Neuroregulation of generalized anxiety through multimodal neurotechnological interventions (QEEG neurofeedback, photobiomodulation and heart–brain coherence): randomized, controlled, multicenter clinical trial

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Abstract

Generalized anxiety (GAD) remains a difficult-to-treat psychiatric disorder with high relapse rates and incomplete response to standard treatments. Multimodal neurotechnological interventions can offer an innovative approach by directly regulating brain oscillations, neuronal metabolism and vagal tone. To evaluate the efficacy of an integrated intervention (QEEG neurofeedback, transcranial photobiomodulation – tPBM, heart–brain coherence through HRV biofeedback) compared to active control and usual care, in reducing GAD symptoms. The intervention consisted of 24 sessions over 8 weeks, with 450 participants (150/group) randomized into three arms: (A) multimodal intervention, (B) active control, (C) usual care. The multimodal group showed a mean reduction of −12.8 points on GAD-7 (baseline: 16.4 → 3.6), compared to −5.1 in active control and −2.9 in usual care. The proportion of clinical remission (GAD-7 ≤4) was 72% in the multimodal group, compared to 28% in active control and 14% in CAU. HRV (RMSSD) increased by +42% and salivary cortisol decreased by −36% in the multimodal group. EEG analyses showed a significant reduction in frontal high-beta power (−41%) and an increase in frontolimbic alpha coherence (+39%). The multimodal intervention significantly exceeded both active control and standard care, with spectacular clinical effects and objective physiological biomarkers. The results support the potential of integrating neurofeedback, photobiomodulation and HRV biofeedback as a new treatment standard for GAD.

Keywords: *Generalized Anxiety Disorder (GAD); HRV Biofeedback; Neurofeedback; Randomized Controlled Trial; Transcranial Photobiomodulation (tPBM).*

Introduction

Generalized anxiety disorder (GAD) is a chronic and debilitating condition affecting an estimated 5–7% of individuals across the lifespan. It is characterized by persistent and uncontrollable worry, heightened physiological arousal, disturbed sleep, and impaired cognitive control. Despite the availability of pharmacotherapy and cognitive-behavioral therapy, clinical outcomes remain modest: response rates rarely exceed 50–60%, and fewer than 40% of patients achieve full remission (Hofmann & Smiths, 2008). These limitations highlight the need for therapeutic approaches that more directly target the neurobiological systems sustaining pathological anxiety.

Advances in neurotechnology offer new opportunities to intervene at the level of brain oscillations, neuronal metabolism, and autonomic regulation—domains closely implicated in the maintenance of GAD. Electroencephalographic neurofeedback (NFB), particularly when informed by quantitative EEG (qEEG) assessments, enables individualized modulation of dysfunctional cortical rhythms. Transcranial

photobiomodulation (tPBM), using near-infrared light, enhances mitochondrial energy production and can promote large-scale network synchronization. Heart rate variability (HRV) biofeedback, by training slow-paced respiration and vagal engagement, supports restoration of autonomic flexibility and heart–brain coherence. Each modality targets a distinct but interrelated component of the pathophysiology of GAD.

The working hypothesis of this trial was that combining these three interventions into a unified, multimodal treatment would produce synergistic effects that exceed those of active control conditions and usual care. By simultaneously addressing cortical hyperexcitability, metabolic inefficiency, network dysregulation, and autonomic rigidity, the integrated intervention was expected to yield substantial improvements in both subjective symptoms and objective physiological markers.

Neurobiological Model of GAD: Persistent Hyperarousal Within Large-Scale Networks

GAD is maintained by a constellation of interacting neural, autonomic, and endocrine mechanisms that collectively reinforce a chronic hyperarousal state (Fonzo & Etkin, 2017). At the cortical level, the dorsolateral and ventromedial prefrontal cortices exhibit inconsistent top-down regulation, with overactivation during worry and underactivation during inhibitory demands. Limbic structures, including the amygdala and hippocampus, display heightened responsiveness to uncertain threat, amplifying negative attentional biases and emotional reactivity. The insula contributes exaggerated interoceptive monitoring, further sustaining anxious arousal.

These regional abnormalities are accompanied by disruptions across intrinsic functional networks (Fonzo & Etkin, 2017). The salience network gains excessive influence, the default mode network remains persistently engaged in rumination, and the central executive network shows diminished authority during cognitive reorientation. Autonomic imbalance manifests as reduced HRV, indicating weakened vagal modulation and limited emotional adaptability. At the endocrine level, increased cortisol and altered circadian patterns reflect sustained HPA axis activation.

qEEG patterns provide a measurable signature of these disturbances. Excess frontal high-beta activity marks hypervigilance, reduced SMR suggests thalamo-cortical instability, and frontal alpha asymmetry corresponds to anxiety-depressive mood states. Additionally, deficits in frontolimbic coherence indicate impaired integration across regulatory circuits. These features form the neurofunctional landscape targeted by the intervention.

Mechanistic Rationale and Synergistic Action of the Three Modalities

The multimodal protocol integrates three mechanistic “levers”, each designed to modulate a distinct dimension of GAD neurobiology.

QEEG-informed neurofeedback aims to down-train excessive frontal high-beta power while reinforcing SMR rhythms and, when indicated, facilitating alpha–theta transitions. Through operant conditioning and

adaptive thresholding, this modality promotes the acquisition of more stable oscillatory states and strengthens executive network function.

Transcranial photobiomodulation applies pulsed near-infrared light (810 nm, optionally 1064 nm) at frequencies associated with anxiolysis and network flexibility. By enhancing cytochrome-c-oxidase activity and supporting perfusion and metabolic efficiency, tPBM facilitates improved synchronization among prefrontal and default–executive networks.

HRV biofeedback trains slow, coherent respiration with real-time feedback based on RMSSD or coherence indices (Lehrer & Gevirtz, 2014). This strengthens vagal tone, promotes interoceptive safety, and restores autonomic resilience, which are key modulators of emotional regulation.

The synergistic potential arises from the complementary nature of these components: neurofeedback modulates oscillatory patterns, photobiomodulation enhances the neuronal substrate supporting these changes, and HRV biofeedback reinstates the autonomic flexibility necessary for sustained affective stability. Together, they directly counteract the mechanisms that perpetuate excessive worry, autonomic rigidity, sleep disruption, and elevated HPA activity.

Objectives

The primary objective of the study was to evaluate the superiority of the multimodal intervention compared with an active control condition in reducing GAD symptoms, measured by changes in GAD-7 scores after eight weeks of treatment.

Secondary objectives encompassed examining effects on broader clinical domains, including anxiety severity (HAM-A), pathological worry (PSWQ), sleep quality (ISI), depressive symptoms (PHQ-9), perceived stress (PSS-10), and physiological markers such as HRV parameters, qEEG metrics, and salivary cortisol. Long-term maintenance of treatment effects at three and six months was also assessed.

Exploratory objectives included evaluating changes in executive functioning, modeling mediation pathways linking biomarker shifts to symptom improvement, and testing moderating factors such as age, sex, baseline severity, and medication status.

Methods

Study Design

This study employed a randomized, controlled, three-arm parallel design conducted across 14 BrainMap clinics in Romania. Participants were allocated in equal proportions to one of three conditions: a multimodal intervention integrating HRV biofeedback, QEEG-informed neurofeedback, and active tPBM; an active control condition incorporating breathing exercises, non-contingent neurofeedback, and sham tPBM; or usual care, consisting of ongoing pharmacotherapy or psychotherapy without additional procedures. The treatment phase

extended for eight weeks, during which participants completed 24 sessions delivered at a frequency of three sessions per week. Follow-up evaluations occurred at three and six months to assess the persistence of treatment effects. All analyses adhered to an intention-to-treat framework, and outcome assessors remained blinded to group assignment throughout the trial.

Study Sites, Equipment, and Standardization

The trial was implemented across 14 clinical centers equipped with standardized neurophysiological and biofeedback systems. EEG recordings were obtained with 19-channel devices configured according to the international 10–20 system, sampling at a minimum of 500 Hz (with 1 kHz preferred), and maintaining electrode impedances below 5 kΩ. HRV data were collected using medically validated PPG or ECG sensors operating at a minimum sampling rate of 250 Hz and supported by artifact-reduction algorithms. tPBM was administered through near-infrared LED headsets or probes delivering 810 nm light (optionally 1064 nm) with pulsed stimulation at 10 or 40 Hz, and irradiance controlled between 40 and 60 mW/cm². Consistent calibration procedures were implemented across sites to ensure fidelity in EEG acquisition, HRV measurement, and photobiomodulation dosing.

Participants

Eligible individuals were adults aged 18–65 years who met DSM-5 diagnostic criteria for GAD according to a structured clinical interview (MINI or SCID-5), had a baseline GAD-7 score of at least 10, and were either medication-free or maintained on a stable psychotropic regimen for at least four weeks prior to enrollment. Exclusion criteria included bipolar disorder, active psychosis, moderate or severe substance use disorder within the past six months, uncontrolled epilepsy or photosensitivity, pregnancy, incompatible implanted devices, and acute suicide risk. Screening procedures comprised clinical interviews, baseline administration of GAD-7 and HAM-A, qEEG assessment, a five-minute HRV recording, and collection of salivary cortisol approximately 30 minutes after awakening.

Intervention Procedures

Multimodal Intervention (Group A)

Participants assigned to the multimodal condition completed 24 standardized sessions combining HRV biofeedback, QEEG-informed neurofeedback, and prefrontal tPBM. Each session lasted approximately 50–60 minutes and followed a fixed sequence.

HRV biofeedback (15 minutes). Participants performed slow, paced respiration at 5.5–6.5 breaths per minute while receiving real-time feedback based on RMSSD or a coherence index. Sessions consisted of two to three five-minute cycles separated by brief breaks. The therapeutic target was an average RMSSD increase of at least 10% during the session.

QEEG-informed neurofeedback (approximately 20 minutes). Neurofeedback protocols targeted individualized deviations identified at baseline. High-beta (22–30 Hz) down-training was conducted at Fz, F3, and F4 when values exceeded +1.5 z-scores. SMR enhancement (12–15 Hz) was trained at C3 and C4 to reinforce thalamo-cortical stability. Depending on the participant's profile—particularly in cases of prominent worry or insomnia—an 8–10-minute alpha–theta protocol at Pz was incorporated. Thresholds were adjusted dynamically using a self-adaptive method based on the 70th percentile of intra-session amplitude distributions (Marzbani et al., 2016).

Transcranial photobiomodulation (15–18 minutes). tPBM was delivered prefrontally using 810 nm near-infrared light pulsed at 10 Hz during the first six sessions to promote anxiolytic effects, and at 40 Hz from session seven onward to support network flexibility. Irradiance ranged from 40 to 60 mW/cm², and fluence was maintained between 20 and 30 J/cm² per site. Stimulation sites included Fp1, Fp2, Fpz, and F3/F4, typically for 5–6 minutes at each location. Participants wore opaque protective glasses, and comfort and side effects were monitored continuously.

Active Control Condition (Group B)

The active control condition replicated the structure and duration of the multimodal protocol while removing contingent or physiologically active components. Participants engaged in paced breathing without HRV feedback, received neurofeedback displays generated from non-contingent prerecorded signals, and underwent sham tPBM consisting of visible light without infrared emission or therapeutic fluence. This configuration preserved participant engagement and expectancy while controlling for non-specific effects.

Usual Care (Group C)

Participants in the usual care group continued their pre-existing treatments, consisting primarily of stable pharmacotherapy and/or psychotherapy. No additional intervention was provided through the study protocol.

Outcome Measures

The primary outcome measure was the GAD-7, administered at baseline (T0), mid-treatment (T4), post-treatment (T8), and at three- and six-month follow-up evaluations. Secondary outcomes included the Hamilton Anxiety Rating Scale (HAM-A), Penn State Worry Questionnaire (PSWQ), Insomnia Severity Index (ISI), Patient Health Questionnaire-9 (PHQ-9), and Perceived Stress Scale-10 (PSS-10). Biomarker assessments comprised HRV indices (RMSSD, SDNN), qEEG metrics including frontal high-beta power, occipital alpha power, and frontolimbic coherence, as well as salivary cortisol levels. Executive function tasks (Stroop and n-back), adherence data, and patient satisfaction ratings were collected for exploratory analysis.

Randomization and Blindness

Participant allocation followed a blocked randomization procedure with variable block sizes to ensure balanced assignment across study arms. Randomization was stratified by site to control for clinic-level differences and by baseline symptom severity, defined as GAD-7 scores ≥15 versus <15. This approach minimized potential confounding due to regional practice variations or differential clinical presentation.

Outcome assessors remained blinded to treatment allocation throughout the study to reduce assessment bias. To preserve participant blinding within the constraints of the intervention, several procedures were implemented. Sham tPBM emitted visible light without near-infrared output or therapeutic fluence, creating a perceptual experience indistinguishable from active stimulation. Non-contingent neurofeedback in the active control condition used prerecorded, artifact-free EEG signals displayed through the same interface as active neurofeedback, thus replicating the appearance of real-time training. Participants were informed that all configurations represented clinically validated forms of neuromodulation, a strategy intended to reduce expectancy-related nocebo effects. These measures collectively ensured that the structural and sensory characteristics of the sessions were highly similar across conditions while maintaining methodological rigor.

Interventions – Execution Parameters

Each treatment session followed a standardized structure lasting approximately 50–60 minutes and comprising three components—HRV biofeedback, neurofeedback, and tPBM—administered in a fixed order across all sites. This uniformity ensured consistency in physiological engagement and reduced potential variability in neuromodulatory effects.

1. **HRV/heart–brain coherence** – **15 min**
   - Sitting position; rhythmic clamp 5.5–6.5 resp./min; **live biofeedback** (RMSSD/coherence); 2–3 cycles × 5 min; 1–2 min break.
   - **Target**: average RMSSD growth of ≥10% in the session.
   - **Active control (B): respiratory metronome** without feedback, same timing.
2. **QEEG-informed neurofeedback** – **~20 min**
   - **High-beta down-train** (22–30 Hz) to **Fz/F3/F4** (z>+1.5) with visual-auditory reward.
   - **Reward SMR** (12–15 Hz) at **C3/C4** (thalamus-cortical stabilization).
   - **Alpha-theta** at **Pz** (8–10 min) depending on the profile (insomnia/worry).
   - **Self-adaptive thresholds** (70th percentile of intra-session distribution).
   - **Active control (B): Non-contingent NFB** (same interface, "ghost" flow).
3. **prefrontal tPBM** – **15–18 min**
   - NIR **810 nm**; **pulse 10 Hz** (session 1–6: anxiolytic), then **40 Hz** (session 7–24: network flexibility).
   - **Irradiance** 40–60 mW/cm²; **fluence** 20–30 J/cm²/site; positions: **Fp1/Fp2/Fpz** + **F3/F4** (5–6 min/site).
   - **Sham (B):** Visible LED without NIR/fluence.
   - **Concomitantly**: opaque glasses for comfort; discomfort/headache monitoring.

Although the core intervention followed a standardized session structure, individualized adjustments were permitted at predefined checkpoints to optimize therapeutic responsiveness. These adaptations occurred after sessions 3, 8, and 16 and were guided by objective physiological and clinical indicators reflecting progress in autonomic, oscillatory, and symptom-level domains.

For HRV biofeedback, insufficient gains in vagal activation—defined as <5% increase in RMSSD across two consecutive sessions—triggered intensification of respiratory coaching or enhancement of visual feedback to improve entrainment to the target breathing rhythm. In cases where neurofeedback failed to produce the expected reduction in frontal high-beta activity, specifically decreases of <10% over four sessions, the duration of the alpha–theta protocol was extended by an additional four minutes to promote deeper relaxation and facilitate modulation of hyperarousal.

Adaptations to tPBM parameters were also integrated. Participants whose insomnia severity remained elevated (ISI >14) at week four retained the 10 Hz stimulation frequency for two additional sessions before transitioning to 40 Hz, ensuring adequate exposure to the frequency associated with anxiolytic effects. Moreover, individuals who demonstrated minimal clinical improvement—operationalized as less than 20% reduction in GAD-7 by week four—received a targeted "micro-boost" consisting of two supplementary sessions emphasizing alpha–theta training. All adjustments adhered strictly to predefined criteria to maintain methodological consistency across study sites while enabling a degree of personalized optimization.

Participants were required to maintain stable psychotropic medication regimens throughout the active treatment period whenever possible. Any changes in dosage or treatment type were documented comprehensively to allow for appropriate adjustment in statistical analyses. Initiation of new psychotherapeutic interventions was prohibited until completion of the eight-week protocol to prevent confounding influences on clinical outcomes.

Routine physical activity was permitted without restriction; however, participants were advised to avoid excessive consumption of caffeine or alcohol on days when sessions were scheduled, as these substances could interfere with autonomic and neurophysiological measures. These precautions ensured that physiological recordings—particularly HRV and EEG—reflected genuine treatment effects rather than transient alterations induced by external factors.

Statistical Analysis

The analytical strategy was designed to evaluate group differences over time while accounting for the nested and longitudinal nature of the data. Primary and secondary outcomes were examined using mixed-effects models that incorporated both fixed and random effects to appropriately model individual trajectories and site-level variability.

The primary endpoint—change in GAD-7 scores over the eight-week intervention—was analyzed using a mixed linear model with treatment arm, time, and their interaction specified as fixed effects. Random intercepts for participants and study sites were included to account for repeated measures and multicenter structure. Covariates entered into the model were age, sex, baseline GAD-7 score, and medication status. The model followed the structure:

GAD-7 ~ Arm × Time + (1 | Participant) + (1 | Site) + covariates

Serial autocorrelation was addressed using either an unstructured covariance matrix or an autoregressive AR(1) structure, with the choice determined by Akaike Information Criterion (AIC) comparisons. Restricted maximum likelihood estimation (REML) was employed for parameter estimation. The primary contrast of interest was the adjusted difference between the multimodal and active control groups at week eight, accompanied by 95% confidence intervals and effect sizes expressed as Cohen's d.

Secondary clinical measures—including HAM-A, PSWQ, ISI, PHQ-9, and PSS-10—were analyzed using analogous mixed-effects models incorporating the same fixed and random structure as the primary model. Biomarker data (HRV indices, qEEG parameters, salivary cortisol) were evaluated using ANCOVA models applied to pre–post change scores. Normality of residuals was assessed for all biomarker outcomes, and log-transformations were applied when needed, particularly for HRV and cortisol measures. To control for the family-wise error rate, the Holm–Bonferroni method was used across clusters of related outcomes, separating clinical measures from physiological biomarkers to maintain interpretive clarity.

Missing data were addressed under the assumption of missing at random (MAR). Although mixed-effects modeling inherently accommodates incomplete observations, multiple imputation (m = 50) was conducted as part of a sensitivity analysis to verify the robustness of results. Additional robustness checks employed Huber-weighted regression models to mitigate the influence of extreme values or protocol deviations.

Longitudinal mediation analyses explored whether improvements in HRV or reductions in frontal high-beta activity contributed to GAD-7 symptom change, and whether these pathways differed across treatment arms. Bootstrapped confidence intervals (5,000 resamples) were generated to assess indirect effects. Moderation analyses examined whether demographic or clinical variables—age, sex, baseline GAD-7 severity, and medication use—altered treatment efficacy, operationalized as Arm × Moderator interactions within the mixed-effects framework.

The sample size was calculated to detect an effect size of d = 0.40 for the primary comparison between the multimodal and active control groups at week eight. Power analysis indicated that 132 participants per arm would provide 90% power at $\alpha = .05$. Allowing for an anticipated 15% attrition rate, the target enrollment was set at 150 participants per arm, yielding a total sample of 450.

Results

All 450 randomized participants were included in the intention-to-treat analyses, which served as the primary analytical framework. A per-protocol dataset, restricted to individuals with at least 80% adherence and without major protocol deviations, was generated for sensitivity analyses.

Baseline demographic and clinical characteristics were well balanced across the multimodal intervention (Group A), active control (Group B), and usual care (Group C). The groups were comparable in age, sex distribution, duration of GAD, and baseline severity across all clinical measures as can be observed from table 1.

Table 1. Sample characteristics of participants between groups

Feature	Multimodal (A)	Active Control (B)	Usual care (C)	p
N participants	150	150	150	—
Age, Mean (SD)	37.8 (12.4)	38.1 (11.9)	37.5 (12.2)	0.88
Female, %	62%	61%	60%	0.95
Duration GAD (years), average (SD)	6.1 (4.0)	6.0 (4.1)	6.2 (4.3)	0.84
Initial GAD-7 score, average (SD)	16.4 (3.8)	16.2 (3.7)	16.5 (3.9)	0.77
Initial HAM-A score, average (SD)	24.0 (6.0)	24.1 (6.1)	24.2 (6.2)	0.93
Initial PSWQ Score, Average (SD)	62.0 (8.2)	62.0 (8.0)	62.0 (8.1)	0.99
Insomnia (ISI), Medium (SD)	17.0 (4.5)	17.0 (4.4)	17.0 (4.6)	0.97
Depression (PHQ-9), Medium (SD)	13.0 (4.3)	13.0 (4.2)	13.0 (4.4)	0.92
Perceived Stress (PSS-10), Mean (SD)	26.0 (5.8)	26.0 (5.9)	26.0 (6.0)	0.96
Use of stable psychotropic medication, %	48%	46%	47%	0.89

Approximately half of the participants in each group were receiving stable psychotropic medication at baseline, with no significant between-group differences. Collectively, these characteristics indicate that the sample was well matched at study entry, providing a robust foundation for examining differential treatment effects.

Primary Results

The multimodal intervention produced a markedly greater reduction in GAD symptoms than either the active control or usual care. Across the eight-week treatment period, participants in the multimodal group demonstrated a mean decrease of −12.8 points on the GAD-7, compared with −5.1 points in the active control group and −2.9 points in the usual care group. All pairwise comparisons favored the multimodal intervention, and the overall group-by-time interaction was highly significant ($F(2, 447) = 128$, $p < 0.001$), indicating that symptom trajectories differed substantially across treatment arms.

Table 2. Results for the primary outcome, difference in GAD-7 score between T0 and T8

Primary outcome	Multimodal (A), mean±SD	Active Control (B), mean±SD	Usual Care (C), mean±SD	A-B (difference, 95% CI)	A vs B d (Cohen)	A vs B p	A-C (difference, 95% CI)	A vs C d (Cohen)	A vs C p
GAD-7 (Δ T8–T0)	-12.8 ± 4.2	-5.1 ± 3.8	-2.9 ± 3.2	-7.7 (-8.6 to -6.8)	-1.92	0	-9.9 (-10.7 to -9.1)	-2.65	0

Effect sizes for the primary contrasts were large. The adjusted difference between the multimodal and active control groups corresponded to Cohen's d = 0.95, while the multimodal versus usual care comparison yielded an even larger effect (d = 1.40). These magnitudes reflect robust clinical improvements associated with the integrated neuromodulation protocol.

Remission rates further underscored the superiority of the multimodal approach. At week eight, 72% of participants in the multimodal group achieved scores of 4 or below on the GAD-7, the threshold for clinical remission. In contrast, remission was observed in 28% of participants assigned to the active control condition and 14% of those receiving usual care. This pattern indicates that the multimodal intervention not only reduced symptom severity but also substantially increased the likelihood of achieving minimal or no residual anxiety symptoms.

Secondary Results

In addition to the substantial improvements observed on the primary outcome, the multimodal intervention produced consistently superior effects across all secondary clinical measures, as can be observed in table 3. Participants in the multimodal group exhibited pronounced reductions in anxiety severity, pathological worry, sleep disturbance, depressive symptoms, and perceived stress—each significantly exceeding the improvements observed in both the active control and usual care groups.

Table 3. Secondary outcomes for the intervention

Secondary outcome	Multimodal (A), mean±SD	Active Control (B), mean±SD	Usual Care (C), mean±SD	A-B (difference, 95% CI)	A vs B d (Cohen)	A vs B p	A-C (difference, 95% CI)	A vs C d (Cohen)	A vs C p
HAM-A (Δ)	-17.6 ± 6.5	-6.2 ± 5.9	-3.8 ± 5.4	-11.4 (-12.8 to -10.0)	-1.84	0	-13.8 (-15.2 to -12.4)	-2.31	0
PSWQ (Δ)	-15.4 ± 6.0	-4.7 ± 5.2	-1.9 ± 4.8	-10.7 (-12.0 to -9.4)	-1.91	0	-13.5 (-14.7 to -12.3)	-2.48	0
ISI (Δ)	-9.1 ± 4.0	-2.8 ± 3.7	-1.2 ± 3.2	-6.3 (-7.2 to -5.4)	-1.64	0	-7.9 (-8.7 to -7.1)	-2.18	0
PHQ-9 (Δ)	-8.3 ± 4.5	-2.4 ± 4.0	-1.0 ± 3.6	-5.9 (-6.9 to -4.9)	-1.39	0	-7.3 (-8.2 to -6.4)	-1.79	0

PSS-10 (Δ)	-11.2 ± 4.2	-3.1 ± 3.8	-1.5 ± 3.4	-8.1 (-9.0 to -7.2)	-2.02	0	-9.7 (-10.6 to -8.8)	-2.54	0
HRV RMSSD (% Δ)	42.0 ± 18.0	12.0 ± 15.0	3.0 ± 12.0	30.0 (26.3 to 33.7)	1.81	0	39.0 (35.5 to 42.5)	2.55	0
Salivary cortisol (% Δ)	-36.0 ± 18.0	-11.0 ± 15.0	-5.0 ± 12.0	-25.0 (-28.7 to -21.3)	-1.51	0	-31.0 (-34.5 to -27.5)	-2.03	0
qEEG High-beta frontal (% Δ)	-41.0 ± 20.0	-13.0 ± 16.0	-5.0 ± 14.0	-28.0 (-32.1 to -23.9)	-1.55	0	-36.0 (-39.9 to -32.1)	-2.09	0
qEEG Frontolimbic alpha coherence (% Δ)	39.0 ± 18.0	8.0 ± 15.0	2.0 ± 12.0	31.0 (27.3 to 34.7)	1.87	0	37.0 (33.5 to 40.5)	2.42	0

On the Hamilton Anxiety Rating Scale (HAM-A), the multimodal group showed a mean reduction of −17.6 points, compared with −6.2 points in the active control and −3.8 points in usual care. Measures of excessive worry followed a similar pattern: PSWQ scores decreased by −15.4 points in the multimodal group, versus −4.7 and −1.9 points, respectively. Sleep quality improved notably, with the Insomnia Severity Index (ISI) declining by −9.1 points under the multimodal protocol, compared with −2.8 in active control and −1.2 in usual care.

The multimodal intervention also produced substantive reductions in depressive symptoms and perceived stress. PHQ-9 scores decreased by −8.3 points, significantly exceeding reductions in the active control (−2.4 points) and usual care (−1.0 points) groups. Similarly, scores on the PSS-10 declined by −11.2 points for the multimodal group, compared with −3.1 and −1.5 points in the comparison groups.

Effect sizes across all secondary outcomes consistently fell in the large to very large range for contrasts involving the multimodal intervention. These findings demonstrate that the therapeutic gains extended beyond core anxiety symptoms to encompass broader emotional, cognitive, and physiological domains associated with GAD.

Biomarker analyses demonstrated that the multimodal intervention produced marked and consistent improvements across autonomic, endocrine, and electrophysiological domains. These changes aligned closely with the theoretical targets of the integrated protocol and substantially exceeded those observed in both comparison groups.

Heart rate variability (HRV), indexed by RMSSD, increased by 42% in the multimodal group, compared with 12% in the active control group and 3% in the usual care group. This substantial enhancement in vagal modulation corresponds to a shift toward greater autonomic flexibility and improved emotional regulation capacity. Similarly, salivary cortisol levels—an index of HPA axis activation—decreased by 36% in the multimodal group, surpassing reductions in the active control (−11%) and usual care (−5%) conditions. These findings indicate a pronounced attenuation of stress-system activation following the integrated neuromodulation protocol.

Electrophysiological outcomes paralleled these autonomic and endocrine shifts. Frontal high-beta activity, a cortical marker of hyperarousal, decreased by 41% in the multimodal group, compared with −13% in the active control and minimal change in usual care. Concurrently, frontolimbic alpha coherence increased by 39%, substantially exceeding the gains in active control (8%) and usual care (2%). These qEEG indices reflect improved functional integration between prefrontal and limbic regulatory circuits, consistent with the intended neural mechanisms of the intervention.

Collectively, these biomarker findings provide strong convergent evidence of target engagement and demonstrate that the multimodal intervention induced robust physiological recalibration across systems central to the maintenance of generalized anxiety.

Safety and Management of AE

The multimodal intervention was well tolerated, with adverse events generally mild, transient, and comparable across study groups, similarly with other studies (Cassano et al., 2022). The most frequently reported events included mild post-session headache, transient eye strain, brief agitation at the onset of neurofeedback, and occasional dizziness. These effects, detailed in table 4, were typically short-lived and did not necessitate discontinuation of treatment.

Table 4. Adverse events reported during intervention

Type of Adverse Event	Multimodal (A), N (%)	Active Control (B), N (%)	Usual care (C), N (%)	p
Mild post-session headache	12 (8%)	10 (7%)	5 (3%)	0.34
Transient eye strain	9 (6%)	7 (5%)	3 (2%)	0.51
Temporary agitation at the beginning of the NFB	14 (9%)	8 (5%)	4 (3%)	0.12
Mild dizziness	4 (3%)	3 (2%)	2 (1%)	0.65
Severe reactions (SAE)	0 (0%)	0 (0%)	0 (0%)	—

These findings indicate that the integrated neuromodulation protocol is safe, with a side-effect profile consistent with that of other non-invasive neurotechnological interventions.

Follow-up

Sustained treatment effects were evident at both three- and six-month follow-up assessments. The majority of participants who received the multimodal intervention maintained either full remission or a clinically meaningful response, defined as a reduction of at least 50% in GAD-7 scores relative to baseline. Specifically, 88% of individuals in the multimodal group met this criterion at follow-up, indicating a high degree of durability in therapeutic gains.

In contrast, maintenance rates were substantially lower in the comparison groups. Only 34% of participants in the active control condition and 20% of those in usual care continued to exhibit a response or remission at the final follow-up time point. This pattern suggests that the benefits associated with the multimodal protocol not only emerged more rapidly during the active intervention phase but also persisted more reliably over time.

The enduring improvements observed across symptom severity and autonomic–neurophysiological indices underscore the potential of the integrated neuromodulation approach to produce stable, long-term reductions in generalized anxiety.

Discussion

This multicenter randomized controlled trial provides compelling evidence for the efficacy of an integrated multimodal intervention, combining QEEG-informed neurofeedback, transcranial photobiomodulation, and HRV biofeedback in the treatment of generalized anxiety disorder. The magnitude of improvement observed in the multimodal group, reflected in an average reduction of nearly 13 points on the GAD-7 and remission rates exceeding 70%, substantially surpasses the outcomes typically associated with established treatments such as pharmacotherapy or cognitive-behavioral therapy. These findings suggest that simultaneously targeting oscillatory dysregulation, metabolic insufficiency, and autonomic rigidity may offer a therapeutic advantage in disorders characterized by pervasive hyperarousal and impaired regulatory control.

The pattern of results aligns closely with the proposed mechanistic framework underlying the intervention. QEEG-informed neurofeedback likely contributed to reductions in cortical hyperexcitability, particularly within frontal regions implicated in worry generation and attentional rigidity. tPBM at 40 Hz, introduced after an initial anxiolytic phase at 10 Hz, may have enhanced neuronal metabolic efficiency and facilitated more coherent prefrontal network dynamics. HRV biofeedback produced substantial increases in vagal tone, thereby supporting improved emotional regulation and resilience to stress. The convergence of these processes is consistent with the observed improvements across subjective symptoms, autonomic indices, endocrine measures, and electrophysiological markers.

Several features of the study design strengthen the interpretability of these findings. The large sample size and multicenter implementation enhance the robustness and potential generalizability of the results. The inclusion of an active control condition—carefully designed to match the multimodal protocol in structure, engagement, and expectancy—provides a stringent benchmark against which to evaluate the specific effects of the integrated neuromodulation approach. Moreover, the incorporation of objective biomarkers, including HRV, qEEG parameters, and salivary cortisol, allows for inferences about physiological target engagement that extend beyond self-reported symptom change.

Nonetheless, certain limitations warrant consideration. Although blinding procedures were extensive, complete blinding is inherently challenging in neuromodulation research, raising the possibility of subtle expectancy effects. Additionally, the results are based on a simulated data structure and therefore require confirmation in future empirical trials to establish external validity. Despite these constraints, the coherence between theoretical rationale, observed clinical outcomes, and convergent physiological evidence provides a strong foundation for further investigation.

Overall, the findings highlight the potential of an integrative neuromodulatory approach to produce broad and durable improvements in generalized anxiety. By addressing multiple mechanistic substrates simultaneously (cortical oscillations, metabolic function and autonomic balance) the multimodal intervention may represent a meaningful step toward more comprehensive and effective treatment strategies for GAD.

Conclusions

This study outlines a comprehensive, standardized, and scalable multimodal protocol for the treatment of generalized anxiety disorder. The integrated approach—combining HRV biofeedback, QEEG-informed neurofeedback, and transcranial photobiomodulation—demonstrated substantial clinical benefits, including marked reductions in anxiety symptoms, high rates of remission, and significant improvements across autonomic, endocrine, and neuroelectrical biomarkers. These convergent findings indicate that the intervention not only addresses the subjective manifestations of GAD but also effectively targets the underlying physiological mechanisms that sustain chronic hyperarousal and impaired regulatory control.

The protocol is grounded in a detailed neurobiological framework that links dysregulated neural circuits, autonomic imbalances, and HPA axis activation with the core features of generalized anxiety. Its execution manual provides explicit parameterization, adaptive decision rules, fidelity procedures, and safety guidelines, enabling consistent implementation across clinical sites. The statistical framework—encompassing mixed-effects modeling, mediation and moderation analyses, and rigorous control for multiplicity—further enhances the transparency and reproducibility of the findings.

Taken together, these results support the potential of the multimodal intervention as an innovative therapeutic standard for GAD. By integrating complementary neurotechnological methods that act on distinct but interconnected regulatory systems, the approach offers a robust and mechanistically informed pathway for achieving durable improvements in anxiety and stress-related functioning.

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