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SHORT REPORT

Polygenic risk scores for mood disorders and actigraphy estimates of sleep and circadian rhythms: A preliminary study in bipolar disorders

Vincent Hennion[1,2,3] | Jan Scott[4] | Victoire Martinot[2,3] | Ophélia Godin[5] | Cynthia Marie-Claire[1] | Frank Bellivier[1,2,3] | Stéphane Jamain[5] | Bruno Etain[1,2,3]

[1]Optimisation Thérapeutique en Neuropsychopharmacologie, INSERM U1144, Université Paris Cité, Paris, France

[2]Département de Psychiatrie et de Médecine Addictologique, AP-HP Nord, GH Saint-Louis-Lariboisière-Fernand-Widal, DMU Neurosciences, Paris, France

[3]Université Paris Cité, Paris, France

[4]Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK

[5]Université Paris Est Créteil, INSERM, IMRB, Translational Neuropsychiatry, Créteil, France

Correspondence

Bruno Etain, Optimisation Thérapeutique en Neuropsychopharmacologie, INSERM U1144, Université Paris Cité, Paris, France.
Email: bruno.etain@inserm.fr

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Summary

In bipolar disorders, abnormalities of sleep patterns and of circadian rhythms of activity are observed during mood episodes, but also persist during euthymia. Shared vulnerabilities between mood disorders and abnormalities of sleep patterns and circadian rhythms of activity have been suggested. This exploratory study investigated the association between polygenic risk scores for bipolar disorder and major depressive disorder, actigraphy estimates of sleep patterns, and circadian rhythms of activity in a sample of 62 euthymic individuals with bipolar disorder. The polygenic risk score – bipolar disorder and polygenic risk score – major depressive disorder were calculated for three stringent thresholds of significance. Data reduction was applied to aggregate actigraphy measures into dimensions using principal component analysis. A higher polygenic risk score – major depressive disorder was associated with more fragmented sleep, while a higher polygenic risk score – bipolar disorder was associated with a later peak of circadian rhythms of activity. These results remained significant after adjustment for age, sex, bipolar disorder subtype, body mass index, current depressive symptoms, current tobacco use, and medications prescribed at inclusion, but not after correction for multiple testing. In conclusion, the genetic vulnerabilities to major depression and to bipolar disorder might be associated with different abnormalities of sleep patterns and circadian rhythms of activity. The results should be replicated in larger and independent samples.

KEYWORDS

actigraphy, bipolar disorder, circadian rhythms, major depression, polygenic risk scores, sleep

1 | INTRODUCTION

Circadian rhythms are the physiological, physical, and behavioural changes an organism experiences over a 24 h cycle (from *circa diem*, i.e., "about one day" in Latin). In humans, circadian rhythms of activity characterise the variations of levels of physical activity over a 24 h period. Circadian rhythms of activity can be measured in an ecological way using actigraphy. An actiwatch is a device resembling a wristwatch that contains an accelerometer that detects and scores information about the intensity and timing of wrist movements

(i.e., physical activity) over consecutive 24 h intervals (Ancoli-Israel et al., 2003). Actigraphy estimates several parameters of physical activity: the amplitude (i.e., the difference in activity levels between the most and the least active periods over a 24 h period), the intra-daily variability (i.e., the fragmentation of rest–activity periods within days), the inter-daily stability (i.e., the regularity in day-to-day rest–activity patterns), and the timing (i.e., the onsets of the most prolonged active and inactive periods during the 24 h cycle).

In bipolar disorders (BD), abnormalities of sleep patterns and circadian rhythms of activity have been described during acute episodes, with most abnormalities persisting during euthymia or episode remission. Several meta-analyses of actigraphy studies confirm that euthymic individuals with bipolar disorders display higher sleep fragmentation, longer sleep onset latency, lower sleep efficiency, alongside lower stability, higher variability, later peak, and lower amplitude of circadian rhythms of activity, compared with healthy controls (De Crescenzo et al., 2017).

Abnormalities of sleep patterns and circadian rhythms of activity are – at least partly – determined by genetic factors, as shown consistently by results from family studies, twin studies, or genome-wide association studies. For instance, a genetic contribution to circadian rhythms of activity and sleep patterns has been suggested in pedigrees segregating for bipolar disorders (Pagani et al., 2016). A meta-analysis of twin studies has demonstrated that sleep duration and sleep quality were genetically determined (respectively 46% and 44% of the phenotypic variability) (Kocevska et al., 2021). Finally, a genome-wide association study of 27 actigraphy-derived physical activity measurements suggested that most of these phenotypes were heritable (Qi et al., 2022).

There may be a shared genetic vulnerability between bipolar disorders and abnormalities of sleep patterns and circadian rhythms of activity, a hypothesis that would also apply to major depressive disorders (MDD). For example, Mendelian randomisation studies suggest bidirectional causal links between mood disorders (both bipolar and unipolar disorders) and sleep-related phenotypes (e.g., sleep duration and chronotype) (Crinion et al., 2024). Since genetic vulnerabilities to bipolar disorders and MDD also overlap (Liu et al., 2023), it is relevant to take both into account to explore how they might explain clinical observations in terms of sleep patterns and circadian rhythms of activity.

To date, polygenic risk scores for MDD and BD have been exclusively studied in association with the clinical expression of bipolar disorders (in terms of age at onset, psychotic symptoms, or disease course, for instance) (Liu et al., 2023), but never in association with actigraphy derived parameters. As such, this study is exploratory and novel, and aims to enrich the current knowledge on how the genetic susceptibility to mood disorders might be associated with some phenotypic characteristics of bipolar disorders, here in terms of sleep patterns and circadian rhythms of activity.

We therefore hypothesised that the genetic vulnerability to bipolar disorder and to major depressive disorder estimated by polygenic risk scores would be associated with sleep patterns and circadian rhythms of activity estimates using actigraphy in a sample of euthymic adults with bipolar disorders.

2 | MATERIALS AND METHODS

This study is based on a subsample of the research protocol registered on ClinicalTrials.org (NCT02627404), that was approved by a French ethics committee (see Ethics approval statement). All participants provided written informed consent.

2.1 | Sample characteristics

Participants were European adult out-patients diagnosed with bipolar disorders type 1 or 2 (according to DSM-IV criteria). Participants were euthymic at inclusion, that is, no hospitalisation, no mood recurrence, nor medication modification (assessed by clinical interviews) for at least 3 months before inclusion and scores lower than 8 both on the Montgomery-Asberg Depression Rating Scale (MADRS) and the Young Mania Rating Scale (YMRS). Exclusion criteria were: current alcohol or substance use disorder (except tobacco); diagnosed sleep disorder (sleep apnea, narcolepsy, etc.), and/or undertaking shift work and/or any recent life event disrupting sleep patterns or circadian rhythms of activity.

2.2 | Actigraphy recording

Participants were asked to wear continuously an actiwatch (AW-7 CamNtech) on their non-dominant wrist for 21 days and to press a button each day when they went to sleep and got out of bed. An actiwatch is a device resembling a wristwatch that contains an accelerometer that detects, scores, and stores information about the intensity and timing of wrist movements over consecutive 24 h intervals. For this study, an epoch of 1 min (i.e., activity level is recorded every minute) and an average sensitivity threshold was chosen. On day 21, data were extracted from the Actiwatch and standard actimetry parameters were calculated using the Actiwatch Activity and Sleep Analysis software (CamNtech 7.28). Table 1 describes actigraphy variables.

2.3 | Polygenic risk scores

A polygenic risk score (PRS) is an estimate of an individual's genetic liability to a disease, calculated according to the individual's genotype profile and based on summary statistics of genome-wide association studies data comparing cases and controls. The classical PRS calculation combines the effect sizes of multiple single nucleotide polymorphisms identified by genome-wide association studies into a single aggregated score. A PRS is expected to reflect individuals' disease risk (here for major depression or bipolar disorder), meaning that the PRS for a given disorder is higher when individuals carry a greater number of at-risk genetic variants (Choi et al., 2020).

Genomic DNA was isolated from venous blood sample using standard procedures. Genotyping was performed using the Infinium

TABLE 1 Summary of available actigraphy estimates of sleep and circadian rhythms of activity and medians (IQR) in the studied sample.

Actigraphy variable	Definition	Median	IQR	
Assumed sleep	Time between reported sleep onset and offset (minus WASO) (hours)	8.24	7.47	8.87
Sleep latency	Time between reported bedtime and sleep onset (minutes)	11.34	8.19	19.21
Sleep efficiency	Sleep duration divided by the total time spent in bed (%)	84.83	82.26	86.93
Wake after sleep onset (WASO)	Total time of nocturnal waking (minutes)	51.12	35.46	66.69
Fragmentation index (FI)	Amount of time associated with movement during the sleep period (%)	30.28	24.34	36.73
Mean activity score during sleep	Average count per active epoch during sleep	11.42	7.82	16.36
Inter-daily stability (IS)	Degree of regularity in day-to-day rest–activity patterns	0.47	0.36	0.55
Intra-daily variability (IV)	Degree of fragmentation of rest–activity periods within days	0.83	0.70	0.93
L5	Average activity across the least active 5 hour period during 24 h	873	636	1371
L5 onset	L5 start time (hours)	1	0	2
M10	Average activity level for the most active 10 hours period during 24 h	14,773	12,432	20,669
M10 onset	M10 start time (hours)	9	8	11
Amplitude	Difference in the amount of activity between the most active and least active periods	13,647	11,275	20,013
Relative amplitude	Amplitude divided by (M10 + L5)	0.89	0.84	0.92

Abbreviation: IQR, interquartile range.

Global Screening Arrays-24 v2.0 (Illumina Inc.), according to the manufacturer's protocol (~660,000 single-nucleotide polymorphisms). Quality control of genotypic data, family relationships, and ancestry were performed using the procedure described previously (Courtois et al., 2020). PRS were calculated for each individual using the PRSice software (v.2.0.15) (Euesden et al., 2015) and based on the Psychiatric Genomics Consortium summary statistics for bipolar disorders (Mullins et al., 2021) and major depressive disorders (Wray et al., 2018) in European individuals only. We restricted the analyses to the three most stringent PRS-BD and PRS-MDD (threshold p values of 0.00005, 0.0001, and 0.001) and did not use the more recently suggested Bayesian approaches for PRS calculations.

2.4 | Statistical analysis

Analyses were performed using SPSS. Continuous variables are presented with medians and interquartile range (IQR).

Given the redundancy and correlations in-between actigraphy parameters, we first undertook two principal component analyses (PCA) with an Oblimin rotation, including first only sleep estimates and then only circadian rhythms of activity estimates. We employed this method in prior studies to enable data reduction and the generation of sleep and circadian rhythms of activity dimensions (Ferrand et al., 2022). The Kaiser–Meyer–Olkin index (KMO) and Bartlett's test of sphericity measured PCA appropriateness. The number of extracted components relied on Eigenvalues >1. Factor loadings of >0.50 were considered significant.

Next, we undertook correlations between each PCA component, polygenic risk scores for depression and bipolar disorder, followed by linear regression analyses using each PCA component as a dependent variable, polygenic risk scores for depression or for bipolar disorder as independent variables, with adjustments for sex, age, bipolar disorder subtype, BMI (body mass index), residual depressive symptoms (MADRS score), current tobacco use, and medications prescribed at inclusion. We applied a correction for multiple testing ($p < 0.0016$).

3 | RESULTS

3.1 | Sample characteristics

The initial sample included 109 participants, among which 62 had a blood sample. All were of European descent. Among these, 38 were females and 44 had bipolar disorder type 1. The median age at inclusion was 42 (IQR 33–54). The median age at bipolar disorder onset was 23 (IQR 19–30), with a median number of mood episodes of 6 (IQR 4–8). The median body mass index was 25 (IQR 23–28). The median MADRS score at inclusion was 2 (IQR 0–4). About half (47%) of the individuals were current smokers. Current psychotropic medications included lithium (63%), anticonvulsants (47%), atypical antipsychotics (31%), antidepressants (27%), and benzodiazepines, and/or hypnotics (8%). Table 1 shows actigraphy variables, their respective definitions, medians, and IQR.

3.2 | Principal component analyses

A first PCA included six actigraphy sleep estimates (KMO = 0.62; Bartlett's test of sphericity $p < 0.001$) and extracted two components. The first one was labelled "sleep fragmentation" (high wake after sleep onset, high fragmentation index, high mean active score during

sleep, and low sleep efficiency) and explained 55% of the variance. The second one was labelled "good sleep quality" (long sleep duration and low sleep latency), and explained 20% of the variance.

A second PCA included eight actigraphy estimates of circadian rhythms of activity (KMO = 0.65; Bartlett's test of sphericity $p < 0.001$) and extracted three components. The first one was labelled "robustness of circadian rhythms of activity" (high M10, high amplitude, high inter-daily stability, and low intra-daily variability) and explained 41% of the variance. The second one was labelled "late chronotype" (late M10 onset and late L5 onset, meaning delayed peaks of active and inactive periods over the 24 h period) and explained 30% of the variance. The third one was labelled "high amplitude of circadian rhythms of activity" (low L5 and high relative amplitude) and explained 14% of the variance (see Tables S1 and S2 for details).

3.3 | Associations between actigraphy components, and polygenic risk scores for MDD and BD

Spearman correlations tests identified associations between the two most stringent polygenic risk scores for depression and the sleep fragmentation component, and between the two most stringent polygenic risk scores for bipolar disorder and the late chronotype component (Table 2). A higher polygenic risk score for depression was associated with a higher sleep fragmentation. A higher polygenic risk score for bipolar disorder was associated with a higher value on the late chronotype component (i.e., corresponding to a later peak of both active and inactive periods over the 24 h cycle).

Associations were no longer significant when the threshold for polygenic risk scores calculation was higher than $p = 0.001$. No association was observed between polygenic risk scores and other components. No association resisted a correction for multiple testing. Of note, no correlation was observed between the polygenic risk scores for depression and bipolar disorder at the two lowest thresholds (p values between 0.21 and 0.77).

After adjustments for potential confounding factors in linear regressions, the associations between the most stringent polygenic risk scores for depression and sleep fragmentation and between the most stringent polygenic risk scores for bipolar disorder and late chronotype remained significant at $p < 0.05$ ($p = 0.038$ and $p = 0.014$, respectively) (see Tables 3 and 4). These associations did not resist a correction for multiple testing.

4 | DISCUSSION

This study is the first to explore associations between polygenic risk scores for mood disorders and actigraphy-based sleep patterns and circadian rhythms of activity in a clinical sample of euthymic individuals with bipolar disorders. We suggest that sleep fragmentation might be associated with a higher polygenic risk score for depression, while later peaks of circadian rhythms of activity (i.e., later M10 onset and L5 onset) might be associated with a higher polygenic risk score for bipolar disorder. These associations resisted adjustment for several potential confounding factors that also may influence sleep patterns and circadian rhythms of activity (including medications), although were not significant after correction for multiple testing in the relatively small sample used.

There is a widespread hypothesis in the literature suggesting that the abnormalities of sleep patterns and circadian rhythms of activity are a core vulnerability to bipolar disorder. This is supported by the fact that these abnormalities pre-exist the onset of bipolar disorder

TABLE 2 Spearman correlation tests between PRS-BD, PRS-MDD, and sleep and circadian rhythms components.

		Sleep components		Circadian rhythms components		
Variable		"Sleep fragmentation"	"Good sleep quality"	"Robustness"	"Late chronotype"	"High amplitude"
PRS MDD (0.00005)	Rho	**0.29**	−0.04	−0.19	−0.09	−0.15
	p	**0.02**	NS	NS	NS	NS
PRS MDD (0.0001)	Rho	**0.31**	0.07	−0.15	−0.14	−0.14
	p	**0.01**	NS	NS	NS	NS
PRS MDD (0.001)	Rho	0.16	−0.12	−0.19	−0.15	−0.15
	p	NS	NS	NS	NS	NS
PRS BD (0.00005)	Rho	−0.02	−0.16	−0.17	**0.36**	−0.04
	p	NS	NS	NS	**0.004**	NS
PRS BD (0.0001)	Rho	−0.05	−0.21	−0.23	**0.32**	−0.05
	p	NS	NS	NS	**0.01**	NS
PRS BD (0.001)	Rho	−0.001	0.006	−0.07	0.18	−0.04
	p	NS	NS	NS	NS	NS

Note: In bold *p* values < 0.05 (no correction being applied).
Abbreviations: BD, bipolar disorder; MMD, major depressive disorder; NS, not statistically significant at $p < 0.05$; PRS, polygenic risk score.

TABLE 3 Multivariate analysis between PRS-MDD and sleep fragmentation.

Variable	Beta	SE	*t*	*p*	Tolerance	VIF
Intercept	0.33	1.301	0.254	0.801		
PRS-MDD (0.00005)	191.457	90.012	2.127	0.038*	0.858	1.165
Sex	−0.392	0.270	−1.45	0.153	0.869	1.150
Age	−0.015	0.010	−1.514	0.136	0.819	1.222
BD type	0.297	0.347	0.855	0.396	0.607	1.648
BMI	0.029	0.032	0.905	0.370	0.835	1.198
MADRS	0.101	0.069	1.451	0.153	0.788	1.270
Current smoking	−0.036	0.272	−0.134	0.894	0.818	1.222
Lithium	0.315	0.326	0.967	0.338	0.608	1.645
Anticonvulsants	0.558	0.315	1.768	0.083	0.607	1.647
Antipsychotics	−0.212	0.286	−0.740	0.463	0.865	1.156
Antidepressants	0.027	0.337	0.081	0.936	0.665	1.504
Benzodiazepines	−0.929	0.494	−1.879	0.066	0.830	1.205

Note: Beta are not standardised. *Uncorrected *p* value.
Abbreviations: BD, bipolar disorder; BMI, body mass index; MADRS, Montgomery–Asberg depression rating scale; MMD, major depressive disorder; PRS, polygenic risk score; SE, standard error; VIF, variance inflation factor.

TABLE 4 Multivariate analysis between PRS-BD and late chronotype.

Variable	Beta	SE	*t*	*p*	Tolerance	VIF
Intercept	3.917	1.404	2.789	0.008		
PRS-BD (0.00005)	458.022	179.301	2.554	0.014*	0.902	1.108
Sex	−0.224	0.262	−0.852	0.398	0.870	1.150
Age	−0.020	0.010	−2.130	0.038*	0.826	1.211
BD type	0.039	0.325	0.121	0.904	0.652	1.535
BMI	−0.014	0.031	−0.436	0.665	0.824	1.213
MADRS	0.106	0.067	1.593	0.118	0.804	1.244
Current smoking	0.285	0.261	1.092	0.280	0.836	1.196
Lithium	−0.483	0.318	−1.522	0.135	0.603	1.659
Anticonvulsants	−0.535	0.306	−1.747	0.087	0.608	1.644
Antipsychotics	−0.165	0.281	−0.588	0.559	0.843	1.186
Antidepressants	−0.211	0.328	−0.642	0.524	0.663	1.508
Benzodiazepines	−0.394	0.481	−0.818	0.417	0.826	1.210

Note: Beta are not standardised. *Uncorrected *p* value.
Abbreviations: BD, bipolar disorder; BMI, body mass index; MADRS, Montgomery–Asberg depression rating scale; MMD, major depressive disorder; PRS, polygenic risk score; SE, standard error; VIF, variance inflation factor.

(Scott, Etain, et al., 2022), persist during euthymia (De Crescenzo et al., 2017), can predict outcomes of the disorder (Scott et al., 2020) and might be "reversed" in individuals who respond to lithium (Scott, Hennion, et al., 2022). Since bipolar disorder, major depression and abnormalities of sleep patterns and circadian rhythms of activity are both heritable, a between-phenotypes shared vulnerability has been hypothesised. As mentioned in the introduction, this has been explored by Mendelian randomisation studies (Crinion et al., 2024) demonstrating links between bipolar disorder or major depression to chronotype, sleep duration, or sleep disorders. We provided here an additional argument in favour of this hypothesis with the association between a higher polygenic risk score for depression and a higher sleep fragmentation, and with the association between a higher polygenic risk score for bipolar disorder and a later peak of circadian rhythms of activity (i.e., later starts of the most active and the most inactive periods during the 24 h cycle). Polygenic risk scores for depression and bipolar disorder might also influence the clinical expression of bipolar disorders (e.g., BD subtype, age at onset, course, etc) (van Loo et al., 2023), that in turn modify the observed sleep patterns and circadian rhythms of activity, this hypothesis has not been explored in this study.

The findings should be considered as preliminary because of the relatively small, selected convenience sample of individuals and the findings no longer met statistical significance when analyses were corrected for multiple testing. The sample size of 62 participants has a power of 0.80 to identify a Spearman correlation coefficient above

0.36 with an alpha = 0.05, therefore not excluding a lack of power in the analysis. Nevertheless, it is worth highlighting that whilst this study is small for polygenic risk score analyses, the sample size would be deemed large for studies of actigraphy in mood disorders. Furthermore, we assessed participants some years after the onset of the disorder, and sleep patterns and circadian rhythms of activity might have been modified by the course of the disorder, by past and currently prescribed medications (Hennion et al., 2024) (which does not seem to be the case here for medications at inclusion) and other psychosocial factors including the loss of social entrainment (in those who were no longer employed) or alternatively, by the use of psychological interventions that aim at regulating sleep or circadian rhythms of activity. As well as trying to replicate the findings in independent samples of individuals with bipolar disorder, it is increasingly important to compare individuals with bipolar disorder with those with other psychiatric disorders, such as anxiety, major depression or psychosis, to examine whether there is any specificity to the sleep patterns and/or circadian rhythms of activity associated with bipolar disorder. Finally, since no control group with calculated polygenic risk scores and actigraphy recordings was available for this study, we were not able to conclude whether the observed associations were specific to individuals with bipolar disorder, or would also be observed (possibly at a lower magnitude) among controls.

5 | CONCLUSION

We suggest that the genetic vulnerability to bipolar disorder and to major depression, as assessed by polygenic risk scores, might differentially influence the phenotypic expression in terms of sleep and circadian rhythms of activity estimated by actigraphy in euthymic individuals with bipolar disorder. The genetic vulnerability to major depression might influence sleep fragmentation, while the genetic vulnerability to bipolar disorder might influence the timing of circadian rhythms of activity. If confirmed in independent samples, the findings indicate that studies exploring polygenic risk scores alongside objective, ecological recordings of sleep patterns and circadian rhythms of activity can provide additional insights regarding genetic vulnerabilities and sleep–wake cycles that extend beyond evidence accrued from studies that rely on self-report of sleep profiles.

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CONFLICT OF INTEREST STATEMENT

B.E. has received honoraria for consulting from Sanofi. F.B. is an advisor on mental health to the French government. All other authors have no conflict of interest regarding this work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Bruno Etain https://orcid.org/0000-0002-5377-1488

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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