

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

Генетические ассоциации ангедонии: новые аспекты взаимосвязи психических и соматических расстройств

doi: 10.17816/CP15494

Original research

Evgeny Kasyanov¹, Darya Pinakhina^{1,2},
Aleksandr Rakitko^{1,3}, Ekaterina Vergasova³,
Danat Yermakovich³, Grigoriy Rukavishnikov¹,
Larisa Malyshko¹, Yaroslav Popov³,
Elena Kovalenko³, Anna Ilinskaya⁴, Anna Kim³,
Nikolay Plotnikov³, Nikolay Neznanov^{1,5},
Valeriy Ilinsky^{1,4}, Aleksandr Kibitov¹,
Galina Mazo¹

¹ V.M. Bekhterev National Medical Research Centre
for Psychiatry and Neurology, Saint Petersburg,
Russia

² ITMO University, Saint Petersburg, Russia

³ Genotek Ltd., Moscow, Russia

⁴ Eligens SIA, Riga, Latvia

⁵ Pavlov First State Medical University of Saint Petersburg,
Saint Petersburg, Russia

Евгений Касьянов¹, Дарья Пинахина^{1,2},
Александр Ракитко^{1,3}, Екатерина Вергасова³,
Данат Ермакович³, Григорий Рукавишников¹,
Лариса Малышко¹, Ярослав Попов³,
Елена Коваленко³, Анна Ильинская⁴, Анна Ким³,
Николай Плотников³, Николай Незнанов^{1,5},
Валерий Ильинский^{1,4}, Александр Кибитов¹,
Галина Мазо¹

¹ ФГБУ «Национальный медицинский исследовательский
центр психиатрии и неврологии им. В.М. Бехтерева»
Минздрава России, Санкт-Петербург, Россия

² ФГАОУ ВО «Национальный исследовательский
университет ИТМО», Санкт-Петербург, Россия

³ ООО «Генотек», Москва, Россия

⁴ Eligens SIA, Рига, Латвия

⁵ ФГБОУ ВО «Первый Санкт-Петербургский
государственный медицинский университет
имени академика И.П. Павлова» Минздрава России,
Санкт-Петербург, Россия

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. website¹. 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 ($p_{HWE} > 1 \times 10^{-5}$), 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, USA². 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, USA³). Gene annotation was performed using GeneCards (Weizmann Institute of Science, Israel⁴). The methods are also described in our earlier article with the results of the Mendelian randomization analysis [30].

In addition, we used ENSEMBL POSTGAP⁵ to annotate variants with $p < 1 \times 10^{-5}$ 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 enrichR⁶. 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>

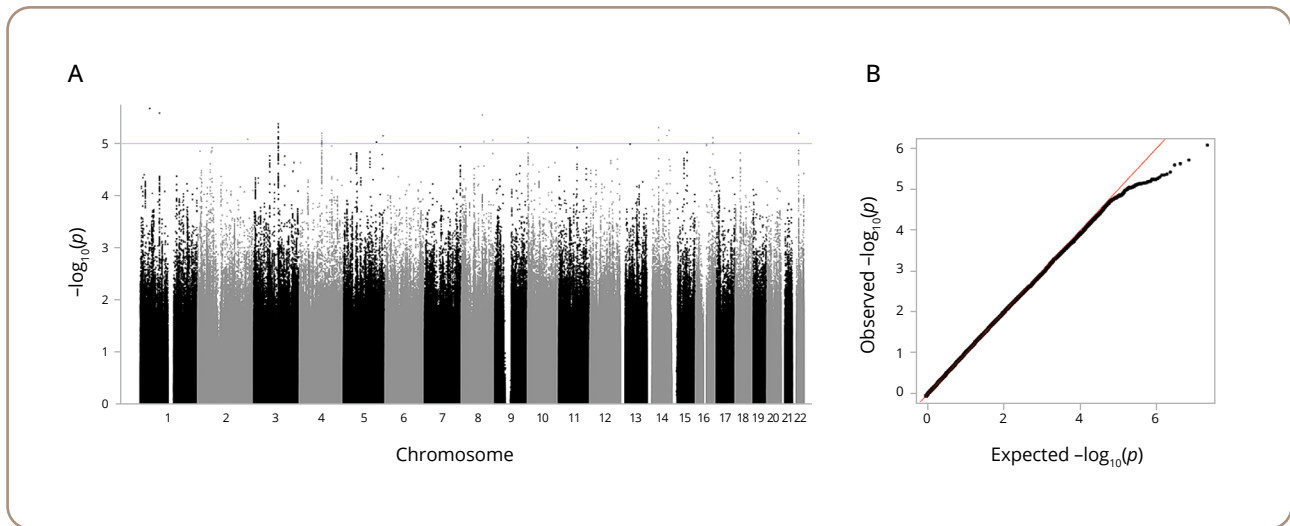


Figure 1. GWAS results of the lifetime anhedonia phenotype.

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. LD Score 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/' files⁷, 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>

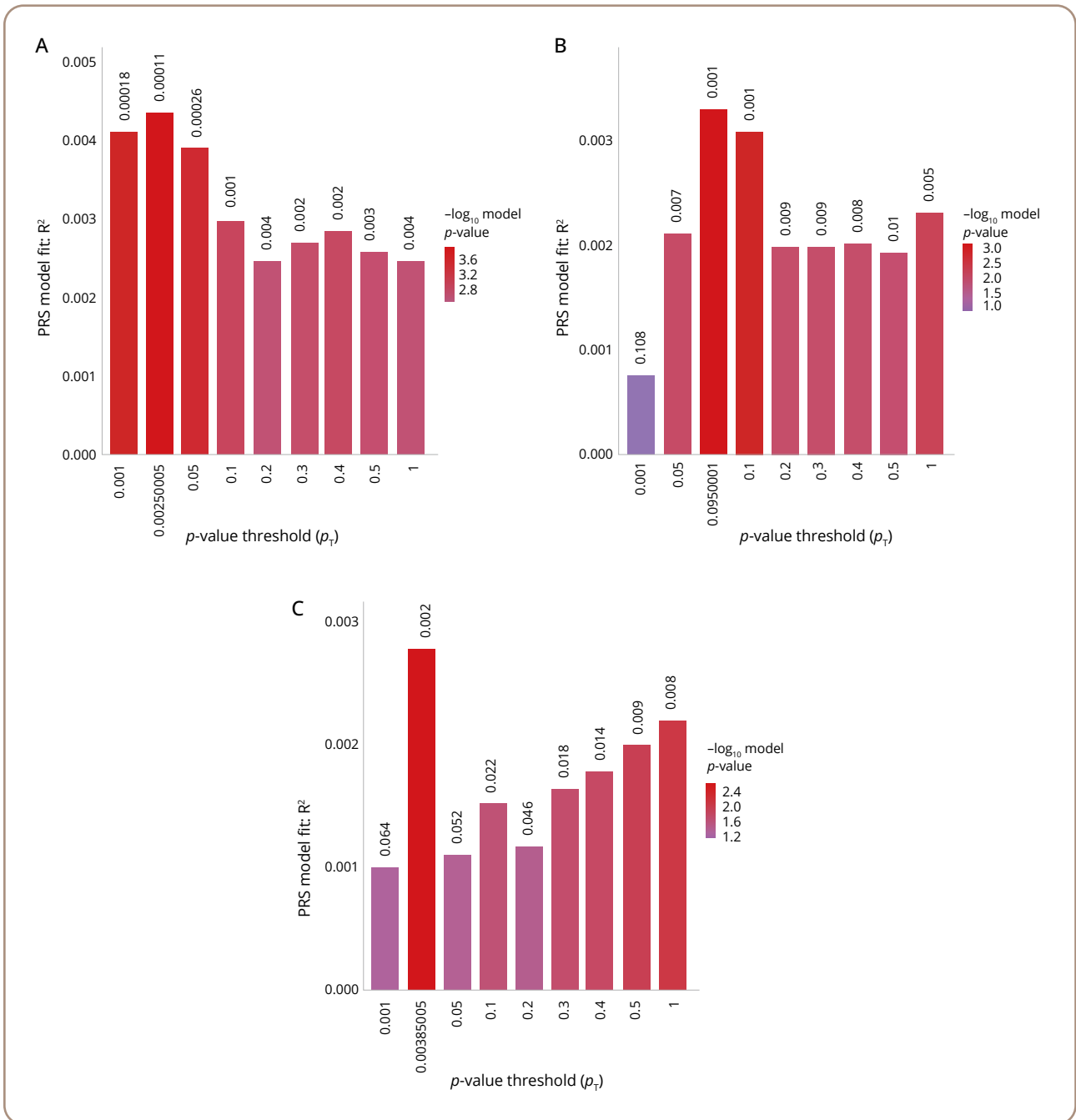


Figure 2. Polygenic risk scores for depression, bipolar disorder, and schizophrenia are significantly associated with the lifetime anhedonia phenotype.

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 $h^2_{\text{snp}}=0.174$ ($SE=0.09$). 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.R²) and other (Null.R²) factors and complete models, considering both factor groups (Full.R²), 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.R²=0.00436498, Full.R²=0.0295311, $p=0.00011262$), BD from PGC (PRS.R²=0.00329757, Full.R²=0.0284637, $p=0.000785365$), and schizophrenia from PGC, second wave (PRS.R²=0.00276988, Full.R²=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 ($p_{\text{adj.}}=0.048$), which includes vitamin K and other hemostatics, due to *DUSP1* — one of the genes the expression of which is affected by vitamin K⁸. 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.

Article history

Submitted: 10.01.2024

Accepted: 08.05.2024

Published Online: 20.06.2024

Authors' contribution: All the authors made a significant contribution to the article, checked and approved its final version prior to publication.

Funding: This work was supported by Russian Science Foundation Grant No. 20-15-00132-П.

Conflict of interest: The authors declare no conflicts of interest.

Supplementary data

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

Figure S1: <https://doi.org/10.17816/CP15494-145181>

Figure S2: <https://doi.org/10.17816/CP15494-145273>

Box S1: <https://doi.org/10.17816/CP15494-145276>

Table S1: <https://doi.org/10.17816/CP15494-145274>

Table S2: <https://doi.org/10.17816/CP15494-145275>

Table S3: <https://doi.org/10.17816/CP15494-145277>

Table S4: <https://doi.org/10.17816/CP15494-145278>

Table S5: <https://doi.org/10.17816/CP15494-145279>

Table S6: <https://doi.org/10.17816/CP15494-145291>

For citation:

Kasyanov ED, Pinakhina DV, Rakitko AS, Vergasova EO, Yermakovich DP, Rukavishnikov GV, Malyshko LV, Popov YaV, Kovalenko EV, Ilinskaya AYu, Kim AA, Plotnikov NA, Neznanov NG, Ilinsky VV, Kibitov AO, Mazo GE. Genetic associations of anhedonia: insights into overlap of mental and somatic disorders. *Consortium Psychiatricum*. 2024;5(2):CP15494. doi: 10.17816/CP15494

Information about the authors

***Evgeny Dmitrievich Kasyanov**, MD, Cand. Sci (Med.), Senior Researcher, Department of social neuropsychiatry, V.M. Bekhterev National Medical Research Center for Psychiatry and Neurology; ORCID: <https://orcid.org/0000-0002-4658-2195>
E-mail: i@kasyan.ru

Darya Vladimirovna Pinakhina, Researcher, Department of social neuropsychiatry, V.M. Bekhterev National Medical Research Center for Psychiatry and Neurology; Researcher, ITMO University; ORCID: <https://orcid.org/0000-0001-9896-6556>

Aleksandr Sergeevich Rakitko, Cand. Sci (Phys Math), Head of Science, Genotek Ltd; Researcher, V.M. Bekhterev National Medical Research Center for Psychiatry and Neurology; ORCID: <https://orcid.org/0000-0003-0567-7734>

Ekaterina Olegovna Vergasova, Bioinformatician, Genotek Ltd; ORCID: <https://orcid.org/0000-0003-0823-0540>

Danat Pavlovich Yermakovich, Researcher, Genotek Ltd; ORCID: <https://orcid.org/0000-0002-0712-6939>

Grigoriy Viktorovich Rukavishnikov, MD, Cand. Sci (Med.), Leading Researcher, Head of the Social Neuropsychiatry Department, V.M. Bekhterev National Medical Research Centre for Psychiatry and Neurology; ORCID: <https://orcid.org/0000-0002-5282-2036>

Larisa Vladimirovna Malyshko, Junior Researcher, Scientific and Organizational Department, V.M. Bekhterev National Medical Research Centre for Psychiatry and Neurology; e-Library SPIN-code: 5156-9223, Scopus Author ID: 57250155600, ORCID: <https://orcid.org/0000-0002-5470-4359>

Yaroslav Vyacheslavovich Popov, Researcher, Genotek Ltd; ORCID: <https://orcid.org/0000-0001-7538-123X>

Elena Vladimirovna Kovalenko, Researcher, Genotek Ltd; ORCID: <https://orcid.org/0000-0001-5678-6557>

Anna Yurievna Ilinskaya, Laboratory manager, Eligens SIA; ORCID: <https://orcid.org/0000-0001-7524-5617>

Anna Aleksandrovna Kim, Researcher, Genotek Ltd; ORCID: <https://orcid.org/0000-0003-4077-4740>

Nikolay Anatolievich Plotnikov, Researcher, Genotek Ltd; ORCID: <https://orcid.org/0000-0001-5585-0035>

Nikolay Grigorievich Neznanov, MD, Dr. Sci (Med.), Professor, Director of V.M. Bekhterev National Medical Research Centre for Psychiatry and Neurology; Head of the Department of Psychiatry and Narcology, Pavlov First State Medical University of Saint Petersburg; e-Library SPIN-code: 108604, ORCID: <https://orcid.org/0000-0001-5618-4206>

Valeriy Vladimirovich Ilinsky, CEO, Eligens SIA; ORCID: <https://orcid.org/0000-0003-4377-2759>

Aleksandr Olegovich Kibitov, MD, Dr. Sci (Med.), Chief Researcher, Head of the Department of Genomics of Mental Disorders; e-Library SPIN-code: 341470, ORCID: <https://orcid.org/0000-0002-8771-625X>

Galina Elevna Mazo, MD, Dr. Sci (Med.), Head of the Institute of Translational Psychiatry, V.M. Bekhterev National Medical Research Center for Psychiatry and Neurology; ORCID: <https://orcid.org/0000-0001-7036-5927>

*corresponding author

Data Availability Statement

The user agreement⁹ 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.

References

1. Craske MG, Meuret AE, Ritz T, et al. Treatment for Anhedonia: A neuroscience driven approach. *Depress Anxiety*. 2016;33(10):927–38. doi: 10.1002/da.22490
2. Der-Avakian A, Markou A. The neurobiology of Anhedonia and other reward-related deficits. *Trends Neurosci*. 2012;35(1):68–77. doi: 10.1016/j.tins.2011.11.005
3. Husain M, Roiser JP. Neuroscience of apathy and Anhedonia: a transdiagnostic approach. *Nat Rev Neurosci*. 2018;19(8):470–84. doi: 10.1038/s41583-018-0029-9
4. Kibitov AO, Mazo GE. [Anhedonia in depression: neurobiological and genetic aspects]. *Zh Nevrol Psikhiatr Im SS Korsakova*. 2021;121(3):146–54. doi: 10.17116/jnevro2021121031146. Russian.
5. Ducasse D, Loas G, Dassa D, et al. Anhedonia is associated with suicidal ideation independently of depression: A meta-analysis. *Depress Anxiety*. 2018;35(5):382–92. doi: 10.1002/da.22709
6. Cuthbert BN, Insel TR. Toward the future of psychiatric diagnosis: the seven pillars of RDoC. *BMC Med*. 2013;11:126. doi: 10.1186/1741-7015-11-126
7. Liu WH, Roiser JP, Wang LZ, et al. Anhedonia is associated with blunted reward sensitivity in first-degree relatives of patients with major depression. *J Affect Disord*. 2016;190:640–8. doi: 10.1016/j.jad.2015.10.050
8. Guffanti G, Kumar P, Admon R, et al. Depression genetic risk score is associated with Anhedonia-related markers across units of analysis. *Transl Psychiatry*. 2019;9(1):236. doi: 10.1038/s41398-019-0566-7
9. Xu C, Chen J, Cui Z, et al. Abnormal Anhedonia as a potential endophenotype in obsessive-compulsive disorder. *Neuropsychiatr Dis Treat*. 2020;16:3001–10. doi: 10.2147/NDT.S268148
10. Hatzigiakoumis DS, Martinotti G, Giannantonio MD, Janiri L. Anhedonia and substance dependence: clinical correlates and treatment options. *Front Psychiatry*. 2011;2:10. doi: 10.3389/fpsy.2011.00010
11. Gorwood P. Neurobiological mechanisms of Anhedonia. *Dialogues Clin Neurosci*. 2008;10(3):291–9. doi: 10.31887/DCNS.2008.10.3/pgorwood
12. Zhang B, Lin P, Shi H, et al. Mapping Anhedonia-specific dysfunction in a transdiagnostic approach: an ALE meta-analysis. *Brain Imaging Behav*. 2016;10(3):920–39. doi: 10.1007/s11682-015-9457-6
13. Pizzagalli DA, Holmes AJ, Dillon DG, et al. Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. *Am J Psychiatry*. 2009;166(6):702–10. doi: 10.1176/appi.ajp.2008.08081201
14. Carter J, Swardfager W. Mood and metabolism: Anhedonia as a clinical target in Type 2 diabetes. *Psychoneuroendocrinology*. 2016;69:123–32. doi: 10.1016/j.psyneuen.2016.04.002
15. Hamer JA, Testani D, Mansur RB, et al. Brain insulin resistance: A treatment target for cognitive impairment and Anhedonia in depression. *Exp Neurol*. 2019;315:1–8. doi: 10.1016/j.expneurol.2019.01.016
16. Trøstheim M, Eikemo M, Meir R, et al. Assessment of Anhedonia in adults with and without mental illness: A systematic review and meta-analysis. *JAMA Netw Open*. 2020;3(8):e2013233. doi: 10.1001/jamanetworkopen.2020.13233
17. Pelle AJ, Pedersen SS, Erdman RAM, et al. Anhedonia is associated with poor health status and more somatic and cognitive symptoms in patients with coronary artery disease. *Qual Life Res*. 2011;20(5):643–51. doi: 10.1007/s11136-010-9792-4
18. Ren H, Fabbri C, Uher R, et al. Genes associated with Anhedonia: a new analysis in a large clinical trial (GENDEP). *Transl Psychiatry*. 2018;8(1):150. doi: 10.1038/s41398-018-0198-3
19. Pain O, Dudbridge F, Cardno AG, et al. Genome-wide analysis of adolescent psychotic-like experiences shows genetic overlap with psychiatric disorders. *Am J Med Genet B Neuropsychiatr Genet*. 2018;177(4):416–25. doi: 10.1002/ajmg.b.32630
20. Ortega-Alonso A, Ekelund J, Sarin AP, et al. Genome-wide association study of psychosis proneness in the Finnish population. *Schizophr Bull*. 2017;43(6):1304–14. doi: 10.1093/schbul/sbx006
21. Ward J, Lyall LM, Bethlehem RAI, et al. Novel genome-wide associations for Anhedonia, genetic correlation with psychiatric disorders, and polygenic association with brain structure. *Transl Psychiatry*. 2019;9(1):327. doi: 10.1038/s41398-019-0635-y
22. Kibitov AO, Mazo GE, Rakitko AS, et al. [GWAS-based polygenic risk scores for depression with clinical validation: methods and study design in the Russian population]. *Zh Nevrol Psikhiatr Im SS Korsakova*. 2020;120(11):131–40. doi: 10.17116/jnevro202012011131. Russian.
23. Kasyanov ED, Verbitskaya EV, Rakitko AS, et al. [Validation of a DSM-5-based screening test using digital phenotyping in the Russian population]. *Zh Nevrol Psikhiatr Im SS Korsakova*. 2022;122(6. Vyp. 2):64–70. doi: 10.17116/jnevro202212206264. Russian.
24. Browning SR, Browning BL. Rapid and accurate haplotype phasing and missing-data inference for whole-genome association studies by use of localized haplotype clustering. *Am J Hum Genet*. 2007;81(5):1084–97. doi: 10.1086/521987
25. 1000 Genomes Project Consortium, Auton A, Brooks LD, Durbin RM, et al. A global reference for human genetic variation. *Nature*. 2015;526(7571):68–74. doi: 10.1038/nature15393
26. McCarthy S, Das S, Kretschmar W, et al. A reference panel of 64,976 haplotypes for genotype imputation. *Nat Genet*. 2016;48(10):1279–83. doi: 10.1038/ng.3643
27. Marees AT, de Kluiver H, Stringer S, et al. A tutorial on conducting genome-wide association studies: Quality control and statistical analysis. *Int J Methods Psychiatr Res*. 2018;27(2):e1608. doi: 10.1002/mpr.1608
28. Chang CC, Chow CC, Tellier LC, et al. Second-generation PLINK: rising to the challenge of larger and richer datasets. *GigaScience*. 2015;4:7. doi: 10.1186/s13742-015-0047-8
29. Cingolani P, Platts A, Wang le L, et al. A program for annotating and predicting the effects of single nucleotide polymorphisms,

⁹ Available from: <https://www.genotek.ru>

- SnPEff: SNPs in the genome of *Drosophila melanogaster* strain w1118; iso-2; iso-3. *Fly (Austin)*. 2012;6(2):80–92. doi: 10.4161/fly.19695
30. Kasyanov ED, Pinakhina DV, Rakitko AS, et al. [Anhedonia in mood disorders and somatic diseases: results of exploratory Mendelian randomization analysis]. *Zh Nevrol Psikhiatr Im SS Korsakova*. 2023;123(4. Vyp. 2):65–73. doi: 10.17116/jnevro202312304265. Russian.
 31. Grote S, Prüfer K, Kelso J, Dannemann M. ABAEnrichment: an R package to test for gene set expression enrichment in the adult and developing human brain. *Bioinformatics*. 2016;32(20):3201–3. doi: 10.1093/bioinformatics/btw392
 32. Hawrylycz MJ, Lein ES, Guillozet-Bongaarts AL, et al. An anatomically comprehensive atlas of the adult human brain transcriptome. *Nature*. 2012;489(7416):391–9. doi: 10.1038/nature11405
 33. Kessler RC, Petukhova M, Sampson NA, et al. Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. *Int J Methods Psychiatr Res*. 2012;21(3):169–84. doi: 10.1002/mpr.1359
 34. Choi SW, Mak TSH, O'Reilly PF. Tutorial: a guide to performing polygenic risk score analyses. *Nat Protoc*. 2020;15(9):2759–72. doi: 10.1038/s41596-020-0353-1
 35. Clark LA, Watson D. Tripartite model of anxiety and depression: Psychometric evidence and taxonomic implications. *J Abnorm Psychol*. 1991;100(3):316–36. doi: 10.1037//0021-843x.100.3.316
 36. Liao A, Walker R, Carmody TJ, et al. Anxiety and Anhedonia in depression: Associations with neuroticism and cognitive control. *J Affect Disord*. 2019;245:1070–8. doi: 10.1016/j.jad.2018.11.072
 37. Appleton KM, Voyias PD, Sallis HM, et al. Omega-3 fatty acids for depression in adults. *Cochrane Database Syst Rev*. 2015(11):CD004692. doi: 10.1002/14651858.CD004692.pub4
 38. Roy T, Lloyd CE. Epidemiology of depression and diabetes: a systematic review. *J Affect Disord*. 2012;142 Suppl:S8–21. doi: 10.1016/S0165-0327(12)70004-6
 39. Barberio B, Zamani M, Black CJ, et al. Prevalence of symptoms of anxiety and depression in patients with inflammatory bowel disease: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. 2021;6(5):359–70. doi: 10.1016/S2468-1253(21)00014-5
 40. Pan A, Sun Q, Okereke OI, et al. Depression and risk of stroke morbidity and mortality: a meta-analysis and systematic review. *JAMA*. 2011;306(11):1241–9. doi: 10.1001/jama.2011.1282. Erratum in: *JAMA*. 2011;306(23):2565.
 41. Mullins N, Forstner AJ, O'Connell KS, et al. Genome-wide association study of more than 40,000 bipolar disorder cases provides new insights into the underlying biology. *Nat Genet*. 2021;53(6):817–29. doi: 10.1038/s41588-021-00857-4
 42. Fabbri C, Kasper S, Kautzky A, et al. Genome-wide association study of treatment-resistance in depression and meta-analysis of three independent samples. *Br J Psychiatry*. 2019;214(1):36–41. doi: 10.1192/bjp.2018.256
 43. Fjukstad KK, Athanasiu L, Bahrami S, et al. Genetic variants associated with cardiometabolic abnormalities during treatment with selective serotonin reuptake inhibitors: a genome-wide association study. *Pharmacogenomics J*. 2021;21(5):574–85. doi: 10.1038/s41397-021-00234-8
 44. Ortega-Azorín C, Coltell O, Asensio EM, et al. Candidate Gene and genome-wide association studies for circulating leptin levels reveal population and sex-specific associations in high cardiovascular risk Mediterranean subjects. *Nutrients*. 2019;11(11):2751. doi: 10.3390/nu11112751
 45. Wood AR, Esko T, Yang J, et al. Defining the role of common variation in the genomic and biological architecture of adult human height. *Nat Genet*. 2014;46(11):1173–86. doi: 10.1038/ng.3097
 46. Wojcik GL, Graff M, Nishimura KK, et al. Genetic analyses of diverse populations improves discovery for complex traits. *Nature*. 2019;570:514–8. doi: 10.1038/s41586-019-1310-4
 47. Wootton RE, Richmond RC, Stuijffand BG, et al. Evidence for causal effects of lifetime smoking on risk for depression and schizophrenia: a Mendelian randomisation study. *Psychol Med*. 2020;50(14):2435–43. doi: 10.1017/S0033291719002678
 48. Mills MC, Tropf FC, Brazel DM, et al. Identification of 371 genetic variants for age at first sex and birth linked to externalising behaviour. *Nat Hum Behav*. 2021;5(12):1717–30. doi: 10.1038/s41562-021-01135-3
 49. Kulminski AM, Loiko E, Loika Y, Culminskaya I. Pleiotropic predisposition to Alzheimer's disease and educational attainment: insights from the summary statistics analysis. *Geroscience*. 2022;44(1):265–80. doi: 10.1007/s11357-021-00484-1
 50. Bogdan R, Pizzagalli DA. The heritability of hedonic capacity and perceived stress: a twin study evaluation of candidate depressive phenotypes. *Psychol Med*. 2009;39(2):211–8. doi: 10.1017/S0033291708003619
 51. Bolzetta F, Veronese N, Stubbs B, et al. The relationship between dietary vitamin K and depressive symptoms in late adulthood: A cross-sectional analysis from a large cohort study. *Nutrients*. 2019;11(4):787. doi: 10.3390/nu11040787
 52. Duric V, Banasr M, Licznarski P, et al. A negative regulator of MAP kinase causes depressive behavior. *Nat Med*. 2010;16(11):1328–32. doi: 10.1038/nm.2219
 53. Liu YX, Wang J, Guo J, et al. DUSP1 is controlled by p53 during the cellular response to oxidative stress. *Mol Cancer Res*. 2008;6(4):624–33. doi: 10.1158/1541-7786.MCR-07-2019
 54. Catani M. The anatomy of the human frontal lobe. *Handb Clin Neurol*. 2019;163:95–122. doi: 10.1016/B978-0-12-804281-6.00006-9
 55. Luby JL, Agrawal A, Belden A, et al. Developmental trajectories of the orbitofrontal cortex and Anhedonia in middle childhood and risk for substance use in adolescence in a longitudinal sample of depressed and healthy preschoolers. *Am J Psychiatry*. 2018;175(10):1010–21. doi: 10.1176/appi.ajp.2018.17070777
 56. Samara Z, Evers EAT, Peeters F, et al. Orbital and medial prefrontal cortex functional connectivity of major depression vulnerability and disease. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2018;3(4):348–357. doi: 10.1016/j.bpsc.2018.01.004
 57. Zhang Y-J, Cai X-L, Hu H-X, et al. Social brain network predicts real-world social network in individuals with social Anhedonia. *Psychiatry Res Neuroimaging*. 2021;317:111390. doi: 10.1016/j.pscychresns.2021.111390