Multimodal Neurotechnological Interventions for Mood Stabilization in Bipolar Disorder: A Multicenter Micro-Randomized Trial with JITAI

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Abstract

Bipolar disorder is characterized by recurrent affective instability and a high likelihood of relapse, underpinned by limbic hyperactivity, reduced prefrontal regulatory capacity, large-scale network dysregulation, and disturbances in autonomic and endocrine function. In response to these multidimensional impairments, this study evaluated a multimodal neurotechnological intervention integrating quantitative EEG–informed neurofeedback, prefrontal transcranial photobiomodulation at 810 nm and 40 Hz, and heart-rate-variability biofeedback. The protocol was delivered within a micro-randomized, Just-In-Time Adaptive Intervention (JITAI) framework designed to target periods of emerging vulnerability. Across 14 clinical sites, 320 adults with bipolar I or II disorder completed a 12-week active intervention followed by 12 weeks of follow-up. Weekly clinician-guided sessions were complemented by multiple daily JITAI prompts for HRV breathing or evening tPBM, triggered through ecological assessments and wearable-derived physiological indicators. The proximal outcome was the 6-hour Mood Volatility Index (MVI), while the principal distal outcome was time to depressive or hypomanic relapse. Secondary clinical measures included depression, mania, sleep, and functioning; biomarker assessments encompassed nocturnal HRV, hair cortisol, prefrontal hemodynamics, and qEEG indices. JITAI-delivered prompts produced a 35% reduction in mood volatility, and survival analyses demonstrated a substantially prolonged relapse-free interval during the intervention period. Significant improvements were also observed in depressive and manic symptomatology, sleep regularity, HRV, and physiological stress markers, accompanied by enhanced prefrontal activation during cognitive load. Mediation analyses indicated that changes in autonomic, endocrine, and neurophysiological measures accounted for nearly half of the observed mood stabilization. Adherence was high, and adverse events were mild and transient, with no serious events reported. Overall, the findings show that combining neurofeedback, 40 Hz photobiomodulation, and HRV biofeedback within a JITAI architecture yields robust clinical and mechanistic benefits, offering a safe and scalable adjunct for stabilizing mood and reducing relapse risk in bipolar disorder.

Keywords: bipolar disorder, mood stabilization, neurofeedback, 40 Hz photobiomodulation, HRV biofeedback, JITAI, micro-randomized trial

Introduction

Bipolar disorder (BD) is a chronic and severe psychiatric illness characterized by recurrent episodes of depression, mania or hypomania, and mixed affective states. Its lifetime prevalence is estimated at approximately 2–3%, and although pharmacological treatments remain the foundation of care, more than half of patients experience relapse within two years. Functional outcomes also often remain incomplete, underscoring the need for a deeper understanding of the disorder's underlying mechanisms.

Contemporary neurobiological models increasingly conceptualize BD as a condition driven by large-scale network dysregulation. Hyperactivity within limbic and reward-related regions, particularly the amygdala and ventral striatum, contributes to heightened emotional reactivity and increased sensitivity to rewarding

stimuli (Phillips & Swartz, 2014). In parallel, multiple prefrontal territories, including the dorsolateral, medial, and ventromedial prefrontal cortices, exhibit reduced activation or inconsistent recruitment, diminishing top-down regulatory control. These imbalances extend across functional networks: an overdominant salience network amplifies emotional "capture," a rigid default-mode network reinforces rumination and self-referential processing, and an underperforming central executive network weakens cognitive flexibility.

Physiological findings mirror these neural alterations. Individuals with BD frequently demonstrate reduced heart-rate variability, elevated hypothalamic–pituitary–adrenal axis activity, often captured through increased hair cortisol, and marked irregularity in sleep–wake patterns. Electrophysiological markers further reveal atypical oscillatory signatures, such as elevated frontal beta activity, abnormal frontal alpha asymmetry, and disrupted coherence patterns.

Viewed through this framework, BD reflects disrupted connectivity between emotional and executive hubs. Hyperreactivity within the amygdala, ventral striatum, and insula fosters exaggerated salience attribution and rapid affective shifts, while diminished or dysregulated prefrontal engagement limits effective modulation of these responses. Altered hippocampal functioning contributes to disturbances in contextual and episodic emotional memory, further destabilizing mood states. Together, these abnormalities culminate in affective lability, circadian mood variability, and deficits in executive processes such as inhibition, updating, and cognitive shifting.

A growing body of evidence highlights the importance of "bottom-up" physiological processes in the maintenance and destabilization of mood states in bipolar disorder. Reduced heart-rate variability, whether indexed through RMSSD or SDNN, reflects diminished vagal regulation and a fragile autonomic organization, thereby increasing susceptibility to abrupt affective shifts (Thayer et al., 2009). In parallel, dysregulation of the hypothalamic–pituitary–adrenal axis, often expressed through markers of allostatic overload (McEwen & Gianaros, 2011), contributes to disruptions in cortisol profiles that may be detectable in both diurnal rhythm and hair-based assessments. Disturbances of circadian rhythm and sleep architecture further compound this vulnerability; low values on the Sleep Regularity Index and reduced interdaily stability have been repeatedly associated with heightened relapse risk.

Electrophysiological oscillations provide additional insight into network functioning, where elevated frontal high-beta activity (22–30 Hz) is commonly linked to cognitive hyperarousal, internal tension, and reactive states. In contrast, sensorimotor rhythm (12–15 Hz) reflects thalamocortical stabilization, while alpha activity (8–12 Hz) represents a central coordinating frequency across networks. Altered frontal alpha asymmetry and impaired alpha coherence have been tied to disruptions in affective regulation and executive control (Marzbani et al., 2016). These oscillatory markers therefore offer accessible windows into the broader functional organization of large-scale brain networks.

Within this mechanistic framework, multiple neuromodulatory modalities target complementary physiological levels. Neurofeedback uses operant conditioning to decrease excessive high-beta activity at frontal sites (Fz/F3/F4), enhance sensorimotor rhythm at central sites (C3/C4), and, when indicated, facilitate alpha–theta protocols at parietal regions (Pz) to support oscillatory recalibration and strengthen prefrontal regulation of limbic circuits (Marzbani et al., 2016). Transcranial photobiomodulation at 810 nm, administered in the evening to promote gentle network entrainment, aims to increase cytochrome c oxidase activity, cerebral perfusion, and metabolic efficiency, thereby enhancing network coherence and flexibility. Heart-rate-variability biofeedback, combined with capnographic monitoring, employs resonance-frequency breathing (5.5–6 breaths per minute) to maintain end-tidal CO_2 within a target range of 35–40 mmHg, supporting increased vagal tone, reducing salience-network hyperresponsiveness, and stabilizing interoceptive signaling.

When integrated, these approaches form a synergistic triad: HRV biofeedback stabilizes the autonomic foundation, neurofeedback adjusts maladaptive oscillatory dynamics, and photobiomodulation provides metabolic support and temporal modulation. Together, they target the autonomic, cortical, and circadian dimensions of bipolar disorder, addressing mechanisms central to both mood stability and relapse prevention.

Pharmacological mood stabilizers such as lithium, valproate, and atypical antipsychotics remain central to the treatment of bipolar disorder and are effective in reducing relapse risk. Nonetheless, many patients continue to experience residual symptoms, functional impairment, or adverse effects despite adequate adherence. These limitations highlight the need for adjunctive, non-pharmacological interventions that act through clearly defined mechanistic pathways.

Within this context, neurofeedback offers a means of retraining maladaptive oscillatory patterns by decreasing excessive frontal high-beta activity and enhancing sensorimotor rhythm or alpha–theta states, thereby strengthening prefrontal regulatory control over limbic reactivity. Transcranial photobiomodulation at 40 Hz supports mitochondrial metabolism, improves cerebral perfusion, and promotes gamma-frequency synchronization, processes that facilitate more efficient prefrontal–limbic interaction (Cassano et al., 2018; Cassano et al., 2022). Heart-rate-variability biofeedback with capnographic monitoring further restores vagal tone and recalibrates interoceptive safety signals through controlled resonance-frequency breathing (Cherland, 2012).

When applied in combination, these modalities provide complementary effects across autonomic, cortical, and circadian regulatory systems. Their integration forms a mechanistically informed adjunct capable of addressing core physiological and network disruptions that persist beyond standard pharmacotherapy in bipolar disorder.

Methodology

The study employed a micro-randomized trial (MRT) structure embedded within a Just-In-Time Adaptive Intervention (JITAI) framework. Over a 12-week active intervention period followed by 12 weeks of follow-up, participants received weekly in-clinic neuromodulation sessions and multiple daily prompts for home-based exercises. JITAI prompts were delivered 3–5 times per day and were triggered by ecological momentary assessments and physiological data obtained from handheld and wearable devices. These prompts recommended brief HRV biofeedback sessions or evening photobiomodulation, depending on momentary indicators of vulnerability such as mood volatility, autonomic status, or circadian irregularity.

A total of 320 adults aged 18–65 years were recruited across 14 clinics. Eligible participants met DSM-5 criteria for bipolar I disorder (54%), bipolar II disorder (38%), or cyclothymia (8%). Inclusion criteria required a history of at least two affective episodes within the preceding five years and evidence of current mood instability. Exclusion criteria included active psychosis, moderate to severe substance-use disorders, photosensitivity, pregnancy, and the presence of implants incompatible with neuromodulatory procedures.

Intervention Protocol

Participants attended standardized weekly sessions comprising approximately 55–60 minutes of multimodal neuromodulation:

- **HRV biofeedback (10–12 minutes):** Sessions targeted an intra-session RMSSD increase of 10–15%.
- **Neurofeedback (≈25 minutes):**
    - Down-training excessive high-beta activity at frontal sites (Fz/F3/F4; >+1.5 z).
    - Enhancing sensorimotor rhythm at C3/C4, delivered in two to three blocks of 6–8 minutes.
    - Implementing alpha–theta training at Pz (8–10 minutes) when insomnia or hyperarousal was present.
- **Transcranial photobiomodulation (15–18 minutes):**

  Applied at 810 nm with an irradiance of 40–60 mW/cm² and a fluence of 20–30 J/cm² per site at Fp1, Fp2, Fpz, F3, and F4. Eye protection was mandatory, and total stimulation time did not exceed 18 minutes.
- **Debriefing (5–8 minutes):** Reinforcement of somatic grounding, review of regulatory strategies, and personalized daily recommendations.

Daily JITAI Prompts - Participants received context-sensitive, algorithm-driven prompts for:

- **HRV training:** 10-minute sessions of resonance-frequency breathing (5.5–6 breaths/min) with real-time RMSSD feedback.

- **Evening tPBM:** 12–15 minutes of prefrontal photobiomodulation administered within two hours of bedtime.

Prompt eligibility was determined by continuously updated indicators spanning the previous 2–6 hours, including elevated Mood Volatility Index (MVI), reduced HRV, low Sleep Regularity Index (SRI), and circadian timing rules (e.g., evening restriction for tPBM).

Safety Procedures

A structured "mania-watch" protocol monitored early signs of hypomanic activation. If participants reported a Young Mania Rating Scale (YMRS) score ≥12 or slept fewer than four hours over two consecutive nights, photobiomodulation was postponed, HRV and SMR-focused neurofeedback were prioritized, and clinical follow-up was initiated. Alpha–theta training was delivered with grounding strategies to prevent dysregulation. For hypomanic symptoms emerging during active phases, tPBM duration was reduced and surveillance intensified.

Outcome Measures

The primary proximal endpoint was the 6-hour Mood Volatility Index (MVI), calculated using ecological momentary assessments and sensor-derived affective, interoceptive, and contextual data. MVI changes were compared between prompted and unprompted windows.

The main distal outcome was time to relapse, defined as meeting diagnostic criteria for a new depressive or hypomanic/manic episode during the 20-week follow-up period. Relapse occurrence was assessed using standardized clinical interviews, and survival analyses were conducted using Cox proportional-hazards models.

Secondary Clinical Outcomes

Assessments were performed at baseline and at weeks 4, 8, and 12, including:

- Montgomery–Åsberg Depression Rating Scale (MADRS)
- Young Mania Rating Scale (YMRS)
- Insomnia Severity Index (ISI)
- Sleep Regularity Index and interdaily stability (actigraphy)
- WHODAS 2.0 functional measures

Biomarkers were analyzed using:

- **HRV (RMSSD)** at rest and during nocturnal recordings
- **qEEG** (19-channel, ICA-corrected): frontal high-beta activity, alpha asymmetry, and coherence
- **Prefrontal fNIRS:** oxyhemoglobin changes during a 2-back working-memory task
- **Hair cortisol** as a marker of cumulative HPA-axis activity
- **Capnography** ($ETCO_2$) during HRV sessions
- **Actigraphy** for sleep regularity metrics

Quality Control

Standardized quality-control procedures were applied across all sites. For EEG, electrode impedances were maintained below 5 kΩ, epoch rejection remained under 20%, and monthly phantom calibrations were performed. Photobiomodulation devices were periodically calibrated for irradiance and frequency. HRV recordings were accepted only with <5% artifact contamination. fNIRS datasets underwent motion correction, and no more than 10% of channels were allowed to be rejected.

Statistical Analysis

Proximal effects on MVI were evaluated using generalized estimating equations and mixed models, comparing prompted versus non-prompted windows while adjusting for time-of-day, day-of-week, and baseline characteristics. Relapse-free survival was examined with Cox models. Clinical outcomes (MADRS, YMRS) were analyzed through mixed-effects modeling under intent-to-treat and per-protocol (≥80% adherence) frameworks. Mediation analyses assessed whether changes in autonomic, hemodynamic, or oscillatory biomarkers accounted for clinical improvement. Moderator analyses incorporated baseline HRV, high-beta z-scores, sleep regularity, and chronotype, and personalization rules were estimated through dWOLS and Q-learning approaches. Sensitivity analyses used multiple imputation (m = 50), and multiplicity adjustments followed Holm correction procedures.

Results

A total of 320 individuals were enrolled in the study with characteristics detailed in table 1. The mean age of the sample was 36.8 years (SD = 10.9), and women represented 57% of participants. Diagnostic distribution reflected the heterogeneity of bipolar spectrum conditions: 54% met criteria for bipolar I disorder, 38% for bipolar II disorder, and 8% for cyclothymia. At study entry, 62% of participants were in a depressive episode, 9% in hypomania, and 29% in a euthymic state.

Table 1. Characteristics of the research sample

Feature	Value
N participants	320
Age, Mean (SD)	36.8 (10.9)
Female, %	57%
BP Type: I/II/Cyclothymic (%)	54 / 38 / 8
Current episode: depressive/hypomanic/euthymic (%)	62 / 9 / 29
Concomitant mood stabilizer, %	71%
PHQ-9 Initial, Medium (SD)	13.6 (5.2)
Initial MADRS, Medium (SD)	24.1 (6.3)
Initial YMRS, Medium (SD)	12.7 (5.0)
Initial Nocturnal RMSSD (ms), Medium (SD)	26.4 (10.8)
Initial SRI, Medium (SD)	57.2 (12.6)

Pharmacological treatment was common, with 71% of participants receiving a mood stabilizer at baseline. Scores on symptom and physiological measures indicated moderate clinical burden: the mean PHQ-9 score was 13.6 (SD = 5.2), while initial MADRS and YMRS means were 24.1 (SD = 6.3) and 12.7 (SD = 5.0), respectively. Baseline nocturnal heart-rate variability was reduced, with an average RMSSD of 26.4 ms (SD = 10.8). Circadian disruption was also evident, as reflected by a mean Sleep Regularity Index of 57.2 (SD = 12.6).

These characteristics collectively illustrate a clinically diverse sample with substantial mood symptoms, autonomic dysregulation, and sleep irregularity at the outset of the intervention.

Proximal Outcome

The primary proximal endpoint of the study was the change in the 6-hour Mood Volatility Index (MVI), calculated from ecological momentary assessments and sensor-derived indicators of affective variability. Analyses comparing windows in which JITAI prompts were delivered with windows without prompts demonstrated a robust effect. Overall, the intervention produced a 35% reduction in MVI (95% CI: –40% to –30%, $p < 0.001$), indicating that the adaptive prompts successfully attenuated short-term affective instability during vulnerable periods.

Table 2. Primary and Secondary Treatment Outcomes

Outcome	Effect	p
Proximal MVI ATE (prompt vs no prompt)	-35.0% (95%CI [-40;-30])	<0.001
Relapse hazard ratio (MRT vs baseline)	0.42 (95% CI [0.34; 0.52])	<0.001
Δ MADRS (8 weeks)	-11.8	<0.001
Δ YMRS (8 weeks)	-6.9	<0.001
RMSSD at night %Δ	27%	<0.001
Sleep Regularity Index (Δ p.p.)	+14.5 p.p.	<0.001
Interdaily stability (IS, actigraphy) – Δ mean	0.62	<0.001

The pronounced reduction in MVI, as observed in table 2, confirms that the JITAI system effectively targeted momentary fluctuations in mood and intervened at times when regulatory support was most needed. In addition to this immediate effect, the micro-randomized trial period was associated with a significant

improvement in relapse-free survival; the hazard ratio of 0.42 (95% CI: 0.34–0.52) demonstrates that participants experienced substantially fewer depressive or hypomanic relapses during the intervention compared with baseline periods.

Secondary clinical outcomes further reinforce the global stabilizing effect of the multimodal protocol. By week 12, depression severity had decreased by 11.8 points on the MADRS, while YMRS scores had declined by 6.9 points, indicating improvement across both depressive and manic symptom domains. Autonomic and circadian markers showed corresponding enhancements, including a 27% increase in nocturnal RMSSD and an improvement of 14.5 percentage points in the Sleep Regularity Index. Interdaily stability measured through actigraphy also increased (mean $\Delta = 0.62$), reflecting more consistent daily rhythms. Together, these outcomes illustrate coordinated progress across emotional, physiological, and circadian systems.

Table 3 details subgroup-level analyses examining whether baseline physiological and clinical characteristics moderated the acute impact of JITAI prompts on mood volatility. The overall pattern demonstrates that the proximal benefit of MVI reduction was broadly consistent but disproportionately larger in groups exhibiting greater initial dysregulation.

Table 3. Proximal effect of MVI on subgroups

Subgroup	ΔMVI effect (%)	95% CI	P Interaction	N
Basal HRV ≤25 ms	-42	[-48, -36]	<0.01	160
Basal HRV >25 ms	-28	[-33, -23]	,	160
SRI <60	-38	[-44, -32]	0.04	170
SRI ≥60	-30	[-35, -25]	,	150
High-beta ≥ +0.5 z	-40	[-46, -34]	0.02	140
High-beta < +0.5 z	-29	[-34, -24]	,	180
Evening chronotype	-36	[-42, -30]	0.3	120
Morning/intermed chronotype.	-33	[-38, -28]	,	200
BP Type I	-37	[-43, -31]	0.2	190
BP Type II/Cyclothymic	-32	[-37, -27]	,	130
No stabilizer disposition	-36	[-42, -30]	0.7	92
With Stabilizer Disposition	-34	[-39, -29]	,	228

Participants with low baseline HRV (≤25 ms RMSSD) showed the strongest response, with a 42% reduction in MVI, compared with a 28% reduction among those with higher HRV. Similarly, individuals with poor sleep regularity (SRI < 60) experienced greater benefit (–38%) than those with more stable circadian patterns (–30%). Elevated frontal high-beta activity at baseline (≥ +0.5 z) also predicted a more pronounced reduction in volatility (–40%) relative to those with lower high-beta levels (–29%). These findings suggest that the JITAI mechanism is particularly effective when autonomic, circadian, or oscillatory markers indicate vulnerability.

Analyses across chronotype, bipolar subtype, and medication status showed consistent reductions in MVI, with no significant interaction effects, indicating that the proximal impact of the intervention was robust

across demographic and diagnostic subgroups. The presence or absence of a mood stabilizer did not meaningfully influence outcome magnitude.

Overall, the subgroup findings validate the rationale of the JITAI system: individuals who exhibit greater physiological fragility or network dysregulation derive proportionally larger benefits from timely, targeted neuromodulatory prompts.

Distal outcome (relapse-free survival)

The principal distal endpoint of the study was time to relapse, defined as the emergence of a new depressive, hypomanic, or manic episode during the 20-week follow-up period. Survival analyses revealed a substantial protective effect associated with participation in the multimodal JITAI-guided intervention. The hazard ratio of 0.42 (95% CI: 0.34–0.52, $p < 0.001$) indicates that, during periods of active engagement with the protocol, participants were approximately 58% less likely to experience a mood episode compared with baseline conditions. This finding demonstrates a clinically meaningful extension of relapse-free intervals and reinforces the durability of treatment effects beyond the immediate proximal window.

Table 4. Hazard relapse by subgroups

Subgroup	HR Relapse (MRT vs Reference)	95% CI	P Interaction
Basal HRV ≤25 ms	0.34	[0.27, 0.43]	0.01
Basal HRV >25 ms	0.52	[0.42, 0.64]	,
SRI <60	0.38	[0.30, 0.47]	0.03
SRI ≥60	0.48	[0.39, 0.59]	,
High-beta ≥ +0.5 z	0.36	[0.29, 0.45]	0.02
High-beta < +0.5 z	0.5	[0.41, 0.62]	,
BP Type I	0.4	[0.33, 0.49]	0.4
BP Type II/Cyclothymic	0.45	[0.36, 0.57]	,

Interpretation of subgroup analyses (Table 4) demonstrates that the survival benefit was consistent across demographic and diagnostic categories, but, as with the proximal outcome, was more pronounced in individuals exhibiting greater baseline physiological or oscillatory dysregulation. Participants with low HRV (≤25 ms RMSSD) showed the strongest reduction in relapse risk (HR = 0.34), whereas those with higher HRV displayed a more modest yet still significant reduction (HR = 0.52). A similar gradient was observed for sleep regularity: participants with an SRI below 60 had a hazard ratio of 0.38, compared with 0.48 among those with more stable rhythms.

Baseline frontal high-beta activity also moderated risk: individuals with elevated high-beta (≥ +0.5 z) experienced a hazard ratio of 0.36, compared to 0.50 in the lower-beta group. These patterns align with the mechanistic rationale of the intervention, suggesting that individuals with greater autonomic, circadian, or cortical instability derive proportionally larger protective effects.

Importantly, no significant interaction emerged across bipolar subtypes (type I vs. type II/cyclothymic) or between medicated and unmedicated participants. This consistency underscores the broad applicability of the protocol and suggests that the multimodal intervention exerts clinically relevant, scalable effects across diverse presentations of bipolar disorder.

Outcomes at week 12

By the end of the 12-week intervention, participants demonstrated substantial improvements across multiple symptom domains. Depressive symptoms showed a clinically meaningful reduction, with mean MADRS scores decreasing by 11.8 points. Manic and hypomanic features also improved, reflected in a 6.9-point reduction on the YMRS. These findings indicate balanced stabilization across both poles of the affective spectrum.

Circadian functioning exhibited parallel progress. The Sleep Regularity Index increased by 14.5 percentage points, indicating more consistent sleep–wake patterns across days. Actigraphy-derived Interdaily Stability showed a mean improvement of 0.62, further supporting the restoration of circadian organization. Functionally, participants reported fewer days of absenteeism (–2.1 days per eight-week interval) and a 12% enhancement in workplace performance, suggesting that symptomatic gains translated into meaningful real-world improvements. Collectively, these clinical results illustrate the broad impact of the multimodal protocol, with benefits spanning depressive and manic symptoms, circadian health, and functional capacity.

Biomarker analyses revealed convergent physiological changes consistent with improved autonomic regulation, endocrine normalization, and enhanced cortical function. Nocturnal HRV increased by 27%, signifying strengthened vagal modulation and more stable autonomic dynamics. Measures of cumulative stress burden also improved: hair cortisol levels decreased by 28%, indicating reduced HPA-axis activation over time.

Neurophysiological assessments demonstrated parallel enhancements. Prefrontal fNIRS recordings obtained during a 2-back task showed an increase of +0.80 μM in oxyhemoglobin concentration, compared with +0.15 μM during control periods, reflecting improved recruitment of executive networks under cognitive load. qEEG analyses indicated reductions in frontal high-beta activity and improvements in alpha coherence, suggesting more stable oscillatory patterns and better-integrated network functioning. Together, these biomarker findings corroborate the clinical outcomes, demonstrating that the intervention not only reduced symptom severity but also addressed underlying physiological and neurocircuit-level dysregulation.

Adverse events and safety

The multimodal intervention demonstrated a favorable safety profile, with adverse events generally mild, transient, and easily managed within the clinical protocol. No serious adverse events were recorded throughout the study as can be observed from table 5.

Table 5. Reported adverse events by the participants throughout the trial

Adverse event	Frequency (N, %)	Severity	Action
Mild headache post-tPBM	7%	Easy	short break
Mild daytime sleepiness	5%	Easy	Evening appointment
Transient agitation (NFB)	6%	Easy	NFB threshold adjustment
Skin/scalp irritation (head tPBM)	3%	Easy	conductive gel/head
Hypomanic turn during the screening period (stratified)	1%	Clinical monitoring	Alert algorithm + clinician contact
SAE	0%	,	,

The most frequently reported effect was mild headache following transcranial photobiomodulation, occurring in 7% of participants; symptoms resolved with brief rest and did not require protocol modification, similar with other studies Cassano et al., 2022. Daytime sleepiness was reported by 5% of participants, typically associated with evening scheduling of sessions, and was mitigated by adjusting appointment times. Transient agitation during neurofeedback occurred in 6% of individuals and was resolved by adjusting training thresholds or incorporating additional grounding strategies. Minor skin or scalp irritation related to tPBM contact points was reported in 3% of participants and improved with the application of conductive gel or repositioning of the device. A small number of participants (1%) exhibited hypomanic symptoms during the screening period. These cases were identified promptly through the study's monitoring system, triggering the predefined alert algorithm and clinician contact. In such instances, tPBM was postponed, HRV and SMR-focused neurofeedback were emphasized, and clinical oversight was intensified.

Adherence to the intervention remained high, ranging from 84% to 86%, underscoring the acceptability of the protocol and the tolerability of its component modalities. Overall, the safety data support the suitability of the integrated neurofeedback, photobiomodulation, and HRV biofeedback program for use in outpatient populations with bipolar disorder.

Discussion

This study demonstrates that a multimodal neurotechnology protocol, delivered within a Just-In-Time Adaptive Intervention (JITAI) framework, can produce substantial improvements in mood stability, relapse prevention, and neurophysiological functioning in individuals with bipolar disorder. The findings provide convergent evidence across clinical outcomes, proximal markers of affective regulation, and objective physiological indicators, reinforcing the mechanistic coherence of the intervention.

At the mechanistic level, the data suggest that the protocol exerted its effects through coordinated modulation of autonomic, cortical, and circadian systems. HRV biofeedback consistently enhanced vagal tone, which is theorized to reduce salience-network overactivation and improve interoceptive stability. Neurofeedback contributed to oscillatory recalibration by reducing excessive frontal high-beta activity and strengthening sensorimotor and alpha–theta dynamics, a pattern associated with improved prefrontal–limbic regulation. Transcranial photobiomodulation at 40 Hz supported metabolic efficiency and gamma synchrony, reflected in increased oxyhemoglobin concentrations within prefrontal regions during cognitive challenge. Together, these processes appear to restore balance across functional networks implicated in emotional reactivity, cognitive control, and circadian rhythm maintenance.

Clinically, improvements were observed across both depressive and hypomanic symptom domains, indicating that the intervention facilitated bidirectional mood stabilization rather than unipolar symptom reduction. Enhancements in sleep regularity and functional outcomes suggest that the benefits extended beyond symptom severity to encompass broader aspects of daily functioning and quality of life. The strong effect on relapse-free survival (HR = 0.42) underscores the relevance of mechanistically informed, momentary interventions for modifying long-term outcomes in bipolar disorder.

Several methodological strengths support the robustness of the findings. The MRT/JITAI design allowed the study to capture fluctuations in real-world emotional and physiological states, enabling analyses that reflect naturalistic patterns of vulnerability. Objective biomarkers, including HRV, fNIRS, hair cortisol, and qEEG, provided multi-system validation of the clinical changes. The multicenter implementation further demonstrates the scalability of the protocol, provided appropriate calibration and fidelity procedures are maintained.

However, certain limitations warrant consideration. Complete blinding of participants is inherently challenging in interventions involving feedback-based neuromodulation, although assessor blinding and the use of active controls mitigate some risk of expectancy effects. The heterogeneity of bipolar subtypes and comorbidities may introduce variability in treatment trajectories, though personalization analyses helped characterize differential responses. The technical infrastructure required for EEG, tPBM, HRV, and fNIRS may limit immediate deployment in settings with fewer resources, emphasizing the importance of training and standardized quality-control procedures.

Future research should explore adaptive enrichment strategies, such as increasing prompt probability in individuals with low HRV or reduced sleep regularity, to further optimize personalization. Additional directions include evaluating the utility of post-protocol booster sessions, integrating the intervention with pharmacological strategies in hybrid treatment algorithms, and conducting economic analyses to quantify cost-effectiveness in relapse prevention. Together, these extensions may enhance the precision, accessibility, and sustainability of multimodal neurotechnology approaches for bipolar disorder.

Conclusion

The present study demonstrates that a multimodal neuromodulatory program, combining neurofeedback, 40 Hz prefrontal photobiomodulation, and HRV biofeedback, delivered through a Just-In-Time Adaptive Intervention architecture, offers a potent and mechanistically coherent approach to stabilizing mood and preventing relapse in bipolar disorder. Across the 12-week intervention, the protocol produced significant improvements in proximal affective stability, as evidenced by a 35% reduction in mood volatility in the hours following JITAI prompts. This immediate stabilizing effect illustrates that timely, context-sensitive neuromodulation can attenuate rapid emotional fluctuations during periods of heightened vulnerability.

These proximal gains translated into meaningful long-term benefits. Participants experienced a substantially reduced risk of depressive or hypomanic relapse, reflected in a hazard ratio of 0.42, indicating durable protection during follow-up. The intervention further supported balanced symptomatic improvement, with reductions in both depressive and manic/hypomanic symptomatology, highlighting its ability to contribute to bidirectional stabilization rather than unipolar symptom reduction. Additional improvements in sleep regularity, circadian stability, and functional capacity confirm that the protocol exerted broad, cross-domain benefits extending into daily behaviors and psychosocial functioning.

The physiological outcomes reinforce the clinical findings. Enhancements in nocturnal HRV and reductions in hair cortisol suggest restoration of autonomic regulation and attenuation of chronic stress signaling. Increases in prefrontal oxyhemoglobin during cognitive load and improvements in oscillatory indices, particularly reductions in frontal high-beta activity and strengthened alpha coherence, are consistent with improved executive network recruitment and more efficient prefrontal–limbic integration. Mediation analyses further indicated that changes in HRV, cortisol, and hemodynamic responses accounted for nearly half of the mood-stabilizing effect, underscoring the mechanistic alignment between physiological normalization and clinical outcomes.

Importantly, the safety profile was favorable. Adverse events were mild, transient, and readily managed within the standardized protocol, and no serious events occurred. The high adherence rate (84–86%) demonstrates strong acceptability of the intervention components, even in a population experiencing significant affective and circadian instability.

Taken together, these findings support the value of a multimodal, mechanism-oriented, and adaptively delivered neuromodulation strategy for bipolar disorder. By acting simultaneously on autonomic, cortical, and circadian systems, and by delivering support precisely during windows of elevated risk, the intervention addresses the core instabilities that maintain mood volatility and predispose individuals to relapse. This integrative approach offers a scalable and promising adjunct to standard pharmacotherapy, with potential to improve long-term outcomes through targeted modulation of the very systems that underpin bipolar disorder's recurrent nature.

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