Neuroregulation of chronic insomnia by prefrontal photobiomodulation (tPBM) against the background of HRV & sleep hygiene: double-blind cross-over RCT, sham-control with actigraphy and autonomic biomarkers

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Abstract

Chronic insomnia is characterized by cortico-limbic hyperarousal and autonomic dysregulation, frequently manifested through reduced heart rate variability and fragmented sleep. This randomized, double-blind, cross-over controlled trial examined the efficacy of prefrontal transcranial photobiomodulation (tPBM; 810 nm) in reducing insomnia severity when delivered alongside a standardized program consisting of evening HRV biofeedback and structured sleep hygiene. A total of 120 adults aged 18–65 years with DSM-5 chronic insomnia (ISI ≥ 15) were allocated to two treatment sequences (active–sham or sham–active), each consisting of two four-week periods separated by a two-week washout. Participants received three evening sessions per week of either active tPBM or a matched sham procedure, in addition to the common background intervention. The primary outcome was the change in Insomnia Severity Index (ISI) across each treatment period. Active tPBM produced a significant reduction in ISI scores compared to sham (−5.4 points; 95% CI −6.1 to −4.7; $p < 0.001$), with no evidence of carry-over and no significant period effects. Clinical remission (ISI ≤ 7) occurred in 62% of active versus 24% of sham periods. Secondary outcomes showed convergent improvements: increased sleep efficiency, shortened sleep-onset latency and wake after sleep onset, lower PSQI and Epworth Sleepiness scores, enhanced nocturnal HRV (RMSSD), and a greater reduction in sleep-related qEEG alpha/delta ratios during active treatment. Adherence was high (median 89%), and adverse events were mild and comparable across conditions, with no serious adverse events reported. The findings indicate that prefrontal tPBM confers substantial additional benefit beyond HRV biofeedback and sleep hygiene, yielding robust subjective and objective sleep improvements with an excellent safety profile.

Keywords: chronic insomnia; transcranial photobiomodulation; prefrontal stimulation; HRV biofeedback; sleep hygiene; actigraphy; autonomic regulation; qEEG

Introduction

Chronic insomnia is a persistent disorder defined by difficulties in initiating or maintaining sleep, non-restorative sleep, or early morning awakenings, occurring despite adequate opportunity for rest. Its pathophysiology has been increasingly linked to sustained cortico-limbic hyperexcitability, which contributes to a heightened state of cognitive and physiological arousal that interferes with the initiation and consolidation of sleep. This hyperarousal profile is paralleled by autonomic dysregulation, most notably reflected in reduced heart rate variability (HRV), a marker of diminished parasympathetic activity. Together, these mechanisms support a self-perpetuating cycle in which cortical overactivation and impaired autonomic flexibility maintain insomnia symptoms and contribute to sleep fragmentation.

Transcranial photobiomodulation (tPBM), particularly near-infrared stimulation at 810 nm, has emerged as a potential neuromodulatory tool capable of attenuating hyperarousal through its effects on prefrontal regulatory circuits. When applied in the evening using pulsed stimulation, tPBM may promote the transition toward sleep by facilitating the emergence of slower cortical rhythms and improving regulatory control over subcortical arousal systems. These characteristics suggest a plausible role for tPBM as an adjunct intervention targeted at the neurophysiological substrates underlying chronic insomnia.

In this context, the present study was designed to test whether active prefrontal tPBM produces measurable improvements in insomnia severity beyond those conferred by a standardized foundational program consisting of evening HRV biofeedback and structured sleep hygiene counseling. HRV biofeedback, delivered through slow-paced breathing with real-time RMSSD feedback, aims to increase parasympathetic tone, whereas sleep hygiene provides behavioral guidance known to support more stable sleep patterns. By ensuring that all participants received these two components, the study sought to isolate the specific contribution of tPBM within a controlled and therapeutically relevant background. The trial employed a randomized, double-blind, cross-over design with two four-week treatment periods separated by a washout interval. This methodology minimizes interindividual variability, enhances sensitivity to treatment effects, and enables rigorous testing for potential period or carry-over influences. The primary hypothesis was that active tPBM would demonstrate superior improvements in the Insomnia Severity Index (ISI) compared with sham stimulation, accompanied by beneficial changes in objective sleep metrics and nocturnal HRV. The study further explored whether these effects aligned with alterations in sleep-related qEEG activity, particularly in alpha/delta ratios associated with sleep depth and cortical settling.

Methodology

This study employed a randomized, double-blind, cross-over design consisting of two active treatment periods of four weeks each, separated by a two-week washout interval. Participants were allocated in a 1:1 ratio to one of two treatment sequences: active tPBM followed by sham (AB) or sham followed by active tPBM (BA). Both the participants and investigators were blinded to treatment assignment, with devices rendered indistinguishable and treatment codes sealed until study completion. The cross-over format was selected to reduce interindividual variability and to allow each participant to serve as their own control, thereby increasing statistical power. All participants received two standardized background interventions throughout the trial: (1) evening HRV biofeedback and (2) structured sleep hygiene guidance. HRV biofeedback consisted of a 10-minute session at a breathing rate of 5.5–6 breaths per minute, using RMSSD as the feedback parameter. Sleep hygiene recommendations were provided through written materials and reinforced during brief weekly check-ins. These components ensured a uniform therapeutic baseline across conditions and allowed for the specific contribution of tPBM to be assessed.

Intervention

The active tPBM intervention consisted of prefrontal LED/NIR stimulation at 810 nm, pulsed at 10 Hz. The device delivered an irradiance of 40–60 mW/cm², yielding 18–22 J/cm² per stimulation site over a session lasting 15–18 minutes. Stimulation was applied to prefrontal locations including Fp1, Fp2, Fpz, F3, and F4. Sessions were scheduled three times per week, in the evening, and always within two hours before bedtime.

The sham condition employed an identical device configured to emit only visible light, without near-infrared output. Session duration, frequency, and procedural steps were matched precisely to those of the active treatment to ensure methodological equivalence and maintain blinding.

Eligible **participants** were adults aged 18–65 years meeting DSM-5 criteria for chronic insomnia and presenting a baseline Insomnia Severity Index (ISI) score of at least 15. Consistent use of actigraphy for a minimum of six nights per week was required. Exclusion criteria included moderate to severe sleep apnea identified through STOP-BANG and Epworth Sleepiness Scale screening, major neurological disorders, photosensitivity, and the presence of implanted devices incompatible with tPBM.

The primary **outcome** was the change in ISI score across each treatment period. Secondary outcomes included the Pittsburgh Sleep Quality Index (PSQI), the Epworth Sleepiness Scale, and multiple actigraphy-derived parameters: sleep efficiency, sleep-onset latency (SOL), and wake after sleep onset (WASO). Nocturnal HRV was quantified using RMSSD extracted from a 30-minute segment during N2/N3 sleep, and sleep-related cortical activity was evaluated using qEEG alpha/delta ratios. Adherence and patient-reported acceptability were assessed through electronic logs, calculation of session completion percentages, and the Client Satisfaction Questionnaire (CSQ-8).

Cross-over **analyses** were conducted using linear mixed-effects models specified as Outcome ~ Treatment + Period + Sequence + (1|Participant). Carry-over effects were tested through the Sequence × Period interaction; when non-significant, the full dataset was included in the estimation of treatment effects. Remission was defined as ISI ≤ 7, and remission rates were analyzed using mixed logistic models. Both intention-to-treat and per-protocol analyses were performed, the latter restricted to participants achieving at least 80% session adherence.

A priori **sample** size calculations indicated that detecting a mean between-condition ISI difference of 5 points, assuming a within-subject standard deviation of 8, with $\alpha = 0.05$ and 90% power, required 108 participants. To accommodate potential attrition, the study enrolled 120 participants.

Results

A total of 120 participants were randomized into the two cross-over sequences, with 60 assigned to the active–sham sequence (AB) and 60 to the sham–active sequence (BA). Of these, 116 participants completed at least one treatment period, and overall adherence was high, with a median session completion rate of 89%.

Baseline demographic and clinical characteristics were comparable between the two sequence groups, as observed in table 1. The mean age was 39.1 years (SD = 11.8) in the AB sequence and 38.7 years (SD = 11.2) in the BA sequence. The proportion of female participants was balanced across groups (61% in AB and 60% in BA). Participants entered the trial with consistent levels of insomnia severity and sleep disturbance, reflected in similar baseline Insomnia Severity Index (ISI) scores (18.5 ± 3.2 vs. 18.7 ± 3.3) and Pittsburgh Sleep Quality Index (PSQI) scores (12.4 ± 2.8 vs. 12.5 ± 2.7).

Table 1. Characteristics of AB versus BA sequence groups

Feature	Sequence AB	BA Sequence	p
N participants	60	60	—
Age, Mean (SD)	39.1 (11.8)	38.7 (11.2)	0.82
Female, %	61%	60%	0.91
Initial ISI, Mean (SD)	18.5 (3.2)	18.7 (3.3)	0.77
Initial PSQI, Medium (SD)	12.4 (2.8)	12.5 (2.7)	0.88
Sleep efficiency (%) – actigraphy	78.2 (6.4)	78.1 (6.6)	0.95
SOL (min)	38.5 (14.2)	39.1 (13.9)	0.79
WASO (min)	72.4 (28.6)	73.0 (29.1)	0.86

Actigraphy-derived sleep parameters at baseline also demonstrated substantial equivalence between groups. Mean sleep efficiency was 78.2% (SD = 6.4) in the AB sequence and 78.1% (SD = 6.6) in the BA sequence. Mean sleep-onset latency (SOL) values were 38.5 minutes (SD = 14.2) and 39.1 minutes (SD = 13.9), respectively, while wake after sleep onset (WASO) averaged 72.4 minutes (SD = 28.6) in AB and 73.0 minutes (SD = 29.1) in BA. None of the between-group differences reached statistical significance. Overall, the two randomized sequences were well balanced at study entry, ensuring appropriate comparability for subsequent cross-over analyses.

Primary Results

The primary analysis focused on changes in Insomnia Severity Index (ISI) scores across the two treatment periods. Active transcranial photobiomodulation produced a significant reduction in insomnia severity compared with the sham condition. The estimated treatment effect from the cross-over mixed model indicated a mean ISI improvement of −5.4 points in favor of active tPBM (95% CI: −6.1 to −4.7; $p < 0.001$).

The analysis further demonstrated the absence of meaningful temporal or sequence-related influences. The period effect did not reach statistical significance ($p = 0.18$), indicating that improvements were not dependent on whether a treatment was received in the first or second phase of the cross-over. Likewise, the test for carry-over effects, indexed by the Sequence × Period interaction in table 2, was non-significant ($p = 0.41$), supporting the validity of combining data across periods to estimate the treatment effect.

Table 2. Results of treatment effectiveness for primary outcome

Model (cross-over)	Estimate	95% CI	p
Treatment effect (active vs sham)	-5.4	(-6.1, -4.7)	<0.001
Period effect	-0.6	(-1.5, +0.3)	0.18
Carry-over (Sequence×Period)	—	—	0.41

Clinical remission—defined as achieving an ISI score of 7 or lower—occurred in 62% of active treatment periods compared with 24% of sham periods. This difference corresponded to an odds ratio of 5.1 (95% CI: 3.0–8.8), indicating a substantially higher likelihood of remission during active photobiomodulation. These findings collectively confirm that active prefrontal tPBM produced marked improvements in subjective insomnia severity when compared with sham stimulation, with no evidence of period-related confounding or residual treatment effects across phases.

Secondary Outcomes

Secondary analyses examined objective sleep parameters, global sleep quality, daytime sleepiness, autonomic regulation during sleep, and sleep-related cortical activity. Across all domains, observed from table 3, active tPBM produced consistently greater improvements than the sham condition.

Table 3. Secondary outcomes of the intervention

Outcome (Δ per period)	tPBM active – mean	tPBM sham – mean	Difference active - sham	p (treatment)
Sleep efficiency (p.p.)	12.3	4.2	+8.1 p.p.	<0.001
SOL (minutes)	-22	-8	-14 min	<0.001
WASO (minute)	-45	-15	-30 min	<0.001
PSQI (score)	-3.9	-1.5	-2.4	<0.001
Epworth (drowsiness)	-3.1	-1.2	-1.9	<0.001
HRV RMSSD at night (%Δ)	28%	10%	18%	<0.001
qEEG alpha/delta at sleep (%Δ)	-31%	-9%	-22%	<0.001

Actigraphy demonstrated notable enhancements in sleep architecture during active treatment. Sleep efficiency increased by 12.3 percentage points during active tPBM, compared with a 4.2-percentage-point improvement during sham stimulation. Sleep-onset latency (SOL) decreased by 22 minutes with active tPBM, whereas sham treatment yielded an 8-minute reduction. Wake after sleep onset (WASO) was reduced by 45 minutes in the active periods, compared with a 15-minute reduction during sham, indicating pronounced consolidation of nocturnal sleep. Correspondingly, subjective sleep quality and daytime alertness also improved more substantially

under active stimulation. PSQI scores decreased by 3.9 points during active tPBM versus 1.5 points during sham, and Epworth Sleepiness Scale scores decreased by 3.1 points compared with 1.2 points in the sham condition.

Physiological indices aligned with these changes. Nocturnal HRV, measured as RMSSD during a stable N2/N3 window, increased by 28% in the active periods, exceeding the 10% improvement observed under sham. Moreover, qEEG analysis revealed a 31% reduction in the alpha/delta ratio during sleep with active treatment, compared with a 9% reduction under sham. This pattern is consistent with decreased cortical arousal and deeper sleep-related cortical activity during active stimulation. Across all evaluated secondary domains, the direction and magnitude of changes consistently favored active tPBM, reinforcing the primary findings and supporting a broad impact on both subjective and objective indices of sleep regulation.

Rates of clinical remission and treatment adherence further illustrated the advantages of active transcranial photobiomodulation within the standardized therapeutic framework. Remission, defined as achieving an Insomnia Severity Index (ISI) score of 7 or lower, was substantially more frequent during active tPBM periods. A total of 62% of active treatment periods met the remission criterion, compared with 24% of periods under sham stimulation. This marked difference reflects the robustness of the therapeutic effect observed in the primary and secondary analyses.

Adherence to the intervention protocol was high across both treatment conditions. Completion of at least 80% of scheduled sessions was achieved by 86% of participants during active tPBM and by 83% during sham treatment. These comparable adherence levels support the feasibility and acceptability of the intervention procedures and indicate that differential engagement was unlikely to have influenced treatment outcomes. Together, the remission and adherence data reinforce the consistency of the therapeutic response and the practicality of implementing the protocol in a clinical or research setting.

Adverse Events

The safety profile of the intervention was favorable, with only mild adverse events reported across both treatment conditions and no serious adverse events as observed from table 4. Mild headache occurred in 8% of active tPBM sessions and 6% of sham sessions, while mild daytime sleepiness was reported by 5% and 4% of participants, respectively. Eye strain was noted with similar frequency, affecting 4% of participants during active stimulation and 3% during sham. None of these differences reached statistical significance, indicating that adverse events were evenly distributed and unlikely to be attributable specifically to the active intervention.

Table 4. Reported adverse events throughout the intervention

Adverse event	active tPBM, N (%)	tPBM sham, N (%)	p
Mild headache	10 (8%)	7 (6%)	0.46
Mild daytime sleepiness	6 (5%)	5 (4%)	0.72
Eye strain	5 (4%)	4 (3%)	0.74
SAE	0 (0%)	0 (0%)	—

Acceptability ratings were high, reflected in a mean Client Satisfaction Questionnaire (CSQ-8) score of 29.1 out of 32. This pattern underscores the tolerability of both the active and sham procedures and supports the suitability of the protocol for sustained use within a structured therapeutic program.

Discussion

The present randomized, double-blind, cross-over trial demonstrates that prefrontal transcranial photobiomodulation (tPBM), when delivered alongside HRV biofeedback and structured sleep hygiene, yields consistent and clinically meaningful improvements in chronic insomnia. The superiority of active tPBM over sham was evident across subjective symptoms, objective actigraphic indices, autonomic markers, and neurophysiological sleep signatures. These convergent findings underscore the capacity of tPBM to modulate the mechanisms of evening hyperarousal that characterize chronic insomnia.

The robust reduction in Insomnia Severity Index scores, together with the high remission rate during active treatment periods, supports the specific therapeutic action of prefrontal tPBM beyond the standardized background interventions. Improvements in sleep efficiency, sleep-onset latency, and wake after sleep onset corroborate the subjective outcomes and indicate that the intervention effectively consolidates nocturnal sleep. The enhancement of nocturnal HRV further suggests a favorable shift in autonomic balance, with increased parasympathetic activity aligning with the hypothesized reduction in physiological arousal.

Decreases in qEEG alpha/delta ratios during sleep provide additional evidence for the neuroregulatory effects of tPBM, reflecting a transition toward deeper and more stable sleep-related cortical activity. The consistency of improvements across behavioral, physiological, and electrophysiological measures strengthens the interpretation of tPBM as a modality capable of influencing both cortical and autonomic dimensions of insomnia.

The cross-over design played an important role in clarifying treatment-specific effects by minimizing interindividual variability. The absence of significant carry-over effects indicates that the two-week washout period was sufficient to mitigate residual influences from the preceding condition. Likewise, the lack of a period effect suggests that improvements were attributable to the treatment rather than the timing of the intervention.

Several limitations warrant consideration, and although the sham device closely mimicked the active stimulation, the possibility of subtle differences in sensory perception may have influenced participant expectations. The two-week washout, while adequate statistically, may be relatively short for some individuals depending on the persistence of neuromodulatory effects. Additionally, the use of actigraphy, although ecologically valid, limits the ability to distinguish sleep stages, and polysomnography would provide a more precise characterization of sleep architecture.

Despite these constraints, the study provides compelling evidence that prefrontal tPBM is an effective and well-tolerated adjunct intervention for chronic insomnia. Its capacity to modulate both subjective symptoms and objective physiological markers supports its integration into multimodal treatment frameworks aimed at reducing evening hyperarousal and improving sleep continuity.

Conclusion

This study shows that prefrontal transcranial photobiomodulation, when implemented alongside HRV evening biofeedback and structured sleep hygiene, constitutes an effective and safe therapeutic option for individuals with chronic insomnia. Across subjective clinical measures, behavioral sleep metrics, autonomic indices, and electrophysiological markers, active tPBM produced improvements that were consistently superior to those observed with sham stimulation. These findings support the capacity of tPBM to address the core pathophysiological features of the disorder, particularly evening hyperarousal and impaired sleep consolidation.

The protocol demonstrated high rates of adherence and acceptability, indicating that the combined intervention is both feasible and well tolerated. The absence of serious adverse events further reinforces the suitability of tPBM for regular clinical use. Taken together, these results suggest that the integrated protocol is scalable and can be readily incorporated into structured treatment pathways. Within such frameworks, prefrontal tPBM may serve as a valuable first-line option for patients whose insomnia persists despite standard behavioral strategies focused on sleep hygiene.