

Scalable fMRI-Informed EEG Neurofeedback for Anhedonic Depression: Associations with Reward-Circuit Function

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Introduction

Anhedonia is a disabling and often persistent feature of major depressive disorder, closely linked to altered reward processing in the ventral striatum (VS) and midbrain dopaminergic nuclei (MDN) circuits¹. Although these brain regions represent clinically relevant targets, their use in scalable interventions is limited by the difficulty of measuring deep reward-system activity outside resource-intensive fMRI settings. The Reward-System EEG-fMRI Pattern (RS-EFP) is an fMRI-informed EEG model of ventral striatal activity², developed to enable EEG-based neurofeedback targeting reward-related circuitry without patient-specific fMRI. In a previously reported open-label clinical trial, RS-EFP upregulation neurofeedback training was followed by reductions in depression and anhedonia symptoms³. Building on these clinical findings, the present work presents two independent studies: Study I examined whether spontaneous RS-EFP fluctuations correspond to ventral striatal activity during concurrent EEG-fMRI in healthy participants; and Study II examined whether symptom change in the fMRI subset of the clinical trial was associated with changes in reward-anticipation responses in ventral striatal and midbrain dopaminergic regions.

Methods

The work included two independent studies. Study I was an observational concurrent EEG-fMRI study in 35 healthy participants, used to test whether spontaneous RS-EFP fluctuations corresponded to ventral striatal fMRI activity during naturalistic movie viewing. Study II was based on a previously reported³ prospective, single-arm, open-label feasibility trial of RS-EFP neurofeedback in 34 patients with anhedonic depression; the present analysis includes 16 patients who completed both pre- and post-training fMRI assessments, providing the first analysis of the trial's fMRI data. Patients completed 10 RS-EFP upregulation neurofeedback sessions using Prism for Depression, with clinical and fMRI assessments before and after training. Clinical outcomes included clinician-administered anhedonia severity using SHAPS-C and depression severity using HDRS-21. Neurofeedback learning was quantified as change in RS-EFP upregulation across training. Neural outcomes were assessed with pre- and post-training fMRI during a monetary incentive delay (MID) task, focusing on reward-anticipation activation (reward cue > no-incentive cue) in the VS and MDN. Analyses tested RS-EFP-fMRI correspondence in healthy participants, pre- to post-training neural changes in patients, and associations among neurofeedback learning, symptom change, and reward-circuit activation.

Results

In Study I, spontaneous RS-EFP fluctuations during naturalistic movie viewing significantly covaried with fMRI activity in ventral striatal clusters, supporting correspondence between the EEG-derived signal and its intended reward-system target. In Study II, patients with greater anhedonia improvement showed significant post-training increases in ventral striatal reward-anticipation activation, whereas less-improved patients did not show comparable changes. Across patients, anhedonia reduction was significantly associated with increased reward-anticipation activation in the

ventral striatal region identified in Study I as covarying with RS-EFP fluctuations ($R = 0.69$, FDR-corrected $P = 0.021$) and in left MDN ($R = 0.65$, FDR-corrected $P = 0.022$), but not in right MDN, orbitofrontal cortex, or non-dopaminergic substantia nigra control regions. Neurofeedback learning, defined as the increase in successful RS-EFP upregulation from the introductory session to the final training sessions, was associated with anhedonia reduction ($R = 0.55$, $P = 0.027$) and with increased left MDN reward-anticipation activation ($R = 0.59$, FDR-corrected $P = 0.033$). Finally, a mediation model indicated that reward-anticipation changes in the VS and left MDN significantly accounted for the association between RS-EFP upregulation learning and anhedonia reduction, leaving no significant residual association between upregulation learning and symptom change.

Conclusions

These findings support RS-EFP neurofeedback as a scalable fMRI-informed approach for targeting reward-system dysfunction in anhedonic depression. Across two independent studies, the RS-EFP corresponded to ventral striatal fMRI activity during naturalistic processing, and clinical improvement following neurofeedback was associated with reward-anticipation changes in ventral striatal and midbrain dopaminergic regions. Together with the statistical mediation results, this pattern suggests a plausible biological mechanism in which successful RS-EFP upregulation is linked to greater reward-anticipation responsiveness within ventral striatal–midbrain circuitry, corresponding with reduced anhedonia. While larger controlled studies are needed to establish efficacy and causal mechanisms, this work supports the use of fMRI-informed EEG signals to bridge mechanistically defined neural targets with scalable real-time neurofeedback interventions.

Figures

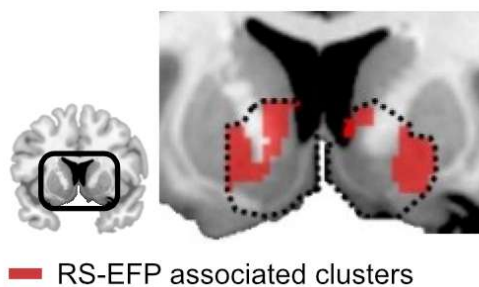


Figure 1. Study-I GLM analysis.

Voxel-wise linear regression revealed RS-EFP associated fMRI activity in the VS (threshold at FDR corrected $P < 0.05$) in healthy participants during passive movie viewing.

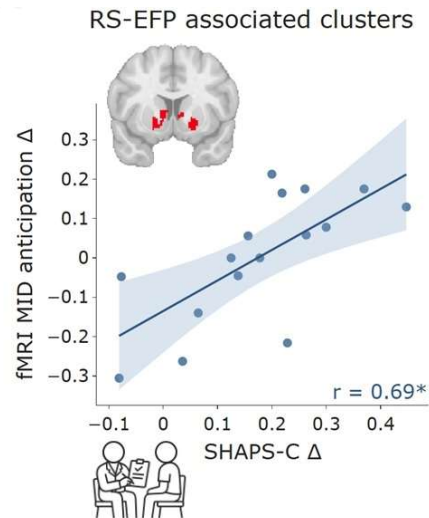


Figure 2. Study-II correlation analysis.

Anhedonia reduction following NF training was correlated with the fMRI activation change in reward-anticipation in RS-EFP associated clusters identified in Study I ($R = 0.69$, FDR corrected $P = 0.021$).

References

1. Pizzagalli DA. Toward a Better Understanding of the Mechanisms and Pathophysiology of Anhedonia: Are We Ready for Translation? *American Journal of Psychiatry*. 2022;179:458-469.
2. Singer N, Poker G, Dunskey N, et al. Development and validation of an fMRI-informed EEG model of reward-related ventral striatum activation. *NeuroImage*. 2023;276:120183-120183.
3. Amital D, Gross R, Goldental N, et al. Reward System EEG–fMRI–Pattern Neurofeedback for Major Depressive Disorder with Anhedonia: A Multicenter Pilot Study. *Brain Sciences*. 2025;15(5):476.