

Research paper

A characteristic cerebellar biosignature for bipolar disorder, identified with fully automatic machine learning



Georgios V. Thomaidis ^{a,*}, Konstantinos Papadimitriou ^b, Sotirios Michos ^c, Evangelos Chartampilas, Prof. ^d, Ioannis Tsamardinos ^e

^a Greek National Health System, Psychiatric Department, Katerini General Hospital, Katerini, Greece

^b Greek National Health System, G. Papanikolaou General Hospital, Organizational Unit - Psychiatric Hospital of Thessaloniki, Thessaloniki, Greece

^c Independent Researcher, Thessaloniki, Greece

^d Laboratory of Radiology, AHEPA General Hospital, University of Thessaloniki, Thessaloniki, Greece

^e Department of Computer Science, University of Crete, Heraklion, Greece

ARTICLE INFO

ABSTRACT

Keywords:

Bipolar disorder
Biosignature
VEPH1
KREMEN2
RNU6-576 P
AutoML
Machine Learning
Psychiatry

Background: Transcriptomic profile differences between patients with bipolar disorder and healthy controls can be identified using machine learning and can provide information about the potential role of the cerebellum in the pathogenesis of bipolar disorder. With this aim, user-friendly, fully automated machine learning algorithms can achieve extremely high classification scores and disease-related predictive biosignature identification, in short time frames and scaled down to small datasets.

Method: A fully automated machine learning platform, based on the most suitable algorithm selection and relevant set of hyper-parameter values, was applied on a preprocessed transcriptomics dataset, in order to produce a model for biosignature selection and to classify subjects into groups of patients and controls. The parent GEO datasets were originally produced from the cerebellar and parietal lobe tissue of deceased bipolar patients and healthy controls, using Affymetrix Human Gene 1.0 ST Array.

Results: Patients and controls were classified into two separate groups, with no close-to-the-boundary cases, and this classification was based on the cerebellar transcriptomic biosignature of 25 features (genes), with Area Under Curve 0.929 and Average Precision 0.955. The biosignature includes both genes connected before to bipolar disorder, depression, psychosis or epilepsy, as well as genes not linked before with any psychiatric disease. Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis revealed participation of 4 identified features in 6 pathways which have also been associated with bipolar disorder.

Conclusion: Automated machine learning (AutoML) managed to identify accurately 25 genes that can jointly – in a multivariate-fashion – separate bipolar patients from healthy controls with high predictive power. The discovered features lead to new biological insights. Machine Learning (ML) analysis considers the features in combination (in contrast to standard differential expression analysis), removing both irrelevant as well as redundant markers, and thus, focusing to biological interpretation.

1. Background

Bipolar disorder (BD) is a mood disorder characterized by unusual fluctuations of mood, thinking, activity and sleep patterns, classified in six subtypes (Alural et al., 2017) (with bipolar disorder types 1 and 2 the most prevalent) and presented as a constellation of phenotypes, with a

variety of cognitive and behavioral features (Duffy et al., 2017). It is a highly hereditary disease, running in families, with an early onset, unpredictable course and detrimental impact due to the great risk of fatal self-destructive events, long term disability and great financial and social burden, despite existing pharmacological and psychotherapeutic treatment strategies (Fountoulakis et al., 2016). For these reasons, the

Abbreviation List: AutoML, Automatic Machine Learning; GEO, Gene Expression Omnibus; AUC, Area Under Curve; AP, Average Precision; TLE, Temporal Lobe Epilepsy; BD, Bipolar Disorder; CNS, Central Nervous System; JADBio, Just Add Data Bio; SES, Statistically EquivalentbioSignatures; LASSO, Least Absolute Shrinkage and Selection Operator; ROC, Receiver Operating Characteristic (curve); CI, Confidence Interval; UMAP, Uniform Manifold Approximation and Projection.

* Corresponding author.

E-mail address: giorgosthomaidis@hotmail.com (G.V. Thomaidis).

<https://doi.org/10.1016/j.ibneur.2023.06.008>

Received 6 January 2023; Received in revised form 19 May 2023; Accepted 29 June 2023

Available online 1 July 2023

2667-2421/© 2023 The Author(s). Published by Elsevier Ltd on behalf of International Brain Research Organization. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

neuroanatomy (Ching et al., 2022), neurogenetics and neurobiology (Charney et al., 2020) of BD are fields of intense research concerning all brain areas and of paramount importance for 45 million patients globally (James et al., 2018). In this context, the cerebellum is a relatively recent target of neurogenetics research in BD, with its main functional roles related to modulation of movement, to emotion and to cognition (Wang et al., 2017). Research has linked the cerebellum to emotional, cognitive and affective processing and their disruption in mood disorders (Adamaszek et al., 2017; Wang et al., 2017). Structural (Chambers et al., 2022; Eker et al., 2014; Mahon et al., 2009; Moorhead et al., 2007; Phillips et al., 2015; Redlich et al., 2014; Romer et al., 2018), functional (Adamaszek et al., 2017; Liang et al., 2013, 2013; Phillips et al., 2015; Shinn et al., 2017; Wang et al., 2017; Y. Wang et al., 2015), neurotransmission (Hossein Fatemi et al., 2005; Maloku et al., 2010), metabolic (Altamura et al., 2013; Cecil et al., 2003; Pinna and Colasanti, 2021; Su et al., 2014), and transcriptomic (C. Chen et al., 2018; Chen et al., 2013; McCarthy et al., 2014) alterations in the cerebellum in BD point to the cerebellum's particular role in the affected brain-wide networks.

Machine learning is now gradually being used in psychiatry, in order to optimize genetic analysis (Bracher-Smith et al., 2021; Karthik and Sudha, 2021), to highlight the most characteristic differences among groups of patients and controls, and to confirm their importance for diagnostic classification into these groups. These complex classification algorithms, produce genetic signatures using data from the analysis of samples from living tissue, blood, saliva, as well as from postmortem brain tissue (prefrontal cortex) (Karthik and Sudha, 2021). The data include SNP (5 studies) (Bracher-Smith et al., 2021) and transcriptomics (2 studies) (Karthik and Sudha, 2021; Wang et al., 2018) analysis results. In this context, transcriptomic data analysis can contribute greatly to psychiatric research (Hernandez et al., 2021). Data from the less explored area of the cerebellum can add new and important biosignatures to the puzzle of BD pathogenesis and progression, and potentially to treatment response and resistance. The main advantages of Machine Learning (as well as multivariate statistical modelling) versus standard univariate statistics (e.g. differential expression analysis) is that Machine Learning models consider the biomarkers in combination, while univariate statistics do not. Machine Learning feature selection algorithms, select biomarkers not based on their (univariate) p-value and their correlation with the outcome, but based on the added-predictive-value they provide to the model. Hence, feature selection algorithms may remove (unconditionally) statistically significant markers that do not provided added-value to the final model (remove redundant markers). They may also discover markers that are not (unconditionally) statistically significant by themselves but become correlated in combination with other markers.

Recently, the field of Automated Machine Learning (AutoML) has emerged (Hutter et al., 2019) that strives to automate the machine learning analysis of a dataset. More specifically, AutoML tools automate the selection of algorithms and their hyper-parameter values (tuning parameters that determine the predictive performance of the produced model), the estimation of out-of-sample predictive performance, and the selection of features to enter the model. They may also provide visualization, interpretations, and explanation of the produced model (Xanthopoulos et al., 2020). AutoML tools, provided they are well-designed, may not only lead to a better predictive model than a human expert, but may do so with minimal human effort and avoid methodological errors in the analysis. The current study is, as far as we know, the first where AutoML and transcriptomic data from the cerebellum were used for biosignature identification and patient classification.

2. Aims of the study

The aim of this analysis is the selection of characteristic transcriptomic biosignatures of bipolar disorder in the cerebellum, using the AutoML platform for optimal performance (Karagiannaki et al., 2022;

Tsamardinos et al., 2022, 2018). The features identified could facilitate the discovery of the genetic networks related to BD, highlight their importance at the local and brain-wide network levels and explore a potential genetic overlap with other central nervous system (CNS) disorders.

3. Methods

3.1. Data acquisition

The datasets employed for the analyses are public transcriptomic data from previous studies (C. Chen et al., 2018; Chen et al., 2013) that analyzed the transcriptomic profiles of the cerebellum and parietal cortex of postmortem brain tissues and produced a set of biosignatures (C. Chen et al., 2018). Patient and control groups were homogenized by tissue sample location (cerebellum), psychiatric diagnosis, sex and age. The data have been retrieved from the online BioDataome database (Lakiotaki et al., 2018), which is constructed by uniformly preprocessed, disease-annotated omics data from GEO and RECOUNT databases, based on a uniform preprocessing pipeline, described in detail at the BioDataome documentation page (Lakiotaki, 2017). We analyzed the BioDataome data, which correspond to the GEO dataset GSE35978. GSE35978 contains expression data from the human cerebellum (produced from GSE35974) and parietal cortex of post mortem brain tissue samples, which have been extracted from unaffected subjects and schizophrenic, bipolar and depressed patients. The brain tissue samples were selected from the Stanley Foundation Brain Collection (Torrey et al., 2000) of the Stanley Medical Research Institute (SMRI). Expression data were obtained by microarray analysis using the “[HuGene-1_0-st] Affymetrix Human Gene 1.0 ST Array [transcript (gene) version]”. The dataset was initially used for the analyses in (C. Chen et al., 2018; Chen et al., 2013). Technical details about the initial postmortem sample (age, Ph, postmortem interval, sex, etc.) are available at the EMBL-EBI page for E-GEOD-35978 (Chen, 2012). Demographic data about a. race/ethnicity, b. side of brain of the samples, c. Bipolar Disorder types, d. Occurrence of psychotic features and e. cause of death of the participants, are available at the Array Collection description (“Brain Research – Tissue Repository,” 2014). Details regarding the description of the original SMRI sample, inclusion and exclusion criteria used for its composition and sample subjects diagnoses and causes of death, are presented in SI, Section A.

3.2. Data Processing

The preprocessed file includes data for 144 samples from the cerebellum and 168 samples from the parietal cortex. The 144 cerebellum samples include unaffected subjects and patients with bipolar disorder, schizophrenia and depression (SI, information on GSE35974 and GSE35978). From the cerebellum group, all 50 unaffected subjects and 37 bipolar disorder patients (sex: females/males, age span: 20–70) were initially chosen (SI, Images 1A-1B and 1C-1D). From the initial heterogeneous groups of patients and controls, a number of subjects were removed, and two new, smaller groups of affected / unaffected subjects were produced, matched for sex (female / male) and for age. At the same time, we aimed to exceed (as much as the sample sizes allowed) the minimum threshold of 30 subjects per group required for the machine learning analysis (SI, Images 2A-2B and 2C-2D). The final dataset includes the following two groups: Group A (BD) with 35 bipolar patients (18 female and 17 male) and Group B (HC) with 37 unaffected controls (19 female and 18 male). The small size of available data excluded the possibility of testing after the initial training; this was balanced by the extremely high AUCs produced during the initial (training) analysis. During the initial microarray analysis, a number of transcriptomes were used as controls (C. Chen et al., 2018; Chen et al., 2013). These have been identified and removed from the csv. of the analysis, and the final datasheet (Diagnosed Subjects x Features) consequently produced. The

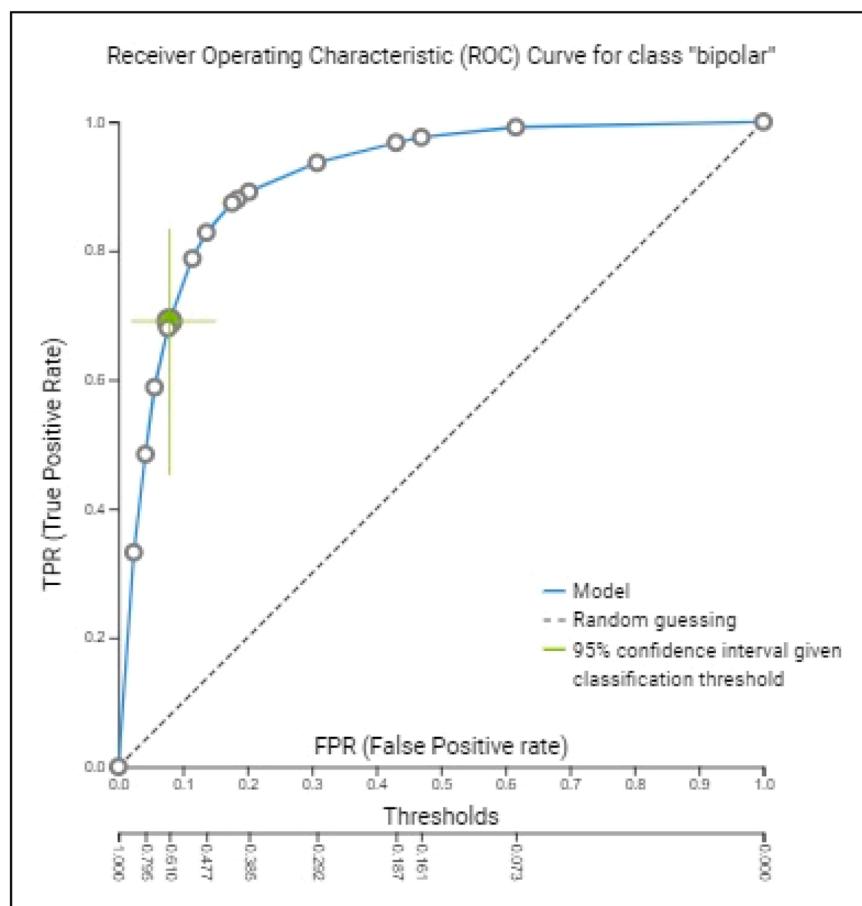


Image 1. Using the best performing model option in the platform, the AUC for the positive class bipolar is 0.929 (~93%), with a 95% CI between 0.868 and 0.977, and the APis 0.955, with a 95% CI between 0.914 and 0.986. Accuracy has been calculated at 0.843, Precision at 0.906 and Specificity at 0.921 (full data in SI, Section B, **Image 3**). The classification threshold (0.61) has been optimized and determined for Accuracy / Balanced Accuracy. Classification as positive is performed when out-of-sample predicted probability is above this given threshold (0.61).

datasets are 2D matrices (features/ genes x diagnosis for any given subject, unaffected or patient).

3.3. Automated Machine Learning

For this study, we applied the fully automatic machine learning (AutoML) platform Just Add Data Bio (JADbio) (Tsamardinos et al., 2022). JADbio tries several hundred Machine Learning pipelines (called **configurations** in the AutoML literature) on a given dataset stemming from different combinations of preprocessing, feature selection, and modeling algorithms, as well as different hyper-parameter values for these algorithms. Specifically, for classification problems JADBio tries the Statistically Equivalent Signature (SES) and the Least Absolute Shrinkage and Selection Operator (Lasso) feature selection algorithms, Decision Trees, Random Forests, Ridge Logistic Regression, and Support Vector Machines with different kernels (Tsamardinos et al., 2022). The configurations are decided automatically based on the type and size of data and the user preferences. The best configuration is determined by estimating the performance of the models it produces using hold-out estimation protocols such as cross-validation. The exact type of cross-validation, is decided upon the characteristics of the dataset, but for small sample studies it is a repeated, stratified Cross-validation, meaning the cross-validation is repeated several times to reduce the variance of the estimation. The final performance reported, as well as the confidence intervals are corrected for a type of the “winner’s curse”, specifically, it is corrected for the estimation bias that stems from the fact that the best out of many configurations is selected. The correction uses the Bootstrap-Bias Corrected CV method (Tsamardinos et al., 2018). In (Tsamardinos et al., 2022), a comparative evaluation on 360 omics datasets of small sample size shows that JADBio does not overestimate performance, on average. JADBio fully automatically returns (a) a final

predictive model, (b) an estimate of the model’s out-of-sample predictive performance, and (c) selects a biosignature (set of measured quantities such as transcriptomic, biochemical, neuroimaging, psychometric or symptom intensity features) that enters the model. In typical omics studies, the set of biomarkers is typically less than 20 (Liu et al., 2013). JADBio has been selected as the system of choice for AutoML because it is designed for high-dimensional/small-sample data and does not overestimate predictive performance. It was also chosen because it has been shown to reduce the number of biomarkers required for prediction by a factor of ~4000, without a decrease in predictive performance, compared to other AutoML platforms (Tsamardinos et al., 2022). In addition, it has been previously applied to modeling problems in oncology, neurology and psychiatry (Adamou et al., 2019, 2018; Bowler et al., 2022; Deutsch et al., 2022; Deutsch and Stres, 2021; Karaglani et al., 2022, 2020, 2020; Karstoft et al., 2020; Nissen et al., 2021; Panagopoulou et al., 2021; Papoutsoglou et al., 2021; Rounis et al., 2021).

There are several metrics of predictive performance for binary classification problems. In the results we use the Area Under the ROC curve (AUC) which equals the probability that the model will correctly rank a pair of a randomly chosen positive and one negative sample, according to their probabilities of being positive. We also use Accuracy defined as the percentage of correct classifications by the model, Sensitivity (percentage of true positives over all positives), Precision (percentage of true positives over all discoveries), and Specificity (percentage of true negative over all negatives). Predictive models output a probability for each new sample. One needs to set a threshold on this probability to classify a subject to BD or not. Notice that AUC is a metric that does not depend on a threshold, while all other metrics discussed above, do depend on the choice of the classification threshold.

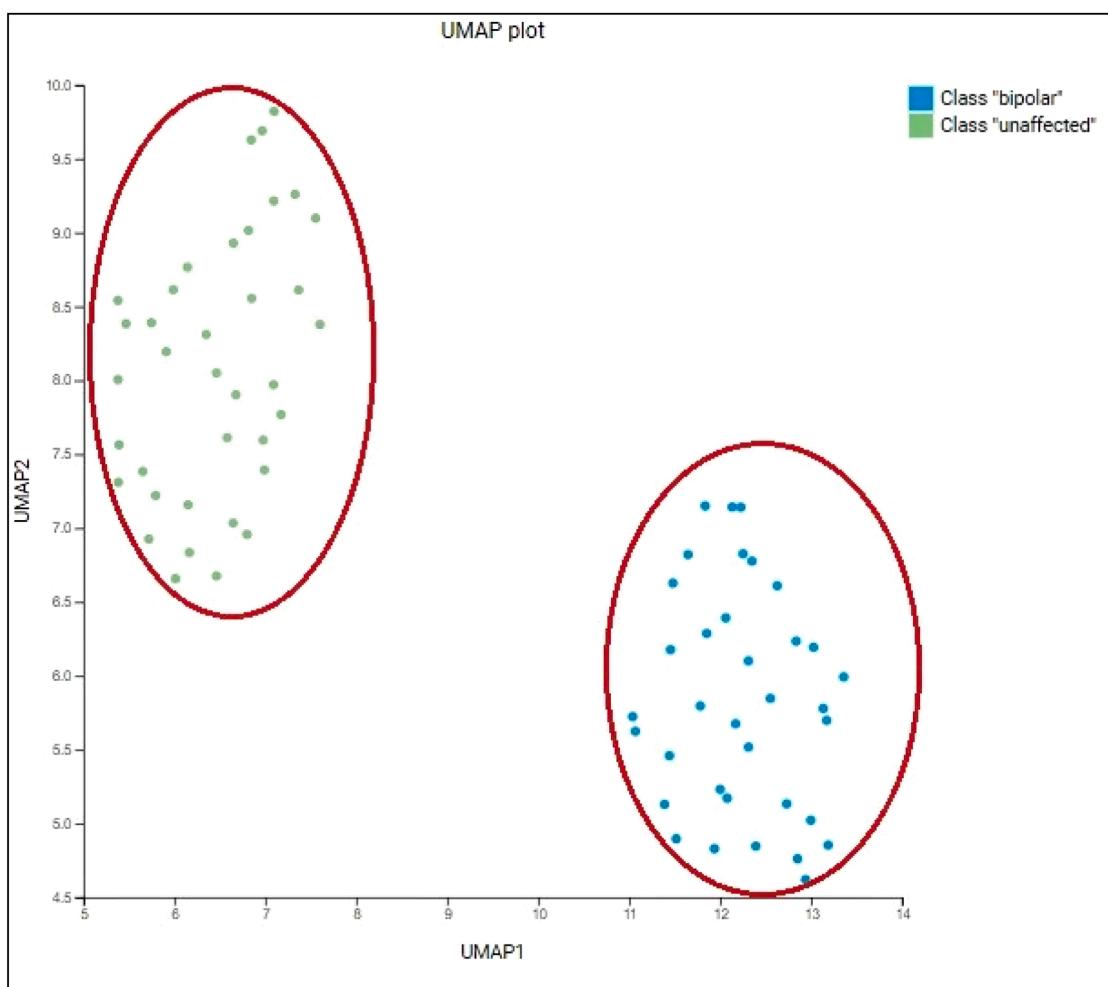


Image 2. Complete separation of BD patients from unaffected controls, in UMAP plots based on all the 25 selected biosignatures. In the Box Plot contrasting the cross-validated predicted probability of belonging to a specific class against the actual class of the samples, the medians are ~0,72 for the class “bipolar” and ~0,18 for the class “unaffected” (SI, Section B, Image 4).

3.4. Statistical analysis of the biosignature genes

After the identification of the biosignature genes, we proceeded to a statistical investigation and analysis, in order to identify differences in the expression of any selected gene between the two groups (bipolar patients and healthy controls). For this analysis, we began with visual exploration of the box and violin plot for every gene, and then computed the basic descriptive statistics of the bipolar disorder and healthy controls groups and the difference of the means between these groups, along with their 99.8% confidence intervals. Finally we performed Welch’s t-test to assess the statistical significance of the observed difference (Additional details on the Statistical Analyses and results are reported in Appendix I).

3.5. KEGG Analysis

KEGG is a reference Knowledge base (Kanehisa et al., 2022), including various objects, for example genes, which can be categorized into genetic pathways, genetic networks, and other systems (Kanehisa et al., 2023). All database entries (for example genes) can be identified by characteristic KEGG identifiers (kid) (Kanehisa et al., 2023). KEGG mapping is the procedure which computationally generates the biological (genetic, metabolic and other) systems in an organism-specific way (Kanehisa et al., 2022, 2023), using the KEGG Mapper Search tool. Specifically, the search matches the genetic loci on KEGG pathway maps

and other network entities and subsequently provides information about the biological functions that these genetic loci are involved in.

In our study we performed a KEGG analysis of the genetic loci (the biosignature genes) that were shown to be significant in differentiating between the two groups. The procedure had the following steps. First we entered the NCBI Entrez Gene ID number of each gene on the KEGG Convert ID tool, in order to generate the KEGG identifiers from the biosignature genes. Then we used the Search tool of the KEGG Mapper. Initially, we inserted the KEGG identifiers of the significant genes and subsequently performed the search. Specific pathways have been identified (see 4.3 in the Results).

4. Results

4.1. Classification between BD patients and unaffected controls

For the analysis, data were uploaded to JADBio version 1.4.14 (April 2021). As the outcome the diagnosis (Bipolar or Unaffected) was selected leading to a classification prediction task. The analysis protocol selected by JADBio performed a repeated 10-fold cross validation without the dropping heuristic (see (“Neuropathology Consortium,” 2014)) to evaluate each configuration. A total of 596 configurations were used to train 5760 predictive models during cross-validation and estimate their performance. The winning configuration (pipeline), i.e., the one exhibiting the highest cross-validated AUC, comprises of a

preprocessing step by removing constant values, selecting features using the Lasso (Least Absolute Shrinkage and Selection Operator) algorithm with hyper-parameters penalty= 0.0, and lambda= 5.509e-02, and predictive modeling algorithm the Ridge Logistic Regression with penalty hyper-parameter lambda = 10.0. The time to complete the analysis was 2 h 16 min. The technical analysis report is in SI-Appendix-2. The results can be used interactively in the unique, shared link automatically created by JADBio for each analysis: <https://app.jadbio.com/share/b2484058-15af-496c-adff-9e4ee1fd4d3f>.

The final predictive model had an AUC for the bipolar class of 0.93 based on 25 selected characteristic biomarkers. Several predictive performance metrics along with the Receiver Operating Characteristic Curve (ROC curve) are shown in [Image 1](#). The classification threshold that maximizes the Accuracy, as well as the Balanced accuracy is 0.61. For that threshold, Accuracy has been calculated at 0.843, Precision at 0.906 and Specificity at 0.921. A 2D visualization of the samples using only the selected biomarkers and the Uniform Manifold Approximation and Projection (UMAP) algorithm is shown in [Image 2](#). The BD and HC groups produced are completely separate, visually depicting the class separation that is implied by a 0.93 AUC.

4.2. Biosignature identification

JADBio selected the most important 25 out of the 28869 features of the dataset using the Lasso algorithm with hyper-parameters penalty= 0.0, and lambda= 5.509e-02. These 25 features constitute the reference signature, used for the classification between BD and controls. The best predictive model deriving from the current analysis is a linear Ridge Logistic Regression model with penalty hyper-parameter lambda = 10.0.

In [Image 3](#), we present the 25 genes along with their standardized

Table 1
Genes ranked by absolute value of their Standardized coefficients.

Gene	Assay Number	Standardized Coefficient
VEPH1	8091678	-0.299
KREMEN2	7992758	-0.285
RNU6-576 P	7925874	0.278
RABGGTA	7978239	-0.268
RNU6-347 P	8063433	0.261
FGD2	8119132	-0.250
GDP5	7950501	-0.244
AURKB	8012403	-0.240
FAM215A	8007548	-0.236
CARD16	7951408	-0.235
FBXO17	8036686	-0.225
RNA5SP273	8147242	0.219
chr6:69375060-69375137	8127423	0.213
chr6:69375060-69375137	8127423	-0.213
NFAM1	8076441	-0.210
PROCA1	8013747	0.200
RNU6-1249 P	8008596	0.200
RNU6-1270 P	8088846	-0.193
chr7:57236783-57236849	8132988	-0.187
ASIC3	8137336	-0.187
PRSS22	7998878	-0.185
FNDC8	8006504	-0.1845
MGC34800	7995310	0.182
HIST1H4A	8117334	0.165
RNU6-1154 P	8143108	-0.161
MIR194-2	7949275	-0.299

coefficients in the model in order of decreasing absolute value. This absolute value expresses the impact each gene has to the predictive model. In particular, the largest absolute values, the highest the feature impact..

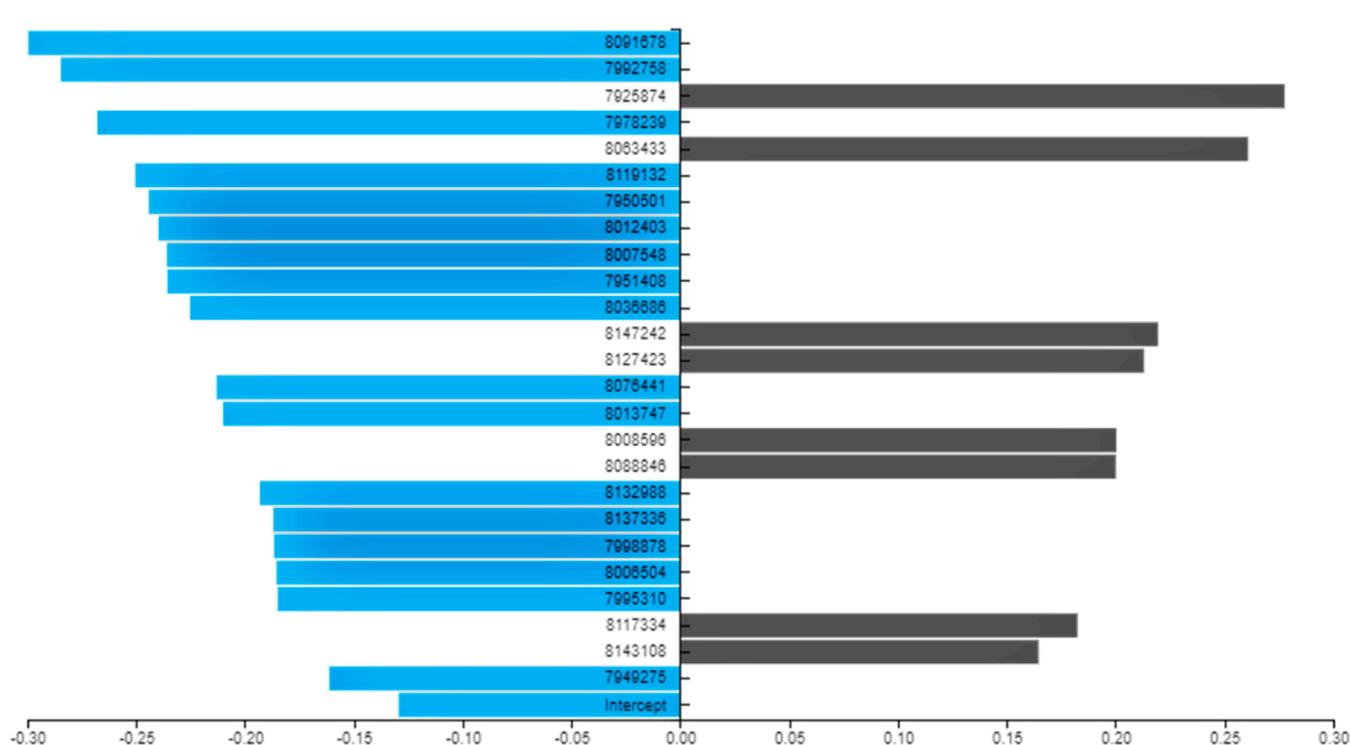


Image 3. In [Image 3](#), we present the 25 genes along with their standardized coefficients in the model in order of decreasing absolute value. From top to the bottom, the 25 selected genes which correspond to each gene number used in the initial study ([Chen et al., 2013](#)) are: VEPH1 (8091678), KREMEN2 (7992758), RNU6-576 P (7925874), RABGGTA (7978239), RNU6-347 P (8063433), FGD2 (8119132), GDP5 (7950501), AURKB (8012403), FAM215A (8007548), CARD16 (7951408), FBXO17 (8036686), RNA5SP273 (8147242), chr6:69375060-69375137 (8127423), NFAM1(8076441), PROCA1 (8013747), RNU6-1249 P (8008596), RNU6-1270 P (8088846), chr7:57236783-57236849 (8132988), ASIC3 (8137336), PRSS22 (7998878), FNDC8 (8006504), MGC34800 (7995310), HIST1H4A (8117334), RNU6-1154 P (8143108). MIR194-2 (7949275). The genes and their respective values, are presented in [Table 1](#). A detailed statistical analysis illustrating both the statistical significance and the effect size of those genes is presented in SI, Appendix 1.

4.3. KEGG analysis

We applied KEGG analytical tools (Kanehisa, 2019, 2000; Kanehisa et al., 2023) to the characteristic features with KEGG identifiers. Four of the genes with KEGG identifiers (MIR194–2, CARD16, ASIC3, H4C1) are involved in 7 KEGG pathways: MIR194–2 in the hsa05206 pathway (“MicroRNAs in cancer”), CARD16 in the hsa04621 pathway (“NOD-like receptor signaling”), ASIC3 in the hsa04750 pathway (“Inflammatory mediator regulation of TRP channel”) and H4C1 in 4 pathways: hsa05034 (“Alcoholism”), hsa04613 (“Neutrophil extracellular trap formation”), hsa05203 (“Viral carcinogenesis”)], hsa05322 (“Systemic lupus erythematosus - Homo sapiens”).

5. Discussion

5.1. Main findings

5.1.1. Genetic biosignature genes and bipolar disorder

The classification between the bipolar and unaffected control groups was completed in < 1 h, with accuracy ~93% and without overlaps between the produced sets of individuals, based on the 25 genes of the genetic biosignature. Potential connections, for some of the biosignature genes, to BD-related symptoms, pathophysiology and treatment and to the regulation of emotion, have been suggested in the existing scientific literature and are briefly presented. A complete description of all the complex potential connections of the identified genes with neuropsychiatric disorders is presented in the SI, Section C.

VEPH1 has been a candidate gene for association with bipolar disorder (Hattori et al., 2009), for neurodevelopmental abnormalities related to BD (Madison et al., 2015) and response to lithium therapy (Stacey et al., 2018). It has also been suggested as a potential link between affective disorders and psychosis (X. Chen et al., 2018). KREMEN2 is implicated in the regulation of Wnt signaling pathways (Lou et al., 2021; Mao et al., 2002; Mao and Niehrs, 2003). Wnt deregulation has been linked to bipolar disorder, (Aghaiizu et al., 2023). For RABGGTA, potential associations between modulation of its expression during exposure to lithium and antipsychotic medication, both first line treatments for BD (Alnafisah et al., 2022; Breen, 2016; Fatemi et al., 2009) have been proposed. FGD2 has been connected with microRNA deregulation inducing manic-like behaviors in rat models (Leem et al., 2023) and is a potential biomarker for suicidality (Le-Niculescu et al., 2013). GDPD5 is differentially expressed in experimental models of mental illness after treatment with valproic acid, a major treatment option in BD (Jiang et al., 2019). CARD16, has been associated with BD (Hossain et al., 2022; Vastrand and Vastrand, 2022) and lithium response (Crueanu et al., 2013). PROCA1 has been connected to BD in twin studies (Amare et al., 2021), to patient response to lithium treatment in BD (Amare, 2018) and to treatment response in mood disorders (Hettwer et al., 2022). ASIC-3, is expressed in crucial brain structures related to emotion and cognition (Wemmie et al., 2013). HIST1H4A gene expression is potentially connected to response to antidepressant therapy (Belzeaux et al., 2012) and depression in mouse models (Yamagata et al., 2017) Finally, a number of small non-coding RNAs and pseudogenes, is included in the biosignature (RNU6–347 P, RNU6–1154 P, MIR194–2). Both classes are a subject of intense research in relation to their participation in the epigenetic modification of DNA during the onset of psychotic disorders, depression and bipolar disorder (Barbash et al., 2017; Yoshino and Dwivedi, 2020).

Another important finding is that RNU6–576 P, MIR194–2 and GDPD5 have been associated with epilepsy (though not until now with bipolar disorder). Both epilepsy and bipolar disorder are characterized by episodic functional deregulation in the CNS (Mula et al., 2010), co-occur (Bakken et al., 2014), share common symptoms and precipitating factors (Bostock et al., 2017; Lyketsos et al., 1993), their treatment with antiepileptics / mood stabilizers partially overlaps (Haggarty et al., 2021), and potential pathophysiological links between epilepsy

and bipolar disorder have been proposed recently (Lopez et al., 2017) regarding aberrant neuronal excitation-inhibition related to ANK-3 gene expression. ANK3 belongs to a cluster of genes with altered expression patterns in the cerebellar vermis, in patients with bipolar disorder (McCarthy et al., 2014; Oraki Kohshour et al., 2022). Significantly, alterations in RNU6–576 P and MIR194–2 expression are connected to temporal lobe epilepsy (An et al., 2016; Barbash et al., 2017; Cava et al., 2018; Niu et al., 2021; Yoshino and Dwivedi, 2020) which shares the most common symptoms and pathways with Bipolar Disorders I and II (Bakken et al., 2014; Bostock et al., 2017; Drange et al., 2020; Haggarty et al., 2021; Lopez et al., 2017; Lyketsos et al., 1993). RNU6–576 P is the most overexpressed small non-coding mRNA in the hippocampus of patients with mesial temporal lobe epilepsy (Niu et al., 2021) and the most important identifying biosignature in the cerebellum of BD patients in this study. The role of MIR-194–2 expression in epilepsy has been studied in the greatest detail, and a constant pattern of down-regulation has been documented, in various epilepsy studies (An et al., 2016; Cava et al., 2018; Li et al., 2014; Mills et al., 2020).

5.1.2. KEGG analysis results and bipolar disorder

The potential associations of the identified KEGG pathways with BD (proposed pathophysiological or treatment mechanisms), have been found in several studies, and are presented briefly. Potential associations between the identified KEGG pathways and other neuropsychiatric disorders are presented in the SI, Section C.

The **hsa05206 pathway** includes MIR194–2 gene and also miR-34a gene (which is not included in the biosignature). miR-34a expression alterations in the cerebellum have been connected to bipolar disorder in previous studies in the same post-mortem sample (Bavamian et al., 2015; C. Chen et al., 2018). The hsa05206 is of particular interest, as both ANK3 (Ankyrin-3) and CACNB3 (voltage-dependent L-type calcium channel subunit beta-3) genes, are directly targeted by miR-34a (Bavamian et al., 2015; C. Chen et al., 2018) and could be connected to the neurobiology of bipolar disorder (Alural et al., 2017; Bavamian et al., 2015; Harrison et al., 2018; Leussis et al., 2013; Yoon et al., 2022). The **hsa04621 pathway** (includes CARD16 gene) implicates immunological deregulation in bipolar disorder (“Bipolar pathways, (Scaini et al., 2019; Szatkiewicz et al., 2014) and depression (Zhang et al., 2022). The **hsa04750 pathway** (includes ASIC3 gene), has been connected to the metabolic syndrome in bipolar disorder and schizophrenia (Winterton, 2022). Interestingly, **hsa05322, hsa05034, hsa05203 and hsa04613 pathways**, involving H4C1, have been all associated with a genetic risk for depression (Huang et al., 2021), with many mechanisms mediated by immunological processes (Shen et al., 2022). Concisely 7 identified KEGG pathways are associated with bipolar disorder or depression.

5.2. Statistical analysis

The visual data exploration and the descriptive statistical analysis of the 25 genes of the biosignature (SI, Appendix 1), reveal the presence of a statistically significant effect in each of the 25 genes of large or very large size (with one medium exception) at a confidence level of 99.8%. Some genes showed reduced levels of expression in the bipolar case, while others were characterized by an increase in their expression. Of course, there was no clear separation between the two groups in any gene. However, this tendency of certain genes to over- or under-express in the bipolar case suggests that these genes share important information regarding the presence of disease, as indicated by the high performance of the biosignature discovered by the JADBio platform.

5.3. Novelty of the study and the classification results

The aim of this study has been the search for differences in the genetic expression in the cerebellum between bipolar patients and healthy controls. The AutoML method applied on the genetic dataset, identified a biosignature with robust prognostic value, confirmed by the

classification results achieved. As far as we know, this is the first study of that kind for bipolar disorder and has resulted to a complete separation between the two groups (Image 2). The biosignature discovered and used for the classification analysis, is consisted of a set of 25 genes with known potential associations to bipolar disorder or other neuropsychiatric diseases with clusters of symptoms overlapping with the symptoms of BD (schizophrenia, major depression) and with overlapping treatment options (schizophrenia, major depression, epilepsy). The AutoML platform JADBIO used in this study, has been successfully tested against different, advanced predictive modeling systems in 360 high dimensional datasets and has been applied to various datasets, in more than 40 published studies (Tsamardinos et al., 2022).

5.4. Limitations of the study

The present study was based on samples from patients with BD type I and II, with an increased analogy of deaths from suicide, and was based on post-mortem tissue sampling and microarray analysis. Any potential diagnostic heterogeneity from the inclusion of BD2 subjects in the sample is not a restrictive factor for the analysis. Some genetic differences between patients with BD I and BD II have been suggested (Gershon, 1982; Heun and Maier, 1993; Kvaløy et al., 2018; McGrath et al., 2004; Sadovnick et al., 1994; Tondo et al., 2022), using family databases, but findings from very large genetic studies have revealed a more complex picture: BD1 and BD2, although partially different in terms of clinical presentation and not genetically identical (Mullins et al., 2021), are genetically similar (Mullins et al., 2021), strongly genetically correlated (Mullins et al., 2021), and so are considered as parts of a genetic spectrum (Coleman et al., 2020) and “sufficiently similar to justify joint analysis” (Coleman et al., 2020), as it is in the case of two very recent major genetic studies of BD, with very large samples comprising more than 40.000 and 185.000 BD patients respectively (Coleman et al., 2020; Mullins et al., 2021). Additionally, the bipolar spectrum is highly heterogeneous, with many different biotypes and their probable neurobiological causes (Ching et al., 2022; Dai et al., 2020; Diaz et al., 2020; Duffy et al., 2017; Guzman-Parra et al., 2021). These different biotypes can be fully represented only in very large samples (Ching et al., 2022).

We observed that 15 out of 31 BD subjects from the Array Collection (“Brain Research – Tissue Repository,” 2014) and 4 out of 9 subjects of the initial Stanley Neuropathology consortium sample, have died of suicide, a rate higher than the statistically expected suicide rate for both BD1 and BD2 subtypes (Novick et al., 2010). A higher suicide rate in the sample could potentially indicate a stronger genetic correlation of the sample to MDD, although suicide is common and also during episodes of mania. Indeed, suicide mainly occurs during the depressive state of the disease and – occasionally – during a manic episode, and could be connected to certain patterns of gene expression (Kung et al., 2010) and biosignature differences (Sher et al., 2022) found also in the cerebellum. Also, its frequency can vary depending on the depressive, manic or mixed state of the disease (Valtonen et al., 2008).

Regarding the estimation of performance, we note that it is very challenging given the number of available samples, the high-dimensionality of the problem, the fact that non-linear algorithms that may overfit are also tried, and that numerous pipelines were tried. Reporting the cross-validation estimate of the winning pipeline is known to be plagued by the “winner’s curse” and be optimistically biased. JADBIO uses several estimation principles that overcome these limitations and do not require one to retain a completely separate hold-out set for statistical validation of the methodology and thus “lose samples to estimation” (Tsamardinos, 2022). It has been shown not to overestimate performance in a large evaluation study (Tsamardinos et al., 2022). However, an external validation dataset would be necessary to confirm the results and to ensure that results transfer to datasets from other laboratories.

Finally, further studies, in more post-mortem samples, using

microarray (Choi et al., 2021), RNA-seq and other methods, are very important, as the genetic characteristics of post-mortem brain tissue samples could be extremely complex in the same area (Cariaga-Martinez and Alelú-Paz, 2016) and divergent from the same characteristics of the living brain, in health and disease; still they remain one of the cornerstones of research on the neurobiology of the CNS and its disorders (Harrison, 2011; Lewis, 2002; McCullumsmith and Meador-Woodruff, 2011; Sullivan et al., 2018).

5.5. Implications of the study

The discovery of a genetic biosignature leading to classification with $AUC > 90\%$ and complete separation between the classification groups (bipolar patients, healthy controls), indicates the existence of differences in the cerebellar genetic expressions of bipolar patients and healthy controls. The biosignature, includes genes with known potential associations with BD and with neuropsychiatric disorders whose symptoms overlap with the symptoms of BD, plus new genes with emerging properties, potentially related to brain function. Future studies, based on advancements in knowledge of the cerebellar transcriptomic landscape (Aldinger et al., 2021), could provide additional insights into the cerebellar region specificity of our findings and of future ones, on the potential connection of bipolar disorder with other neuropsychiatric diseases which have similar cerebellar genetic profiles, on the potential effect of medications (ex. lithium) to gene expression in the cerebellum, on the interaction of brain-wide networks affected by BD, with cerebellar-based networks leading to alterations of the cerebellar gene expression, and on the role of cerebellar-based networks in the regulation and deregulation of emotional states.

6. Conclusions

The AutoML classification analysis of the expression data from the cerebellum of bipolar patients and healthy individuals produced a robust genetic biosignature and resulted in the complete separation between the patient and control groups. These results point to the existence of a discrete genetic expression profile in the cerebellum of bipolar patients, compared to controls. Also, they support the further application of AutoML, as a promising tool for genetic research in neuropsychiatric disorders.

CRediT authorship contribution statement

Georgios V. Thomaidis: Conceptualization, Methodology, Data curation, Writing – original draft preparation, Validation of results. **Konstantinos Papadimitriou:** Investigation of gene functions in the CNS. **Sotirios Michos:** Statistical Analysis. **Evangelos Chartampilas:** Investigation about Bipolar Disorder cerebellar biology. **Ioannis Tsamardinos:** Software, Supervision, Writing – review & editing

Declaration of Competing Interest

None.

Acknowledgements

NA.

Authors' information

Ioannis Tsamardinos is Professor of Data Science and Bioinformatics in the University of Crete, Department of Computer Science, Heraclion, Greece. He has more than 10.000 citations in the field. Georgios V. Thomaidis is a Psychiatrist (MD, MSc), researcher and trainer of psychiatric residents, with post-graduate studies (MSc level) in Nanoscience and Complex Systems. He practices Psychiatry at the Department of

Psychiatry of Katerini General Hospital (ex. Psychiatric Hospital of Petra Olympus, Pieria).

Sotirios Michos, PhD Electronic Engineering, is a researcher in the fields of Network Science and Bioinformatics.

Konstantinos Papadimitriou, is a molecular biologist (MSc) and resident Psychiatrist in the Psychiatric Hospital of Thessaloniki, Greece. Evangelos Chartampilas is a Clinical Radiologist, researcher and trainer of Radiology residents at the Radiology Department Aristotle University of Thessaloniki, Greece.

Authors' contributions

G.V.T. designed the experiment, interpreted the results and wrote the main manuscript text. I.T. designed the software for the experiment and reviewed the manuscript. S.M., K.P. and E.C. performed equally the acquisition and analysis of data. S.M and K.P contributed equally to the methods section.

Preprint

A preprint version of the article can be found at:

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.ibneur.2023.06.008](https://doi.org/10.1016/j.ibneur.2023.06.008).

References

- Adamaszek, M., D'Agata, F., Ferrucci, R., Habas, C., Keulen, S., Kirkby, K.C., Leggio, M., Mariën, P., Molinari, M., Moulton, E., Orsi, L., Van Overwalle, F., Papadelis, C., Priori, A., Sacchetti, B., Schutter, D.J., Styliadis, C., Verhoeven, J., 2017. Consensus paper: cerebellum and emotion. *Cerebellum* 16, 552–576. <https://doi.org/10.1007/s12311-016-0815-8>.
- Adamou, M., Antoniou, G., Greasidou, E., Lagani, V., Charonyktakis, P., Tsamardinos, I., 2018. Mining free-text medical notes for suicide risk assessment, in: Proceedings of the 10th Hellenic Conference on Artificial Intelligence. pp. 1–8.
- Adamou, M., Antoniou, G., Greasidou, E., Lagani, V., Charonyktakis, P., Tsamardinos, I., Doyle, M., 2019. Toward automatic risk assessment to support suicide prevention. *Crisis* 40, 249–256. <https://doi.org/10.1027/0227-5910/a000561>.
- Aghaizu, N.D., Jolly, S., Samra, S.K., Kalmar, B., Craessaerts, K., Greensmith, L., Salinas, P.C., De Strooper, B., Whiting, P.J., 2023. Microglial expression of the Wnt signaling modulator *DKK2* differs between human Alzheimer's disease brains and mouse neurodegeneration models. *ENEURO* 0306-22.2022 eneurop 10. <https://doi.org/10.1523/ENEURO.0306-22.2022>.
- Aldinger, K.A., Thomson, Z., Phelps, I.G., Haldipur, P., Deng, M., Timms, A.E., Hirano, M., Santpere, G., Roco, C., Rosenberg, A.B., Lorente-Galdos, B., Gulden, F.O., O'Day, D., Overman, L.M., Lisgo, S.N., Alexandre, P., Sestan, N., Doherty, D., Dobyns, W.B., Seelig, G., Glass, I.A., Millen, K.J., 2021. Spatial and cell type transcriptional landscape of human cerebellar development. *Nat. Neurosci.* 24, 1163–1175. <https://doi.org/10.1038/s41593-021-00872-y>.
- Alnafisah, R.S., Reigle, J., Eladawi, M.A., O'Donovan, S.M., Funk, A.J., Meller, J., Mccullumsmith, R.E., Shukla, R., 2022. Assessing the effects of antipsychotic medications on schizophrenia functional analysis: a postmortem proteome study. *Neuropsychopharmacology* 47, 2033–2041. <https://doi.org/10.1038/s41386-022-01310-8>.
- Altamura, A.C., Bertoldo, A., Marotta, G., Paoli, R.A., Caletti, E., Dragogna, F., Buoli, M., Baglivo, V., Mauri, M.C., Brambilla, P., 2013. White matter metabolism differentiates schizophrenia and bipolar disorder: a preliminary PET study. *Psychiatry Res. Neuroimaging* 214, 410–414. <https://doi.org/10.1016/j.jpsychresns.2013.08.011>.
- Altural, B., Genc, S., Haggarty, S.J., 2017. Diagnostic and therapeutic potential of microRNAs in neuropsychiatric disorders: Past, present, and future. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 73, 87–103. <https://doi.org/10.1016/j.pnpbp.2016.03.010>.
- Amare, A.T., 2018. *Genetic Predictors of Response to Pharmacotherapy in Patients with Mood Disorders: Steps on the Path to Personalised Psychiatry* (Doctoral Thesis). University of Adelaide.
- Amare, A.T., Schubert, K.O., Hou, L., Clark, S.R., Papiol, S., Cearns, M., Heilbronner, U., Degenhardt, F., Tekola-Ayiele, F., Hsu, Y.-H., Shekhtman, T., Adli, M., Akula, N., Akiyama, K., Ardaul, R., Arias, B., Aubry, J.-M., Backlund, L., Bhattacharjee, A.K., Bellivier, F., Benabarre, A., Bengesser, S., Biernacka, J.M., Birner, A., Brichant-Petitjean, C., Cervantes, P., Chen, H.-C., Chillotti, C., Cichon, S., Cruceanu, C., Czerski, P.M., Dalkner, N., Dayer, A., Del Zompo, M., DePaulo, J.R., Étaine, B., Jamain, S., Falkai, P., Forstner, A.J., Frisen, L., Frye, M.A., Fullerton, J.M., Gard, S., Garnham, J.S., Goes, F.S., Grigorioiu-Serbanescu, M., Grof, P., Hashimoto, R., Hauser, J., Herms, S., Hoffmann, P., Hofmann, A., Jiménez, E., Kahn, J.-P., Kassem, L., Kuo, P.-H., Kato, T., Kelsoe, J.R., Kittel-Schneider, S., Kliwicki, S., König, B., Kusumi, I., Laje, G., Landén, M., Lavebratt, C., Leboyer, M., Leckband, S., Tortorella, A., Manchia, M., Martinsson, L., McCarthy, M.J., McElroy, S.L., Colom, F., Mitjans, M., Mondimore, F.M., Monteleone, P., Nievergelt, C.M., Nöthen, M.M., Novák, T., O'Donovan, C., Ozaki, N., Ösby, U., Pfennig, A., Potash, J. B., Reif, A., Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium, Wray, N.R., Ripke, S., Mattheisen, M., Trzaskowski, M., Byrne, E.M., Abdellaoui, A., Adams, M.J., Agerbo, E., Air, T.M., Andlauer, T.F.M., Bacanu, S.A., Baekvad-Hansen, M., Beekman, A.T.F., Bigdeli, T.B., Binder, E.B., Blackwood, D.H.R., Bryois, J., Buttenschøn, H.N., Bybjerg-Grauholt, J., Cai, N., Castelao, E., Christensen, J., varregaard, Clarke, T.-K., Coleman, J.R.I., Colodro-Conde, L., Couvy-Duchesne, B., Craddock, N., Crawford, G.E., Davies, G., Deary, I.J., Degenhardt, F., Derk, E.M., Direk, N., Dolan, C.V., Dunn, E.C., Eley, T.C., Escott-Price, V., Kiadeh, F. H., Finucane, H.K., Forstner, A.J., Frank, J., Gaspar, H.A., Gill, M., Goes, F.S., Gordon, S.D., Grove, J., Hall, L.S., Hansen, C.S., Hansen, T.F., Herms, S., Hickie, I.B., Hoffmann, P., Homuth, G., Horn, C., Hottenga, J.-J., Hougaard, D.M., Ising, M., Jansen, R., Jorgenson, E., Knowles, J.A., Kohane, I.S., Kraft, J., Kretschmar, W.W., Krogh, J., Kutalik, Z., Li, Y., Lind, P.A., MacIntyre, D.J., MacKinnon, D.F., Maier, R. M., Maier, W., Marchini, J., Mbarek, H., McGrath, P., McGuffin, P., Medland, S.E., Mehta, D., Middeldorp, C.M., Mihalov, E., Milaneschi, Y., Milani, L., Mondimore, F. M., Montgomery, G.W., Mostafavi, S., Mullins, N., Nauck, M., Ng, B., Nivard, M.G., Nyholt, D.R., O'Reilly, P.F., Oskarsson, H., Owen, M.J., Painter, J.N., Pedersen, C.B., Pedersen, M.G., Peterson, R.E., Pettersson, E., Peyrot, W.J., Pistis, G., Posthuma, D., Quiroz, J.A., Qvist, P., Rice, J.P., Riley, B.P., Rivera, M., Mirza, S.S., Schoevers, R., Schulte, E.C., Shen, L., Shi, J., Shyn, S.I., Sigurdsson, E., Sinnamon, G.C.B., Smit, J. H., Smith, D.J., Stefansson, H., Steinberg, S., Streit, F., Strohmaier, J., Tansey, K.E., Teismann, H., Teumer, A., Thompson, W., Thomson, P.A., Thorgeirsson, T.E., Traylor, M., Treutlein, J., Trubetskoy, V., Uitterlinden, A.G., Umbricht, D., Van der Auwer, S., van Hemert, A.M., Viktorin, A., Visscher, P.M., Wang, Y., Webb, B.T., Weinshheimer, S.M., Wellmann, J., Willemsen, G., Witt, S.H., Wu, Y., Xi, H.S., Yang, J., Zhang, F., Arolt, V., Baune, B.T., Berger, K., Boomsma, D.I., Cichon, S., Dannowski, U., de Geus, E.J.C., DePaulo, J.R., Domenici, E., Domschke, K., Esko, T., Grabe, H.J., Hamilton, S.P., Hayward, C., Heath, A.C., Kendler, K.S., Kloiber, S., Lewis, G., Li, Q.S., Lucae, S., Madden, P.A.F., Magnusson, P.K., Martin, N.G., McIntosh, A.M., Metspalu, A., Mors, O., Mortensen, P.B., Müller-Mylhsok, B., Nordentoft, M., Nöthen, M.M., O'Donovan, M.C., Paciga, S.A., Pedersen, N.L., Penninx, B.W.J.H., Perlis, R.H., Porteous, D.J., Potash, J.B., Preisig, M., Rietschel, M., Schaefer, C., Schulze, T.G., Smoller, J.W., Stefansson, K., Tiemeier, H., Uher, R., Völzke, H., Weissman, M.M., Werge, T., Lewis, C.M., Levinson, D.F., Breen, G., Borglum, A.D., Sullivan, P.F., Reininghaus, E., Rouleau, G.A., Rybakowski, J.K., Schalling, M., Schofield, P.R., Schweizer, B.W., Severino, G., Shilling, P.D., Shimoda, K., Simhandl, C., Slaney, C.M., Squassina, A., Stamm, T., Stopkova, P., Maj, M., Turecki, G., Vieta, E., Veeh, J., Witt, S.H., Wright, A., Zandi, P. P., Mitchell, P.B., Bauer, M., Alda, M., Rietschel, M., McMahon, F.J., Schulze, T.G., Baune, B.T., 2021. Association of polygenic score for major depression with response to lithium in patients with bipolar disorder. In: *Mol. Psychiatry*, 26, pp. 2457–2470. <https://doi.org/10.1038/s41380-020-0689-5>.
- An, N., Zhao, W., Liu, Y., Yang, X., Chen, P., 2016. Elevated serum miR-106b and miR-146a in patients with focal and generalized epilepsy. *Epilepsy Res* 127, 311–316. <https://doi.org/10.1016/j.eplepsyres.2016.09.019>.
- Bakken, I.J., Revdal, E., Nesvåg, R., Brenner, E., Knudsen, G.P., Surén, P., Ghaderi, S., Gunnar, N., Magnus, P., Reichborn-Kjennerud, T., Camilla, Stoltenberg, Trostad, L. I., Häberg, S.E., Brodtkorb, E., 2014. Substance use disorders and psychotic disorders in epilepsy: A population-based registry study. *Epilepsy Res* 108, 1435–1443. <https://doi.org/10.1016/j.eplepsyres.2014.06.021>.
- Barbash, S., Simchovitz, A., Buchman, A.S., Bennett, D.A., Shifman, S., Soreq, H., 2017. Neuronally-expressed microRNA-targeted pseudogenes compete with coding genes in the human brain. *e1199–e1199 Transl. Psychiatry* 7. <https://doi.org/10.1038/tp.2017.163>.
- Bavamian, S., Mellios, N., Lalonde, J., Fass, D.M., Wang, J., Sheridan, S.D., Madison, J. M., Zhou, F., Rueckert, E.H., Barker, D., Perlis, R.H., Sur, M., Haggarty, S.J., 2015. Dysregulation of miR-34a links neuronal development to genetic risk factors for bipolar disorder. *Mol. Psychiatry* 20, 573–584. <https://doi.org/10.1038/mp.2014.176>.
- Belzeaux, R., Bergon, A., Jeanjean, V., Loriod, B., Formisano-Tréziny, C., Verrier, L., Loundou, A., Baumstarck-Barraud, K., Boyer, L., Gall, V., Gabert, J., Nguyen, C., Azorin, J.-M., Naudin, J., Ibrahim, E.C., 2012. Responder and nonresponder patients exhibit different peripheral transcriptional signatures during major depressive episode. *e185–e185 Transl. Psychiatry* 2. <https://doi.org/10.1038/tp.2012.112>.
- Bostock, E.C.S., Kirkby, K.C., Garry, M.I., Taylor, B.V.M., 2017. Systematic Review Of Cognitive Function In Euthymic Bipolar Disorder And Pre-surgical Temporal Lobe Epilepsy. *Front. Psychiatry* 8, 133. <https://doi.org/10.3389/fpsyg.2017.00133>.
- Bowler, S., Papoutsoglou, G., Karanikas, A., Tsamardinos, I., Corley, M.J., Ndhlovu, L.C., 2022. A machine learning approach utilizing DNA methylation as an accurate classifier of COVID-19 disease severity. *Sci. Rep.* 12, 17480. <https://doi.org/10.1038/s41598-022-22201-4>.
- Bracher-Smith, M., Crawford, K., Escott-Price, V., 2021. Machine learning for genetic prediction of psychiatric disorders: a systematic review. *Mol. Psychiatry* 26, 70–79.
- Breen, M., 2016. Blood-based biomarkers in psychiatric diseases (Doctoral Thesis). University of Southampton.
- Cariaga-Martinez, A., Alelú-Paz, R., 2016. False data, positive results in neurobiology: moving beyond the epigenetics of blood and saliva samples in mental disorders. *s12952-016-0064-x J. Negat. Results Biomed.* 15, 21. <https://doi.org/10.1186/s12952-016-0064-x>.

- Cava, C., Manna, I., Gambardella, A., Bertoli, G., Castiglioni, I., 2018. Potential Role of miRNAs as Theranostic Biomarkers of Epilepsy. *Mol. Ther. - Nucleic Acids* 13, 275–290. <https://doi.org/10.1016/j.omtn.2018.09.008>.
- Cecil, K.M., DellBello, M.P., Sellars, M.C., Strakowski, S.M., 2003. Proton magnetic resonance spectroscopy of the frontal lobe and cerebellar vermis in children with a mood disorder and a familial risk for bipolar disorders. *J. Child Adolesc. Psychopharmacol.* 13, 545–555. <https://doi.org/10.1089/104454603322724931>.
- Chambers, T., Escott-Price, V., Legge, S., Baker, E., Singh, K.D., Walters, J.T.R., Caseras, X., Anney, R.J.L., 2022. Genetic common variants associated with cerebellar volume and their overlap with mental disorders: a study on 33,265 individuals from the UK-Biobank. *Mol. Psychiatry* 27, 2282–2290. <https://doi.org/10.1038/s41380-022-01443-8>.
- Charney, A.W., Mullins, N., Park, Y.J., Xu, J., 2020. On the diagnostic and neurobiological origins of bipolar disorder. *Transl. Psychiatry* 10, 118. <https://doi.org/10.1038/s41398-020-0796-8>.
- Chen, C., 2012. Expression data from the human cerebellum and parietal cortex brain. *Chen, C., Cheng, L., Gennan, K., Bibiri, F., Zhang, C., Badner, J.A., Members of the Bipolar Disorder Genome Study (BiGS) Consortium, Gershon, E.S., Liu, C., 2013. Two gene co-expression modules differentiate psychotics and controls. Mol. Psychiatry* 18, 1308–1314. <https://doi.org/10.1038/mp.2012.146>.
- Chen, C., Meng, Q., Xia, Y., Ding, C., Wang, L., Dai, R., Cheng, L., Gunaratne, P., Gibbs, R. A., Min, S., Coarfa, C., Reid, J.G., Zhang, C., Jiao, C., Jiang, Y., Giase, G., Thomas, A., Fitzgerald, D., Brunetti, T., Shieh, A., Xia, C., Wang, Yongjun, Wang, Yunpeng, Badner, J.A., Gershon, E.S., White, K.P., Liu, C., 2018. The transcription factor POU3F2 regulates a gene coexpression network in brain tissue from patients with psychiatric disorders. *Sci. Transl. Med.* 10, eaat8178 <https://doi.org/10.1126/scitranslmed.aat8178>.
- Chen, X., Long, F., Cai, B., Chen, Xiaohong, Chen, G., 2018. A novel relationship for schizophrenia, bipolar and major depressive disorder Part 3: Evidence from chromosome 3 high density association screen. *J. Comp. Neurol.* 526, 59–79. <https://doi.org/10.1002/cne.24311>.
- Ching, C.R.K., Hibar, D.P., Gurholt, T.P., Nunes, A., Thomopoulos, S.I., Abé, C., Agartz, I., Brouwer, R.M., Cannon, D.M., Zwarts, S.M.C., Eyler, L.T., Favre, P., Hajek, T., Haukvik, U.K., Houenou, J., Landén, M., Lett, T.A., McDonald, C., Nabulsi, L., Patel, Y., Pauling, M.E., Paus, T., Radua, J., Soeiro-de-Souza, M.G., Tronchin, G., Haren, N.E.M., Vieta, E., Walter, H., Zeng, L., Alda, M., Almeida, J., Alnæs, D., Alonso-Lana, S., Altimus, C., Bauer, M., Baune, B.T., Bearden, C.E., Bellani, M., Benedetti, F., Berk, M., Bilderbeck, A.C., Blumberg, H.P., Boen, E., Bollettini, I., Mar Bonnin, C., Brambilla, P., Canales-Rodríguez, E.J., Caseras, X., Dandash, O., Dannlowski, U., Delvecchio, G., Díaz-Zuluaga, A.M., Dima, D., Duchesnay, É., Elvsåshagen, T., Fears, S.C., Frangou, S., Fullerton, J.M., Glahn, D.C., Goikolea, J.M., Green, M.J., Grotzeger, D., Gruber, O., Haarman, B.C.M., Henry, C., Howells, F.M., Ives-Deliperi, V., Jansen, A., Kircher, T.T.J., Knöchel, C., Kramer, B., Lafer, B., López-Jaramillo, C., Machado-Vieira, R., MacIntosh, B.J., Melloni, E.M.T., Mitchell, P.B., Nenadic, I., Nery, F., Nugent, A.C., Oertel, V., Ophoff, R.A., Ota, M., Owers, B.J., Pham, D.L., Phillips, M.L., Pineda-Zapata, J.A., Poletti, S., Polosan, M., Pomarol-Clotet, E., Pouchon, A., Quidé, Y., Rive, M.M., Roberts, G., Ruhe, H.G., Salvador, R., Sarró, S., Satterthwaite, T.D., Schene, A.H., Sim, K., Soares, J.C., Stäblein, M., Stein, D.J., Tamnes, C.K., Thomaidis, G.V., Upegui, C.V., Veltman, D.J., Wessa, M., Westlye, L.T., Whalley, H.C., Wolf, D.H., Wu, M., Yatham, L.N., Zarate, C.A., Thompson, P.M., Andreassen, O.A., ENIGMA Bipolar Disorder Working Group, 2022. What we learn about bipolar disorder from large-scale neuroimaging: findings and future directions from the ENIGMA Bipolar Disorder Working Group. *Hum. Brain Mapp.* 43, 56–82. <https://doi.org/10.1002/hbm.25098>.
- Choi, J., Bodensteiner, D.F., Geraci, J., Andreazzia, A.C., 2021. Evaluation of postmortem microarray data in bipolar disorder using traditional data comparison and artificial intelligence reveals novel gene targets. *J. Psychiatr. Res.* 142, 328–336. <https://doi.org/10.1016/j.jpsychires.2021.08.011>.
- Coleman, J.R.I., Gaspar, H.A., Bryois, J., Breen, G., Byrne, E.M., Forstner, A.J., Holmans, P.A., de Leeuw, C.A., Mattheisen, M., McQuillin, A., Whitehead Pavlidès, J.M., Pers, T.H., Ripke, S., Stahl, E.A., Steinberg, S., Stahl, E.A., Steinberg, S., Trubetskoy, V., Trzaskowski, M., Wang, Y., Abbott, L., Abdellaoui, A., Adams, M.J., Adolfsson, A.N., Agerbo, E., Akil, H., Albani, D., Alliey-Rodriguez, N., Als, T.D., Andlauer, T.F.M., Anjorin, A., Antilla, V., Van der Auwera, S., Awasthi, S., Bacanu, S.-A., Badner, J.A., Bækvad-Hansen, M., Barchas, J., Bass, N., Bauer, M., Beekman, A.T.F., Belliveau, R., Bergen, S.E., Bigdely, T.B., Binder, E.B., Boen, E., Boocoock, J., Budde, M., Bunney, W., Burmeister, M., Buttenschøn, H.N., Bybjerg-Grauholm, J., Byerley, W., Cai, N., Casas, M., Castelao, E., Cerrato, F., Cervantes, P., Chambert, K., Charney, A.W., Chen, D., Christensen, J.H., Churchhouse, C., St Clair, D., Clarke, T.-K., Colodro-Conde, L., Coryell, W., Couvy-Duchesne, B., Craig, D.W., Crawford, G.E., Cruceanu, C., Czerski, P.M., Dale, A.M., Davies, G., Deary, I.J., Degenhardt, F., Del-Favero, J., DePaulo, J.R., Derk, E.M., Direk, N., Djurovic, S., Dobbyn, A.L., Dolan, C., Dumont, A., Dunn, E.C., Eley, T.C., Elvsåshagen, T., Escott-Price, V., Fan, C.C., Finucane, H.K., Fischer, S.B., Flickinger, M., Foo, J.C., Foroud, T.M., Forty, L., Frank, J., Fraser, C., Freimer, N.B., Frisén, L., Gade, K., Gage, D., Garnham, J., Giambartolomei, C., Goes, F.S., Goldstein, J., Gordon, S.D., Gordon-Smith, K., Green, E.K., Green, M.J., Greenwood, T.A., Grove, J., Guan, W., Hall, L.S., Hamshere, M.L., Hansen, C.S., Hansen, T.F., Hautzinger, M., Heilbronner, U., van Hemert, A.M., Herms, S., Hickie, I.B., Hipolito, M., Hoffmann, P., Holland, D., Homuth, G., Horn, C., Hottenga, J.-J., Huckins, L., Ising, M., Jamain, S., Jansen, R., Johnson, J.S., de Jong, S., Jorgenson, E., Juréus, A., Kandaswamy, R., Karlsson, R., Kennedy, J.L., Hassan Kiadeh, F.F., Kittel-Schneider, S., Knowles, J.A., Kogevinas, M., Kohane, I.S., Koller, A.C., Kraft, J., Kretschmar, W.W., Krogh, J., Kupka, R., Kutalik, Z., Lavebratt, C., Lawrence, J., Lawson, W.B., Leber, M., Lee, P., Levy, S.E., Li, J.Z., Li, Y., Lind, P.A., Liu, C., Olde Loohuis, L.M., Maaser, A., MacIntyre, D.J., MacKinnon, D.F., Mahon, P.B., Maier, W., Maier, R.M., Marchini, J., Martinsson, L., Mbarek, H., McCarroll, S., McGrath, P., McGuffin, P., McInnis, M.G., McKay, J.D., Medeiros, H., Medland, S.E., Mehta, D., Meng, F., Middeldorp, C.M., Mihailov, E., Milaneschi, Y., Milani, L., Mirza, S.S., Mondimore, F.M., Montgomery, G.W., Morris, D.W., Mostafavi, S., Mühlleisen, T.W., Mullins, N., Nauck, M., Ng, B., Nguyen, H., Nievergelt, C.M., Nivard, M.G., Nwulia, E.A., Nyholt, D.R., O'Donovan, C., O'Reilly, P.F., Ori, A.P.S., Oruc, L., Osby, U., Oskarsson, H., Painter, J.N., Parra, J.G., Pedersen, C.B., Pedersen, M.G., Perry, A., Peterson, R.E., Pettersson, E., Peyrot, W.J., Pfennig, A., Pistics, G., Purcell, S.M., Quiroz, J.A., Qvist, P., Regeer, E.J., Reif, A., Reinbold, C.S., Rice, J.P., Riley, B.P., Rivas, F., Rivera, M., Roussos, P., Ruderfer, D.M., Ryu, E., Sánchez-Mora, C., Schatzberg, A.F., Scheftner, W.A., Schoevers, R., Schork, N.J., Schulte, E.C., Shekhtman, T., Shen, L., Shi, J., Shilling, P.D., Shyn, S.I., Sigurdsson, E., Slaney, C., Smeland, O.B., Smit, J.H., Smith, D.J., Sobell, J.L., Spijkerman, A.T., Steffens, M., Strauss, J.S., Streit, F., Strohmaier, J., Szelinger, S., Tansey, K.E., Teismann, H., Teumer, A., Thompson, R.C., Thompson, W., Thomson, P.A., Thorgeirsson, T.E., Traylor, M., Treutlein, J., Uitterlinden, A.G., Umbricht, D., Vedder, H., Viktorin, A., Visscher, P.M., Wang, W., Watson, S.J., Webb, B.T., Weickert, C.S., Weickert, T.W., Weinshheimer, S.M., Wellmann, J., Willemse, G., Witt, S.H., Wu, Y., Xi, H.S., Xu, W., Yang, J., Young, A.H., Zandi, P., Zhang, P., Zhang, F., Zollner, S., Adolfsson, R., Agartz, I., Alda, M., Arolt, V., Backlund, L., Baune, B.T., Bellivier, F., Berger, K., Berrettini, W.H., Biernacka, J.M., Blackwood, D.H.R., Boehnke, M., Boomstra, D.I., Corvin, A., Craddock, N., Daly, M.J., Dannlowski, U., Domenici, E., Domischke, K., Esko, T., Etain, B., Frye, M., Fullerton, J.M., Gershon, E.S., de Geus, E.J.C., Gill, M., Goes, F., Grabe, H.J., Grigoroiu-Serbanescu, M., Hamilton, S.P., Hauser, J., Hayward, C., Heath, A.C., Hougaard, D.M., Hultman, C.M., Jones, I., Jones, L.A., Kahn, R.S., Kendler, K.S., Kirov, G., Kloiber, S., Landén, M., Leboyer, M., Lewis, G., Li, Q.S., Lissowska, J., Lucae, S., Madden, P.A.F., Magnusson, P.K., Martin, N.G., Mayoral, F., McElroy, S.L., McIntosh, A.M., McMahon, F.J., Melle, I., Metspalu, A., Mitchell, P.B., Morken, G., Mors, O., Mortensen, P.B., Müller-Myhsok, B., Myers, R., Neale, B.M., Nimgaonkar, V., Nordentoft, M., Nöthen, M.M., O'Donovan, M.C., Odegaard, K.J., Owen, M.J., Paciga, S.A., Pato, C., Pato, M.T., Pedersen, N.L., Penninx, B.W.J.H., Perlis, R.H., Porteous, D.J., Posthuma, D., Potash, J.B., Preisig, M., Ramos-Quiroga, J.A., Ribasés, M., Rietschel, M., Rouleau, G.A., Schaefer, C., Schalling, M., Schofield, P.R., Schulze, T.G., Serretti, A., Smoller, J.W., Stefansson, H., Stefansson, K., Stordal, E., Tiemeier, H., Turecki, G., Uher, R., Vaaler, A.E., Vieta, E., Vincent, J.B., Völzke, H., Weissman, M.M., Werge, T., Andreassen, O.A., Børglum, A.D., Cichon, S., Edenberg, H.J., Di Florio, A., Kelsoe, J., Levinson, D.F., Lewis, C.M., Nurnberger, J.I., Ophoff, R.A., Scott, L.J., Sklar, P., Sullivan, P.F., Wray, N.R., Byrne, E.M., Forstner, A.J., Holmans, P.A., de Leeuw, C., A., Mattheisen, M., McQuillin, A., Whitehead Pavlidès, J.M., Pers, T.H., Ripke, S., Stahl, E.A., Steinberg, S., Trubetskoy, V., Trzaskowski, M., Wang, Y., Abbott, L., Abdellaoui, A., Adams, M.J., Adolfsson, A.N., Agerbo, E., Akil, H., Albani, D., Alliey-Rodriguez, N., Als, T.D., Andlauer, T.F.M., Anjorin, A., Antilla, V., Van der Auwera, S., Awasthi, S., Bacanu, S.-A., Badner, J.A., Bækvad-Hansen, M., Barchas, J., Bass, N., Bauer, M., Beekman, A.T.F., Belliveau, R., Bergen, S.E., Bigdely, T.B., Binder, E.B., Boen, E., Boocoock, J., Budde, M., Bunney, W., Burmeister, M., Buttenschøn, H.N., Bybjerg-Grauholm, J., Byerley, W., Cai, N., Casas, M., Castelao, E., Cerrato, F., Cervantes, P., Chambert, K., Charney, A.W., Chen, D., Christensen, J.H., Churchhouse, C., St Clair, D., Clarke, T.-K., Colodro-Conde, L., Coryell, W., Couvy-Duchesne, B., Craig, D.W., Crawford, G.E., Cruceanu, C., Czerski, P.M., Dale, A.M., Davies, G., Deary, I.J., Degenhardt, F., Del-Favero, J., DePaulo, J.R., Derk, E.M., Direk, N., Djurovic, S., Dobbyn, A.L., Dolan, C., Dumont, A., Dunn, E.C., Eley, T.C., Elvsåshagen, T., Escott-Price, V., Fan, C.C., Finucane, H.K., Fischer, S.B., Flickinger, M., Foo, J.C., Foroud, T.M., Forty, L., Frank, J., Fraser, C., Freimer, N.B., Frisén, L., Gade, K., Gage, D., Garnham, J., Giambartolomei, C., Goes, F.S., Goldstein, J., Gordon, S.D., Gordon-Smith, K., Green, E.K., Green, M.J., Greenwood, T.A., Grove, J., Guan, W., Hall, L.S., Hamshere, M.L., Hansen, C.S., Hansen, T.F., Hautzinger, M., Heilbronner, U., van Hemert, A.M., Herms, S., Hickie, I.B., Hipolito, M., Hoffmann, P., Holland, D., Homuth, G., Horn, C., Hottenga, J.-J., Huckins, L., Ising, M., Jamain, S., Jansen, R., Johnson, J.S., de Jong, S., Jorgenson, E., Juréus, A., Kandaswamy, R., Karlsson, R., Kennedy, J.L., Hassan Kiadeh, F.F., Kittel-Schneider, S., Knowles, J.A., Kogevinas, M., Kohane, I.S., Koller, A.C., Kraft, J., Kretschmar, W.W., Krogh, J., Kupka, R., Kutalik, Z., Lavebratt, C., Lawrence, J., Lawson, W.B., Leber, M., Lee, P., Levy, S.E., Li, J.Z., Li, Y., Lind, P.A., Liu, C., Olde Loohuis, L.M., Maaser, A., MacIntyre, D.J., MacKinnon, D.F., Mahon, P.B., Maier, W., Maier, R.M., Marchini, J., Martinsson, L., Mbarek, H., McCarroll, S., McGrath, P., McGuffin, P., McInnis, M.G., McKay, J.D., Medeiros, H., Medland, S.E., Mehta, D., Meng, F., Middeldorp, C.M., Mihailov, E., Milaneschi, Y., Milani, L., Mirza, S.S., Mondimore, F.M., Montgomery, G.W., Morris, D.W., Mostafavi, S., Mühlleisen, T.W., Mullins, N., Nauck, M., Ng, B., Nguyen, H., Nievergelt, C.M., Nivard, M.G., Nwulia, E.A., Nyholt, D.R., O'Donovan, C., O'Reilly, P.F., Ori, A.P.S., Oruc, L., Osby, U., Oskarsson, H., Painter, J.N., Parra, J.G., Pedersen, C.B., Pedersen, M.G., Perry, A., Peterson, R.E., Pettersson, E., Peyrot, W.J., Pfennig, A., Pistics, G., Purcell, S.M., Quiroz, J.A., Qvist, P., Regeer, E.J., Reif, A., Reinbold, C.S., Rice, J.P., Riley, B.P., Rivas, F., Rivera, M., Roussos, P., Ruderfer, D.M., Ryu, E., Sánchez-Mora, C., Schatzberg, A.F., Scheftner, W.A., Schoevers, R., Schork, N.J., Schulte, E.C., Shekhtman, T., Shen, L., Shi, J., Shilling, P.D., Shyn, S.I., Sigurdsson, E., Slaney, C., Smeland, O.B., Smit, J.H., Sobell, J.L., Spijkerman, A.T., Steffens, M., Strauss, J.S., Streit, F., Strohmaier, J., Szelinger, S., Tansey, K.E., Teismann, H., Teumer, A., Thompson, R.C., Thompson, W., Thomson, P.A., Thorgeirsson, T.E., Traylor, M., Treutlein, J., Uitterlinden, A.G., Umbricht, D., Vedder, H., Viktorin, A., Visscher, P.M., Wang, W., Watson, S.J., Webb, B.T., Weickert, C.S., Weickert, T.W., Weinshheimer, S.M., Wellmann, J., Willemse, G., Witt, S.H., Wu, Y., Xi, H.S., Xu, W., Yang, J., Young, A.H., Zandi, P., Zhang, P., Zhang, F., Zollner, S., Adolfsson, R., Agartz, I., Alda, M., Arolt, V., Backlund, L., Baune, B.T., Bellivier, F., Berger, K.,

- Berrettini, W.H., Biernacka, J.M., Blackwood, D.H.R., Boehnke, M., Boomsma, D.I., Corvin, A., Craddock, N., Daly, M.J., Dannowski, U., Domenici, E., Domschke, K., Esko, T., Etain, B., Frye, M., Fullerton, J.M., Gershon, E.S., de Geus, E.J.C., Gill, M., Goes, F., Grabe, H.J., Grigorou-Serbanescu, M., Hamilton, S.P., Hauser, J., Hayward, C., Heath, A.C., Hougaard, D.M., Hultman, C.M., Jones, I., Jones, L.A., Kahn, R.S., Kendler, K.S., Kirov, G., Kloiber, S., Landén, M., Leboyer, M., Lewis, G., Li, Q.S., Lisowska, J., Lucae, S., Madden, P.A.F., Magnusson, P.K., Martin, N.G., Mayoral, F., McElroy, S.L., McIntosh, A.M., McMahon, F.J., Melle, I., Metspalu, A., Mitchell, P.B., Morken, G., Mors, O., Mortensen, P.B., Müller-Myhsok, B., Myers, R., Neale, B.M., Niogaonkar, V., Nordentoft, M., Nöthen, M.M., O'Donovan, M.C., Oedegaard, K.J., Owen, M.J., Paciga, S.A., Pato, C., Pato, M.T., Pedersen, N.L., Penninx, B.W.J.H., Perlis, R.H., Porteous, D.J., Posthuma, D., Potash, J.B., Preisig, M., Ramos-Quiroga, J.A., Ribasés, M., Rietschel, M., Rouleau, G.A., Schaefer, C., Schalling, M., Schofield, P.R., Schulze, T.G., Serretti, A., Smoller, J.W., Stefansson, H., Stefansson, K., Stordal, E., Tiemeier, H., Turecki, G., Uher, R., Vaaler, A.E., Vieta, E., Vincent, J.B., Völzke, H., Weissman, M.M., Werge, T., Andreassen, O.A., Børglum, A.D., Cichon, S., Edenberg, H.J., Di Florio, A., Kelsoe, J., Levinson, D.F., Lewis, C.M., Nurnberger, J.I., Ophoff, R.A., Scott, L.J., Sklar, P., Sullivan, P.F., Wray, N.R., 2020. The genetics of the mood disorder spectrum: genome-wide association analyses of more than 185,000 cases and 439,000 controls. In: *Biol. Psychiatry*, 88, pp. 169–184. <https://doi.org/10.1016/j.biopsych.2019.10.015>.
- Cruceanu, C., Ambalavanan, A., Spiegelman, D., Gauthier, J., Lafrenière, R.G., Dion, P.A., Alda, M., Turecki, G., Rouleau, G.A., 2013. Family-based exome-sequencing approach identifies rare susceptibility variants for lithium-responsive bipolar disorder. *Genome* 56, 634–640. <https://doi.org/10.1139/gen-2013-0081>.
- Dai, Y., O'Brien, T.D., Pei, G., Zhao, Z., Jia, P., 2020. Characterization of genome-wide association study data reveals spatiotemporal heterogeneity of mental disorders. *BMC Med. Genom.* 13, 192. <https://doi.org/10.1186/s12920-020-00832-8>.
- Deutsch, L., Sotridis, A., Murovec, B., Plavec, J., Mekjavić, I., Debevec, T., Stres, B., 2022. Exercise and interorgan communication: short-term exercise training blunts differences in consecutive daily urine 1H NMR metabolomic signatures between physically active and inactive individuals. *Metabolites* 12, 473. <https://doi.org/10.3390/metabol12060473>.
- Deutsch, L., Stres, B., 2021. The importance of objective stool classification in Fecal 1H NMR metabolomics: exponential increase in stool crosslinking is mirrored in systemic inflammation and associated to fecal acetate and methionine. *Metabolites* 11, 172. <https://doi.org/10.3390/metabol11030172>.
- Diaz, A.P., Bauer, I.E., Sanches, M., Soares, J.C., 2020. Neuroanatomic and Functional Neuroimaging Findings. In: Young, A.H., Juruena, M.F. (Eds.), *Bipolar Disorder: From Neuroscience to Treatment, Current Topics in Behavioral Neurosciences*. Springer International Publishing, Cham, pp. 173–196. https://doi.org/10.1007/7854_2020_174.
- Drange, O.K., Sæther, S.G., Finseth, P.I., Morken, G., Vaaler, A.E., Arntsen, V., Henning, O., Andreassen, O.A., Elvsåshagen, T., Malt, U.F., Bøen, E., 2020. Differences in course of illness between patients with bipolar II disorder with and without epileptiform discharges or other sharp activity on electroencephalograms: a cross-sectional study. *BMC Psychiatry* 20, 582. <https://doi.org/10.1186/s12888-020-02968-4>.
- Duffy, A., Vandeleur, C., Heffer, N., Preisig, M., 2017. The clinical trajectory of emerging bipolar disorder among the high-risk offspring of bipolar parents: current understanding and future considerations. *Int. J. Bipolar Disord.* 5, 37. <https://doi.org/10.1186/s40435-017-0106-4>.
- Eker, C., Simsek, F., Yilmazer, E.E., Kitis, O., Cinar, C., Eker, O.D., Coburn, K., Gonul, A.S., 2014. Brain regions associated with risk and resistance for bipolar I disorder: a voxel-based MRI study of patients with bipolar disorder and their healthy siblings. *Bipolar Discord.* 16, 249–261. <https://doi.org/10.1111/bdi.12181>.
- Fatemi, S.H., Reutiman, T.J., Folsom, T.D., 2009. The role of lithium in modulation of brain genes: relevance for aetiology and treatment of bipolar disorder. *Biochem. Soc. Trans.* 37, 1090–1095. <https://doi.org/10.1042/BST0371090>.
- Fountoulakis, K.N., Grunze, H., Vieta, E., Young, A., Yatham, L., Blier, P., Kasper, S., Moeller, H.J., 2016. The International College of Neuro-Psychopharmacology (CINP) treatment guidelines for Bipolar disorder in adults (CINP-BD-2017), part 3: The clinical guidelines. *Int. J. Neuropsychopharmacol.* pyw109. <https://doi.org/10.1093/ijnp/pyw109>.
- Gershon, E.S., 1982. A family study of schizoaffective, bipolar I, Bipolar II, unipolar, and normal control probands. *Arch. Gen. Psychiatry* 39, 1157. <https://doi.org/10.1001/archpsyc.1982.04290100031006>.
- Guzman-Parra, J., Streit, F., Forstner, A.J., Strohmaier, J., González, M.J., Gil Flores, S., Cabaleiro, F.J., del Río Noriega, F., Pérez Pérez, F., Haro González, J., Orozco Diaz, G., de Diego-Otero, Y., Moreno-Kustner, B., Auburger, G., Degenhardt, F., Heilmann-Heimbach, S., Herms, S., Hoffmann, P., Frank, J., Foo, J.C., Sirignano, L., Witt, S.H., Cichon, S., Rivas, F., Mayoral, F., Nöthen, M.M., Andlauer, T.F.M., Rietschel, M., 2021. Clinical and genetic differences between bipolar disorder type 1 and 2 in multiplex families. *Transl. Psychiatry* 11, 31. <https://doi.org/10.1038/s41398-020-01146-0>.
- Haggarty, S.J., Karmacharya, R., Perlis, R.H., 2021. Advances toward precision medicine for bipolar disorder: mechanisms & molecules. *Mol. Psychiatry* 26, 168–185. <https://doi.org/10.1038/s41380-020-0831-4>.
- Harrison, P.J., 2011. Using our brains: the findings, flaws, and future of postmortem studies of psychiatric disorders. *Biol. Psychiatry* 69, 102–103. <https://doi.org/10.1016/j.biopsych.2010.09.008>.
- Harrison, P.J., Geddes, J.R., Tunbridge, E.M., 2018. The emerging neurobiology of bipolar disorder. *Trends Neurosci.* 41, 18–30. <https://doi.org/10.1016/j.tins.2017.10.006>.
- Hattori, E., Toyota, T., Ishitsuka, Y., Iwayama, Y., Yamada, K., Ujike, H., Morita, Y., Kodama, M., Nakata, K., Minabe, Y., Nakamura, K., Iwata, Y., Takei, N., Mori, N., Naitoh, H., Yamanouchi, Y., Iwata, N., Ozaki, N., Kato, T., Nishikawa, T., Kashiba, A., Suzuki, M., Shioe, K., Shinohara, M., Hirano, M., Nanko, S., Akahane, A., Ueno, M., Kaneko, N., Watanabe, Y., Someya, T., Hashimoto, K., Iyo, M., Itokawa, M., Arai, M., Nankai, M., Inada, T., Yoshida, S., Kunugi, H., Nakamura, M., Iijima, Y., Okazaki, Y., Higuchi, T., Yoshikawa, T., 2009. Preliminary genome-wide association study of bipolar disorder in the Japanese population. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 150B, 1110–1117. <https://doi.org/10.1002/ajmg.b.30941>.
- Hernandez, L.M., Kim, M., Hoftman, G.D., Haney, J.R., de la Torre-Ubieta, L., Pasanuic, B., Gandal, M.J., 2021. Transcriptomic insight into the polygenic mechanisms underlying psychiatric disorders. *Biol. Psychiatry* 89, 54–64. <https://doi.org/10.1016/j.biopsych.2020.06.005>.
- Hettwer, M.D., Larivière, S., Park, B.Y., van den Heuvel, O.A., Schmaal, L., Andreassen, O.A., Ching, C.R.K., Hoogman, M., Buitelaar, J., van Rooij, D., Veltman, D.J., Stein, D.J., Franke, B., van Erp, T.G.M., ENIGMA ADHD Working Group, ENIGMA Autism Working Group, van Rooij, D., ENIGMA Bipolar Disorder Working Group, ENIGMA Major Depression Working Group, ENIGMA OCD Working Group, van den Heuvel, O.A., ENIGMA Schizophrenia Working Group, van Erp, T.G.M., Jahanshad, N., Thompson, P.M., Thomopoulos, S.I., Bethlehem, R.A.I., Bernhardt, B.C., Eickhoff, S.B., Valk, S.L., 2022. Coordinated cortical thickness alterations across six neurodevelopmental and psychiatric disorders. *Nat. Commun* 6851. <https://doi.org/10.1038/s41467-022-34367-6>.
- Heun, R., Maier, W., 1993. The distinction of bipolar II disorder from bipolar I and recurrent unipolar depression: results of a controlled family study. *Acta Psychiatr. Scand.* 87, 279–284. <https://doi.org/10.1111/j.1600-0447.1993.tb03372.x>.
- Hossain, Md.B., Islam, Md.K., Adhikary, A., Rahaman, A., Islam, Md.Z., 2022. Bioinformatics approach to identify significant biomarkers, drug targets shared between parkinson's disease and bipolar disorder: a pilot study, 117793222210792. *Bioinforma. Biol. Insights* 16. <https://doi.org/10.1177/1177932221079232>.
- Hosseini Fatemi, S., Stary, J.M., Earle, J.A., Araghi-Niknam, M., Eagan, E., 2005. GABAergic dysfunction in schizophrenia and mood disorders as reflected by decreased levels of glutamic acid decarboxylase 65 and 67 kDa and Reelin proteins in cerebellum. *Schizophr. Res.* 72, 109–122. <https://doi.org/10.1016/j.schres.2004.02.017>.
- Huang, M., de Koning, T.J., Tijssen, M.A.J., Verbeek, D.S., 2021. Cross-disease analysis of depression, ataxia and dystonia highlights a role for synaptic plasticity and the cerebellum in the pathophysiology of these comorbid diseases. *Biochim. Biophys. Acta BBA - Mol. Basis Dis.* 1867, 165976. <https://doi.org/10.1016/j.bbadi.2020.165976>.
- Hutter, F., Kotthoff, L., Vanschoren, J. (Eds.), 2019. *Automated Machine Learning: Methods, Systems, Challenges, The Springer Series on Challenges in Machine Learning*. Springer International Publishing, Cham. <https://doi.org/10.1007/978-3-030-05318-5>.
- James, S.L., Abate, D., Abate, K.H., Abay, S.M., Abbafati, C., Abbasi, N., Abbastabar, H., Abd-Allah, F., Abdela, J., Abdellalim, A., Abdollahpour, I., Abdulkader, R.S., Abebe, Z., Abera, S.F., Abil, O.Z., Abraha, H.N., Abu-Raddad, L.J., Abu-Rmeileh, N.M.E., Accrombessi, M.M.K., Acharya, D., Acharya, P., Ackerman, I.N., Adamu, A.A., Adebayo, O.M., Adekanmbi, V., Adetokunboh, O.O., Adib, M.G., Adsuar, J.C., Afanvi, K.A., Afarideh, M., Afshin, A., Agarwal, G., Agesa, K.M., Aggarwal, R., Aghayan, S.A., Agrawal, S., Ahmadi, A., Ahmadi, M., Ahmadieh, H., Ahmed, M.B., Aichour, A.N., Aichour, I., Aichour, M.T.E., Akinyemiju, T., Akseer, N., Al-Aly, Z., Al-Eyadhy, A., Al-Mekhlafi, H.M., Al-Raddadi, R.M., Alahdab, F., Alam, K., Alam, T., Alashi, A., Alavian, S.M., Alene, K.A., Aljianzadeh, M., Alizadeh-Navaei, R., Aljunid, S.M., Alkerwi, A., Alla, F., Allebeck, P., Alouani, M.M.L., Altirkawi, K., Alvis-Guzman, N., Amare, A.T., Aminde, L.N., Ammar, W., Amoako, Y.A., Anber, N.H., Andrei, C.L., Androudi, S., Animut, M.D., Anjomshoa, M., Ansha, M.G., Antonio, C.A.T., Anvari, P., Arabloo, J., Arauz, A., Aremu, O., Ariani, F., Armoon, B., Arnlöv, J., Arora, A., Artaman, A., Aryal, K.K., Asayesh, H., Asghar, R.J., Ataro, Z., Atre, S.R., Ausloos, M., Avila-Burgos, L., Avokpaho, E.F.G.A., Awasthi, A., Ayala Quintanilla, B.P., Ayer, R., Azzopardi, P.S., Babazadeh, A., Badali, H., Badawi, A., Bali, A.G., Ballesteros, K.E., Ballew, S.H., Banach, M., Banoub, J.A.M., Banstola, A., Barac, A., Barboza, M.A., Barker-Collo, S.L., Bärnighausen, T.W., Barrero, L.H., Baune, B.T., Bazargan-Hejazi, S., Bedi, N., Beghi, E., Behzadifar, Masoud, Behzadifar, Meysam, Béjot, Y., Belachew, A.B., Belay, Y.A., Bell, M.L., Bello, A.K., Bensenor, I.M., Bernabe, E., Bernstein, R.S., Beuran, M., Beyranvand, T., Bhala, N., Bhattachari, S., Bhaumik, S., Bhutta, Z.A., Biadgo, B., Bijani, A., Bikbov, B., Bilano, V., Bililign, N., Bin Sayeed, M.S., Bisanzio, D., Blacker, B.F., Blyth, F.M., Bou-Orm, I.R., Boufous, S., Bourne, R., Brady, O.J., Brainin, M., Brant, L.C., Brazinova, A., Breitborde, N.J.K., Brenner, H., Briant, P.S., Briggs, A.M., Britton, G., Brugha, T., Buchbinder, R., Busse, R., Butt, Z.A., Cahuana-Hurtado, L., Cano, J., Cádenas, R., Carrero, J.J., Carter, A., Carvalho, F., Castañeda-Orjuela, C.A., Castillo Rivas, J., Castro, F., Catalá-López, F., Cercy, K.M., Cerin, E., Chaiah, Y., Chang, A.R., Chang, H.-Y., Chang, J.-C., Charlson, F.J., Chatterjee, A., Chaturvedi, P., Chiang, P.-C., Chin, K.L., Chitheer, A., Choi, J.-Y.J., Chowdhury, R., Christensen, H., Christopher, D.J., Cicuttini, F.M., Ciobanu, L.G., Cirillo, M., Claro, R.M., Collado-Mateo, D., Cooper, C., Coresh, J., Cortesi, P.A., Cortinovis, M., Costa, M., Cousin, E., Criqui, M.H., Cromwell, E.A., Cross, M., Crump, J.A., Dadi, A.F., Dandona, L., Dandona, R., Dargan, P.I., Daryani, A., Das Gupta, R., Das Neves, J., Dasa, T.T., Davey, G., Davis, A.C., Davitoiu, D.V., De Courten, B., De La Hoz, F.P., De Leo, D., De Neve, J.-W., Degefa, M.G., Degenhardt, L., Deiparine, S., Dellavalle, R.P., Demoz, G.T., Deribe, K., Dervenis, N., Des Jarlaids, D.C., Dessie, G.A., Dey, S., Dharmaratne, S.D., Dinberu, M.T., Dirac, M.A., Djalalinia, S., Doan, L., Dokova, K., Doku, D.T., Dorsey, E.R., Doyle, K.E., Driscoll, T.R., Dubey, M., Dubljanin, E., Duken, E.E., Duncan, B.B., Duraes, A.R., Ebrahimi, H., Ebrahimpour, S., Echko, M.

- M., Edvardsson, D., Effiong, A., Ehrlich, J.R., El Bcheraoui, C., El Sayed Zaki, M., El-Khatib, Z., Elkout, H., Elyazar, I.R.F., Enayati, A., Endries, A.Y., Er, B., Erskine, H.E., Eshrat, B., Eskandarieh, S., Esteghamati, A., Esteghamati, S., Fakhim, H., Fallah Omrani, V., Faramarzi, M., Fareed, M., Farhad, F., Farid, T.A., Farinha, C.S.E. sá, Farioli, A., Faro, A., Farvid, M.S., Farzadfar, F., Feigin, V.L., Fentahun, N., Fereshtehnejad, S.-M., Fernandes, E., Fernandes, J.C., Ferrari, A.J., Feyissa, G.T., Filip, I., Fischer, F., Fitzmaurice, C., Foigt, N.A., Foreman, K.J., Fox, J., Frank, T.D., Fukumoto, T., Fullman, N., Fürst, T., Furtado, J.M., Futran, N.D., Gall, S., Ganji, M., Gankpe, F.G., Garcia-Basteiro, A.L., Gardner, W.M., Gebremedhin, A.T., Gebremichael, T.G., Gelano, T.F., Geleijnse, J.M., Genova-Maleras, R., Geramo, Y.C., Getting, P.W., Gezae, K.E., Ghadiri, K., Ghasemi Falavarjani, K., Ghasemi-Kasman, M., Ghimire, M., Ghosh, R., Ghoshal, A.G., Giampaoli, S., Gill, P.S., Gill, T., K., Ginawi, I.A., Giussani, G., Gnedovskaya, E.V., Goldberg, E.M., Goli, S., Gómez-Dantés, H., Gona, P.N., Gopalani, S.V., Gorman, T.M., Goulart, A.C., Goulart, B.N.G., Grada, A., Grams, M.E., Gross, G., Gugnani, H.C., Guo, Y., Gupta, P.C., Gupta, Rahul, Gupta, Rajeev, Gupta, T., Gyawali, B., Haagsma, J.A., Hachinski, V., Hafezi-Nejad, N., Haghparasht Bidgoli, H., Hagos, T.B., Hailu, G.B., Haj-Mirzaian, Arvin, Haj-Mirzaian, Arya, Hamadeh, R.R., Hamidi, S., Handal, A.J., Hankey, G.J., Hao, Y., Harb, H.L., Harikrishnan, S., Haro, J.M., Hasan, M., Hassankhani, H., Hassen, H.Y., Havmoeller, R., Hawley, C.N., Hay, R.J., Hay, S.I., Hedayatizadeh-Omrani, A., Heibati, B., Hendrie, D., Henok, A., Hertelius, C., Heydarpour, S., Hibstu, D.T., Hoang, H.T., Hoek, H.W., Hoffman, H.J., Hole, M.K., Homae Rad, E., Hoogar, P., Hosgood, H.D., Hosseini, S.M., Hosseiniad, M., Hostic, M., Hostic, S., Hotez, P.J., Hoy, D.G., Hsairi, M., Htet, A.S., Hu, G., Huang, J.J., Huynh, C.K., Iburg, K.M., Ikeda, C.T., Ileanu, B., Ilesamni, O.S., Iqbal, U., Iravani, S.S.N., Irvine, C.M.S., Islam, S.M.S., Islami, F., Jacobsen, K.H., Jahangiry, L., Jahanmehr, N., Jain, S.K., Jakovljevic, M., Javanbakht, M., Jayatilleke, A.U., Jeemon, P., Jha, R.P., Jha, V., Ji, S.J., Johnson, C.O., Jonas, J.B., Jozwiak, J.J., Jungari, S.B., Jürissohn, M., Kabir, Z., Kadel, R., Kahsay, A., Kalani, R., Kanchan, T., Karami, M., Karami Matin, B., Karch, A., Karem, C., Karimi, N., Karimi, S.M., Kasaeian, A., Kassa, D.H., Kassa, G.M., Kassa, T.D., Kassebaum, N.J., Katikireddi, S.V., Kawakami, N., Karyani, A.K., Keighobadi, M.M., Keijoro, P.N., Kemmer, L., Kemp, G.R., Kengne, A.P., Keren, A., Khader, Y.S., Khafaei, B., Khafaei, M.A., Khajavi, A., Khalil, I.A., Khan, E.A., Khan, M.S., Khan, M.A., Khang, Y.-H., Khazaei, M., Khoja, A.T., Khosravi, A., Khosravi, M.H., Kiadaliri, A.A., Kiirthio, D.N., Kim, C.-I., Kim, D., Kim, P., Kim, Y.-E., Kim, Y.J., Kimkoti, R.W., Kinfu, Y., Kisa, A., Kissimova-Skarbek, K., Kivimäki, M., Knudsen, A.K.S., Kocarnik, J.M., Kochhar, S., Kokubo, Y., Kolola, T., Kopeck, J.A., Kosen, S., Kotsakis, G.A., Koul, P.A., Koyanagi, A., Kravchenko, M.A., Krishan, K., Krohn, K.J., Kuato Defo, B., Kucuk Bicer, B., Kumar, G.A., Kumar, M., Kyu, H.H., Lad, D.P., Lad, S., Lafranconi, A., Lalloo, R., Lallukka, T., Lami, F.H., Lansingh, V.C., Latifi, A., Lau, K.M.-M., Lazarus, J.V., Leasher, J.L., Ledesma, J.R., Lee, P.H., Leigh, J., Leung, J., Levi, M., Lewycka, S., Li, S., Li, Y., Liao, Y., Liben, M.L., Lim, L.-L., Lim, S., Liu, S., Lodha, R., Looker, K.J., Lopez, A.D., Lorkowski, S., Lotufo, P.A., Low, N., Lozano, R., Lucas, T.C.D., Lucchesi, L.R., Lunevicius, R., Lyons, R.A., Ma, S., Macarayan, E.R.K., Mackay, M.T., Madotto, F., Magdy Abd El Razek, H., Magdy Abd El Razek, M., Maghavani, D.P., Mahotra, N.B., Mai, H.T., Majdan, M., Majdzadeh, R., Majeed, A., Malekzadeh, R., Malta, D.C., Mamun, A.A., Manda, A.-L., Manguerra, H., Manhertz, T., Mansournia, M.A., Mantovani, L.G., Mapona, C.S., Maravilla, J.C., Marenes, W., Marks, A., Martins-Melo, F.R., Martopullo, I., März, W., Marzan, M.B., Mashamba-Thompson, T.P., Massenburg, B.B., Mathur, M.R., Matsushita, K., Maulik, P.K., Mazidi, M., McAlinden, C., McGrath, J.J., McKee, M., Mehendiratta, M.M., Mehrotra, R., Mehta, K.M., Mehta, V., Mejia-Rodriguez, F., Mekonen, T., Melese, A., Melku, M., Meltzer, M., Memiah, P.T.N., Memish, Z.A., Mendoza, W., Mengistu, D.T., Mengistu, G., Mensah, G.A., Mereta, S.T., Meretoja, A., Meretoja, T., J., Mestrovic, T., Mezerji, N.M.G., Miazkowski, B., Miazkowski, T., Millear, A.I., Miller, T.R., Miltz, B., Mini, G.K., Mirarefin, M., Mirrakhimov, E.M., Misganaw, A.T., Mitchell, P.B., Mitiku, H., Moazen, B., Mohajer, B., Mohammad, K.A., Mohammadi, N., Mohammadnia-Afrouzi, M., Mohammed, M.A., Mohammed, S., Mohebi, F., Moitra, M., Mokdad, A.H., Molokhia, M., Monasta, L., Moodley, Y., Moosazadeh, M., Moradi, G., Moradi-Lakeh, M., Moradinazar, M., Moraga, P., Morawska, L., Moreno Velásquez, I., Mordago-Da-Costa, J., Morrison, S.D., Moschos, M.M., Mountjoy-Venning, W.C., Mousavi, S.M., Mruts, K.B., Muche, A.A., Muchie, K.F., Mueller, U.O., Muhammed, O.S., Mukhopadhyay, S., Muller, K., Mumford, J.E., Murhekar, M., Musa, J., Musa, K.I., Mustafa, G., Nabhan, A.F., Nagata, C., Naghavi, M., Naheed, A., Nahviouj, A., Naik, G., Naik, N., Najafi, F., Naldi, L., Nam, H.S., Nangia, V., Nansseu, J.R., Nascimento, B.R., Natarajan, G., Neamati, N., Negoi, I., Negoi, R.I., Neupane, S., Newton, C.R.J., Nganjuri, J.W., Nguyen, A.Q., Nguyen, Ha, Thu, Nguyen, H.L.T., Nguyen, Huong Thanh, Nguyen, L.H., Nguyen, M., Nguyen, N.B., Nguyen, S.H., Nichols, E., Ningrum, D.N.A., Nixon, M.R., Nolutshungu, N., Nomura, S., Norheim, O.F., Noroozi, M., Norrvig, B., Noubiap, J.J., Nouri, H.R., Nourollahpour Shiadeh, M., Nowroozi, M.R., Nsoesie, E.O., Nyasulu, P.S., Odell, C.M., Ofori-Asenso, R., Ogbo, F.A., Oh, I.-H., Oladimeji, O., Olagunju, A.T., Olagunju, T.O., Olivares, P.R., Olsen, H.E., Olusanya, B.O., Ong, K.L., Ong, S.K., Oren, E., Ortiz, A., Ota, E., Osttavnon, S.S., Øverland, S., Owolabi, M.O., P, A., Pacella, R., Pakpour, A.H., Pana, A., Panda-Jonas, S., Parisi, A., Park, E.-K., Parry, C.D.H., Patel, S., Pati, S., Patil, S.T., Patle, A., Patton, G.C., Paturi, V.R., Paulson, K.R., Pearce, N., Pereira, D.M., Perico, N., Pesudovs, K., Pham, H.Q., Phillips, M.R., Pigott, D.M., Pillay, J.D., Piradov, M.A., Pirsahab, M., Pishgar, F., Plana-Ripoll, O., Plass, D., Polinder, S., Popova, S., Postma, M.J., Pourshams, A., Poustchi, H., Prabhakaran, D., Prakash, S., Prakash, V., Purcell, C.A., Purwar, M.B., Qorbani, M., Quisberg, D.A., Radfar, A., Rafay, A., Rafiei, A., Rahim, F., Rahimi, K., Rahimi-Movaghara, A., Rahimi-Movaghara, V., Rahman, M., Rahman, M.H. ur, Rahman, M.A., Rahman, S.U., Rai, R.K., Rajati, F., Ram, U., Ranjan, P., Ranta, A., Rao, P.C., Rawaf, D.L., Rawaf, S., Reddy, K.S., Reiner, R.C., Reinig, N., Reitsma, M.B., Remuzzi, G., Renzaho, A.M.N., Resnikoff, S., Rezaei, S., Rezai, M.S., Ribeiro, A.L., Roberts, N.L.S., Robinson, S.R., Roever, L., Ronfani, L., Rosenthal, G., Rostami, A., Roth, G.A., Roy, A., Rubagotti, E., Sachdev, P.S., Sadat, N., Saddik, B., Sadeghi, E., Saeedi Moghaddam, S., Safari, H., Safari, Y., Safari-Faramani, R., Safdar, M., Safi, S., Safiri, S., Sagar, R., Sahebkar, A., Sahraian, M.A., Sajadi, H.S., Salam, N., Salama, J.S., Salamat, P., Saleem, K., Saleem, Z., Salimi, Y., Salomon, J.A., Salvi, S.S., Salz, I., Samy, A.M., Sanabria, J., Sang, Y., Santomauro, D.F., Santos, I.S., Santos, J.V., Santrius Milicevic, M.M., Sao Jose, B.P., Sardana, M., Sarker, A.R., Sarrafzadegan, N., Sartorius, B., Sarvi, S., Sathan, B., Satpathy, M., Sawant, A.R., Sawhney, M., Saxena, S., Saylan, M., Schaeffner, E., Schmidt, M.I., Schneider, I.J.C., Schöttker, B., Schwebel, D.C., Schwendicke, F., Scott, J.G., Sekeria, M., Sepanlou, S.G., Serván-Mori, E., Seyedinousavi, S., Shabaninejad, H., Shafee, A., Shahbazi, M., Shaheen, A.A., Shaikh, M.A., Shams-Beyranvand, M., Shamis, M., Shamisizadeh, M., Sharafi, H., Sharifi, M., Sharif-Alhosseini, M., Sharma, M., Sharma, R., She, J., Sheikh, A., Shi, P., Shibuya, K., Shigematsu, M., Shiri, R., Shirkoohi, R., Shishani, K., Shiu, I., Shokraneh, F., Shoman, H., Shrire, M.G., Si, S., Siabani, S., Siddiqi, T.J., Sigfusdottir, I.D., Sigurvinssdottir, R., Silva, J.P., Silveira, D.G.A., Singam, S.N.S., Singh, J.A., Singh, N.P., Singh, P., Sinha, D.N., Skiadaresi, E., Slepak, E.L.N., Sliwa, K., Smith, D.L., Smith, M., Soares Filho, A.M., Sobahi, B.H., Sobhani, S., Sobngwi, E., Soneji, S.S., Soofi, M., Soosareei, M., Sorensen, R.J.D., Soriano, J.B., Soyiri, I.N., Spasato, L.A., Sreramareddy, C.T., Srinivasan, V., Stanaway, J.D., Stein, D.J., Steiner, C., Steiner, T.J., Stokes, M.A., Stovner, L.J., Subart, M.L., Sudaryanto, A., Sufiyan, M.B., Sunguya, B.F., Sur, P.J., Sutradhar, I., Sykes, B.L., Sylte, D.O., Tabares-Seisdedos, R., Tadakamadla, S.K., Tadesse, B.T., Tandon, N., Tassew, S.G., Tavakkoli, M., Taveira, N., Taylor, H.R., Tehrani-Banishamini, A., Tekalign, T.G., Teklemedhin, S.W., Tekle, M.G., Temesgen, H., Temsah, M.-H., Temsah, O., Terkawi, A.S., Teweldeemedhin, M., Thankappan, K.R., Thomas, N., Tilahun, B., To, Q.G., Tonelli, M., Topor-Madry, R., Topouzis, F., Torre, A.E., Tortajada-Girbés, M., Touvier, M., Tovani-Palone, M.R., Towbin, J.A., Tran, B.X., Tran, K.B., Troeger, C.E., Truelsen, T.C., Tsilimbaris, M.K., Tsoi, D., Tudor Car, L., Tuzcu, E.M., Ukwaja, K.N., Ullah, I., Undurraga, E.A., Unutzer, J., Updike, R.L., Usman, M.S., Uthman, O.A., Vaduganathan, M., Vaezi, A., Valdez, P.R., Varughese, S., Vasankari, T.J., Venketasubramanian, N., Villafaina, S., Violante, F.S., Vladimirov, S.K., Vlassov, V., Vollset, S.E., Vosoughi, K., Vujcic, I.S., Wagnew, F.S., Waheed, Y., Waller, S.G., Wang, Y., Wang, Y.-P., Weiderpass, E., Weintraub, R.G., Weiss, D.J., Weldegebre, F., Weldegeberg, K.G., Werdecker, A., West, T.E., Whiteford, H.A., Widecka, J., Wijeratne, T., Wilner, L.B., Wilson, S., Winkler, A.S., Wiyeh, A.B., Wiysonge, C.S., Wolfe, C.D.A., Woolf, A.D., Wu, S., Wu, Y.-C., Wyper, G.M.A., Xavier, D., Xu, G., Yadigir, S., Yadollahpour, A., Yahyazadeh Jabbari, S.H., Yamada, T., Yan, L.L., Yano, Y., Yaseri, M., Yasin, Y.J., Yesnaneh, A., Yimer, E.M., Yip, P., Yisma, E., Yonemoto, N., Yoon, S.-J., Yotebieng, M., Younis, M.Z., Youseffard, M., Yu, C., Zadnik, V., Zaidi, Z., Zaman, S., B., Zamani, M., Zare, Z., Zeleke, A.J., Zenebe, Z.M., Zhang, K., Zhao, Z., Zhou, M., Zodpey, S., Zucker, I., Vos, T., Murray, C.J.L., 2018. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. In: *The Lancet*, 392, pp. 1789–1858. [https://doi.org/10.1016/S0140-6736\(18\)32279-7](https://doi.org/10.1016/S0140-6736(18)32279-7).
- Jiang, X., Detera-Wadleigh, S.D., Akula, N., Mallon, B.S., Hou, L., Xiao, T., Felsenfeld, G., Gu, X., McMahon, F.J., 2019. Sodium valproate rescues expression of TRANK1 in iPSC-derived neural cells that carry a genetic variant associated with serious mental illness. *Mol. Psychiatry* 24, 613–624. <https://doi.org/10.1038/s41380-018-0207-1>.
- Kanehisa, M., Sato, Y., Kawashima, M., 2022. KEGG mapping tools for uncovering hidden features in biological data. *Protein Sci.* 31, 47–53. <https://doi.org/10.1002/pro.4172>.
- Kanehisa, M., Furumichi, M., Sato, Y., Kawashima, M., Ishiguro-Watanabe, M., 2023. KEGG for taxonomy-based analysis of pathways and genomes. *Nucleic Acids Res.* 51, D587–D592. <https://doi.org/10.1093/nar/gkac963>.
- Kanehisa, M., 2019. Toward understanding the origin and evolution of cellular organisms. *Protein Sci.* 28, 1947–1951. <https://doi.org/10.1002/pro.3715>.
- Kanehisa, M., 2000. KEGG: kyoto encyclopedia of genes and genomes. *Nucleic Acids Res.* 28, 27–30. <https://doi.org/10.1093/nar/28.1.27>.
- Karagiannaki, I., Gourlia, K., Lagani, V., Pantazis, Y., Tsamardinos, I., 2022. Learning biologically-interpretable latent representations for gene expression data: pathway activity score learning algorithm. *Mach. Learn.* <https://doi.org/10.1007/s10994-022-06158-z>.
- Karagliani, M., Gourlia, K., Tsamardinos, I., Chatzaki, E., 2020. Accurate blood-based diagnostic biosignatures for Alzheimer's disease via automated machine learning. *J. Clin. Med.* 9, 3016. <https://doi.org/10.3390/jcm9093016>.
- Karagliani, M., Panagopoulou, M., Cheimonidi, C., Tsamardinos, I., Maltezos, E., Papapanas, N., Papazoglou, D., Mastorakos, G., Chatzaki, E., 2022. Liquid biopsy in type 2 diabetes mellitus management: building specific biosignatures via machine learning. *J. Clin. Med.* 11, 1045. <https://doi.org/10.3390/jcm11041045>.
- Karstoft, K.-I., Tsamardinos, I., Eskelund, K., Andersen, S.B., Nissen, L.R., 2020. Applicability of an automated model and parameter selection in the prediction of screening-level PTSD in Danish soldiers following deployment: development study of transferable predictive models using automated machine learning. *JMIR Med. Inform.* 8, e17119 <https://doi.org/10.2196/17119>.
- Karthik, S., Sudha, M., 2021. Predicting bipolar disorder and schizophrenia based on non-overlapping genetic phenotypes using deep neural network. *Evol. Intell.* 14, 619–634. <https://doi.org/10.1007/s12065-019-00346-y>.
- Kung, C.-H., Lee, S.-Y., Chang, Y.-H., Wu, J.Y.-W., Chen, S.-L., Chen, S.-H., Chu, C.-H., Lee, I.-H., Yeh, T.-L., Yang, Y.-K., Lu, R.-B., 2010. Poorer sustained attention in bipolar I than bipolar II disorder. *Ann. Gen. Psychiatry* 9, 8. <https://doi.org/10.1186/1744-859X-9-8>.

- Kvaløy, K., Page, C.M., Holmen, T.L., 2018. Epigenome-wide methylation differences in a group of lean and obese women – A HUNT Study. *Sci. Rep.* 8, 16330. <https://doi.org/10.1038/s41598-018-34003-8>.
- Lakiotaki, K., 2017. Download, preprocess, annotate and analyze omics data sets [WWW Document]. URL (<http://dataome.mensxmachina.org/docs>) (accessed 3.30.23).
- Lakiotaki, K., Vorniotakis, N., Tsagris, M., Georgakopoulos, G., Tsamardinos, I., 2018. BioDataome: a collection of uniformly preprocessed and automatically annotated datasets for data-driven biology. *Database* 2018. <https://doi.org/10.1093/database/bay011>.
- Leem, K.H., Kim, S., Kim, H.W., Park, H.J., 2023. Downregulation of microRNA -330-5p induces manic-like behaviors in REM sleep-deprived rats by enhancing tyrosine hydroxylase expression. *CNS Neurosci. Ther. CNS* 14121. <https://doi.org/10.1111/cns.14121>.
- Le-Niculescu, H., Levey, D.F., Ayalew, M., Palmer, L., Gavrin, L.M., Jain, N., Winiger, E., Bhosrekar, S., Shankar, G., Radel, M., Bellanger, E., Duckworth, H., Olesek, K., Vergo, J., Schweitzer, R., Yard, M., Ballew, A., Shekhar, A., Sandusky, G.E., Schork, N.J., Kurian, S.M., Salomon, D.R., Niculescu, A.B., 2013. Discovery and validation of blood biomarkers for suicidality. *Mol. Psychiatry* 18, 1249–1264. <https://doi.org/10.1038/mp.2013.95>.
- Leussis, M.P., Berry-Scott, E.M., Saito, M., Jhuang, H., de Haan, G., Alkan, O., Luce, C.J., Madison, J.M., Sklar, P., Serre, T., Root, D.E., Petryshen, T.L., 2013. The ANK3 Bipolar Disorder Gene Regulates Psychiatric-related Behaviors That Are Modulated By Lithium And Stress. *Biol. Psychiatry* 73, 683–690. <https://doi.org/10.1016/j.biopsych.2012.10.016>.
- Lewis, D., 2002. The Human Brain Revisited Opportunities And Challenges In Postmortem Studies Of Psychiatric Disorders. *Neuropsychopharmacology* 26, 143–154. [https://doi.org/10.1016/S0893-133X\(01\)00393-1](https://doi.org/10.1016/S0893-133X(01)00393-1).
- Li, M.-M., Jiang, T., Sun, Z., Zhang, Q., Tan, C.-C., Yu, J.-T., Tan, L., 2014. Genome-wide microRNA expression profiles in hippocampus of rats with chronic temporal lobe epilepsy. *Sci. Rep.* 4, 4734. <https://doi.org/10.1038/srep04734>.
- Liang, M.-J., Zhou, Q., Yang, K.-R., Yang, X.-L., Fang, J., Chen, W.-L., Huang, Z., 2013. Identify Changes Of Brain Regional Homogeneity In Bipolar Disorder And Unipolar Depression Using Resting-state fMRI. *PLoS One* 8, e79999. <https://doi.org/10.1371/journal.pone.0079999>.
- Liu, C.-H., Ma, X., Wu, X., Zhang, Y., Zhou, F.-C., Li, F., Tie, C.-L., Dong, J., Wang, Y.-J., Yang, Z., Wang, C.-Y., 2013. Regional homogeneity of resting-state brain abnormalities in bipolar and unipolar depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 41, 52–59. <https://doi.org/10.1016/j.pnpbp.2012.11.010>.
- Lopez, A.Y., Wang, X., Xu, M., Maheshwari, A., Curry, D., Lam, S., Adesina, A.M., Noebels, J.L., Sun, Q.-Q., Cooper, E.C., 2017. Ankyrin-G isoform imbalance and interneuronopathy link epilepsy and bipolar disorder. *Mol. Psychiatry* 22, 1464–1472. <https://doi.org/10.1038/mp.2016.233>.
- Lou, X., Meng, Y., Hou, Y., 2021. A literature review on function and regulation mechanism of DKK4. *J. Cell. Mol. Med.* 25, 2786–2794. <https://doi.org/10.1111/jcmm.13672>.
- Lyketsos, C.G., Stoline, A.M., Longstreet, P., Ranen, N.G., Lesser, R., Fisher, R., Folstein, M., 1993. Mania in temporal lobe epilepsy. *Cogn. Behav. Neurol.* 6, 19–25.
- Madison, J.M., Zhou, F., Nigam, A., Hussain, A., Barker, D.D., Nehme, R., van der Ven, K., Hsu, J., Wolf, P., Fleishman, M., O'Dushlaine, C., Rose, S., Chamberlain, K., Lau, F.H., Ahfeldt, T., Rueckert, E.H., Sheridan, S.D., Fass, D.M., Nemeth, J., Mullen, T.E., Daheron, L., McCarroll, S., Sklar, P., Perlis, R.H., Haggarty, S.J., 2015. Characterization of bipolar disorder patient-specific induced pluripotent stem cells from a family reveals neurodevelopmental and mRNA expression abnormalities. *Mol. Psychiatry* 20, 703–717. <https://doi.org/10.1038/mp.2015.7>.
- Mahon, K., Wu, J., Malhotra, A.K., Burdick, K.E., DeRosse, P., Ardekani, B.A., Szczepko, P., 2009. A voxel-based diffusion tensor imaging study of white matter in bipolar disorder. *Neuropsychopharmacology* 34, 1590–1600. <https://doi.org/10.1038/npp.2008.216>.
- Malóku, E., Covelio, I.R., Hanbauer, I., Guidotti, A., Kadriu, B., Hu, Q., Davis, J.M., Costa, E., 2010. Lower number of cerebellar Purkinje neurons in psychosis is associated with reduced reelin expression. *Proc. Natl. Acad. Sci. USA* 107, 4407–4411. <https://doi.org/10.1073/pnas.0914483107>.
- Mao, B., Niehrs, C., 2003. Kremen2 modulates Dickkopf2 activity during Wnt/IRP6 signaling. *Gene* 302, 179–183. [https://doi.org/10.1016/S0378-1119\(02\)01106-X](https://doi.org/10.1016/S0378-1119(02)01106-X).
- Mao, B., Wu, W., Davidson, G., Marhold, J., Li, M., Mechler, B.M., Delius, H., Hoppe, D., Stannek, P., Walter, C., Glinka, A., Niehrs, C., 2002. Kremen proteins are Dickkopf receptors that regulate Wnt/β-catenin signalling. *Nature* 417, 664–667. <https://doi.org/10.1038/nature756>.
- McCarthy, M.J., Liang, S., Spadoni, A.D., Kelsoe, J.R., Simmons, A.N., 2014. Whole brain expression of bipolar disorder associated genes: structural and genetic analyses. *PLoS One* 9, e100204. <https://doi.org/10.1371/journal.pone.0100204>.
- McCullumsmith, R.E., Meador-Woodruff, J.H., 2011. Novel approaches to the study of postmortem brain in psychiatric illness: old limitations and new challenges. *Biol. Psychiatry* 69, 127–133. <https://doi.org/10.1016/j.biopsych.2010.09.035>.
- McGrath, B.M., Wessels, P.H., Bell, E.C., Ulrich, M., Silverstone, P.H., 2004. Neurobiological findings in bipolar II disorder compared with findings in bipolar I disorder. *Can. J. Psychiatry* 49, 794–801. <https://doi.org/10.1177/070674370404901202>.
- Mills, J.D., van Vliet, E.A., Chen, B.J., Janitz, M., Anink, J.J., Baayen, J.C., Idema, S., Devore, S., Friedman, D., Diehl, B., Thom, M., Scott, C., Thijss, R., Aronica, E., Devinsky, O., 2020. Coding and non-coding transcriptome of mesial temporal lobe epilepsy: Critical role of small non-coding RNAs. *Neurobiol. Dis.* 134, 104612. <https://doi.org/10.1016/j.nbd.2019.104612>.
- Moorhead, T.W.J., McKirdy, J., Sussmann, J.E.D., Hall, J., Lawrie, S.M., Johnstone, E.C., McIntosh, A.M., 2007. Progressive gray matter loss in patients with bipolar disorder. *Biol. Psychiatry* 62, 894–900. <https://doi.org/10.1016/j.biopsych.2007.03.005>.
- Mula, M., Marotta, A.E., Monaco, F., 2010. Epilepsy and bipolar disorders. *Expert Rev. Neurother.* 10, 13–23. <https://doi.org/10.1586/ern.09.139>.
- Mullins, N., Forstner, A.J., O'Connell, K.S., Coombes, B., Coleman, J.R.I., Qiao, Z., Als, T. D., Bigdeli, T.B., Børte, S., Bryois, J., Charney, A.W., Drange, O.K., Gandal, M.J., Hagenaars, S.P., Ikeda, M., Kamitaki, N., Kim, M., Krebs, K., Panagiotaropoulou, G., Schilder, B.M., Sloofman, L.G., Steinberg, S., Trubetskoy, V., Winsvold, B.S., Won, H.-H., Abramova, L., Adorjan, K., Agerbo, E., Al Eissa, M., Albani, D., Alliey-Rodriguez, N., Anjorin, A., Antilla, V., Antoniou, A., Awasthi, S., Baek, J.H., Bækvd-Hansen, M., Bass, N., Bauer, M., Beins, E.C., Bergen, S.E., Birner, A., Becker, Pedersen, C., Bøen, E., Boks, M.P., Bosch, R., Brum, M., Brumpton, B.M., Brunkhorst-Kanaan, N., Budde, M., Bybjerg-Grauholt, J., Byerley, W., Cairns, M., Casas, M., Cervantes, P., Clarke, T.-K., Cruceanu, C., Cuellar-Barboza, A., Cunningham, J., Curtis, D., Czerski, P.M., Dale, A.M., Dalkner, N., David, F.S., Degenhardt, F., Djurovic, S., Dobbyn, A.L., Douzenis, A., Elvsåshagen, T., Escott-Price, V., Ferrier, I. N., Fiorentino, A., Foroud, T.M., Forty, L., Frank, J., Frei, O., Freimer, N.B., Frisén, L., Gade, K., Garnham, J., Gelernter, J., Giørtz Pedersen, M., Gizer, I.R., Gordon, S.D., Gordon-Smith, K., Greenwood, T.A., Grove, J., Guzman-Parraga, J., Ha, K., Haraldsson, M., Hautzinger, M., Heilbronner, U., Hellgren, D., Herms, S., Hoffmann, P., Holmes, P.A., Huckins, L., Jamain, S., Johnson, J.S., Kalman, J.L., Kamatani, Y., Kennedy, J.L., Kittel-Schneider, S., Knowles, J.A., Kogevinas, M., Koromina, M., Kranz, T.M., Kranzler, H.R., Kubo, M., Kupka, R., Kushner, S.A., Lavebratt, C., Lawrence, J., Leber, M., Lee, H.-J., Lee, P.H., Levy, S.E., Lewis, C., Liao, C., Lucae, S., Lundberg, M., MacIntyre, D.J., Magnusson, S.H., Maier, W., Maihofer, A., Malaspina, D., Maratou, E., Martinsson, L., Mattheisen, M., McCarroll, S.A., McGregor, N.W., McGuffin, P., McKay, J.D., Medeiros, H., Medland, S.E., Millischer, V., Montgomery, G.W., Moran, J.L., Morris, D.W., Mühlleisen, T.W., O'Brien, N., O'Donovan, C., Olde Loohuis, L.M., Oruc, L., Papio, S., Pardinas, A.F., Perry, A., Pfennig, A., Porichis, E., Potash, J.B., Quested, D., Raj, T., Rapaport, M.H., DePaulo, J.R., Regeer, E.J., Rice, J.P., Rivas, F., Rivera, M., Roth, J., Roussos, P., Ruderer, D.M., Sánchez-Mora, C., Schulz, E.C., Senner, F., Sharp, S., Shilling, P.D., Sigurdsson, E., Sirignano, L., Slaney, C., Smeland, O.B., Smith, D.J., Sobell, J.L., Soholm Hansen, C., Soler Artigas, M., Spijker, A.T., Stein, D., Strauss, J.S., Świątkowska, B., Terao, C., Thorgeirsson, T.E., Toma, C., Tooney, P., Tsermpini, E.-E., Vawter, M.P., Vedder, H., Walters, J.T.R., Witt, S.H., Xi, S., Xu, W., Yang, J.M.K., Young, A.H., Young, H., Zandi, P.P., Zhou, H., Zillich, L., HUNT All-In Psychiatry, Adolfsson, R., Agartz, I., Alda, M., Alfredsson, L., Babadjanova, G., Backlund, L., Baune, B.T., Bellivier, B., Bengesser, S., Berrettini, W.H., Blackwood, D., H.R., Boehnke, M., Borglum, A.D., Breen, G., Carr, V.J., Catts, S., Corvin, A., Craddock, N., Dannlowski, U., Dikeos, D., Esko, T., Etain, B., Ferentinos, P., Frye, M., Fullerton, J.M., Gawlik, M., Gershon, E.S., Goes, F.S., Green, M.J., Grigoroiu-Serbanescu, M., Hauser, J., Henskens, F., Hillert, J., Hong, K.S., Hougaard, D.M., Hultman, C.M., Hveem, K., Iwata, N., Jablensky, A.V., Jones, I., Jones, L.A., Kahn, R. S., Kelsoe, J.R., Kirov, G., Landén, M., Leboyer, M., Lewis, C.M., Li, Q.S., Lissowska, J., Lochner, C., Loughland, C., Martin, N.G., Mathews, C.A., Mayoral, F., McElroy, S.L., McIntosh, A.M., McMahon, F.J., Melle, I., Michie, P., Milani, L., Mitchell, P.B., Morken, G., Mors, O., Mortensen, P.B., Mowry, B., Müller-Mylsok, B., Myers, R.M., Neale, B.M., Nievergelt, C.M., Nordentoft, M., Nöthen, M.M., O'Donovan, M.C., Odegaard, K.J., Olsson, T., Owen, M.J., Paciga, S.A., Pantelis, C., Pato, C., Pato, M.T., Patrinos, G.P., Perlis, R.H., Posthuma, D., Ramos-Quiroga, J.A., Reif, A., Reininghaus, E.Z., Ribasés, M., Rietschel, M., Ripke, S., Rouleau, G.A., Saito, T., Schall, U., Schalling, M., Schofield, P.R., Schulze, T.G., Scott, L.J., Scott, R. J., Serretti, A., Shannon Weickert, C., Smoller, J.W., Stefansson, H., Stefansson, K., Stordal, E., Streit, F., Sullivan, P.F., Turecki, G., Vaaler, A.E., Vieta, E., Vincent, J.B., Waldman, I.D., Weickert, T.W., Werge, T., Wray, N.R., Zwart, J.A., Biernacka, J.M., Nurnberger, J.I., Cichon, S., Edenberg, H.J., Stahl, E.A., McQuillin, A., Di Florio, A., Ophoff, R.A., Andreassen, O.A., 2021. Genome-wide association study of more than 40,000 bipolar disorder cases provides new insights into the underlying biology. *Nat. Genet.* 53, 817–829. <https://doi.org/10.1038/s41588-021-00857-4>.
- Nissen, L.R., Tsamardinos, I., Eskelund, K., Gradus, J.L., Andersen, S.B., Karstoft, K.-I., 2021. Forecasting military mental health in a complete sample of Danish military personnel deployed between 1992–2013. *J. Affect. Disord.* 288, 167–174. <https://doi.org/10.1016/j.jad.2021.04.010>.
- Niu, X., Zhu, H.-L., Liu, Q., Yan, J.-F., Li, M.-L., 2021. MiR-194-5p serves as a potential biomarker and regulates the proliferation and apoptosis of hippocampus neuron in children with temporal lobe epilepsy. *J. Chin. Med. Assoc.* 84, 510–516. <https://doi.org/10.1097/JCMA.0000000000000518>.
- Novick, D.M., Swartz, H.A., Frank, E., 2010. Suicide attempts in bipolar I and bipolar II disorder: a review and meta-analysis of the evidence. *Bipolar Disord.* 12, 1–9. <https://doi.org/10.1111/j.1399-5618.2009.00786.x>.
- Oraki Kohshour, M., Papio, S., Ching, C.R.K., Schulze, T.G., 2022. Genomic and neuroimaging approaches to bipolar disorder. *BJPsych Open* 8, e36. <https://doi.org/10.1192/bjopen.2021.1082>.
- Panagopoulou, M., Karaglani, M., Manolopoulos, V.G., Iliopoulos, I., Tsamardinos, I., Chatzaki, E., 2021. Deciphering the Methylation Landscape in Breast Cancer: Diagnostic and Prognostic Biosignatures through Automated Machine Learning. *Cancers* 13, 1677. <https://doi.org/10.3390/cancers13071677>.
- Papoutsoglou, G., Karaglani, M., Lagani, V., Thomson, N., Røe, O.D., Tsamardinos, I., Chatzaki, E., 2021. Automated machine learning optimizes and accelerates predictive modeling from COVID-19 high throughput datasets. *Sci. Rep.* 11, 15107. <https://doi.org/10.1038/s41598-021-94501-0>.
- Phillips, J.R., Hewedi, D.H., Eissa, A.M., Moustafa, A.A., 2015. The cerebellum and psychiatric disorders. *Front. Public Health* 3. <https://doi.org/10.3389/fpubh.2015.00066>.
- Pinna, A., Colasanti, A., 2021. The neurometabolic basis of mood instability: the parvalbumin interneuron link—a systematic review and meta-analysis. *Front. Pharmacol.* 12, 689473. <https://doi.org/10.3389/fphar.2021.689473>.

- Redlich, R., Almeida, J.J.R., Grotegerd, D., Opel, N., Kugel, H., Heindel, W., Arolt, V., Phillips, M.L., Dannlowski, U., 2014. Brain morphometric biomarkers distinguishing unipolar and bipolar depression: a voxel-based morphometry-pattern classification approach. *JAMA Psychiatry* 71, 1222. <https://doi.org/10.1001/jamapsychiatry.2014.1100>.
- Romer, A.L., Knodt, A.R., Houts, R., Brigidi, B.D., Moffitt, T.E., Caspi, A., Hariri, A.R., 2018. Structural alterations within cerebellar circuitry are associated with general liability for common mental disorders. *Mol. Psychiatry* 23, 1084–1090. <https://doi.org/10.1038/mp.2017.57>.
- Rounis, K., Makrakis, D., Papadaki, C., Monastirioti, A., Vamvakas, L., Kalbakis, K., Gourlia, K., Xanthopoulos, I., Tsamardinos, I., Mavroudis, D., Agelaki, S., 2021. Prediction of outcome in patients with non-small cell lung cancer treated with second line PD-1/PDL-1 inhibitors based on clinical parameters: Results from a prospective, single institution study. *PLOS ONE* 16, e0252537. <https://doi.org/10.1371/journal.pone.0252537>.
- Sadovnick, A.D., Remick, R.A., Lam, R., Zis, A.P., Yee, I.M.L., Huggins, M.J., Baird, P.A., 1994. Mood disorder service genetic database: Morbidity risks for mood disorders in 3,942 first-degree relatives of 671 index cases with single depression, recurrent depression, bipolar I, or bipolar II. *Am. J. Med. Genet.* 54, 132–140. <https://doi.org/10.1002/ajmg.1320540208>.
- Scaini, G., Barichello, T., Fries, G.R., Kennon, E.A., Andrews, T., Nix, B.R., Zunta-Soares, G., Valvassori, S.S., Soares, J.C., Quevedo, J., 2019. TSPO upregulation in bipolar disorder and concomitant downregulation of mitophagic proteins and NLRP3 inflammasome activation. *Neuropsychopharmacology* 44, 1291–1299. <https://doi.org/10.1038/s41386-018-0293-4>.
- Shen, X., Caramaschi, D., Adams, M.J., Walker, R.M., Min, J.L., Kwong, A., Hemani, G., Genetics of DNA Methylation Consortium, Barbu, M.C., Whalley, H.C., Harris, S.E., Deary, I.J., Morris, S.W., Cox, S.R., Relton, C.L., Marioni, R.E., Evans, K.L., McIntosh, A.M., 2022. DNA methylome-wide association study of genetic risk for depression implicates antigen processing and immune responses. *Genome Med.* 36. <https://doi.org/10.1186/s13073-022-01039-5>.
- Sher, L., Sublette, M.E., Grunbaum, M.F., Mann, J.J., Oquendo, M.A., 2022. Plasma testosterone levels and subsequent suicide attempts in males with bipolar disorder. *Acta Psychiatr. Scand.* 145, 223–225. <https://doi.org/10.1111/acps.13381>.
- Shinn, A.K., Roh, Y.S., Ravichandran, C.T., Baker, J.T., Öngür, D., Cohen, B.M., 2017. Aberrant Cerebellar Connectivity in Bipolar Disorder With Psychosis. *Biol. Psychiatry Cogn. Neurosci. Neuroimaging* 2, 438–448. <https://doi.org/10.1016/j.bpsc.2016.07.002>.
- Stacey, D., Schubert, K.O., Clark, S.R., Amare, A.T., Milanesi, E., Maj, C., Leckband, S.G., Shekhtman, T., Kelsoe, J.R., Gurwitz, D., Baune, B.T., 2018. A gene co-expression module implicating the mitochondrial electron transport chain is associated with long-term response to lithium treatment in bipolar affective disorder. *Transl. Psychiatry* 8, 183. <https://doi.org/10.1038/s41398-018-0237-0>.
- Su, L., Cai, Y., Xu, Y., Dutt, A., Shi, S., Bramon, E., 2014. Cerebral metabolism in major depressive disorder: a voxel-based meta-analysis of positron emission tomography studies. *BMC Psychiatry* 14, 321. <https://doi.org/10.1186/s12888-014-0321-9>.
- Sullivan, K., Pantazopoulos, H., Liebson, E., Woo, T.-U., Baldessarini, R.J., Hedreen, J., Beretta, S., 2018. What can we learn about brain donors? Use of clinical information in human postmortem brain research. *Handb. Clin. Neurol.* 150, 181–196.
- Szatkiewicz, J.P., O'Dushlaine, C., Chen, G., Chambert, K., Moran, J.L., Neale, B.M., Fromer, M., Ruderfer, D., Akterin, S., Bergen, S.E., Kähler, A., Magnusson, P.K.E., Kim, Y., Crowley, J.J., Rees, E., Kirov, G., O'Donovan, M.C., Owen, M.J., Walters, J., Scolnick, E., Sklar, P., Purcell, S., Hultman, C.M., McCarroll, S.A., Sullivan, P.F., 2014. Copy number variation in schizophrenia in Sweden. *Mol. Psychiatry* 19, 762–773. <https://doi.org/10.1038/mp.2014.40>.
- Tondo, L., Miola, A., Pinna, M., Contu, M., Baldessarini, R.J., 2022. Differences between bipolar disorder types 1 and 2 support the DSM two-syndrome concept. *Int. J. Bipolar Disord.* 10, 21. <https://doi.org/10.1186/s40345-022-00268-2>.
- Torrey, E.F., Webster, M., Knable, M., Johnston, N., Yolken, R.H., 2000. The Stanley Foundation brain collection and Neuropathology Consortium. *Schizophr. Res.* 44, 151–155. [https://doi.org/10.1016/S0920-9964\(99\)00192-9](https://doi.org/10.1016/S0920-9964(99)00192-9).
- Tsamardinos, I., 2022. Don't lose samples to estimation. *Patterns* 3, 100612. <https://doi.org/10.1016/j.patter.2022.100612>.
- Tsamardinos, I., Charonyktakis, P., Papoutsoglou, G., Borboudakis, G., Lakiotaki, K., Zenklusen, J.C., Juhl, H., Chatzaki, E., Lagani, V., 2022. Just Add Data: automated predictive modeling for knowledge discovery and feature selection. *Npj Precis. Oncol.* 6, 38. <https://doi.org/10.1038/s41698-022-00274-8>.
- Tsamardinos, I., Greasidou, E., Borboudakis, G., 2018. Bootstrapping the out-of-sample predictions for efficient and accurate cross-validation. *Mach. Learn.* 107, 1895–1922. <https://doi.org/10.1007/s10994-018-5714-4>.
- Valtonen, H.M., Suominen, K., Haukka, J., Mantere, O., Leppmki, S., Arvilommi, P., Isomets, E.T., 2008. Differences in incidence of suicide attempts during phases of bipolar I and II disorders. *Bipolar Disord.* 10, 588–596. <https://doi.org/10.1111/j.1399-5618.2007.00553.x>.
- Vastrad, B., Vastrand, C., 2022. Identification of Key Genes and Biological Pathways in Bipolar Disorder by Bioinformatics and Next Generation Sequencing Data Analysis (preprint). *Bioinformatics*. <https://doi.org/10.1101/2022.04.29.489994>.
- Wang, D., Liu, S., Warrell, J., Won, H., Shi, X., Navarro, F.C.P., Clarke, D., Gu, M., Emani, P., Yang, Y.T., Xu, M., Gandal, M.J., Lou, S., Zhang, J., Park, J.J., Yan, C., Rhee, S.K., Manakongtreeep, K., Zhou, H., Nathan, A., Peters, M., Mattei, E., Fitzgerald, D., Brunetti, T., Moore, J., Jiang, Yan, Girdhar, K., Hoffman, G.E., Kalayci, S., Güümü, Z.H., Crawford, G.E., PsychENCODE Consortium, Roussos, P., Akbarian, S., Jaffe, A.E., White, K.P., Weng, Z., Sestan, N., Geschwind, D.H., Knowles, J.A., Gerstein, M.B., Ashley-Koch, A.E., Crawford, G.E., Garrett, M.E., Song, L., Safi, A., Johnson, G.D., Wray, G.A., Reddy, T.E., Goes, F.S., Zandi, P., Bryois, J., Jaffe, A.E., Price, A.J., Ivanov, N.A., Collado-Torres, L., Hyde, T.M., Burke, E.E., Kleiman, J.E., Tao, R., Shin, J.H., Akbarian, S., Girdhar, K., Jiang, Yan, Kundakovic, M., Brown, L., Kassim, B.S., Park, R.B., Wiseman, J.R., Zharovsky, E., Jacobov, R., Devillers, O., Flatow, E., Hoffman, G.E., Lipska, B.K., Lewis, D.A., Haroutunian, V., Hahn, C.-G., Charney, A.W., Dracheva, S., Kozlenkov, A., Belmont, J., DelValle, D., Francoeur, N., Hadjimichael, E., Pinto, D., van Bakel, H., Roussos, P., Fullard, J.F., Bendl, J., Hauberg, M.E., Mangravite, L.M., Peters, M.A., Chae, Y., Peng, J., Niu, M., Wang, X., Webster, M.J., Beach, T.G., Chen, C., Jiang, Yi, Dai, R., Shieh, A.W., Liu, C., Grennan, K.S., Xia, Y., Vadukupuram, R., Wang, Y., Fitzgerald, D., Cheng, L., Brown, Miguel, Brown, Mimi, Brunetti, T., Goodman, T., Alsayed, M., Gandal, M.J., Geschwind, D.H., Won, H., Polioudakis, D., Wamsley, B., Yin, J., Hadzic, T., De La Torre Ubieto, L., Swarup, V., Sanders, S.J., State, M.W., Werling, D.M., An, J.-Y., Sheppard, B., Willsey, A.J., White, K.P., Ray, M., Giase, G., Kefi, A., Mattei, E., Purcaro, M., Weng, Z., Moore, J., Pratt, H., Huey, J., Borrman, T., Sullivan, P.F., Giusti-Rodriguez, P., Kim, Y., Sullivan, P., Szatkiewicz, J., Rhee, S.K., Armoskus, C., Camarena, A., Farnham, P.J., Spitsyna, V.N., Witt, H., Schreiner, S., Evgrafov, O.V., Knowles, J.A., Gerstein, M., Liu, S., Wang, D., Navarro, F.C.P., Warrell, J., Clarke, D., Emani, P.S., Gu, M., Shi, X., Xu, M., Yang, Y.T., Kitchen, R.R., Gürsoy, G., Zhang, J., Carlyle, B.C., Nairn, A.C., Li, M., Pochareddy, S., Sestan, N., Skarica, M., Li, Z., Sousa, A.M.M., Santpere, G., Choi, J., Zhu, Y., Gao, T., Miller, D.J., Cherskov, A., Yang, M., Amiri, A., Coppola, G., Mariotti, J., Scuderi, S., Szekely, A., Vaccarino, F.M., Wu, F., Weissman, S., Roychowdhury, T., Abyzov, A., 2018. Comprehensive functional genomic resource and integrative model for the human brain. In: *Science*, 362, p. eaat8464. <https://doi.org/10.1126/science.aat8464>.
- Wang, Y., Wang, J., Jia, Y., Zhong, S., Niu, M., Sun, Y., Qi, Z., Zhao, L., Huang, L., Huang, R., 2017. Shared and specific intrinsic functional connectivity patterns in unmedicated bipolar disorder and major depressive disorder. *Sci. Rep.* 7, 3570. <https://doi.org/10.1038/s41598-017-03777-8>.
- Wang, Y., Zhong, S., Jia, Y., Zhou, Z., Wang, B., Pan, J., Huang, L., 2015. Interhemispheric resting state functional connectivity abnormalities in unipolar depression and bipolar depression. *Bipolar Disord.* 17, 486–495. <https://doi.org/10.1111/bdi.12315>.
- Wemmie, J.A., Taucher, R.J., Kreple, C.J., 2013. Acid-sensing ion channels in pain and disease. *Nat. Rev. Neurosci.* 14, 461–471. <https://doi.org/10.1038/nrn3529>.
- Winterton, A., 2022. The Oxytocin Genetic Pathway Links Severe Mental Illness and Metabolic Syndrome.
- Xanthopoulos, I., Tsamardinos, I., Christophides, V., Simon, E., Salinger, A., 2020. Putting the Human Back in the AutoML Loop, in: *EDBT/ICDT Workshops*.
- Yamagata, H., Uchida, S., Matsuo, K., Harada, K., Kobayashi, A., Nakashima, M., Nakano, M., Otsuki, K., Abe-Higuchi, N., Higuchi, F., Watanuki, T., Matsubara, T., Miyata, S., Fukuda, M., Mikuni, M., Watanabe, Y., 2017. Identification of commonly altered genes between in major depressive disorder and a mouse model of depression. *Sci. Rep.* 7, 3044. <https://doi.org/10.1038/s41598-017-03291-x>.
- Yoon, S., Piguel, N.H., Penzes, P., 2022. Roles and mechanisms of ankyrin-G in neuropsychiatric disorders. *Exp. Mol. Med.* 54, 867–877. <https://doi.org/10.1038/s12276-022-00798-w>.
- Yoshino, Y., Dwivedi, Y., 2020. Non-Coding RNAs in psychiatric disorders and suicidal behavior. *Front. Psychiatry* 11, 543893. <https://doi.org/10.3389/fpsyg.2020.543893>.
- Zhang, J., Xie, S., Chen, Y., Zhou, X., Zheng, Z., Yang, L., Li, Y., 2022. Comprehensive analysis of endoplasmic reticulum stress and immune infiltration in major depressive disorder. *Front. Psychiatry* 13, 1008124. <https://doi.org/10.3389/fpsyg.2022.1008124>.