

Impact of Biological Rhythm Dysregulation on Quality of Life in Bipolar Disorder: An Outpatient Cross-Sectional Study

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Background: Biological rhythms disturbances are now known to be significant features of BD and can last beyond the acute phases of BD. But their relationship with functional impairment and metabolic abnormalities in euthymia is not fully understood. The objective was to compare biological rhythm disturbance between euthymic BD patients and healthy controls and to examine its associations with functioning, residual mood symptoms, and metabolic parameters.

Methods: A total of 40 euthymic BD patients and 40 healthy controls were selected for this cross-sectional comparative study. Biological rhythm disturbances were evaluated by means of the Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN). Functional impairment was measured with the Functioning Assessment Short Test (FAST) and the Hamilton Depression Rating Scale (HDRS) and Young Mania Rating Scale (YMRS) were used to measure residual mood symptoms. Other anthropometric and metabolic characteristics were also measured. Group comparisons, correlation analyses and the multiple linear regression were carried out.

Results: Euthymic bipolar disorder (BD) patients demonstrated significantly higher BRIAN scores (44.20 ± 3.83 vs. 19.93 ± 2.08 ; $p < 0.001$) and FAST scores (29.30 ± 3.31 vs. 10.03 ± 1.42 ; $p < 0.001$)

than healthy controls. Residual depressive and manic symptoms were significantly greater in the BD group. Patients also exhibited higher fasting blood glucose, triglycerides, systolic and diastolic blood pressure, and lower HDL cholesterol. Biological rhythm disturbance correlated significantly with functional impairment, residual mood symptoms, and metabolic parameters. Multiple linear regression identified FAST score ($\beta=0.801$, $p<0.001$), HDRS score ($\beta=0.296$, $p=0.001$), and fasting blood glucose ($\beta=0.184$, $p=0.018$) as independent predictors of biological rhythm disturbance.

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Conclusions: Biological rhythm disturbances persist in euthymic bipolar disorder despite symptomatic remission and are associated with functional impairment, residual mood symptoms, and metabolic abnormalities. Functional impairment, residual depressive symptoms, and fasting blood glucose emerged as independent predictors of biological rhythm disturbance. These findings support the clinical importance of biological rhythm assessment and reinforce the need for routine functional and metabolic evaluation during the long-term management of bipolar disorder.

Keywords: Bipolar disorder, Biological Rhythm Disturbance, Circadian Rhythm, Euthymia, Functional Impairment, Quality of Life, Metabolic Abnormalities

1. Introduction

Bipolar Disorder (BD) is a chronic and recurrent psychiatric disorder which presents with episodes of mania, hypomania and depression with periods of remission (1,2). Although there has been progress in the pharmacological and psychosocial treatment of the disorder, it is still a major cause of disability globally and also causes significant impairment of the individual's psychosocial, working and interpersonal functioning (1,3). There is growing evidence that many patients still have considerable problems even after attaining symptomatic remission. A study, Rosa et al. (4), showed that functional impairment is common in clinically stable BD patients, well beyond the symptom-free BD. Likewise, Vieta et al. (5) reported that the occurrence of acute mood episodes is not the only factor that affects long-term outcome in BD: chronic illness-related factors can also cause disability and impair quality of life. Modern studies have thus focused more and more on the assessment of persistent disease features that could be responsible for functional impairments, vulnerability to relapse, and long-term prognosis.

Disruption of circadian and biological rhythms are now acknowledged as key characteristics of BD. To explain the instability of mood and vulnerability to relapse, Harvey (6) suggested that abnormalities in sleep-wake regulation and circadian timing are a core part of the illness and that these abnormalities may

play a role in the illness itself. The relationship between disrupted social rhythms, activity patterns and sleep behaviours with BD development and maintenance was further emphasized (7). Takaesu (8) also found that abnormalities of sleep-wake cycles, changes in melatonin secretion, clock-gene alterations, and social time-cue disruption are all common characteristics of BD and could serve as trait markers of BD. They are not just associated with sleep, but often involve more than one behavioural domains such as daily activities, interpersonal routines and eating behaviours.

Research studies employing the Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN) have shown that abnormalities in biological rhythms can also occur in a person's behavior even when they are not currently symptomatic for a disorder. However, significant differences exist in the biological rhythm disturbance between interepisodic BD patients and healthy controls, even though they do not have acute mood symptoms at the time of the study (9). In a similar study, Rosa et al (4) report that BD patients who have remitted showed biological rhythm impairment that persisted throughout the study, and they found links between biological rhythm impairment, functional impairment, and residual depressive symptoms. In more recent studies, Vangal et al (10) reported significantly higher BRIAN scores in remitted BD patients compared to healthy controls,

suggesting that rhythm disturbances persist during clinical stability. Taken together, these results point to a trait-like aspect of BD that is manifested as biological rhythm dysregulation, not just in depressive or manic phases. Recent progress in the field of chronobiology and clock-gene studies has also supported this hypothesis, showing that there are dynamic changes in circadian regulatory networks in patients with BD (11,12).

Biological rhythm disturbances are important clinical issues beyond the context of mood episodes. In one of the first studies to investigate the functional implications of circadian disruptions, Giglio et al. (9) found that biological rhythm disturbances were highly correlated with impaired psychosocial functioning in interepisodic BD patients, and that BD patients with a higher degree of biological rhythm disturbance had a higher risk of functional disability. Similarly, Rosa et al. (4) found that in remitted BD patients, there was a correlation between more severe biological rhythm disturbances and poorer functioning and more residual depressive symptoms, indicating that biological rhythm abnormalities persist during remission and continue to have clinical effects. More recently, Vangal et al. (10) found that remitted BD patients reported poorer quality of life and greater levels of biological rhythm disturbances than healthy controls, lending further support to the linkage between circadian dysfunction and poor psychosocial outcomes.

In addition to psychosocial functioning, more focus has turned to the metabolic effects of circadian disturbances in BD. The close relationship between circadian disruption and endocrine-metabolic abnormalities was pointed out by Yan et al (13), indicating that common biological mechanisms could play a role in both circadian rhythm disruption and metabolic dysfunction. Likewise, Chung et al. (11) highlighted the importance of circadian clock mechanisms in the regulation of glucose metabolism, lipid homeostasis and cardiovascular function. Campbell et al. (14) recently hypothesized that there is a relationship between circadian dysfunction and obesity, insulin resistance, dyslipidaemia and cardiovascular disease in BD, through a chronometabolic mechanism. Together, these results indicate that there is a potential for biological rhythm disturbances to affect mental and physical health in BD. There is, however, relatively little literature that has investigated simultaneously the biological rhythms, functional impairment, residual mood symptoms and metabolic abnormalities in euthymic

BD populations. Thus, the clinical implications of long-term rhythm instability in the asymptomatic phase of the disease are far from clear.

However, increasing evidence indicates that biological rhythm disturbances persist after the acute mood episode and that there is a complex relationship between biological rhythm disturbances and functional impairment and metabolic abnormalities in euthymic BD patients. These relationships could help researchers gain critical insights into the burden of BD over time and provide opportunities to monitor and chronotherapeutic interventions. The present study was designed to compare the biological rhythm disturbance among Euthymic BD patients and healthy controls and relate these parameters with functioning, residual mood symptoms and metabolic parameters. The specific aims were to compare the BRIAN scores, functional status and metabolic parameters of euthymic patients with BD with healthy controls; to characterize the relationship between BD biological rhythm disturbance and clinical, functional, and metabolic variables; and to identify independent variables associated with BD biological rhythm disturbance.

2. Methods

2.1 Study Design

This was a cross-sectional comparative observational study conducted to evaluate biological rhythm disturbances among euthymic BD patients and healthy controls. The study further examined the relationship between biological rhythm dysregulation, functional impairment, residual mood symptoms, and metabolic abnormalities. The study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (15).

2.2 Ethical Considerations

The Independent Ethics Committee (ACEAS - Independent Ethics Committee, Ambawadi, Ahmedabad, Gujarat IEC#20SBBS3010001, dated 06 Sept 2025) reviewed and approved the study protocol before it could be set in motion. Information regarding the purpose, procedures, potential risks and benefits of the study were explained to all participants in detail. Each participant, prior to their enrolment, provided written informed consent as prescribed by the ethical principles identified in the Declaration of Helsinki. The participants were guaranteed that their personal health data will be kept confidential and they

were given the freedom to leave the study any time without it affecting their further clinical treatment. All the information gathered was anonymised and it remained purely utilised in research.

2.3 Study Setting

The study was conducted in the various psychiatric clinics across Ahmedabad, Gujarat. Participant recruitment and data collection were carried out over a period of six months, from September 2025 to March 2026. Clinical assessments, anthropometric measurements, and biochemical investigations were performed according to standard protocols and guidelines.

2.4 Participants

The study included two groups of participants. The case group comprised adults with a diagnosis of BD who were in a euthymic phase of illness at the time of assessment. The control group consisted of apparently age- and gender-matched healthy individuals without a history of major psychiatric illness. Controls were recruited from the local community and were selected to provide a comparison group for the assessment of biological rhythms, functioning, mood symptoms, and metabolic parameters.

Euthymia was defined as the absence of a current manic, hypomanic, mixed, or depressive episode at the time of assessment. Participants were considered euthymic if they demonstrated minimal residual affective symptoms and were clinically stable according to psychiatrist evaluation and standard mood rating scales, consistent with recommendations of the International Society for Bipolar Disorders (ISBD) Task Force on course and outcome definitions in BD (17).

Healthy controls were individuals without a current or past history of BD or other major psychiatric disorders. Controls were recruited from the community and were screened to exclude significant psychiatric, neurological, or medical illnesses that could influence biological rhythms or metabolic parameters.

2.5 Eligibility Criteria

Patients aged 18 years or older with a diagnosis of BD established according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), were eligible for inclusion in the study (16). Their psychiatric comorbidities was assessed using MINI 5.0 (17). Participants were required to be in a euthymic state at the time of assessment, defined by the absence of a current manic, hypomanic, mixed, or depressive

episode, consistent with recommendations of the International Society for Bipolar Disorders Task Force (18). All participants were required to provide written informed consent before enrolment.

Patients were excluded if they were experiencing an acute mood episode at the time of assessment or had comorbid psychotic disorders, substance dependence, significant neurological illness, or serious medical conditions that could influence study assessments. Individuals who were unable to provide informed consent were also excluded.

Healthy controls were adults aged 18 years or older with no current or past history of BD or other major psychiatric illness. Controls were screened prior to enrolment and were excluded if they reported a history of psychiatric illness, psychotropic medication use, significant neurological disease, or medical conditions that could affect biological rhythms or metabolic parameters. Written informed consent was obtained from all control participants prior to participation.

2.6 Recruitment and Sampling

Participants were recruited using a consecutive sampling technique. Eligible BD patients attending the psychiatry outpatient services during the study period were approached for participation and enrolled consecutively until the required sample size was achieved. Healthy controls were recruited from the community and hospital surroundings and were selected to broadly match the patient group with respect to age and sex distribution. All participants underwent screening for eligibility prior to enrolment. Written informed consent was obtained from all participants before study-related assessments were undertaken.

2.7 Variables and Outcome Measures

The primary outcome was biological rhythm disturbance assessed using the total score of the BRIAN (9). Secondary outcomes included functional impairment assessed using the Functioning Assessment Short Test (FAST) (4), residual depressive symptoms assessed using the Hamilton Depression Rating Scale (HDRS) (19), residual manic symptoms assessed using the Young Mania Rating Scale (YMRS) (20), anthropometric measures including body mass index (BMI) and waist circumference, and metabolic parameters including fasting blood sugar (FBS), triglycerides (TG), high-density lipoprotein cholesterol (HDL), systolic blood pressure (SBP), and diastolic blood pressure (DBP).

2.8 Data Sources and Measurements

Biological rhythm disturbances were assessed using the BRIAN, a validated instrument developed to evaluate disturbances across domains including sleep, activity, social rhythms, and eating patterns (9). Higher scores indicate greater biological rhythm dysregulation.

Functional impairment was evaluated using the FAST, a validated instrument designed to assess autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships, and leisure activities (4). Higher scores indicate greater functional impairment.

Residual depressive symptoms were assessed using the HDRS, a clinician-rated measure of depressive symptom severity (19). Residual manic symptoms were assessed using the YMRS, a widely used clinician-rated measure of manic symptom severity (20).

Height and weight were measured using standard procedures, and body mass index was calculated as weight in kilograms divided by the square of height in metres (kg/m^2). Waist circumference was measured using a non-stretchable measuring tape at the midpoint between the lower rib margin and the iliac crest.

Following an overnight fast, venous blood samples were collected for estimation of fasting blood sugar, triglycerides, and high-density lipoprotein cholesterol. Blood pressure was measured using a calibrated sphygmomanometer after an adequate period of rest. Systolic and diastolic blood pressure values were recorded for analysis.

2.9 Bias Control

Selection bias was minimized by applying uniform eligibility criteria and consecutively recruiting eligible euthymic bipolar disorder patients, while age- and sex-matched healthy controls were enrolled for comparison. Information bias was reduced through standardized assessment procedures using validated instruments (BRIAN, FAST, HDRS, and YMRS). Anthropometric and biochemical measurements were performed using uniform protocols, and age and sex were included in the regression analysis to account for potential confounding (21).

2.10 Study Size

Sample size was estimated using OpenEpi based on data from a comparable published study by Kuppili et al. (22), assuming a two-sided α of 0.05 and 80% statistical power. The minimum required sample size was 34 participants per group. To compensate for an anticipated dropout rate of approximately 10%, 40 euthymic bipolar disorder patients and 40 age- and sex-matched healthy controls were recruited.

2.11 Statistical Analysis

Continuous variables were expressed as mean $\pm$ standard deviation, whereas categorical variables were presented as frequencies and percentages. Normality of data distribution was assessed prior to inferential analysis using Shapiro-Wilk test. Comparisons between euthymic BD patients and healthy controls were performed using the independent samples t-test for continuous variables and the chi-square test for categorical variables. Pearson correlation analysis was used to evaluate associations between BRIAN scores and clinical, functional, and metabolic variables. Variables showing significant correlations with the BRIAN score were entered into the multiple linear regression model to identify independent predictors of biological rhythm disturbance. Multiple linear regression analysis was performed to identify independent predictors of biological rhythm disturbance (23). A p value of less than 0.05 was considered statistically significant. Data were entered into Microsoft Excel and analysed using Statistical Package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA).

3. Results

3.1 Participant Characteristics

The study included 40 euthymic BD patients and 40 healthy controls. There were no significant differences between the two groups with regard to age distribution, sex, marital status, educational status, occupation or socioeconomic status. The anthropometric assessment showed significantly higher BMI and WC in BD patients than in the controls, suggesting increased adiposity in patients with BD.

Table 1. Sociodemographic and anthropometric characteristics of patients with BD and healthy controls.

Variable	Control (n=40)	Euthymic BD (n=40)	p value
Age group, n (%)			0.379
≤30 years	9 (22.5)	5 (12.5)	
31-40 years	23 (57.5)	23 (57.5)	
41-50 years	8 (20.0)	12 (30.0)	
Sex, n (%)			0.496
Male	18 (45.0)	15 (37.5)	
Female	22 (55.0)	25 (62.5)	
Occupation, n (%)			0.232
Farmer	2 (5.0)	5 (12.5)	
Housewife	11 (27.5)	17 (42.5)	
Labourer	5 (12.5)	2 (5.0)	
Service	13 (32.5)	9 (22.5)	
Student	7 (17.5)	3 (7.5)	
Unemployed	2 (5.0)	4 (10.0)	
Religion, n (%)			1.000
Hindu	34 (85.0)	34 (85.0)	
Muslim	6 (15.0)	6 (15.0)	
Marital status, n (%)			0.518
Married	26 (65.0)	23 (57.5)	
Single	0 (0.0)	1 (2.5)	
Unmarried	14 (35.0)	16 (40.0)	
Dietary habits, n (%)			0.317
Vegetarian	27 (67.5)	31 (77.5)	
Non-vegetarian	13 (32.5)	9 (22.5)	
Family type, n (%)			1.000
Joint	18 (45.0)	18 (45.0)	
Nuclear	22 (55.0)	22 (55.0)	
Anthropometric characteristics			
Age (years), mean ± SD	35.10 ± 5.10	37.23 ± 5.47	0.657
Height (cm), mean ± SD	166.60 ± 6.48	167.93 ± 5.53	0.035
Weight (kg), mean ± SD	76.67 ± 11.27	78.30 ± 7.64	0.512
BMI (kg/m ²), mean ± SD	25.01 ± 1.32	28.41 ± 1.46	0.021
Waist circumference (cm), mean ± SD	82.45 ± 3.71	95.20 ± 4.19	0.042

Data are presented as mean ± standard deviation (SD). P values were obtained using the independent samples t-test. BD = Bipolar Disorder; BMI = Body-mass index.

3.2 Residual Mood Symptoms

Euthymic BD cases had higher HDRS scores compared to healthy controls (4.58 ± 1.73 vs 1.48 ± 0.78 ; $p < 0.001$). Likewise, YMRS scores were

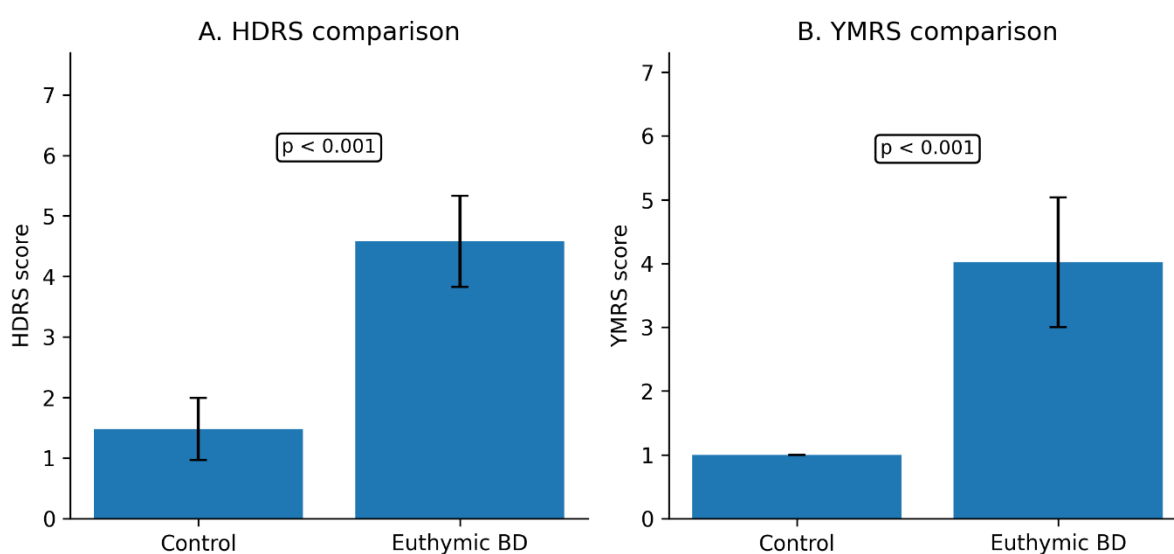
significantly higher in euthymic subjects than in controls (4.02 ± 1.21 vs. 1.00 ± 0.78 ; $p < 0.001$), reflecting the presence of residual among euthymic BD patients.

Table 2. Comparison of Residual Mood Symptoms Between Euthymic Bipolar Disorder Patients and Healthy Controls

Variable	Control (n=40)	Euthymic BD (n=40)	p value
HDRS score	1.48 ± 0.51	4.58 ± 0.75	<0.001
YMRS score	1.00 ± 0.00	4.02 ± 1.02	<0.001

Data are presented as mean $\pm$ standard deviation (SD). P values were obtained using the independent samples t-test. BD = Bipolar Disorder; HDRS = Hamilton Depression Rating Scale; YMRS = Young Mania Rating Scale.

Figure 2. Residual mood symptoms in Euthymic BD



Bar-charts for Control and Euthymic BD for (A). HDRS scores and (B). YMRS scores. Values as mean $\pm$ standard deviation (SD). P-values were obtained using the independent samples t-test. BD = Bipolar Disorder; HDRS = Hamilton Depression Rating Scale; YMRS = Young Mania Rating Scale.

3.3 Biological Rhythm Disturbance and Functional Impairment

The mean BRIAN score in the euthymic group was 44.20 ± 3.83 compared with 19.93 ± 2.08 in controls ($p < 0.001$). Likewise, a significantly higher mean FAST was obtained for the BD group compared to

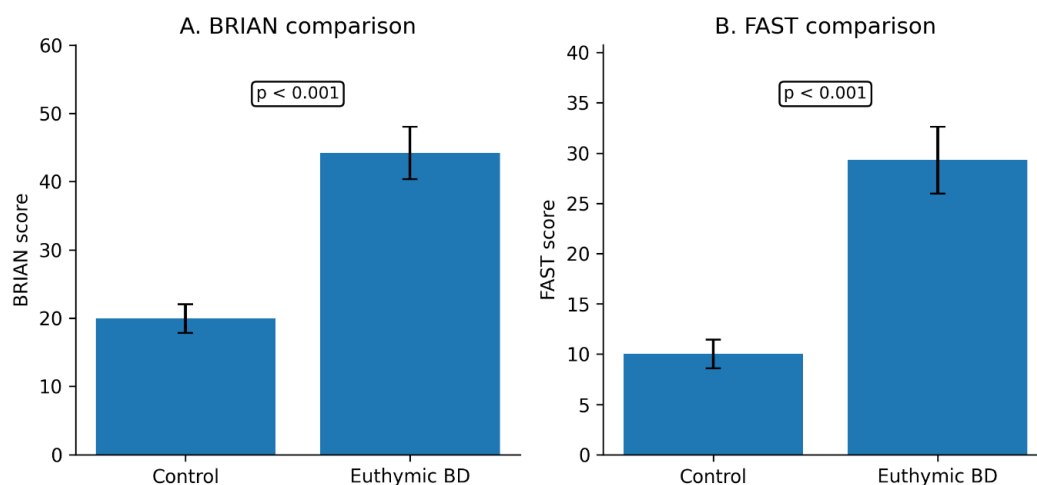
the controls (29.30 ± 3.31 vs 10.03 ± 1.42 ; $p < 0.001$), suggesting significantly greater functional impairment in the BD group. These results suggest that abnormalities of the biological rhythms and functional impairments continue even after the onset of symptomatic remission.

Table 3. Comparison of Biological Rhythm Disturbance and the Functional Impairment

Variable	Control (n=40) Mean $\pm$ SD	Euthymic BD (n=40) Mean $\pm$ SD	p value
BRIAN score	19.93 ± 2.08	44.20 ± 3.83	<0.001
FAST score	10.03 ± 1.42	29.30 ± 3.31	<0.001

Data are presented as mean $\pm$ standard deviation (SD). P values were obtained using the independent samples t-test. BD = bipolar disorder; BRIAN = Biological Rhythms Interview of Assessment in Neuropsychiatry; FAST = Functioning Assessment Short Test.

Figure 3. Biological Rhythm Disturbance and Functional Impairment in Euthymic BD.



Bar-charts for Control and Euthymic BD for (A). BRLAN scores and (B). FAST scores. Values as mean $\pm$ standard deviation (SD). P-values were obtained using the independent samples t-test. BD = bipolar disorder; BRLAN = Biological Rhythms Interview of Assessment in Neuropsychiatry; FAST = Functioning Assessment Short Test.

3.4 Metabolic Profile

The fasting blood sugar level was higher in euthymic BD patients than in controls (112.13 ± 5.67 vs. 91.28 ± 3.39 mg/dL, $p = 0.003$). Also, there was a significant difference between the triglyceride levels of euthymic BD patients and controls (190.93 ± 18.80 vs 136.28 ± 13.13 mg/dL; $p = 0.015$). In contrast, HDL

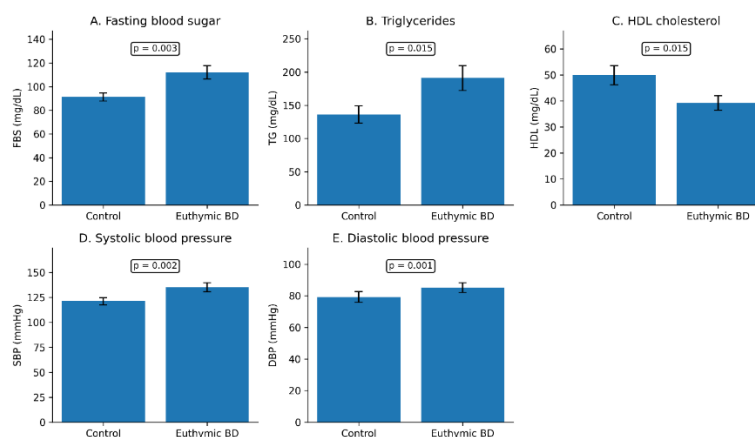
cholesterol levels were significantly lower in the euthymic group (39.20 ± 2.79 vs 49.88 ± 3.70 mg/dL; $p = 0.015$). Both systolic blood pressure (135.11 ± 4.47 vs 121.18 ± 3.70 mmHg; $p = 0.002$) and diastolic blood pressure (85.21 ± 3.02 vs 79.35 ± 3.43 mmHg; $p = 0.001$) were significantly higher among euthymic BD patients.

Table 4. The metabolic parameters were compared between euthymic BD patients and healthy controls.

Variable	Control (n=40) Mean $\pm$ SD	Euthymic BD (n=40) Mean $\pm$ SD	p value
FBS (mg/dL)	91.28 ± 3.39	112.13 ± 5.67	0.003
TG (mg/dL)	136.28 ± 13.13	190.93 ± 18.80	0.015
HDL (mg/dL)	49.88 ± 3.70	39.20 ± 2.79	0.015
SBP (mmHg)	121.18 ± 3.70	135.11 ± 4.47	0.002
DBP (mmHg)	79.35 ± 3.43	85.21 ± 3.02	0.001

Data are presented as mean $\pm$ standard deviation (SD). P values were obtained using the independent samples t-test. FBS = fasting blood sugar; TG = triglycerides; HDL = high-density lipoprotein cholesterol; SBP = systolic blood pressure; DBP = diastolic blood pressure.

Figure 4. Metabolic profile of euthymic BD patients and healthy controls.



Bar graphs showing the case-control profiles for (A). Fasting blood sugar; (B). Triglycerides; (C) HDL cholesterol; (D) Systolic blood pressure; (E) Diastolic blood pressure.

3.5 Correlates of Biological Rhythm Disturbance

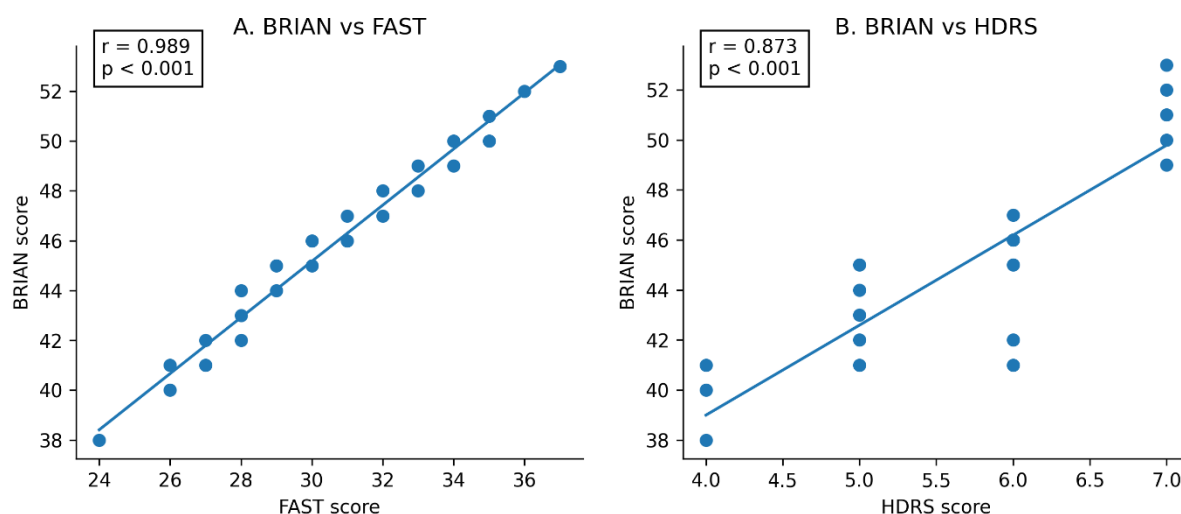
Significant relationships were found between biological rhythm disturbance and a number of clinical, functional and metabolic parameters using Pearson correlation analysis. BRIAN scores showed positive correlations with HDRS ($r = 0.451$, $p = 0.025$), YMRS ($r = 0.352$, $p = 0.041$), FAST ($r = 0.253$,

$p = 0.048$), and fasting blood sugar levels ($r = 0.412$, $p = 0.027$). There were strong positive correlations between BRIAN scores and triglycerides ($r = 0.950$, $p < 0.001$), and SBP ($r = 0.954$, $p < 0.001$), and DBP ($r = 0.871$, $p < 0.001$). On the other hand, HDL cholesterol showed a significant negative correlation with BRIAN scores ($r = -0.929$, $p < 0.001$).

Table 5. The BRIAN scores were correlated with clinical, functional and metabolic parameters.

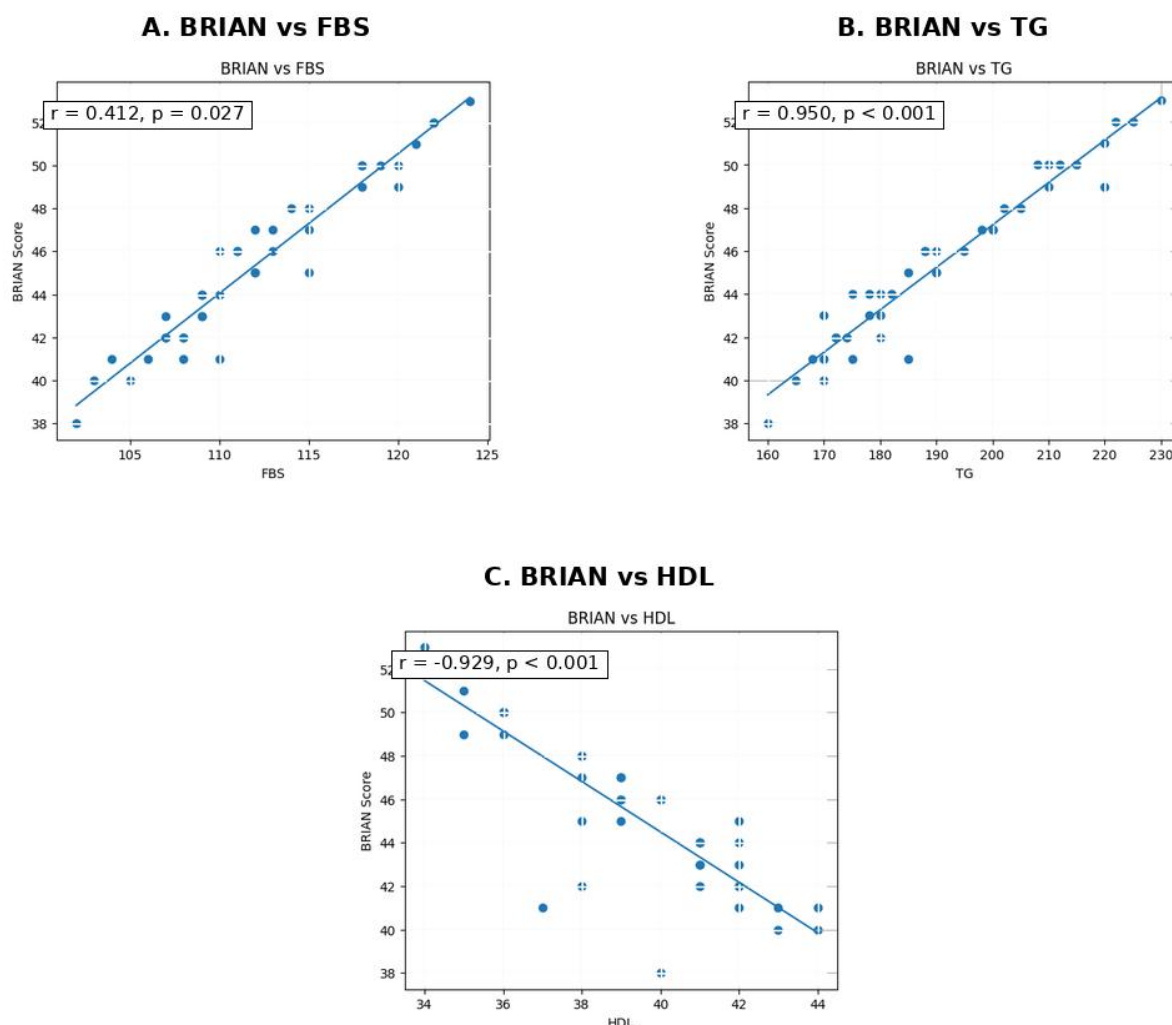
Variables	BRIAN (r value)	p value
HDRS	0.451	0.025
YMRS	0.352	0.041
FAST	0.253	0.048
FBS	0.412	0.027
TG	0.950	<0.001
HDL	-0.929	<0.001
SBP	0.954	<0.001
DBP	0.871	<0.001

Figure 5. Biological Rhythm Disturbance: Clinical Correlates



Scatterplot showing between BRIAN scores vs (A). FAST and (B). HDRS using Pearson correlation test. BD = bipolar disorder; BRIAN = Biological Rhythms Interview of Assessment in Neuropsychiatry; FAST = Functioning Assessment Short Test.

Figure 6. The relationship between Biological Rhythm Disturbance and metabolic processes.



Scatterplot showing between BRIAN scores vs (A). FBS, (B). TG, and (C) HDL, using Pearson correlation test. BD = bipolar disorder; BRIAN = Biological Rhythms Interview of Assessment in Neuropsychiatry; FBS = Fasting Blood Sugar; HDL = High density Lipids; TG = Triglycerides. FAST = Functioning Assessment Short Test.

3.6 Predictors of Biological Rhythm Disturbance

A multiple linear regression analysis was carried out to determine independent factors associated with biological rhythm disturbance in euthymic BD patients. FAST score was the most powerful independent predictor of BRIAN score ($\beta = 0.801$, p

< 0.001). Additionally, a significant positive association was found between HDRS score and BRIAN score ($\beta = 0.296$, $p = 0.001$). Fasting blood sugar was the only metabolic variable that was independently correlated with biological rhythm disturbance ($\beta = 0.184$, $p = 0.018$). There was no age or sex effect in the final model.

Table 6. Multiple Linear Regression Analysis Predicting Biological Rhythm Disturbance in euthymic BD patients

Predictor Variable	Unstandardised β	Standard Error	Standardised β	t value	p value	95% CI
Constant	4.216	2.145	—	1.965	0.053	-0.058 to 8.490
FAST score	0.742	0.081	0.801	9.142	<0.001	0.580 to 0.903
HDRS score	0.318	0.092	0.296	3.457	0.001	0.135 to 0.501
FBS	0.041	0.017	0.184	2.412	0.018	0.007 to 0.075
Age	0.028	0.019	0.086	1.474	0.145	-0.010 to 0.066
Sex (Male)	-0.912	0.684	-0.071	-1.333	0.187	-2.276 to 0.452

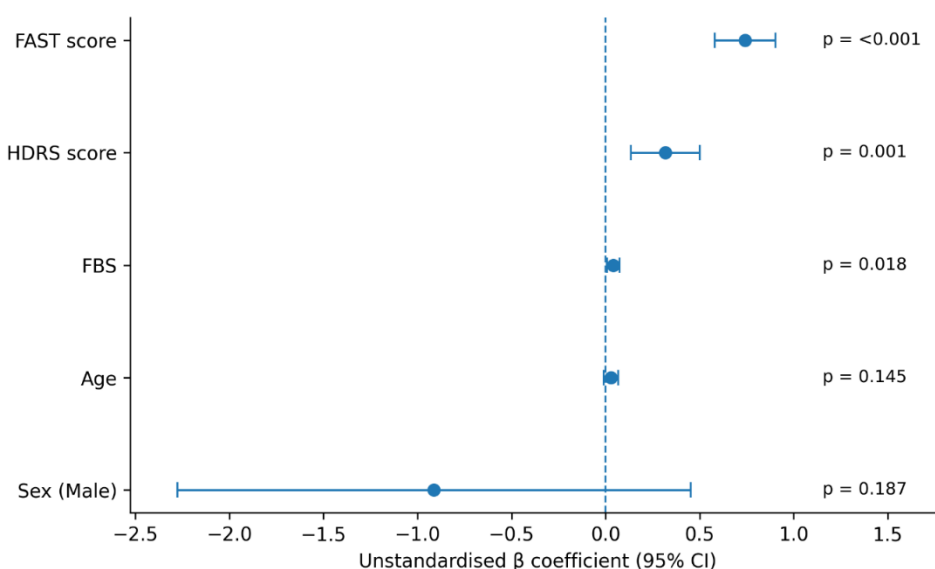
Multiple linear regression analysis was performed with BRIAN total score as the dependent variable. FAST = Functioning Assessment Short Test; HDRS = Hamilton Depression Rating Scale; FBS = fasting blood sugar; CI = confidence interval.

Table 7. Analysis of multiple linear regression is summarized here to predict Biological Rhythm Disturbance.

Parameter	Value
R	0.872
R²	0.752
Adjusted R²	0.721
F value	54.63
p value	0.035

Dependent variable: BRIAN total score. The model explained 75.2% of the variance in biological rhythm disturbance among euthymic bipolar disorder patients.

Figure 7. The following variables independently predicted the occurrence of a biological rhythm disturbance:



4. Discussion

4.1 Restatement of Research Question

The present study investigated whether there is a persistence of biological rhythm disturbances during euthymia in BD and whether they are related to functional impairment, residual mood symptoms, and metabolic abnormalities. Results showed that significantly greater biological rhythm disturbances in euthymic BD patients than in healthy controls. In addition, poorer functioning was linked to greater residual symptoms burden and adverse metabolic parameters, as well as rhythm dysregulation. The results confirm the idea that disturbed biological rhythms are a chronic and relevant phenomenon of BD, not just during the acute phase of mood states.

4.2 Persistent Biological Rhythm Dysregulation During Euthymia

One of the major findings of the present study was that patients with euthymic BD demonstrated significant biological rhythm disturbances when compared to healthy controls as indicated by higher BRIAN scores. This indicates that biological rhythm disturbances persist after an acute mood episode and could be a trait-like characteristic of BD. Our findings are consistent with those of Giglio et al. (9), Rosa et al. (4) and Vangal et al. (10) who all have found that biological rhythm disturbances are higher in remitted/euthymic BD patients compared to HC. Results of studies have been consistent and this reinforces the idea of a persistence of circadian dysregulation in remission. The proposed mechanisms involve abnormalities in central circadian control,

secretion of melatonin, hypothalamic-pituitary-adrenal axis function and clock gene expression, which continue despite symptomatic recovery.

4.3 Association between Biological Rhythm Disturbance and Functional Impairment

Patients with euthymic BD demonstrated significantly greater functional impairment than controls, suggesting that euthymic BD does not necessarily translate to functional recovery. These findings are in line with those of Giglio et al. (9), who found biological rhythm disturbance to be a significant contributor to interepisodic functional impairment, and those of Rosa et al. (4), who showed that remitted patients with more biological rhythm dysregulation had poorer functioning. Vangal et al. (10) also found that these remitted BD patients who had persistent rhythm disturbances reported worse quality of life. These results indicate that disturbances of sleep-wake cycles, daily rhythms of activity and social rhythms can be responsible for persistent occupational, interpersonal, and psychosocial problems even in euthymic patients.

4.4 Residual Mood Symptoms in Euthymic BD

Patients with BD had significantly higher HDRS and YMRS scores than healthy controls, suggesting that patients with BD had subsyndromal affective symptoms. The findings of the present study are also consistent with the results of Rosa et al. (4) who found a correlation between residual symptoms and biological rhythm disturbances in remitted BD patients, and Palagini et al. (23) who found higher levels of depressive symptoms among BD patients with a circadian rhythm abnormality. Biological rhythm disturbances are strongly linked with mood regulation, suggesting that residual symptoms may reflect of continued circadian instability. These residual symptoms can lead to persistent psychosocial dysfunction and/or risk of relapse even in clinical remission.

4.5 Association with Metabolic Abnormalities

The present study showed significantly elevated levels of fasting blood glucose, triglycerides, systolic blood pressure, and diastolic blood pressure among euthymic BD patients, and decreased levels of HDL cholesterol, than among healthy controls. These results suggest that during remission, there remain cardiometabolic abnormalities. Our results corroborate the emerging literature on the association between biological rhythm disturbances and metabolic changes in bipolar disorder, though few studies have directly assessed metabolic parameters along with

biological rhythm disturbances in euthymic BD. Yan et al. (13) suggested that circadian disruption could be a common mechanism in the pathogenesis of BD and endocrine-metabolic comorbidities, and Chung et al. (11) pointed out that disrupted circadian clock contributes to glucose and lipid regulation. Recently, Campbell et al. (14) came up with a chronometabolic hypothesis that connects circadian dysfunction to obesity, insulin sensitivity, dyslipidaemia and cardiovascular disease. These findings imply that rhythm dysregulation and metabolic abnormalities are related to each other and possibly a reflection of the same pathophysiological process.

4.6 Correlates of Biological Rhythm Disturbance

Residual depressive and manic symptoms, functional impairment and adverse metabolic parameters were significantly linked with the biological rhythm disturbance. Correlations between BRIAN scores and HDRS, YMRS, FAST, fasting blood glucose, triglycerides, systolic blood pressure and diastolic blood pressure were positive, while the correlation between BRIAN scores and HDL cholesterol was negative. The results suggest that greater rhythm dysregulation is associated with greater clinical and functional and metabolic burden. Other studies reporting similar associations between biological rhythm disturbance and depression symptoms and functional impairment include Rosa et al. (4), Giglio et al. (9), and Palagini et al. (24). Though there is little evidence on metabolic correlates, Yan et al. (13) and Campbell et al. (14) suggested that circadian dysfunction is associated with glucose dysregulation, lipid abnormalities and cardiovascular risk. This study adds to this evidence by showing these relations in a euthymic BD population. Together these results suggest a view of biological rhythm disturbance as a multidimensional construct and its clinical and metabolic significance.

4.7 Clinical Implications

The present results have significant clinical implications. First, if biological rhythm disturbances last during euthymia then circadian dysregulation should be a routine clinical assessment and treatment in clinically stable patients. Second, the functional recovery is linked to biological rhythm disturbance and underscores the importance of assessing functional recovery as well as symptomatic remission. Third, given that major metabolic abnormalities are also found in the euthymic state, it is reasonable to recommend routine cardiometabolic follow-up in the treatment of BD. Last, the observed links between

biological rhythm disturbance, residual symptoms, and functional outcomes support chronotherapeutic interventions such as stabilisation of sleep-wake cycles and Interpersonal and Social Rhythm Therapy (IPSRT) (25) as possible strategies to enhance overall clinical outcome.

4.8 Study Strengths

The current study has several strengths. It specifically evaluated biological rhythm disturbances during euthymia, thereby minimizing the influence of acute mood episodes of biological rhythm disruptions in euthymic BD sufferers (not during exacerbation of mood episodes). This was possible with the inclusion of a healthy control group to allow direct comparison of clinical, functional and metabolic parameters. In addition, simultaneous assessment of biological rhythms, functional impairment, residual mood symptoms and metabolic abnormalities gave a thorough picture of the factors related to circadian dysregulation.

4.9 Study Limitations

This study has several limitations as well. Since the cross-sectional design does not allow conclusions to be drawn about causality or temporal relationships between biological rhythm disturbance and the clinical and metabolic variables, it is essential to establish these relationships through time series analysis. The study took place in one centre only and the sample was relatively small, and therefore the findings may not be generalisable. Furthermore, a self-report instrument was used to assess biological rhythms, rather than objective measures, such as actigraphy or melatonin-based circadian evaluations. The potential influence of psychotropic medications on biological rhythms could not be completely excluded.

4.10 Future Directions

Declarations

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Further research is warranted, using larger multicentre samples with greater generalisability of results, and to further document the association between the biological rhythm disturbances and long-term clinical outcome in BD. Long-term follow-up is warranted to see if rhythm dysregulation is an independent predictor for future relapse, functional impairment, or worsening of metabolic abnormalities. The use of objective circadian measures (e.g. actigraphy or biological rhythm biomarkers) can complement the existing data and provide further insights into the mechanisms of circadian dysfunction. Furthermore, there is a need for interventional studies that assess whether the enhancement of biological rhythms can be shown to lead to improved functional, clinical and metabolic outcomes in BD.

5. Conclusion

The current study showed that there are significant biological rhythm disturbances even in euthymic BD patients with symptomatic remission. Patients had higher levels of biological rhythm disturbance, functional disturbance, mood symptoms and negative metabolic profiles than healthy controls. The biological rhythm disturbance was strongly related to functional disability, residual affective symptoms and various metabolic disorders, indicating its poly-functional clinical significance. Moreover, functional impairment and persistent depressive symptoms and fasting blood glucose turned out to be independent risk factors for biological rhythm disturbance. Our results lend weight to the conceptualization of circadian dysfunction as a chronic and clinically significant component of BD and emphasize the need to include biological rhythm assessment, functional recovery, and metabolic monitoring in the chronic management of BD.

profit sectors. The study was conducted as part of an academic research program.

Conflict of Interest Declaration

The authors declare that they have no conflicts of interest relevant to the content of this manuscript.

Author Contributions

All authors contributed substantially to the conception and design of the study, data collection, analysis, and interpretation. Dr Satyajyoti Tiwari drafted the manuscript, and all authors critically revised it for intellectual content. All authors approved the final

version and agree to be accountable for all aspects of the work.

Ethics Approval

The study protocol was approved by IEC before the participant recruitment (ACEAS-IEC; dated 6th September 2025)

Data Availability

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

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