Major Depressive Disorder and Bipolar Disorder Subtypes Differ in their Genetic Correlations with Physical Activity, Circadian Rhythm, and Sleep

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Article

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Abstract

Alterations in biological rhythms are features of mood disorders. Patients suffering from major depressive disorder (MDD) show decreased physical activity compared to healthy controls. Bipolar disorder (BIP) patients differ in their activity patterns during different mood phases, and in comparison to their non-affected relatives and healthy controls. In both MDD and BIP, circadian rhythms can be disrupted, accompanied by sleep problems and changes in sleep duration. It is unclear whether the observed associations are due to common etiology or if they are influenced by the current mood state in which they are observed. Here, we used summary statistics from large-scale genome-wide association analysis (GWAS) to test the genetic correlations of MDD, BIP-I, and BIP-II with physical activity (overall physical activity, moderate activity, sedentary behavior), circadian rhythm (relative amplitude) and sleep features (sleep duration, daytime sleepiness). MDD showed positive genetic correlations with sedentary behavior, and negative correlations with overall physical activity and moderate activity, while BIP-I showed associations in the opposite direction. MDD and BIP-II had negative genetic correlations with relative amplitude. All mood disorders were positively genetically correlated with daytime sleepiness. The correlational patterns show that MDD and BIP-I differ the most in their correlations with biological rhythms with BIP-II seemingly occupying a intermediate position. Furthermore, our 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 depressive disorder (MDD) and Bipolar disorder (BIP) are common, often long-lasting conditions that can cause harm to those affected and the people close to them [1, 2]. MDD is characterized by depressed mood and loss of interest, while BIP is characterized by manic (BIP-I) or hypomanic (BIP-II) symptoms in addition to depressive episodes [3]. Alterations in physical activity, circadian rhythm and sleep are among the symptoms of both MDD and BIP; in depression, disturbed sleep, tiredness, and psychomotor retardation/agitation are often observed, while increased energy and movement and a decreased need to sleep are recognized during (hypo-) manic episodes [4].

Research linking physical activity, circadian rhythm, and sleep features (hereafter referred to together as biological rhythms) has identified different patterns in various mood disorder states or phases (depressed, manic, hypomanic, euthymic). For example, in unipolar depression, lower levels of physical activity or increased sedentary behavior have been observed compared to healthy controls [5, 6]. BIP (subtype not examined) is shown to be associated with lower mean activity levels compared to controls [7, 8]; comparison of the different mood states within BIP discovered significantly higher levels of activity during manic than euthymic and depressed states [9, 10]. In BIP-I and BIP-II, increased frequency of exercise during manic and hypomanic episodes in comparison to depressed episodes have also been shown [11].
Physical activity patterns also reflect circadian rhythms, disruption of which is seen in various psychiatric disorders [12]. One measure of circadian rhythm is relative amplitude, which quantifies the relative difference between the most and least active hours in a 24-hour cycle [13]. Several studies observe a link between mood disorders and low relative amplitude, finding reduced activity during the day and higher activity in the evening, representing a disrupted circadian rhythm [13, 14]. In MDD patients, a diminished relative amplitude is shown compared to healthy controls [15]. In BIP, patterns of circadian rhythm are reported to be less stable and with peak activity arising earlier in the day in comparison to healthy controls [16, 17, 10].

Alterations in circadian function are in turn linked to sleep and sleep-wake cycles; sufficient sleep is usually considered to increase health and well-being [18]. Sleep disturbances such as insomnia, abnormal sleep latency, and poor sleep efficiency can affect mental health and are described as symptoms in MDD and BIP [19, 20]. Sleep problems and circadian disruptions can also cause daytime sleepiness, which is often reported in patients suffering from MDD and in BIP during euthymic states [21, 22].

Associations between mood disorders and biological rhythms are clinically observed but it is unclear if these relationships are due to common etiology. Genetic studies offer the opportunity to investigate these relationships independent of the current mood state. Mood disorders are known to be heritable, with estimates for MDD at 40% and BIP at 80% [23]. BIP-I and BIP-II are genetically highly correlated ($r_g = 0.87$); MDD and BIP-I ($r_g = 0.31$) have a lower genetic correlation than MDD and BIP-II ($r_g = 0.69$) [24]. For biological rhythms, heritability estimates ($h^2$) are heterogeneous, ranging from small (<30%) to high (78%) for physical activity, from 40–54% for chronotype, and 31–49% for normal sleep [25, 26, 27] due to factors such as variation in age and study design. Several twin and family studies offer insight into the genetic relationship of mood disorders and biological rhythms: In twin studies, negative genetic associations have been reported between depressive symptoms and physical activity [28] and sleep duration [29]. In a study of 26 high-density bipolar families, 43 circadian rhythms and sleep phenotypes showed significant heritability ($h^2$ ranging from 15–75%), 12 were associated with BIP-I [30]. Taken together, these studies suggest the possibility of shared underlying genetic factors between mood disorders and various aspects of the body’s biological rhythms.

While twin and family studies allow investigation of genetic relatedness of disorders and traits in related individuals in whom all the disorders and traits in question have been investigated, genetic correlation studies based on genome-wide association study (GWAS) results allow testing of those associations in independent samples in whom only a specific disorder or trait has been assessed. Several studies have begun to use GWAS summary statistics to investigate the relationship between mood disorders and biological rhythms. For example, in one study, genetic correlation of depressive symptoms, but not BIP, with daytime sleepiness has been observed [31]. Using a polygenic risk score (PRS) approach a association between a PRS for low relative amplitude and MDD was shown [32]. Meanwhile, two recent studies found a negative genetic correlation of MDD with overall activity and walking and a positive genetic correlation of BIP with moderate activity and walking [33]; and a high genetic overlap of sleep-
related phenotypes (insomnia, chronotype, sleep duration) with schizophrenia, bipolar disorder and depression [34].

The present study aims to explore the shared genetic etiology of MDD, BIP-I, and BIP-II with biological rhythms using summary statistics from the latest GWASs. In particular, we investigated BIP subtypes using summary statistics from the largest GWAS on BIP [35]. Differences in genetic correlations of MDD, BIP-I, and BIP-II with biological rhythms are examined to identify overlap as well as differences between the disorders and their relationship with biological rhythms.

Methods

GWAS summary statistics

Table 1 gives an overview of the GWAS summary statistics used in this analysis. For MDD the latest publicly available summary statistics were applied (excluding 23andMe) as described in [36]. BIP-I and BIP-II summary statistics were derived from the latest Psychiatric Genomics Consortium (PGC) GWAS on BIP in 40 000 cases [35].

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

Summary statistics for overall physical activity, moderate activity, sedentary behavior, and sleep duration based on objective accelerometer measurements as described in [37] were utilized. Overall physical activity represents the average activity over the time of assessment, moderate activity is characterized by periods of high activity, and sedentary behavior is described as sitting or lying behavior [37]. Summary statistics for relative amplitude based on objective accelerometer measures from [32] were used. The relative amplitude measure employed for this analysis was linear, with lower values reflecting a more
disrupted pattern of movement with reduced daytime activity and increased nighttime activity [32]. Summary statistics from the largest GWAS for self-reported daytime sleepiness were applied [31].

**Genetic Correlation Analysis**

Genetic correlations of mood disorders (MDD, BIP-I, BIP-II), with overall physical activity, moderate activity, sedentary behavior, sleep duration, relative amplitude, and daytime sleepiness were calculated using the bivariate genetic correlation method in 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 [38]. We used the LD Scores of the 1 000 Genomes Project for use with European samples. Default settings were applied for the filtering process: INFO score > 0.9, Minor Allele Frequency (MAF) > 0.01, and 0 < P < = 1. Indels, ambiguous, duplicated SNPs, and SNPs having no match in the LDScore reference panel were removed. For each mood disorder (MDD, 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; corrected values are indicated in Fig. 1 and reported in Table S1.1-S1.3.

**Analysis of Differences in Correlations**

To compare the above calculated correlations between MDD, BIP-I, and BIP-II, we employed the block jackknife extension of LDSC [38], 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 analyzed: MDD vs. BIP-I, MDD vs. BIP-II, and BIP-I vs. BIP-II in their correlations with biological rhythm traits. For each comparison six tests were conducted. Bonferroni correction (p < 0.05/6 = 0.0083) for the number of biological rhythm traits was applied; corrected values are indicated in Fig. 1 and reported in Table S2.1-S2.3.

**Results**

Genetic correlations of MDD, BIP-I, and BIP-II with biological rhythm traits and the differences between the mood disorders in their correlations are presented in Fig. 1.

**Genetic Correlations of MDD with Biological Rhythms**

Significant negative correlations of MDD with overall physical activity ($r_g = -0.11$, $p = 0.0001$), moderate activity ($r_g = -0.09$, $p = 0.04$) and with relative amplitude ($r_g = -0.30$, $p = 4.40 	imes 10^{-12}$) were found. A significant positive correlation of MDD with daytime sleepiness ($r_g = 0.17$, $p = 3.17 	imes 10^{-11}$) was observed. MDD was not significantly correlated with sedentary behavior ($r_g = 0.03$, $p = 0.40$), 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 behavior ($r_g = -0.11$, $p = 0.003$). 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 behavior ($r_g = -0.03$, $p = 0.61$), and sleep duration ($r_g = 0.02$, $p = 0.77$) (see Table S1.3).

**Differences between Correlations**

**Comparing correlations of MDD and BIP-I with Biological Rhythms**

MDD 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 behavior ($z = 2.95$, $p = 0.003$), and relative amplitude ($z = -4.15$, $p = 3.36 \times 10^{-5}$). MDD and BIP-I did not differ significantly in their correlations with sleep duration and daytime sleepiness (see Table S2.1).

**Comparing correlations of MDD and BIP-II with Biological Rhythms**

MDD and BIP-II differed significantly in their genetic correlations with moderate activity ($z = -2.70$, $p = 0.007$). The correlations of MDD and BIP-II with overall physical activity, sedentary behavior, 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 behavior, sleep duration yielded no significant differences (see Table S2.3).

**Discussion**

In the present study, we found shared genetic architecture between MDD, BIP-I, and BIP-II and biological rhythms; the observed clinical comorbidities appear to have a root in common genetic variation. Although
MDD, BIP-I, and BIP-II are highly correlated, direction and strength of their genetic associations with biological rhythms differ, underlining the importance of examining the subgroups of mood disorders.

The observed negative correlations between MDD and increased activity (overall physical activity and moderate activity) reflect clinical observations that mean activity is decreased in MDD patients [5, 40]. Recent studies using genome-wide data have found that physical activity can decrease the risk for depression [41, 42], and also report negative genetic correlations of MDD with overall physical activity and walking [33]. A recent twin study found a genetic relationship between decreased depression and increased activity [43]. The positive genetic correlation of BIP-I and BIP-II with moderate activity and the negative correlation of BIP-I with sedentary behavior are in line with findings showing a positive genetic correlation of BIP (without specification of subtypes) with moderate activity and walking [33] based on a previous BIP GWAS [44]. A Mendelian Randomization study investigating the causal relationship between physical activity and BIP, found that a increase in physical activity is associated with decreased liability to developing BIP [45]. The observed genetic correlation of BIP-I and BIP-II with increased activity, may reflect the genetic factors underlying the respective manic and hypomanic features [7, 10]. Placing the present findings on BIP-I and BIP-II in the context of the genetic literature, it should be noted that the BIP data used in earlier works is based on GWAS where the large majority of the patients were diagnosed with BIP-I [44]; the present analysis uses a larger dataset and separately examines BIP-II.

We observed negative correlations of MDD, and BIP-II, with relative amplitude (lower relative amplitude indicates a more disrupted circadian rhythm); circadian rhythm disruption plays a prominent role in MDD and BIP disease etiology and treatment. Genetic studies provide evidence for a close relationship between circadian, MDD and BIP genes [for reviews, see 46, 47, 48], with one hypothesis being that mood symptoms (such as depressive or manic symptoms) arise from dysregulation of circadian clock genes [49, 50]. Our findings confirm and provide a potential background for clinical observations of less stable patterns of movement and disrupted circadian rhythms in MDD and BIP [51, 52, 15]. We note that the strongest and most statistically significant correlation in the present analysis was between MDD and relative amplitude, suggesting this relationship as a target for further investigation and characterization.

Symptoms such as insufficient sleep duration and frequent awakenings are often reported in mood disorders [53, 54]. Neither MDD, nor either BIP subtypes were found to be significantly correlated with objectively measured sleep duration, leaving it an open question whether and to what extent common genetic factors might contribute to their relationship. The literature so far is also unclear. For example, a GWAS conducted on sleep duration found a significant genetic correlation of sleep duration and BIP, but not with depressive symptoms [55]; further investigations of these relationships await. We also observed that MDD, BIP-I and BIP-II are significantly positively correlated with daytime sleepiness, the only subjective measure used in this analysis. Our use of larger summary statistics appears to clarify prior results which had shown genetic correlations between daytime sleepiness and depression, but not BIP [31]. Although a consequence of a disrupted circadian rhythm and insufficient sleep can be increased daytime sleepiness (both often reported in MDD and BIP [56, 22]), the present results hint at a more fundamental shared etiology, which bears further examination.
In comparing correlations, the most prominent differences were found between MDD 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 in MDD (low activity) and BIP-I (high activity). BIP-II showed an intermediate correlational pattern, with the only significant differences in relative amplitude and daytime sleepiness to BIP-I and a significant difference in moderate activity to MDD. Notably, MDD and BIP-II showed 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 MDD with respect to increased activity phenotypes. It is of interest to note that the strongest similarities between the mood disorders are observed in daytime sleepiness suggesting that daytime sleepiness shares common genetic etiology with all mood disorder types. It should be kept in mind, that daytime sleepiness was the only biological rhythms measure, that was assessed by self-report, which might have contributed to this result; highlighting the value of objectively assessing traits in large scale studies. This similarity, as well as the same direction of effect with respect to relative amplitude, may reflect the common genetic underpinnings, and the quantitative measures which differentiate them from healthy controls. In summary, the discovered similarities and differences appear to be clues to delineating these mood disorders with respect to each other, on a continuum or otherwise.

A limitation of this study is the sample size of some of the used GWASs; the power of BIP-II and relative amplitude summary statistics is lower than the other GWASs, which is of note for the statistical comparison of the genetic correlations. Although still well powered, not all genetic correlations or differences between genetic correlations were significant after corrections for multiple testing (see Fig. 1, Table S1.1-S2.3). With larger samples available, the analysis of causality with methods like MR will become possible as the number of identified significant SNPs associated with newer phenotypes such as physical activity and relative amplitude is expected to increase. Continued efforts are needed to acquire increased sample sizes of under-characterized subtypes and these emerging phenotypes.

The present 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 the current disorder state or medication status. 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. 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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Conflict of Interests

All authors declare that they have no conflict of interest.

Supplementary Information

Supplementary information is available at MP’s website.

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**Figures**

Figure 1

Genetic Correlations of MDD, BIP-I, BIP-II with Biological Rhythms. \( rg \) = genetic correlation coefficient; lines indicate standard error limits of \( rg \); ** indicate \( q < 0.05 \), * indicate \( p < 0.05 \); for comparison of correlations: ^^ indicate \( q < 0.05 \), ^ indicate \( p < 0.05 \).

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