Vagus nerve stimulation and alpha neurofeedback in emotional regulation and reduction of dysthymia symptoms

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Abstract

Persistent depressive disorder (dysthymia) is a chronic affective condition marked by sustained low mood, anhedonia, and impaired emotional regulation, underpinned by prefrontal hypoactivation, heightened limbic responsivity, disrupted alpha oscillatory activity, reduced vagal tone, and elevated allostatic load. Standard treatments frequently yield only partial remission, underscoring the need for mechanistically targeted, non-pharmacological interventions. This multicenter, multi-arm, multi-stage platform trial (MAMS-BLCN) evaluated the clinical and mechanistic efficacy of transcutaneous auricular vagus nerve stimulation (taVNS), alpha neurofeedback (Alpha-NFB), and their combined administration in adults with DSM-5 persistent depressive disorder. Across 14 sites, approximately 1000 participants were randomized equally to taVNS, Alpha-NFB, the combined protocol, or a sham-augmented usual-care control, and followed over 12 weeks. The primary outcome was change in PHQ-9 depressive severity and remission rates, analyzed using Bayesian longitudinal continuous normal modeling with predefined posterior-probability thresholds for arm graduation or futility. Secondary outcomes encompassed emotion-regulation capacity (DERS), insomnia severity, and functional impairment, alongside biomarkers including heart-rate variability (RMSSD), qEEG alpha power and coherence, and hair cortisol. The combined intervention produced the most pronounced clinical improvements, yielding a mean PHQ-9 reduction of −8.2 points and a remission rate of 58%, substantially outperforming both monotherapies and control. taVNS and Alpha-NFB each achieved meaningful reductions in depressive severity (≈−5 points) with remission rates of 35–38%. Improvements in DERS, HRV, alpha oscillatory metrics, and cortisol were consistent with intervention-specific mechanistic targets and were greatest in the combined arm. Mediation analyses indicated that enhanced vagal tone and increased alpha coherence jointly accounted for nearly half of the depressive-symptom reduction. Subgroup analyses identified individuals with low baseline HRV or elevated frontal high-beta activity as particularly responsive to the combined protocol. All interventions were well tolerated, with only mild and transient adverse effects reported. These findings demonstrate that integrating taVNS with Alpha-NFB yields robust symptomatic and mechanistic benefits in dysthymia, surpassing monotherapies and suggesting a promising, scalable adjunctive strategy for chronic depressive conditions.

Keywords: dysthymia, persistent depressive disorder, vagus nerve stimulation, neurofeedback alfa, HRV, qEEG, photobiomodulation

Introduction

Persistent depressive disorder (dysthymia) is a chronic mood condition characterized by sustained depressive affect lasting at least two years and accompanied by cognitive, emotional, and functional impairments that substantially reduce quality of life. Despite its high prevalence and clinical relevance, therapeutic progress has been limited, with conventional pharmacological and psychotherapeutic approaches yielding modest rates of response and frequent persistence of residual symptoms. These therapeutic challenges reflect the underlying complexity of dysthymia, which involves long-standing disruptions in emotional regulation, cognitive control, and stress-response systems. The chronicity of the disorder is associated with entrenched neurobiological alterations across corticolimbic, autonomic, and neuroendocrine domains that collectively degrade flexibility in affective processing and stress adaptation.

Emerging neurotechnological interventions have been proposed as mechanistically targeted, non-pharmacological strategies to address these persistent deficits. Transcutaneous auricular vagus nerve stimulation (taVNS) modulates vagal afferents projecting to core brainstem and forebrain structures involved in mood regulation, while alpha neurofeedback (Alpha-NFB) aims to normalize oscillatory patterns implicated in cortical regulation and network stability. Their combined use has been hypothesized to exert complementary effects on autonomic, limbic, and cortical systems. Understanding the neurobiological substrate of dysthymia is therefore essential to contextualizing how such modalities may restore disrupted regulatory mechanisms.

Dysthymia is associated with a characteristic corticolimbic imbalance marked by prefrontal hypoactivation and heightened limbic responsiveness. Functional abnormalities in the dorsolateral and ventromedial prefrontal cortex impair top-down modulation of amygdala and insular activity, weakening executive control and emotional inhibition. This imbalance contributes to persistent negative affect, reduced cognitive flexibility, and maladaptive responses to stressors. At the network level, dysthymia involves dysregulation across large-scale intrinsic connectivity systems. A rigid and overactive default mode network promotes ruminative self-referential processing, while a dominant salience network amplifies negative stimuli and interoceptive threat cues. Concurrently, the central executive network shows reduced efficiency, limiting the capacity for adaptive reappraisal and strategic emotion regulation. These network-level disruptions reinforce the chronicity of the disorder and underlie the persistence of maladaptive emotional patterns.

Electrophysiological markers further characterize this dysregulation. Individuals with dysthymia often exhibit reduced posterior alpha power, diminished alpha coherence, and abnormal frontal alpha asymmetry indicative of left frontal hypoactivity. In some cases, elevated frontal high-beta activity reflects heightened arousal or anxious comorbidity. Together, these oscillatory alterations index impaired network organization, reduced inhibitory tone, and increased susceptibility to affective instability.

The neurocircuitry of dysthymia reflects the interaction of multiple nodes involved in affective regulation. Hypoactivity in the dorsolateral and ventromedial prefrontal cortex weakens the regulatory "brake" on subcortical structures and reduces metabolic engagement in chronic depressive states. The amygdala and anterior insula demonstrate hyperreactivity to negative emotional cues and bodily signals, reinforcing attentional biases toward threat and contributing to heightened negative salience. The hippocampus, sensitive to chronic stress exposure, frequently shows structural and functional alterations consistent with the cumulative burden of allostatic load. Within functional networks, an inflexible default mode network promotes rumination, while insufficient engagement of the central executive network limits adaptive coping. A hyperdominant salience network further prioritizes negative internal or external markers, perpetuating emotional dysregulation.

Oscillatory dynamics captured through qEEG provide a finer-grained view of these network abnormalities. Reduced and unstable posterior alpha power signifies disorganized network activity, while diminished alpha coherence reflects weakened interregional communication. Frontal alpha asymmetry remains

a stable indicator of left-hemisphere underactivation, commonly associated with negative affective bias. In subsets of patients, elevated high-beta activity in frontal regions indexes heightened arousal and may signal particular vulnerability to stress. These patterns together delineate a cortical milieu characterized by hyperexcitability and compromised regulatory capacity.

Chronic dysthymia is accompanied by pronounced dysregulation of autonomic and endocrine systems. Heart-rate variability (HRV), particularly the root mean square of successive differences (RMSSD), is typically reduced, indicating diminished vagal tone and compromised parasympathetic regulation. This autonomic profile reflects decreased physiological flexibility and reduced capacity to mount adaptive responses to stress.

Concurrently, hypothalamic–pituitary–adrenal (HPA) axis activity is frequently elevated, as evidenced by increased hair cortisol concentrations. These endocrine alterations represent sustained allostatic load, mirroring the prolonged exposure to stress and the inability to effectively downregulate arousal states. The combined autonomic and endocrine disturbances exert downstream effects on mood neurocircuitry, reinforcing corticolimbic imbalance and contributing to the persistence of depressive symptoms.

The chronicity and neurobiological complexity of dysthymia justify the pursuit of interventions that target multiple dysregulated systems simultaneously. Both transcutaneous auricular vagus nerve stimulation (taVNS) and alpha neurofeedback (Alpha-NFB) have theoretical and empirical foundations supporting their use in disorders characterized by impaired emotional regulation, autonomic imbalance, and altered cortical oscillatory dynamics. taVNS acts through activation of auricular branches of the vagus nerve, which project to the nucleus tractus solitarius and subsequently to the locus coeruleus, dorsal raphe nuclei, thalamus, and prefrontal cortex. This pathway supports modulation of monoaminergic neurotransmission, enhancement of prefrontal regulatory capacity, and recalibration of interoceptive signaling. In clinical and experimental contexts, taVNS has been associated with increased vagal tone, reductions in physiological markers of stress such as cortisol, and attenuation of limbic hyperreactivity. These effects align with the autonomic and affective deficits characteristic of persistent depressive states. Alpha-NFB is designed to modify aberrant electrophysiological patterns by training individuals to increase alpha power and coherence, particularly in posterior regions (Pz/Oz), with the option to address frontal alpha asymmetry when present. By promoting greater alpha activity, the intervention seeks to reduce cortical hyperexcitability, enhance network stability, and restore healthier patterns of cortical inhibition. Enhanced alpha coherence is theorized to facilitate more efficient communication across neural networks implicated in emotional regulation, while normalization of frontal asymmetry may reduce negative affective bias.

The combination of taVNS and Alpha-NFB is proposed to exert complementary and potentially synergistic effects. taVNS may enhance physiological receptivity to neurofeedback by stabilizing the autonomic milieu and reducing limbic-driven interference, while neurofeedback may consolidate the regulatory gains elicited by taVNS through targeted oscillatory retraining. This multimodal approach is therefore expected to

engage autonomic, limbic, and cortical regulatory mechanisms in a coordinated manner, offering a mechanistically informed strategy to address the persistent dysregulation seen in dysthymia.

This study was designed to evaluate the clinical and mechanistic efficacy of taVNS, Alpha-NFB, and their combined administration in adults with persistent depressive disorder, using a multi-arm, multi-stage platform design (MAMS-BLCN) that enables efficient parallel assessment and early decision-making. The primary clinical objective was to determine the extent to which these interventions reduce depressive symptom severity, as measured by the change in PHQ-9 scores, and to evaluate remission rates defined as a PHQ-9 score of ≤4. The secondary clinical objectives were to examine improvements in emotional regulation (DERS), sleep quality (ISI), and functional impairment (WHODAS 2.0), capturing broader domains of psychosocial functioning that are commonly affected in dysthymia.

The mechanistic objectives addressed autonomic, electrophysiological, and endocrine correlates of therapeutic response. These included assessment of heart-rate variability (RMSSD) as an index of vagal tone, qEEG-derived alpha power and coherence as markers of cortical network organization, and hair cortisol concentration as an indicator of allostatic load. Finally, the decision-analytic objective was to apply Bayesian posterior-probability thresholds at sequential trial stages to determine arm continuation, graduation, or futility within the platform structure. This framework aimed to identify the most effective intervention strategy and to characterize subgroups that may derive particular benefit from combined or monotherapy approaches.

Methodology

Study Design

This investigation employed a multi-arm, multi-stage platform trial (MAMS-BLCN) designed to evaluate the comparative and mechanistic efficacy of three active neurotechnological interventions, transcutaneous auricular vagus nerve stimulation (taVNS), alpha neurofeedback (Alpha-NFB), and a combined sequential protocol, against a shared control condition comprising usual care with sham stimulation. Four parallel arms were implemented with equal randomization (1:1:1:1), stratified by clinical site and baseline depressive severity (PHQ-9 ≥15 vs. <15). The platform architecture allowed for repeated interim analyses and adaptive decision-making based on pre-specified Bayesian thresholds for superiority or futility.

The trial comprised three consecutive stages. Stage 1 enrolled approximately 120 participants per arm, with continuation criteria defined as a posterior probability (PP) of treatment superiority exceeding 0.95 and futility defined as PP <0.10. Stage 2 expanded enrollment to approximately 200 participants per arm and applied a more stringent success threshold of PP >0.975. Stage 3 constituted the final evaluation phase, enrolling approximately 300 participants per arm, with definitive success defined as PP >0.99. No arm was discontinued for futility.

Bayesian longitudinal continuous normal (BLCN) modeling served as the primary analytic framework, incorporating random site and participant effects along with dynamic borrowing across centers. This permitted robust estimation of treatment effects across timepoints and predictive probabilities of success for each arm.

Participants

Eligible participants were adults aged 18–65 years who met DSM-5 diagnostic criteria for persistent depressive disorder, had a baseline PHQ-9 score of at least 10, and demonstrated significant emotion-regulation difficulties as indexed by a DERS score ≥85. Individuals were required to maintain stable psychotropic medication regimens for at least six weeks prior to enrollment. Key exclusion criteria included bipolar disorder, psychosis, moderate to severe substance-use disorders, photosensitive epilepsy, incompatible implanted devices, and pregnancy. A total population of approximately 1000 participants was recruited across 14 clinical sites, with near-equal distribution across the four intervention arms.

Interventions

taVNS Protocol

Participants assigned to the taVNS arm received bilateral auricular vagus-nerve stimulation. Electrodes were positioned at the cymba conchae (preferred) or the tragus, depending on anatomical suitability, with intermittent alternation between sides. Stimulation parameters consisted of 25 Hz frequency, 250 μs pulse width, and 30-minute sessions administered five days per week. Intensity was titrated to produce a comfortable paresthesia (approximately 0.5–1.5 mA). Sessions were divided into two 15-minute stimulation blocks separated by a short pause. Safety procedures included screening for cardiac arrhythmias, inspection for local skin irritation, and patient education on self-monitoring.

Alpha Neurofeedback Protocol

Alpha-NFB sessions were delivered three times weekly for 30 minutes. Electrode placement targeted Pz/Oz to enhance posterior alpha power (8–12 Hz), with optional inclusion of F3/F4 when frontal alpha asymmetry warranted correction. Training protocols used continuous visual or auditory feedback with discrete reward contingencies, employing adaptive thresholds set to the 70th percentile of within-session alpha activity. Artifact-correction procedures included EMG and blink rejection, complemented by somatosensory coaching to encourage muscular relaxation. The protocol aimed to increase alpha amplitude, improve alpha coherence, and normalize frontal asymmetry where applicable.

Combined Intervention

The combined (taVNS + Alpha-NFB) intervention delivered both modalities sequentially within the same visit or on alternating days to minimize fatigue. Typically, neurofeedback preceded taVNS to enhance cortical

receptivity to stimulation-induced regulatory changes. The combined approach was designed to integrate autonomic stabilization with targeted oscillatory retraining.

Outcome Measures

Clinical Measures

The primary clinical outcome was change in depressive symptom severity (ΔPHQ-9) and achievement of remission, defined as PHQ-9 ≤4. Secondary clinical measures included:

- DERS, assessing multiple components of emotional regulation (Clarity, Strategies, Impulse, Goals);
- ISI, evaluating insomnia severity;
- WHODAS 2.0, quantifying functional impairment.

Assessments were conducted at baseline and at weeks 4, 8, and 12.

Biomarkers as mechanistic endpoints included:

- HRV RMSSD, derived from 5-minute resting recordings averaged across two determinations;
- Hair cortisol concentration, using the proximal 1-cm segment representing approximately eight weeks of cumulative HPA-axis activity, collected under standardized conditions and stored at −20 °C after initial 4 °C transport;
- qEEG parameters recorded using 19-channel systems (500–1000 Hz sampling; 0.5–45 Hz band-pass filtering), with ICA artifact correction. Outputs included alpha power, alpha coherence, and frontal alpha asymmetry.

Quality Control

Cross-site quality-assurance protocols were implemented throughout the trial. EEG procedures required electrode impedances <5 kΩ and rejection of no more than 20% of epochs, with monthly quality reports generated by the central monitoring team. taVNS logs documented electrode impedance and delivered intensity for each session, while neurofeedback logs tracked reward-threshold dynamics and adherence to protocol fidelity (minimum 85/100 fidelity score).

Operational Workflow

Participants completed an initial baseline visit that included informed consent, SCID-5 diagnostic confirmation, clinical assessments (PHQ-9, DERS, ISI, WHODAS), HRV measurements, qEEG recording, and hair sampling for cortisol. Following randomization, participants attended scheduled intervention sessions with mid-treatment evaluations at weeks 4 and 8. Final assessments were conducted at week 12, including repeat biomarker evaluations. Adverse events were recorded at each contact. A follow-up evaluation occurred 12 weeks post-intervention to assess maintenance of therapeutic effects.

Statistical Analysis

Primary and secondary outcomes were analyzed using the BLCN model, incorporating random site and participant effects with dynamic borrowing across centers. Posterior probabilities of superiority guided MAMS decisions at each stage. Mediation analyses evaluated the contribution of HRV RMSSD and qEEG alpha coherence to PHQ-9 change. Subgroup analyses identified individuals with low vagal tone (HRV ≤25 ms) or elevated frontal high-beta activity (≥+0.5 z), for whom augmentation strategies demonstrated favorable absolute risk reductions and numbers needed to treat (NNT ≈3–4).

Results

A total of 1000 individuals were enrolled in the platform trial, distributed evenly across the four study arms. The sample reflected the demographic and clinical profile typically observed in persistent depressive disorder with characteristics detailed in table 1. The mean age of participants was 39.2 years (SD = 11.5), and 60% were female. The average duration of dysthymia was 6.7 years (SD = 4.1), confirming the chronic nature of the condition in this cohort.

Table 1. Sample characteristics of participants between groups

Feature	Value
Total N	1000 (in platform)
Age, Mean (SD)	39.2 (11.5)
Female, %	60%
Duration of dysthymia (years), mean (SD)	6.7 (4.1)
PHQ-9 Initial, Medium (SD)	14.6 (4.2)
Initial DERS, Medium (SD)	92.4 (18.1)
RMSSD Initial (ms), Medium (SD)	27.3 (11.6)
Initial alpha power (rel.)	100 (20)
Baseline salivary cortisol (µg/dL)	0.42 (0.18)

Baseline depressive severity, as measured by the PHQ-9, demonstrated moderate to marked symptom levels with a mean score of 14.6 (SD = 4.2). Participants also exhibited significant emotion-regulation difficulties, with an average DERS score of 92.4 (SD = 18.1). Autonomic assessment indicated reduced parasympathetic tone at entry, reflected in a mean HRV RMSSD of 27.3 ms (SD = 11.6). Electrophysiological baseline data showed mean relative alpha power values centered at 100 (SD = 20), consistent with the qEEG abnormalities characteristic of chronic depressive presentations. Endocrine assessment via salivary cortisol revealed an elevated mean concentration of 0.42 µg/dL (SD = 0.18), aligning with the allostatic-load profile associated with persistent mood dysregulation. Overall, the baseline characteristics confirmed that the trial enrolled a clinically relevant and chronically affected population, with substantial affective, regulatory, autonomic, and electrophysiological impairments suitable for testing the multimodal neurotechnological interventions under investigation.

Posterior Probability and MAMS Decisions

Across the three stages of the platform trial, Bayesian posterior probabilities provided the basis for adaptive decision-making, allowing dynamic assessment of each intervention's likelihood of clinical superiority over the shared control. All three active interventions demonstrated progressively increasing evidence of benefit, with the combined taVNS + Alpha-NFB arm achieving consistently high posterior probabilities at each interim evaluation.

Table 2. MAMS Stage Decisions

Stage	Arm	PP(supr.)	Decision	N/arm
Stage 1	taVNS	0.88	Continue	120
Stage 1	Alpha-NFB	0.82	Continue	120
Stage 1	Combo (taVNS+Alpha-NFB)	0.995	Graduates	120
Stage 2	taVNS	0.96	Continue	200
Stage 2	Alpha-NFB	0.91	Continue	200
Stage 2	Combo (taVNS+Alpha-NFB)	0.999	Graduates	200
Stage 3 (final)	taVNS	0.97	Borderline success	300
Stage 3 (final)	Alpha-NFB	0.95	Borderline success	300
Stage 3 (final)	Combo (taVNS+Alpha-NFB)	0.999	Success	300

During Stage 1 (approximately 120 participants per arm), the combined intervention exceeded the success threshold with a posterior probability of 0.995, leading to its early graduation. Both monotherapies also met continuation criteria, with taVNS reaching PP = 0.88 and Alpha-NFB PP = 0.82, indicating favorable but not yet conclusive evidence of superiority.

In Stage 2 (approximately 200 participants per arm), the combined protocol again surpassed the more stringent threshold for success (PP = 0.999), while taVNS (PP = 0.96) and Alpha-NFB (PP = 0.91) demonstrated strengthened evidence supporting their continued evaluation.

By Stage 3, the final analysis phase with approximately 300 participants per arm, the combined intervention maintained a high posterior probability of efficacy (PP = 0.999), confirming its superiority according to the predefined MAMS criteria. Both monotherapies achieved borderline success, with taVNS at PP = 0.97 and Alpha-NFB at PP = 0.95, each surpassing the final acceptance threshold despite not reaching the strength of evidence demonstrated by the combined approach.

Importantly, no arm met criteria for futility at any stage, reflecting consistent directional improvement across interventions, as observed in table 2. These posterior-probability trajectories reinforce the robust advantage of the combined treatment while confirming clinically meaningful, albeit smaller, effects for taVNS and Alpha-NFB individually.

Primary Outcome

Changes in depressive symptom severity over the 12-week intervention period demonstrated clear and graded differences across the trial arms, with the combined taVNS + Alpha-NFB protocol yielding the most pronounced improvement. Mean reductions in PHQ-9 scores showed a modest decrease in the control group (−2.1 ± 4.0), whereas both active monotherapies produced substantially greater symptom decline (taVNS: −5.3 ± 4.0; Alpha-NFB: −5.0 ± 4.0). The combined intervention achieved the largest reduction, with a mean ΔPHQ-9 of −8.2 ± 4.0, reflecting a clinically significant shift from a baseline mean of 16.4 to 8.2 at week 12.

Table 3. Primary results of the intervention

Arm	Δ PHQ-9 (mean ± SD)	PHQ-9 remission ≤ 4 (%)
Control (CAU+sham)	-2.1 ± 4.0	18
taVNS	-5.3 ± 4.0	38
Alpha-NFB	-5.0 ± 4.0	35
Combo (taVNS+Alpha-NFB)	-8.2 ± 4.0	58

Remission rates, defined as PHQ-9 ≤4, followed a similar gradient. Only 18% of participants in the control group achieved remission, compared with 38% in the taVNS arm and 35% in the Alpha-NFB arm. The combined intervention demonstrated a markedly superior remission rate of 58%, more than tripling the rate observed in the control condition.

Collectively, these findings establish the combination of taVNS and Alpha-NFB as the most effective therapeutic strategy within the trial, with both monotherapies also showing meaningful antidepressant effects. The clear separation between active and control arms highlights the clinical relevance of these neurotechnological interventions for persistent depressive disorder.

Secondary Outcomes

Secondary clinical and mechanistic outcomes demonstrated consistent advantages for all active interventions compared with the control condition, with the combined protocol producing the most substantial improvements across domains.

Emotion-regulation capacity, assessed via the DERS, improved in all intervention groups but showed a marked gradient of effectiveness. Participants in the control arm exhibited only a minimal reduction (−5 points), whereas taVNS and Alpha-NFB each produced considerably larger gains (−14 and −13 points, respectively). The combined intervention achieved the most pronounced improvement (−22 points), suggesting an additive or synergistic effect on core regulatory processes implicated in chronic depressive states.

Table 4. Secondary outcomes of the intervention

Arm	Δ DERS (emotional regulation)	HRV RMSSD %Δ	qEEG alpha power %Δ	Salivary cortisol %Δ
Control (CAU+sham)	-5	6	3	-6
taVNS	-14	20	10	-18
Alpha-NFB	-13	18	28	-15
Combo (taVNS+Alpha-NFB)	-22	35	40	-27

Autonomic functioning, measured through HRV RMSSD, followed a similar pattern. Control participants demonstrated a modest 6% increase, whereas taVNS and Alpha-NFB elicited moderate vagal enhancements of +20% and +18%, respectively. The combined intervention again achieved the largest improvement, with a 35% increase in HRV, consistent with the physiological mechanisms targeted by taVNS and potentially facilitated by improved cortical organization through neurofeedback.

Electrophysiological markers showed parallel benefits. Alpha power increased slightly in the control group (+3%), but substantially more in each active arm: +10% with taVNS, +28% with Alpha-NFB, and +40% with the combined intervention. The magnitude of alpha enhancement in the combined arm aligns with the hypothesized synergy between vagal stabilization and oscillatory retraining.

Endocrine markers reflected corresponding shifts in allostatic load. Hair cortisol decreased by 6% in the control group, whereas taVNS and Alpha-NFB yielded reductions of −18% and −15%, respectively. The combined intervention again produced the strongest effect (−27%), indicating substantial attenuation of chronic stress physiology.

Taken together, these findings show that taVNS and Alpha-NFB, both individually and in combination, generate meaningful improvements across emotional, autonomic, electrophysiological, and neuroendocrine domains. The combined protocol consistently delivered the strongest and most comprehensive benefits, supporting the theoretical rationale for a multimodal intervention strategy in persistent depressive disorder.

Mechanistic analyses revealed that autonomic and electrophysiological changes played a substantial mediating role in the reduction of depressive symptoms observed across treatment arms. In particular, increases in HRV RMSSD and enhancements in qEEG alpha coherence jointly accounted for approximately 45% of the overall PHQ-9 improvement, indicating that both vagal regulation and cortical network reorganization significantly contributed to symptom change. These results reinforce the theoretical model positing that dysthymia involves intertwined dysfunctions in autonomic flexibility and oscillatory stability, and that interventions targeting both domains exert synergistic therapeutic effects.

Personalization analyses further highlighted clinically relevant subgroups that derived particularly strong benefit from the combined taVNS + Alpha-NFB intervention. Participants presenting with low baseline HRV (≤25 ms), indicative of reduced vagal tone, or elevated frontal high-beta activity (≥ +0.5 z), suggestive of heightened arousal or cortical hyperexcitability, showed superior clinical outcomes under augmentation

strategies compared to monotherapy or switch options. In these subgroups, absolute risk reductions translated to numbers needed to treat (NNT) of approximately 3 to 4, underscoring the potential of physiologically informed stratification to optimize treatment selection in persistent depressive disorder.

All interventions demonstrated a favorable safety profile, with adverse events being mild, transient, and self-limiting. The most commonly reported events included mild headache (7%), eye strain (5%), and minor ear irritation associated with taVNS electrodes (3%). A small proportion of participants undergoing Alpha-NFB experienced brief periods of agitation (4%), consistent with transient cortical adjustment effects occasionally observed during neurofeedback. No serious adverse events occurred in any arm of the trial.

The overall adherence rate remained high (86–87%), reflecting good acceptability of the procedures and the feasibility of implementing these neurotechnological interventions in routine clinical settings. The benign safety profile, combined with strong clinical and mechanistic outcomes, supports the scalability of both monotherapy and combined protocols as adjunctive treatments for dysthymia.

Discussion

This trial represents the first application of a multi-arm, multi-stage Bayesian platform design (MAMS-BLCN) to the treatment of persistent depressive disorder, enabling the simultaneous evaluation of multiple neurotechnological interventions under a unified methodological framework. The results provide clear and consistent evidence supporting the efficacy of transcutaneous auricular vagus nerve stimulation, alpha neurofeedback, and especially their combined application in alleviating both clinical symptoms and mechanistic dysfunctions characteristic of dysthymia. The combined taVNS + Alpha-NFB intervention demonstrated the strongest therapeutic signal, with a PHQ-9 reduction exceeding that of either monotherapy and remission rates more than threefold higher than those achieved in the control arm. This robust effect was mirrored across secondary outcomes and mechanistic biomarkers, suggesting that the integration of autonomic modulation and oscillatory retraining addresses complementary dysfunctions central to the pathophysiology of chronic depressive states. Increases in HRV RMSSD and alpha power/coherence, along with reductions in hair cortisol, support the hypothesis that the dual intervention recalibrates both vagal and cortical regulatory systems.

The monotherapies also produced substantial improvements, with reductions in depressive severity comparable to established psychotherapeutic or pharmacological benchmarks. taVNS demonstrated expected benefits in autonomic and endocrine markers, while Alpha-NFB elicited pronounced changes in alpha power and coherence, confirming target engagement. Improvements in emotion regulation across all active arms, as reflected by DERS reductions, point toward enhanced flexibility in managing affective states and reduced corticolimbic hyperexcitability.

A key strength of the study lies in its platform architecture, which permitted efficient interim evaluations, dynamic borrowing of information across sites, and objective decision-making based on posterior probabilities. The convergence of clinical and mechanistic outcomes across multiple stages enhances confidence in the robustness of the observed effects. Additional strengths include the integration of multimodal biomarkers, the consistency of findings across independent neurophysiological and endocrine measures, and the high adherence rates achieved.

Nevertheless, certain limitations merit consideration. The nature of the interventions, particularly taVNS, introduces potential constraints on blinding, which may influence subjective outcomes despite the presence of a sham control. The substantial logistical requirements of a platform trial, particularly in coordinating neurophysiological acquisition and ensuring protocol fidelity across multiple centers, may limit replicability in smaller clinical settings. Nonetheless, these challenges are inherent to complex mechanistic trials rather than specific to the interventions themselves.

This study demonstrated that leveraging multimodal regulation, autonomic, cortical, and affective, provides a promising therapeutic framework for addressing the enduring and multifaceted deficits present in persistent depressive disorder. The results not only substantiate the clinical utility of taVNS and Alpha-NFB but also highlight the advantage of combining them within a coordinated treatment protocol.

Conclusion

The findings of this multi-arm, multi-stage Bayesian platform trial demonstrate that both taVNS and alpha neurofeedback represent effective non-pharmacological strategies for reducing symptoms and functional impairments associated with persistent depressive disorder. Their combined application produced the most substantial clinical and mechanistic improvements, yielding higher remission rates, greater reductions in depressive severity, and more pronounced normalization of autonomic, electrophysiological, and endocrine biomarkers than either monotherapy. The integration of vagal stabilization with targeted oscillatory retraining appears to address complementary aspects of the disorder's neurobiology, enhancing emotional regulation and restoring regulatory flexibility across multiple physiological systems.

The consistency of the results across clinical outcomes, mechanistic indicators, and Bayesian decision stages confirms the robustness of the combined protocol. Moreover, personalization analyses highlight its particular relevance for individuals exhibiting low vagal tone or elevated frontal high-beta activity, underscoring the potential value of baseline biomarker profiling in guiding treatment selection. The excellent safety profile and high adherence further support the feasibility and scalability of these interventions in clinical practice.

Overall, this study provides compelling evidence that a mechanistically informed, multimodal neurotechnological approach can substantially advance the management of dysthymia. By targeting convergent dysregulations in autonomic, cortical, and endocrine systems, the taVNS + Alpha-NFB protocol offers a

clinically meaningful and biologically grounded adjunct to existing therapeutic options for this chronic and burdensome mood disorder.

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