

Real-World Clinical Outcomes of Limbic Self-Neuromodulation for Symptom Relief in Anxiety Disorders

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Introduction

Anxiety is characterized by heightened arousal in response to perceived threats, whether real or imagined, and encompasses a spectrum of conditions marked by excessive fear and worry. Anxiety disorders are among the most prevalent mental health conditions worldwide, affecting approximately 4.4% of the global population [1]. Traditional treatments include pharmacotherapy, psychotherapy, or their combination. Although combined treatment is often considered the first-line intervention, its effectiveness and tolerability vary considerably across individuals. Consequently, many patients fail to achieve adequate symptom relief, highlighting the need for non-pharmacological, brain-informed interventions that target relevant cognitive processes. Neurofeedback guided by an amygdala-related EEG-fMRI pattern (Amyg-EFP-NF) aims to strengthen regulatory control over limbic responses by facilitating downregulation of the Amyg-EFP, potentially through improvements in emotion regulation [2]. Present real-world study examined patients seeking treatment for anxiety-related symptoms using Amyg-EFP-NF in a public clinic. This clinical setting provided an opportunity to evaluate the effectiveness and utility of Amyg-EFP-NF under naturalistic treatment conditions. We retrospectively tested three primary hypotheses: 1) patients would show significant clinical improvement, reflected in reduced anxiety symptoms; 2) patients would exhibit measurable neural changes across NF sessions (i.e., neuromodulation capacity), reflected in progressively greater downregulation of the Amyg-EFP signal over sessions; 3) neural changes would predict clinical outcomes, such that greater neuromodulation capacity would be associated with greater symptom reduction.

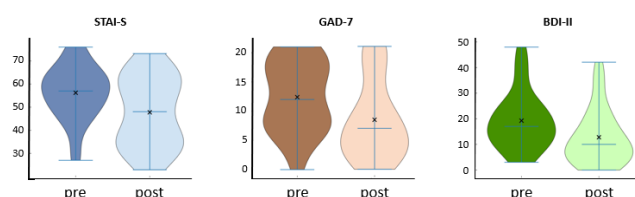
Methods

Forty-three consecutive patients in our clinic with anxiety disorders (enrollment: 2018 – 2025 years, mean age: 42.8 ± 15.8 years; 24 males) completed 20 Amyg-EFP-NF sessions over ~10 weeks. Diagnoses, including generalized anxiety disorder, social anxiety disorder, health anxiety, and specific phobias, were confirmed using clinician-provided medical records. Outcomes were assessed using standardized self-report questionnaires, including State-Trait Anxiety Inventory (STAI), Generalized Anxiety Disorder Scale (GAD-7), and Beck's Depression Inventory (BDI). Questionnaires were administered electronically via the Qualtrics™ platform at baseline (S1) and immediately post-intervention (S20). EEG data were acquired using a g.Nautilus™ electrode cap and g.tech amplifier (g.tech™ medical engineering GmbH, Austria). Signals were sampled at 250 Hz and processed using a custom OpenViBE-based pipeline. Amyg-EFP amplitude was computed online from the Pz electrode using a previously validated machine-learning algorithm that identifies EEG time-frequency patterns associated with amygdala activity [3]. Each session consisted of five *Rest* (60 s) / *Regulate* (120 s) cycles, during which patients received real-time feedback via either a visual display (lower bar height), an audio-visual virtual scenario (e.g., avatars placed in a less noisy virtual hospital waiting room), or auditory feedback (reduced musical volume).

Results

Clinical symptom improvement

To evaluate changes in clinical symptoms following NF training, paired-samples t-tests were conducted for state anxiety (STAI-S),



generalized anxiety (GAD-7), and depression (BDI-II). Significant reductions were observed across all measures from pre- to post-treatment (see Figure 1 and Table below).

	<i>Pre-</i>	<i>Post-</i>	<i>t</i>	<i>p</i>	<i>d</i>
STAI-S	55.9 ± 11.5	47.6 ± 14.2	3.88	.0004	0.71
GAD-7	12.4 ± 6.0	8.3 ± 6.4	4.36	.0001	0.67
BDI-II	19.2 ± 10.7	12.6 ± 10.3	6.07	.0000	0.6

Neurofeedback regulation performance over training NF performance was quantified using a *learning slope*, reflecting overall change between *Rest* and *Regulate* conditions across the treatment course. For each patient, delta scores (*Regulate* – *Rest*) across all 20 NF sessions were entered into a linear regression model with session number as the predictor. The resulting regression coefficient served as an individual learning index, with more negative slopes indicating greater improvement in EFP downregulation over time. A repeated-measures ANOVA revealed a significant main effect of condition ($p < .001$), with substantially lower Amyg-EFP values during the *Regulate* compared to the *Rest* condition. The large effect size (partial $\eta^2 = 0.70$) indicates that this difference accounts for approximately 70% of the variance, suggesting that, on average, patients successfully downregulated amygdala-related activity during NF. To assess how regulatory capacity evolved over training, a linear mixed-effects model was fitted with Session as a categorical factor. The analysis revealed a significant main effect of Session ($p < .001$), indicating that NF performance changed over time. Pairwise comparisons relative to S1 showed no significant improvements during SS 2–6 (all $p > .05$). From S7 onward, performance was consistently higher than in S1 (SS 7–8: $p < .05$; SS 9–20: $p < .01$), suggesting that reliable NF learning emerged only after several sessions (Figure 2). Finally, a linear mixed-effects model was fitted with mean downregulation capacity (delta scores) as the dependent variable, and Session number entered as a continuous within-subject predictor, with age and sex included as covariates. The analysis revealed a significant main effect of session, indicating systematic changes in regulation capacity across training ($p < .001$). Neither age ($p = .769$) nor sex ($p = .246$) was significantly associated with regulation performance.

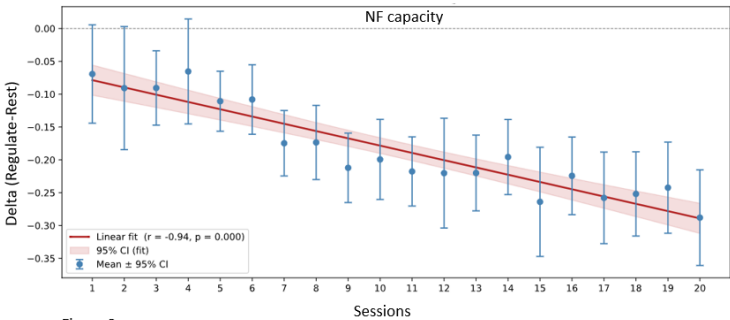


Figure 2

Association between NF learning and clinical outcomes Linear regression analyses indicated that steeper learning slopes were associated with greater anxiety-related symptom reduction (Figure 3). Steeper learning slopes were associated with larger reductions in state anxiety scores ($p = .016$, $R^2 = .137$). A similar pattern was observed for generalized anxiety symptoms, such that steeper learning slopes were associated with greater symptom reduction; however, this relationship was only marginally significant ($p = .054$, $R^2 = .069$). Learning slopes were not significantly associated with changes in depressive symptoms ($p = .372$, $R^2 = .003$).

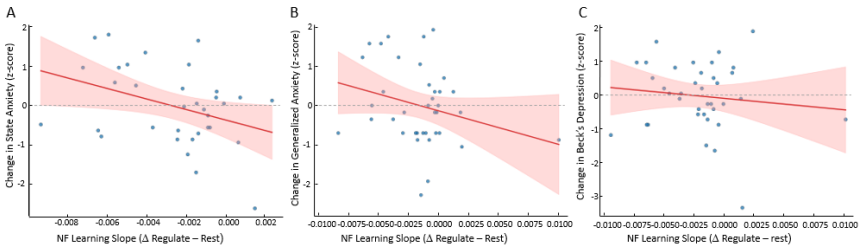


Figure 3

Conclusions

These findings suggest that a clinical protocol of Amyg-EFP-NF enabled participants to learn downregulation of amygdala-related EEG signals, resulting in corresponding alleviation of anxiety symptoms. Effect sizes were comparable to those reported for established treatments, including psychotherapy ($d \approx 0.5$ – 0.8) and pharmacotherapy ($d \approx 0.3$ – 0.6). Together, this retrospective analysis of real-world data demonstrates the potential of Amygdala-EFP-NF as an accessible and scalable brain-informed intervention for diverse anxiety disorders.

[1] Goodwin et al., 2020; [2] Berboth & Morawetz, 2021; [3] Keynan et al., 2016