20	48 to 8	32 to 6	44 to 11
Course	Referred to GHPU, diagnosed with Pulm. TB with PE	D/C with significant improvement	D/C with significant improvement	D/C with significant improvement

Note: PMA — Psychomotor Activity; LZM — Lorazepam; D/C — Discharged; MECT — Modified Electric Convulsive Treatment; THP — Trihexyphenidyl; TLC — Total Leucocyte Count; ANC — Absolute Neutrophil Count; SGOT — Serum Glutamic Oxaloacetic Transaminase; SGPT — Serum Glutamic Pyruvic Transaminase; WNL — Within Normal Limits; YMRS — Young Mania Rating Scale; GHPU — General Hospital Psychiatry Unit; TB — Tuberculosis; PE — Pleural Effusion. The arrows (↑) show the increase in level, the arrows (↓) show the drop in level.

- Taylor and Fink described DM as a variant of catatonia (i.e., excited catatonia) [14];
- Dunayevich and Keck stated that DM is similar to schizophrenia [15].

Bond has defined the criteria for a diagnosis of DM [4, 16], which include the following:

- acute onset with or without premonitory signs of irritability, insomnia or emotional withdrawal;
- the presence of the hypomanic or manic syndrome (as defined by DSM-III criteria) at some point in the illness;
- development of signs and symptoms of delirium;

Table 2. Pathophysiology of DM

Pathophysiology of delirium	Pathophysiology of catatonia	Pathophysiology of mania
↓Acetylcholine — leads to decreased awareness	↓GABA binding in the lateral orbitofrontalcortex — leads to echolalia/echopraxia	↓Prefrontal cortex activity — leads to socially inappropriate behaviour
↑Dopamine — leads to perceptual disturbance	Aberrations in glutamate signaling at posterior parietal cortex — leads to posturing	↑Dopamine — leads to manic symptoms of elevated mood, increased energy and psychosis
↑GABA — leads to sleep disturbance	Abnormal dopamine signaling in corticothalamic loops — leads to autonomic dysregulation of malignant catatonia	
↑Serotonin — leads to confusion	The increase in glutamate at NMDA-receptors in frontal lobe leads to inhibition of GABA. Therefore, NMDA-receptor antagonists may lead to treatment of catatonia by inhibiting glutamate and increasing GABA	

Note: The arrows (↑) show the increase in level, the arrows (↓) show the drop in level.

- a personal history of either mania or depression;
- a family history of major affective disorder;
- responsivity to standard treatments for mania.

Research does not offer comments on any specific pathophysiology of DM. However, its pathophysiology can be hypothesized on the basis of the known neuropathophysiology of its three principal clinical features as stated below (Table 2) [10].

In all 4 cases, a past history of manic episode was present [17]. The patient's presentation in hospital during the episode had an acute onset, and the symptoms had a rapid progression. The common clinical features included:

- manic symptoms — decreased need for sleep, irritability/aggression, increased PMA, increased talkativeness, increased goal directed behaviour-hyper-religiosity, hypersexuality, emotional lability, grandiosity;
- delirium signs-disorientation to time/place/person, impaired recall of recent events, impaired attention;
- catatonic signs of negativism/echopraxia/echolalia.

The haematological and neuroimaging findings were within normal range, except in one case, where there was comorbidity of pulmonary tuberculosis. There was a good response to intravenous Lorazepam or MECT in all cases, similarly to that found in other studies [17, 18]. MECT yielded drastic improvement whenever used. There was a good response to antipsychotics and mood stabilizers upon stabilization of the acute stage with intravenous Lorazepam or MECT. In all the cases, patients had followed up in OPD post discharge, with continuous remission of symptoms. The patients were prescribed oral antipsychotics and/or mood stabilizers, and/or benzodiazepines.

A clinician should strongly consider the diagnosis of Delirious mania whenever delirium, mania, and psychosis are present concurrently; the additional presence of catatonia further bolsters the confirmation of DM [19]. In cases where the risk of harm to self or others is high, benzodiazepines and/or MECT may provide immediate relief [3, 18].

CONCLUSION

DM can be rightfully called a severe, but rare condition that involves severe incessant agitation. This leads to the referring of cases to emergency. Misdiagnosis is likely in such cases, with the most common differential being the manic episode. Ignorance of this condition and its different modalities of treatment can turn into an ordeal for the treating clinicians, leading to mismanagement and morbidity, or mortality.

Our current classificatory system does not mention DM under a major heading due to its complex symptomatology. In all cases of DM, all potential underlying etiologies must be investigated. Atypical antipsychotics and mood stabilizers may be used to treat less severe forms of DM. Early recognition and definitive treatment of DM in an acute setting can be life-saving. This case series will be of help to clinicians in identifying cases of DM and providing treatment at the early stages, leading to a faster response and minimized morbidity.

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