Depression and Bipolar Disorder Subtypes Differ in their Genetic Correlations with Biological Rhythms

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Article

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Abstract

Major Depression and Bipolar Disorder Type I (BIP-I) and Type II (BIP-II), are mood disorders characterized by the occurrence of depressed, manic, and hypomanic episodes in which specific changes of physical activity, circadian rhythm, and sleep are observed. While it is known that genetic factors contribute to variation in both mood disorders and these biological rhythms, it is an open question to what extent there is an overlap between their underlying genetics.

Here, we used data from genome-wide association studies to examine the genetic relationship between mood disorders and biological rhythms. Linkage Disequilibrium Score Regression was applied to test 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). Furthermore, we compared depression, BIP-I, and BIP-II in their correlations with biological rhythms to discover commonalities and differences.

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.

The present results suggest that the clinically observed associations between mood disorders and biological rhythms have shared genetic underpinnings. Future research considering possible joint mechanisms may offer potential avenues for improving disease detection and treatment.

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 [1, 2]. MD is characterized by depressive episodes, while BIP is characterized by manic (BIP-I) or hypomanic (BIP-II) episodes, generally alternating with depressive episodes [3].

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.) [4]. 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 [3].

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 [5, 6]. The same is found for individuals with BIP [7, 8]. 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 [9, 10]. 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**) [11].

Circadian mechanisms govern many biological processes and their importance is being increasingly recognized in the etiology, diagnosis, and treatment of mood disorders [12]. A parameter often used to describe circadian rhythms is relative amplitude, which quantifies rest-activity patterns using the most active continuous 10 hours and least active continuous 5 hours of a day [13]. A healthy person is active during the day and less active at night (high relative amplitude) while patients suffering from mood disorders can present with the opposite pattern (low relative amplitude), indicating a disrupted circadian rhythm [14, 15]. Lower relative amplitudes are found in both depression and BIP compared to healthy individuals [13, 16].

Sleep is a recurring biological process holding many functions of great importance for the human body (e.g., restoration and memory functioning) [17]. Sleep problems, insufficient sleep, irregularity of sleep-wake cycles, and differences in sleep duration, are well described in MD and BIP [18, 19], as is daytime sleepiness, which is also reported to be increased in patients suffering from MD and BIP [20, 21].

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 40-54% for chronotype, and 31-49% for normal sleep due to factors such as variation in age and study design [22 - 24]. 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 = 5,952 twins, n = 756 twins) [25, 26] as well as with sleep duration (n = 894 twins) [27]. 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 [28].

Advances in molecular genetic methods have led to an increase in sample size, power, and number of genome-wide association studies (GWASs) of many disorders and traits, also enabling *in silico* testing for genetic overlap of various phenotypes based on those results [29]. Molecular genetic studies offer the opportunity to investigate commonalities in genetic predisposition independent of the current mood state. 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 [30] and negative correlations between MD and physical activity [31]. In contrast, for BIP (subtypes unspecified), positive associations have been found with physical activity, but none with daytime sleepiness [30, 31].

The present study aims to explore whether depression, BIP-I, and BIP-II share genetic etiology with biological rhythms using summary statistics from the most current respective GWASs [30, 32 - 35]. 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.

Materials And Methods

GWAS Samples

Table 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 [29].

For depression, the latest publicly available summary statistics were used as described in [32], 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 [33].

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 [36]. 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) [11]. 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) [30]. 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.

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 [37]. 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 S1.1-S1.3**) indicating good interpretability and power for genetic correlation analyses, as recommended by the authors of LDSC [38]. 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.

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 [37], as previously described in [39]. 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 vs. 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.

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 1**. Bonferroni corrected p-values are indicated in **Figure 1** and reported in **Tables S1.1-S2.3**.

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 S1.1**).

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 S1.2**).

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 ($r_g = 0.02$, $p = 0.77$) (see **Table S1.3**).

Differences between Correlations

Comparing correlations of Depression and BIP-I with Biological Rhythms

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 S2.1**).

Comparing correlations of Depression and BIP-II with Biological Rhythms

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 S2.2**).

Comparing correlations of BIP-I and BIP-II with Biological Rhythms

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 S2.3**).

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.

Epidemiological and clinical studies have repeatedly reported an inverse relation between higher levels of activity and depression [40, 41]. 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 [26], and also confirms an earlier study using GWAS data which reported negative genetic correlations of MD with overall physical activity as well as walking [31].

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 [31] based on an earlier BIP GWAS [42]. 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 [42]; 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 [9, 10]; 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 [13 - 16]. 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 [43 - 45]; 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) [35]. 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 [29]. This study found that participants with an increased PRS for a disrupted circadian rhythm showed in turn an increased PRS for MD [35]. Further studies applying methods leveraging genome-wide data approaches are expected to provide further insight into these relationships.

Symptoms such as insufficient sleep duration and frequent awakenings are often reported in mood disorders [46]. Genetic studies report a high genetic overlap of sleep-related phenotypes (e.g., insomnia, chronotype, sleep duration) with MD and BIP [47, 48]. An earlier GWAS using self-report measures of sleep duration reported a significant genetic correlation with BIP, but not with depressive symptoms [49]; 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 [30]. The same study examined BIP as well in a smaller sample but did not look at the subtypes separately [30]; 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 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 S1.1-S1.3**) and we could expect more significant findings with larger samples. As increased samples become available, the analysis of causality with methods like Mendelian Randomization will become possible as the number of identified significant SNPs associated with objective phenotypes such as physical activity and relative amplitude is expected to increase. 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) [50]. 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. Continued efforts are needed to acquire increased sample sizes of under-characterized subtypes and these emerging phenotypes on a population-wide scale. In addition, expanding the assessment of objective phenotypes (e.g., recording locomotor activity for longer periods) will increase the stability of these measures and lead to more robust insights.

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. The causality behind this bears further investigation. 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. 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.

Declarations

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Disorders; from converging epigenetic signatures to novel targets for therapeutic intervention” [01EW1904]. All authors declare that they have no conflict of interest.

Author Contributions

LS and JCF proposed the analysis plan. LS, JCF, JF, and FS undertook the statistical analysis. LS, JCF, MR, LZ, SHW, and FS did the literature review for the paper. LS and JCF 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.

Data Availability

Summary statistics for depression, BIP-I, and BIP-II were obtained from the Downloads section on the Psychiatric Genomics Consortium Webpage (<https://www.med.unc.edu/pgc/download-results/>, March 19th, 2020 and November 20th, 2020) [32, 33]. 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:ff479f44-bf35-48b9-9e67-e690a2937b22> (retrieved March 13th, 2020) [34]. 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) [35, 30].

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) or can be made available by the corresponding author based on reasonable request.

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Tables

Table 1. Overview of GWAS Summary Statistics Analyzed

<u>Phenotype</u>	<u>Reference</u>	<u>Sample</u>
Depression	Howard et al. (2019)	170,756 MDD cases (excluding 23andMe)
BIP-I BIP-II	Mullins et al. (2021)	25,060 BIP-I cases and 6,781 BIP-II cases
Relative Amplitude	Ferguson et al. (2018)	71,500 participants UK Biobank cohort
Overall Physical Activity Moderate Activity Sedentary Behaviour Sleep Duration	Doherty et al. (2018)	91,105 participants UK Biobank cohort
Daytime Sleepiness	Wang et al. (2019)	452,071 participants UK Biobank cohort

Figures

Figure 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 ; ** $q < 0.05$, * $p < 0.05$; for comparison of correlations: ^^ $q < 0.05$, ^ $p < 0.05$.

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