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Original Research Article

Longitudinal Changes in Cardiac Autonomic Function Across Manic and Euthymic States in Bipolar Disorder: A Prospective Heart Rate Variability Study from South India

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Abstract

Background: Bipolar disorder (BD) is a chronic mood disorder associated with substantial psychiatric and medical comorbidity. Increasing evidence suggests that autonomic nervous system dysfunction may contribute to the elevated cardiovascular morbidity and mortality observed in individuals with BD. Heart rate variability (HRV), a non-invasive marker of autonomic regulation, provides valuable insights into sympathetic-parasympathetic balance during different mood states.

Aim: To evaluate longitudinal changes in heart rate variability among patients with bipolar disorder during manic episodes and subsequent euthymic states.

Methods: A prospective longitudinal observational study was conducted among 12 patients diagnosed with bipolar affective disorder presenting with mania. Diagnosis was confirmed using the Mini International Neuropsychiatric Interview (MINI 5.0.0) and ICD-10 criteria. Severity of mania was assessed using the Bech-Rafaelsen Mania Scale. HRV recordings were obtained during the manic phase and repeated after achieving euthymia. Time-domain, frequency-domain, and non-linear HRV parameters were analyzed using Kubios HRV software. Statistical analyses included paired t-tests, Wilcoxon signed-rank tests, effect size estimation, and Spearman correlation analyses.

Results: Mean heart rate was higher during mania (89 beats/min) compared with euthymia (80.1 beats/min), while mean RR intervals were shorter during mania (689 ms vs. 754 ms). Frequency-domain parameters demonstrated reduced low-frequency and high-frequency power during mania. Non-linear HRV indices also showed reduced complexity during manic episodes. Although most differences did not reach statistical significance ($p>0.05$), several variables demonstrated moderate effect sizes, suggesting clinically meaningful autonomic alterations. Correlation analyses revealed weak associations between manic symptom severity and HRV parameters.

Conclusion: Patients with bipolar disorder exhibited lower HRV during manic episodes compared with euthymic states, indicating reduced autonomic flexibility and potential cardiovascular vulnerability. Longitudinal HRV assessment may serve as a useful biomarker for monitoring autonomic dysfunction and cardiovascular risk in bipolar disorder.

Keywords: Bipolar Disorder, Heart Rate Variability, Mania, Euthymia, Autonomic Nervous System, Cardiovascular Risk.

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Introduction

Bipolar disorder (BD) is a severe recurrent psychiatric illness characterized by episodes of mania, hypomania, depression, and periods of euthymia [1]. The disorder affects approximately 1–3% of the global population and contributes substantially to disability, impaired quality of life, and premature mortality [1-2]. While psychiatric manifestations remain the primary focus of clinical management, growing evidence suggests that cardiovascular disease represents one of the leading

causes of excess mortality among individuals with BD [3]. Several biological mechanisms have been proposed to explain this association, including chronic inflammation, oxidative stress, metabolic abnormalities, hypothalamic-pituitary-adrenal axis dysregulation, and autonomic nervous system dysfunction [4-6]. Among these, disturbances in autonomic regulation have emerged as an important pathway linking psychiatric symptoms to cardiovascular outcomes [5].

Heart rate variability (HRV) refers to beat-to-beat fluctuations in cardiac rhythm resulting from dynamic interactions between sympathetic and parasympathetic nervous systems [7]. Reduced HRV is considered a marker of impaired autonomic flexibility and has been associated with increased risks of arrhythmias, myocardial infarction, and sudden cardiac death [8]. Previous studies have demonstrated reduced HRV in mood disorders, including major depressive disorder and bipolar disorder [9]. However, the majority of investigations have employed cross-sectional designs comparing patients with healthy controls [10]. Relatively few studies have examined within-subject changes across different mood states in bipolar disorder [11]. Understanding these longitudinal changes may provide valuable insights into state-dependent autonomic alterations and potential mechanisms underlying cardiovascular vulnerability.

The present study therefore evaluated HRV parameters in patients with bipolar disorder during manic episodes and following remission into euthymia, thereby allowing each participant to serve as his or her own control.

Aim: To investigate longitudinal changes in heart rate variability among patients with bipolar disorder from mania to euthymia.

Objectives

1. To compare time-domain HRV parameters during mania and euthymia.
2. To evaluate frequency-domain HRV changes across mood states.
3. To assess non-linear HRV indices during mania and euthymia.
4. To examine the relationship between manic symptom severity and HRV measures.
5. To explore potential cardiovascular implications of autonomic dysfunction in bipolar disorder.

Methodology

Study Design and Setting: This prospective longitudinal observational study was conducted in the Department of Psychiatry of a tertiary care teaching hospital in Tamil Nadu, India. Ethical approval was obtained from the Institutional Ethics Committee before commencement of the study.

Study Population: Twelve patients diagnosed with bipolar affective disorder presenting with a manic episode were recruited consecutively from inpatient psychiatric services.

Inclusion Criteria

- Age between 18 and 65 years.
- Diagnosis of bipolar affective disorder according to ICD-10 criteria.
- Current manic episode confirmed using MINI 5.0.0.
- Ability to provide informed consent.

Exclusion Criteria

- Presence of additional Axis I or Axis II psychiatric disorders.
- History of myocardial infarction, stroke, or structural cardiac disease.
- Diabetes mellitus.
- Substance use disorder within the previous six months.
- Previous electroconvulsive therapy.
- Severe psychomotor agitation preventing HRV recording.

Clinical Assessment: Sociodemographic and clinical details were collected using a structured proforma. Diagnostic confirmation was performed using MINI version 5.0.0. Severity of mania was assessed using the Bech-Rafaelsen Mania Scale. Participants underwent reassessment following achievement of euthymia.

Heart Rate Variability Assessment: HRV recordings were obtained using a Polar H10 chest strap. Participants refrained from caffeinated beverages for at least 12 hours before testing. Recordings were obtained between 11:00 AM and 3:00 PM in a quiet environment. Subjects remained in a supine resting position with spontaneous breathing for 20 minutes. Raw RR interval data were transferred to Elite HRV software and subsequently analyzed using Kubios HRV Standard version 3.5.0. Time-domain, frequency-domain, and non-linear parameters were extracted.

Statistical Analysis: Data were analyzed using Jamovi statistical software. Continuous variables were expressed as mean ± standard deviation. Paired comparisons between mania and euthymia were performed using paired Student's t-test and Wilcoxon signed-rank test. Cohen's d was calculated to estimate effect size. Spearman's rank correlation coefficient was used to assess associations between HRV measures and manic symptom severity. Statistical significance was defined as $p < 0.05$.

Results

Table 1: Sociodemographic and Clinical Characteristics of Participants

Variable	Value
Sample size	12
Male	75%
Female	25%
Mean age of onset	28 ± 7.47 years
Previous suicide attempts	25%
≥2 hospitalizations	66%
BMI ≥25 kg/m²	41%

The study population predominantly consisted of males (75%). The average age of illness onset was 28 years. One-fourth of participants reported a previous suicide attempt, while more than two-thirds had experienced multiple psychiatric hospitalizations.

Table 2: Course of Illness Characteristics

Episode Type	Range
Mania	1–4
Mixed Episodes	0–1
Depressive Episodes	0–2

Participants demonstrated considerable heterogeneity in illness course, with manic episodes being the most frequent polarity observed.

Table 3: Comparison of HRV Parameters between Mania and Euthymia

Parameter	Mania	Euthymia	p value
Mean RR (ms)	689	754	0.058
Mean HR (bpm)	89	80.1	0.947
SDNN (ms)	53	52.6	0.506
RMSSD (ms)	59.9	59.7	0.502
LF (ms²)	4091	5765	0.380
HF (ms²)	2065	2492	0.422
LF/HF Ratio	3.35	2.82	0.678

During mania, participants exhibited shorter RR intervals and higher heart rates, indicating increased sympathetic activity. Frequency-domain analysis demonstrated reduced low-frequency and high-frequency power during mania compared with euthymia.

Table 4: Correlation between Mania Severity and HRV Measures

Parameter	Spearman r	p value
RMSSD	-0.418	0.176
HF Power	-0.401	0.197
SD2/SD1	0.545	0.067
DFA α1	0.396	0.238

Severity of manic symptoms demonstrated weak-to-moderate correlations with HRV indices; however, none reached statistical significance.

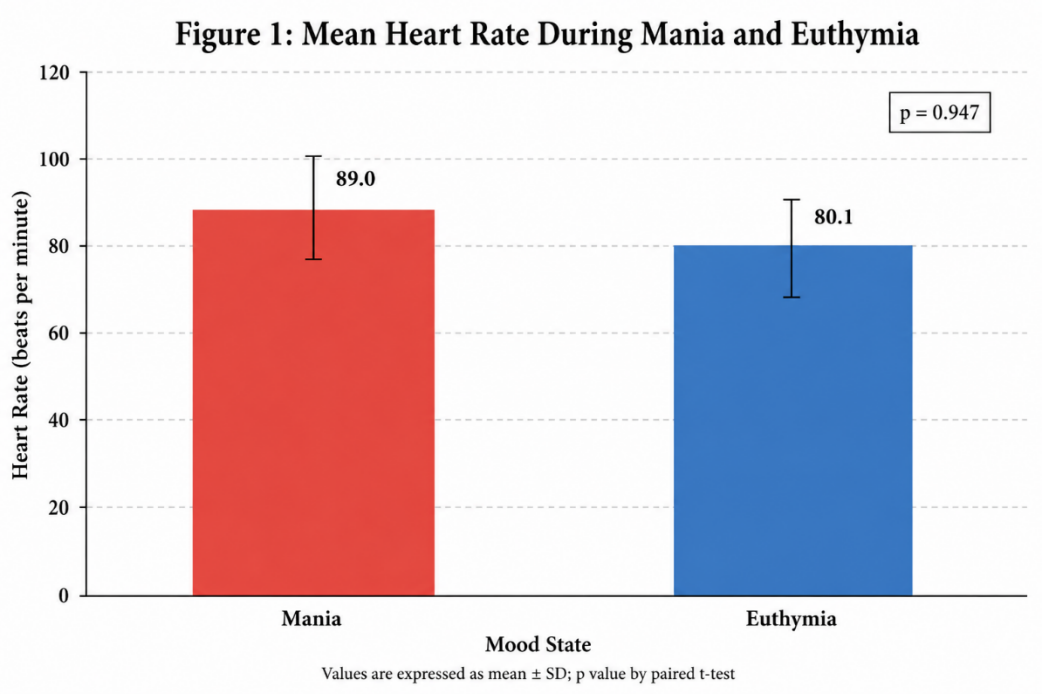

Figure 1: Mean heart rate during mania and euthymia.

Figure 1 illustrates the comparison of mean heart rate between the manic and euthymic phases of bipolar disorder. Patients demonstrated a higher mean heart rate during mania (89.0 beats/min) compared to euthymia (80.1 beats/min), indicating a trend toward increased sympathetic nervous system activity during the acute manic state. Although the difference did not achieve statistical significance (p = 0.947), the observed elevation in heart rate during mania suggests reduced autonomic stability and supports the hypothesis of autonomic dysregulation in bipolar disorder.

The reduction in heart rate observed during euthymia may reflect partial restoration of autonomic balance following clinical remission (Figure 1).

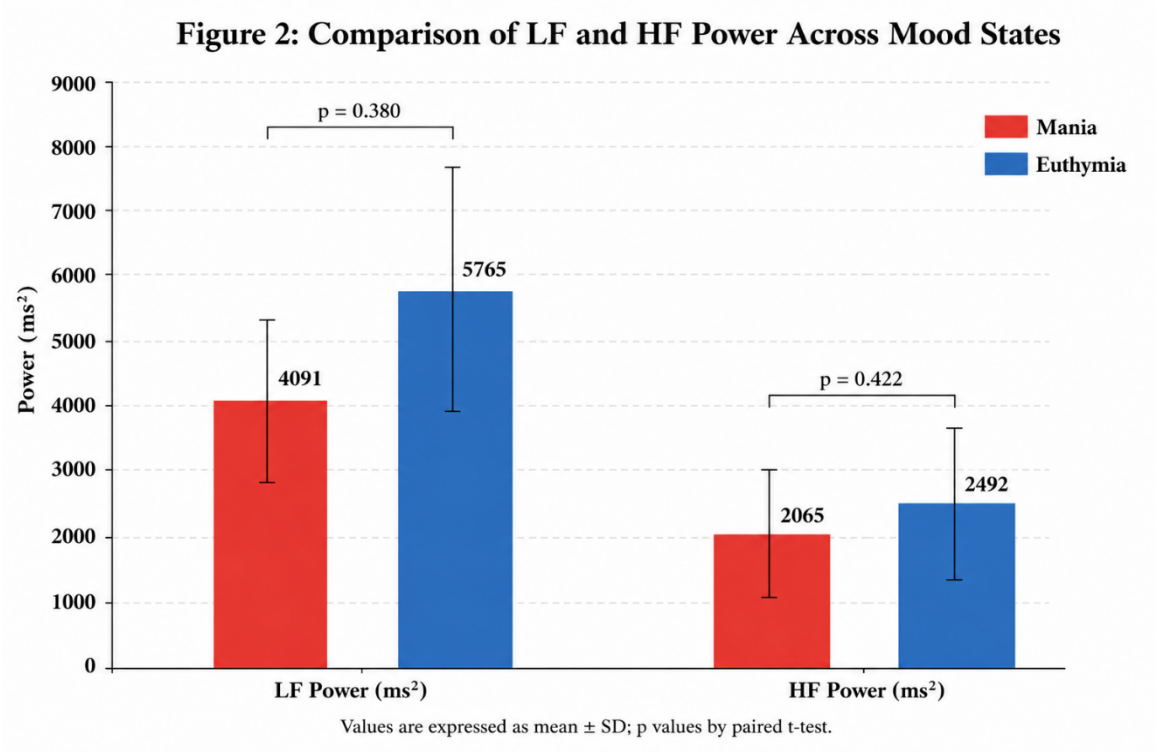

Figure 2: Comparison of LF and HF power across mood states.

Figure 2 compares the frequency-domain heart rate variability parameters, namely low-frequency (LF) power and high-frequency (HF) power, between the manic and euthymic phases of bipolar disorder. Both LF and HF power were lower during mania (4091 ms² and 2065 ms², respectively) compared with euthymia (5765 ms² and 2492 ms², respectively). Although these differences did not reach statistical significance (LF: p = 0.380; HF: p = 0.422), the observed trend suggests reduced autonomic modulation during manic episodes. The decrease in both LF and HF power during mania may reflect impaired sympathovagal regulation and reduced cardiac autonomic adaptability, while the higher values observed during euthymia indicate partial restoration of autonomic balance (Figure 2).

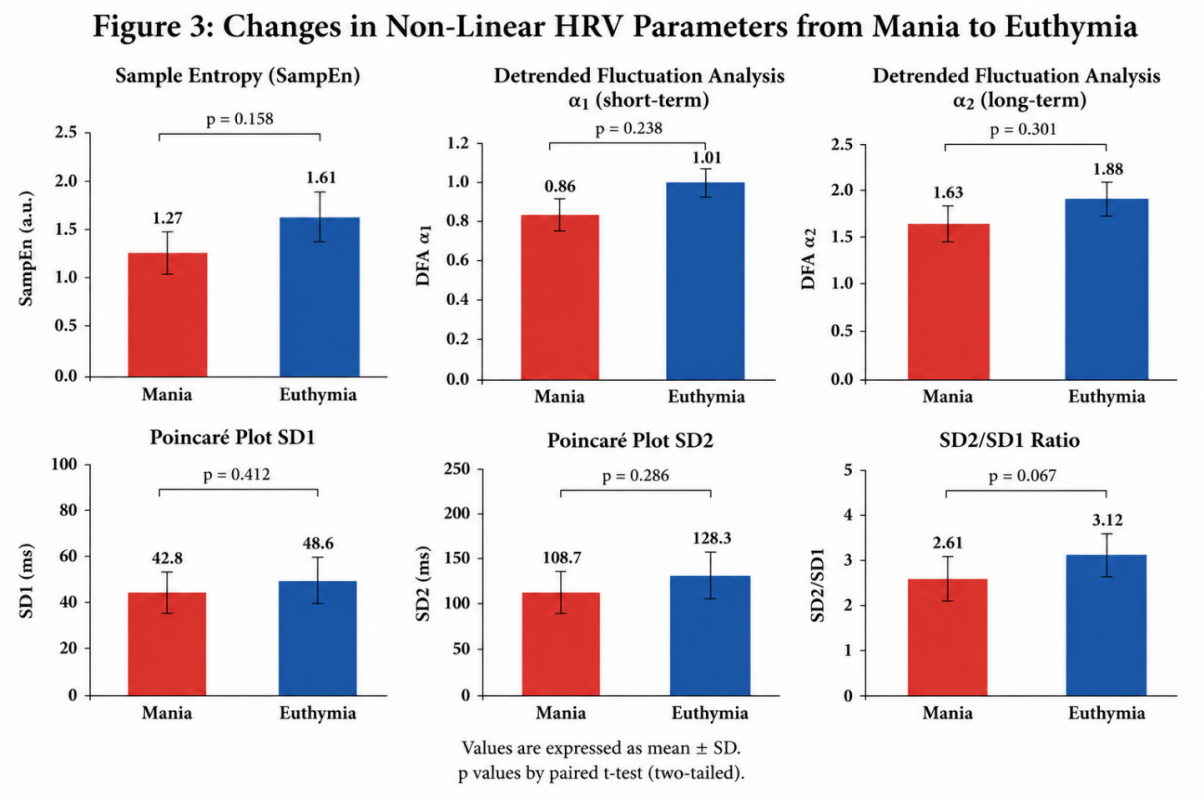

Figure 3: Changes in non-linear HRV parameters from mania to euthymia.

Figure 3 illustrates the comparison of non-linear HRV parameters between the manic and euthymic phases of bipolar disorder. Most non-linear indices, including Sample Entropy, SD1, SD2, and DFA measures, showed a trend toward improvement during euthymia compared with mania. Although these differences were not statistically significant, the findings suggest greater autonomic complexity and improved cardiac autonomic regulation during the euthymic state. The observed changes support the presence of autonomic nervous system dysregulation during manic episodes (Figure 3).

Discussion

The present study examined longitudinal changes in autonomic function among patients with bipolar disorder transitioning from mania to euthymia. The findings suggest a trend toward reduced HRV during manic episodes, reflecting impaired autonomic regulation. The observed reduction in RR intervals and increase in heart rate during mania are consistent with enhanced sympathetic activation. Similar findings have been reported by Kemp et al., who demonstrated autonomic dysregulation among individuals experiencing acute manic states [2-14]. Reduced HRV during mania may indicate diminished vagal modulation and decreased cardiac adaptability [15-17].

Time-domain measures such as SDNN and RMSSD did not differ significantly between mood states [18]. Nevertheless, the observed trends are clinically relevant because lower HRV has repeatedly been linked with adverse cardiovascular outcomes. The lack of statistical significance may be attributable to the modest sample size.

Frequency-domain analyses demonstrated lower LF and HF power during mania. Previous studies have suggested that HF power predominantly reflects parasympathetic activity, whereas LF power represents combined sympathetic and parasympathetic influences [19-21]. The reduction in both parameters observed in the present study suggests generalized autonomic dysregulation rather than isolated sympathetic activation [22]. Non-linear HRV measures provide insight into the

complexity of cardiac regulation. Although entropy measures and Poincaré plot indices did not differ significantly, their direction of change suggests reduced physiological complexity during manic states. Similar observations have been reported in studies evaluating autonomic dysfunction across psychiatric disorders [23].

An important finding of the present study is the persistence of autonomic abnormalities despite clinical improvement [24-25]. Although HRV improved during euthymia, several parameters remained lower than values typically reported in healthy populations. This observation raises the possibility that autonomic dysfunction may represent a trait marker rather than solely a state marker of bipolar disorder.

Cardiovascular disease remains a major contributor to premature mortality among individuals with bipolar disorder. Reduced HRV has been identified as an independent predictor of cardiovascular morbidity and mortality. Therefore, routine cardiovascular screening and lifestyle interventions should be considered as part of comprehensive bipolar disorder management.

The longitudinal design represents a major strength of this study because each participant served as his or her own control, minimizing confounding influences related to age, sex, and genetic factors.

Strengths

The present study possesses several notable strengths. Its prospective longitudinal design enabled the assessment of autonomic changes within the same individuals as they transitioned from mania to euthymia, thereby minimizing inter-individual variability and allowing each participant to serve as their own control.

A comprehensive evaluation of heart rate variability was performed using time-domain, frequency-domain, and non-linear analyses, providing a multidimensional assessment of cardiac autonomic function. Furthermore, the use of standardized and validated psychiatric diagnostic instruments, including the Mini International Neuropsychiatric Interview (MINI) and the Bech–Rafaelsen Mania Scale, enhanced the diagnostic accuracy and reliability of clinical assessments. Together, these methodological strengths improve the internal validity of the study and contribute to a more detailed understanding of autonomic dysfunction across different mood states in bipolar disorder.

Limitations

The present study has certain limitations. The small sample size and single-center design may limit the generalizability of the findings. The absence of a healthy control group restricted comparative evaluation of HRV parameters. In addition, psychotropic medications may have influenced autonomic function, and the short follow-up period may not have captured long-term changes in heart rate variability among patients with bipolar disorder.

Conclusion

Patients with bipolar disorder exhibited reduced heart rate variability during manic episodes compared with euthymic states, suggesting impaired autonomic regulation during acute illness. Although most differences did not achieve statistical significance, consistent reductions across multiple HRV domains indicate potential cardiovascular vulnerability. HRV may serve as a valuable biomarker for monitoring autonomic function and cardiovascular risk in bipolar disorder. Larger multicenter studies are warranted to validate these findings and establish the clinical utility of HRV-guided risk assessment.

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