Reward System EEG-fMRI-Pattern Neurofeedback for Major Depressive Disorder with Anhedonia: A multicenter pilot study.

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Abstract

Background: Up to 75% of Major Depressive Disorder (MDD) patients exhibit persistent anhedonia symptoms related to abnormalities in the positive valence system. Accumulated evidence points to brain dysfunction of the reward system including of the ventral striatum, in MDD patients with anhedonia. The EEG-fMRI-Pattern (EFP) biomarker for the ventral striatum known as the Reward System (RS)-EFP, is a machine-learning driven EEG representation of simultaneously acquired fMRI activation in the ventral striatum. The RS-EFP was validated on healthy subjects showing its functional relevance as a target in Neurofeedback (NF); a closed-loop system for self-neuromodulation, and as a neural probe for reward processing.

Objective: Evaluate the safety and efficacy of a dedicated NF device (termed Prism) which incorporates the RS-EFP biomarker for use in self-neuromodulation training (RS-EFP-NF) for alleviating depression in MDD patients with anhedonia.

Methods: 49 adults (age range, M=39.9±11.03) with DSM-5 diagnosis of MDD with anhedonia (per SHAPS-C score?25) on stable therapy, were screened for administration of ten sessions of RS-EFP-NF twice a week on nonconsecutive days. Depression and Anhedonia severity was assessed respectively by HDRS-17 and SHAPS-C, at baseline, midway and at the end of treatment.

Results: 34 patients (77%) completed the protocol and were included in the analyses. No device related adverse events were serious or required treatment. As expected depression symptoms were reduced at end of treatment as indicated by the HDRS-17 with reduction of 8 points on average (95% CI: -10.5 to -5.41, p<0.0001), clinical improvement rate of 78.47%, remission of 32.25%. Furthermore, anhedonia as indicated by SHAPS-C was diminished, showing an average reduction of 6.3 points (95% CI: -8.51 to -4.14, p<0.0001).

Conclusions: Self-neuromodulation using RS-EFP-NF is a promising and safe treatment for MDD with anhedonia. The intervention demonstrates substantial clinical effects on both depression and anhedonia symptoms, with high patient acceptability. The RS-EFP-NF (Prism for depression) approach may address a critical treatment gap for anhedonia symptoms that often persist despite conventional therapies. Larger controlled implementation, efficacy and dosing studies are warranted. Clinical Trial: N/A

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Conclusion: Self-neuromodulation using RS-EFP-NF is a promising and safe treatment for MDD with anhedonia. The intervention demonstrates substantial clinical effects on both depression and anhedonia symptoms, with high patient acceptability. The RS-EFP-NF (Prism for depression) approach may address a critical treatment gap for anhedonia symptoms that often persist despite conventional therapies. Larger controlled implementation, efficacy and dosing studies are warranted.

Keywords: EFP Neurofeedback, self-neuromodulation, depression, anhedonia, depression treatment, reward system, ventral striatum, biomarker, personalized treatment

Introduction:

Background

The diagnosis of major depressive disorder(MDD) requires at least five depressive symptoms, one of

which may be anhedonia - which is the loss of pleasure or interest in daily activities, perceived as rewarding during a premorbid state [1]. Anhedonia can be present in up to 70% of MDD diagnoses [2,3]. With a 14.5 million prevalence of MDD, approximately 10.3 million adults with MDD would be considered to have an anhedonic depression. Importantly, anhedonia is positively related to the severity of MDD [4], prolonged disease course [5], worse long-term prognosis [5,6] and a higher suicide rate [1,7]. Anhedonia has been found to be a predictor of poor outcomes in patients taking antidepressant medications, particularly serotonin uptake inhibitors(SSRIs) [8,9]; as these medications fail to address reward related symptoms associated with anhedonia [10,11]. There is a clinical need for therapies specifically designed to treat anhedonia related MDD [12].

As shown consistently across human imaging studies, depression in general and anhedonic symptoms specifically are associated with deficient-activation of the Ventral Striatum (VS); a core aspect in the subcortical reward circuit [13,14]. Decades of experimental research in animals and humans have emphasized the role of the meso-cortico-limbic circuit in different subdomains of reward system processes, including anticipation and consumption of reward, valuation and deciding on an effort to pursue a possible reward and learning from it for future occurrences [14,15,16,17]. Many of these studies refer to the role of neuroanatomical connections and dopamine secretion in the meso-limbic circuit [18]. Although other, nondopaminergic mechanisms also play a role in reward pleasure ("liking"), dopamine has received attention due to its critical effects on reward anticipation and incentive (“wanting”) of pleasurable stimuli [19].Therefore, anhedonia is reflected both at the molecular level, involving deficits in dopamine production, and at the structural level, indicating impaired processing within meso-cortico-limbic structures [20].
Despite the high prevalence of anhedonia in MDD and its association with worse outcomes, few interventions specifically target reward system dysfunction. The growing neurobiological understanding of its mechanism supports the idea that interventions targeting the reward system could be beneficial for MDD with anhedonia. Prior studies using behavioral activation techniques and pharmacological agents directed at reward-related neural circuits have shown notable improvements in depressive symptoms by mitigating anhedonia [9,21]. Furthermore, interventions such as Positive Affect Treatment (PAT), Positive Affect Stimulation Sustainment (PASS), and Positive Activity Intervention (PAI) have shown effectiveness in enhancing positive affect and reducing depressive symptoms compared to interventions solely targeting a negative affect [20,22].
A recently developed, innovative form of Neurofeedback (NF), named Prism for Depression™ (Gray Matters Health, Haifa, Israel) follows this reward system approach for treatment of depression with anhedonia. Uniquely, this approach targets the relevant neural mechanism by analytically integrating simultaneous EEG and fMRI recordings to create a group level biomarker for VS activation during reward processing. By utilizing machine learning for estimating fMRI activity in the VS from the simultaneously acquired EEG data, a set of coefficients (named Reward System EEG-fMRI-Pattern; RS-EFP) are derived. This EFP serves as an fMRI-informed measure of EEG signals related to reward system activity during the processing of pleasurable stimuli. This RS-EFP biomarker is used as the self-neuromodulation target during EEG-NF via Prism for Depression™, emphasizing the active role patients play in modulating their own neural activity. Unlike conventional NF approaches that target general EEG patterns, the RS-EFP method uniquely provides anatomically specific feedback derived from deep brain reward structures, potentially offering more precise neuromodulation of anhedonia-related neural circuits.

The RS-EFP was validated in healthy individuals [23]. That analysis demonstrated upregulation of the VS and additional functionally relevant reward related regions (such as the insula and anterior cingulate cortex [ACC]) of the brain) in response to reward stimuli than in EFP models derived from other anatomical regions of the brain [23].

The goal of this study was to prospectively evaluate the safety and clinical efficacy of the RS-EFP-NF integrated in a dedicated device and audiovisual feedback interface (i.e. Prism for Depression™) in MDD patients with anhedonia.

Methods:

Participants and recruitment:

Inclusion criteria were: Primary Diagnosis of MDD with Anhedonia, with SHAPS-C score ≥ 25. MDD diagnosis determined via the Neuropsychiatric Interview (MINI for DSM-5).
Ages 22 to 50; Any gender; High school diploma or equivalent; Right-handed getting MRI(Chapman and Chapman 1987); Normal or corrected-to-normal vision and hearing; Ability to give signed, informed consent; Ability to adhere to the study schedule. Concomitant psychotropic medications allowed if they are at a stable dose for 4 weeks prior the study.

Exclusion criteria were: A history of psychotic disorder or Bipolar I; Moderate or severe substance use disorder within 3 months of screening; Lifetime diagnosis of autism or intellectual disability was allowed at the investigators discretion; Benzodiazepines which cannot be ceased for the duration of the study (with a washout period of at least 2 weeks prior to the first Prism training session) or which cannot be replaced with short-acting benzodiazepines that are taken only for sleeping during the night at equivalent daily dose of up to 3 mg; Current diagnosis of PTSD; treatment resistant depression, defined as episodes that did not have a ≥50% symptom reduction to at least two full trials of optimally dosed antidepressant monotherapy or to at least optimally dosed antidepressant monotherapy and one trial of augmentation. Patient were excluded with any past or current use of DA (Dopamine Agonist)-acting drugs (e.g., bupropion, stimulants, low doses of anti-psychotics used as an augmentation strategy). Recent initiation of any evidence- based MDD psychotherapy was excluded but continuation of established therapy was allowed.

Participants were recruited from four medical centers in Israel (Ramban Medical Center, Sheba Medical Center, Sourasky Medical Center, and Barzilai Medical Center). The fMRIs were done at Sourasky Medical Center, and the NF only at the other three medical centers. The research protocol was approved by the ethics committee of each participating clinical site. The study was registered on the Israel Ministry of Health website MOH_2022-02-22_010631. The study took place from February 22, 2023, to March 6, 2024. The planned sample size of 30 was chosen for MDD patients with anhedonia based on the rule of thumb recommendation [24].

The Consensus on the Reporting of Experimental Design of clinical and cognitive-behavioral NF studies (CRED-nf) best practices checklist was used (Appendix 1).

Study design, device description, outcome measures, statistical methods

Study design:

The study was a prospective, single arm, open label treatment trial with Prism for Depression™ aimed at assessing its safety and efficacy, in MDD patients with anhedonia. The goal was to train individuals to up-regulate their RS-EFP biomarker, (i.e. self-neuromodulation) while probing various sub-domain of reward processing. This study consisted of subjects participating in the following visits: screening and eligibility confirmation; baseline clinical assessment; 10 Prism sessions; mid study clinical assessment; post Prism clinical assessments. The study also included two optional fMRI scans, (before and after the 10 sessions) which are not included in the current report.

Device description:

Using the RS-EFP signal and the NF training protocol, Prism aims to target the different components of depression related to the reward processing, and through that targeting anhedonia related processes corresponding to reward anticipation and consumption. During the Prism training, the patient is instructed to control an interactive audio-visual scenario presented on a screen (based on principles presented in [25,26]). The patient is informed about the success level of RS-EFP up-modulation by audio-visual feedback. During each of the 10 sessions, the participant is seated in front of a monitor, wearing a wireless EEG headset, and watching an interactive scene with avatars of a woman and a dog. The Prism training protocol specifically emphasizes self-neuromodulation, where patients actively learn to control their brain activity through the NF interface. The participant is instructed to find a personally effective mental strategy – such as a memory of an experience, a song, or other sensation that evokes a happy/excited/satisfied emotion – to make the woman take the dog for a walk. As the participant engages in various strategies, Prism reads the patient's attached 8-electrode EEG and computes the EFP biomarker. When the biomarker level goes up, the avatars gradually go for a walk, giving a real-time representation of the patient's RS-related brain activity and teaching control in an evolutional and repetitive way. The session structure and the scenario were designed to follow the main sub-domains for reward processing which are the reward anticipation and consumption (corresponding to "wanting" and "liking").
Each Prism session has 5 cycles (3 min each) where each cycle is composed of three repeated blocks. In the first stage of each block, the patient watches an animation of a dog trying to get its owner's attention, creating anticipation for what will happen next (anticipation stage). Self-neuromodulation success at this stage of anticipation will result in taking the scenario to the next level, where the owner is taking the dog for an outside walk and an auditory - visual reward is played (rewarding feedback for incentive/wanting related activity). Then, if the feedback system detects that the RS-EFP is getting higher in response to the reward, the patient will get additional auditory - visual reward (feedback for reward consumption). At that point, the patient is asked to maintain the level of mental and neural response to reward consumption. If they succeed, they will get an additional reward (brain state holding feedback; For additional details please see Figures 1-2). The processing during this time period is a mixture reflecting incentive and consumption.

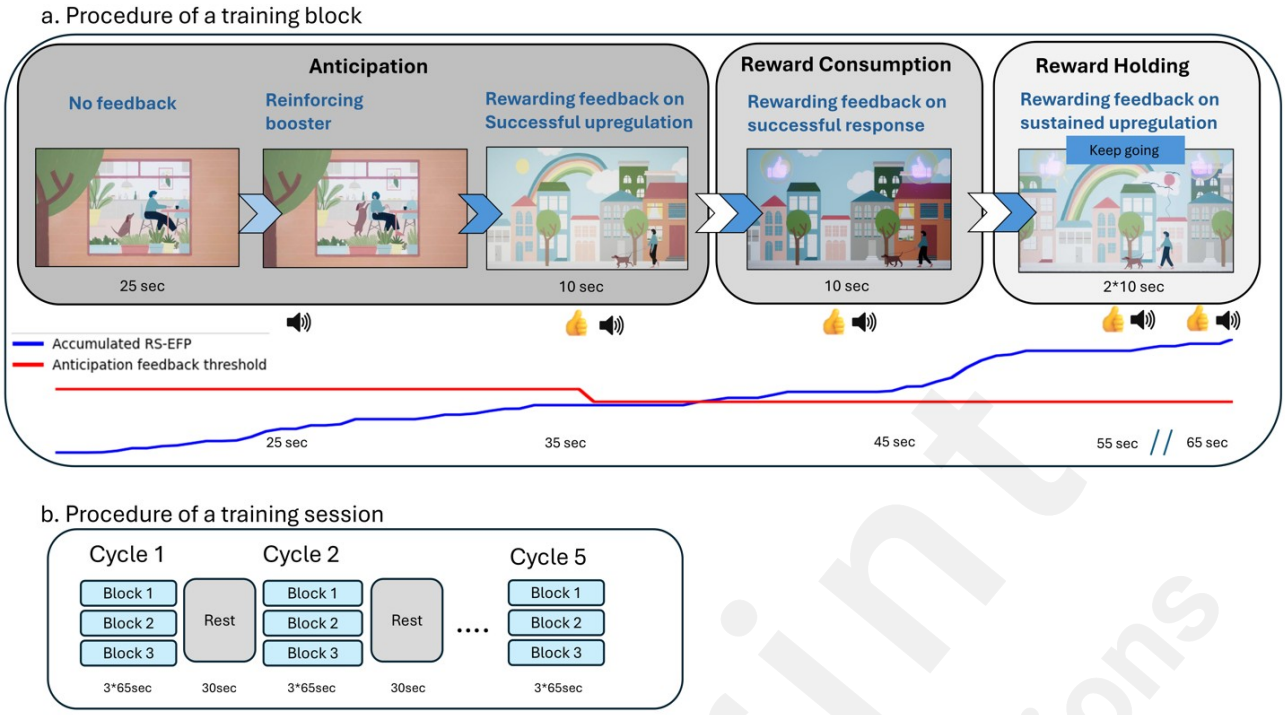


Figure 1: Prism for Depression™ design. (a) **Feedback interface design and monitoring**. Each training block progresses through Anticipation (25 sec), Reward Consumption (10 sec), and Reward Holding (20 sec) phases. The blue line represents accumulated RS-EFP signal, with the red line showing the anticipation threshold. (b) **NF session protocol.** Each training session consists of 5 cycles, with 3 blocks per cycle separated by rest periods.

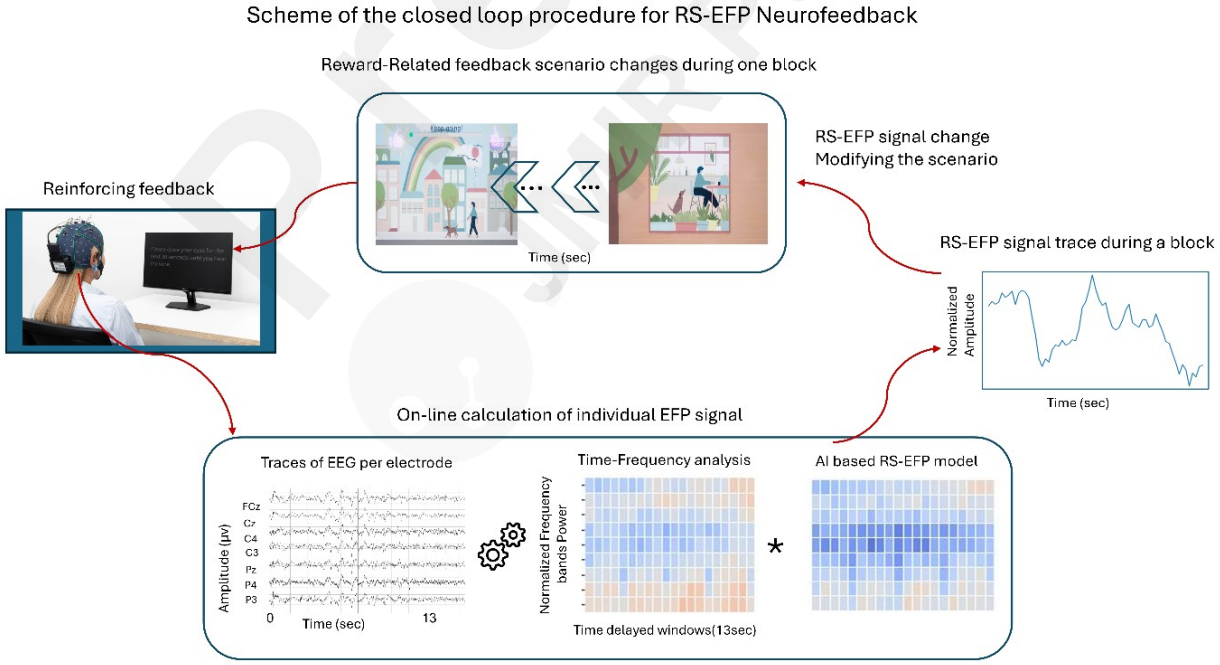


Figure 2: Schematic representation of the closed loop RS-EFP-NF procedure. The system captures EEG signals from the trainee, processes them through time-frequency analysis and an AI-based RS-EFP model, and generates real-time feedback that directly modifies the audiovisual scenario, creating a continuous learning loop for reward system activation.

Outcome measures:

The primary outcome measure was the Hamilton Depression Rating Scale (HDRS-17) change from baseline. Clinically meaningful improvement defined as a 4-6-point reduction and clinically substantial improvement defined as a 7-12 point reduction [27]. The following hypotheses were tested for the primary efficacy endpoint:

- Null Hypothesis: Mean change from baseline to the post Prism training visit in Clinician HDRS-17 (week 6), HDRS≥ -4.
- Alternative Hypothesis: Mean change from baseline to the post Prism training visit in HDRS-17 (week 6), HDRS< -4.

Other endpoints for HDRS included: Proportion of responders (at least 50% reduction from baseline in HDRS total score); proportion of remitters (HDRS total score of 7 or lower at the post NF training visit).

Secondary efficacy endpoints included measuring anhedonia change from baseline to the post NF training visit via the clinician administered Snaith Hamilton Pleasure Scale (SHAPS-C); the Clinical Global Impression-Improvement (CGI-I) score at each visit until the post NF training visit; the change from baseline to the post NF training visit in Quick Inventory Depressive Symptomatology (QIDS-SR-16); the change from baseline to the post NF training visit in General Anxiety Disorder-7 (GAD-7) and the change from baseline to the post NF training visit in Patient Health Questionnaire (PHQ-9).

Safety endpoints included the frequency, severity, and causality of adverse events (AEs), related and unrelated to Prism NF training.

Statistical methods:

Statistical analyses were performed using SAS®V9.4 (SAS Institute Cary, NC, USA). The following analysis sets defined for this study were as follows: Full Analysis (FA) set which consisted of all subjects enrolled who receive at least one Prism session; Efficacy Analysis (EF) set which consisted of all subjects from the FA set who in addition met the inclusion criteria of the protocol even retrospectively and had 10 sessions and; Per Protocol (PP) analysis set which will consist of all subjects from the EF set who finished the study without major protocol violations and had at least 10 completed sessions where a signal was recorded and detected. If there was no statistically significant difference in the EF, FA or PP, the EF only was presented. Study data was summarized with descriptive statistics and presented in tables and figures. For comparison of means (continuous variables), the two-sample t-test or the Wilcoxon rank sum test was used as appropriate. For comparison of proportions (categorical variables), the chi-squared test or Fisher's exact test was used as appropriate. A hierarchy approach was adopted for the primary and secondary endpoints to control type I error due to multiple endpoint testing. Thus, the primary endpoint was first analyzed and only if successful would the secondary endpoints be analyzed. Analysis of the primary endpoint - the change from baseline to the post NF training visit (6 weeks) in HDRS-17 was modeled using a linear mixed model for repeated measures. The change from baseline in HDRS-17 was modelled as a function of visit (categorical: Mid NF, Post NF), baseline HDRS-17 value was entered as a covariate, site was entered as a random effect but if the model does not converge it was entered as a fixed effect. LSmean HDRS-17 scores per visit were calculated and presented with level of significance (testing the null hypothesis that the LSmean=0) and 95% confidence interval. The mean change in

HDRS-17 during the post NF training visit (6 weeks) was compared to the performance goal of -4, rejecting the null hypothesis if the upper bound of the 95% confidence interval of the LSmean of the post NF training visit (6 weeks) is lower than -4. The mean change from baseline SHAPS-C, CGI-I, QIDS-SR-16, GAD-7, PHQ-9 to the post NF training visit, were modeled using ANCOVA (a repeated measures model was used for SHAPS-C and CGI-I) with the baseline value as a covariate (except for CGI-I). LSMEANS were calculated and presented with 95% confidence intervals and level of significance (testing the null hypothesis that the LSmean=0) for each variable. Poolability was assessed by adding the variable site to the primary endpoint analysis model as an additional covariate (in the EF and FA sets) and was tested at a significance level of 10%.

Results:

The disposition of the subjects is detailed in Table 2. Forty-nine (49) participants were screened. 44 were enrolled into the full analysis set (FA). Three withdrew prior to any sessions, and 7 withdrew before the final efficacy outcome measures. The Efficacy Analysis (EF) set included 34 subjects and was identical to the per protocol (PP) or completer set. There were no major protocol violations. There was no statistically significant difference between the sites for the primary endpoint. Therefore, the data from the sites was pooled.

Table 1 shows the disposition of patients based on FA, EF, and PP:

	Number of Subjects
Screened	49
Screen Failures	5
FA analysis set	44
Completed 1 session	1
Completed 3 sessions	2
Completed 4 sessions	1
Completed 6 sessions	1
Completed 7 sessions	2
Did not start NF sessions	3
EF analysis set	34
Major Protocol Violation	0
PP analysis set	34

Safety analysis (AEs):

While 25% of the subjects experienced AEs (20 AEs in total), the majority were mild in nature with: 12 mild, 7 moderate and 1 severe. One of these AEs was related to the Prism software (headache), with 2 possibly related to the fMRI device. Most AEs were unrelated to the Prism device and included: sore throat, nausea, fever, cold and abdominal pain. One patient had an SAE which manifested as abdominal pain ultimately resulting in kidney stone removal (unrelated to the device or therapy).

Demographic and baseline characteristics (FA set)

Table 2 shows the baseline characteristics of enrolled in the trial. Table 3 shows the baseline values for the primary and secondary endpoints evaluated.

Table 2: Demographic and baseline characteristics – FA set (N=44)

			FA Set
Age (years)		**N**	44
		Mean (SD)	39.9 (11.03)
		Median [Range]	39.1 [21.5;64.6]
Gender	**Male**	**% (n/N)**	25.0% (11/44)
	Female	**% (n/N)**	75.0% (33/44)
Ethnicity	**Not of Hispanic or Latino origin**	**% (n/N)**	100% (44/44)
Race	**Caucasian**	**% (n/N)**	93.2% (41/44)
	Other	**% (n/N)**	6.8% (3/44)
Years of Education	**Did not finish High School**	**% (n/N)**	2.3% (1/44)
	High school diploma or equivalent	**% (n/N)**	40.9% (18/44)
	Some college, no degree	**% (n/N)**	15.9% (7/44)
	Associate degree (for example: AA, AS)	**% (n/N)**	4.5% (2/44)
	Bachelor's degree (for example: BA, BS)	**% (n/N)**	31.8% (14/44)
	Master's degree (For example: MA, MS)	**% (n/N)**	4.5% (2/44)
Marital Status	**Married**	**% (n/N)**	40.9% (18/44)
	Divorced	**% (n/N)**	29.5% (13/44)
	Single	**% (n/N)**	29.5% (13/44)
Laterality	**Right**	**% (n/N)**	95.5% (42/44)

	Ambidextrous	**% (n/N)**	4.5% (2/44)
Duration of current episode		**Mean (SD) in months**	72 (88.8)
Concomitant Meds	**SSRI/SNRI**	**% (n/N)**	66% (29/44)
	Cannabis	**% (n/N)**	16% (7/44)
	Benzodiazepine	**% (n/N)**	30% (13/44)
	Other	**% (n/N)**	36.4% (16/44)
Comorbidities	**Fibromyalgia**	**% (n/N)**	20.5% (9/44)
	Insomnia	**% (n/N)**	6.8% (3/44)
	PTSD	**% (n/N)**	4.5% (2/44)
	Migraine	**% (n/N)**	4.5% (2/44)
	Irritable bowel syndrome (IBS)	**% (n/N)**	4.5% (2/44)

Table 3: Baseline values of primary and secondary endpoints:

Primary and secondary endpoints	**Baseline value**
HDRS-17	19.1±6.26
SHAPS-C	38.8±6.85
QIDS-SR-16	15.5±5.03
GAD-7	11.4±5.74
PHQ-9	12.4±4.7

Clinical outcomes (EF set):

Primary efficacy outcomes

As shown in Table 3, the baseline HDRS-17 score was 19.1±6.26, and baseline SHAPS-C was 38.8±6.85, indicating moderate depression with significant anhedonia. The HDRS-17 primary endpoint, change from baseline to the post Prism NF training visit (6 weeks), is found in Table 4. The adjusted mean (LSmean) change from baseline for HDRS-17 was -8.00 [95% CI: -10.5; -5.41]; P<0.0001. The proportion of subjects who had a clinically meaningful reduction (at least 4 points reduction) from baseline in HDRS was 78.47% [95% CI: 58.83; 89.25%]. The proportion of patients achieving remission (HDRS≤7) was 32.25% (11/34) [95% CI: 17.39%; 50.53%] (post-hoc analysis). The proportion of subjects with at least a 50% reduction in HDRS-17 score (responders) was 38.24% (13/34) [95% CI: 22.17%; 56.44%]. Based on the primary outcome results for HDRS-17 the null hypothesis ($H_{0:}$ mean HDRS≥ -4) was rejected.

Secondary efficacy outcomes

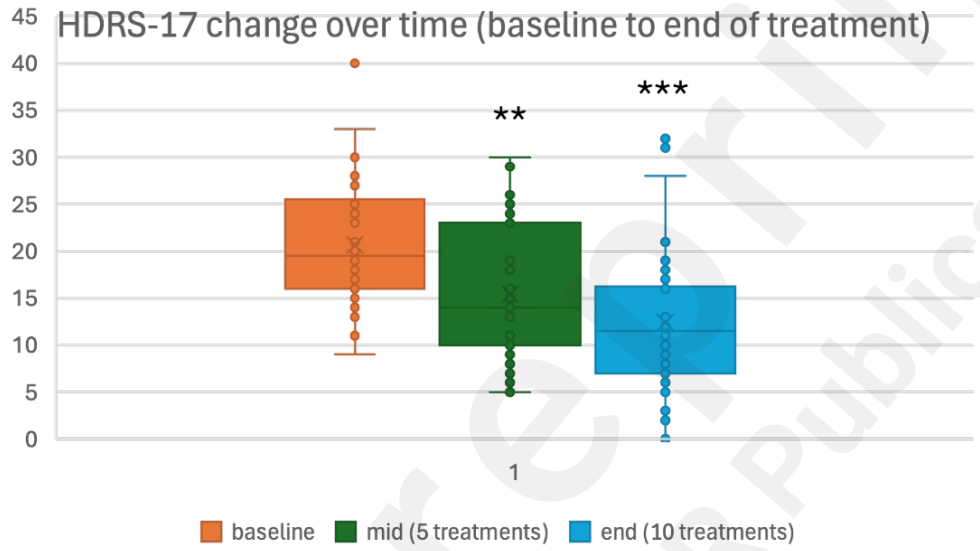
The changes from baseline in SHAPS-C, QIDS-SR-16, GAD-7, and PHQ-9 to 6 weeks (post training) for the EF set were found to demonstrate statistically significant improvements based on the repeated measures ANCOVA model described above. Notably, the proportion of subjects with at least a 50% reduction in SHAPS-C score was 76.5% (26/34) [95% CI: 58.83%; 89.35%]. (Table 4).

Table 4: Change from baseline HDRS-17, SHAPS-C, CGI-I, QIDS-SR-16, GAD-7 and PHQ-9 – EF set (mean difference)

Instrument	Baseline to 6 weeks assessment	
	LS means (95% CI)	P-value
HDRS-17	-8.0 (-10.5 to -5.41)	<0.0001
SHAPS-C	-6.3 (-8.51 to -4.14)	<0.0001
CGI-I	2.5 (2.22 to .,72)	<0.0001
QIDS-SR-16	-4.3 (-5.97 to -2.62)	<0.0001
GAD-7	-3.3 (-4.47 to -2.12)	<0.0001
PHQ-9	-4.7 (-7.94 to -1.40)	<0.0001

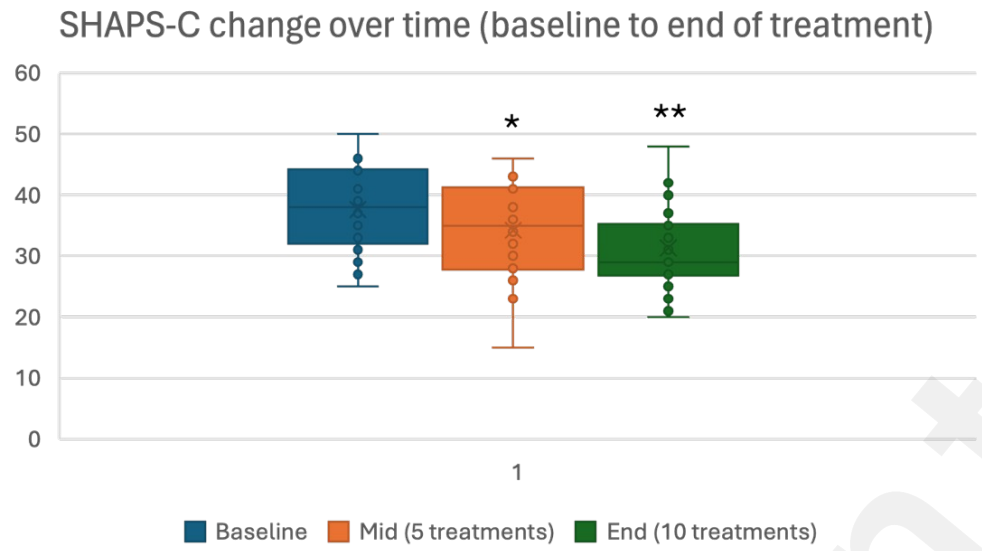
Figures 3 and 4 show the change in baseline to mid-point of training and from baseline to end of training for HDRS-17 and SHAPS-C. Both HDRS-17 and SHAPS-C scores showed progressive improvement from baseline through mid-treatment and end-of-treatment assessments. There appeared to be a dose response to Prism training, which did not reach a plateau level after ten treatments.

Figure 3: Change in HDRS-17 score over time (mean±SE))



**P<0.0001; ***P<0.0001

Figure 4: Change in SHAPS-C score over time (mean±SE)



*P=0.0032; **P<0.0001

Effect sizes and clinical significance

The effect sizes (standardized mean difference/Cohen's d) evaluated from baseline in HDRS-17, SHAPS-C, QIDS-SR-16, GAD-7, and PHQ-9 score to 6 weeks post training for the EF set were found to show statistically significant improvements and demonstrated moderate (0.5 to 0.8) to large (>0.8) effect sizes (Table 5).

Table 5: Effect sizes baseline to end of treatment (6 weeks).

Instrument	Effect size	P value
HDRS-17	1.22 [95% CI: 0.7 to 1.74]	<0.00001
SHAPS-C	0.92 [95% CI: 0.42 to 1.42]	0.0003
QIDS-SR-16	0.81 [95% CI: 0.31 to 1.3]	0.001
GAD-7	0.54 [95% CI: 0.06 to 1.03]	0.03
PHQ-9	0.75 [95% CI: 0.03 to 1.47]	0.04

Patient Satisfaction

A 5-item Patient Satisfaction questionnaire was used in this study, aiming to gauge the subjective satisfaction from the therapy and the study conduct. Table 6 presents descriptive statistics of the responses per question in each of the analysis sets (1=not satisfied through 5=very satisfied). Overall, subject satisfaction with the Prism training was high with 85.3% giving a score of 3 or higher out of a maximum score of 5.

Table 6: Subject satisfaction with Prism

		Mean (SD)
EF	To what extent you were satisfied from the NF training in this trial?	3.6 (1.05)
	In your opinion, how effective was the NF training?	3.6 (1.13)
	Would you recommend the use of the PRISM system (used in this trial) to your friends/family members?	3.7 (1.24)

Discussion:

The pilot study of Prism for Depression™ sessions in MDD patients with anhedonia demonstrated favorable outcomes across three key domains: (1) Safety: Only one device-related adverse event occurred (headache), which resolved without treatment. This favorable safety profile compares well with other biological and neuromodulation-based treatments, which often report higher rates of adverse events; (2) Efficacy: This self-neuromodulation intervention produced significant reductions in both depression and anhedonia with large effect sizes on clinician-rated measures (HDRS-17, SHAPS-C) and moderate improvements in self-reported measures of depression and anxiety (QIDS-SR-16, PHQ-9 and GAD-7); and (3) Acceptability: The majority of participants (>85%) reported satisfaction with the treatment, perceived it as effective, and would recommend it to others. This high completion rate (77%) compares favorably to typically higher dropout rates seen with treatments like TMS and pharmacotherapy.

Addressing the Anhedonia Treatment Gap

As it relates to clinically meaningful change, this study met the threshold identified in the STAR*D report (4–6-point reduction) for HDRS-17, with an average reduction of 8.0 points (95% CI: -10.5 to -5.41, $p<0.0001$), placing it in the range defined as "clinically substantial improvement." Notably, 78.5% of patients achieved clinically meaningful improvement (≥4-point HDRS reduction) and 32.25% achieved remission (HDRS≤7). The high proportion of patients showing clinical improvement suggests the intervention effectively addresses the core depressive symptoms in this population. The observed effect sizes were large for depression (HDRS-17, Cohen's d=1.22) and anhedonia (SHAPS-C, Cohen's d=0.92) measures, indicating substantial clinical impact that would be meaningful for both clinicians and patients.

The significant reduction in anhedonia symptoms (SHAPS-C average reduction of 6.3 points, 95% CI: -8.51 to -4.14, $p<0.0001$) addresses a critical treatment gap. The improvement through VS upregulation further supports the suggested mechanism for anhedonia of diminished reward processing. Future research should delineate the sub-processes of anhedonia, i.e., incentive versus hedonic components, which represent distinct but related aspects of reward processing. More precise

biomarkers targeting specific regions within the reward circuit (e.g., different parts of the VS; medial vs lateral, or ventromedial prefrontal cortex/orbitofrontal cortex connections) could substantially improve treatment personalization and outcome prediction. Such precision would allow tailoring of the intervention to address individual deficits in reward anticipation versus consumption.

Despite 66.6% of participants receiving concomitant SSRI/SNRI medications, these individuals showed robust decreases in depression and anhedonia as measured by HDRS-17 and SHAPS-C. Indeed, SSRI/SNRI medications are known to have limited benefit for anhedonia and may even have pro-anhedonic effects in some individuals[28,29]. This suggests that RS-EFP-NF may address symptom dimensions not adequately targeted by conventional pharmacotherapy.

Notably, improvement demonstrated a progressive pattern from baseline through mid-treatment to end-of-treatment (Figure 3), suggesting a cumulative benefit pattern possibly pointing to the benefit of booster sessions. This temporal dynamic has important implications for treatment prediction and relapse prevention, though further controlled studies of dosage and frequency are necessary. Based on the data analysis of mean, median, and mode (on the improvements from baseline to end of therapy) for the various instruments used, there does not appear to be a ceiling effect, suggesting that increasing the number of sessions or duration of sessions may have an additional positive effect on effectiveness.

Comparison with Existing Treatment Approaches

The remission rate of 32.25% compares favorably to typical ranges (11-30%) for effective depression treatments as reported by Mendlewicz et al. 2008[30]. Current pharmacotherapies, particularly SSRIs/SNRIs, often improve mood symptoms but leave residual anhedonia symptoms, representing a specific treatment challenge.

Conventional NF approaches for depression target either process/non-neuroanatomically defined EEG patterns (e.g., alpha asymmetry) or amygdala-fMRI-NF upregulation[31]. demonstrated the efficacy of real-time fMRI amygdala NF for MDD, focusing on emotion regulation rather than reward processing. In contrast, RS-EFP's focus on reward system activity offers a more neuroanatomically and process targeted approach to anhedonia. As mentioned above, this can be further improved for subprocesses of reward processing through more granular assessment of reward anticipation versus consumption deficits.

While NF has not been included in MDD treatment guidelines, a recent systematic review and meta-analysis concluded that patients with depression showed significant cognitive, clinical, and neural improvements following electroencephalogram NF (EEG-NF) training[32]. The studies examined EEG-NF without targeting deep brain structures associated with anhedonia. A recent meta-analysis including both fMRI and EEG NF demonstrated a reduction in self-reported depression[33]. The advantage of Prism is that it combines both EEG and fMRI through machine learning, making the technology affordable and specific to evaluating the functionality of the brain reward system.

This approach could fit into the treatment landscape as a complement to existing options, particularly for patients with inadequate response to standard treatments. The importance of self-driven treatment, enhancing sense of agency over one's condition and targeting endogenous mental processes represents a unique benefit of NF compared to passive treatments.

The Potential for Scalable Clinical Implementation/Feasibility

The RS-EFP-NF approach offers a non-invasive intervention that delivers a targeted approach to address reward system-related processes that underlie depression. This aligns with the Research Domain Criteria [RDoC] framework[34], which encourages focusing on fundamental neurobiological dimensions across traditional diagnostic categories rather than symptom-based diagnoses alone. Its potential for broader implementation stems from minimal training requirements for both therapists and patients, supervision possible by non-physician personnel, well-defined treatment protocol with potential for real-life skill translation (through mental strategy development), and low adverse event profile. Though longer follow-up is needed to confirm translation of learned skills to everyday situations.

Patient-centered self-regulation skills learned during treatment could potentially extend beyond the sessions. Practical advantages include accessibility and the potential for integration into existing treatment pathways, especially with psychotherapy. NF interventions have shown promising results when combined with traditional psychotherapeutic approaches[35]. In treatment-resistant depression, this could be especially beneficial, considering that despite many existing pharmacological and psychological approaches, not everyone responds adequately.

Methodological Considerations and Limitations

Several limitations should be considered when interpreting these results. The single-arm design without a control/comparison group limits causal inferences and cannot account for non-specific effects such as expectancy, therapist attention, or natural symptom fluctuation. The sample characteristics (predominantly female, non-treatment-resistant, specific age range, multiple sites but in one country) limit worldwide generalizability.

The fixed treatment parameters (10 sessions) prevent determination of optimal dosing and boostering strategies. The absence of follow-up assessments leaves questions about durability of observed benefits and skill translation, which could be addressed in future home-based approaches. Additionally, we were unable to determine specific mechanisms underlying the observed clinical improvements, which would require subprocess assessments through questionnaires and experimental tasks specifically designed to differentiate between reward anticipation, reward valuation, and reward consumption processes. Such assessments would significantly improve treatment personalization by identifying which components of the reward system are most compromised in individual patients.

To address these limitations, a randomized controlled trial is currently underway (NCT05869708). Future research should focus on optimal treatment protocols (session number, frequency, duration), maintenance strategies and relapse prevention approaches, long-term durability of clinical benefits, applicability to more diverse populations (including treatment-resistant cases), and comparative effectiveness versus and in combination with standard treatments.

Conclusion

In conclusion, these promising initial results suggest that RS-EFP-NF represents a novel approach to addressing the critical unmet need for effective anhedonia-targeted interventions in MDD, potentially offering patients a new pathway to recovery through direct engagement with reward system dysfunction. The approach demonstrates safety and promising clinical benefit in MDD with anhedonia, addressing an important gap in current treatment options. If confirmed through controlled

trials, this approach could represent a valuable addition to the therapeutic options for depression with anhedonia, particularly for patients with residual anhedonic symptoms despite standard treatments.

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Conflicts of interest:
AT is the medical director for Gray Matters Health, the developer and manufacturer of the Prism device. JV is a reimbursement and outcomes expert consultant hired by Gray Matters Health. Tal Harmelech is a neuroscience and medical affairs expert consultant hired by Gray Matters Health. Talma Hendler is the inventor of the EEG-fMRI-Pattern (EFP) digital biomarker used in the Prism device.

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Supplementary Files