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Longitudinal Investigation of Phenotypic, Genetic and Epigenetic Factors in Mood Disorders

Inauguraldissertation
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vorgelegt von
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ABBREVIATIONS

APA	American Psychiatric Association
BDNF	Brain-derived neurotrophic factor
BIP	Bipolar disorder
BIP-I	Bipolar I disorder
BIP-II	Bipolar II disorder
CBT	Cognitive-behavioral therapy
CHR	Chromosome
CIDI	Composite International Diagnostic Interview
CIMH	Central Institute of Mental Health
CpG	Cytosine-phosphate-guanine
DMR	Differentially methylated region
DNA	Deoxyribonucleic acid
DNAm	DNA methylation
DSM-5	Diagnostic and Statistical Manual of Mental Disorders 5
ECS	Electroconvulsive stimulation
ECT	Electroconvulsive therapy
EWAS	Epigenome-wide association study
FDR	False discovery rate
GBD	Global Burden of Disease
GO	Gene Ontology
GWAS	Genome-wide association study
HDRS	Hamilton Depression Rating Scale
ICD-10	International Statistical Classification of Diseases version 10
ICD-11	International Statistical Classification of Diseases version 11
LD	Linkage Disequilibrium
LDSC	Linkage Disequilibrium Score Regression
MAF	Minor Allele Frequency
MAGMA	Multi-marker Analysis of GenoMic Annotation
MD	Major Depression
MDD	Major Depressive Disorder
MINI	Mini International Neuropsychiatric Interview
PCs	Principal components
PRS	Polygenic risk scores
QC	Quality control
SCAN	Schedules for Clinical Assessment in Neuropsychiatry
SCID	Structured Clinical Interview for DSM Disorders
SD	Sleep Deprivation Therapy
SNPs	Single nucleotide polymorphisms
VIF	Variance inflation factor
WHO	World Health Organization

PREAMBLE

This cumulative doctoral thesis consists of two publications, with me as first author. The first study, titled "*Depression and bipolar disorder subtypes differ in their genetic correlations with biological rhythms*", was published in Scientific Reports and is presented in chapter 2 of this thesis. The second study, entitled "*Methylome-wide change associated with response to electroconvulsive therapy in depressed patients*", was published in Translational Psychiatry and is presented in chapter 3.

Sirignano, L., Streit, F., Frank, J., Zillich, L., Witt, S. H., Rietschel, M., & Foo, J. C. (2022). Depression and bipolar disorder subtypes differ in their genetic correlations with biological rhythms. *Scientific reports*, *12*(1), 15740. https://doi.org/10.1038/s41598-022-19720-5

Sirignano, L., Frank, J., Kranaster, L., Witt, S. H., Streit, F., Zillich, L., Sartorius, A., Rietschel, M., & Foo, J. C. (2021). Methylome-wide change associated with response to electroconvulsive therapy in depressed patients. *Translational psychiatry*, *11*(1), 347. https://doi.org/10.1038/s41398-021-01474-9

Darstellung der Eigenleistung der Doktorandin/des Doktoranden

bei kumulativen Dissertationen

Name der Doktorandin/des Doktoranden Lea Maria Anke Sirignano

Titel der Dissertation
Longitudinal Investigation of Phenotypic, Genetic and Epigenetic Factors in Mood Disorders

Betreut durch Prof. Dr. med. Marcella Rietschel

☒ Ich möchte eine kumulative Dissertation einreichen und bitte den Promotionsausschuss zu prüfen, ob die vorgeschlagenen Publikationen quantitativ und qualitativ ausreichen, um die Anforderungen an eine kumulative Dissertation zu erfüllen.

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Publikation 1 Depression and Bipolar Disorder Subtypes Differ in their Genetic Correlations with Biological Rhythms (weitere Informationen siehe Anlage 1)

Publikation 2 Methylome-wide change associated with response to electroconvulsive therapy in depressed patients (weitere Informationen siehe Anlage 1)

Publikation 3

2. Zusammenfassung des Beitrags der Doktorandin/des Doktoranden zu der in jedem Manuskript berichteten Arbeit

Arbeitsschritte	Publikation 1	Publikation 2	Publikation 3
Konzeption (%)	90	80	
Literaturrecherche (%)	100	95	
Ethikantrag (%)	-	-	
Tierversuchsantrag (%)	-	-	
Datenerhebung (%)	-	-	
Datenauswertung (%)	100	90	
Ergebnisinterpretation (%)	90	90	
Verfassen des Manuskripttextes (%)	90	95	
Revision (%)	95	95	
Geben Sie an, welche Abbildungen/ Tabellen aus Ihrer Doktorarbeit entstanden sind.	alle	alle	
Geben Sie im Einzelnen an, welche Daten/Zahlen/Tabellen auf Forschungsergebnissen von anderen beruhen.	Tabelle 1	keine	

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1 INTRODUCTION

1.1 Depression and Bipolar Disorders

Depression and Bipolar Disorders (BIP) are mood disorders in which mood is severely disturbed and can range from depression to mania (World Health Organisation (WHO), 2022a). The average lifetime prevalence of depression is estimated to be ~15% and can vary across countries (Bromet et al., 2011; Kessler et al., 2003); ~280 million individuals worldwide are affected by depression (WHO, 2023). Lifetime prevalences for BIP vary between 0.4 - 2.4% for the different subtypes (Merikangas et al., 2011), with ~40 million people affected worldwide in 2019 (WHO, 2022b). Mental disorders, including mood disorders are one of the major contributors to the global burden of disease (GBD 2019 Diseases and Injuries Collaborators, 2020). Both disorders' direct and indirect costs are high and are expected to increase (Arias et al., 2022; Olesen et al., 2012).

1.1.1 Definition and Diagnosis

The diagnosis of psychiatric disorders is not based on objectively measurable (bio-) markers – as they are not available yet. As such, the diagnoses of depression and BIP are made according to one of the two current international classification systems: (1) the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (American Psychiatric Association (APA), 2013) or (2) the International Classification of Diseases, 10th (WHO, 1993) or the latest 11th edition (WHO, 2022a). Diagnosis can be made based on structured clinical interviews to assess the presence of symptoms for example with the Structured Clinical Interview for DSM-5 (SCID-5-CV) (First et al., 2019), Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (Aboraya et al., 1998), Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998), or the Composite International Diagnostic Interview (CIDI) (Wittchen, 1994).
If a certain set of symptoms is present during a defined time period (i.e., two weeks for depressive episode), a diagnosis is given (APA, 2013; WHO, 2022a). Characteristic symptoms of a major depressive episode are loss of interest and enjoyment, fatigue, loss of energy, changes in appetite, sleep patterns, feelings of worthlessness or guilt, and thoughts of death or suicide (APA, 2013; WHO, 2022a). In manic episodes mood is elevated, euphoric, or irritable. Symptoms are increased energy and psychomotor activity, accelerated thinking, pressure of speech, distractibility, impairment of concentration, decreased need for sleep, overconfidence, and grandiosity (APA, 2013; WHO, 2022a). Ordinary work and social activities are disrupted during a manic episode (APA, 2013; WHO, 2022a). In a hypomanic episode, symptoms are less intense, do not cause significant functional impairment or hospitalization, and no psychotic symptoms occur (APA, 2013; WHO, 2022a). Based on the occurrence of depressive, manic and hypomanic episodes the classification systems distinguish between depression or major depressive disorder (MDD), bipolar I (BIP-I), and bipolar II (BIP-II) disorder (APA, 2013; WHO, 2022a). The symptoms for MDD, BIP-I, and BIP-II must not be better explained by another medical condition or substance use, and for BIP not better by a schizoaffective, or other schizophrenic or psychotic disorder (APA, 2013). The key symptoms for the different mood disorder subtypes according to DSM-5 (APA, 2013) and ICD-11 (WHO, 2022a) are summarized in Table 1.1.

Table 1.1. Key Symptoms for the Three Mood Disorder Subtypes According to DSM-5 (APA, 2013) and ICD-11 (WHO, 2022a).

DSM-5	ICD-11
Major Depressive Episode	*Depressive Episode*
• Five or more symptoms, at least one is (1) or (2) 1. Depressed mood 2. Markedly diminished interest or pleasure in activities 3. Significant weight loss/ gain or decrease/ increase in appetite 4. Insomnia or hypersomnia 5. Psychomotor agitation or retardation 6. Fatigue or loss of energy 7. Feelings of worthlessness or excessive or inappropriate guilt 8. Diminished concentration or indecisiveness 9. Recurrent thoughts of death, suicidal ideation, plans or a suicide attempt	• At least five symptoms, at least one symptom from the Affective Cluster. Affective Cluster: Depressed mood; Markedly diminished interest or pleasure in activities Cognitive-behavioural Cluster: Reduced ability to concentrate; Beliefs of low self-worth or excessive and inappropriate guilt; Hopelessness about the future; Recurrent thoughts of death, recurrent suicidal ideation, or evidence of attempted suicide Neurovegetative Cluster: Significantly disrupted sleep or excessive sleep; Significant change in appetite or significant weight change; Psychomotor agitation or retardation; Reduced energy, fatigue, or marked tiredness
Bipolar I Disorder	*Bipolar type I disorder*
• At least one manic episode with: a. Distinct period of abnormally and persistently elevated, expansive or irritable mood and abnormally and persistently increased activity or energy b. At least three manic symptoms (four if the mood is only irritable) during this period: 1. Inflated self-esteem or grandiosity 2. Decreased need for sleep 3. More talkative than usual or pressure to talk 4. Flight of ideas or racing thoughts 5. Distractibility 6. Increase in goal directed activity or psychomotor agitation 7. Excessive involvement in activities with high potential for painful consequences	• A history of at least one manic or mixed episode, manic episode presenting with: - Euphoria, irritability or expansiveness, and, increased activity or subjective experience of increased energy - *Several of the following symptoms*: Increased talkativeness or pressured speech; Flight of ideas; Increased self-esteem or grandiosity; Decreased need for sleep; Distractibility; Impulsive reckless behaviour; Increase in sexual drive, sociability or goal-directed activity
Bipolar II Disorder	*Bipolar type II disorder*
• At least one hypomanic episode (weaker than a manic episode, see above) and at least one major depressive episode (see above) • Never a manic episode	• A history of at least one hypomanic episode (like a manic episode, but weaker, see above) and at least one depressive episode • No history of manic or mixed episodes

Episodes of mood disorders are recurrent, and depressive, manic, or hypomanic episodes can alternate (see Figure 1.1).

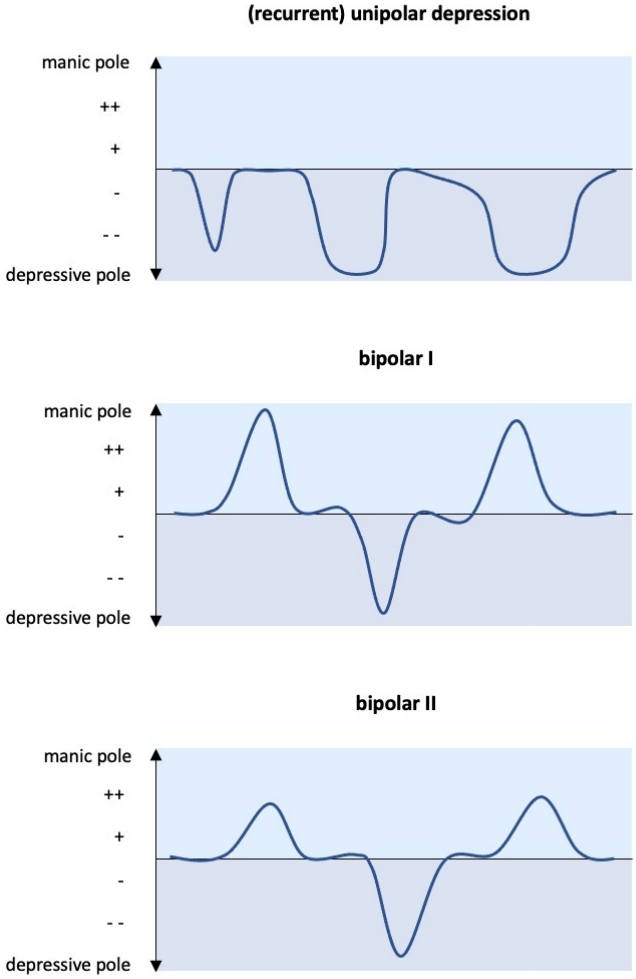


Figure 1.1. Trajectories of (Recurrent) Unipolar Depression, BIP-I, and BIP-II. These mood disorder trajectories are published in Laux, G. (2017). Grundlagen affektiver Störungen. In H. Möller, G. Laux, & H. Kapfhammer (Eds.), *Psychiatrie, Psychosomatik, Psychotherapie* (5 ed., pp. 1703-1710) and reprinted with permission from Springer Nature. The figure was adapted only showing the three subtypes of mood disorders relevant for this work; in addition the background of the figures were changed. Headers and axis labelling were translated from German to English.

An obvious shortcoming of the current classification systems is that patients with the same diagnosis will likely display differences in symptom constellation, i.e., symptoms across the same diagnosis might differ between patients (Fried & Nesse, 2015). This means that mood disorders are phenotypically highly heterogeneous – in a vicious circle – making it difficult to identify their biological underpinnings, whereas identifying those would improve diagnosis, identification of subgroups, understanding of the etiology, and treatment immensely.

1.1.2 Treatment

There are different types of treatments for mood disorders: (1) psychotherapy, (2) medication, and (3) non-pharmacological somatic interventions (DGBS & DGPPN, 2019; Leitlinien, 2022).
The most commonly used psychotherapy is Cognitive Behavioral Therapy (CBT), which is effective in achieving remission of depressive symptoms (Gautam et al., 2020). In BIP, psychotherapy is beneficial during depressive episodes or in euthymic and remitted states (DGBS & DGPPN, 2019).
Medication to treat depressed states also in BIP are called antidepressants; in BIP, other substances such as the mood stabilizer lithium can be applied to treat manic states (DGBS & DGPPN, 2019; Leitlinien, 2022). The efficacy of antidepressants has been shown repeatedly (Cipriani et al., 2018). However, approximately one-third of patients fail to attain remission, even after being treated with multiple antidepressants (Rush et al., 2006). In addition, the average latency time for antidepressants is two weeks, during which symptoms persist and the risk of self-harm increases (Katz et al., 2004; Tadić et al., 2016).
Non-pharmacological treatments include Electroconvulsive therapy (ECT) and Sleep Deprivation Therapy (SD) (DGBS & DGPPN, 2019; Leitlinien, 2022); ECT will be described in more detail as relevant to this work. ECT is very successful (i.e., > 50% response rate) in MDD and BIP (Bahji et al., 2019; Perugi et al., 2017), especially in patients with treatment-resistant depression (Khalid et al., 2008). During the process of ECT, cerebral seizures are induced under general anesthesia (Jaffe, 2002). Different mechanisms of action are proposed for ECT, including alterations in neurotransmitters (i.e., serotonin, dopamine and noradrenaline), neuroplasticity, and beneficial hormone changes in stress hormones (i.e., cortisol) (Singh & Kar, 2017). While existing treatments have reduced or even remitted the symptoms of mood disorders, they are applied in a “trial and error” manner (McMahon, 2014) due to the limited understanding of the etiology.

1.1.3 Etiology of Depression and Bipolar Disorder

So far, no sufficient understanding of the etiology of mood disorders exists. Well-studied environmental risk factors in mood disorders are childhood trauma, physical health, chronic stress, stressful life events, and social isolation (Rowland & Marwaha, 2018; for a list see Leitlinien, 2022). Genetic factors are also crucial in the development of mood disorders; formal genetic studies have reported heritability estimates for depression of ~40% and for bipolar disorders of ~80% (for reviews, see Forstner et al., 2020; Sullivan et al., 2012). Heritability describes the variance in a specific phenotype due to genetic differences between individuals within a population (Wray & Visscher, 2008). Psychiatric disorders differ in heritability and frequency (Sullivan et al., 2012) (see Figure 1.2).

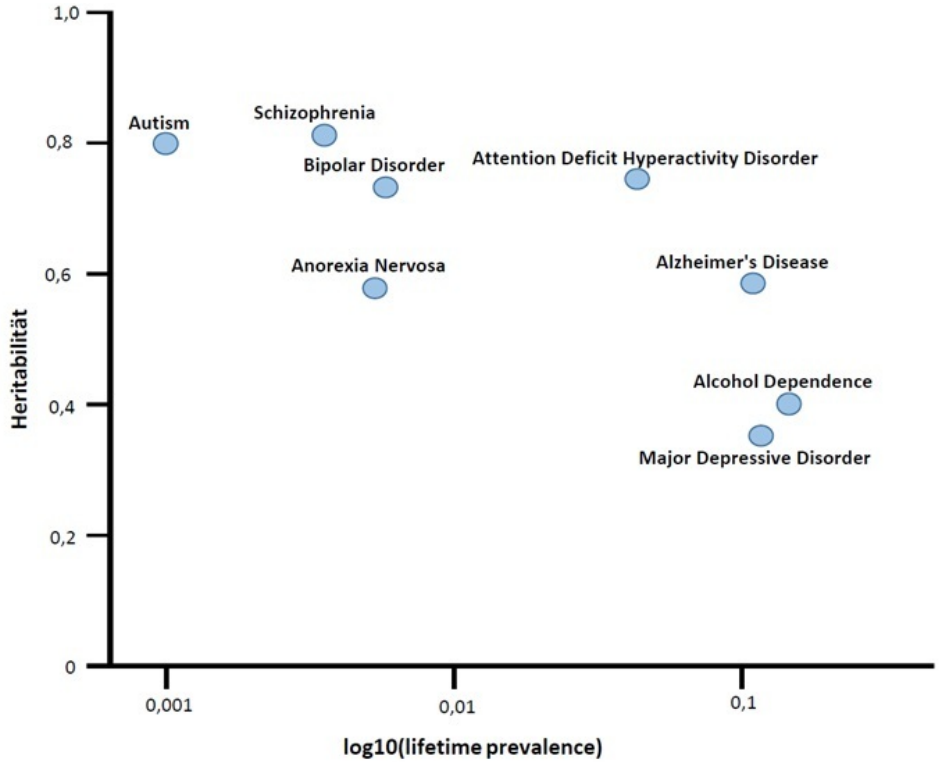


Figure 1.2. Heritability Plotted by Lifetime Prevalence of Nine Psychiatric Disorders reprinted and adapted with permission from Springer Nature: Nature Reviews Genetics: Sullivan et al. (2012).

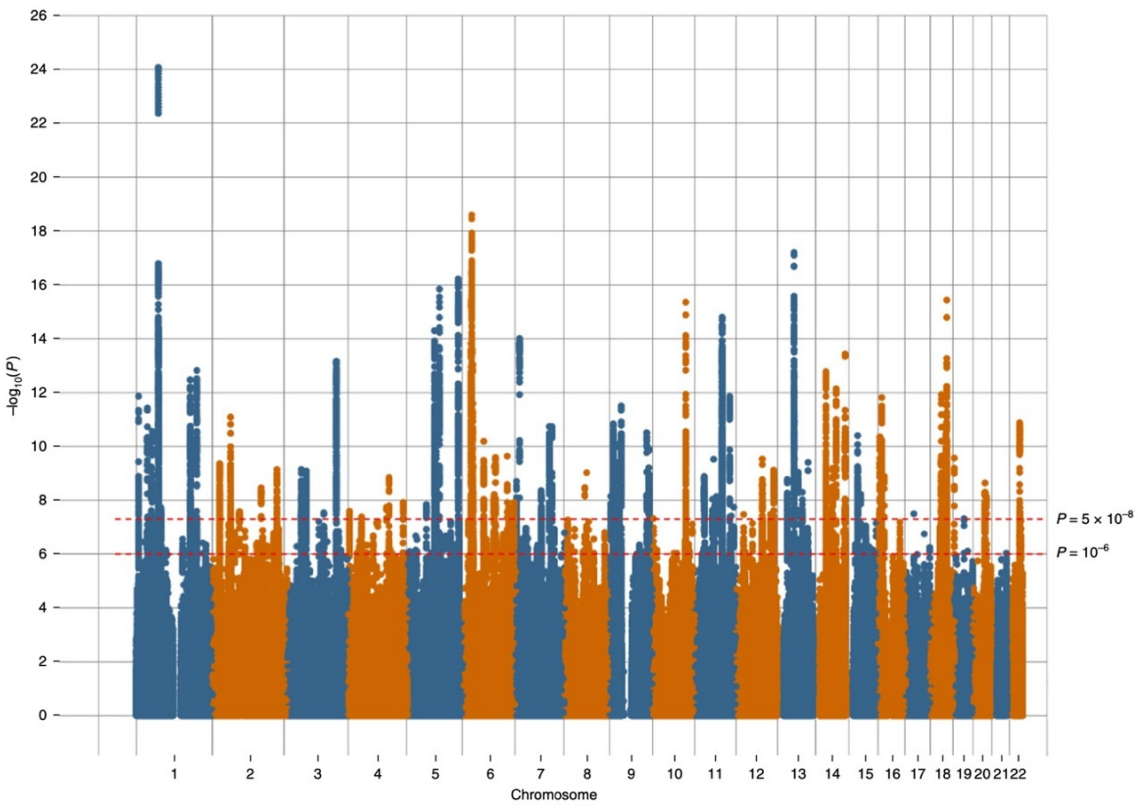
It has been shown that psychiatric disorders including depression and BIP are not inherited in a monogenic, i.e., Mendelian way where one single mutation is responsible for the disorder, but that psychiatric disorders are genetically complex (for a review, see Visscher et al., 2021). This means many variants with small effects which are also present in the healthy and general population contribute to disease risk in conjunction with environmental factors (Visscher et al., 2021).
Integrative models such as the vulnerability-stress model (Ingram & Luxton, 2005) or gene-environment interaction (Ottman, 1996) exist to disentangle the relationship between environmental and genetic factors. However, it is not well understood to which extent the factors contribute and how they interact/ are additive. Also, no objective biomarker for mood disorders exists, indicating the disorder. The field of psychiatric genetics offers genome-wide methods to identify genetic variation across the whole genome, enhancing our understanding of the etiology. The following paragraph will focus on some of these methods and highlight relevant findings.

1.2 Genome-wide Approaches

As genetic factors play a substantial role in the etiology of mood disorders, a promising approach is to search for their genetic basis on the molecular level (for reviews, see Gordovez & McMahon, 2020; Kendall et al., 2021; McIntosh et al., 2019; O`Connell & Coombes, 2021). Different genetic variation types exist; the most frequent ones are single nucleotide polymorphisms (SNPs) (Frazer et al., 2009). SNPs involve a replacement of a single nucleotide (A, T, C, G) at a specific location in the DNA (Deoxyribonucleic acid) sequence. There are approximately 11 million SNPs in the human genome, of which 7 million have a minor allele frequency (MAF) greater than

5% and 4 million have a (MAF) of 1-5 % (Frazer et al., 2009). Those variants only have inferior effects on complex phenotypes, and it is assumed that many of these SNPs across the whole genome contribute to the disorder (Gratten et al, 2014).
In 2005, genome-wide association studies (GWASs) leveraging SNPs across the whole genome became increasingly feasible for complex disorders (Hirschhorn & Daly, 2005). GWASs use genotype data, which can be acquired with sequencing or microarray technologies. One popular microarray is the Illumina Infinium Global Screening Array-24 Kit (GSA); the chip covers ~ 700,000 – 1 million SNPs across the whole genome (Illumina, Inc., San Diego, CA, USA).
A GWAS investigates if and which SNPs across the whole genome are more common in individuals with a disorder compared to individuals without that disorder (Uffelmann et al., 2021). Comparing these two groups is one way to conduct a GWAS; if the phenotype of interest is non-binary, for example sleep or physical activity, a linear regression is applied to the SNP data (Uffelmann et al., 2021). GWAS findings provide an effect size representing the relatedness of each SNP with the phenotype, resulting in an output of thousands of tested SNPs (Uffelmann et al., 2021). This amount of association testing requires multiple testing correction; a significance level of $5x10^{-8}$ is usually applied (Pe'er et al., 2008; Uffelmann et al., 2021). This in turn also requires large sample sizes for risk variants to pass the significance threshold (Spencer et al., 2009). A Manhattan plot is commonly used to present GWAS findings, where on the x-axis the chromosomes are given, the dots represent the SNPs across the whole genome, and the y-axis indicates the level of significance (Uffelmann et al., 2021). Figure 1.3 A-B shows the Manhattan plots of the depression GWAS from Howard et al. (2019) (A) and the BIP GWAS from Mullins et al. (2021) (B).

A



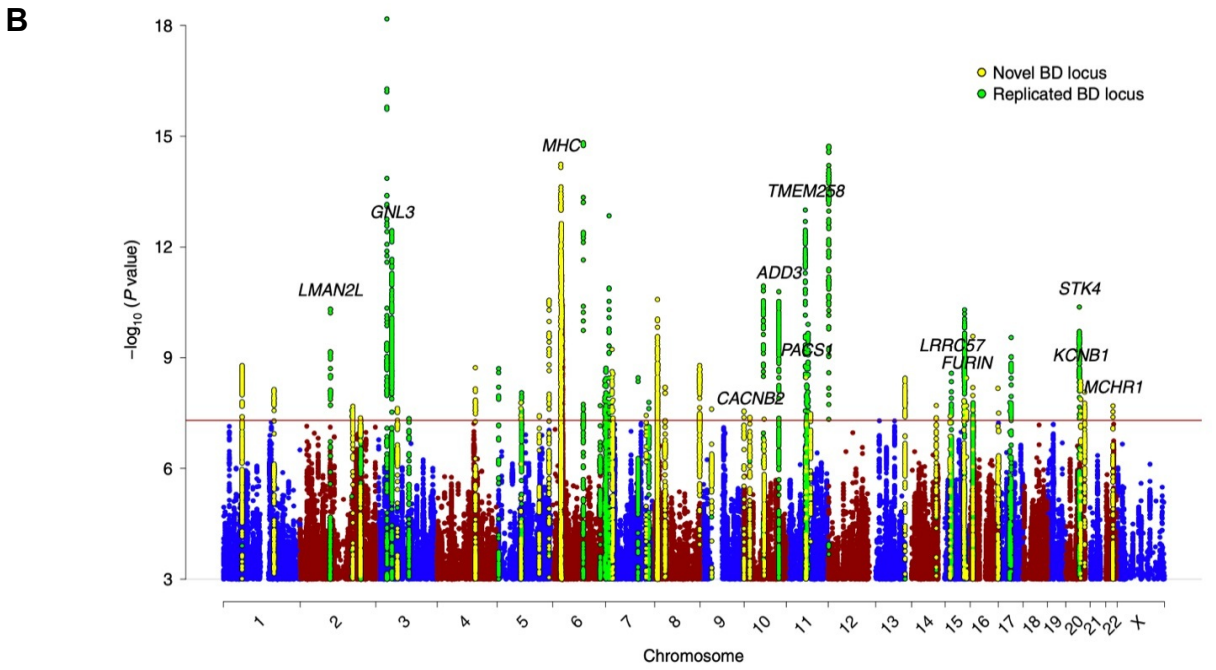


Figure 1.3. Manhattan Plot of the GWAS of Depression (A) and BIP (B) reprinted with permission from Springer Nature: Nature Neuroscience: Howard et al. (2019) and Nature Genetics: Mullins et al. (2021).

A GWAS on depression published in 2019 identified 102 genetic variants associated with depression, of which 87 survived multiple testing correction (Howard et al., 2019). Another meta-analysis on depression in 2021, including the data from the Million Veteran Program, identified 77 novel loci more than before (Levey et al., 2021). A GWAS of BIP published in 2021 led to substantial progress in the field of psychiatric genetics (Mullins et al., 2021). The study comprised genetic data from over 41,000 BIP cases, the most substantial genetic dataset of BIP patients worldwide (Mullins et al., 2021), identifying 64 genetic loci, of which 33 were novel. Just recently, a GWAS of antidepressant response was published (Pain et al., 2022). Even though the sample size was compared to other GWAS in the field small (N = 5,151 remission, N = 5,218 percentage improvement) and no significant single variants were identified, the study provided evidence for the polygenic architecture of therapy response and revealed meaningful insight into the underlying biology of therapy response. GWAS are not only conducted in pathological phenotypes, but also in phenotypes related to psychiatric disorders such as physical activity, sleep, and circadian rhythm (e.g., Doherty et al., 2018; Ferguson et al., 2018). The UK Biobank, a large-scale biomedical cohort study, collected objective phenotype data using actigraphy and genotype data (Bycroft et al., 2018); making it feasible to conduct GWASs in these related phenotypes. A GWAS on objectively collected physical activity and sleep behaviors identified 14 genetic variants associated with different types of physical activity (e.g., overall physical activity, sedentary behavior) and sleep duration in a sample of 91,105 UK Biobank participants (Doherty et al., 2018). Also, a GWAS of relative amplitude, a measure of circadian rhythms derived from actigraphy data, provides evidence for a shared polygenic architecture with mood phenotypes (Ferguson et al., 2018). Another study investigating the genetic underpinnings of daytime sleepiness found 42 loci linked with the phenotype; genetic links were found with insomnia, psychiatric disorders, and several other health conditions, including obesity and type 2 diabetes (Wang et al., 2019).

With these genome-wide findings, insights into the biology of the disorders can be gained by applying gene-level, pathway, and enrichment analysis, as shown on the right side of Figure 1.4 (McIntosh et al., 2019).

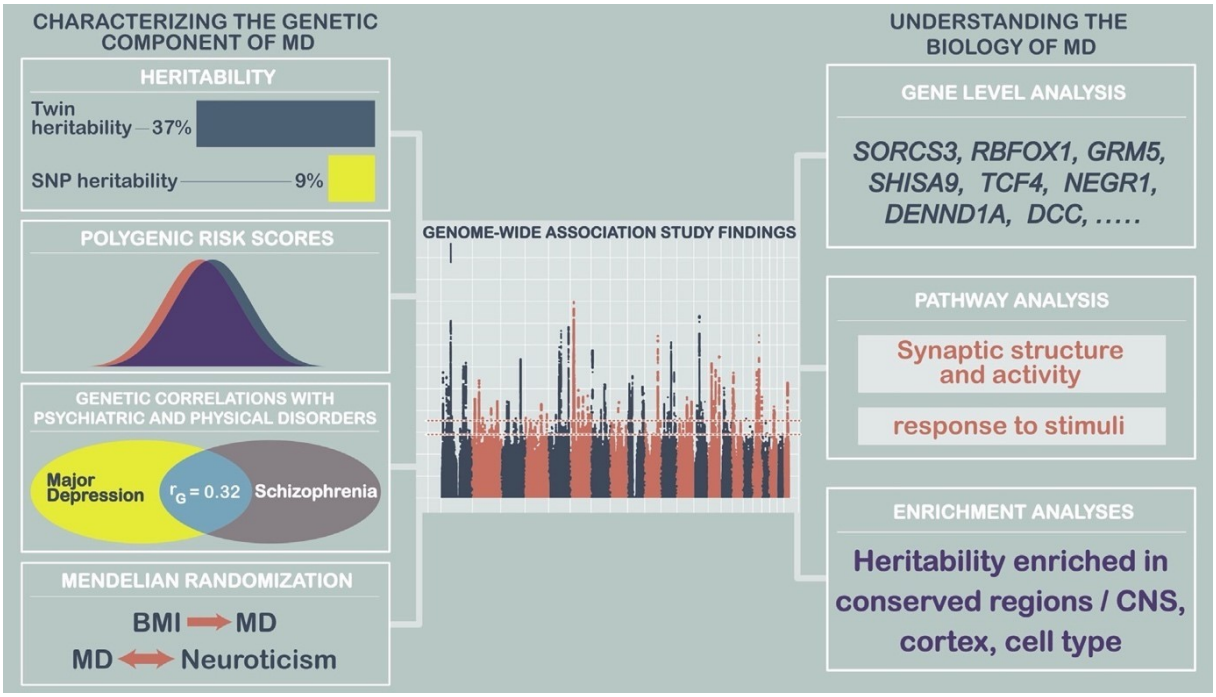


Figure 1.4. Overview of Methods for Genetic Characterization and Biologic Understanding of Major Depression (MD), published in McIntosh, Sullivan & Lewis (2019), *Neuron, 102*(1), 91-103, reprinted with permission from Elsevier.

In the depression GWAS of Howard et al. (2019), these analysis revealed an association of the depression phenotype with genes and gene sets implicated in neurotransmission, stimuli response, and functioning of the central nervous system (Howard et al., 2019). Enrichment analysis in the latest BIP GWAS showed enrichment in gene sets associated with neuronal components and synaptic signaling (Mullins et al., 2021). In addition, enriched gene targets for pharmaceutical agents (i.e., antipsychotic, mood stabilizing and anti-epileptic drugs) were found.
Furthermore, GWAS data can be used to learn more about the architecture of the disorders (see left side of Figure 1.4), including SNP heritability, polygenic risk scores (PRSs), Mendelian Randomization (MR), and estimation of genetic correlations (McIntosh et al., 2019). Genetic correlations across disorders or related phenotypes can be estimated with tools such as LD score regression representing the genetic relatedness of two phenotypes (Bulik-Sullivan et al., 2015a). The correlation scores can range from -1 to 1 (Bulik-Sullivan et al., 2015a). A positive correlation means that people with genetic variants for one trait also tend to have an increased risk for the other trait. On the other hand, a negative correlation means that people with genetic variations for one trait tend to have a lower risk of developing the other trait (Kendall et al., 2021). Compared to formal genetic studies, these methods can be applied in independent groups where not all phenotypes of interest were assessed in the same person (Bulik-Sullivan et al., 2015a). Based on these independent GWAS findings, biological subgroups can be built by quantifying the genetic overlap between disorders with clinical symptoms and associated phenotypes. The following paragraph will focus on relevant genetic correlation findings of mood disorders.

1.2.1 Genetic Overlap of Mood Disorders

Several studies have explored the genetic relationship between psychiatric diagnosis and their overlap with other traits (e.g., Bulik-Sullivan et al., 2015a; The Brainstorm Consortium, 2018; Tylee et al., 2022). In 2019, the PGC Cross Disorder Group GWAS showed a strong genetic correlation between schizophrenia and BIP with a correlation estimate (r_g) of 0.70 (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019). MD showed a moderate genetic correlation with schizophrenia (r_g = 0.34) and BIP (r_g = 0.36), and the highest correlation with Autism Spectrum Disorder (r_g = 0.45). Genetic studies analyzing mood disorder subtypes show that BIP-I and BIP-II are highly correlated (r_g = 0.87) (Coleman et al., 2020a), while BIP-I shares a stronger genetic relationship with schizophrenia (r_g = 0.66), whereas BIP-II a stronger one with MD (r_g = 0.66) (Mullins et al., 2021). Figure 1.5 shows the genetic correlations between eight psychiatric disorders representing the central role of MD.

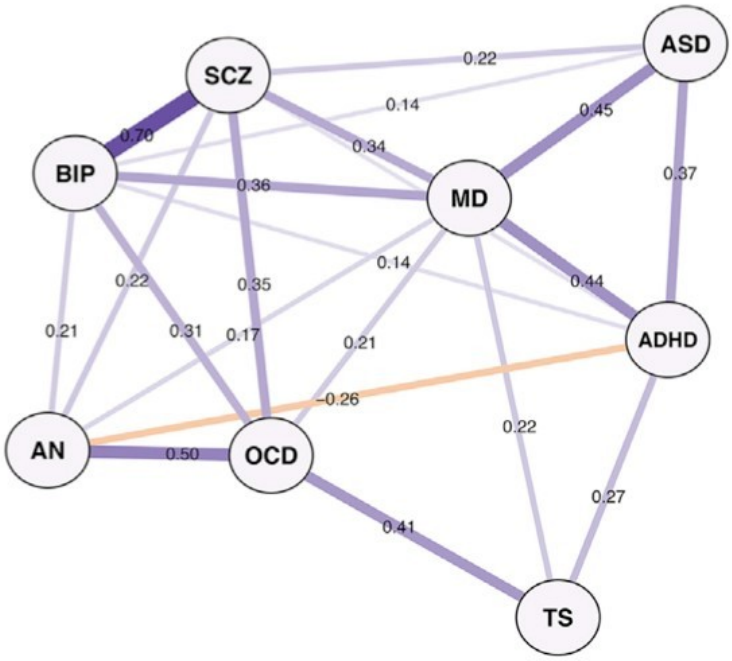


Figure 1.5: Genetic Overlap of Eight Psychiatric Disorders published in Cross-Disorder Group of the Psychiatric Genomics Consortium (2019), *Cell, 179*(7), 1469–1482, reprinted with permission from Elsevier. The links between the disorders are depicted in purple and orange, representing positive and negative correlations. The links' thickness indicates the correlation's strength, with thicker links representing stronger associations. SCZ = Schizophrenia; ASD = Autism Spectrum Disorder; ADHD = Attention-deficit/hyperactivity Disorder; AN = Anorexia Nervosa; OCD = Obsessive-compulsive Disorder; TS = Tourette Syndrome.

Mood disorders are genetically overlapping with other psychiatric disorders, continuous traits, and symptoms of psychiatric disorders: strong genetic overlap has been found between depressive symptoms with neuroticism (r_g = 0.75) and subjective well-being (r_g = -0.81) (Okbay et al., 2016). Weaker genetic correlations have been shown between depression and BIP with objectively measured traits such as sleep duration (depression: r_g = -0.06, BIP: r_g = 0.20) (Dashti et al., 2019) and physical activity (MDD: r_g = -0.1, BIP: r_g = 0.03) (Dennison et al., 2021).

The reported findings, representing only a fraction of the existing literature, provide evidence for the shared polygenic architecture of mood disorders and related traits, contrasting traditional classification systems treating mood disorders as distinct entities. Based on genetic data, especially from well-characterized samples with deep phenotype collection, subgroups of psychiatric disorders could be built to be more reflective of the disorders and enhance our understanding of their underlying etiology.

1.3 Epigenetics

The term epigenetic refers to changes in gene expression or cell phenotypes that occur without changes in the underlying DNA sequence (Rakyan et al., 2011). Epigenetic markers across the whole genome exist, which can be stable but can change through influences of the environment (Rakyan et al., 2011). This adds another layer of information when investigating mood disorders' biological roots compared to genetic data with epigenetic data, changes in epigenetic markers can be observed over time. Among others (i.e., DNA hydroxymethylation, histone modifications), one known mechanism of epigenetic modification is DNA methylation (DNAm), where a methyl group is added to a cytosine base usually in the context of Cytosine-phosphate-Guanine sites (CpGs) (Rakyan et al., 2011). CpG islands are DNA regions enriched for CpGs and are typically found near gene promoter regions (Rakyan et al., 2011). Methylated CpG islands in promoter regions may affect gene expression by suppression of the binding of transcription factors and proteins necessary for gene expression (Singer, 2019), see also Figure 1.6.

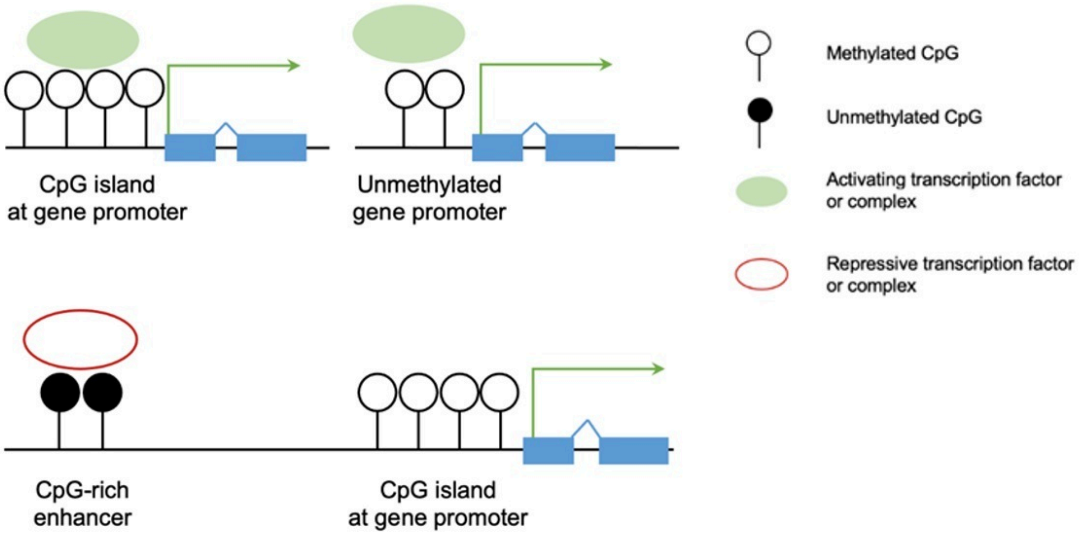
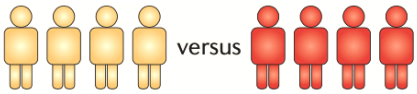
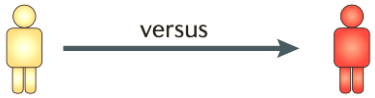


Figure 1.6. CpG Residues and Islands in Enhancer Elements and Dynamic Changes in CpG Methylation. This overview is reprinted and adapted with permission of the American Thoracic Society. Copyright © 2023 American Thoracic Society. All rights reserved. Singer (2009), A Practical Guide to the Measurement and Analysis of DNA Methylation, *Am J Respir Cell Mol Biol, 61*(4), 417–428. The figure was adapted only showing the right side of the original figure.

Similar to genetic data, for the quantification of DNAm array-based technologies (i.e., BeadChips) are frequently used as sequencing is more resource-intensive (Wei et al., 2021). These chips cover CpG sites in different regulatory regions, the Illumina EPIC

BeadChip v1.0 contains ~850,000 CpG sites (Moran et al., 2016), the recently released later version, the Illumina EPIC BeadChip v2.0 more than 935,000 CpG sites (Illumina, Inc., San Diego, CA, USA) of the approximately 28 million that exist in the human genome (Lövkvist et al., 2016). The resulting data are signals of light intensity; values of this intensity can range from 0 (complete lack of methylation) to 1 (complete methylation) (Du et al., 2010).
There are different ways to profile epigenetic variation; similar to GWAS, epigenome-wide association studies (EWASs) are conducted for binary and non-binary phenotypes, but as DNAm is not stable over time, longitudinal EWAS (e.g., before and after treatment) can be conducted (Rakyan et al., 2011). Table 1.2 presents commonly used study designs in which epigenetic variation can be observed.

Table 1.2. Different Study Designs of EWASs reprinted and adapted with permission from Springer Nature: Nature Reviews Genetics: Raykan et al. (2011). The figure was adapted and only represents study designs relevant for this work.

	Key advantages	Key disadvantages
Case versus control (singletons) 	Many cohorts exist	Cannot easily control for environmental and genetic confounders
Prospectively sampled, longitudinal 	Can establish causality	Slow and difficult to establish

In an EWAS, CpG sites are tested instead of SNPs using logistic and linear regression models to assess the association between DNAm and the phenotype of interest (Wei et al., 2021). DNAm depends on cell-type and tissue (Lokk et al., 2014) and is significantly influenced by age (Horvath, 2013) and smoking (Zeilinger et al., 2013). These factors must be taken into account when conducting an EWAS.
Same as for GWAS summary statistics, the generated data from conducting an EWAS can be used to calculate methylation risk scores (MRSs), analyze differentially methylated regions (DMRs), and pathways to enhance our understanding of the underlying biology of the disorders (Campagna et al., 2021). In recent years, the number of downstream analysis tools such as methylation quantitative trait loci analysis, and methylation age acceleration has grown (not in detail discussed in this work, for a review, see Campagna et al., 2021).

1.3.1 Epigenome-wide Association Studies in Mood Disorders and Treatment Response

As epigenetic changes can modulate the interaction between genes and environment, epigenetic research in psychiatric disorders is steadily increasing (Wei et al., 2021). In 2022, a meta-analysis was published using EWAS data including peripheral blood samples from individuals with (N = 298) and without MDD (N = 63). The differentially methylated CpGs and DMRs associated with MDD were related to immunological and

signaling pathways reported earlier in studies of depression (Li et al., 2022). Another EWAS in a population-based cohort of N = 7,948 individuals identified 3 differential methylated sites associated with depressive symptoms (Story Jovanova et al., 2018). In an epigenetic prediction study, the authors used MRS for MDD to distinguish MDD cases from healthy controls. Also, the MRS for MDD was associated with prevalent and incident MDD (Barbu et al., 2021). In addition, pathway analysis revealed that CpGs from the MRSs were enriched for genes involved in neurogenesis and neurodevelopment processes (Barbu et al., 2021). In BIP, epigenetic studies have been conducted in a number of different genes (e.g., *BDNF*, *SLC6A4*, *KCNQ3*) and associations between BD-related characteristics (e.g., psychosis, lithium response) with epigenetic markers have been reported (for a review, see Ludwig & Dwivedi, 2016). Also a few epigenome-wide studies in BIP exist (e.g., Hesam-Shariati et al., 2022; Li et al., 2015). Several studies investigated the epigenetics of treatment response, chiefly in antidepressants (for reviews, see Lisoway et al., 2018; Martinez-Pinteno et al., 2021; Webb et al., 2020), some in other treatments such as ECT (Moschny et al., 2020; Neyazi et al., 2018). One recent EWAS on the use of antidepressants assessed via self-report was conducted in the Generation Scotland (N = 6428) and the Netherlands Twin Register (N = 2449) cohort. In the Generation Scotland cohort 10 differentially methylated sites were found for antidepressant use, located particularly in genes associated with mental disorders and inborn immunity (Barbu et al., 2022).
So far, several epigenetic studies have been conducted, especially in depression phenotypes linking to relevant immunological and neurological pathways. However, most studies on mood disorders and antidepressant response have not been conducted longitudinally and rely on heterogeneous patient groups. The discovery of changes in epigenetic variation over time in homogenous samples is essential to understand the contribution of epigenetic markers to the pathophysiology of mood disorders and their response to treatment.

1.4 Aims

The following two studies investigate whether genetic and epigenetic data serve as biological markers to characterize mood disorders and response to therapy. The biological meaning of the discovered markers is further explored.

2 STUDY 1: DEPRESSION AND BIPOLAR DISORDER SUBTYPES DIFFER IN THEIR GENETIC CORRELATIONS WITH BIOLOGICAL RHYTHMS[1]

2.1 Abstract

Major Depression and Bipolar Disorder Type I (BIP-I) and Type II (BIP-II), are characterized by depressed, manic, and hypomanic episodes in which specific changes of physical activity, circadian rhythm, and sleep are observed. It is known that genetic factors contribute to variation in mood disorders and biological rhythms, but unclear to what extent there is an overlap between their underlying genetics. In the present study, data from genome-wide association studies were used to examine the genetic relationship between mood disorders and biological rhythms. We tested the genetic correlation of depression, BIP-I, and BIP-II with physical activity (overall physical activity, moderate activity, sedentary behaviour), circadian rhythm (relative amplitude), and sleep features (sleep duration, daytime sleepiness). Genetic correlations of depression, BIP-I, and BIP-II with biological rhythms were compared to discover commonalities and differences. A gene-based analysis tested for associations of single genes and common circadian genes with mood disorders. Depression was negatively correlated with overall physical activity and positively with sedentary behaviour, while BIP-I showed associations in the opposite direction. Depression and BIP-II had negative correlations with relative amplitude. All mood disorders were positively correlated with daytime sleepiness. Overall, we observed both genetic commonalities and differences across mood disorders in their relationships with biological rhythms: depression and BIP-I differed the most, while BIP-II was in an intermediate position. Gene-based analysis suggested potential targets for further investigation. The present results suggest shared genetic underpinnings for the clinically observed associations between mood disorders and biological rhythms. Research considering possible joint mechanisms may offer avenues for improving disease detection and treatment.

1 Published as: Sirignano, L., Streit, F., Frank, J., Zillich, L., Witt, S. H., Rietschel, M., & Foo, J. C. (2022). Depression and bipolar disorder subtypes differ in their genetic correlations with biological rhythms. *Scientific reports*, *12*(1), 15740. https://doi.org/10.1038/s41598-022-19720-5

2.2 Introduction

Major Depression (MD) and Bipolar disorder (BIP) are common (lifetime prevalence MD: 20.6%, BIP-I: 0.6%, and BIP-II: 0.4%), often chronic disorders that can cause harm to those affected and the people close to them (Hasin et al., 2018; Merikangas et al., 2011). MD is characterized by depressive episodes, while BIP is characterized by manic (BIP-I) or hypomanic (BIP-II) episodes, generally alternating with depressive episodes (APA, 2013). Changes in physical activity, circadian rhythm, and sleep, hereafter referred to collectively as "biological rhythms", are often observed in mood disorders. Biological rhythms is a term used to summarize a series of body functions determined by the internal circadian clock (e.g., activity, sleep, body temperature, etc.) (Salvatore et al., 2012). Different patterns of biological rhythms are generally observed during different mood episodes (depressed, manic, hypomanic). The cardinal symptoms of a depressive episode are a persistent feeling of sadness and/or loss of interest in almost all activities. Further symptoms include feelings of worthlessness or guilt, suicidality, poor concentration, loss of weight, tiredness and loss of energy, disturbances of sleep, and psychomotor alterations. Manic episodes and hypomanic episodes (which are less intense) are characterized by an ongoing inappropriate elevated or irritable mood. Further symptoms include an excessive sense of self-worth or grandiosity, being more talkative and more easily distracted, reduced need for sleep, and markedly increased energy and activity levels and/or psychomotor agitation (APA, 2013). There is an increasing number of studies investigating such alterations of biological rhythms in mood disorders with objective assessments. Actigraphy studies observe lower activity levels in individuals with MD compared to healthy controls (Minaeva et al., 2020; Schuch et al., 2017). The same is found for individuals with BIP (De Crescenzo et al., 2017; Janney et al., 2014). When comparing the different mood states (depressed, manic, hypomanic) within BIP, significantly higher levels of activity during manic and hypomanic phases are observed than in depressed phases (Faurholt-Jepsen et al., 2016; Scott et al., 2017). However, actigraphy studies evaluate not only overall physical activity levels but investigate various other types of activity such as 'sedentary behaviour' or 'moderate activity' (for details, see Materials and Methods) (Doherty et al., 2017). Circadian mechanisms govern many biological processes and their importance is being increasingly recognized in the etiology, diagnosis, and treatment of mood disorders (Walker et al., 2020). A parameter commonly used as a proxy for circadian rhythms of body movement is relative amplitude; it is often used in actigraphy studies, where based on movement acceleration data, the average activity for the least active continuous 5 h of a day is subtracted from the average for the most active continuous 10 h; this is divided by their sum (Lyall et al., 2018). High relative amplitude values are often observed in healthy individuals reporting to be more active during the day and less active during the night, while patients with mood disorders usually describe the opposite pattern, reflected in low relative amplitude values (Carpenter et al., 2021; Murray et al., 2020). Relative amplitude is a rest-activity parameter which can be used to describe the circadian rhythm/ disruption of activity, but does not represent the circadian rhythms of different physiological body functions. Lower relative amplitudes are found in both depression and BIP compared to healthy individuals (Difrancesco et al., 2019; Lyall et al., 2018). Sleep is a recurring biological process holding many functions of great importance for the human body (e.g., restoration and memory functioning) (Watson et al., 2015). Sleep problems, insufficient sleep, irregularity of sleep–wake cycles, and differences in sleep duration, are well described in MD and BIP (Gold & Sylvia, 2016; Murphy & Peterson, 2015), as is daytime sleepiness, which is also reported to be increased in

patients suffering from MD and BIP (Chellappa et al., 2009; Walz et al., 2013). Both mood disorders and biological rhythms have a genetic basis with heritability estimates for MD at 40% and BIP at 80%; for biological rhythms, those estimates are heterogeneous, ranging from small (< 30%) to high (78%) for physical activity, from 40 to 54% for chronotype, and 31–49% for normal sleep due to factors such as variation in age and study design (Bauman et al., 2012; Coleman et al., 2020a; Yamazaki & Goel, 2020). It is uncertain whether changes in biological rhythms typically observed are a mere consequence of a given mood episode (e.g., a patient who is depressed and has lost interest would move less, showing decreased activity) or due to common etiology. This raises the question of whether genes increasing the liability for MD, BIP-I, and BIP-II overlap with genes predisposing individuals to altered biological rhythms and if so, whether this overlap differs between the different mood disorder subtypes. The few formal genetic studies which have addressed these questions so far suggest a possible shared etiology. Twin studies observed negative genetic correlations of depressive symptoms with physical activity (n = 5952 twins, n = 756 twins) (De Moor et al., 2008; Johnson et al., 2020) as well as with sleep duration (n = 894 twins) (Watson et al., 2014). In a family study of 26 high-density bipolar families, analyses of actigraphy data revealed 13 trait-like associations with BIP-I, demonstrating lower activity levels than in their non-BIP-I relatives (Pagani et al., 2016). Genetic associations between mood disorders and circadian rhythms have largely been studied in circadian related clock genes (e.g., *ARNTL*, *CLOCK*, *CRY*, *PER*, etc.) (Bunney et al., 2015; McClung, 2007), given the many aspects of physiological processes under the control of the central circadian clock (for reviews, see Rijo-Ferreira & Takahashi, 2019; Takahashi, 2017; Zhang et al., 2014). Advances in molecular methods now offer the possibility to investigate such associations not only on a single-variant level but also on the gene- and genome-wide level. Increases in sample size, power, and number of genome-wide association studies (GWASs) of many disorders and traits have enabled *in silico* testing for genetic overlap of various phenotypes on a large scale (Uffelmann et al., 2021). In previous studies using such GWAS data to examine the overlap between mood disorders and altered biological rhythms, positive associations have been observed between depressive symptoms and daytime sleepiness (Wang et al., 2019) and negative correlations between MD and physical activity (Dennison et al., 2021). In contrast, for BIP (subtypes unspecified), positive associations have been found with physical activity, but none with daytime sleepiness (Dennison et al., 2021; Wang et al., 2019). The present study aims to explore whether depression, BIP-I, and BIP-II share an overall genetic etiology with biological rhythms using summary statistics from the most current respective GWASs (Doherty et al., 2018; Ferguson et al., 2018; Howard et al., 2019; Mullins et al., 2021; Wang et al., 2019) independent of the current mood state. Differences in genetic correlations of depression, BIP-I, and BIP-II with biological rhythms are examined to identify commonalities as well as differences between the disorders and their relationship with biological rhythms. To gain deeper insight, associations of mood disorders and biological rhythms with single genes, particularly with known circadian genes, and the overlap of genes between mood disorders and biological rhythms, are explored.

2.3 Materials and Methods

2.3.1 GWAS Samples

Table 2.1 gives an overview of the GWAS summary statistics and cohorts used in this analysis. Summary statistics comprise aggregate p-values and association data for every single nucleotide polymorphism (SNP) analysed in a GWAS (Uffelmann et al., 2021). For depression, the latest publicly available summary statistics were used as described in (Howard et al., 2019), the meta-analysis comprised 33 cohorts (excluding 23andme cohort), resulting in summary statistics of 170,756 depression cases and 329,443 controls. Summary statistics for BIP-I and BIP-II were derived from the latest Psychiatric Genomics Consortium GWAS on BIP consisting of 57 cohorts with a total number of 41,917 BIP cases and 371,549 controls, including 25,060 BIP-I, 6,781 BIP-II cases (Mullins et al., 2021). Biological rhythms summary data were obtained from studies carried out in the UK Biobank (UKB) cohort. The UKB is a national cohort consisting of over 500,000 participants (40–69 years old) with genetic and deep phenotype data (Sudlow et al., 2015). Biological rhythms were assessed in a subset of the UKB cohort including 103,720 individuals who wore accelerometers for 7 days. Based on this accelerometer data the UKB accelerometer expert working group extracted or classified several physical activity parameters: overall physical activity (measuring the mean activity over the whole assessment), moderate activity (activities requiring higher levels of energy such as exercising), sedentary behaviour (activities requiring low energy consumption like sitting or lying), relative amplitude (for circadian rhythm), and sleep duration (the time spent in behaviour classified as sleep) (Doherty et al., 2017). Daytime sleepiness was assessed subjectively in the whole UKB sample with a self-reported question, asking participants if they were likely to doze off or fall asleep during the day unintentionally (rating on a 4-point scale) (Wang et al., 2019). The current analysis used summary data from GWASs based on these biological rhythm parameters were made available by the UKB. All original studies and used datasets are included in the Data Availability section, where detailed information on cohorts and datasets can be found.

Table 2.1. Overview of GWAS Summary Statistics Analyzed.

Phenotype	**Reference**	**Sample**
Depression	Howard et al. (2019)	170,756 Depression cases (excluding 23andMe)
BIP-I BIP-II	Mullins et al. (2021)	25,060 BIP-I cases and 6,781 BIP-II cases
Overall Physical Activity Moderate Activity Sedentary Behaviour Sleep Duration	Doherty et al. (2018)	91,105 participants UK Biobank cohort
Relative Amplitude	Ferguson et al. (2018)	71,500 participants UK Biobank cohort

Daytime Sleepiness	Wang et al. (2019)	452,071 participants UK Biobank cohort

2.3.2 Analysis

2.3.2.1 Genetic Correlation Analysis

Genetic correlations of depression, BIP-I, and BIP-II, with overall physical activity, moderate activity, sedentary behaviour, sleep duration, relative amplitude, and daytime sleepiness were calculated using the bivariate genetic correlation method in Linkage Disequilibrium Score Regression (LDSC) software (https://github.com/bulik/ldsc). LDSC is a regression-based analysis tool that can estimate the genetic correlation between two traits using GWAS summary statistics (Bulik-Sullivan et al., 2015b). We used the Linkage Disequilibrium (LD) Scores of the 1,000 Genomes Project for use with European samples. Default settings were applied for the filtering process: information metric (INFO score) > 0.9, indicating high quality of imputation, Minor Allele Frequency (MAF) > 0.01, and removing out of bounds summary statistic p-values. Indels, ambiguous, duplicated SNPs, and SNPs having no match in the LD Score reference panel were removed. SNP heritability analyses using LDSC revealed a Z-score of > 4 for all used GWAS summary statistics (see Tables 2.S1.1–2.S1.3) indicating good interpretability and power for genetic correlation analyses, as recommended by the authors of LDSC (Zheng et al., 2017). For each mood disorder (depression, BIP-I, and BIP-II) genetic correlations with the six biological rhythm traits were estimated for which Bonferroni correction ($p < 0.05/6 = 0.0083$) was applied.

2.3.2.2 Analysis of Differences in Correlations

To compare the above calculated correlations between depression, BIP-I, and BIP-II, we employed the block jackknife extension of LDSC (Bulik-Sullivan et al., 2015b), as previously described in (Hübel et al., 2019). A z-test was conducted using the LDSC extension computing a z-value (z), standard error (SE), and p-value for each comparison. The following comparisons were analysed: depression vs. BIP-I, depression vs. BIP-II, and BIP-I versus BIP-II in their correlations with biological rhythm traits. For each comparison, six tests were conducted and Bonferroni correction ($p < 0.05/6 = 0.0083$) for the number of biological rhythm traits was applied.

2.3.2.3 Gene Association Analysis and Targeted Examination of Circadian Genes

A genome-wide gene-based analysis for mood disorders and biological rhythms was conducted using the Multi-marker Analysis of GenoMic Annotation (MAGMA) (de Leeuw et al., 2015). MAGMA is a computational tool that allows gene-based and geneset analysis of GWAS data and is widely used to detect genes and pathways associated with phenotypes and diseases. The gene-based analysis is based on a multiple regression model, using data of all single variants annotated to a gene, deriving one p-value per gene to determine if the genetic variation in this gene is associated with the phenotype (for further details see de Leeuw et al., 2015). Default settings were used. Lists of genes were reduced to the number of genes available in all mood disorders and biological rhythms summary statistics (n = 17,861 genes). Bonferroni correction was applied for all tested genes ($p < 0.05/17{,}861 = 2.80 \times 10^{-6}$) to determine genes significantly associated with mood disorders and biological rhythms. The overlap of genes associated with each of the mood disorders and

biological rhythms was then examined based on filtered gene sets with a suggestive threshold of $p < 1 \times 10^{-5}$. Next, utilizing MAGMA results, we took a targeted look at associations of mood disorders with common circadian genes (*ARNTL*, *CLOCK*, *CRY1*, *CRY2*, *DBP*, *NPAS2*, *NR1D1*, *NR1D2*, *PER1*, *PER2*, *PER3*, *RORA*, *RORB*, *RORC*) (Takahasi, 2017) applying a Bonferroni corrected significance threshold, correcting for the number of tested circadian genes ($p < 0.05/14 = 0.004$).

2.4 Results

Genetic correlations of depression, BIP-I, and BIP-II with biological rhythm traits and the differences between the mood disorders in their correlations are presented in Figure 2.1. Bonferroni corrected p-values are indicated in Figure 2.1 and reported in Tables 2.S1.1–2.S2.3. Bonferroni corrected p-values from the gene-based analysis of all 17,861 tested genes and common circadian genes are shown in Supplementary Tables 2.S3.1–2.S4.9.

2.4.1 Genetic Correlations of Depression with Biological Rhythms

Significant negative correlations of depression with overall physical activity ($r_g = -0.11$, $p = 0.0001$), moderate activity ($r_g = -0.09$, $p = 0.04$) and with relative amplitude ($r_g = -0.30$, $p = 4.40 \times 10^{-12}$) were found. A significant positive correlation of depression with daytime sleepiness ($r_g = 0.17$, $p = 3.17 \times 10^{-11}$) was observed. Depression was not significantly correlated with sedentary behaviour ($r_g = 0.03$, $p = 0.40$), and sleep duration ($r_g = 0.05$, $p = 0.11$) (see Table 2.S1.1).

2.4.2 Genetic Correlations of BIP-I with Biological Rhythms

BIP-I was positively correlated with overall physical activity ($r_g = 0.07$, $p = 0.02$), moderate activity ($r_g = 0.23$, $p = 4.98 \times 10^{-6}$), and daytime sleepiness ($r_g = 0.11$, $p = 0.0002$) and negatively correlated with sedentary behaviour ($r_g = -0.11$, $p = 0.003$). BIP-I was not significantly correlated with sleep duration ($r_g = -0.03$, $p = 0.39$) and relative amplitude ($r_g = -0.05$, $p = 0.31$) (see Table 2.S1.2).

2.4.3 Genetic Correlations of BIP-II with Biological Rhythms

BIP-II was positively correlated with moderate activity ($r_g = 0.19$, $p = 0.04$) and daytime sleepiness ($r_g = 0.22$, $p = 2.36 \times 10^{-5}$), and negatively correlated with relative amplitude ($r_g = -0.23$, $p = 0.006$). BIP-II was not significantly correlated with overall physical activity ($r_g = -0.03$, $p = 0.62$), sedentary behaviour ($r_g = -0.03$, $p = 0.61$), and sleep duration ($r_g = 0.02$, $p = 0.77$) (seeTable 2.S1.3).

2.4.4 Differences between Correlations

Depression and BIP-I differed significantly in their correlations with overall physical activity ($z = -4.33$, $p = 1.50 \times 10^{-5}$), moderate activity ($z = -4.80$, $p = 1.57 \times 10^{-6}$), sedentary behaviour ($z = 2.95$, $p = 0.003$), and relative amplitude ($z = -4.15$, $p = 3.36 \times 10^{-5}$). Depression and BIP-I did not differ significantly in their correlations with sleep duration and daytime sleepiness (see Table 2.S2.1). Depression and BIP-II differed significantly in their genetic correlations with moderate activity ($z = -2.70$, $p = 0.007$). The correlations of depression and BIP-II with overall physical activity, sedentary

behaviour, sleep duration, relative amplitude, and daytime sleepiness did not differ significantly (see Table 2.S2.2). BIP-I and BIP-II differed significantly in their correlation with relative amplitude (z = 2.17, p = 0.03) and daytime sleepiness (z = − 2.31, p = 0.02). Comparing correlations of BIP-I and BIP-II with respect to overall physical activity, moderate activity, sedentary behaviour, sleep duration yielded no significant differences (see Table 2.S2.3).

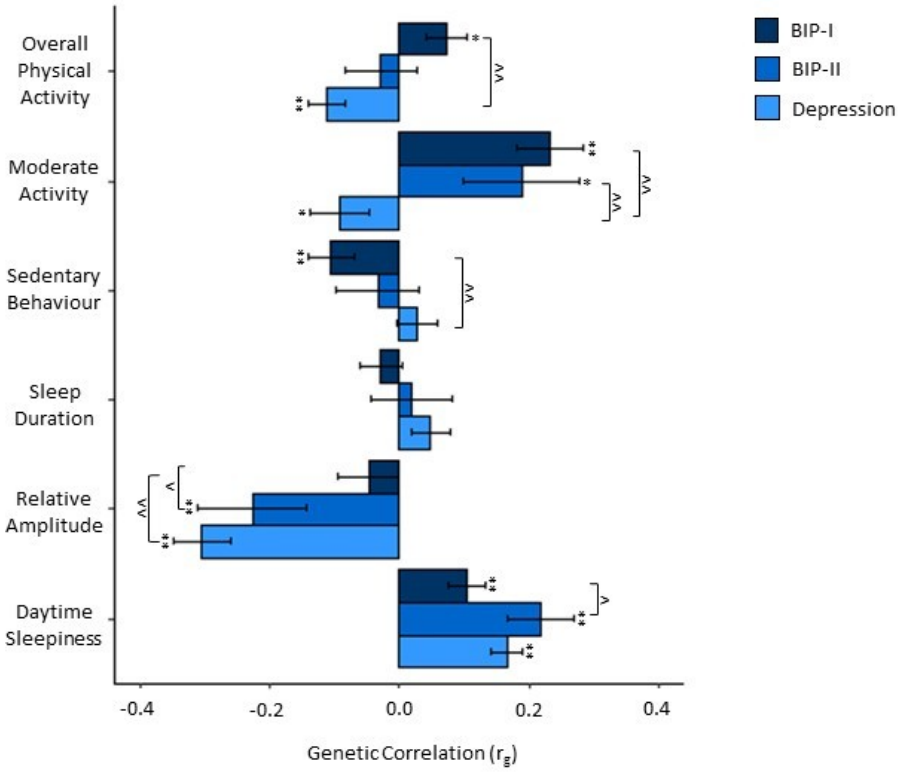


Figure 2.1. Genetic Correlations of Depression, BIP-I, BIP-II with Biological Rhythms. r_g = genetic correlation coefficient; error bars indicate standard error limits of r_g; ** $p_{adj} < 0.05$, * $p < 0.05$; for comparison of correlations: ^^ $p_{adj} < 0.05$, ^ $p < 0.05$.

2.4.5 Gene Association Analysis and Examination of Circadian Genes.

100 genes were significantly ($p_{adj} < 0.05$) associated with depression; the top-ranked were *HIST1H2BN*, *HIST1H3J*, and *SORCS3* (see Table 2.S3.1). BIP-I was significantly associated with 122 genes, the top-ranked were *CACNA1C*, *MAD1L1*, and *PLEC* (see Table 2.S3.2). SLIT3 was the only gene significantly associated with BIP-II (see Table 2.S3.3). The overlap of genes associated with mood disorders and biological rhythms ($p < 1 \times 10^{-5}$) is presented in Fig. 2.2. Depression showed an overlap with sedentary behaviour in the gene *MEF2C* ($Z_{dep} = 4.53$, $p_{dep} = 2.95 \times 10^{-6}$; $Z_{sb} = 4.43$, $p_{sb} = 4.77 \times 10^{-6}$, with relative amplitude in *CCDC36* ($Z_{dep} = 4.30$, $p_{dep} = 8.66 \times 10^{-6}$; $Z_{ra} = 4.41$, $p_{ra} = 5.28 \times 10^{-6}$), and with daytime sleepiness in *ERBB4* ($Z_{dep} = 6.97$, $p_{dep} = 1.63 \times 10^{-12}$; $Z_{ds} = 4.39$, $p_{ds} = 5.80 \times 10^{-6}$). BIP-I showed an overlap with sleep duration in *MSRA* ($Z_{bip\text{-}I} = 5.69$, $p_{bip\text{-}I} = 6.26 \times 10^{-9}$; $Z_{sd} = 5.12$, $p_{sd} = 1.53 \times 10^{-7}$) and daytime sleepiness in *CADM2* ($Z_{bip\text{-}I} = 5.00$, $p_{bip\text{-}I} = 2.93 \times 10^{-7}$; $Z_{ds} = 5.90$, $p_{ds} = 1.83 \times 10^{-9}$). BIP-II associated genes did not overlap with biological rhythms genes at

the p-value threshold of $p < 1 \times 10^{-5}$. In the targeted examination of circadian genes, significant associations ($p_{adj} < 0.05$) of depression with *NR1D1* (Z = 4.23, p = 1.16 × 10^{-5}) and *PER1* (Z = 2.94, p = 0.002) were observed. BIP-I was associated with *ARNTL* (Z = 3.35, p = 0.0004), *CRY2* (Z = 3.15, p = 0.0008), and *RORB* (Z = 3.05, p = 0.001). BIP-II showed no significant association with any circadian gene. All circadian genes associated with mood disorders are presented in Supplementary Tables 2.S4.1–2.S4.3.

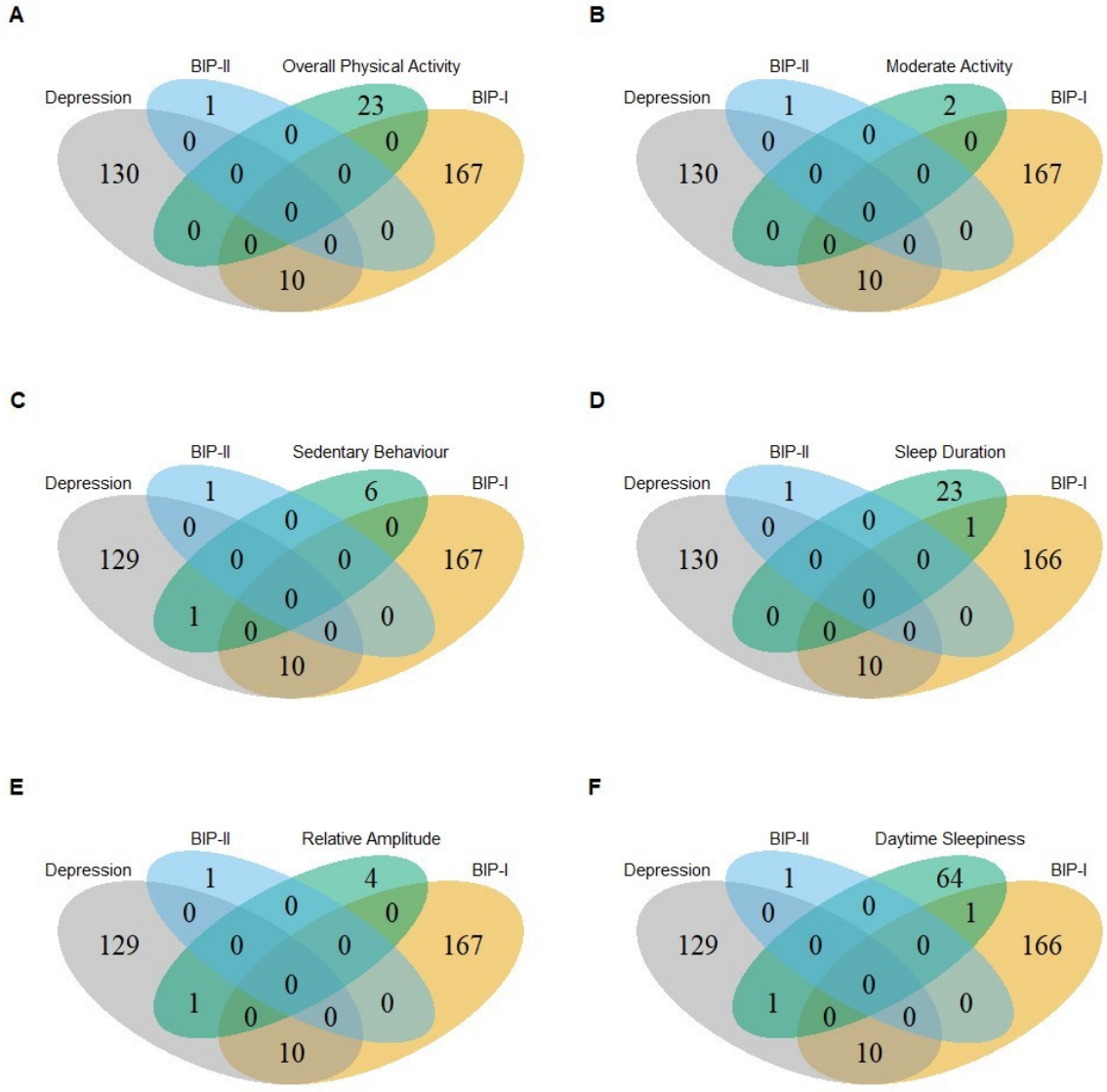


Figure 2.2. Venn Diagrams Showing Overlap of Genes Associated of Depression, BIP-I, BIP-II, with Biological Rhythms: A.) Overall Physical Activity, B.) Moderate Activity, C.) Sedentary Behaviour, D.) Sleep Duration, E.) Relative Amplitude, F.) Daytime Sleepiness. Gene-based associations were determined using MAGMA, and 17,861 genes available in all GWASs were tested. For the presented overlap, association was assigned based on a suggestive threshold $p < 1 \times 10^{-5}$.

2.5 Discussion

In the present study, we used data from independent GWASs of mood disorders and biological rhythms and demonstrate that they have common genetic roots. Our results show that depression, BIP-I, BIP-II have commonalities but also distinct differences in their genetic correlations with biological rhythms. Notably, our study is the first to differentiate between the BIP subtypes BIP-I and BIP-II, revealing specific patterns of the two subtypes with biological rhythms. Our gene-level analysis shows that depression and BIP-I share genes with biological rhythms and that both mood disorders are associated with known circadian genes. Epidemiological and clinical studies have repeatedly reported an inverse relation between higher levels of activity and depression (Burton et al., 2013; Choi et al., 2019). Our findings now show that this inverse relationship has -at least partially- a common genetic basis. Our finding of a negative genetic correlation between increased physical activity (moderate activity) and depression is in line with the results from a recent twin study showing a genetic relationship between decreased depression and increased activity (Johnson et al., 2020), and also confirms an earlier study using GWAS data which reported negative genetic correlations of MD with overall physical activity as well as walking (Dennison et al., 2021). BIP-I and BIP-II were positively genetically correlated with moderate activity and negatively with sedentary behaviour, implying that both BIP-I and BIP-II share genetic properties with increased physical activity. Our findings agree with previous findings showing a positive genetic correlation of BIP with moderate activity and walking (Dennison et al., 2021) based on an earlier BIP GWAS (Stahl et al., 2019). Placing the present findings in context, it should be noted that earlier works are based on BIP GWAS aggregating all subtypes in wherein the large majority of the patients were diagnosed with BIP-I (Stahl et al., 2019); the present analysis uses a larger dataset and separately examines BIP-II. Actigraphy studies suggest positive associations between physical activity and BIP during manic and hypomanic phases (Faurholt-Jepsen et al., 2016; Scott et al., 2017); our results indicate that those relationships are partially due to shared genetic factors and not solely a result of the mood state in which they are observed. Interestingly, our investigation of relative amplitude found negative genetic correlations with both depression and BIP-II, but not with BIP-I, which is a reflection of findings at the phenotypic level (Carpenter et al., 2021; Difrancesco et al., 2019; Lyall et al., 2018; Murray et al., 2020). We note that the strongest and most statistically significant correlation in the present analysis was between depression and relative amplitude, suggesting this relationship as a target for further investigation and characterization. Physiological and molecular studies suggest that disruption of the molecular clock is strongly involved in mood symptoms observed in MD and BIP (Bunney et al., 2015; Melo et al., 2017; Shou et al., 2017); the present findings appear to suggest a connection on a wider genomic level. One study recently took such an approach using genome-wide data to investigate these relationships with polygenic risk scores (PRS) (Ferguson et al., 2018). A PRS is a single score capturing the sum of an individual's risk alleles weighted by GWAS summary statistics to quantify the genetic predisposition of an individual for a certain phenotype (Uffelmann et al., 2021). This study found that participants with an increased PRS for a disrupted circadian rhythm showed in turn an increased PRS for MD (Ferguson et al., 2018). It should be noted that the measure relative amplitude, on which the summary statistics were based, is a composite index representing the difference between most and least active hours of the day and does not fully describe rest-activity cycles. More comprehensive measures will be needed to better investigate the links between circadian rhythmicity and mood disorders. Symptoms such as insufficient sleep

duration and frequent awakenings are often reported in mood disorders (Byrne et al., 2019). Genetic studies report a high genetic overlap of sleep-related phenotypes (e.g., insomnia, chronotype, sleep duration) with MD and BIP (Jansen et al., 2019; Jones et al., 2019a). An earlier GWAS using self-report measures of sleep duration reported a significant genetic correlation with BIP, but not with depressive symptoms (Dashti et al., 2019); in the present study, significant genetic correlations of objectively measured sleep duration were not observed with MD or either BIP subtypes. This may be due to the difference in assessment methodology but may also be clarified when larger samples of objectively measured sleep duration become available. Here, we observed that depression, BIP-I, and BIP-II are significantly positively correlated with daytime sleepiness. With respect to MD, this confirms findings of an earlier study that found a genetic correlation between daytime sleepiness and depressive symptoms (Wang et al., 2019). The same study examined BIP as well in a smaller sample but did not look at the subtypes separately (Wang et al., 2019); the increased sample size and power in the present study enabled detection of significant correlations of daytime sleepiness in BIP-I and BIP-II, which is a novel finding. When we compared the genetic correlations between mood disorders, the most prominent differences were found between depression and BIP-I, which showed genetic correlations with opposite directions for all objectively assessed traits besides relative amplitude, although in the same direction, correlation strength differed significantly. These differences may be causally linked to the clinical symptoms observed during the depressive episodes in MD (generally low activity) and during manic episodes (high activity) in BIP-I. BIP-II showed an intermediate correlational pattern, with the only significant differences in relative amplitude and daytime sleepiness being with BIP-I and a significant difference in moderate activity to depression. Notably, depression and BIP-II showed a closer resemblance in sleep duration, relative amplitude, and daytime sleepiness than BIP-I and BIP-II, which suggests a stronger link between genetics of depressed features with these phenotypes. At the same time, BIP-I and BIP-II are more similar to each other when compared to depression with respect to increased activity phenotypes. It is of interest that the strongest similarities between the mood disorders were observed in daytime sleepiness, suggesting that it shares common genetic etiology with all mood disorder types. In summary, the discovered similarities and differences appear to be clues to delineating these mood disorders with respect to each other. The gene-based analysis revealed several genome-wide significant genes associated with depression (topranked: *HIST1H2BN*, *HIST1H3J*, *SORCS3*) and BIP-I (top-ranked: *CACNA1C*, *MAD1L1*, *PLEC*); and BIP-II was significantly associated with *SLIT3*. These genes have been reported previously for the respective GWAS (Howard et al., 2019; Mullins et al., 2021). Analysis of overlapping genes suggests potential pleiotropic targets for the investigation of mood disorders and biological rhythms. Depression and sedentary behaviour showed an overlap in *MEF2C*, a protein-coding gene involved in processes such as cell differentiation and neurogenesis; studies implicate *MEF2C* in neuropsychiatric disorders (e.g., schizophrenia and autism) (Zhang & Zhao, 2022) and it is also involved in muscle activity and exercise (Wu et al., 2001). *CCDC36*, the gene overlapping between depression and relative amplitude, is important for meiosis and other cellular processes; it has been reported to contribute to both MD and attention deficit and hyperactivity disorder (Powell et al., 2021). The overlapping gene between depression and daytime sleepiness was *ERBB4*, part of the Tyr protein kinase family, was found to be associated with schizophrenia endophenotypes (Greenwood et al., 2019). Also, a study investigating sleep regulation via the *EGFR* signalling pathway found genetic variants in *ERBB4* to be associated with excessive daytime sleepiness (Lee et al., 2019). BIP-I and sleep duration were both associated with *MSRA*, which is

engaged in protein repair processes; *MSRA* was associated with nine psychiatric disorders in a study investigating pleiotropic effects (Lu et al., 2021); it has also been linked to neuroticism (Luciano et al., 2018) and sleep behavior (Jones et al., 2019b). *CADM2*, which was overlapping in BIP-I and daytime sleepiness, belongs to the immunoglobulin superfamily and has been implicated in various genetic studies investigating psychological and physical traits, such as obesity (Morris et al., 2019), cognitive function (Ibrahim-Verbaas et al., 2016), and physical activity (Klimentidis et al., 2018). Findings from the targeted examination of clock genes revealed several significant associations with depression (*NR1D1* and *PER1*) and BIP-I (*ARNTL*, *CRY2*, *RORB*) underlining the close relationship with mood disorders. *NR1D1* regulates the expression of core clock genes and is involved in metabolic and immunological processes; it has been reported to be associated with both depression (Gammie, 2021) and bipolar disorder (Scott & McClung, 2021). *PER1* is involved in the transcription and translation of core clock components and is involved in a wide range of physiological functions (e.g., metabolism, sleep, and the endocrine and immune systems); changes in *PER1* expression have been found in patients with depression compared to healthy controls (Scott & McClung, 2021). *ARNTL* acts as an activator of transcriptional processes in the circadian clock machinery and is known as a metabolic modulator (Hatanaka et al., 2010); it has been implicated in affective disorders (Scott & McClung, 2021). *CRY2*, a repressor of transcription in the circadian clock machinery, has been shown to be related to depression (Zhang et al., 2022), and bipolar disorder (Sjöholm et al., 2010). The nuclear receptor *RORB* has been shown to be associated with bipolar disorder (Colombo et al., 2022). Even though circadian genes did not reach genome-wide significance, they support findings from previous studies indicating a close genetic relationship between mood disorders and circadian rhythms on a genome-wide gene level. The present study had certain limitations. We used the largest currently available cohorts for the respective phenotypes; however, sample sizes and statistical power of the GWASs differed. In particular, BIP-II and relative amplitude samples were smaller than for the other GWASs. All GWASs included exceed the SNP heritability Z-score threshold of 4 which is recommended for genetic correlation analyses (see Tables 2.S1.1–2.S1.3) and we could expect more significant findings with larger samples. Another limitation that bears mentioning is that it cannot be excluded that some of the individuals in the biological rhythms dataset were suffering from a mood disorder (lifetime or acute) (Davis et al., 2020). However, in the light of the relatively low lifetime frequency of BIP and the decreased likelihood that individuals with MD or BIP have participated in the accelerometer recording during an acute mood episode, it is unlikely that the genetic correlation between biological rhythms and mood disorders could result from the biorhythms observed in these individuals at the time of assessment. These results show that clinically observed relationships of mood disorders and biological rhythms have a common genetic basis, and indicate that alterations in biological rhythms observed in mood disorder patients are linked to the genetic vulnerability for the specific disorder, and not only to the current mood episode. Biological rhythms should be given more attention in the study of mood disorders and require greater consideration with respect to assessment and treatment. Links between mood disorders and genetic components underlying other physiological traits also under circadian control (e.g., hormonal secretion, body temperature) should be investigated to enhance our understanding of this complex relationship. As sample sizes of GWASs increase, overlapping genes and pathways can be identified with more certainty, enabling investigation of the causality of the observed genetic relationship between mood disorders and biological rhythms. To further extend these findings, future studies in the field could investigate this

relationship also on the individual level, assessing mood disorders and biological rhythm phenotypes with more refined approaches such as ambulatory assessment, while at the same time incorporating genetic data. Furthermore, incorporating epigenetic and gene expression assessments into research designs will allow exploration of underlying mechanisms, in particular those that change over time. Implementation of these multimodal assessments will not only give deeper insight into shared mechanisms but also shed light on how they interact with the environment. If shared genetic factors jointly affect biological rhythms and liability to mood disorders, further investigation may allow targeting of these factors in treatment, providing potential avenues of improvement for therapeutic approaches.

2.6 Data availability

Summary statistics for depression were downloaded from the Downloads section on the Psychiatric Genomics Consortium Webpage (https://www.med.unc.edu/pgc/download-results/, March 19th, 2020) (Howard et al., 2019). BIP-I and BIP-II summary statistics were obtained from the authors of the original GWAS (November, 2020) (Mullins et al., 2021). The summary statistics for overall physical activity, moderate activity, sedentary behaviour, and sleep duration were downloaded via the following link: https://ora.ox.ac.uk/objects/uuid:f479f44-bf35-48b9-9e67-e690a2937b22 (retrieved March 13th, 2020) (Doherty et al., 2018). Relative amplitude summary statistics were retrieved from http://researchdata.gla.ac.uk/928/ (January 1st, 2020) and for daytime sleepiness from the Sleep Disorder Knowledge Portal (SDKP) website http://www.sleepdisordergenetics.org (June 9th, 2020) Ferguson et al., 2018; Wang et al., 2019).

2.7 Code availability

Code used for this analysis can be found here: https://github.com/bulik/ldsc/wiki/Heritability-and-Genetic-Correlation (retrieved February 4th, 2022) and https://ctg.cncr.nl/sofware/magma (retrieved July 16th, 2022) or can be made available by the corresponding author based on reasonable request.

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The authors declare no competing interests.

2.9 Author Contributions

L.S. and J.C.F. proposed the analysis plan. L.S., J.C.F., J.F., and F.S. undertook the statistical analysis. L.S., J.C.F., M.R., L.Z., S.H.W., and F.S. did the literature review for the paper. L.S. and J.C.F. drafted the manuscript, and all authors contributed, revised, and edited the final manuscript critically. All authors agreed to the publication of the final version of the manuscript.

2.10 Supplementary Information

2.10.1 Supplementary Tables

Some of the tables in Supplementary Tables 2.S1.1-2.S4.9 had to be reduced to save space. The full tables are available under https://www.nature.com/articles/s41598-022-19720-5#Sec14.

Supplementary Table 2.S1.1: LDSC Genetic Correlations of Depression with Biological Rhythms.

p1	p2	rg	se	z	p	h2_obs	h2_obs_se	p_adjust	Z
Depression	Overall Physical Activity	-0,112	0,0292	-3,8339	0,00012614	0,1442	0,0082	0,00075684	17,5853659
Depression	Moderate Activity	-0,0925	0,0447	-2,071	0,038355	0,0493	0,0059	0,23013	8,3559322
Depression	Sedentary Behaviour	0,0266	0,0315	0,8439	0,3987	0,1158	0,0084	1	13,7857143
Depression	Sleep Duration	0,0484	0,0305	1,5895	0,11194	0,1314	0,0074	0,67164	17,7567568
Depression	Relative Amplitude	-0,3044	0,044	-6,9237	4,4003E-12	0,0536	0,0061	2,6402E-11	8,78688525
Depression	Daytime Sleepiness	0,166	0,025	6,6385	3,1683E-11	0,0484	0,0023	1,901E-10	21,0434783

p1 and p2 represent the traits which are correlated; rg = estimate for this genetic correlation; h2_obs shows heritability estimate for p2; p = unadjusted p-value; p_adjust = Bonferroni adjusted p-value.

Supplementary Table 2.S1.2: LDSC Genetic Correlations of BIP-I with Biological Rhythms.

p1	p2	rg	se	z	p	h2_obs	h2_obs_se	p_adjust	Z
BIP-I	Overall Physical Activity	0,0725	0,0315	2,3049	0,0212	0,1443	0,0086	0,1272	16,7790698
BIP-I	Moderate Activity	0,2315	0,0507	4,5655	4,9834E-06	0,0487	0,0067	2,99E-05	7,26865672
BIP-I	Sedentary Behaviour	-0,105	0,0362	-2,8998	0,0037336	0,118	0,0089	0,0224016	13,258427
BIP-I	Sleep Duration	-0,028	0,0325	-0,8613	0,38907	0,1328	0,0078	1	17,025641
BIP-I	Relative Amplitude	-0,0476	0,0465	-1,0253	0,30524	0,0545	0,0068	1	8,01470588
BIP-I	Daytime Sleepiness	0,1052	0,0285	3,6854	0,00022833	0,0481	0,0025	0,00136998	19,24

p1 and p2 represent the traits which are correlated; rg = estimate for this genetic correlation; h2_obs shows heritability estimate for p2; p = unadjusted p-value; p_adjust = Bonferroni adjusted p-value.

Supplementary Table 2.S1.3: LDSC Genetic Correlations of BIP-II with Biological Rhythms.

p1	p2	rg	se	z	p	h2_obs	h2_obs_se	p_adjust	Z
BIP-II	Overall Physical Activity	-0,0283	0,0565	-0,5002	0,6169	0,1431	0,0088	1	16,2613636
BIP-II	Moderate Activity	0,1884	0,0897	2,1013	0,035616	0,0474	0,0067	0,213696	7,07462687
BIP-II	Sedentary Behaviour	-0,0336	0,065	-0,5162	0,60573	0,1179	0,0091	1	12,956044
BIP-II	Sleep Duration	0,0186	0,0628	0,2966	0,76674	0,1315	0,0081	1	16,2345679
BIP-II	Relative Amplitude	-0,2269	0,0827	-2,7443	0,0060647	0,0553	0,0068	0,0363882	8,13235294
BIP-II	Daytime Sleepiness	0,2187	0,0517	4,2278	2,3595E-05	0,0477	0,0026	0,00014157	18,3461538

p1 and p2 represent the traits which are correlated; rg = estimate for this genetic correlation; h2_obs shows heritability estimate for p2; p = unadjusted p-value; p_adjust = Bonferroni adjusted p-value.

Supplementary Table 2.S2.1: Comparison of Depression and BIP-I with Biological Rhythms.

Cor_1	Cor_2	nblocks	var	se	estimate	z	p	p_adjust
Depression/Overall Physical Activity	BIP-I/Overall Physical Activity	200	0,00174332	0,04175314	-0,18076444	-4,32936203	1,4954E-05	8,9725E-05
Depression/Moderate Activity	BIP-I/Moderate Activity	200	0,00417296	0,06459848	-0,31019243	-4,80185378	1,572E-06	9,4322E-06
Depression/Sedentary Behaviour	BIP-I/Sedentary Behaviour	200	0,00195548	0,04422086	0,13050974	2,9513161	0,00316423	0,01898537
Depression/Sleep Duration	BIP-I/Sleep Duration	200	0,00175122	0,04184759	0,0755216	1,80468193	0,07112447	0,42674682
Depression/Relative Amplitude	BIP-I/Relative Amplitude	200	0,00384098	0,06197562	-0,25705032	-4,14760408	3,3597E-05	0,00020158
Depression/Daytime Sleepiness	BIP-I/Daytime Sleepiness	200	0,00123401	0,03512845	0,05700963	1,62289036	0,10461284	0,62767706

Cor_1 and Cor_2 repesent the correlations which were compared; p = unadjusted p-value; p_adjust = Bonferroni adjusted p-value.

Supplementary Table 2.S2.2: Comparison of Depression and BIP-II with Biological Rhythms.

Cor_1	Cor_2	nblocks	var	se	estimate	z	p	p_adjust
Depression/Overall Physical Activity	BIP-II/Overall Physical Activity	200	0,00359755	0,05997959	-0,07826553	-1,30486937	0,19193733	1
Depression/Moderate Activity	BIP-II/Moderate Activity	200	0,00948269	0,09737911	-0,26248904	-2,69553735	0,00702752	0,04216512
Depression/Sedentary Behaviour	BIP-II/Sedentary Behaviour	200	0,0041812	0,06466218	0,06802786	1,05205026	0,29277649	1
Depression/Sleep Duration	BIP-II/Sleep Duration	200	0,00451017	0,06715781	0,03075463	0,45794568	0,64699147	1
Depression/Relative Amplitude	BIP-II/Relative Amplitude	200	0,00703754	0,08389003	-0,0743351	-0,88610173	0,37556271	1
Depression/Daytime Sleepiness	BIP-II/Daytime Sleepiness	200	0,00308053	0,05550248	-0,05767435	-1,03913098	0,29874383	1

Cor_1 and Cor_2 repesent the correlations which were compared; p = unadjusted p-value; p_adjust = Bonferroni adjusted p-value.

Supplementary Table 2.S2.3: Comparison of BIP-I and BIP-II with Biological Rhythms.

Cor_1	Cor_2	nblocks	var	se	estimate	z	p	p_adjust
BIP-I/Overall Physical Activity	BIP-II/Overall Physical Activity	200	0,00318038	0,05639486	0,10249892	1,81752237	0,06913717	0,41482299
BIP-I/Moderate Activity	BIP-II/Moderate Activity	200	0,00686819	0,08287455	0,04770339	0,57560968	0,56487904	1
BIP-I/Sedentary Behaviour	BIP-II/Sedentary Behaviour	200	0,00400933	0,06331927	-0,06248188	-0,98677505	0,32375293	1
BIP-I/Sleep Duration	BIP-II/Sleep Duration	200	0,00388673	0,06234366	-0,04476697	-0,71806771	0,47271554	1
BIP-I/Relative Amplitude	BIP-II/Relative Amplitude	200	0,00711118	0,0843278	0,18271522	2,16672588	0,03025576	0,18153457
BIP-I/Daytime Sleepiness	BIP-II/Daytime Sleepiness	200	0,00246758	0,0496747	-0,11468398	-2,30869999	0,02096023	0,12576141

Cor_1 and Cor_2 repesent the correlations which were compared; p = unadjusted p-value; p_adjust = Bonferroni adjusted p-value.

Supplementary Table 2.S3.1: Tested Genes in MAGMA Associated with Depression.

GENE	CHR	START	STOP	NSNPS	NPARAM	N	ZSTAT	P	GENENAME	P_ADJ
8341	6	27805544	27821533	33	7	500199	8,0988	2,7756E-16	*HIST1H2BN*	4,9575E-12
8356	6	27858093	27858570	1	1	500199	7,6587	9,392E-15	*HIST1H3J*	1,67751E-10
22986	10	106400859	107024993	1959	54	500199	7,5068	3,0286E-14	*SORCS3*	5,40938E-10
6925	18	52889562	53303252	767	61	500199	7,4834	3,6219E-14	*TCF4*	6,46908E-10
7745	6	28109688	28127250	43	7	500199	7,4741	3,8858E-14	*ZKSCAN8*	6,94043E-10
84547	6	28249314	28270326	62	14	500199	7,2795	1,6748E-13	*PGBD1*	2,99136E-09
11118	6	26365387	26378548	98	9	500199	7,1675	3,8181E-13	*BTN3A2*	6,81951E-09
80345	6	28092334	28097864	13	4	500199	7,0005	1,2751E-12	*ZSCAN16*	2,27746E-08
2066	2	212240442	213403879	4688	205	500199	6,9659	1,632E-12	*ERBB4*	2,91492E-08
7718	6	28048482	28057341	28	6	500199	6,9581	1,7247E-12	*ZNF165*	3,08049E-08
7746	6	28193029	28201265	23	9	500199	6,9243	2,1907E-12	*ZSCAN9*	3,91281E-08
7741	6	28234788	28246001	16	4	500199	6,9123	2,3848E-12	*ZSCAN26*	4,25949E-08
2915	11	88237256	88796846	1824	47	500199	6,7172	9,2632E-12	*GRM5*	1,6545E-07
54664	7	12250848	12276890	176	8	500199	6,6289	1,6911E-11	*TMEM106B*	3,02047E-07
387032	6	28212404	28227030	36	13	500199	6,6131	1,8813E-11	*ZKSCAN4*	3,36019E-07
145173	13	31774112	31906413	350	27	500199	6,4717	4,8461E-11	*B3GALTL*	8,65562E-07
1813	11	113280317	113346413	186	28	500199	6,3582	1,0205E-10	*DRD2*	1,82272E-06
81697	6	27878963	27880174	4	2	500199	6,3232	1,2811E-10	*OR2B2*	2,28817E-06
54715	16	5289469	7763342	15414	628	500199	6,3162	1,3407E-10	*RBFOX1*	2,39462E-06
257194	1	71868625	72748533	2024	99	500199	6,3074	1,4186E-10	*NEGR1*	2,53376E-06
3009	6	27834570	27835359	6	3	500199	6,2817	1,6748E-10	*HIST1H1B*	2,99136E-06
115708	14	103995509	104003410	21	4	500199	6,275	1,7479E-10	*TRMT61A*	3,12192E-06
1630	18	49866542	51062273	4880	118	500199	6,2666	1,8453E-10	*DCC*	3,29589E-06
84251	1	66999066	67210768	786	25	500199	6,184	3,1241E-10	*SGIP1*	5,57996E-06
9753	6	28346598	28367544	66	11	500199	6,1581	3,6819E-10	*ZSCAN12*	6,57624E-06

Supplementary Table 2.S3.2: Tested Genes in MAGMA Associated with BIP-I.

GENE	CHR	START	STOP	NSNPS	NPARAM	N	ZSTAT	P	GENENAME	P_ADJ
775	12	2079952	2807115	1924	173	475038	6,4934	4,1963E-11	*CACNA1C*	7,5E-07
8379	7	1855428	2272583	1590	31	475038	6,3352	1,185E-10	*MAD1L1*	2,12E-06
5339	8	144989321	145050913	149	9	475038	6,1663	3,4943E-10	*PLEC*	6,24E-06
3992	11	61567097	61584529	20	3	475038	6,1591	3,6575E-10	*FADS1*	6,53E-06
746	11	61556602	61560085	6	2	475038	6,1501	3,872E-10	*TMEM258*	6,92E-06
84875	8	145051320	145060635	15	3	475038	6,1162	4,7924E-10	*PARP10*	8,56E-06
9415	11	61583675	61634826	130	16	475038	6,0824	5,9201E-10	*FADS2*	1,06E-05
783	10	18429373	18830688	1445	109	475038	6,0611	6,7611E-10	*CACNB2*	1,21E-05
9640	15	85291818	85349663	115	16	475038	6,0215	8,6418E-10	*ZNF592*	1,54E-05
9881	3	36868308	36986548	235	21	475038	5,9727	1,1665E-09	*TRANK1*	2,08E-05
745	11	61520121	61555990	57	12	475038	5,9601	1,2605E-09	*MYRF*	2,25E-05
84942	15	85185607	85197521	30	6	475038	5,9338	1,4797E-09	*WDR73*	2,64E-05
3745	20	47988505	48099181	388	36	475038	5,9254	1,5577E-09	*KCNB1*	2,78E-05
55690	11	65837747	66012218	272	14	475038	5,8578	2,3447E-09	*PACS1*	4,19E-05
55830	3	52728500	52740099	14	3	475038	5,8409	2,5955E-09	*GLT8D1*	4,64E-05
55193	3	52579368	52719866	292	11	475038	5,8322	2,735E-09	*PBRM1*	4,88E-05
9671	12	108523511	108644314	312	25	475038	5,7744	3,8624E-09	*WSCD2*	6,9E-05
6196	6	166822854	167275948	1549	134	475038	5,7487	4,4971E-09	*RPS6KA2*	8,03E-05
4828	15	85198360	85201802	10	4	475038	5,7306	5,0053E-09	*NMB*	8,94E-05
4482	8	9911830	10286401	1483	67	475038	5,6924	6,2631E-09	*MSRA*	0,000112
28972	3	52739792	52742198	4	2	475038	5,6659	7,3122E-09	*SPCS1*	0,000131
6787	3	52744796	52804965	117	10	475038	5,6657	7,3213E-09	*NEK4*	0,000131
26354	3	52719936	52728513	11	3	475038	5,658	7,6579E-09	*GNL3*	0,000137
404037	19	19366450	19373596	16	3	475038	5,5742	1,2432E-08	*HAPLN4*	0,000222
3362	1	19991780	20006055	38	8	475038	5,5519	1,4126E-08	*HTR6*	0,000252

Supplementary Table 2.S3.3: Tested Genes in MAGMA Associated with BIP-II.

GENE	CHR	START	STOP	NSNPS	NPARAM	N	ZSTAT	P	GENENAME	P_ADJ
6586	5	168088738	168728133	2087	164	370856	5,6556	7,7665E-09	*SLIT3*	0,000139
2064	17	37844167	37884915	42	8	370856	4,2548	0,000010462	*ERBB2*	0,186862
162417	17	42082032	42086436	11	3	370856	4,2157	0,000012449	*NAGS*	0,222352
3009	6	27834570	27835359	4	2	370856	4,0504	0,000025569	*HIST1H1B*	0,456688
51473	6	24171983	24383520	742	48	370856	4,0078	0,000030645	*DCDC2*	0,54735
8368	6	27840926	27841289	1	1	370856	3,9929	0,00003263	*HIST1H4L*	0,582804
201229	17	26205340	26220409	13	3	370856	3,972	0,000035631	*LYRM9*	0,636405
8341	6	27805544	27821533	26	4	370856	3,963	0,000037009	*HIST1H2BN*	0,661018
11074	6	30070674	30080867	71	16	370856	3,925	0,000043358	*TRIM31*	0,774417
55898	15	91473410	91497323	77	11	370856	3,8646	0,000055635	*UNC45A*	0,993697
55876	17	38060848	38074903	44	4	370856	3,7967	0,00007333	*GSDMB*	1
11118	6	26365387	26378548	86	7	370856	3,7804	0,000078284	*BTN3A2*	1
9863	7	77646374	79083121	4971	246	370856	3,7797	0,000078495	*MAGI2*	1
8340	6	27775257	27775709	2	1	370856	3,7511	0,000088027	*HIST1H2BL*	1
81697	6	27878963	27880174	4	2	370856	3,7487	0,000088877	*OR2B2*	1
6650	16	577816	604636	76	19	370856	3,7317	0,000095077	*CAPN15*	1
2242	15	91427665	91439006	31	6	370856	3,6996	0,00010798	*FES*	1
84547	6	28249314	28270326	55	10	370856	3,616	0,00014961	*PGBD1*	1
5045	15	91411885	91426687	28	6	370856	3,5947	0,00016237	*FURIN*	1
64326	1	175913967	176176386	477	25	370856	3,5703	0,00017829	*RFWD2*	1
148113	19	19649057	19657468	16	2	370856	3,5652	0,00018181	*CILP2*	1
51079	19	19626550	19639858	24	3	370856	3,5526	0,00019073	*NDUFA13*	1
347732	5	134303596	134347397	52	12	370856	3,5383	0,00020133	*CATSPER3*	1
1996	1	50513686	50669442	180	29	370856	3,5335	0,00020506	*ELAVL4*	1
3024	6	26017260	26018040	3	2	370856	3,5334	0,0002051	*HIST1H1A*	1

Supplementary Table 2.S3.4: Tested Genes in MAGMA Associated with Overall Physical Activity.

GENE	CHR	START	STOP	NSNPS	NPARAM	N	ZSTAT	P	GENENAME	P_ADJ
284058	17	44107282	44302740	939	4	91105	6,7047	1,0094E-11	*KANSL1*	1,8E-07
4137	17	43971702	44105700	763	5	91105	6,6475	1,491E-11	*MAPT*	2,66E-07
1394	17	43697710	43913194	1060	9	91105	6,5421	3,0331E-11	*CRHR1*	5,42E-07
9884	17	44316744	44415160	480	6	91105	6,4773	4,6698E-11	*LRRC37A*	8,34E-07
162540	17	43922256	43924438	17	2	91105	6,4718	4,8429E-11	*SPPL2C*	8,65E-07
100506084	17	44351550	44439416	207	7	91105	6,3367	1,174E-10	*ARL17B*	2,1E-06
8028	10	21813540	22032559	210	30	91105	6,1094	5E-10	*MLLT10*	8,93E-06
4905	17	44668035	44834830	102	11	91105	5,7646	4,0921E-09	*NSF*	7,31E-05
9842	17	43513266	43568146	153	8	91105	5,5409	1,5046E-08	*PLEKHM1*	0,000269
201176	17	43471268	43510282	98	6	91105	5,4936	1,9691E-08	*ARHGAP27*	0,000352
1879	5	158122916	158526788	770	56	91105	5,2394	8,0568E-08	*EBF1*	0,001439
7473	17	44839872	44896126	112	20	91105	5,1054	1,6509E-07	*WNT3*	0,002949
5101	13	66876966	67804468	2214	129	91105	4,9425	3,8566E-07	*PCDH9*	0,006888
23035	16	71678827	71757798	166	16	91105	4,6247	0,000001876	*PHLPP2*	0,033507
150356	22	41605861	41636935	94	6	91105	4,5992	2,1207E-06	*CHADL*	0,037878
83746	22	41601312	41627276	90	5	91105	4,5884	2,2329E-06	*L3MBTL2*	0,039882
11281	7	39017609	39504390	1476	63	91105	4,4934	3,5055E-06	*POU6F2*	0,062612
4163	5	112357796	112824527	1933	59	91105	4,4418	4,4608E-06	*MCC*	0,079674
2033	22	41488614	41576081	154	16	91105	4,4295	4,7218E-06	*EP300*	0,084336
100861540	7	99282302	99332819	103	6	91105	4,3212	7,7594E-06	*CYP3A7-CYP3A51P*	0,138591
151126	2	180306709	180726232	1615	99	91105	4,3004	8,5246E-06	*ZNF385B*	0,152258
1551	7	99302660	99332853	68	5	91105	4,2877	9,0247E-06	*CYP3A7*	0,16119
100289187	7	99195702	99208456	21	6	91105	4,2826	9,2373E-06	*GS1-259H13.2*	0,164987
1577	7	99245813	99277636	49	13	91105	4,2584	0,000010293	*CYP3A5*	0,183843
26289	1	77747662	78025654	1040	66	91105	4,2226	0,000012074	*AK5*	0,215654

Supplementary Table 2.S3.5: Tested Genes in MAGMA Associated with Moderate Activity.

GENE	CHR	START	STOP	NSNPS	NPARAM	N	ZSTAT	P	GENENAME	P_ADJ
341	19	45417577	45422606	11	4	91105	4,3872	5,7405E-06	*APOC1*	0,102531
89782	3	197687071	197770591	253	16	91105	4,3032	8,4163E-06	*LMLN*	0,150324
23030	19	4969123	5153609	602	38	91105	4,158	0,00001605	*KDM4B*	0,286669
4828	15	85198360	85201802	11	4	91105	4,1127	0,000019551	*NMB*	0,3492
55345	4	113460489	113558151	190	21	91105	4,0756	0,000022951	*ZGRF1*	0,409928
1475	3	122044011	122060816	55	10	91105	4,0466	0,000025978	*CSTA*	0,463993
9640	15	85291818	85349663	132	18	91105	4,0106	0,00003028	*ZNF592*	0,540831
7380	22	45680868	45691755	43	9	91105	3,9546	0,000038334	*UPK3A*	0,684684
101929008	7	45818810	45822386	9	2	91105	3,952	0,000038743	*LOC101929008*	0,691989
348	19	45409039	45412650	6	3	91105	3,9052	0,000047078	*APOE*	0,84086
51151	5	33944721	33984780	72	12	91105	3,8236	0,000065756	*SLC45A2*	1
150356	22	41605861	41636935	94	6	91105	3,8076	0,000070166	*CHADL*	1
83746	22	41601312	41627276	90	5	91105	3,8007	0,000072136	*L3MBTL2*	1
2033	22	41488614	41576081	154	16	91105	3,7837	0,00007725	*EP300*	1
4008	13	76194570	76434006	698	49	91105	3,7553	0,000086583	*LMO7*	1
284058	17	44107282	44302740	939	4	91105	3,7522	0,000087634	*KANSL1*	1
84942	15	85185607	85197521	30	6	91105	3,7451	0,000090147	*WDR73*	1
284018	17	65987217	65989765	2	1	91105	3,7451	0,000090159	*C17orf58*	1
4137	17	43971702	44105700	763	5	91105	3,7254	0,000097485	*MAPT*	1
3838	17	66031848	66042970	36	5	91105	3,7241	0,000097994	*KPNA2*	1
3742	12	4918342	4961093	237	28	91105	3,7129	0,00010245	*KCNA6*	1
162540	17	43922256	43924438	17	2	91105	3,6807	0,00011632	*SPPL2C*	1
9469	10	73724120	73773322	154	13	91105	3,6759	0,00011849	*CHST3*	1
100506084	17	44351550	44439416	207	7	91105	3,6663	0,00012306	*ARL17B*	1
1394	17	43697710	43913194	1060	9	91105	3,6511	0,00013054	*CRHR1*	1

Supplementary Table 2.S3.6: Tested Genes in MAGMA Associated with Sedentary Behaviour.

GENE	CHR	START	STOP	NSNPS	NPARAM	N	ZSTAT	P	GENENAME	P_ADJ
83698	7	71244476	71912136	2057	62	91105	6,1662	3,4968E-10	*CALN1*	6,25E-06
1946	5	106712590	107006596	768	91	91105	4,6761	0,000001462	*EFNA5*	0,026113
83891	4	186130773	186285120	494	30	91105	4,5847	2,2727E-06	*SNX25*	0,040593
23030	19	4969123	5153609	602	38	91105	4,5227	3,0535E-06	*KDM4B*	0,054539
4208	5	88014058	88199922	353	27	91105	4,4273	4,7709E-06	*MEF2C*	0,085213
338761	12	49726200	49730971	15	5	91105	4,4177	4,9877E-06	*C1QL4*	0,089085
491	3	10365707	10733131	1437	125	91105	4,3937	5,5711E-06	*ATP2B2*	0,099505
9910	1	174128552	174964445	1953	23	91105	4,2533	0,000010533	*RABGAP1L*	0,18813
8476	1	227177566	227506193	1694	23	91105	4,1481	0,000016764	*CDC42BPA*	0,299422
63931	1	174982094	174992591	18	5	91105	4,1213	0,000018835	*MRPS14*	0,336412
29988	9	130159417	130170177	23	4	91105	4,0949	0,000021113	*SLC2A8*	0,377099
4482	8	9911830	10286401	1613	70	91105	4,0647	0,000024049	*MSRA*	0,429539
50809	1	21069170	21113808	106	17	91105	4,0485	0,000025773	*HP1BP3*	0,460332
9551	7	99055784	99063824	15	4	91105	4,047	0,000025936	*ATP5J2*	0,463243
1551	7	99302660	99332853	68	5	91105	4,0024	0,000031356	*CYP3A7*	0,56005
10898	7	99036563	99054996	45	7	91105	3,9977	0,000031975	*CPSF4*	0,571105
11333	7	98992296	99006305	18	5	91105	3,9852	0,00003371	*PDAP1*	0,602094
100861540	7	99282302	99332819	103	6	91105	3,981	0,000034312	*CYP3A7-CYP3A51P*	0,612847
10095	7	98972298	99004226	62	9	91105	3,9685	0,000036168	*ARPC1B*	0,645997
284716	1	42846468	42889900	151	10	91105	3,9668	0,000036416	*RIMKLA*	0,650426
54810	1	78510646	78604129	245	24	91105	3,9646	0,000036766	*GIPC2*	0,656678
5630	12	49688796	49692481	9	3	91105	3,9132	0,000045532	*PRPH*	0,813247
100526740	7	99014362	99063824	118	13	91105	3,8969	0,000048706	*ATP5J2-PTCD1*	0,869938
407738	3	68040734	68594772	1956	85	91105	3,8849	0,000051196	*FAM19A1*	0,914412
79634	2	175260457	175294303	114	8	91105	3,8529	0,000058361	*SCRN3*	1

Supplementary Table 2.S3.7: Tested Genes in MAGMA Associated with Sleep Duration.

GENE	CHR	START	STOP	NSNPS	NPARAM	N	ZSTAT	P	GENENAME	P_ADJ
5090	9	128509617	128729656	285	17	91105	6,0981	5,3671E-10	*PBX3*	9,59E-06
26053	7	69063905	70257885	2579	82	91105	5,9356	1,4641E-09	*AUTS2*	2,62E-05
5300	19	9945883	9960365	26	7	91105	5,9208	1,6017E-09	*PIN1*	2,86E-05
284058	17	44107282	44302740	939	4	91105	5,8341	2,7041E-09	*KANSL1*	4,83E-05
93145	19	9964394	10047070	231	24	91105	5,8188	2,9637E-09	*OLFM2*	5,29E-05
4137	17	43971702	44105700	763	5	91105	5,8128	3,0722E-09	*MAPT*	5,49E-05
1394	17	43697710	43913194	1060	9	91105	5,7663	4,0527E-09	*CRHR1*	7,24E-05
79109	9	128199673	128469513	485	25	91105	5,7287	5,0604E-09	*MAPKAP1*	9,04E-05
9884	17	44316744	44415160	480	6	91105	5,7223	5,256E-09	*LRRC37A*	9,39E-05
100506084	17	44351550	44439416	207	7	91105	5,6912	6,306E-09	*ARL17B*	0,000113
162540	17	43922256	43924438	17	2	91105	5,6377	8,6181E-09	*SPPL2C*	0,000154
4482	8	9911830	10286401	1613	70	91105	5,1203	1,5256E-07	*MSRA*	0,002725
4905	17	44668035	44834830	102	11	91105	5,046	2,2554E-07	*NSF*	0,004028
23338	5	133860003	133918918	160	26	91105	4,9164	4,4078E-07	*JADE2*	0,007873
9842	17	43513266	43568146	153	8	91105	4,7319	1,1122E-06	*PLEKHM1*	0,019865
57688	5	60628100	60841999	341	22	91105	4,7185	0,000001188	*ZSWIM6*	0,021219
201176	17	43471268	43510282	98	6	91105	4,689	0,000001373	*ARHGAP27*	0,024523
1806	1	97543299	98386615	2280	127	91105	4,6519	1,6446E-06	*DPYD*	0,029374
114781	6	38136227	38608202	1144	70	91105	4,5934	0,00000218	*BTBD9*	0,038937
23500	6	39760159	39872653	369	45	91105	4,5518	2,6594E-06	*DAAM2*	0,0475
1676	1	10520588	10532613	16	4	91105	4,4349	4,6065E-06	*DFFA*	0,082277
3231	2	177053307	177055635	4	2	91105	4,3545	6,6679E-06	*HOXD1*	0,119095
23085	12	1100404	1605099	1817	43	91105	4,2832	9,2111E-06	*ERC1*	0,164519
4211	2	66662257	66799891	321	43	91105	4,2744	9,5834E-06	*MEIS1*	0,171169
7473	17	44839872	44896126	112	20	91105	4,2615	0,000010151	*WNT3*	0,181307

Supplementary Table 2.S3.8: Tested Genes in MAGMA Associated with Relative Amplitude.

GENE	CHR	START	STOP	NSNPS	NPARAM	N	ZSTAT	P	GENENAME	P_ADJ
408050	16	16326389	16388668	14	8	71500	5,7032	5,8781E-09	*NOMO3*	0,000105
10641	3	50384918	50388486	1	1	71500	5,1796	1,112E-07	*NPRL2*	0,001986
375341	3	49306030	49314864	12	4	71500	4,7593	9,7127E-07	*C3orf62*	0,017348
200942	3	49208987	49213919	7	2	71500	4,6087	2,0262E-06	*KLHDC8B*	0,03619
339834	3	49235861	49295636	79	12	71500	4,4053	5,2823E-06	*CCDC36*	0,094347
11334	3	50362341	50365668	2	1	71500	4,2204	0,000012193	*TUSC2*	0,217779
57553	22	18270415	18507325	899	61	71500	4,1835	0,000014353	*MICAL3*	0,256359
8502	2	159313476	159537941	620	24	71500	4,1148	0,000019372	*PKP4*	0,346003
51447	3	48725436	48754711	47	6	71500	3,9894	0,000033125	*IP6K2*	0,591646
84276	3	49459766	49466777	8	4	71500	3,9886	0,000033225	*NICN1*	0,593432
646498	3	49215069	49229291	21	5	71500	3,9742	0,000035312	*C3orf84*	0,630708
54870	3	49067140	49131504	57	12	71500	3,9648	0,000036726	*QRICH1*	0,655963
3615	3	49061758	49066875	4	2	71500	3,8743	0,000053455	*IMPDH2*	0,95476
7375	3	49314577	49377536	72	10	71500	3,8536	0,000058205	*USP4*	1
4208	5	88014058	88199922	316	25	71500	3,845	0,00006027	*MEF2C*	1
65010	3	48663156	48672926	13	2	71500	3,6834	0,00011507	*SLC26A6*	1
6631	6	34724871	34741634	56	9	71500	3,681	0,00011617	*SNRPC*	1
1951	3	48673896	48700348	26	4	71500	3,652	0,00013009	*CELSR3*	1
25805	10	28966424	28971868	10	5	71500	3,634	0,00013951	*BAMBI*	1
3987	2	109150811	109303702	417	24	71500	3,6256	0,00014414	*LIMS1*	1
65121	1	12851546	12856777	11	6	71500	3,6116	0,00015218	*PRAMEF1*	1
100652824	2	202937978	203061886	302	27	71500	3,5993	0,00015951	*KIAA2012*	1
8028	10	21813540	22032559	188	29	71500	3,5266	0,00021047	*MLLT10*	1
64771	6	34555065	34664625	205	17	71500	3,5199	0,00021583	*C6orf106*	1
51517	3	48700419	48723366	31	4	71500	3,5064	0,00022713	*NCKIPSD*	1

Supplementary Table 2.S3.9: Tested Genes in MAGMA Associated with Daytime Sleepiness.

GENE	CHR	START	STOP	NSNPS	NPARAM	N	ZSTAT	P	GENENAME	P_ADJ
100506084	17	44351550	44439416	161	16	452071	7,183	3,4106E-13	*ARL17B*	6,09E-09
9884	17	44316744	44415160	324	15	452071	6,9096	2,43E-12	*LRRC37A*	4,34E-08
10207	1	62208149	62629592	2022	136	452071	6,7547	7,1578E-12	*INADL*	1,28E-07
1394	17	43697710	43913194	1318	21	452071	6,7228	8,9133E-12	*CRHR1*	1,59E-07
284058	17	44107282	44302740	1065	15	452071	6,4682	4,9603E-11	*KANSL1*	8,86E-07
4137	17	43971702	44105700	877	11	452071	6,4236	6,6552E-11	*MAPT*	1,19E-06
162540	17	43922256	43924438	25	5	452071	6,3302	1,224E-10	*SPPL2C*	2,19E-06
26130	9	128024073	128127290	295	36	452071	6,1851	3,1028E-10	*GAPVD1*	5,54E-06
283455	12	117890817	118406399	2571	264	452071	6,1743	3,3232E-10	*KSR2*	5,94E-06
4905	17	44668035	44834830	155	31	452071	6,1094	5E-10	*NSF*	8,93E-06
7473	17	44839872	44896126	201	55	452071	6,1094	5E-10	*WNT3*	8,93E-06
64766	1	33282368	33324480	131	36	452071	6,1094	5E-10	*S100PBP*	8,93E-06
66037	2	198591603	198651036	121	28	452071	6,1094	5E-10	*BOLL*	8,93E-06
9842	17	43513266	43568146	175	22	452071	6,0771	6,1177E-10	*PLEKHM1*	1,09E-05
149345	1	201857797	201861715	16	9	452071	6,0556	6,9955E-10	*SHISA4*	1,25E-05
1793	10	128768965	129250780	2773	184	452071	5,9465	1,3698E-09	*DOCK1*	2,45E-05
253559	3	85008133	86123579	4854	106	452071	5,8991	1,8278E-09	*CADM2*	3,26E-05
201176	17	43471268	43510282	171	23	452071	5,8245	2,8648E-09	*ARHGAP27*	5,12E-05
1981	3	184032283	184053146	59	29	452071	5,8167	3,0013E-09	*EIF4G1*	5,36E-05
25802	1	201865584	201915716	212	47	452071	5,7646	4,0922E-09	*LMOD1*	7,31E-05
10743	17	17584787	17714767	424	71	452071	5,7495	4,4754E-09	*RAI1*	7,99E-05
116987	2	236402733	237040444	2951	227	452071	5,462	2,3536E-08	*AGAP1*	0,00042
5334	2	198669426	199014608	1010	51	452071	5,4406	2,6544E-08	*PLCL1*	0,000474
55705	1	201798288	201853422	210	39	452071	5,4151	3,0625E-08	*IPO9*	0,000547
2646	2	27719470	27746556	89	22	452071	5,2936	5,9975E-08	*GCKR*	0,001071

Supplementary Table 2.S4.1: Selected Circadian Genes in MAGMA Associated with Depression.

GENE	CHR	START	STOP	NSNPS	NPARAM	N	ZSTAT	P	GENENAME	P_ADJ	P_ADJ_1
9572	17	38249037	38256978	17	7	500199	4,2307	0,000011647	*NR1D1*	0,208027	0,000163
5187	17	8043788	8059723	33	9	500199	2,9447	0,0016163	*PER1*	1	0,022628
9575	4	56294068	56413076	451	16	500199	2,4169	0,0078265	*CLOCK*	1	0,109571
8863	1	7844413	7905241	248	31	500199	1,4911	0,06797	*PER3*	1	0,95158
6095	15	60780483	61521502	2256	226	500199	1,4755	0,07004	*RORA*	1	0,98056
1408	11	45868669	45904799	70	14	500199	1,3255	0,092498	*CRY2*	1	1
406	11	13299325	13408813	290	40	500199	1,3002	0,096771	*ARNTL*	1	1
9975	3	23986751	24022109	101	16	500199	1,1057	0,13442	*NR1D2*	1	1
4862	2	101436613	101613289	574	65	500199	0,63226	0,26361	*NPAS2*	1	1
6096	9	77112252	77303534	484	46	500199	0,50097	0,3082	*RORB*	1	1
6097	1	151778547	151804348	61	14	500199	0,48091	0,31529	*RORC*	1	1
1407	12	107385142	107487635	256	17	500199	0,13253	0,44728	*CRY1*	1	1
8864	2	239152679	239198678	138	22	500199	-0,10305	0,54104	*PER2*	1	1
1628	19	49133817	49140639	12	4	500199	-0,18535	0,57352	*DBP*	1	1

Supplementary Table 2.S4.2: Selected Circadian Genes in MAGMA Associated with BIP-I.

GENE	CHR	START	STOP	NSNPS	NPARAM	N	ZSTAT	P	GENENAME	P_ADJ	P_ADJ_1
406	11	13299325	13408813	252	31	475038	3,3474	0,00040793	*ARNTL*	1	0,005711
1408	11	45868669	45904799	66	13	475038	3,1533	0,0008073	*CRY2*	1	0,011302
6096	9	77112252	77303534	401	34	475038	3,0454	0,0011618	*RORB*	1	0,016265
6097	1	151778547	151804348	57	13	475038	2,1959	0,014051	*RORC*	1	0,196714
6095	15	60780483	61521502	1942	207	475038	1,878	0,030189	*RORA*	1	0,422646
1628	19	49133817	49140639	9	3	475038	1,7813	0,037433	*DBP*	1	0,524062
5187	17	8043788	8059723	32	9	475038	1,6327	0,051268	*PER1*	1	0,717752
9572	17	38249037	38256978	14	5	475038	0,9764	0,16443	*NR1D1*	1	1
9975	3	23986751	24022109	76	12	475038	0,13407	0,44667	*NR1D2*	1	1
8864	2	239152679	239198678	111	16	475038	-0,30149	0,61848	*PER2*	1	1
8863	1	7844413	7905241	210	25	475038	-0,38598	0,65025	*PER3*	1	1
9575	4	56294068	56413076	401	13	475038	-0,41448	0,66074	*CLOCK*	1	1
4862	2	101436613	101613289	493	61	475038	-0,79885	0,78781	*NPAS2*	1	1
1407	12	107385142	107487635	213	16	475038	-1,0892	0,86196	*CRY1*	1	1

Supplementary Table 2.S4.3: Selected Circadian Genes in MAGMA Associated with BIP-II.

GENE	CHR	START	STOP	NSNPS	NPARAM	N	ZSTAT	P	GENENAME	P_ADJ	P_ADJ_1
9572	17	38249037	38256978	12	4	370856	0,73294	0,2318	*NR1D1*	1	1
406	11	13299325	13408813	248	34	370856	0,66576	0,25278	*ARNTL*	1	1
1408	11	45868669	45904799	64	12	370856	0,64184	0,26049	*CRY2*	1	1
9975	3	23986751	24022109	81	13	370856	0,58764	0,27839	*NR1D2*	1	1
9575	4	56294068	56413076	393	12	370856	0,56791	0,28505	*CLOCK*	1	1
8863	1	7844413	7905241	210	25	370856	0,51408	0,3036	*PER3*	1	1
4862	2	101436613	101613289	487	61	370856	0,32692	0,37187	*NPAS2*	1	1
6097	1	151778547	151804348	57	13	370856	0,10011	0,46013	*RORC*	1	1
6096	9	77112252	77303534	355	33	370856	-0,17458	0,5693	*RORB*	1	1
5187	17	8043788	8059723	32	9	370856	-0,19872	0,57876	*PER1*	1	1
1628	19	49133817	49140639	8	3	370856	-0,20932	0,5829	*DBP*	1	1
8864	2	239152679	239198678	111	16	370856	-0,31734	0,62451	*PER2*	1	1
1407	12	107385142	107487635	210	16	370856	-1,2464	0,8937	*CRY1*	1	1
6095	15	60780483	61521502	1918	201	370856	-2,4595	0,99304	*RORA*	1	1

Supplementary Table 2.S4.4: Selected Circadian Genes in MAGMA Associated with Overall Physical Activity.

GENE	CHR	START	STOP	NSNPS	NPARAM	N	ZSTAT	P	GENENAME	P_ADJ	P_ADJ_1
9575	4	56294068	56413076	433	14	91105	2,5487	0,0054065	*CLOCK*	1	0,075691
8863	1	7844413	7905241	234	27	91105	2,4209	0,0077401	*PER3*	1	0,108361
6097	1	151778547	151804348	60	13	91105	2,1147	0,017227	*RORC*	1	0,241178
1628	19	49133817	49140639	14	4	91105	1,8341	0,033323	*DBP*	1	0,466522
6095	15	60780483	61521502	2130	209	91105	1,2537	0,10497	*RORA*	1	1
406	11	13299325	13408813	271	34	91105	1,2019	0,11469	*ARNTL*	1	1
9572	17	38249037	38256978	15	5	91105	0,68672	0,24613	*NR1D1*	1	1
8864	2	239152679	239198678	131	20	91105	0,16069	0,43617	*PER2*	1	1
9975	3	23986751	24022109	99	14	91105	0,13424	0,44661	*NR1D2*	1	1
1408	11	45868669	45904799	69	13	91105	0,11211	0,45537	*CRY2*	1	1
4862	2	101436613	101613289	551	58	91105	0,038269	0,48474	*NPAS2*	1	1
6096	9	77112252	77303534	439	36	91105	-0,35696	0,63944	*RORB*	1	1
5187	17	8043788	8059723	32	9	91105	-1,0896	0,86205	*PER1*	1	1
1407	12	107385142	107487635	235	18	91105	-1,7187	0,95716	*CRY1*	1	1

Supplementary Table 2.S4.5: Selected Circadian Genes in MAGMA Associated with Moderate Activity.

GENE	CHR	START	STOP	NSNPS	NPARAM	N	ZSTAT	P	GENENAME	P_ADJ	P_ADJ_1
8863	1	7844413	7905241	234	27	91105	3,1028	0,00095849	*PER3*	1	0,013419
9975	3	23986751	24022109	99	14	91105	2,1398	0,016185	*NR1D2*	1	0,22659
9575	4	56294068	56413076	433	14	91105	1,4957	0,067371	*CLOCK*	1	0,943194
8864	2	239152679	239198678	131	20	91105	1,4541	0,072961	*PER2*	1	1
4862	2	101436613	101613289	551	58	91105	1,4309	0,076222	*NPAS2*	1	1
1628	19	49133817	49140639	14	4	91105	0,63054	0,26417	*DBP*	1	1
6097	1	151778547	151804348	60	13	91105	0,60849	0,27143	*RORC*	1	1
6096	9	77112252	77303534	439	36	91105	0,33441	0,36904	*RORB*	1	1
5187	17	8043788	8059723	32	9	91105	0,20692	0,41804	*PER1*	1	1
1408	11	45868669	45904799	69	13	91105	0,045675	0,48178	*CRY2*	1	1
1407	12	107385142	107487635	235	18	91105	-0,35164	0,63744	*CRY1*	1	1
406	11	13299325	13408813	271	34	91105	-1,1152	0,86762	*ARNTL*	1	1
6095	15	60780483	61521502	2130	209	91105	-1,3481	0,91118	*RORA*	1	1
9572	17	38249037	38256978	15	5	91105	-1,7831	0,96272	*NR1D1*	1	1

Supplementary Table 2.S4.6: Selected Circadian Genes in MAGMA Associated with Sedentary Behaviour.

GENE	CHR	START	STOP	NSNPS	NPARAM	N	ZSTAT	P	GENENAME	P_ADJ	P_ADJ_1
9575	4	56294068	56413076	433	14	91105	2,324	0,010064	*CLOCK*	1	0,140896
6095	15	60780483	61521502	2130	209	91105	1,3776	0,084164	*RORA*	1	1
1408	11	45868669	45904799	69	13	91105	1,0139	0,15532	*CRY2*	1	1
8864	2	239152679	239198678	131	20	91105	0,94036	0,17352	*PER2*	1	1
6096	9	77112252	77303534	439	36	91105	0,85459	0,19639	*RORB*	1	1
406	11	13299325	13408813	271	34	91105	0,80932	0,20916	*ARNTL*	1	1
8863	1	7844413	7905241	234	27	91105	-0,067317	0,52684	*PER3*	1	1
9975	3	23986751	24022109	99	14	91105	-0,10946	0,54358	*NR1D2*	1	1
6097	1	151778547	151804348	60	13	91105	-0,60396	0,72706	*RORC*	1	1
1628	19	49133817	49140639	14	4	91105	-0,82027	0,79397	*DBP*	1	1
4862	2	101436613	101613289	551	58	91105	-0,89556	0,81476	*NPAS2*	1	1
9572	17	38249037	38256978	15	5	91105	-1,4975	0,93286	*NR1D1*	1	1
5187	17	8043788	8059723	32	9	91105	-1,8804	0,96998	*PER1*	1	1
1407	12	107385142	107487635	235	18	91105	-2,537	0,99441	*CRY1*	1	1

Supplementary Table 2.S4.7: Selected Circadian Genes in MAGMA Associated with Sleep Duration.

GENE	CHR	START	STOP	NSNPS	NPARAM	N	ZSTAT	P	GENEN-AME	P_ADJ	P_ADJ_1
6097	1	151778547	151804348	60	13	91105	1,6148	0,053177	*RORC*	1	0,744478
8863	1	7844413	7905241	234	27	91105	1,5346	0,062437	*PER3*	1	0,874118
406	11	13299325	13408813	271	34	91105	1,5296	0,063056	*ARNTL*	1	0,882784
9575	4	56294068	56413076	433	14	91105	1,357	0,087385	*CLOCK*	1	1
1628	19	49133817	49140639	14	4	91105	1,1016	0,13532	*DBP*	1	1
9572	17	38249037	38256978	15	5	91105	1,0676	0,14285	*NR1D1*	1	1
6096	9	77112252	77303534	439	36	91105	0,86191	0,19437	*RORB*	1	1
9975	3	23986751	24022109	99	14	91105	0,63363	0,26316	*NR1D2*	1	1
1407	12	107385142	107487635	235	18	91105	0,53018	0,29799	*CRY1*	1	1
1408	11	45868669	45904799	69	13	91105	0,31012	0,37824	*CRY2*	1	1
5187	17	8043788	8059723	32	9	91105	-0,048011	0,51915	*PER1*	1	1
8864	2	239152679	239198678	131	20	91105	-0,14488	0,5576	*PER2*	1	1
6095	15	60780483	61521502	2130	209	91105	-0,85244	0,80302	*RORA*	1	1
4862	2	101436613	101613289	551	58	91105	-1,6783	0,95335	*NPAS2*	1	1

Supplementary Table 2.S4.8: Selected Circadian Genes in MAGMA Associated with Relative Amplitude.

GENE	CHR	START	STOP	NSNPS	NPARAM	N	ZSTAT	P	GENENAME	P_ADJ	P_ADJ_1
9575	4	56294068	56413076	418	14	71500	1,8195	0,034419	*CLOCK*	1	0,481866
1408	11	45868669	45904799	68	14	71500	1,1508	0,1249	*CRY2*	1	1
6096	9	77112252	77303534	407	35	71500	0,92174	0,17833	*RORB*	1	1
9572	17	38249037	38256978	15	5	71500	0,80422	0,21064	*NR1D1*	1	1
1407	12	107385142	107487635	181	13	71500	0,2233	0,41165	*CRY1*	1	1
6095	15	60780483	61521502	1930	205	71500	0,13518	0,44624	*RORA*	1	1
4862	2	101436613	101613289	479	62	71500	-0,085162	0,53393	*NPAS2*	1	1
5187	17	8043788	8059723	30	9	71500	-0,090015	0,53586	*PER1*	1	1
406	11	13299325	13408813	264	35	71500	-0,42675	0,66522	*ARNTL*	1	1
8864	2	239152679	239198678	127	20	71500	-0,4509	0,67397	*PER2*	1	1
6097	1	151778547	151804348	60	13	71500	-0,67047	0,74872	*RORC*	1	1
1628	19	49133817	49140639	3	2	71500	-0,68081	0,752	*DBP*	1	1
8863	1	7844413	7905241	217	26	71500	-0,88596	0,81218	*PER3*	1	1
9975	3	23986751	24022109	79	14	71500	-1,2784	0,89944	*NR1D2*	1	1

Supplementary Table 2.S4.9: Selected Circadian Genes in MAGMA Associated with Daytime Sleepiness.

GENE	CHR	START	STOP	NSNPS	NPARAM	N	ZSTAT	P	GENEN-AME	P_ADJ	P_ADJ_1
8863	1	7844413	7905241	281	30	452071	2,029	0,021227	*PER3*	1	0,297178
6095	15	60780483	61521502	3232	331	452071	1,5897	0,055955	*RORA*	1	0,78337
5187	17	8043788	8059723	57	22	452071	1,2371	0,10802	*PER1*	1	1
4862	2	101436613	101613289	796	93	452071	1,0461	0,14776	*NPAS2*	1	1
1628	19	49133817	49140639	17	8	452071	1,0373	0,1498	*DBP*	1	1
6096	9	77112252	77303534	654	72	452071	0,72214	0,23511	*RORB*	1	1
9572	17	38249037	38256978	23	11	452071	0,67918	0,24851	*NR1D1*	1	1
9975	3	23986751	24022109	143	34	452071	0,54118	0,29419	*NR1D2*	1	1
406	11	13299325	13408813	430	78	452071	0,39834	0,34519	*ARNTL*	1	1
9575	4	56294068	56413076	556	22	452071	0,25782	0,39827	*CLOCK*	1	1
1407	12	107385142	107487635	331	29	452071	0,089211	0,46446	*CRY1*	1	1
6097	1	151778547	151804348	96	29	452071	-0,70273	0,75889	*RORC*	1	1
8864	2	239152679	239198678	195	41	452071	-1,5553	0,94007	*PER2*	1	1
1408	11	45868669	45904799	99	25	452071	-1,9662	0,97536	*CRY2*	1	1

Interpretation of Parameters of MAGMA Analysis in Accordance with Parameter Interpretation from the MAGMA manual (https://ctg.cncr.nl/software/MAGMA/doc/manual_v1.10.pdf).

Parameter	Definition
GENE	Gene ID as specified in the annotation file.
CHR	Chromosome the gene is located on.
START/STOP	Annotation basepairs of where the gene starts and ends on that chromosome.
NSNPS	Number of SNPs annotated to that gene.
NPARAM	Number of relevant parameters used in the regression model.
N	Used sample size for analysis of that gene.
ZSTAT	Z-value presenting the measure of gene association.
P	Unadjusted p-value of that gene.
GENEAME	Name of located and examined gene.
P_ADJ	Bonferroni adjusted p-value for all genes (n = 17861).
P_ADJ_1	Secondary Bonferroni adjusted p-value for all circadian genes (n = 14).

3 METHYLOME-WIDE CHANGE ASSOCIATED WITH RESPONSE TO ELECTROCONSULIVE THERAPY IN DEPRESSED PATIENTS[2]

3.1 Abstract

Electroconvulsive therapy (ECT) is a quick-acting and powerful antidepressant treatment considered to be effective in treating severe and pharmacotherapy-resistant forms of depression. Recent studies have suggested that epigenetic mechanisms can mediate treatment response and investigations about the relationship between the effects of ECT and DNA methylation have so far largely taken candidate approaches. In the present study, we examined the effects of ECT on the methylome associated with response in depressed patients (n = 34), testing for differentially methylated CpG sites before the first and after the last ECT treatment. We identified one differentially methylated CpG site associated with the effect of ECT response (defined as >50% decrease in Hamilton Depression Rating Scale score, HDRS), TNKS ($q < 0.05$; $p = 7.15 \times 10^{-8}$). When defining response continuously (ΔHDRS), the top suggestive differentially methylated CpG site was in FKBP5 ($p = 3.94 \times 10^{-7}$). Regional analyses identified two differentially methylated regions on chromosomes 8 (Šídák's p = 0.0031) and 20 (Šídák's $p = 4.2 \times 10^{-5}$) associated with ΔHDRS. Functional pathway analysis did not identify any significant pathways. A confirmatory look at candidates previously proposed to be involved in ECT mechanisms found CpG sites associated with response only at the nominally significant level ($p < 0.05$). Despite the limited sample size, the present study was able to identify epigenetic change associated with ECT response suggesting that this approach, especially when involving larger samples, has the potential to inform the study of mechanisms involved in ECT and severe and treatment-resistant depression.

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3.2 Introduction

Depression is a major contributor to global burden of disease and despite worldwide research efforts, the heterogeneous nature of the disorder makes it difficult to definitively unravel its underlying etiology and the factors influencing treatment response (Krishnan & Nestler, 2008; WHO, 2017). Electroconvulsive therapy (ECT) is an intervention with rapid and striking antidepressant effects and is the treatment of choice for patients with severe and treatment-resistant depression (Jaffe, 2002; Singh & Kar, 2017). Studying biological changes associated with response to ECT in such a subgroup of severely depressed patients is a promising approach to gain insights into the underlying mechanisms of depression and treatment response. DNA methylation is thought to be involved in disease pathology through its influence on gene expression and cellular function (Jones, 2012; Meissner et al., 2008). There is evidence that pre-treatment methylation profiles may predict likelihood of achieving remission (Webb et al., 2020) and the literature on DNA methylation in depression has pointed to several possible genes of interest (e.g., *BDNF*, *SLC6A4*, *NR3C1*, *FKBP5*, etc. for reviews, see Chen et al., 2017; Lisoway et al., 2018; Menke et al., 2012; Webb et al., 2020) as being related to antidepressant response. Investigating change of methylation levels during treatment may inform the biological processes underlying both depression and antidepressant response. Examining these changes in ECT patients offers an optimal research setting as: (1) treatment effects are substantial and occur soon after the intervention, and (2) ECT patients represent a subgroup of patients with the most severe form of depression. It is likely that this subgroup is not only clinically but also genetically more homogenous, especially as these patients tend to show a higher genetic burden for major depression than those with less severe forms (Foo et al., 2019). The few studies exploring differences in methylation related to ECT are only beginning to give insight into the factors involved. A translational study observed that the response to electroconvulsive stimulation (ECS) in rats was predicted by higher p11 promoter methylation and found this also to be the case in two human samples (n = 11; n = 65) in response to ECT (Neyazi et al., 2018). Another candidate gene is brain-derived neurotrophic factor (*BDNF*) which is involved in neuroplastic changes associated with stress and depression (Levy et al., 2018; Pittenger & Duman, 2008). Methylation differences of the promoter region of *BDNF* have been observed in many psychiatric disorders (Zheleznyakova et al., 2016), and also after use of antidepressant medication (Tadic et al., 2014). Studies in animals and humans also propose an involvement of *BDNF* in response to ECT: after ECS/ECT, alterations of *BDNF* levels have been found in rats (Sartorius et al., 2009), and in humans, differences in expression of *BDNF* have been described (Kleimann et al., 2015; Stelzhammer et al., 2013). Furthermore, associations between pre-treatment *BDNF* levels and ECT outcome have been described, but whether *BDNF* levels are indicative of response remains to be determined (Rocha et al., 2016; van Zutphen et al., 2019). Research on ECT-related changes in methylation levels has largely focused on candidate genes. However, as ECT is a non-specific treatment with widespread, yet uncertain effects on biological processes, the selection of predefined candidates, relying on prior knowledge may not give the full picture. As such, an approach investigating the whole methylome is expected to yield new and relevant insights. Few studies have made use of these technologies in ECT samples to date. Moschny et al. (2020) examined longitudinal DNA methylation before and after ECT in a small group of patients (8 responders and 4 non-responders). They did not find any significant differences in global DNA methylation, but identified eight genes potentially implicated in either ECT response or its mechanism through analysis of single probe variance, and two genes

whose methylation changed during treatment course. In the present study, we aimed to identify changes in methylation levels associated with the effects of ECT and to find potential biomarkers for antidepressant response. We obtained and compared epigenome-wide DNA methylation levels of ECT patients (n = 34) before and after ECT. Differentially methylated CpG sites and regions associated with response were examined. Pathway analyses were employed to search for functional pathways affected by ECT. Finally, we took a targeted look at methylation in genes which have been previously implicated in ECT response and depression-related studies.

3.3 Materials and Methods

This study was approved by the Ethics Committee (II), Medical Faculty Mannheim, University of Heidelberg. All patients provided written consent after a detailed explanation of the content of the study. All experimental procedures were performed in accordance with the Declaration of Helsinki.

3.3.1 Participants

Patients (n = 34) diagnosed with a major unipolar depressive episode (based on International Classification of Diseases version 10, ICD-10), older than 18 years, and assigned to ECT treatment were recruited at the Department of Psychiatry and Psychotherapy at the Central Institute of Mental Health (CIMH) in Mannheim, Germany, between 2014 and 2016. Criteria for assignment to ECT were treatment-resistant depression (i.e., failure of two adequate dose-duration antidepressants from different classes, or psychotherapy in the current episode), positive experience of ECT from a previous episode, or severe depression with (a) psychotic symptoms, (b) severe suicidality, or (c) the refusal of food or fluid intake. Patients were excluded if they had any substance-use related disorders (other than tobacco and alcohol use disorders) or a lifetime diagnosis of schizophrenia. All participants were of Caucasian descent. The patients kept the same medication regimens throughout ECT treatment. This sample is a subset of a sample reported in a previous genetic study in ECT patients (Foo et al., 2019). Descriptive and clinical characteristics of the participants are described in Table 3.1.

3.3.2 Depression and DNA Methylation Assessment

The 21-item version of the Hamilton Depression Rating Scale (HDRS) was administered and blood was collected from patients prior to the first (T1) and after the last (T2) session of ECT (average sessions: 10.82, range: 5–25 sessions). T2 was between 1 and 7 days after the last ECT session. Time of collection was kept constant between 8:30 and 9:30 a.m. at both timepoints to keep it close to the clinical interview conducted around the same time, as well as preclude any potential confounding effects arising from ward routines and circadian fluctuations (Liu & Chung, 2015; Rijo-Ferreira & Takahashi, 2019). Standard procedures for extraction and processing were followed. DNA extraction was performed using the Chemagic Magnetic Separation Module 1 (Chemagen Biopolymer-Technologie AG; Baesweiler, Germany). All genomic DNA samples were stored at −20 °C prior to analysis. Epigenome-wide DNA methylation was measured using the Illumina Infinium Methylation EPIC array (>850,000 CpG sites). The arrays were processed at the Genome Analysis Center at the

HelmholtzZentrum München and Max-Planck-Institute for Psychiatry in Munich, Germany.

Table 3.1. Patient Demographics.

	Responders (n=25)	*Non-Responders (n=9)*	*P-value (group comparison)*
Sex (M/F)	16/9	2/7	0.05[1]
Smoking (NS/S)	22/3	4/5	0.02[1]
	Mean (SD)	*Mean (SD)*	
Age	65.8 (18.7)	55.8 (15.4)	0.16[2]
BMI	24.8 (3.9)	26.6 (5.3)	0.30[2]
Baseline HDRS	28.7 (5.4)	27.0 (6.0)	0.43[2]
Baseline HDRS (Min - Max)	19 - 38	21 - 41	
ΔHDRS	21.1 (6.2)	6.1 (6.7)	8.21×10^{-7} [2]
Number of ECT Sessions	10.2 (4.7)	12.4 (6.4)	0.28[2]
Number of Weeks (T1 - T2)	4.6 (1.9)	5.5 (2.6)	0.28[2]
ECT Sessions per Week	2.2 (0.1)	2.2 (0.1)	0.45[2]

[1]Fisher's Exact Test; [2]t-test; M = Male; F = Female; NS = Non-Smoker; S = Smoker; BMI = Body Mass Index; HDRS = Hamilton Depression Rating Scale; ECT = Electroconvulsive therapy; SD = Standard Deviation.

3.3.3 ECT Treatment

ECT was conducted with a Thymatron IV device (Somatics, LLC. Lake Bluff, IL, USA). Anesthetic drugs used were: s-ketamine (~1.0 mg/kg) (Hoyer et al., 2014; Kranaster et al., 2011) and succinylcholine for muscle relaxation (~1.0 mg/kg). Seizure thresholds were titrated at the initial session; dosing in subsequent sessions was given at >2.5 above this threshold. If patients did not show a clinical improvement or seizures were insufficient, energy used was increased. Patients received 2–3 ECT sessions per week. All patients started with unilateral stimulation with the possibility to change to bilateral stimulation at the discretion of the ECT supervisor.

3.3.4 Statistical Analysis

Data processing, quality control (QC) and other statistical analyses were performed using R (versions 3.4.4 and 3.6.3) analysis software (https://cran.r-project.org/).

3.3.4.1 Data Preprocessing, QC, and Filtering

Methylation values were extracted using an updated version of the pipeline indicated in (Lehne et al., 2015), adapted in-house for use with the Illumina Infinium EPIC array. Illumina background correction was applied to all intensity values. A detection p-value threshold of $p < 10^{-16}$ was used and intensity values with detection $p \geq 10^{-16}$ were designated as missing data. The proportion of missing data points was determined, allowing the calculation of sample and CpG site-specific call rates. Samples with insufficient DNA quality as denoted by a call rate of <95% were excluded. Intensity values were quantile normalized for each of the six probe types present on the array separately. Intensity values were converted to methylation beta values according to the manufacturer's recommendation. White blood cell fractions were estimated according to (Houseman et al., 2012). Five of the six resulting estimates were subsequently included as covariates in downstream analyses to control for influences of cell type distribution on DNA methylation. The estimate for granulocytes showed the highest variance inflation factor (VIF) and was omitted to avoid collinearity issues. CpG

sites were filtered by removing cross-hybridizing probes, probes with high missing rate (>0.02), and probes linked to X- and Y-chromosomes. Correction for batch effects and other technical parameters was done by performing a principal component analysis on internal control probe intensity values and including the first 10 extracted principal components (PCs) as covariates in the downstream analyses. Prior to analysis, all methylation beta values were logit transformed (base 2) to M-values, which were used in downstream analysis as recommended in (Du et al., 2010).

3.3.4.2 Differentially Methylated Single CpG Sites

Association testing of methylation M-values for each CpG site was done using a mixed linear model approach as implemented in the limma R package. Participant ID was used as a blocking factor, and estimated cell fractions, 10 control probe PCs, age, sex, and smoking status were included as additional covariates to adjust for confounding factors. It was observed that sex was highly correlated with the 5th control probe PC, thus this PC was not included in the statistical models to avoid collinearity issues. The main effects of interest specified included: (1) response (responders vs. non-responders), (2) timepoint (change after intervention), and (3) the interaction between timepoint and response (the difference in change between response groups). Models were calculated with response specified both as a binary (>50% decrease in HDRS score) and continuous variable (i.e., change in HDRS score, ΔHDRS). In addition, we examined the relationship between baseline (T1) methylation and response (both binary and continuous) in additional models. Significance was defined as false discovery rate (FDR) $q < 0.05$. Results at a suggestive threshold of $p < 10^{-5}$ were also reported.

3.3.4.3 Differentially Methylated Regions

Differentially methylated region (DMR) analysis was performed on the results of the above analyses using the comb-p package (Pedersen et al., 2012). Comb-p parameters were specified as: seed p-value = 0.001 and a maximum distance between probes of 500 base pairs. These parameters follow those used in previous studies in the field (Mooney et al., 2020; Roberts et al., 2019) and results from simulation experiments (Mallik et al., 2019).

3.3.4.4 Pathway Analysis

A Gene Ontology (GO) enrichment analysis was performed on the results of the different models using the missMethyl (v1.12.0) R package. We examined CpG sites at the suggestive threshold of 1×10^{-5}.

3.3.4.5 Targeted Examination of Methylation Change in Candidate CpG Sites

Change in methylation of candidate genes from the literature was examined in an exploratory search. First, we selected: (1) candidates implicated in reviews of DNA methylation and antidepressant medication, i.e., *BDNF*, *MAOA*, *SLC6A2*, *SLC6A4*, *HTR1A*, *HTR1B*, *IL6*, *IL11* (Webb et al., 2020); *SLC6A4*, *NR3C1*, *FKBP5*, and *OXTR* (Chen et al., 2017); and (2) candidates specific to ECT, i.e., *S100A10* (p11) (Neyazi et al., 2018), *RNF175*, *RNF213*, *TBC1D14*, *TMC5*, *WSCD1*, *AC018685.2*, *AC098617.1*, *CLCN3P1*, *AQP10*, and *TRERF1* (Moschny et al., 2020). Autosomal CpG sites which were annotated to these candidate genes in the UCSC Genome Browser NCBI curated RefSeq (retrieved: August 10, 2018) were extracted from the results of the single site

analyses above (for each variable of interest in both binary and continuous models). Furthermore, to examine their predictive value in our sample, association between baseline methylation and response was also examined. A secondary FDR correction was applied to the list of all candidate CpG sites to control for false positives.

3.4 Results

Descriptive statistics of the sample are shown in **Table 3.1**. In the sample analyzed, using binary criteria, (defined as decrease of HDRS score of more than 50%) 25 were responders and 9 were non-responders to ECT. Levene's test found no significant differences between group variances. Briefly, as also reported for the total sample in (Foo et al., 2019), binary response to ECT was positively correlated with sex (being male) while continuous response (ΔHDRS score) was also associated with male sex and positively correlated with increased age.

3.4.1 Single CpG Site Analysis

3.4.1.1 Binary Response

In the binary response model, one significantly differentially methylated site ($q < 0.05$), cg10005358, mapped to *TNKS*, was observed as an effect of response. Eight sites reached a suggestive threshold of $p < 1 \times 10^{-5}$ (see Table 3.2). No significantly differentially methylated CpG sites were observed for the effect of timepoint (at $p < 1 \times 10^{-5}$; 22 CpG sites), or interaction effect (at $p < 1 \times 10^{-5}$; 12 CpG sites). Several CpG sites annotated to the same gene appeared among the top hits of these effects of interest (see Tables 3.2 and 3.S1.1–3.S1.3, e.g., *TNKS*, *PCM1*, *RAPGEF2*, *RAB21*; all suggestive at $p < 1 \times 10^{-5}$).

3.4.1.2 Continuous Response (ΔHDRS)

In the continuous response model, no effects yielded significantly differentially methylated CpG sites at $q < 0.05$. At a suggestive threshold of $p < 1 \times 10^{-5}$, 7, 9, and 5 differentially methylated CpG sites were observed for the effects of ΔHDRS, timepoint, and ΔHDRS × timepoint, respectively (see Table 3.2 and Tables 3.S2.1–3.S2.3). *FKBP5* (CHR 6: cg01294490) was the top hit for both effect of ΔHDRS ($p = 4.46 \times 10^{-7}$) and effect of interaction of ΔHDRS × timepoint ($p < 3.94 \times 10^{-7}$). *FXR2* (CHR 17: cg02936535) was also observed among the top hits for all effects of interest (ΔHDRS $p = 3.79 \times 10^{-6}$; timepoint $p = 6.78 \times 10^{-6}$; ΔHDRS × timepoint $p = 7.38 \times 10^{-6}$).

3.4.1.3 Baseline Methylation and Response

Methylation at baseline was not significantly associated with either binary or continuous response. At a suggestive threshold of $p < 1 \times 10^{-5}$ baseline methylation was associated with binary response at 9 CpG sites and with ΔHDRS at 6 CpG sites (see Tables 3.S3.1 and 3.S3.2).

3.4.2 Differentially Methylated Region Analysis

Two DMRs were identified as associated with effect of ΔHDRS in the continuous response model. One significant DMR on chromosome 8 was identified (3 probes,

Šídák's corrected p = 0.0031) and another on chromosome 20 (13 probes, Šídák's corrected p = 4.2×10^{-5}). The DMR on chromosome 8 (CHR 8: 127568854-127569023) is located in the *LRATD2* (*FAM84B*) gene, while the chromosome 20 DMR (CHR 20: 36148620-36148861) is located in the *BLCAP* gene and in the promoter region of *NNAT* (791 base pairs upstream of the transcription start site, TSS). Two other regions on chromosomes 14 and 19 were nominally significant but did not remain significant after Šídák correction (see Table 3.3 and Figure 3.1). Analysis of the results from timepoint and timepoint × ΔHDRS models, as well as all binary response models, did not identify significant DMRs.

3.4.3 Pathway Analysis

No significant pathways were observed in any of the models.

3.4.4 Candidate Analysis

In the binary model, at nominal significance (p < 0.05 uncorrected), 43, 37, and 36 CpG sites were associated with response, timepoint, and response × timepoint interaction, respectively. The top 3 candidate CpG sites associated with binary response were: *FKBP5* (cg01294490, p = 8.74×10^{-5}), *BDNF-AS* (cg02386995, p = 1.51×10^{-4}), and *NR3C1* (cg23273257, p = 0.0012), but no CpG site tested survived secondary FDR correction for multiple testing. In the continuous response model, 41, 43, and 42 CpG sites were nominally associated with ΔHDRS, timepoint and ΔHDRS × timepoint interaction, respectively. The top 3 candidate CpG sites associated with continuous response were, *FKBP5* (cg01294490, p = 4.46×10^{-7}), *BDNF* (cg15710245, p = 0.0033), and *BDNF-AS* (cg09878183, p = 0.0034). The site annotated to *FKBP5* survived the secondary correction for multiple testing (q = 0.0004).

Table 3.2. Top 10 Differentially Methylated CpG Sites Associated With Binary Response and ΔHDRS.

CpG	*CHR*[1]	*Base Pair Position*	*p-value*	*FDR*[2]	*Annotated Genes*
Binary Response					
cg10005358	8	9505300	7.2×10^{-8}	0.0498	*TNKS*
cg22813821	12	72148853	2.2×10^{-6}	0.5940	*RAB21*
cg11062168	15	35262789	2.6×10^{-6}	0.5940	*AQR*
cg12305855	4	160216262	5.1×10^{-6}	0.6072	*RAPGEF2*
cg19869734	2	107154571	9.8×10^{-6}	0.6072	
cg08133350	19	50321326	9.9×10^{-6}	0.6072	*MED25*
cg23870282	3	72897792	1.0×10^{-5}	0.6072	*SHQ1*
cg00101693	10	70715578	1.0×10^{-5}	0.6072	*DDX21*
cg23367665	1	231414306	1.1×10^{-5}	0.6072	
cg00511318	17	56406260	1.1×10^{-5}	0.6072	*TSPOAP1;TSPOAP1-AS1*
ΔHDRS					
cg01294490	6	35656906	4.5×10^{-7}	0.3106	*FKBP5*
cg10515948	2	242674491	1.3×10^{-6}	0.4558	*D2HGDH*

cg02936535	17	7514491	3.8×10^{-6}	0.7870	*FXR2*
cg11385008	2	11621166	6.1×10^{-6}	0.7870	
cg16377817	5	170845627	8.2×10^{-6}	0.7870	*FGF18*
cg06668695	15	80213874	8.6×10^{-6}	0.7870	*ST20-MTHFS;ST20;ST20-AS1*
cg08790000	11	67255752	9.0×10^{-6}	0.7870	*AIP*
cg16306546	21	44183372	1.0×10^{-5}	0.7870	*PDE9A*
cg19307750	1	241372556	1.1×10^{-5}	0.7870	*RGS7*
cg03611990	6	96980568	1.2×10^{-5}	0.7870	*UFL1*

[1]Chromosome; [2]False Discovery Rate; CpG = cytosine-phosphate-guanine (CpG).

Table 3.3. Differentially Methylated Regions Associated with ΔHDRS.

CHR[1]	*Base Pair Start - End*	*Min p-value*	*Number of Probes*	*Šídák's p-value*	*Annotated Genes*
20	36148620 - 36148861	2.4×10^{-4}	13	4.2×10^{-5}	*BLCAP,NNAT*
8	127568854 - 127569023	2.4×10^{-4}	3	0.0031	*LRATD2 (FAM84B)*
19	39402922 - 39402937	3.0×10^{-4}	3	0.4673	*CCER2*
14	91720372 - 91720373	7.9×10^{-4}	1	1	*GPR68*

[1]Chromosome.

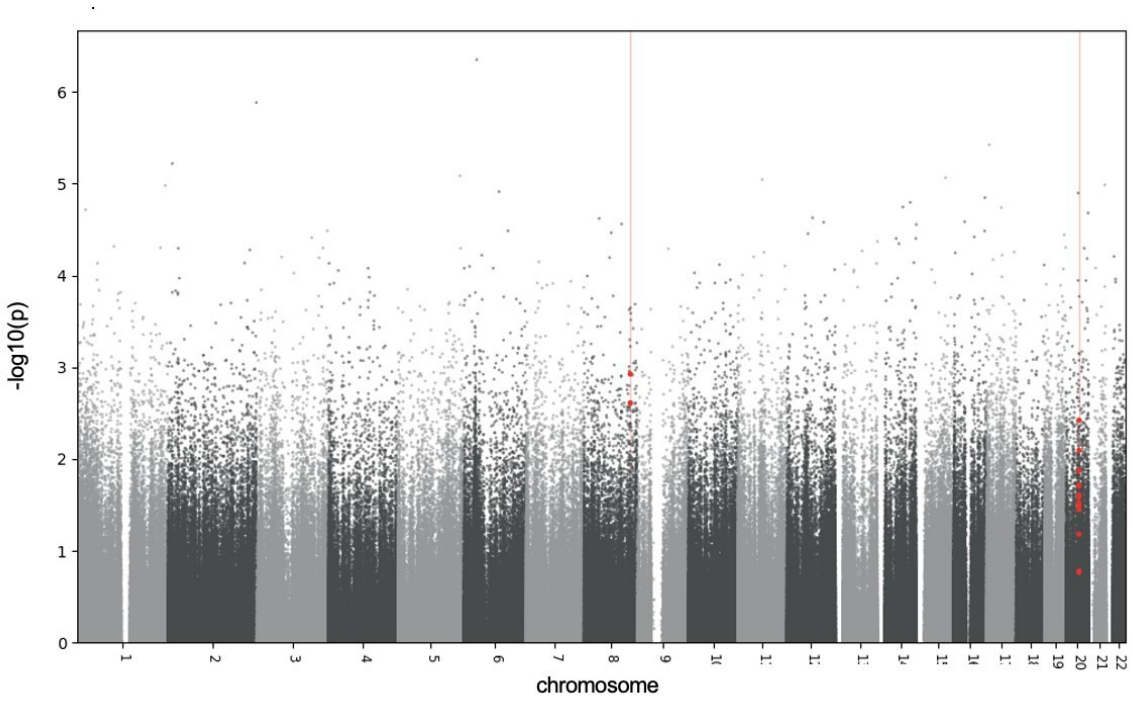

Figure 3.1. Manhattan Plot Showing Differentially Methylated Regions for the Effect of ΔHDRS.

3.5 Discussion

The present study examined treatment-associated changes of DNA methylation levels in 34 patients in an epigenome-wide manner. By investigating the relationship between response status and change in methylation levels, this study identified several potential CpG sites involved in ECT response and outlines potential differences between response groups. The top CpG site associated with binary response is located in TNKS, which is a protein-coding gene associated with blood pressure, alcohol consumption, implicated in cancer pathology, and involved in various processes such as the Wnt signaling pathway, telomere length, and vesicle trafficking (*TNKS* Gene-GeneCards, 2021). Telomere length, a marker associated with aging is also known to be associated with psychiatric disorders (Darrow et al., 2016) including major depressive disorder (Ridout et al., 2016), as well as depressive symptoms (Humphreys et al., 2020). In several genome-wide association studies (GWASs) of depression-related traits, *TNKS* was found to be associated with ($p = 7.68 \times 10^{-10}$) (Jones et al., 2019a), bipolar disorder ($p = 3 \times 10^{-6}$) (Stahl et al., 2019), and positive affect ($p = 0.0003$) (Baselmans et al., 2019). Among the top 5 CpG sites suggestively associated with binary response, genes associated with processes such as cell adhesion, cell growth, apoptosis in malignant tumors, protein metabolism (*RAB21*) (*RAB21* Gene-GeneCards, 2021), and signaling in glucose metabolism (AQR) (Song et al., 2018) were found. *RAB21* was previously reported to be associated with remission ($p = 0.0103$) in a GWAS of selective serotonin reuptake inhibitors in MDD patients (Ji et al., 2013) and *AQR* as related to neuroticism ($p = 9.58 \times 10^{-8}$) and worry ($p = 2.06 \times 10^{-6}$) (Nagel et al., 2018), a well-known symptom in depression. *RAPGEF2*, a protein-coding gene suggested to be involved in signal transmission, in BDNF receptor pathway signaling (*RAPGEF2* Gene-GeneCards, 2021) in schizophrenia (Han & Gage, 2016), and is found to be a target for regulated miRNAs in MDD (Garbett et al., 2015). *PCM1*, located in a chromosomal region on *8p*, which has been implicated in various neuropsychiatric disorders including schizophrenia and depression (Tabares-Seisdedos & Rubenstein, 2009), is a protein-coding gene critical for cell division, and is involved in the proliferation and neurogenesis of neuroprecursors (Zhang et al., 2016). The top site in the continuous response analysis was located in *FKBP5*, a gene which is known to be an important endogenous regulator of the stress hormone system possibly linked to stress-related psychiatric disorders such as depression (Binder, 2009). *FKBP5* demethylation resulting from childhood trauma has been linked to longterm stress hormone system deregulation and effects on immune function and brain areas associated with stress regulation (Klengel et al., 2013). Depressive phenotypes are shown to be associated with the age-related decrease in *FKBP5* methylation (Zannas et al., 2019). Altered epigenetic and genetic *FKBP5* regulation may contribute to stress-related disease risk. Findings related to *FKBP5* have pointed to it as important in the interaction with environment in stress-related disorders such as major depression (Zannas et al., 2016). The present study found an association between methylation in a CpG site in *FKBP5* and the reduction in patients' HDRS scores. Although the CpG site identified here has not been associated with antidepressant response in previous studies, the findings support *FKBP5* as an important gene requiring further investigation in the present context. Among the top 5 CpG sites suggestively associated with continuous response were CpG sites annotated to *D2HGDH* and *FXR2*. *D2HGDH* encodes for the enzyme D-2-hydroxyglutarate dehydrogenase, and is suggested to be downregulated in depressed patients during remission (Scifo et al., 2018). Proteins of the FXR family have commonly been reported in autism spectrum disorders, and evidence from GWASs in

mood disorders and schizophrenia suggests that Fragile X mental retardation syndrome-related proteins are involved in the development of mental disorders (Khlghatyan & Beaulieu, 2018). Two DMRs associated with continuous response were identified. The DMR on chromosome 8 lies in *LRATD2* (*FAM84B*), which is known to be involved in gastric and prostate cancer (Wong et al., 2017; Zhang et al., 2019). In a recent large genome-wide gene-environment analysis, its paralog, *LRATD1*, was observed to be associated with unipolar depression and response to trauma exposure (Coleman et al., 2020b). The DMR on chromosome 20 is located in *BLCAP* and in the promoter region of *NNAT*. *BLCAP* encodes a protein that regulates cell proliferation and reduces cell growth by stimulating apoptosis (*BLCAP* NCBI, 2021) and NNAT is involved in brain development and neuronal differentiation (*NNAT* NCBI, 2021). Together with the single site results, these findings are in line with previous works in the field of ECT; alterations in mechanisms such as neurogenesis and neuroinflammatory immune response are proposed to be among the mechanisms of ECT action (Mindt et al., 2020; Nakamura et al., 2013; van Buel et al., 2015). Several candidate genes proposed in the literature were found harboring CpG sites with nominally significant changes between T1 and T2, and T1 methylation values for a number of them were also nominally associated with response (both binary and continuous) (see Tables 3.S4.1–3.S6.2); the roles they play remain unclear. The present results appear to lend support to previous research which has suggested the importance of these candidates but these results are preliminary and further investigation is warranted. Also, the identification of *FKBP5* in the present study suggests that future research should assess and control for factors such as childhood trauma and stress (Klengel et al., 2013; Weder et al., 2014). This study had several limitations. Although the largest study to date, the present sample size was limited, and it is expected that future studies using a similar approach in larger samples will be able to further clarify our results. Sample size notwithstanding, we identified a single significantly differentially methylated CpG site, as well as some suggestive ones which need further investigation. While we assessed methylation levels in whole blood, ECT is applied to the brain; both central and peripheral mechanisms may be affected by the global nature of the treatment and care should be taken with the interpretation of these findings (Hannon et al., 2015). The possible effect of anesthesia and pharmacotherapy is a potential confounding factor in methylation studies. However, medication in each patient was kept constant during the ECT course, and there were no differences between patients regarding anesthesia administration or treatment dosage. Therefore, the observed changes are unlikely to have resulted from these medications. The genes implicated in our findings have been previously involved in the etiology of depression and treatment response, but confirmation in larger samples is needed. Multi-center approaches and collaborative efforts could help in obtaining the sample sizes required to allow a more robust characterization of ECT response and give insights into the biological processes underlying the striking antidepressant effects of ECT.

3.6 Acknowledgements

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[031L0190A] and through ERA-NET NEURON, “SynSchiz-linking synaptic dysfunction to disease mechanisms in schizophrenia-a multilevel investigation” [01EW1810], through ERA-NET NEURON “EMBED-impact of Early life MetaBolic and psychosocial strEss on susceptibility to mental Disorders; from converging epigenetic signatures to novel targets for therapeutic intervention” [01EW1904], and by a grant of the Dietmar-Hopp Foundation. The funders had no role in the design of the study nor in its execution, analyses, interpretation of results, and decision to prepare and submit the manuscript for publication.
The authors declare no competing interests.

3.7 Supplementary Material

Supplementary Tables 3.S1.1-3.S6.2 had been reduced to save space. The full summary statistics showing all 1,000 (3.S1.1-3.S3.2) and 799 (3.S4.1-3.S6.2) sites are available under https://www.nature.com/articles/s41398-021-01474-9#Sec21.

Supplementary Table 3.S1.1: Differently Methylated CpG Sites (Top 1000) Associated with the Effect of Binary Response.

CHR	BP	cg	Gene	logFC	AveExpr	t	P.Value	adj.P.Val	B
8	9505300	cg10005358	*TNKS*	-2,50339814	3,71617987	-6,33888769	0,00000007	0,04984269	0,38090000
12	72148853	cg22813821	*RAB21*	18,27267496	-9,04291036	5,36742335	0,00000220	0,59397780	-0,63766151
15	35262789	cg11062168	*AQR*	1,24704957	0,82877236	5,32380033	0,00000256	0,59397780	-0,68482957
4	160216262	cg12305855	*RAPGEF2*	1,56144136	2,78331410	5,12401040	0,00000510	0,60720699	-0,90196697
2	107154571	cg19869734		-1,35361536	2,69733310	-4,93375389	0,00000980	0,60720699	-1,11013171
19	50321326	cg08133350	*MED25*	15,70383776	-8,40712773	4,92985412	0,00000993	0,60720699	-1,11440970
3	72897792	cg23870282	*SHQ1*	1,29698995	-4,65771751	4,92734082	0,00001002	0,60720699	-1,11716695
10	70715578	cg00101693	*DDX21*	1,29177113	-4,11062461	4,92642865	0,00001005	0,60720699	-1,11816770
1	231414306	cg23367665		-1,07317337	3,48840287	-4,89888252	0,00001104	0,60720699	-1,14839832
17	56406260	cg00511318	*TSPOAP1; TSPOAP1-AS*	4,96730281	-4,94454699	4,89636741	0,00001113	0,60720699	-1,15115943
4	108746407	cg02823293	*SGMS2*	0,86901647	-3,58630089	4,87545413	0,00001195	0,60720699	-1,17412378
6	111804752	cg10830518	*REV3L; TRAF3IP2-AS1*	1,87978817	-5,74772835	4,86210230	0,00001251	0,60720699	-1,18879006
5	138731441	cg09469111	*PROB1*	0,67062724	2,39647210	4,83169040	0,00001387	0,60720699	-1,22220941
11	72417121	cg26730831	*ARAP1*	-1,10112181	3,08226403	-4,81125004	0,00001486	0,60720699	-1,24468090
12	65218052	cg13039115	*TBC1D30*	9,60141515	-4,75026565	4,79385058	0,00001576	0,60720699	-1,26381499
10	131640139	cg04217539	*EBF3*	0,98068736	3,19171478	4,79116811	0,00001591	0,60720699	-1,26676532
8	145634833	cg20962000	*CPSF1*	12,10269537	-7,39428740	4,78893040	0,00001603	0,60720699	-1,26922657
3	113415262	cg17171448	*USF3*	19,37865511	-7,60895378	4,77015079	0,00001708	0,60720699	-1,28988520
11	66521467	cg12450728	*C11orf80*	-1,09586866	2,90732222	-4,72868916	0,00001965	0,60720699	-1,33551247
6	31865909	cg05495984	*EHMT2;C2*	2,02116746	-3,77366783	4,72401495	0,00001996	0,60720699	-1,34065761
3	30648096	cg12541591	*TGFBR2*	1,17161012	-3,86696181	4,71693148	0,00002044	0,60720699	-1,34845519
2	27580174	cg25462815	*GTF3C2*	1,09798228	-3,58469037	4,69653736	0,00002189	0,60720699	-1,37090815
15	80213874	cg06668695	*ST20MTHFS;ST20;ST20-AS1*	-0,71727461	3,34763480	-4,69295750	0,00002216	0,60720699	-1,37484981
22	25564248	cg24671382	*KIAA1671*	0,72235148	3,17110202	4,67873525	0,00002325	0,60720699	-1,39051049
9	116172877	cg12829978	*POLE3;C9orf43*	12,81633299	-7,61181588	4,67843189	0,00002327	0,60720699	-1,39084455

Supplementary Table 3.S1.2: Differently Methylated CpG Sites (Top 1000) Associated With the Effect of Timepoint in the Binary Response Model.

CHR	BP	cg	Gene	logFC	AveExpr	t	P.Value	adj.P.Val	B
8	17829063	cg21318700	*PCM1*	0,78931571	3,34137260	6,03955768	0,00000021	0,14419653	3,70205870
8	9505300	cg10005358	*TNKS*	-1,09021176	3,71617987	-5,75175913	0,00000057	0,19926023	3,11562995
16	71687460	cg20022220	*PHLPP2*	0,98991693	3,32240555	5,42819361	0,00000178	0,30168708	2,45138839
12	72148853	cg22813821	*RAB21*	8,67772028	-9,04291036	5,31099709	0,00000267	0,30168708	2,21006713
4	140561951	cg02431535		-0,78120211	3,31513264	-5,30531425	0,00000273	0,30168708	2,19836064
1	32208634	cg13182731	*ADGRB2*	0,86222008	5,42124106	5,26863940	0,00000310	0,30168708	2,12280484
6	111804752	cg10830518	*REV3L;TRAF3IP2-AS1*	0,97002458	-5,74772835	5,22762723	0,00000357	0,30168708	2,03830454
10	131813485	cg10847915		1,05398996	5,72430853	5,20366047	0,00000388	0,30168708	1,98892250
10	70715578	cg00101693	*DDX21*	0,65199713	-4,11062461	5,18082591	0,00000419	0,30168708	1,94187382
16	81047029	cg20765446	*CENPN*	-0,47771378	2,97303557	-5,16970280	0,00000436	0,30168708	1,91895618
5	17406866	cg23118697	*LOC101929544*	-0,42449666	2,25241744	-5,10124269	0,00000552	0,30168708	1,77792212
5	93382458	cg18331133	*FAM172A*	-0,42436862	3,63861771	-5,09815218	0,00000558	0,30168708	1,77155648
14	21439883	cg10960632		0,83787800	-5,32605918	5,05960152	0,00000637	0,30168708	1,69216340
1	31821436	cg14805250	*ZCCHC17*	0,51462558	2,82040181	5,05048851	0,00000657	0,30168708	1,67339907
8	1805190	cg04003839	*ARHGEF10*	-0,50478822	3,73006232	-5,04780669	0,00000663	0,30168708	1,66787729
7	134779210	cg23231197	*AGBL3;C7orf49*	0,42733041	3,51104392	5,02463086	0,00000718	0,30168708	1,62016475
6	39311540	cg23881245	*KIF6*	0,34265472	3,11020338	5,00579486	0,00000766	0,30168708	1,58139495
7	20369301	cg11621808	*LOC101927811; ITGB8*	-0,93036709	-3,92806240	-4,97421211	0,00000853	0,30168708	1,51640750
6	6009011	cg25307691	*NRN1*	8,74212878	-8,66305043	4,97155007	0,00000861	0,30168708	1,51093103
1	181007669	cg22450342	*MR1*	0,41685018	1,36188900	4,94814897	0,00000933	0,30168708	1,46279766
5	173111423	cg14873776		-0,78661741	3,40370751	-4,94414620	0,00000946	0,30168708	1,45456602
8	37553131	cg12440566	*ZNF703*	-1,53925653	-6,96878760	-4,94217850	0,00000952	0,30168708	1,45051966
4	174357286	cg12145043	*SCRG1*	-0,46492531	2,41068896	-4,86353786	0,00001245	0,33668906	1,28890998
10	53149004	cg17730149	*PRKG1*	0,81141534	2,18119251	4,86103610	0,00001255	0,33668906	1,28377250
4	20605725	cg01749295	*SLIT2*	-0,85175116	2,74265499	-4,85574359	0,00001278	0,33668906	1,27290496

Supplementary Table 3.S1.3: Differently Methylated CpG Sites (Top 1000) Associated With the Effect of the Interaction Between Binary Response and Timepoint.

CHR	BP	cg	Gene	logFC	AveExpr	t	P.Value	adj.P.Val	B
4	160216262	cg12305855	*RAPGEF2*	-1,12372240	2,78331410	-6,19281164	0,00000012	0,07673741	3,17091193
8	9505300	cg10005358	*TNKS*	1,40923252	3,71617987	5,99253115	0,00000024	0,07673741	2,81341484
8	17829063	cg21318700	*PCM1*	-0,95785181	3,34137260	-5,90732042	0,00000033	0,07673741	2,66032294
15	50979356	cg03965827	*TRPM7*	-0,75193739	-3,85727023	-5,61092470	0,00000094	0,16344705	2,12393715
10	70715578	cg00101693	*DDX21*	-0,82317126	-4,11062461	-5,27207203	0,00000306	0,37729540	1,50531837
14	24605782	cg18070079	*PSME1*	-0,82596150	-4,97074908	-5,21419961	0,00000374	0,37729540	1,39931195
14	103442892	cg20521220	*CDC42BPB*	0,78463679	3,72130386	5,19144029	0,00000404	0,37729540	1,35760662
10	133572424	cg11969919		-0,57422899	2,77959643	-5,14146057	0,00000481	0,37729540	1,26599624
8	41272824	cg00447085		-0,90455035	1,69277290	-5,13750763	0,00000487	0,37729540	1,25874949
3	72897792	cg23870282	*SHQ1*	-0,78262629	-4,65771751	-4,99315372	0,00000800	0,50430653	0,99406200
3	124278885	cg11463851	*KALRN*	1,09394008	-4,55721325	4,97904972	0,00000839	0,50430653	0,96820186
7	27865298	cg04913392	*TAX1BP1*	-1,05724034	3,48918836	-4,96920731	0,00000868	0,50430653	0,95015628
12	95867614	cg15390415	*METAP2*	0,74861892	-4,07777765	4,91836046	0,00001033	0,50653735	0,85694553
11	47289814	cg12195149	*NR1H3;MADD*	0,37749387	2,29565452	4,91684556	0,00001038	0,50653735	0,85416893
2	32503081	cg01195127	*YIPF4*	0,43686570	-3,83117576	4,88372154	0,00001162	0,50653735	0,79346557
19	50321326	cg08133350	*MED25*	-9,26328418	-8,40712773	-4,88357394	0,00001163	0,50653735	0,79319511
19	10509456	cg05151419	*CDC37*	0,70390045	3,30592989	4,86415752	0,00001242	0,50886126	0,75762097
5	138731441	cg09469111	*PROB1*	-0,40018954	2,39647210	-4,84203758	0,00001339	0,50886126	0,71710244
1	149982400	cg00941229	*OTUD7B*	-10,11073646	-8,29807528	-4,83165203	0,00001387	0,50886126	0,69808217
1	110284817	cg16780480	*GSTM3*	-0,39274243	2,74884155	-4,80015039	0,00001543	0,51697641	0,64040516
8	98635123	cg06607266		-0,63386903	3,34687188	-4,75776681	0,00001781	0,51697641	0,56284637
14	69658356	cg01028283	*EXD2*	0,44638882	-4,02080975	4,75595186	0,00001792	0,51697641	0,55952633
8	128138702	cg13819913		-0,69149030	3,49137751	-4,75292215	0,00001810	0,51697641	0,55398441
1	231414306	cg23367665		0,61876407	3,48840287	4,74347633	0,00001869	0,51697641	0,53670812
14	74428069	cg05178711	*COQ6;ENTPD5*	0,62244331	3,48214152	4,73875807	0,00001899	0,51697641	0,52807955

Supplementary Table 3.S2.1: Differently Methylated CpG Sites (Top 1000) Associated With the Effect of Continuous Response (ΔHDRS).

CHR	BP	cg	Gene	logFC	AveExpr	t	P.Value	adj.P.Val	B
6	35656906	cg01294490	*FKBP5*	0,08383636	-4,36393228	5,82247695	0,00000045	0,31062540	6,13049273
2	242674491	cg10515948	*D2HGDH*	0,08882513	-4,77560698	5,51602270	0,00000131	0,45584339	5,08399689
17	7514491	cg02936535	*FXR2*	-0,07255416	3,49687656	-5,21056371	0,00000379	0,78702579	4,05335840
2	11621166	cg11385008		-0,03934593	1,69005330	-5,07514486	0,00000604	0,78702579	3,60141269
5	170845627	cg16377817	*FGF18*	-0,03994700	0,60958946	-4,98467799	0,00000823	0,78702579	3,30144572
15	80213874	cg06668695	*ST20-MTHFS;ST20;ST20-AS1*	-0,03645135	3,34763480	-4,97152478	0,00000861	0,78702579	3,25797126
11	67255752	cg08790000	*AIP*	0,03476560	2,78962312	4,95820225	0,00000901	0,78702579	3,21397400
21	44183372	cg16306546	*PDE9A*	0,04661389	2,91696006	4,91881304	0,00001031	0,78702579	3,08411292
1	241372556	cg19307750	*RGS7*	0,05343684	1,90029721	4,91338054	0,00001050	0,78702579	3,06622890
6	96980568	cg03611990	*UFL1*	-0,03225041	0,63906016	-4,86864389	0,00001223	0,78702579	2,91920086
20	33699516	cg20990011		-0,07208232	3,33879370	-4,85844008	0,00001266	0,78702579	2,88572833
16	85882028	cg27440995		0,06472914	3,35674202	4,82434434	0,00001422	0,78702579	2,77405287
14	90422831	cg15356780	*TDP1*	0,03839915	-3,87599218	4,78913361	0,00001602	0,78702579	2,65900839
14	70084982	cg00736295	*SUSD6*	0,07198386	3,18290146	4,75499665	0,00001798	0,78702579	2,54775324
17	40688138	cg25664725	*NAGLU*	0,04789374	-4,39248384	4,75030889	0,00001827	0,78702579	2,53249741
1	22517402	cg09005414		0,03138383	1,68324065	4,73429890	0,00001928	0,78702579	2,48043504
20	61041274	cg09864990	*GATA5*	0,04681100	1,90711112	4,71067548	0,00002088	0,78702579	2,40373025
12	70637393	cg08307766	*LINC01481;CNOT2*	0,31672029	-6,54218967	4,67484834	0,00002355	0,78702579	2,28766727
8	42011981	cg00325212	*AP3M2*	0,04347984	1,95106913	4,66989715	0,00002395	0,78702579	2,27165344
12	101187374	cg08327548	*ANO4*	-0,09804418	0,40840612	-4,65128989	0,00002636	0,78702579	2,19790409
16	30126595	cg05329317	*MAPK3*	0,02992757	1,78219714	4,64501402	0,00002603	0,78702579	2,19126859
8	103524071	cg06503422		-0,03964290	3,34004990	-4,62786935	0,00002757	0,78702579	2,13597663
14	106932032	cg26426220		-0,05902638	2,91727049	-4,62457219	0,00002788	0,78702579	2,12535207
6	121655782	cg10721490	*TBC1D32*	-0,04527513	-4,01982981	-4,57704310	0,00003268	0,78702579	1,97251955
3	194527730	cg25235301		0,03752004	2,86676321	4,57616000	0,00003278	0,78702579	1,96968566

Supplementary Table 3.S2.2: Differently Methylated CpG Sites (Top 1000) Associated With the Effect of Timepoint in the Continuous Response Model.

CHR	BP	cg	Gene	logFC	AveExpr	t	P.Value	adj.P.Val	B
4	41072974	cg02650667	*APBB2*	0,92617565	2,93057311	5,36633620	0,00000220	0,57550028	-0,57843340
9	86095810	cg23102092	*FRMD3*	1,11374454	2,55672121	5,29044691	0,00000301	0,57550028	-0,75044953
17	7514491	cg02936535	*FXR2*	-0,74716408	3,49687656	-5,04120819	0,00000678	0,57550028	-0,93794572
2	62116573	cg00458927	*CCT4;COMMD1*	0,91308442	2,29726963	5,02657536	0,00000713	0,57550028	-0,95422126
15	41047711	cg18385233	*RMDN3*	-2,16853749	-6,33165689	-5,02539430	0,00000716	0,57550028	-0,95553520
21	18913093	cg17761826	*CXADR*	-0,77708849	2,86687935	-5,01437714	0,00000744	0,57550028	-0,96779397
11	64052200	cg04056144	*BAD;GPR137*	-6,60757826	-8,11594055	-4,99701838	0,00000789	0,57550028	-0,98711646
12	59366940	cg16491571		-0,75267487	2,79003651	-4,97249661	0,00000858	0,57550028	-1,01442721
21	44183372	cg16306546	*PDE9A*	0,50134361	2,91696006	4,97023289	0,00000865	0,57550028	-1,01694924
7	116663691	cg14145892	*ST7*	0,60551911	2,31963920	4,92570471	0,00001007	0,57550028	-1,06658623
8	70551020	cg16208342	*SULF1*	-0,90832787	3,10207824	-4,90726711	0,00001073	0,57550028	-1,08715378
10	16479076	cg07570421	*PTER*	-1,01123240	-4,86029802	-4,90375938	0,00001085	0,57550028	-1,09106764
10	131813485	cg10847915		1,09737683	5,72430853	4,88934250	0,00001140	0,57550028	-1,10715667
7	19148187	cg19193956		-0,72095346	-2,79574918	-4,84999875	0,00001303	0,57550028	-1,15108646
16	74484275	cg08012845	*GLG1*	-0,52907953	3,66785868	-4,84245280	0,00001337	0,57550028	-1,15951555
12	50015929	cg20119464	*PRPF40B*	0,55505677	-3,29764242	4,80934458	0,00001496	0,57550028	-1,19651082
9	100264941	cg14382750	*TMOD1*	-0,50298866	-3,43232810	-4,80496434	0,00001518	0,57550028	-1,20140674
14	21439883	cg10960632		0,88686705	-5,32605918	4,80051721	0,00001541	0,57550028	-1,20637773
16	71687460	cg20022220	*PHLPP2*	0,98237435	3,32240555	4,79269807	0,00001583	0,57550028	-1,21511871
2	27994528	cg14093101	*MRPL33*	1,16556625	-5,51947181	4,78019362	0,00001651	0,57550028	-1,22909929
22	43485393	cg15811549	*TTLL1*	1,71470274	-7,23705054	4,75186820	0,00001817	0,60315534	-1,26077660
17	6982120	cg19840965	*CLEC10A*	0,42714723	2,91198467	4,70355089	0,00002138	0,67002598	-1,31483352
1	23765292	cg23595342	*ASAP3*	0,35570818	2,59816103	4,68102373	0,00002307	0,67002598	-1,34004421
2	11621166	cg11385008		-0,38513550	1,69005330	-4,66722210	0,00002416	0,67375387	-1,35549177
3	25646267	cg11841863	*TOP2B*	0,82659930	2,51409494	4,70108539	0,00002232	0,67002598	-1,38724182

Supplementary Table 3.S2.3: Differently Methylated CpG Sites (Top 1000) Associated With the Effect of the Interaction Between Continuous Response (ΔHDRS) and Timepoint.

CHR	BP	cg	Gene	logFC	AveExpr	t	P.Value	adj.P.Val	B
6	35656906	cg01294490	*FKBP5*	-0,04849954	-4,36393228	-5,85720379	0,00000039	0,27480324	5,84536573
6	121655782	cg10721490	*TBC1D32*	0,03116082	-4,01982981	5,47786751	0,00000149	0,52088854	4,53211267
2	11621166	cg11385008		0,02362853	1,69005330	5,29983873	0,00000278	0,64554922	3,92262015
21	44183372	cg16306546	*PDE9A*	-0,02787893	2,91696006	-5,11562256	0,00000525	0,73864125	3,29762800
17	7514491	cg02936535	*FXR2*	0,04017040	3,49687656	5,01655932	0,00000738	0,73864125	2,96422818
19	58557436	cg27497487	*ZSCAN1*	0,01976342	2,67567630	4,90418451	0,00001084	0,73864125	2,58853804
2	242674491	cg10515948	*D2HGDH*	-0,04527427	-4,77560698	-4,88898791	0,00001141	0,73864125	2,53794883
16	4321381	cg00246366	*TFAP4*	-0,09254395	-6,43457050	-4,86279182	0,00001248	0,73864125	2,45086753
2	131116277	cg12242994	*PTPN18*	0,02544641	3,12790304	4,85686570	0,00001273	0,73864125	2,43119005
21	18913093	cg17761826	*CXADR*	0,04062451	2,86687935	4,85194342	0,00001295	0,73864125	2,41485204
5	170211126	cg10816243	*GABRP*	-0,05312884	5,09088377	-4,83302352	0,00001381	0,73864125	2,35210661
15	50979356	cg03965827	*TRPM7*	-0,03245973	-3,85727023	-4,76013159	0,00001767	0,73864125	2,11117829
11	64052200	cg04056144	*BAD;GPR137*	0,33993002	-8,11594055	4,75816217	0,00001779	0,73864125	2,10468701
19	54370839	cg17382541	*MYADM*	-0,02863732	-3,91679217	-4,75292402	0,00001811	0,73864125	2,08742654
11	129938383	cg09693101	*APLP2*	0,01962735	3,11505436	4,75022043	0,00001827	0,73864125	2,07852050
13	114748575	cg24926364	*RASA3*	0,01576246	2,78156231	4,73349009	0,00001933	0,73864125	2,02344939
14	95830027	cg00775576		-0,02418524	2,00441024	-4,72248755	0,00002006	0,73864125	1,98727119
16	11376309	cg05385299	*PRM1*	0,04407957	3,33728454	4,70944442	0,00002096	0,73864125	1,94442350
3	171704056	cg15268191		-0,11441773	-3,36524078	-4,70967101	0,00002249	0,73864125	1,90787253
7	116663691	cg14145892	*ST7*	-0,03108941	2,31963920	-4,68095052	0,00002307	0,73864125	1,85097226
16	79632625	cg06834240	*MAF*	0,03771101	-3,18709408	4,66959442	0,00002397	0,73864125	1,81378710
14	70084982	cg00736295	*SUSD6*	-0,04061635	3,18290146	-4,66544757	0,00002431	0,73864125	1,80021687
3	48885314	cg07754938	*PRKAR2A;PRKAR2A-AS1*	-0,69831312	-11,05251927	-4,65201275	0,00002543	0,73864125	1,75628403
16	85122186	cg07244716	*KIAA0513*	-0,01535719	2,14592412	-4,63297884	0,00002710	0,73864125	1,69412469
14	39901091	cg11221049	*FBXO33*	-0,05421981	-4,76835351	-4,62718761	0,00002763	0,73864125	1,67523159

Supplementary Table 3.S3.1: Differently Methylated CpG Sites (Top 1000) Associated With the Effect of Binary Response at Baseline.

CHR	BP	cg	Gene	logFC	AveExpr	t	P.Value	adj.P.Val	B
8	143546524	cg20063965	*ADGRB1*	-1,09861374	-1,18481123	-7,30234472	0,00000131	0,49695968	0,18325000
10	651119	cg18502238	*DIP2C*	-1,34426895	2,26562945	-7,00812131	0,00000223	0,49695968	0,04154362
10	102289529	cg03734035	*NDUFB8*	10,56709125	-8,93239616	6,91255104	0,00000265	0,49695968	-0,00655722
1	40746645	cg13140809	*ZMPSTE24*	-0,82665756	2,57957723	-6,78678700	0,00000334	0,49695968	-0,07145964
10	131640139	cg04217539	*EBF3*	0,71217646	3,23445213	6,64850534	0,00000432	0,49695968	-0,14497940
22	31368615	cg15843413	*TUG1*	-1,29127190	3,62561151	-6,59215209	0,00000480	0,49695968	-0,17560253
21	45209618	cg18095213	*RRP1*	5,01388369	-7,81682093	6,52624156	0,00000544	0,49695968	-0,21191383
13	39612443	cg08408316	*PROSER1;NHLRC3*	-1,98735049	-6,37677668	-6,50077717	0,00000570	0,49695968	-0,22608677
17	74865178	cg05057634	*MGAT5B*	-0,88524520	-2,42287353	-6,23725905	0,00000943	0,58268736	-0,37757665
6	154876352	cg14350969		0,62921045	2,24241126	6,20600494	0,00001001	0,58268736	-0,39613821
8	124428770	cg12901472	*WDYHV1*	1,48151478	-4,17651289	6,09973553	0,00001230	0,58268736	-0,46021500
11	120434922	cg10514733	*GRIK4*	-0,83421027	-2,45383393	-6,03999387	0,00001382	0,58268736	-0,49689844
19	49588359	cg12236003	*SNRNP70*	0,70365971	-4,31978936	6,01185008	0,00001460	0,58268736	-0,51434628
13	114325720	cg23627248	*GRK1*	-0,48981993	4,10112871	-5,97753601	0,00001562	0,58268736	-0,53576461
11	120434880	cg21893358	*GRIK4*	-1,17630662	-1,65450793	-5,91727521	0,00001758	0,58268736	-0,57376694
1	3304584	cg09904793	*PRDM16*	0,99465702	2,79754779	5,90540687	0,00001800	0,58268736	-0,58131013
11	67188389	cg08173356	*CARNS1*	6,20605943	-7,65224564	5,89703284	0,00001829	0,58268736	-0,58664408
16	16042767	cg17199483	*ABCC1*	-1,06277971	-2,48318358	-5,89591212	0,00001834	0,58268736	-0,58735868
18	35250260	cg04176047		-0,57743782	2,84557761	-5,88271052	0,00001882	0,58268736	-0,59578927
3	142314877	cg19893077	*PLS1*	-15,37110020	-9,38624626	-5,87870045	0,00001897	0,58268736	-0,59835488
5	170039198	cg03443549	*KCNIP1*	0,51261330	3,10940915	5,87820715	0,00001899	0,58268736	-0,59867064
3	185446099	cg08983650	*IGF2BP2;IGF2BP2-AS1*	1,78025631	3,46606340	5,82094328	0,00002126	0,58268736	-0,63555421
12	68754612	cg15553697		0,89082543	3,17004795	5,81594110	0,00002147	0,58268736	-0,63879772
1	213128487	cg08623556	*VASH2*	0,68698096	2,07005428	5,81131233	0,00002167	0,58268736	-0,64180220
10	126848218	cg00087005	*CTBP2*	-16,61858235	-8,93931654	-5,77592349	0,00002325	0,58268736	-0,66487144

Supplementary Table 3.S3.2: Differently Methylated CpG Sites (Top 1000) Associated With the Effect of Continuous Response (ΔHDRS) at Baseline.

CHR	BP	cg	Gene	logFC	AveExpr	t	P.Value	adj.P.Val	B
4	111559355	cg17707140	*PITX2*	0,06584674	-1,99454706	6,91187746	0,00000265	0,83196787	4,73060723
3	9439396	cg13216995	*THUMPD3-AS1 SETD5;SETD5*	-0,92659117	-12,54928086	-6,84001930	0,00000303	0,83196787	4,59666226
9	116853875	cg15407190		-0,03149182	2,24000774	-6,65709170	0,00000425	0,83196787	4,25245160
7	150747107	cg02920383	*ASIC3*	0,04063914	3,41035304	6,59554975	0,00000477	0,83196787	4,13561062
19	2603622	cg13839160	*GNG7*	-0,03661081	2,65607680	-6,45122122	0,00000627	0,85431670	3,85955558
5	137225509	cg05201789	*PKD2L2*	0,03109691	3,02170052	6,23840727	0,00000941	0,85431670	3,44734436
19	50162772	cg00506277		0,05376233	3,08412060	6,18317698	0,00001047	0,85431670	3,33937181
19	49588359	cg12236003	*SNRNP70*	0,03652116	-4,31978936	6,12970077	0,00001161	0,85431670	3,23444259
5	115697214	cg05931423		0,06919784	3,77953201	6,11703270	0,00001190	0,85431670	3,20953042
17	46800674	cg04618333	*PRAC2;PRAC1*	-0,05452150	-4,66649113	-6,03041433	0,00001409	0,85431670	3,03862857
4	155471803	cg16373290	*PLRG1*	-0,11268820	-4,97180558	-6,03028055	0,00001409	0,85431670	3,03836387
6	33181031	cg02775469		-0,05480803	-4,23772547	-6,00848648	0,00001471	0,85431670	2,99520879
12	30816511	cg06937319	*IPO8*	-0,04466307	4,01661955	-5,96105297	0,00001614	0,86157008	2,90107198
10	27609286	cg11203244	*ARMC4P1*	0,03146065	2,70402498	5,81476556	0,00002154	0,86157008	2,60893925
12	121838009	cg09926889	*RNF34*	0,03201499	-4,33847177	5,76341498	0,00002385	0,86157008	2,50575515
14	104376199	cg21567958		-0,03389450	2,21467364	-5,71044016	0,00002650	0,86157008	2,39896599
5	140080544	cg22976331	*ZMAT2*	-0,05268811	-2,73370231	-5,69121172	0,00002754	0,86157008	2,36011946
10	5488628	cg27367170	*NET1*	-0,03222257	-2,18145326	-5,65541163	0,00002958	0,86157008	2,28767440
7	158059976	cg19547192	*PTPRN2*	-0,08241269	4,33239027	-5,64281145	0,00003034	0,86157008	2,26213990
2	75929513	cg16505623	*GCFC2*	0,03794954	2,71348162	5,60502056	0,00003273	0,86157008	2,18544213
20	62360072	cg25255847	*ZGPAT*	-0,06334262	-1,09980139	-5,59098136	0,00003366	0,86157008	2,15690588
16	87350553	cg08862203	*C16orf95;LOC101928659*	-0,04708858	-4,47709116	-5,52903999	0,00003814	0,86157008	2,03072636
21	44183372	cg16306546	*PDE9A*	0,03219240	2,91277493	5,47862693	0,00004223	0,86157008	1,92770216
1	32469340	cg19837700		0,03416420	-3,53274117	5,47235718	0,00004277	0,86157008	1,91486892
4	12441385	cg03870405		-0,04342333	1,40626379	-5,46844350	0,00004311	0,86157008	1,90685594

Supplementary Table 3.S4.1 Differentially Methylated Candidate CpG Sites Associated With the Effect of Binary Response.

Rank	CHR	BP	cg	Gene	logFC	AveExpr	t	P.Value	adj.P.Val	B	2-FDR
77	6	35656906	cg01294490	*FKBP5*	1,41395365	-4,36393228	4,27911820	0,00008735	0,76616477	-1,83034803	0,06023519
133	11	27679976	cg02386994	*BDNF-AS;BDNF*	0,50061001	1,94906470	4,11045918	0,00015078	0,78437954	-2,01510058	0,06023519
912	5	142658828	cg23273257	*NR3C1*	0,89211113	3,93428091	3,43982371	0,00120193	0,91003882	-2,73373698	0,32011428
1477	17	78320968	cg22354918	*RNF213*	0,64651490	3,47394885	3,27374519	0,00195566	0,91584983	-2,90532780	0,39064284
4518	4	7009356	cg20963865	*TBC1D14*	-0,72338815	3,16284415	-2,85092341	0,00637334	0,98101347	-3,32480118	0,86989948
5369	5	142784278	cg07515400	*NR3C1*	0,81448537	-3,86641097	2,78172233	0,00766685	0,99431484	-3,39062441	0,86989948
5757	11	27656516	cg06322831	*BDNF-AS;LINC00678*	-0,70127223	1,96809417	-2,75367120	0,00825717	0,99808819	-3,41705027	0,86989948
7207	4	6996897	cg10316586	*TBC1D14*	-0,97764779	3,69902097	-2,66065058	0,01052755	0,99999469	-3,50357943	0,86989948
9107	5	142783621	cg15910486	*NR3C1*	0,95706812	-4,05739118	2,55914760	0,01364771	0,99999469	-3,59597485	0,86989948
9901	17	5974352	cg06150297	*WSCD1*	0,97389746	-5,28383488	2,52491972	0,01487651	0,99999469	-3,62663291	0,86989948
10605	17	6023861	cg18340535	*WSCD1*	0,40159907	2,37108211	2,49398448	0,01607267	0,99999469	-3,65411829	0,86989948
12532	4	6988322	cg09884257	*TBC1D14*	0,74072374	-4,53392941	2,42192672	0,01920349	0,99999469	-3,71729612	0,86989948
12585	5	142784721	cg21702128	*NR3C1*	0,33137688	-3,16434172	2,42035013	0,01927775	0,99999469	-3,71866496	0,86989948
12980	16	19428088	cg17880841	*TMC5*	-1,05429449	3,77289042	-2,40745202	0,01989508	0,99999469	-3,72984149	0,86989948
13946	11	27529576	cg09025927	*LIN7C;BDNF-AS*	-0,49752309	2,98378443	-2,37661569	0,02144365	0,99999469	-3,75640182	0,86989948
14061	6	42421084	cg10260072	*TRERF1*	-0,82969348	-3,84686223	-2,37325304	0,02161890	0,99999469	-3,75928441	0,86989948
14364	5	142814827	cg08818984	*NR3C1*	4,28792796	-4,63639728	2,36314242	0,02215360	0,99999469	-3,76793519	0,86989948
15891	11	27661223	cg06351568	*BDNF-AS*	-0,50518803	2,88792292	-2,32188515	0,02446045	0,99999469	-3,80297733	0,86989948
16707	5	142784323	cg06968181	*NR3C1*	3,07668217	-4,73617472	2,30010604	0,02576279	0,99999469	-3,82130627	0,86989948
17135	17	5982765	cg20792590	*WSCD1*	0,34893381	2,41117865	2,28958117	0,02641404	0,99999469	-3,83012137	0,86989948
17215	17	28530849	cg20209182	*SLC6A4*	-0,33831997	1,68136157	-2,28777060	0,02652753	0,99999469	-3,83163501	0,86989948
18833	6	35633557	cg21789597	*FKBP5;MIR5690*	-1,00264906	2,28669478	-2,25007532	0,02908861	0,99999469	-3,86415991	0,86989948
19226	6	35611611	cg04137760	*FKBP5*	-0,82809531	3,60985424	-2,23937668	0,02972651	0,99999469	-3,87178418	0,86989948
19380	17	78336957	cg22672496	*RNF213; LOC100294362*	-0,73844046	3,16148352	-2,23600094	0,02996192	0,99999469	-3,87456243	0,86989948
20620	17	78354382	cg00029678	*RNF213; LOC100294362*	0,51675666	3,28442036	2,20922088	0,03188872	0,99999469	-3,89649798	0,86989948

Supplementary Table 3.S4.2: Differentially Methylated Candidate CpG Sites Associated With the Effect of Timepoint in the Binary Response Model.

Rank	CHR	BP	cg	Gene	logFC	AveExpr	t	P.Value	adj.P.Val	B	2-FDR
723	11	27656516	cg06322831	*BDNF-AS;LINC00678*	-0,44793332	1,96809417	-3,66475967	0,00061032	0,58783737	-1,10533856	0,48764234
2799	6	35633557	cg21789597	*FKBP5;MIR5690*	-0,67001218	2,28669478	-3,13142428	0,00296766	0,73964431	-2,09307569	0,59563550
2851	17	78320968	cg22354918	*RNF213*	0,29572175	3,47394885	3,12001229	0,00303521	0,74214487	-2,10651894	0,59563550
3288	5	142784721	cg21702128	*NR3C1*	0,20112057	-3,16434172	3,06068889	0,00358556	0,75893693	-2,21045593	0,59563550
3902	4	6996897	cg10316586	*TBC1D14*	-0,52785254	3,69902097	-2,99312414	0,00432584	0,77130210	-2,32743957	0,59563550
4443	17	6023861	cg18340535	*WSCD1*	0,22725579	2,37108211	2,94051029	0,00499876	0,78411062	-2,41747479	0,59563550
4607	11	27743348	cg02527472	*BDNF*	-0,88763870	-3,45639909	-2,92476785	0,00521833	0,78921469	-2,44422875	0,59563550
6196	6	35656906	cg01294490	*FKBP5*	0,44440436	-4,36393228	2,80223218	0,00726018	0,81657048	-2,64945860	0,72511096
7581	11	27679976	cg02386994	*BDNF-AS;BDNF*	0,15877656	1,94906470	2,71633847	0,00910790	0,83616584	-2,79000636	0,78486755
8126	5	142814827	cg08818984	*NR3C1*	2,34032603	-4,63639728	2,68735768	0,00982312	0,84207700	-2,83678715	0,78486755
10123	5	142658828	cg23273257	*NR3C1*	0,32257002	3,93428091	2,59148038	0,01257258	0,86568816	-2,98917110	0,88289285
10624	17	78319834	cg23464217	*RNF213*	-0,24241367	3,51543508	-2,57053167	0,01325997	0,86900486	-3,02196838	0,88289285
13331	6	42226950	cg16654680	*TRERF1*	-0,24190006	3,05306126	-2,46951344	0,01707989	0,89291827	-3,17753285	0,93618514
13363	6	42290322	cg22540431	*TRERF1*	-0,46242601	3,04553549	-2,46838379	0,01712774	0,89307154	-3,17924778	0,93618514
15442	4	6911012	cg01810502	*TBC1D14*	-1,68188085	-6,52699137	-2,40360009	0,02008286	0,90607434	-3,27666084	0,93618514
15789	17	28558098	cg16647683	*SLC6A4*	-0,32321645	3,81967453	-2,39327111	0,02059428	0,90853726	-3,29202038	0,93618514
15833	17	78313945	cg24542230	*RNF213*	-0,21432514	3,23508032	-2,39222798	0,02064658	0,90867192	-3,29356889	0,93618514
16148	5	142779552	cg06613263	*NR3C1*	0,35770630	2,15008622	2,38346685	0,02109053	0,91024905	-3,30655542	0,93618514
17640	5	142784982	cg14558428	*NR3C1*	-1,42829248	-6,41356761	-2,34281710	0,02326452	0,91938592	-3,36635630	0,93878462
19020	6	42334807	cg14308028	*TRERF1*	-0,14847970	1,56244452	-2,30744004	0,02531749	0,92771450	-3,41778579	0,93878462
19422	17	28547550	cg10146136	*SLC6A4*	0,27272267	2,37531211	2,29764288	0,02591391	0,93007206	-3,43192615	0,93878462
20560	5	142784278	cg07515400	*NR3C1*	0,31912906	-3,86641097	2,27092893	0,02760427	0,93501022	-3,47025519	0,93878462
20627	4	6990245	cg09949789	*TBC1D14*	0,18172867	2,51673257	2,26987684	0,02767280	0,93501022	-3,47175786	0,93878462
20975	5	142814934	cg26720913	*NR3C1*	2,14329021	-5,92554002	2,26187859	0,02819879	0,93701816	-3,48316460	0,93878462
22498	6	35569471	cg07633853	*FKBP5*	-3,25792551	-3,40431157	-2,23071247	0,03043315	0,94344238	-3,52989391	0,97264343

Supplementary Table 3.S4.3: Differentially Methylated Candidate CpG Sites Associated With the Effect of Interaction Between Binary Response and Timepoint.

Rank	CHR	BP	cg	Gene	logFC	AveExpr	t	P.Value	adj.P.Val	B	2-FDR
184	6	35656906	cg01294490	*FKBP5*	-0,80177747	-4,36393228	-4,07490482	0,00016898	0,63484535	-0,67248135	0,13501398
339	11	27679976	cg02386994	*BDNF-AS;BDNF*	-0,27940816	1,94906470	-3,85278173	0,00034123	0,67770082	-1,06433973	0,13631988
786	5	142658828	cg23273257	*NR3C1*	-0,55143776	3,93428091	-3,57074009	0,00081217	0,71931562	-1,55079405	0,20218397
953	17	78320968	cg22354918	*RNF213*	-0,41128880	3,47394885	-3,49750004	0,00101219	0,73408899	-1,67469258	0,20218397
1465	11	27656516	cg06322831	*BDNF-AS;LINC00678*	0,50719532	1,96809417	3,34460775	0,00159121	0,75560437	-1,92964437	0,25208963
1725	5	142784278	cg07515400	*NR3C1*	-0,57274005	-3,86641097	-3,28497867	0,00189304	0,76274190	-2,02762396	0,25208963
3496	17	6023861	cg18340535	*WSCD1*	-0,28865963	2,37108211	-3,01045135	0,00412344	0,82061556	-2,46693452	0,47066128
5085	5	142814827	cg08818984	*NR3C1*	-3,08729736	-4,63639728	-2,85736282	0,00626389	0,85675293	-2,70259331	0,55122185
5438	16	19428088	cg17880841	*TMC5*	0,73845803	3,77289042	2,83182250	0,00670853	0,85839237	-2,74119968	0,55122185
5578	5	142784721	cg21702128	*NR3C1*	-0,23001638	-3,16434172	-2,82136504	0,00689890	0,86073802	-2,75694642	0,55122185
7013	17	78319834	cg23464217	*RNF213*	0,31881576	3,51543508	2,72485531	0,00890700	0,88389349	-2,90056738	0,64697227
7686	17	28547550	cg10146136	*SLC6A4*	-0,39567220	2,37531211	-2,68679567	0,00983749	0,88778328	-2,95633953	0,65501286
9505	17	78313945	cg24542230	*RNF213*	0,28883482	3,23508032	2,59846467	0,01235073	0,90510878	-3,08381747	0,75909507
13208	4	7009356	cg20963865	*TBC1D14*	0,37127004	3,16284415	2,45724564	0,01760602	0,92887029	-3,28167386	0,99022151
16951	5	142783621	cg15910486	*NR3C1*	-0,52215649	-4,05739118	-2,34475611	0,02315643	0,95160155	-3,43375659	0,99022151
17320	6	35633557	cg21789597	*FKBP5;MIR5690*	0,62113072	2,28669478	2,33730435	0,02366378	0,95256458	-3,44630926	0,99022151
17938	4	6998522	cg27050991	*TBC1D14*	-0,41596661	3,53288043	-2,31954934	0,02459725	0,95519984	-3,46713581	0,99022151
18122	5	142781723	cg27122725	*NR3C1*	-10,91827613	-8,88833426	-2,32774175	0,02430510	0,95479556	-3,47328797	0,99022151
18623	11	27661223	cg06351568	*BDNF-AS*	0,29840053	2,88792292	2,30320070	0,02557404	0,95691996	-3,48864499	0,99022151
19180	6	35631736	cg07061368	*FKBP5*	-0,60427493	2,47080274	-2,29003897	0,02638541	0,95850734	-3,50588067	0,99022151
20613	4	6990245	cg09949789	*TBC1D14*	-0,22415090	2,51673257	-2,25661337	0,02854987	0,96501788	-3,54932645	0,99022151
21045	6	35611611	cg04137760	*FKBP5*	0,49476107	3,60985424	2,24691612	0,02920665	0,96616172	-3,56184246	0,99022151
21602	17	28558098	cg16647683	*SLC6A4*	0,37462675	3,81967453	2,23581082	0,02997523	0,96693075	-3,57612671	0,99022151
21708	4	6996897	cg10316586	*TBC1D14*	0,48870126	3,69902097	2,23353824	0,03013470	0,96715737	-3,57904334	0,99022151
22977	17	78354382	cg00029678	*RNF213; LOC100294362*	-0,30740605	3,28442036	-2,20703885	0,03205044	0,97201428	-3,61288932	0,99022151

Supplementary Table 3.S5.1: Differentially Methylated Candidate CpG Sites Associated With the Effect of Continuous Response (ΔHDRS).

Rank	CHR	BP	cg	Gene	logFC	AveExpr	t	P.Value	adj.P.Val	B	2-FDR
1	6	35656906	cg01294490	*FKBP5*	0,08383636	-4,36393228	5,82247695	0,00000045	0,31062540	6,13049273	0,00035603
2767	11	27722620	cg15710245	*BDNF*	0,14806137	-3,68069793	3,09290687	0,00327604	0,81905500	-2,39094527	0,91522675
2891	11	27543806	cg09878183	*BDNF-AS*	0,04231235	3,71722413	3,07587691	0,00343640	0,81905500	-2,43513066	0,91522675
8264	6	42262319	cg03654948	*TRERF1*	0,03133123	3,32181267	2,68555905	0,00986922	0,83115166	-3,40087828	0,91669176
8295	17	78320968	cg22354918	*RNF213*	0,02706997	3,47394885	2,68462967	0,00989309	0,83115166	-3,40306515	0,91669176
8833	6	35633557	cg21789597	*FKBP5;MIR5690*	-0,05741968	2,28669478	-2,65280296	0,01080465	0,83374666	-3,46353225	0,91669176
9789	11	27679976	cg02386994	*BDNF-AS;BDNF*	0,01677697	1,94906470	2,61765223	0,01175960	0,83700351	-3,55918302	0,91669176
11683	11	27543361	cg09646437	*BDNF-AS*	0,01565992	1,92647862	2,54687513	0,01407732	0,84013717	-3,72093107	0,91669176
12127	4	6996897	cg10316586	*TBC1D14*	-0,04510493	3,69902097	-2,53076184	0,01465997	0,84248544	-3,75728413	0,91669176
13568	19	55880286	cg15681462	*IL11*	-0,03004227	-0,60877680	-2,48518482	0,01642856	0,84348320	-3,85915138	0,91669176
15857	17	78252222	cg16236626	*RNF213*	-0,02156172	2,80644218	-2,42110988	0,01924200	0,84567724	-3,99993610	0,91669176
16553	16	55702465	cg06064664	*SLC6A2*	-0,03178286	1,65733430	-2,40295645	0,02011446	0,84684862	-4,03930048	0,91669176
16735	4	154680808	cg09760963	*RNF175*	-0,05296898	-0,40554324	-2,39829670	0,02034408	0,84733198	-4,04936730	0,91669176
17245	16	55690309	cg24280449	*SLC6A2*	-0,02042749	-3,43838052	-2,38602804	0,02095995	0,84733198	-4,07579871	0,91669176
17312	17	5976451	cg04257841	*WSCD1*	0,01975391	2,00140205	2,38444494	0,02104062	0,84735203	-4,07920154	0,91669176
18950	5	142814934	cg26720913	*NR3C1*	0,22423955	-5,92554002	2,34614214	0,02307952	0,84894528	-4,16098777	0,91669176
20172	19	55881981	cg13114229	*IL11*	-0,02793388	-1,66778293	-2,32006797	0,02456690	0,84926710	-4,21606063	0,91669176
20866	3	8811601	cg17036624	*OXTR*	-0,05053315	0,44463825	-2,30530643	0,02544640	0,85010861	-4,24702153	0,91669176
22426	17	78362330	cg12813919	*RNF213; LOC100294362*	0,02716635	3,70530724	2,27470336	0,02735972	0,85090884	-4,31070337	0,91669176
22658	4	6955750	cg19271725	*TBC1D14*	0,02319249	3,25994239	2,27002894	0,02766297	0,85170327	-4,32037006	0,91669176
23251	16	55689449	cg14112935	*SLC6A2*	-0,04414581	0,52148964	-2,25807155	0,02845234	0,85327557	-4,34502495	0,91669176
25779	5	142781498	cg07733851	*NR3C1*	-0,04281410	-0,88782957	-2,21295450	0,03161377	0,85514167	-4,43710068	0,91669176
27035	16	55690873	cg04874129	*SLC6A2*	-0,02252371	-2,10481414	-2,19184019	0,03319719	0,85623403	-4,47967112	0,91669176
27234	5	142759375	cg03746860	*NR3C1*	-0,02944934	2,93074916	-2,18840122	0,03346162	0,85638599	-4,48657314	0,91669176
27451	4	6990245	cg09949789	*TBC1D14*	0,01785011	2,51673257	2,18489814	0,03373287	0,85638599	-4,49359470	0,91669176

Supplementary Table 3.S5.2: Differentially Methylated Candidate CpG Sites Associated With the Effect of Timepoint in the Continuous Response Model.

Rank	CHR	BP	cg	Gene	logFC	AveExpr	t	P.Value	adj.P.Val	B	2-FDR
43	6	35656906	cg01294490	*FKBP5*	0,68329103	-4,36393228	4,45838267	0,00004848	0,72770927	-1,58925998	0,03873253
635	6	35633557	cg21789597	*FKBP5;MIR5690*	-0,82629430	2,28669478	-3,60802791	0,00073667	0,86421208	-2,56650597	0,29430128
2434	11	27722620	cg15710245	*BDNF*	1,57198917	-3,68069793	3,08511167	0,00334855	0,95516303	-3,07493503	0,71120169
2654	17	78313945	cg24542230	*RNF213*	-0,27713097	3,23508032	-3,05304467	0,00366296	0,95741733	-3,10729700	0,71120169
3254	5	142814934	cg26720913	*NR3C1*	3,02620550	-5,92554002	2,97465627	0,00455180	0,97020840	-3,18571074	0,71120169
3781	4	6953947	cg20087425	*TBC1D14*	0,55778459	2,64634775	2,91626379	0,00534069	0,98213321	-3,24345241	0,71120169
6156	17	78269421	cg20225842	*RNF213*	0,26813678	3,17161588	2,72873776	0,00881684	0,99582812	-3,42470871	0,88432237
6452	6	35642470	cg06409316	*FKBP5*	0,57346504	3,09934150	2,71008856	0,00925801	0,99627692	-3,44236446	0,88432237
6953	6	42290322	cg22540431	*TRERF1*	-0,54004452	3,04553549	-2,68199397	0,00996108	0,99627692	-3,46882956	0,88432237
9670	17	78354577	cg25841344	*RNF213; LOC100294362*	0,21110173	3,23873823	2,54926004	0,01399290	0,99996218	-3,59162347	0,97582617
10179	17	5976451	cg04257841	*WSCD1*	0,22294893	2,00140205	2,52834295	0,01474931	0,99996218	-3,61062424	0,97582617
11295	4	6996897	cg10316586	*TBC1D14*	-0,47175061	3,69902097	-2,48677232	0,01636385	0,99996218	-3,64809272	0,97582617
12236	6	35569471	cg07633853	*FKBP5*	-3,79542233	-3,40431157	-2,45403725	0,01782491	0,99996218	-3,67903156	0,97582617
12704	11	27543806	cg09878183	*BDNF-AS*	0,35690841	3,71722413	2,43755734	0,01848113	0,99996218	-3,69193551	0,97582617
13476	5	142779552	cg06613263	*NR3C1*	0,39096611	2,15008622	2,41240300	0,01965611	0,99996218	-3,71412352	0,97582617
15382	17	78362330	cg12813919	*RNF213; LOC100294362*	0,29965593	3,70530724	2,35728783	0,02246870	0,99996218	-3,76220545	0,97582617
16749	11	27543361	cg09646437	*BDNF-AS*	0,15187945	1,92647862	2,32066985	0,02453162	0,99996218	-3,79373698	0,97582617
18879	17	78252222	cg16236626	*RNF213*	-0,21513655	2,80644218	-2,26955960	0,02769359	0,99996218	-3,83718204	0,97582617
19064	17	78320968	cg22354918	*RNF213*	0,24316098	3,47394885	2,26561861	0,02795183	0,99996218	-3,84050419	0,97582617
19621	6	78173227	cg23424273	*HTR1B*	-4,47224379	-9,30980751	-2,25375959	0,02874187	0,99996218	-3,85047676	0,97582617
20288	17	78368528	cg05505076	*RNF213; LOC100294362*	0,29564316	3,39571394	2,23831226	0,02980065	0,99996218	-3,86341194	0,97582617
20980	6	42419091	cg24135939	*TRERF1*	-0,18566592	-3,81100310	-2,22366213	0,03083658	0,99996218	-3,87562177	0,97582617
21438	6	42262319	cg03654948	*TRERF1*	0,27495151	3,32181267	2,21416357	0,03152515	0,99996218	-3,88350788	0,97582617
24516	5	142759375	cg03746860	*NR3C1*	-0,30865817	2,93074916	-2,15489161	0,03613692	0,99996218	-3,93217329	0,97582617
26114	11	27602211	cg21381354	*BDNF-AS*	0,20343734	2,48081370	2,12604742	0,03858848	0,99996218	-3,95551104	0,97582617

Supplementary Table 3.S5.3: Differentially Methylated Candidate CpG Sites Associated With the Effect of Interaction Between Continuous Response (ΔHDRS) and Timepoint.

Rank	CHR	BP	cg	Gene	logFC	AveExpr	t	P.Value	adj.P.Val	B	2-FDR
1	6	35656906	cg01294490	*FKBP5*	-0,04849954	-4,36393228	-5,85720379	0,00000039	0,27480324	5,84536573	0,00031497
1400	17	78313945	cg24542230	*RNF213*	0,01605636	3,23508032	3,27398129	0,00195434	0,96459745	-2,41495516	0,78075995
4132	6	35633557	cg21789597	*FKBP5;MIR5690*	0,03542959	2,28669478	2,88733017	0,00582060	0,96459745	-3,42671182	0,95254631
4394	11	27722620	cg15710245	*BDNF*	-0,07883339	-3,68069793	-2,86360171	0,00615955	0,96459745	-3,48614462	0,95254631
4938	11	27679976	cg02386994	*BDNF-AS;BDNF*	-0,01039764	1,94906470	-2,82104819	0,00690479	0,96459745	-3,59151714	0,95254631
9323	11	27602211	cg21381354	*BDNF-AS*	-0,01334159	2,48081370	-2,58066157	0,01292347	0,96620129	-4,16497654	0,95254631
9406	6	42262319	cg03654948	*TRERF1*	-0,01729022	3,32181267	-2,57712309	0,01304014	0,96686611	-4,17313250	0,95254631
10679	17	78269421	cg20225842	*RNF213*	-0,01340962	3,17161588	-2,52582381	0,01484287	0,96812190	-4,29041503	0,95254631
11550	5	142759375	cg03746860	*NR3C1*	0,01930169	2,93074916	2,49415810	0,01606579	0,96865780	-4,36190679	0,95254631
11805	11	27543806	cg09878183	*BDNF-AS*	-0,01965893	3,71722413	-2,48507189	0,01643317	0,96865780	-4,38229218	0,95254631
12398	17	78320968	cg22354918	*RNF213*	-0,01429403	3,47394885	-2,46506723	0,01726898	0,96865780	-4,42697041	0,95254631
14605	17	78252222	cg16236626	*RNF213*	0,01228635	2,80644218	2,39900650	0,02030895	0,96938608	-4,57250499	0,95254631
14765	16	19428088	cg17880841	*TMC5*	0,02907839	3,77289042	2,39432996	0,02054140	0,97015526	-4,58268992	0,95254631
14798	4	6953947	cg20087425	*TBC1D14*	-0,02472971	2,64634775	-2,39309794	0,02060303	0,97071537	-4,58537048	0,95254631
17215	17	78362330	cg12813919	*RNF213; LOC100294362*	-0,01599955	3,70530724	-2,32958588	0,02401431	0,97188055	-4,72207442	0,95254631
17257	17	5976451	cg04257841	*WSCD1*	-0,01109447	2,00140205	-2,32872483	0,02406384	0,97188055	-4,72390764	0,95254631
19225	5	142814934	cg26720913	*NR3C1*	-0,12545891	-5,92554002	-2,28255362	0,02685709	0,97311538	-4,82141209	0,95254631
23874	17	78336957	cg22672496	*RNF213; LOC100294362*	0,02034700	3,16148352	2,18940704	0,03338409	0,97311538	-5,01329891	0,95254631
23932	11	27528703	cg25227335	*LIN7C;BDNF-AS*	0,01922114	-2,47664888	2,18832071	0,03346783	0,97311538	-5,01549830	0,95254631
26162	11	27720709	cg09492354	*BDN*	-0,02762639	-5,51924578	-2,15038704	0,03651052	0,97311538	-5,09173551	0,95254631
27295	17	78368528	cg05505076	*RNF213; LOC100294362*	-0,01520414	3,39571394	-2,13056965	0,03819474	0,97406849	-5,13112567	0,95254631
27692	17	28535040	cg06961290	*SLC6A4*	-0,03443544	3,87634681	-2,12402891	0,03876537	0,97406849	-5,14406008	0,95254631
27973	11	27603196	cg07991565	*BDNF-AS*	-0,01851640	3,02560181	-2,11952299	0,03916281	0,97406849	-5,15295141	0,95254631
28821	11	27744049	cg15462887	*BDNF*	0,01339282	-3,14211859	2,10655709	0,04032642	0,97406849	-5,17844886	0,95254631
28985	5	142658828	cg23273257	*NR3C1*	-0,01653435	3,93428091	-2,10387641	0,04057073	0,97406849	-5,18370418	0,95254631

Supplementary Table 3.S6.1: Differentially Methylated Candidate CpG Sites Associated With the Effect of Binary Response at Baseline.

Rank	CHR	BP	cg	Gene	logFC	AveExpr	t	P.Value	adj.P.Val	B	2-FDR
1308	4	7009356	cg20963865	*TBC1D14*	-0,50925229	3,17371376	-3,73371316	0,00167645	0,85748512	-2,29970349	0,92555459
4808	4	6996897	cg10316586	*TBC1D14*	-0,49802459	3,78089138	-3,13536187	0,00608538	0,86586881	-2,87578481	0,92555459
7504	5	63258434	cg16807523	*HTR1A*	-0,86088470	-3,36936575	-2,93262323	0,00936827	0,86586881	-3,07556643	0,92555459
8521	5	142782072	cg06521673	*NR3C1*	0,38625959	-4,58201491	2,87232299	0,01064101	0,86586881	-3,13512124	0,92555459
9543	6	35656906	cg01294490	*FKBP5*	0,62162148	-4,32998821	2,81717346	0,01195054	0,86586881	-3,18958705	0,92555459
10405	17	78320968	cg22354918	*RNF213*	0,30155466	3,45173606	2,77606231	0,01302664	0,86586881	-3,23016908	0,92555459
10537	5	142802329	cg17349736	*NR3C1*	0,44310721	2,38412997	2,76935910	0,01321073	0,86586881	-3,23678345	0,92555459
13128	11	27740495	cg04481212	*BDNF*	-0,74403602	-3,36516225	-2,66648936	0,01636969	0,86586881	-3,33814609	0,92555459
13773	19	55880286	cg15681462	*IL11*	-0,48567284	-0,62356754	-2,64402993	0,01714986	0,86586881	-3,36022864	0,92555459
14010	17	78336732	cg27373669	*RNF213; LOC100294362*	-0,54242837	1,73440777	-2,63639382	0,01742312	0,86586881	-3,36773169	0,92555459
14422	5	142784323	cg06968181	*NR3C1*	2,64925516	-4,78748384	2,62130605	0,01797532	0,86814037	-3,38254872	0,92555459
14761	11	27721668	cg20954537	*BDNF*	0,46828767	-3,71674173	2,60973171	0,01841020	0,86814037	-3,39390795	0,92555459
14928	6	35612351	cg08586216	*FKBP5*	0,35923536	3,99071754	2,60322881	0,01865892	0,86814037	-3,40028703	0,92555459
16050	17	6023861	cg18340535	*WSCD1*	0,24478099	2,36402741	2,56870344	0,02003395	0,86965197	-3,43411671	0,92555459
16137	16	55689449	cg14112935	*SLC6A2*	-0,81352033	0,50041993	-2,56556998	0,02016341	0,87071895	-3,43718366	0,92555459
16982	16	55689442	cg24261673	*SLC6A2*	-0,74548087	0,08476857	-2,53943720	0,02127447	0,87198397	-3,46273821	0,92555459
17185	11	27661223	cg06351568	*BDNF-AS*	-0,27324257	2,83898038	-2,53369122	0,02152644	0,87243892	-3,46835118	0,92555459
17392	11	27528430	cg24924243	*LIN7C;BDNF-AS*	4,64707347	-8,93253531	2,52766897	0,02179357	0,87279141	-3,47423166	0,92555459
19646	4	6949557	cg08840052	*TBC1D14*	0,22666236	1,67328504	2,46667603	0,02468184	0,87359528	-3,53364144	0,92555459
22618	5	142658828	cg23273257	*NR3C1*	0,42042756	3,97583297	2,39770540	0,02838202	0,87413008	-3,60045376	0,92555459
22960	5	142793924	cg01751279	*NR3C1*	-0,49402284	2,37207549	-2,39014033	0,02881819	0,87457583	-3,60775531	0,92555459
23591	5	142783621	cg15910486	*NR3C1*	0,59265353	-4,02734501	2,37573379	0,02966627	0,87473991	-3,62164429	0,92555459
23772	11	27722774	cg15914769	*BDNF*	0,26812607	-4,22596369	2,37192125	0,02989459	0,87473991	-3,62531634	0,92555459
23988	3	8809501	cg04523291	*OXTR*	-0,55579200	-1,90385949	-2,36729326	0,03017395	0,87473991	-3,62977177	0,92555459
24891	17	78369689	cg15637226	*RNF213; LOC100294362*	-0,30419918	0,87407285	-2,34919889	0,03128982	0,87473991	-3,64716982	0,92555459

Supplementary Table 3.S6.2: Differentially Methylated Candidate CpG Sites Associated With the Effect of Continuous Response (ΔHDRS) at Baseline.

Rank	CHR	BP	cg	Gene	logFC	AveExpr	t	P.Value	adj.P.Val	B	2-FDR
2041	6	35656906	cg01294490	*FKBP5*	0,03696575	-4,32998821	3,53252186	0,00259001	0,86245477	-2,19091282	0,94332903
2292	11	27721668	cg20954537	*BDNF*	0,02911534	-3,71674173	3,47990597	0,00290160	0,86245477	-2,30254139	0,94332903
5111	5	63258434	cg16807523	*HTR1A*	-0,04612190	-3,36936575	-3,10825238	0,00644908	0,86245477	-3,08191908	0,94332903
5685	6	42419718	cg08336315	*TRERF1*	-0,24403100	-5,74871345	-3,06012230	0,00714648	0,86245477	-3,18133364	0,94332903
5845	4	6955750	cg19271725	*TBC1D14*	0,02031755	3,27287626	3,04937871	0,00731194	0,86245477	-3,20346681	0,94332903
6230	4	6996897	cg10316586	*TBC1D14*	-0,02509895	3,78089138	-3,02301246	0,00773403	0,86245477	-3,25769121	0,94332903
7459	4	7009356	cg20963865	*TBC1D14*	-0,02270936	3,17371376	-2,93501859	0,00932180	0,86245477	-3,43764372	0,94332903
8426	5	142781498	cg07733851	*NR3C1*	-0,03755335	-0,87777684	-2,87973169	0,01047701	0,86245477	-3,54985163	0,94332903
9960	17	78322547	cg08676585	*RNF213*	0,02997684	3,89358382	2,80133038	0,01235573	0,86245477	-3,70773337	0,94332903
12827	11	27744557	cg10022526	*BDNF*	-0,02759990	-3,55310704	-2,68056982	0,01589924	0,86245477	-3,94778945	0,94332903
13923	6	35694245	cg00052684	*FKBP5*	0,02157104	-0,20927792	2,63941659	0,01731572	0,86434208	-4,02865287	0,94332903
14517	4	6967215	cg05810879	*TBC1D14*	-0,03517328	3,47372446	-2,61953301	0,01804258	0,86434208	-4,06753996	0,94332903
20329	5	142783621	cg15910486	*NR3C1*	0,03130842	-4,02734501	2,45272742	0,02539289	0,87010397	-4,38871056	0,94332903
21650	19	55880286	cg15681462	*IL11*	-0,02349487	-0,62356754	-2,41948900	0,02716198	0,87010397	-4,45155133	0,94332903
22519	17	78369689	cg15637226	*RNF213; LOC100294362*	-0,01594819	0,87407285	-2,40062610	0,02821686	0,87010397	-4,48703102	0,94332903
23505	17	28562220	cg22584138	*SLC6A4*	-0,03276440	0,23709674	-2,37917897	0,02946296	0,87010397	-4,52720729	0,94332903
23791	6	42375400	cg11905586	*TRERF1*	0,01823743	-2,05067108	2,37320453	0,02981917	0,87010397	-4,53836751	0,94332903
23816	17	5982344	cg19753798	*WSCD1*	0,01947685	2,52922839	2,37273211	0,02984750	0,87010397	-4,53924938	0,94332903
25388	17	28564117	cg12074493	*SLC6A4*	-0,18115134	-5,22015193	-2,34103343	0,03180757	0,87010397	-4,59822261	0,94332903
26618	5	142762613	cg05483455	*NR3C1*	-0,04353070	3,77118668	-2,31720318	0,03335961	0,87010397	-4,64229346	0,94332903
27692	11	27543361	cg09646437	*BDNF-AS*	0,01034621	1,91335629	2,29838700	0,03463468	0,87010397	-4,67692816	0,94332903
27730	11	27529576	cg09025927	*LIN7C;BDNF-AS*	-0,01626470	2,95643964	-2,29770419	0,03468179	0,87010397	-4,67818227	0,94332903
28645	3	8810206	cg11171527	*OXTR*	-0,04272000	-3,22016855	-2,28115909	0,03584176	0,87010397	-4,70851089	0,94332903
29308	11	27528430	cg24924243	*LIN7C;BDNF-AS*	0,22131622	-8,93253531	2,27038269	0,03661658	0,87010397	-4,72820325	0,94332903
31331	6	42391208	cg01673485	*TRERF1*	0,02152278	1,01574131	2,23717786	0,03910281	0,87010397	-4,78856925	0,94332903

Abbreviations.

Parameter	Definition
Rank	Position of the Candidate CpG Site in the Unfiltered Result File
CHR	Annotated Chromosome Number
BP	Chromosomal Position (hg19)
cg	Illumina cg Number of CpG Site
Gene	Annotated Gene
logFC	Log Fold Change
P.Value	Uncorrected p-value of Single Site Association Test
adj.P.Value	p-value After Adjustment for Multiple Testing (False Discovery Rate)
2-FDR	Secondary FDR Correction of p-values in the Candidate Result File

4 DISCUSSION

The presented work provides evidence that subgroups of mood disorders and treatment response can be characterized based on genetic and epigenetic data. Clinically pre-defined groups, subtypes of mood disorders (depression, BIP-I, BIP-II), and response to ECT treatment were investigated and showed that: (1) depression, BIP-I, and BIP-II share common genetic variation with biological rhythms (i.e., circadian rhythm, physical activity, and sleep), (2) treatment groups (i.e., responders vs. non-responders) are associated with different DNAm patterns. In the first study, genome-wide data from GWASs of depression, BIP-I and BIP-II, and biological rhythms were used. Different patterns of genetic correlations for depression, BIP-I, and BIP-II were found: depression was associated with decreased physical activity, whereas BIP-I was associated with increased physical activity. BIP-II held an intermediate position between the two subtypes, showing a negative albeit weaker association with physical activity than depression. The same was true for circadian rhythms; all three mood disorder subtypes were associated with the genetic risk for a disrupted circadian rhythm. The association was strongest in depression and weakest in BIP-I. Furthermore, specific genes were identified that were overlapping in mood disorders and biological rhythms (i.e., *MEF2C*, *CCDC36*, *ERBB4*, *CADM2*) and were previously involved in cell differentiation, neurogenesis, meiosis, and other neuropsychiatric disorders. These results provide genetic evidence for previous clinical observations regarding mood disorders and biological rhythms.
The second study aimed to identify epigenetic signatures characterizing responders and non-responders to ECT treatment. DNAm patterns before and after ECT were investigated. Differentially methylated single sites were found for binary response (responder vs. non-responders) and continuous response (ΔHDRS). The identified epigenetic marks were annotated to genes (e.g., *TNKS*, *FKBP5*) previously associated with mood disorders, affective states, and cellular processes. Moreover, differentially methylated regions were identified for genes (i.e., *LRATD2* (*FAM84B*); *BLCAP*) previously associated with cancer, cell growth, and apoptosis. For the first time, this study identified differential genome-wide epigenetic signatures of ECT treatment response groups measured longitudinally. The following paragraphs will discuss two studies main findings', including additional considerations.

4.1 Biological Characterization of Mood Disorders

Clinical observations regarding biological rhythms in mood disorders are dependent on the current mood state in which they are observed. For example, for physical activity, different patterns are observed during depressed and (hypo-) manic phases: decreased physical activity during depressed episodes and increased physical activity in (hypo-) manic phases (Faurholt-Jepsen et al., 2016; Scott et al., 2017). Also, it has been repeatedly shown that lower levels of physical activity, a disrupted circadian rhythm, and increased sleep problems are observed in patients during depressed phases compared to healthy controls (Difrancesco et al., 2019; Murphy & Peterson, 2015). However, it is unclear, if these symptoms occur because of the different mood states they are observed in or if they are due to a genetic predisposition. As genetic variants do not change over time, genetic data is state-independent; thus, using genome-wide data, genetic correlations can quantify the associations of mood disorders and biological rhythms regardless of the present state of mood. The genetic

associations found in study 1 reflected clinical observations of biological rhythms in mood disorders. For example, the reported genetic association between BIP-I and increased physical activity provides evidence that the increased physical activity in BIP is not only due to the specific phase (i.e. (hypo-) manic) they are observed in but also due to a shared genetic predisposition of BIP and increased physical activity. Another advantage is that the genetic correlations estimated in study 1 are based on common genetic variation, where biological rhythm parameters were collected in the general population. Thus, mood disorders and biological rhythms data were captured in separate samples. Not all phenotypes must be assessed in a clinical sample or the same individuals to quantify their genetic relationships. In light of prevention and subgroup stratification, this could become increasingly feasible as the assessment of the genotype data of one person would be sufficient to estimate their individual risk for all phenotypes GWAS data exists on, and the overlap could be quantified without any phenotype assessment of this person. Also, investigating shared genetic roots between symptoms across psychiatric disorders using GWASs data can enhance our understanding of etiology and comorbidities and reshape their current nosology (Andreassen et al., 2023). It is known that psychiatric disorders are comorbid, share traits across conditions (i.e., trans-diagnostic traits) and that symptoms are interrelated (e.g., Barr et al., 2022; Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019; Shi et al., 2023). However, according to traditional classification systems, psychiatric disorders are distinct, and symptoms are evaluated as categories, neglecting their interrelation (APA, 2013; WHO, 2022a). Research focusing on the shared genetic overlap across psychiatric disorders has grown. The Cross-disorder analysis group from the Psychiatric Genomics Consortium (PGC) found significant genetic overlap between 11 psychiatric disorders in the following features: compulsive behaviors, internalizing symptoms, psychotic, and neurodevelopmental. In line with the findings in study 1, they found negative associations between internalizing symptoms and physical movement and a positive genetic correlation of BIP with movement (Grotzinger et al., 2022).

EWAS data can also be used to characterize mood disorders, although compared to genetics, methods to analyze aggregated additive signals are fairly new, and EWAS data sets are not as large and powerful as GWAS data. First approaches, such as the MRS for MDD (Barbu et al., 2021), still need larger samples for sufficient prediction of mood disorders. However, DNAm data is a valuable source to characterize subgroups of mood disorder patients. It can model changes in DNAm due to environmental factors and identify reversibility markers if observed during an intervention (Wei et al., 2021).

So far, study 2 is one of the few longitudinal EWAS investigating the effects of ECT. Most of the studies investigating DNAm changes in treatment response are designed cross-sectional (e.g., Barbu et al., 2022; Engelmann et al., 2022). In study 2, DNAm changes were investigated longitudinally (i.e., before and after ECT) and epigenome-wide to search for epigenetic reversibility markers that change in response to ECT. Evidence was found that DNAm at specific sites in the genome differs between response groups. ECT is a vital somatic treatment with a high response rate (Bahji et al., 2019), inducing robust changes in the phenotype, which might have been the reason for our significant results in this small sample. Also, patients assigned to ECT are a fairly homogenous group, reducing variability within the tested response groups as they were all treatment-resistant patients.

The biological characterization of mood disorders and treatment response using genetic and epigenetic data is not limited to aggregated additive signals. These signals are biological correlates, i.e., specific genes, which can enhance our understanding of the underlying biological systems.

4.2 Identification of Treatment Targets in Mood Disorders

4.2.1 Genes Associated with Mood Disorders and Biological Rhythms

Based on genetic correlations, it was shown that mood disorders and biological rhythms share common genetic roots on a broad scale, including a large number of SNPs. In the next step, genes were examined (i.e., genes affecting more than one phenotype) occurring in both mood disorders and biological rhythms. In study 1, some specific genes yielded enough statistical power to show significant associations with mood disorders and biological rhythms. For example, *MEF2C* was significantly associated with depression and sedentary behavior. This gene has been linked previously to schizophrenia, autism, and exercise (Wu et al., 2001; Zhang & Zhao, 2022). The *MEF2C* gene is located on chromosome 5; it regulates various genes involved in the differentiation of muscle cells. Alterations at this locus are related to cognitive disability, stereotypic movements, and epilepsy (*MEF2C* Gene-GeneCards, 2022). MEF2 proteins are enriched in neurons and expressed in different parts of the brain (e.g., cerebellum, cerebral cortex and hippocampus, etc.) (Potthoff & Olson, 2007). Another interesting gene was *MSRA*, which overlapped with BIP-I and sleep duration; its pleiotropic effects have been studied before and it has been linked to nine psychiatric disorders (Lu et al., 2021). *MSRA* lies on chromosome 8 and translates into an enzyme named Methionine sulfoxide reductase A, responsible for protein repair and protecting against oxidative stress (*MSRA* Gene-GeneCards, 2022). Its overlapping association could be due to the role of oxidative stress in BIP and sleep (Brown & Naidoo, 2010; Jiménez-Fernández et al., 2022). Further studies need to clarify this complex relationship. Our study was a first step to identify genes related to mood disorders and biological rhythms, future studies investigating the influence of those genes on cellular processes and pathways are needed to develop novel treatment approaches.

4.2.2 *FKBP5* and *TNKS* in ECT Response

The top sites associated with continuous and binary response were located in the genes *FKBP5* and *TNKS*. *FKBP5* codes for a protein called FK506-Binding Protein 51, which is known for binding on the glucocorticoid receptor (GR) to regulate the effects of cortisol and other stress hormones (for a review, see Binder, 2009). Several studies show its implications in response to trauma and the development of mental disorders (Klengel et al., 2013; Zannas et al., 2016). *TNKS* regulates telomeres and cell proliferation, telomere length is a marker implicated in several psychiatric disorders (Darrow et al., 2016; *TNKS* Gene-GeneCards, 2021). It has also been found in GWASs of BIP (Stahl et al., 2019) and positive affect (Baselmans et al., 2019). The identified genes give insight into the molecular basis of treatment response and could be a starting point for developing treatment response biomarkers. Also, both genes have been found in other genetic and epigenetic studies, underlines the importance of complementary approaches to identify relevant biological systems.

4.3 Methodological Considerations

4.3.1 Genetic Correlations

Genetic correlations are feasible, have low computational time, are applied to independent samples, and can determine if two traits are rooted in a shared genetic

background (Bulik-Sullivan et al., 2015a). However, this methodological approach has some limitations: different biases can occur, such as differences in genetic ancestry or assortative mating can lead to spurious genetic correlations if not adequately accounted for (van Rheenen et al., 2019). Also, ascertainment bias, self-selection, misclassification and errors in the diagnosis or classification of traits can affect the accuracy of genetic correlation estimates (van Rheenen et al., 2019). Most importantly, genetic correlations cannot differentiate between cause and effect.
One method to disentangle cause and effect to use in study 1 would have been Mendelian Randomization (MR). MR tests the causal effect of an explanatory variable on a dependent outcome using genetic variants as instrumental variables (Maier et al., 2018). However, MR often lacks in power and underlies several assumptions such as the no-pleiotropy assumption which are usually violated in studies of complex traits (Maier et al., 2018). One solution to the cause-and-effect problem could be careful phenotypic assessments, including the acquisition of intra-individual variability and longitudinal studies in the field of epigenetics.

4.3.2 Longitudinal Methylation

Measuring longitudinal DNAm is one study design in epigenetics, where DNAm is measured repeatedly over an extended period of time in the same individuals (Campagna et al., 2021; Rakyan et al., 2011). This makes it feasible to investigate the dynamical trajectories of DNAm and their role in various biological processes and diseases. For example, if an EWAS is conducted across the lifespan and assessments are executed before the disorder occurs, results can even hint at causality (Rakyan et al., 2011). So far, several birth cohorts exist, which started to collect methylation data and disease-related phenotypes at timepoint of birth and continue to follow them up across participants' lifespan (e.g., Avon Longitudinal Study of Parents and Children, see https://www.bristol.ac.uk/alspac/, Norwegian Mother, Father and Child Cohort Study, see https://www.fhi.no/en/ch/studies/moba/). However, longitudinal EWAS cannot stand alone, even though they can modulate dynamic processes it remains challenging to derive clear downstream effects from EWAS data. An approach that could help here is the application of multi-omics analysis, e.g., the integration of genotype, methylation and gene expression data (Hasin et al., 2017).

4.4 Limitations

Both studies arrive with some limitations. In the first study, even though the most substantial genome-wide sample of mood disorders and biological rhythms to the time the study was conducted, was used, the size of the sample and its statistical power were still limited, especially for BIP-II and relative amplitude. Study 2 was the first longitudinal collection of DNAm data in a cohort undergoing ECT, but the number of patients included in the study was rather small. As discussed in *section 4.3*, the methods used in study 1 are sufficient tools to analyze these datasets but may not always reflect entirely the underlying biology and do not draw conclusions for causality. The same accounts for the methods used in study 2; an EWAS can identify associations between epigenetic modifications and the phenotype of interest but cannot be used to establish causality. In contrast to DNA, which should be the same at each timepoint and in each cell of the body, DNAm shows a lot of variability due to cell-type, tissue, and lifestyle factors such as smoking (Horvath, 2013; Lokk et al., 2014; Zeilinger et al., 2013). In study 2, the DNAm analysis was conducted based on

peripheral blood. Peripheral blood is often used in DNAm studies because it is feasible to access. However, psychiatric disorders are considered brain disorders. Also, in this specific study, the treatment of choice was ECT, which is applied to the brain. Hence, it cannot be excluded that findings that were made in blood cannot be replicated in the brain. Here, it needs to be kept in mind that depression is a systemic disorder (Sotelo & Nemeroff, 2017); thus, it can be assumed that DNAm changes should be seen in peripheral blood samples and not only in the brain.

4.5 Outlook

The identification of biological correlates of psychiatric disorders requires well-characterized clinical samples. So far, diagnosis is categorical and based on clinical interviews. However, innovative methods such as Ambulatory Assessment (AA) have been developed to assess more continuous and objective phenotypes (for reviews, see Carpenter et al., 2016; Trull & Ebner-Priemer, 2013; Wenzel et al., 2016). AA captures subjective and objective parameters such as current symptom severity, physical activity, and speech in real time using electronic devices (e.g., smartphones, sensors); collecting such deep phenotype data is crucial and expanding clinical diagnosis and identifying fluctuations and trajectories of individual patients over time. GWASs data of deep phenotypes increases, research initiatives such as the UKBiobank (Sudlow et al., 2015) published their GWAS findings on physical activity, sleep, and relative amplitude collected with AA (e.g., Doherty et al., 2018; Ferguson et al., 2018). Also, the largest GWAS on speech parameters was published in June 2023, reporting a SNP heritability of 17% for voice pitch (Gisladottir et al., 2023). Furthermore, available case-control studies could be used to conduct sub-phenotype analysis in cases including trans-diagnostic traits, comorbidities, specific symptoms, and treatment response. Some GWASs have already been performed in those phenotypes, for example, in cardinal symptoms of psychiatric disorders (Mallard et al., 2022), emotional dysregulation (Powers et al., 2016), cognitive function (Davies et al., 2018), and treatment-resistant patients undergoing ECT (Clements et al., 2021).
Also, larger samples are needed to investigate the (epi-) genetic basis of mood disorders and treatment response. To increase sample size, GWASs and EWASs data rely on meta-analytical methods, combining the results of several cohorts, which requires a collaborative effort. The Psychiatric Genomics Consortiuum (PGC, https://pgc.unc.edu/) consists of several working groups for the different psychiatric disorders, where samples are exchanged and meta-analyzed. Recently, a new working group was built on the Genetics of Electroconvulsive Therapy and Severe Depressive Disorders (Gen-ECT-ic) (Soda et al., 2020). Apart from the PGC, the International Consortiuum on Lithium Genetics (ConLiGen) investigates the genetic underpinnings of lithium response in bipolar patients (Schulze et al., 2010). Not only lager, but more ancestral diverse samples are needed. So far, most of the available GWASs and EWASs are based on samples with European ancestry (Peterson et al., 2019). Increased ancestral diversity could give a comprehensive insight into human genetics, increase the accuracy of effect sizes, and enhance the identification of causal variants (Peterson et al., 2019). Lately, GWASs in e.g., schizophrenia, depression, and opioid use disorder have been conducted in samples of different ancestry (Giannakopoulou et al., 2021; Lam et al., 2019; Kember et al., 2022); other studies using multi-ancestry datasets will follow.
To understand the biological roots of mood disorders and treatment response, different levels of data must be assessed and incorporated into our analysis. Multi-omics aims to gain insight into the underlying biological processes by combining several data

levels, e.g., genomic, epigenetic, transcriptomic, proteomic, and metabolomics (for reviews, see Hasin et al., 2017; Sathyanarayanan et al., 2023). Studies investigating different omics data in mood disorders and treatment response are increasing (e.g., Fabbri et al., 2021; Fuh et al., 2023; Ju et al., 2019; von Mücke-Heim et al., 2023; Wang et al., 2023). Also, investigating the functionality of markers and genes found here is essential. This could be done by testing specific markers in different tissues, cells, and species with methods from in vivo, and animal research to understand how and in which part of the body they act (Sathyanarayanan et al., 2023).
Artificial intelligence has made extraordinary progress in the past few years; the emerging analytical tools can be applied to different kinds of data, including (epi-) genetic data. For example, machine learning in psychiatry has been used to stratify subgroups of psychiatric disorders, e.g., in psychosis (Enrico et al., 2021) and schizophrenia (Cao et al., 2020) and treatment response (Joyce et al., 2021).
These different data and methods generate abundant biological knowledge; one crucial goal is translating this knowledge into clinical practice. Most of this data is currently not used in practice. An example of the realization of precision psychiatry in practice is pharmacogenetic testing. Pharmacogenomic studies investigate how genetic differences between individuals affect their response to a prescribed medication. Different genes have been tested in several psychiatric medications (further details can be found here: https://www.pharmgkb.org/). Current guidelines suggest the testing of *CYP2D6* and *CYP2C19* for commonly-used antidepressant and antipsychotic medications (for a review, see Bousman et al., 2021); they also have been studied in the past in response to citalopram usually prescribed to treat depression and anxiety disorders (for a review, see Chang et al., 2014). Another example are PRSs which could be used in the field of prevention, rated as beneficial in the next five years by 87% of US psychiatrists in 2021 (Pereira et al., 2022). However, researchers still perceive the implementation of PRS into clinical practice as challenging (Murray et al., 2021). Apart from genetic risk prediction, results from EWASs and individual epigenetic data could be used for monitoring and modulation of treatment response (Wei et al., 2021).

4.6 Conclusion

Subgroups of mood disorders and treatment response were characterized based on genome-wide genetic and epigenetic data. Both studies showed that mood disorders, their associated symptoms, and the response to antidepressant treatment have a complex genetic architecture involving specific genes and cellular processes. Biological targets for future investigations were suggested and underline the importance of genome-wide approaches. As the fields of genetics, multi-omics, and artificial intelligence are rapidly growing and developing new methods, one can be optimistic that a more holistic biological understanding of mood disorders and treatment response can be achieved.

5 SUMMARY

5.1 English Summary

Mood disorders such as depression and bipolar disorders are leading causes of the global disease burden. They are characterized by severe changes in mood ranging from depression to mania. Despite decades of research, the etiology of mood disorders is not fully understood. Due to the lack of biomarkers, diagnosis and treatment protocols are still made on the basis of clinical interviews and the subjective description of symptoms by the patient, which are both prone to bias. At present, mood disorders are understood as multifactorial, where an interplay of environmental and genetic factors is causing the disorder. In search for the genetic underpinnings of mood disorders, formal genetic studies showed that mood disorders are heritable (depression ~40%, bipolar disorder ~80%). Genome-wide association studies revealed that many different genetic variants are associated with depression and bipolar disorders and that psychiatric disorders share partly common genetic roots. Also, environmental factors can act via epigenetic modifications, such as DNA methylation. Several studies found differentially methylated markers in individuals with mood disorders compared to healthy controls. In addition, response to antidepressant treatment is related to DNA methylation changes. The overall aim of the two studies was to investigate whether the characterization of mood disorder and treatment response groups is possible with genome-wide and epigenome-wide data. Implicated genes and pathways and their potential role in the development of mood disorders were further investigated.

In the first study, genome-wide data from depression, bipolar disorders (i.e., bipolar I disorder, bipolar II disorder), and biological rhythms were dissected by quantification of their genetic overlap. This was done with biostatistical methods to estimate the genetic correlations, calculate differences in correlations for the different mood disorder subtypes, and conduct gene-level analysis. The biological meaning of the overlapping genes was further researched using genetic databanks. In the second study, differential DNA methylation was analyzed to classify responders and non-responders to Electroconvulsive therapy and identify changes in DNA methylation over time. First, an epigenome-wide association study was conducted, looking at the interaction of treatment group and time, followed by differentially methylated regions and pathway analysis.

The results of study 1 show genetic associations of mood disorder subtypes with biological rhythms. Different and similar correlation patterns of mood disorders with biological rhythms were investigated; showing the strongest differences in correlations with biological rhythms between depression and bipolar I disorder, bipolar II disorder takes a position in between the two mood disorders. These findings show that the associations previously observed in clinical studies are already rooted in genetic differences between the mood disorder subtypes and are not solely due to the specific episode they are observed in. The predisposition for increased activity in bipolar I disorder and the weaker negative association with circadian rhythm implies that the genetic underpinnings of bipolar I disorder may be protective regarding disturbed biological rhythms compared to depression. Furthermore, we identified genes that were associated with both mood disorders and biological rhythms (i.e., *MEF2C*, *CCDC36*, *ERBB4*, *MSRA*, *CADM2*) previously implicated in cell differentiation,

neurogenesis, meiosis, and neuropsychiatric disorders. Also, circadian genes such as *NR1D1*, *PER1*, and *ARNTL* were related to depression and bipolar disorder. Results of the second study included differential methylation associated with response groups located in *TNKS*, which is involved in cellular processes, and telomere length and has been found in previous genome-wide association studies of bipolar disorder and positive affect. Under the nominal significant hits, we found *FKBP5*, previously associated with stress and stress-related disorders, and *RAB21*, linked to response to antidepressants, suggesting that similar genes might be implicated in the epigenetic response to different antidepressant treatments. The two differentially associated regions annotated to *LRATD2* (*FAM84B*) and *BLCAP* are involved in cancer, cellular processes, brain development, and neuronal differentiation.

In conclusion, these studies provide evidence that subgroups of mood disorders and treatment response of Electroconvulsive therapy can be characterized with genome-wide genetic and epigenetic data. Both studies identified genetic and epigenetic markers, which could be potential starting points for further research on the etiology and treatment of mood disorders.

5.2 German Summary – Zusammenfassung in deutscher Sprache

Stimmungsstörungen wie Depressionen und bipolare Störungen sind die Hauptursachen für die weltweite Krankheitslast. Sie sind durch schwere Stimmungsschwankungen gekennzeichnet, die von Depression bis zu Manie reichen können. Trotz jahrzehntelanger Forschung ist die Ätiologie von Stimmungsstörungen noch nicht vollständig geklärt. Da es keine Biomarker gibt, werden Diagnose und Behandlungsprotokolle immer noch auf der Grundlage klinischer Befragungen und der subjektiven Beschreibung der Symptome durch den Patienten erstellt, die beide anfällig für Verzerrungen sind. Gegenwärtig werden Stimmungsstörungen als multifaktorielle Erkrankungen verstanden, bei denen ein Zusammenspiel von Umwelt- und genetischen Faktoren die Störung verursacht. Auf der Suche nach den genetischen Grundlagen von Stimmungsstörungen haben formal genetische Studien gezeigt, dass Stimmungsstörungen vererbbar sind (Depression ~40 %, bipolare Störung ~80 %). Genomweite Assoziationsstudien haben gezeigt, dass viele verschiedene genetische Varianten mit Depressionen und bipolaren Störungen assoziiert sind und, dass psychiatrische Störungen teilweise gemeinsame genetische Wurzeln haben. Auch Umweltfaktoren können über epigenetische Veränderungen, wie die DNA-Methylierung, wirken. In mehreren Studien wurden bei Personen mit Stimmungsstörungen im Vergleich zu gesunden Kontrollpersonen unterschiedlich methylierte Marker gefunden. Darüber hinaus steht das Ansprechen auf eine antidepressive Behandlung mit DNA-Methylierungsveränderungen in Zusammenhang. Das übergeordnete Ziel der beiden Studien bestand darin, zu untersuchen, ob die Charakterisierung von Gruppen mit Stimmungsstörungen und Gruppen des Ansprechens auf eine Behandlung mit genomweiten und epigenomweiten Daten möglich ist. Die dabei beteiligten Gene und Signalwege und ihre mögliche Rolle bei der Entwicklung von Stimmungsstörungen wurden weiter untersucht.

In der ersten Studie wurden genomweite Daten zu Depressionen, bipolaren Störungen (d.h. Bipolar-I-Störung, Bipolar-II-Störung) und biologischen Rhythmen durch Quantifizierung ihrer genetischen Überlappung untersucht. Dies geschah mit biostatistischen Methoden, um die genetischen Korrelationen zu schätzen,

Unterschiede in den Korrelationen für die verschiedenen Subtypen von Stimmungsstörungen zu berechnen und Analysen auf Genebene durchzuführen. Die biologische Bedeutung, der sich überschneidenden Gene wurde mit Hilfe genetischer Datenbanken weiter erforscht. In der zweiten Studie wurde die differentielle DNA-Methylierung analysiert, um Respondierende und Nicht-Respondierende auf Elektrokrampftherapie zu klassifizieren und Veränderungen der DNA-Methylierung im Verlauf zu identifizieren. Zunächst wurde eine epigenomweite Assoziationsstudie durchgeführt, in der die Wechselwirkung zwischen Behandlungsgruppe und Zeit untersucht wurde, gefolgt von differenziell methylierten Regionen und einer Analyse der Signalwege.

Die Ergebnisse von Studie 1 zeigen genetische Assoziationen zwischen den Subtypen von Stimmungsstörungen und biologischen Rhythmen. Es wurden unterschiedliche und ähnliche Korrelationsmuster von Stimmungsstörungen mit biologischen Rhythmen untersucht; die stärksten Unterschiede in den Korrelationen mit biologischen Rhythmen zeigen sich zwischen Depression und der Bipolar-I-Störung, während die Bipolar-II-Störung eine Position zwischen den beiden Stimmungsstörungen einnimmt. Diese Ergebnisse zeigen, dass die zuvor in klinischen Studien beobachteten Zusammenhänge bereits auf genetische Unterschiede zwischen den Subtypen der Stimmungsstörung zurückzuführen sind und nicht ausschließlich auf die spezifische Episode, in der sie beobachtet werden. Die Veranlagung zu erhöhter Aktivität bei der Bipolar-I-Störung und die schwächere negative Assoziation mit zirkadianen Rhythmen deutet darauf hin, dass die genetischen Grundlagen der Bipolar-I-Störung im Vergleich zur Depression schützend für gestörte biologische Rhythmen sein könnte. Darüber hinaus haben wir Gene identifiziert, die sowohl mit Stimmungsstörungen als auch mit biologischen Rhythmen assoziiert sind (z.B. *MEF2C*, *CCDC36*, *ERBB4*, *MSRA*, *CADM2*), die zuvor mit Zelldifferenzierung, Neurogenese, Meiose und neuropsychiatrischen Störungen in Verbindung gebracht wurden. Auch zirkadiane Gene wie *NR1D1*, *PER1* und *ARNTL* wurden mit Depression und bipolaren Störungen in Verbindung gebracht. Zu den Ergebnissen der zweiten Studie gehörte eine differentielle Methylierung im Zusammenhang mit den Behandlungsgruppen in *TNKS*, das an zellulären Prozessen und der Telomerlänge beteiligt ist und in früheren genomweiten Assoziationsstudien zu bipolaren Störungen und positivem Affekt gefunden wurde. Unter den nominell signifikanten Treffern fanden wir *FKBP5*, das bereits vorher mit Stress und stressbedingten Störungen in Verbindung gebracht wurde, und *RAB21*, das mit der Reaktion auf Antidepressiva in Verbindung gebracht wurde, was darauf hindeutet, dass ähnliche Gene an der epigenetischen Reaktion auf verschiedene antidepressive Behandlungen beteiligt sein könnten. Die beiden differenziell assoziierten Regionen, annotiert zu *LRATD2* (*FAM84B*) und *BLCAP*, sind an Krebs, zellulären Prozessen, Gehirnentwicklung und neuronaler Differenzierung beteiligt.

Zusammenfassend lässt sich sagen, dass diese Studien belegen, dass Untergruppen von Stimmungsstörungen und dem Ansprechen auf die Elektrokrampftherapie mit genomweiten genetischen und epigenetischen Daten charakterisiert werden können. In beiden Studien wurden genetische und epigenetische Marker identifiziert, die potenzielle Ansatzpunkte für die weitere Erforschung der Ätiologie und Behandlung von Stimmungsstörungen sein könnten.

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