Neuro-regulation of depression with associated anxiety through adaptive protocols (SMART): starting with Neurofeedback or tPBM and augmentation/switch decisions based on early response

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Abstract

This study examines an adaptive treatment strategy for major depressive episodes with anxious distress using a Sequential Multiple Assignment Randomized Trial (SMART) framework. Given the heterogeneity of therapeutic response, the design aimed to identify optimal treatment sequences involving neurofeedback (NFB) and prefrontal transcranial photobiomodulation (tPBM). Six hundred participants across 14 clinical centers were randomized to begin with either NFB or tPBM. At week 4, treatment decisions were based on early response, defined as a ≥35% reduction in PHQ-9 scores. Responders continued their initial modality, whereas non-responders were re-randomized to either augmentation (combination of NFB and tPBM) or a full switch to the alternative modality. The primary endpoint was remission at week 8 (PHQ-9 ≤ 4), with secondary outcomes including changes in PHQ-9, GAD-7, and ISI scores, as well as heart rate variability (HRV) and frontal high-beta activity. Early response rates were 45% for the NFB-start arm and 40% for the tPBM-start arm. Among non-responders, augmented strategies produced the highest remission rates: 72% for NFB→Augment and 65% for tPBM→Augment, compared with 54% and 50% in the respective switch regimens. Augmented pathways were also associated with greater improvements in HRV and larger reductions in high-beta activity. Follow-up assessments at 12 weeks showed sustained remission, particularly among participants receiving augmentation. Adverse events were mild, with no serious events reported. Results demonstrate that, within an adaptive treatment framework, augmentation at week 4 yields superior symptomatic and physiological outcomes compared with switching strategies. The results support a pragmatic, personalized algorithm for managing depression with comorbid anxiety, positioning NFB→Augment as the most effective dynamic treatment regimen.

Keywords: neurofeedback; transcranial photobiomodulation; adaptive treatment; SMART design; depressive disorder; anxious distress; dynamic treatment regimen; neuromodulation biomarkers.

Introduction

Major depressive episodes characterized by anxious distress represent a clinically complex and heterogeneous subgroup, often marked by fluctuating symptom patterns, variable treatment trajectories, and reduced responsiveness to standard monotherapy. Conventional approaches that apply a uniform intervention across all patients tend to overlook the substantial variability in neurophysiological profiles, symptom severity, and early treatment response present within this population. As a result, therapeutic outcomes remain inconsistent, underscoring the need for personalized strategies capable of adjusting dynamically to individual progress.

Sequential Multiple Assignment Randomized Trial (SMART) designs offer a methodological framework suited to constructing and evaluating adaptive, multi-stage treatment regimens. By integrating early response markers into predefined decision rules, SMART methodologies allow for the systematic comparison of alternative

therapeutic pathways and the identification of optimal dynamic treatment regimens. This structure enables investigators to tailor interventions based on patient-specific evolution, thereby increasing both clinical efficiency and ecological validity.

Within this context, two non-pharmacological neuromodulation therapies—neurofeedback (NFB) and transcranial photobiomodulation (tPBM)—have emerged as promising options. NFB aims to reshape maladaptive neural oscillatory patterns, particularly those associated with dysregulated fronto-limbic connectivity. Protocol components such as high-beta down-training, enhancement of sensorimotor rhythm, and alpha–theta modulation target distinct neurophysiological processes linked to affective regulation. Conversely, tPBM utilizes near-infrared light (810 nm) to modulate prefrontal cortical metabolism and facilitate improved neuronal synchronization, potentially supporting cognitive-emotional integration and resilience. Although each modality can be effective as a standalone intervention, their mechanistic complementarity suggests that sequential or combined administration may yield additive or synergistic benefits.

The present SMART trial was designed to evaluate two stages of therapeutic decision-making: an initial randomization to either NFB or tPBM, followed by an adaptive augmentation or switch strategy at four weeks for individuals who do not show early clinical improvement. By integrating symptom trajectories, neurophysiological biomarkers, and dynamic treatment decisions, the study seeks to determine which sequences produce the most favorable outcomes and whether augmentation consistently outperforms switching. This approach ultimately aims to generate an evidence-based, scalable algorithm that can inform clinical practice and support personalized intervention pathways for depression with associated anxiety.

Methodology

This study employed a multicenter Sequential Multiple Assignment Randomized Trial (SMART) design intended to identify optimal adaptive treatment strategies for individuals experiencing a major depressive episode with anxious distress. Fourteen clinical sites participated, collectively enrolling 600 adults. The trial was structured into two distinct stages, with treatment decisions contingent upon early clinical response assessed at the four-week mark.

In Stage 1 (weeks 0–4), participants were randomized in a 1:1 ratio to begin treatment with either neurofeedback (NFB Start) or transcranial photobiomodulation (tPBM Start). Early clinical response was determined at week 4 using the PHQ-9, with response defined as a reduction of at least 35% from baseline. Responders continued with their initial treatment assignment through week 8. Non-responders underwent a second randomization (1:1) to one of two adaptive pathways: augmentation—continuing the initial therapy while adding the alternative modality—or full switch, characterized by discontinuation of the initial modality and

transition to the other treatment. Stage 2 thus encompassed weeks 4–8, after which all participants were followed for an additional 12 weeks to assess maintenance of clinical gains.

Eligible participants were adults aged 18–65 years meeting DSM-5 criteria for a major depressive episode with anxious distress. Minimum symptom thresholds included PHQ-9 ≥ 10 and GAD-7 ≥ 8. Exclusion criteria comprised bipolar disorder, psychotic disorders, moderate to severe substance use disorder within the previous six months, photosensitivity, uncontrolled epilepsy, pregnancy, and the presence of implanted medical devices incompatible with the interventions. These criteria were selected to ensure clinical stability and reduce risk associated with neuromodulation procedures.

The NFB protocol consisted of 20–25-minute sessions incorporating three components: high-beta (22–30 Hz) down-training at Fz, F3, and F4; enhancement of sensorimotor rhythm (SMR) at C3 and C4; and an alpha–theta protocol at Pz. The tPBM intervention delivered near-infrared light (810 nm) at 10–40 Hz pulsing and 40–60 mW/cm² power density, generating 18–25 J/cm² per site across prefrontal regions (FP1, FP2, FPz, F3, F4). All participants engaged in a brief 10–12-minute session of heart rate variability (HRV) coherence training at the start of each visit. Treatment frequency was standardized to three sessions per week across the entire 8-week intervention period.

Clinical and physiological measures were collected at baseline (T0), week 4 (W4), week 8 (W8), and week 12 follow-up (FU12). The primary endpoint was PHQ-9 remission at week 8, defined as a total score of ≤4. Secondary outcomes included changes in PHQ-9, GAD-7, and ISI scores, as well as HRV indices (RMSSD) and frontal high-beta power derived from qEEG. Adherence and adverse events were monitored throughout.

A total sample of 600 participants provided >90% power to detect differences of at least 10 percentage points between dynamic treatment regimens at a significance level of $\alpha = 0.05$. Power estimates accounted for an anticipated 10% attrition rate and multiple comparison adjustments.

Dynamic treatment regimens (DTRs) were compared using inverse probability of treatment weighting (IPTW) to derive marginal estimates for each pathway. Personalization analyses employed Q-learning and doubly weighted ordinary least squares (dWOLS) to examine how baseline characteristics—including age, symptom severity, HRV, and high-beta activity—interacted with treatment stage decisions. Results were expressed using absolute risk differences, odds ratios, numbers needed to treat (NNT), and 95% confidence intervals. Symptom trajectories were modeled using mixed-effects regression incorporating time and DTR as interacting factors.

Results

The study enrolled a total of 600 participants who met the predefined diagnostic and symptom severity criteria. The demographic and clinical characteristics at baseline reflected a population with moderate to

moderately severe depressive and anxiety symptoms, consistent with the targeted phenotype of major depressive episodes accompanied by anxious distress. The mean age of the cohort was 38.9 years (SD = 11.6), and women represented 62% of the sample, indicating a gender distribution aligned with epidemiological patterns observed in depressive and anxiety disorders. The average duration of the current depressive episode was 7.4 months (SD = 5.2), suggesting that participants typically presented with symptoms of substantial persistence prior to enrollment.

Baseline clinical measures revealed a mean PHQ-9 score of 15.0 (SD = 4.1), placing the sample within the moderate severity range. Correspondingly, anxiety severity was elevated, with a mean GAD-7 score of 12.1 (SD = 4.5). Sleep-related difficulties were also common, as reflected by an average ISI score of 15.8 (SD = 4.7), consistent with clinically significant insomnia symptoms frequently associated with anxious depression. Physiological markers collected at intake demonstrated a mean HRV RMSSD of 26.9 ms (SD = 11.8), indicative of reduced parasympathetic modulation, a pattern often observed in depressive and anxiety disorders. Frontal high-beta activity, expressed as a relative value and normalized to 100 (SD = 20), provided an electrophysiological baseline associated with heightened arousal and cognitive-emotional dysregulation.

Table 1. Characteristics of the participants in the trial

Feature	Value
Total N	600
Age, Mean (SD)	38.9 (11.6)
Female, %	62%
Episode Duration (Monday), Average (SD)	7.4 (5.2)
PHQ-9 Initial, Medium (SD)	15.0 (4.1)
GAD-7 Initial, Medium (SD)	12.1 (4.5)
Initial ISI, Mean (SD)	15.8 (4.7)
HRV RMSSD Initial (ms), Medium (SD)	26.9 (11.8)
High-beta frontal initial (rel.), medium (SD)	100 (20)

Together, these characteristics depict a clinically and neurophysiologically impaired cohort suitable for evaluating adaptive neuromodulatory treatment strategies. The homogeneity in diagnostic profile, as observed from table 1, combined with variability in symptom intensity and biomarkers, offered an appropriate foundation for examining differential responsiveness across dynamic treatment regimens.

During the first four weeks of treatment, participants received either neurofeedback (NFB Start) or transcranial photobiomodulation (tPBM Start) according to the initial randomization scheme. The early-response evaluation at week 4 was a pivotal decision point within the SMART design, as treatment continuation, augmentation, or switching depended on whether individuals achieved clinically meaningful improvement.

A ≥35% reduction in PHQ-9 scores from baseline served as the operational definition of early response. This threshold allowed for the identification of participants who were benefiting sufficiently from their initial modality and those requiring treatment adaptation. Of the 300 participants assigned to begin with NFB, 135 individuals (45%) met the response criterion at week 4, while 165 participants (55%) did not. In the group starting with tPBM, 120 of the 300 participants (40%) were classified as responders, whereas 180 (60%) were non-

responders. These proportions indicate that both interventions were capable of producing early symptomatic improvement, with a modest numerical advantage observed in table 2 for the NFB Start arm.

Table 2. Early response rates between groups, at week 4

Initial Arm	N randomized	Respondents W4, N (%)	Non-respondents W4, N (%)
Start NFB	300	135 (45%)	165 (55%)
Start tPBM	300	120 (40%)	180 (60%)

The distribution of responders and non-responders provided the foundation for Stage-2 re-randomization in the non-responder subgroup. Responders from both arms subsequently continued their initial treatment uninterrupted through week 8, while non-responders were allocated to either an augmentation strategy—adding the alternative modality—or a complete modality switch. Overall, the Stage-1 results highlight meaningful early treatment differentiation and support the use of early symptom change as an informative decision rule within adaptive neuromodulatory treatment pathways.

Week 8 represented the principal evaluation point for determining treatment effectiveness across the dynamic treatment regimens (DTRs). Remission was defined as achieving a PHQ-9 score of ≤4, a stringent threshold indicating near-complete resolution of depressive symptoms. The remission rates varied substantially across the adaptive pathways, as observed in table 3, illustrating the differential impact of augmentation versus switching strategies among week-4 non-responders.

Participants following the NFB→Augment regimen demonstrated the highest remission rate, reaching 72%. This outcome corresponded to an odds ratio of 2.2 when compared with the NFB→Switch pathway and yielded a number needed to treat (NNT) of approximately six, indicating a clinically meaningful advantage of augmentation. Similarly, the tPBM→Augment pathway produced a remission rate of 65%, outperforming the tPBM→Switch regimen, which reached 50%, and corresponding to an odds ratio of 1.8 with an estimated NNT of eight.

Table 3. Primary outcome, remission at week 8

Adaptive Regime (DTR)	PHQ-9 Δ W8–T0 (mean)	PHQ-9 remission ≤4 (%)	GAD-7 Δ (mean)	ISI Δ (mean)	HRV RMSSD %Δ	High-beta %Δ
DTR1 NFB→Augment	-10.8	72	-7.2	-6.4	32	-35
DTR2 NFB→Switch	-8.5	54	-5.1	-4	20	-22
DTR3 tPBM→Augmentation	-10	65	-6.6	-5.6	28	-30
DTR4 tPBM→Switch	-7.9	50	-4.8	-3.6	17	-18

In contrast, the switch strategies yielded comparatively lower remission rates: 54% for NFB→Switch and 50% for tPBM→Switch. Although these outcomes still reflect considerable symptomatic improvement, they consistently underperformed relative to their corresponding augmentation strategies.

Responders from Stage 1 who continued their initial treatment maintained favorable remission rates as well—68% among those beginning with NFB and 60% among those starting with tPBM—suggesting that both modalities were effective for individuals demonstrating early benefit. Taken together, the primary outcome analysis indicates that augmentation at week 4 provides a robust advantage over switching for non-responders, regardless of initial treatment modality. These findings support the clinical utility of combining neuromodulation modalities when early response is insufficient, strengthening the rationale for adaptive, response-informed treatment algorithms.

Symptom evolution from baseline to week 8 demonstrated distinct patterns across the four dynamic treatment regimens, reflecting the differential impact of augmentation versus switching strategies on both depressive and anxiety symptoms, as well as sleep disturbance. Across all regimens, PHQ-9 scores showed substantial reductions by week 8, yet the magnitude of change varied systematically. Participants in the NFB→Augment pathway exhibited the most pronounced improvement, with a mean decrease of −10.8 points. The tPBM→Augment regimen produced a similarly robust reduction of −10.0 points. By contrast, switch strategies resulted in more modest symptom improvement, with mean PHQ-9 changes of −8.5 points in the NFB→Switch group and −7.9 points in the tPBM→Switch group. These patterns closely paralleled the remission data, reinforcing the superiority of augmentation for those not responding adequately by week 4.

A similar gradient emerged in anxiety trajectories as measured by the GAD-7. The NFB→Augment regimen generated the largest mean reduction (−7.2), followed by tPBM→Augment (−6.6). Switch pathways again produced smaller decreases, with NFB→Switch showing −5.1 and tPBM→Switch −4.8. These results indicate that augmentative strategies not only enhanced depressive symptom resolution but also conferred broader anxiolytic effects.

Sleep quality, indexed by the ISI, followed the same hierarchical pattern. Mean ISI reductions were −6.4 for NFB→Augment and −5.6 for tPBM→Augment, compared with −4.0 and −3.6 for NFB→Switch and tPBM→Switch, respectively. This consistent pattern across domains suggests that the combined neuromodulation approach more effectively addresses the multidimensional symptom profile characteristic of depression with anxious distress. Overall, the symptomatic trajectories highlight that early non-responders benefit substantially more from augmentation than from switching, with augmentation producing larger and more comprehensive improvements across depressive, anxiety, and sleep-related symptoms. These findings underscore the clinical value of using early symptom change to guide adaptive neuromodulatory treatment decisions.

Physiological and electrophysiological indices assessed at week 8 revealed clear, modality-dependent patterns that paralleled the clinical trajectories observed across the dynamic treatment regimens. Heart rate

variability (HRV), measured via the root mean square of successive differences (RMSSD), demonstrated notable improvements in all groups, with the magnitude of change varying according to the adaptive pathway. The largest increases were observed in participants assigned to augmentation strategies. The NFB→Augment regimen produced a 32% increase in RMSSD, while the tPBM→Augment pathway yielded a 28% increase. These changes indicate enhanced parasympathetic modulation and improved autonomic regulation.

Participants in the switch conditions exhibited more modest gains. RMSSD increased by 20% in the NFB→Switch pathway and by 17% in the tPBM→Switch condition. Although these improvements remain clinically meaningful, they consistently fell below those achieved with augmentation, mirroring the differential symptomatic response.

A comparable pattern emerged in the electrophysiological domain. Frontal high-beta activity—an index associated with cognitive-emotional hyperarousal—decreased across all four regimens. Reductions were most pronounced in augmentation pathways, with a 35% decrease in the NFB→Augment group and a 30% decrease in the tPBM→Augment group. Participants in the switch pathways demonstrated smaller but still measurable reductions: −22% in the NFB→Switch group and −18% in the tPBM→Switch group. The biomarker findings underscore the physiological advantages conferred by augmentation when early clinical response is insufficient. The consistent alignment between symptom reduction and improvements in autonomic and cortical markers reinforces the mechanistic complementarity of NFB and tPBM and supports the rationale for combining both modalities within an adaptive treatment framework.

Sustained clinical improvement was evaluated 12 weeks after the completion of the active treatment phase to determine the durability of treatment effects across the dynamic regimens. Remission maintenance rates demonstrated a clear gradient that closely mirrored both the symptomatic and biomarker outcomes observed at week 8. Participants in the augmentation pathways exhibited the highest stability of remission. The NFB→Augment group showed an 84% maintenance rate, indicating that the vast majority of individuals who achieved remission by week 8 retained their improved status at follow-up. The tPBM→Augment regimen similarly demonstrated strong durability, with 78% of participants remaining in remission at FU12.

In contrast, remission maintenance was less robust in the switch pathways. The NFB→Switch group maintained remission in 68% of cases, while the tPBM→Switch group demonstrated the lowest follow-up maintenance rate at 64%. Although these figures still reflect meaningful longer-term benefit, they consistently underscored the relative advantage of augmented interventions for individuals who required treatment adjustment after week 4. Overall, the follow-up results indicate that augmentation not only produces superior acute outcomes but also supports longer-term clinical stability. These findings highlight the value of integrating both neuromodulation modalities for sustaining symptomatic improvement in patients with depression and associated anxiety.

Adverse events were systematically monitored throughout the study to evaluate the tolerability and safety profile of both neurofeedback and transcranial photobiomodulation across all treatment pathways and can be consulted in table 4. Overall, the interventions were well tolerated, with only mild, transient adverse events reported and no serious adverse events (SAEs) documented.

Table 4. Reported adverse events by the participats

Adverse event	Total frequency (N, %)	Management
Mild post-session headache	38 (6.3%)	short break
Eye strain	29 (4.8%)	visual breaks
Transient agitation (NFB)	31 (5.2%)	NFB threshold adjustment
Mild drowsiness	25 (4.2%)	Evening appointment
SAE	0 (0%)	—

The most frequently reported adverse event was mild post-session headache, occurring in 38 participants (6.3%). These episodes generally resolved with short rest periods and did not necessitate treatment discontinuation. Eye strain was reported by 29 participants (4.8%) and was typically managed through brief visual breaks during or after sessions. Transient agitation specific to NFB occurred in 31 participants (5.2%). These instances were addressed effectively by adjusting neurofeedback thresholds or session parameters. Mild drowsiness was reported by 25 participants (4.2%), most commonly following tPBM sessions; scheduling adjustments—such as moving sessions to later in the day—were sufficient to mitigate this effect.

Importantly, no serious adverse events occurred in the sample (0%). Adherence remained high, with a median of 87%, indicating that participants found both modalities acceptable and manageable within the treatment schedule. These observations demonstrate a favorable safety and tolerability profile for both neuromodulation interventions, further supporting their use within adaptive treatment frameworks for depression with anxious distress.

Discussion

The findings of this multicenter SMART trial provide a clear and coherent picture of how adaptive neuromodulatory strategies can optimize treatment outcomes for individuals with major depressive episodes accompanied by anxious distress. By structuring therapeutic decisions around early clinical response, the study demonstrates that treatment sequences incorporating augmentation at the four-week decision point yield substantially superior outcomes compared with switch-based strategies. This superiority was consistent across all evaluative domains: symptom reduction, remission rates, physiological markers, and follow-up stability.

One of the most salient observations is the robust performance of augmentation regimens, particularly NFB→Augment, which consistently produced the highest remission rates and the most pronounced

improvements in HRV and reductions in high-beta activity. These findings highlight the additive benefits of combining neurofeedback and tPBM in individuals who did not respond sufficiently during the initial treatment phase. The mechanistic complementarity of the two interventions—NFB targeting maladaptive oscillatory dynamics and tPBM enhancing prefrontal metabolic and synchronization processes—may explain the synergy observed in augmentation pathways. The biomarker trajectories further support this interpretation, indicating that combined neuromodulation exerts broader and more integrated regulatory effects on autonomic and cortical functioning.

The results also underscore the importance of early response as a clinically meaningful indicator that can guide subsequent treatment decisions. Responders to both initial modalities showed high remission rates by week 8, suggesting that early symptom improvement reliably predicts continued benefit. Conversely, among non-responders, switching to the alternate modality alone resulted in comparatively weaker outcomes, indicating that transitioning between single modalities may not provide sufficient therapeutic leverage when early progress is limited.

Personalization analyses built into the SMART framework offer preliminary insight into which patients may benefit most from augmentation strategies. Early indicators—such as lower baseline HRV and elevated frontal high-beta activity—appeared to be associated with greater gains under augmentative treatment. While these exploratory findings require further validation, they point toward the potential utility of integrating biomarkers into individualized treatment algorithms.

The strengths of the study include its large sample size, multicenter design, and rigorous decision-making structure, all of which increase the generalizability and applicability of the findings. The incorporation of objective biomarkers alongside symptom measures offers an enriched understanding of treatment mechanisms and their physiological correlates. Additionally, the consistent safety profile and high adherence rates across modalities reinforce the feasibility of integrating these interventions into real-world therapeutic settings.

Considering the limitations, blinding was inherently imperfect, particularly for neurofeedback, which may introduce expectancy effects. Furthermore, the augmented pathways required more resources than single-modality treatments, which may influence scalability in some clinical contexts. Finally, although the study establishes the superiority of augmentation over switching, it does not determine whether different forms of augmentation, dose intensities, or sequencing patterns might produce additional optimization.

Overall, the results contribute substantially to the evidence base for adaptive neuromodulatory treatments in depressive disorders with comorbid anxiety. They support the clinical value of using early treatment response to steer therapeutic decisions and demonstrate that combining NFB and tPBM for non-responders provides a particularly effective strategy. The findings thus offer a practical, data-driven model for individualized treatment planning within this complex clinical population.

Conclusion

This multicenter SMART trial provides compelling evidence that adaptive neuromodulatory treatment strategies can meaningfully enhance clinical outcomes in major depressive episodes with associated anxious distress. By integrating early treatment response into a structured decision-making algorithm, the study demonstrates that patient-specific adjustment—particularly through augmentation at week 4—offers a clear therapeutic advantage over switching strategies.

The NFB→Augment pathway consistently emerged as the most effective dynamic treatment regimen, yielding superior remission rates, stronger reductions in depressive, anxiety, and insomnia symptoms, and more pronounced improvements in HRV and frontal high-beta activity. These convergent findings underscore the synergistic potential of combining neurofeedback and prefrontal photobiomodulation in cases where monotherapy fails to produce adequate early response. Moreover, the durability of remission observed at the 12-week follow-up reinforces the longer-term clinical stability conferred by augmentation strategies.

The results also validate the central premise of adaptive treatment: early symptom trajectories provide actionable information that can be used to tailor interventions to individual needs. The consistency of outcomes across clinical and physiological domains further indicates that the algorithm evaluated here is both coherent and scalable, offering a pragmatic framework suitable for real-world clinical application.

While acknowledging resource considerations and the challenge of imperfect blinding, the study's overall strengths (large sample size, multicenter implementation, objective biomarkers, and high adherence) support the reliability and applicability of the findings. The evidence indicates that a structured, response-guided approach to neuromodulation—starting with either NFB or tPBM and proceeding to augmentation in early non-responders—constitutes a robust and personalized therapeutic strategy. This model offers a viable and efficient pathway for optimizing outcomes in patients with depression and comorbid anxiety and provides a foundation for further refinement of individualized neuromodulatory care.