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Limbic Self-Neuromodulation as a Novel Treatment Option for Emotional Dysregulation in Premenstrual Dysphoric Disorder (PMDD); a Proof-of-Concept Study

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ABSTRACT

Aim: To assess the efficacy of a novel neurofeedback (NF) method, targeting limbic activity, to treat emotional dysregulation related to premenstrual dysphoric disorder (PMDD).

Method: We applied a NF probe targeting limbic activity using an fMRI-inspired EEG model (termed Amyg-EFP-NF) in a double-blind randomized controlled trial. A frontal alpha asymmetry probe (AAS-NF), served as active control.

Twenty-seven participants diagnosed with PMDD (mean age=33.57 years, SD=5.67) were randomly assigned to Amyg-EFP-NF or AAS-NF interventions with a 2:1 ratio, respectively. The treatment protocol consisted of 11 NF sessions through three menstrual cycles, and a follow-up assessment 3 months thereafter. The primary outcome measure was improvement in the Revised Observer Version of the Premenstrual Tension Syndrome Rating Scale (PMTS-OR).

Results: A significant group by time effect was observed for the core symptom subscale of the PMTS-OR, with significant improvement observed at follow-up for the Amyg-EFP group compared with the AAS group ($F(1,15)=4.968$, $p=.042$). This finding was specifically robust for reduction in anger ($F(1,15)=22.254$, $p<.001$). A significant correlation was found between learning scores and overall improvement in core symptoms ($r=.514$, $p=.042$) suggesting an association between mechanism of change and clinical improvement.

Conclusion: Our preliminary findings suggest that Amyg-EFP-NF may serve as an affordable and accessible non–invasive treatment option for emotional dysregulation in women suffering from PMDD. Our main limitations were the relatively small number of participants and the lack of a sham-NF placebo arm.

Key words: Amygdala Electrical Fingerprint, Emotional Dysregulation, Neurofeedback, Premenstrual Dysphoric Disorder (PMDD)

INTRODUCTION

Premenstrual dysphoric disorder (PMDD) causes significant suffering and disability in 2%–8% of females of reproductive age worldwide (1–3). Evidence suggests that changes in reproductive steroid levels during the premenstrual phase of the menstrual cycle, specifically during the luteal phase, trigger emotional dysregulation in susceptible subjects, causing the hallmark symptoms of PMDD – affective lability, depression, anxiety and anger (4,5). Indeed, one of the underlying processes thought to be at the crux of PMDD is impaired emotional regulation (ER), a multifaceted construct, including the awareness, understanding, and acceptance of one's emotions; the ability to control impulsive behaviors when experiencing negative emotions; and the ability to modify strategies for managing emotions according to situational demands and goals (6–8).

The most efficacious treatments for PMDD are considered to be selective serotonin reuptake inhibitors (SSRI's) and contraceptives with shortened to no hormone-free interval (9,10), but their use is frequently limited due to disturbing side-effects (11). Considering the mass disease burden associated with PMDD (12), there is public health impetus for developing new treatment options for this disorder (13).

The neuronal system associated with ER is traced back to the limbic system, a central hub of emotional response, and specifically to amygdala activity, which is disturbed in multiple disorders of ER including PMDD (14,15). The identification of amygdala hyperactivity as a key neural substrate in emotion dysregulation and PMDD (16), suggests a potential for ameliorating ER symptoms by the use of self-neuromodulation procedures that adjust amygdala neuronal activity. Regulation of amygdala activity can be obtained volitionally via a closed-loop brain-computer-interface guided procedure of reinforcement learning termed neurofeedback (NF), using real-time functional magnetic resonance imaging (fMRI). However, applying this technique in clinical settings has a major scalability disadvantage (e.g., accessibility, mobility, and cost-effectiveness). To overcome these difficulties, we applied a validated NF approach of fMRI-inspired electroencephalogram (EEG) model of amygdala activity termed Electrical-Finger-Print (Amyg-EFP) (17,18),that combines the anatomical advantages of fMRI (especially for targeting limbic activation) with the scalability of EEG, i.e., enhanced anatomical precision and widespread availability, respectively.

Amyg-EFP has already shown promising results in both healthy and clinical populations. Specifically, repetitive Amyg-EFP training showed improved indices of ER among individuals undergoing a stressful military training program (19), and improved ER abilities in individuals with tenacious and chronic post-traumatic stress disorder (20).

In this study we sought to test the Amyg-EFP-NF probe, as a mechanism-based therapeutic intervention to alleviate impaired ER in participants diagnosed with PMDD. We applied a double-blind randomized controlled trial with an active control of EEG-NF using frontal alpha asymmetry (AAS-NF), which has previously been used in a variety of psychiatric disorders including depression (21). Our exploratory hypothesis was that participants undergoing Amyg-EFP-NF training will be able to better regulate negative emotions in the luteal phase, compared to those trained by AAS-NF.

Methods

Participant Selection and Symptom ratings

Patients were recruited via on-line advertising and clinician's referrals. Inclusion criteria included: females at reproductive age, with a regular menstrual cycle (i.e., 21–35 days), who were initially positively screened for PMDD using the Premenstrual Symptoms Screening Tool (PSST) (22). The participants were then diagnosed with "provisional PMDD" according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) (4) in a clinical interview by a senior psychiatrist. Prospective affirmation of the diagnosis was made by documenting two symptomatic menstrual cycles using the Daily Record of Severity of Problems questionnaire (DRSP) (23) by email (via the Qualtrics software – Qualtrics, Provo, UT). A cycle was considered symptomatic if meeting the following criteria: at least a moderate level of severity (score of 4) for at least two days (out of the 5 premenstrual days evaluated) in at least 5 symptoms, one of which had to be a core symptom (depression, anxiety, lability or anger), and a similar score in one or more of the impairment items; an average of no greater than mild (score of 3) on any of the symptoms during the postmenstrual phase (days 6-10) (23). Alternatively, we considered a cycle symptomatic if we calculated a 30% decrease (or more) from the luteal to the follicular phase in the mean score of at least five symptoms, including at least one core symptom, and a similar 30% decrease in at least one of the impairment items; an absolute luteal phase mean score equal to or greater than 2.5 (24,25). Exclusion criteria included: current pregnancy, moderate to severe polycystic ovary disease, endometriosis, usage of a hormonal intrauterine device (IUD), recent initiation (less than 3 months) of antidepressant pharmacological treatment or hormonal contraceptive treatment, current diagnosis of a major depressive episode, psychotic disorder, substance dependence or abuse other than nicotine in the 30 days prior to screening. A previous or current diagnosis of an anxiety disorder was not exclusionary.

Patients were evaluated by a clinician upon initiation of training (described below), and following every cycle thereafter, before ovulation and shortly after onset of menses, using the Revised Observer Premenstrual Tension Syndrome Rating Scale (PMTS-OR). This scale is widely used as an outcome measure in clinical trials of treatment of Premenstrual Syndrome. We used the updated version that includes 11 items (O=observer, R=revised), checking the core symptoms of PMDD – mood

lability, anger, depression, and anxiety, as well as other common symptoms including change in sleep pattern, increased appetite, poor concentration and more. The scale is simple to complete and was found to be reliable, valid and sensitive to change.(26). Importantly, The PMTS-OR reflects emotional dysregulation in two ways: first, a specific item relates to lability of mood (in contrast with scales assessing depression that usually focus only on the quality of mood, e.g., the Montgomery-Asberg Depression Rating Scale (MADRS)(27)). Second – the PMTS-OR is administered in both the follicular and the luteal phase, and only patients with no (or minimal) symptoms in the follicular phase were included in this study, thus pointing to the temporary dysregulation of emotional symptoms that characterizes PMDD. A follow-up evaluation was obtained three months after the completion of NF training to evaluate the lasting effect of the treatment. Improvement in the PMTS-OR served as the primary outcome measure.

Study Design

The study was conducted at the psychiatric outpatient clinic and the Sagol Brain Institute, at the Tel Aviv Sourasky Medical Center as an explorative trial. All participants signed informed consent forms, approved by the local ethics committee. The study conforms to the provisions of the Declaration of Helsinki.

Following diagnosis confirmation, patients were randomly assigned using a computerized algorithm to either Amyg-EFP-NF or AAS-NF interventions on a 2:1 ratio, to promise a suitable number of participants in the test group. Patients and evaluators were blinded to study intervention type (known only to the technician applying the NF treatment).

The treatment protocol consisted of 11 NF sessions of either Amyg-EFP-NF or AAS - NF performed over three consecutive reproductive cycles: In the 1st cycle six NF sessions were performed, two per week for the first three weeks starting on day 6-10 of the follicular phase; In the 2nd cycle, three NF session were performed – one per week for three weeks starting on day 6-10 of the follicular phase; and in the 3rd cycle, two "maintenance" NF sessions were performed – one in the week after ovulation (early luteal phase) and the second on day 2-3 of the following follicular phase. As there are no prior studies with this intervention in this population, timing of sessions wasn't based on precedent but assumed that learning would be easier on symptom-

free days, followed by rest in the late luteal phase, and focusing on more intense learning at the beginning of the trial.

Neurofeedback training procedure

Patients were trained to downregulate Amyg-EFP signal or AAS index using two interfaces for feedback: an auditory interface in which a neural signal correlated with the volume of a soft piano tune (performed with eyes closed) (28), and a 3D audio-visual animated scenario (29) in which the neural signal correlated with the level of unrest in a virtual waiting room indicated by the number of virtual characters aggregating in front of a receptionist and the loudness of their voice (30).

The paradigm across the 11 sessions followed a similar block design that constituted of a 3-minute global baseline and consecutive conditions: (1) attend (2) regulate (3) washout. During "attend", participants were instructed to passively view the interface animation or listen to a tune and were explained that, at this time, the feedback was not influenced by their brain activity. During "regulate", participants were instructed to find the mental strategy that would cause the feedback to change accordingly (make figures sit down and lower their voices or reduce the tune volume). During "washout" participants tap their thumb according to a 3-digit number that appears on the screen (an animated scenario) or open their eyes while a graph displaying their performance in the last trial appears on the screen (auditory interface). Following the global baseline; the auditory interface included 4 cycles (each with 5 minutes regulate), and the animated interface included 5 cycles (1 minute attend, 1 minute regulate, 30s washout). The combined sessions included 3 minutes global baseline followed by 3 auditory cycles (each with 3 minutes regulate), and 2 animated cycles (1 minute attend, 1 minute regulate, 30s washout). In sessions 1 + 3 the animation interface was used and in sessions 2 + 4 the auditory interface. Sessions 5-11 combined both interfaces while sessions 5, 6, 9 and 10 also contained 2 cycles of "transfer training" at the end of the session (1 minute attend, 1 minute regulate), which requires participants to perform the learned regulation without receiving feedback. The two different interfaces were implemented to keep participants engaged throughout NF training.

EEG acquisition

EEG data was acquired using the V-Amp™ EEG amplifier (Brain Products™,

Munich Germany) and the BrainCap™ electrode cap with sintered Ag/AgCI ring electrodes (Falk Minow Services™, Herrsching-Breitburnn, Germany). Electrodes were positioned according to the standard 10/20 system. The reference electrode was between Fz and Fcz. Raw EEG signal was sampled at 250 Hz and recorded using the Brain Vision Recorder™ software (Brain Products). The RecView software makes it possible to remove cardio-ballistic artifacts from the EEG data in real time using a built-in automated implementation of the average artifact subtraction method (31). RecView™ was custom modified to enable export of the corrected EEG data in real time through a TCP/IP socket. Preprocessing algorithm and Amyg-EFP calculation models were compiled from Matlab R2013b™ to Microsoft.NET™ to be executed within the Brain Vision RecView™ EEG Recorder system. Data were then transferred to a MATLAB.NET-compiled Dynamic Link Library (DLL) that calculated the value of the targeted signal power every 3s.

Amyg-EFP model

The Amyg-EFP model was previously developed to enable the prediction of localized limbic related activity using EEG only (18). This was done by applying machine learning algorithms on EEG data acquired simultaneously with fMRI. The procedure resulted in a *Time-Delay X Frequency X weight* coefficient matrix. EEG data recorded from electrode Pz at a given time-point are multiplied by the coefficient matrix to produce the predicted amygdala fMRI-BOLD activity. Keynan (2016) validated the reliability of the Amyg-EFP in predicting amygdala BOLD activity by conducting simultaneous EEG-fMRI recordings using a new sample not originally used to develop the model (32).

NF on-line calculation of Amyg-EFP and AAS

Online EEG processing was conducted via the RecView software (Brain Products). Amyg-EFP data were collected from electrode Pz and the AAS - EEG Alpha band (8-12Hz) was extracted from electrodes F3, F4 and transmitted to the RecView system. The current study used the asymmetry score developed by Davidson (33), in a similar manner to that of Rosenfeld (34). Rosenfeld defined R as alpha power at cortical site F4 and L as alpha power at cortical site F3 (using the standard 10-20 electrode placement standard). The asymmetry score can be computed either as A1=logR-logL or as A2=R-L/(R+L) as the two scores are highly correlated (≥.98) (35).

Similar to previous studies (19,30,36), NF success measure was assessed by calculating a personal NF success index for each subject in each session using the following formula (Cohen's d) (37):

Effect size = (mean baseline – mean regulate) / √(SD baseline ^{2} + SD regulate^2).

The NF learning index is a continuous measure that can range from positive (meaning up regulation) to negative (meaning down regulation). We consider any negative value of this index as successful down regulation as it is calculated as the delta between the average of the NF cycles and the average of the baseline cycles, divided by the standard deviation of the baseline and regulation cycles. The baseline in auditory sessions was the global baseline, and in the animation scenario, the baseline was the active baseline block in each training cycle.

Data Analysis

Clinical outcome: changes in clinical assessment were analyzed using PMTS-OR scores at baseline, following each month of training, and at follow up, for a total of five repeated measures. Changes in scores for the four core symptom subscales (anger, depression, mood lability, and anxiety) in the PMTS-OR, as well as their total, were then compared between groups. Our approach included two complementary analyses: per protocol (PP) analyses, including only completers of the full study protocol including follow up, as well as the intent-to-treat (ITT) analyses. This approach allows maximizing power, reducing type I error probability, and providing for data that may not be normally distributed or not missing completely at random, such as skewed dropout, with ITT, which provides information as to the potential effects of assigning patients to a specific condition. PP analyses complement this by directly examining the effects on patients of clinical protocols administered as intended(38). PP analyses were conducted using a repeated-measures ANOVA, with a time (5) X group (2) design, for each outcome, or dependent, variable. Thereafter we conducted general linear mixed models (GLMM) analyses on the ITT sample. Maximum Likelihood (ML) method was used. Fixed effects included group, time, and group by time interaction. No random effects were included. For ANOVA, main effects of time and group status were examined as well as interaction of time by group status to gauge effects for the relationship between NF and symptom change. Several control analyses were conducted: PP and ITT repeated measures analyses were conducted for NF trials at the same five time-points to gauge any group by time

interactions in participants' learning of the NF target response. None of these analyses yielded significant group by time effects, supporting the specificity and validity of the clinical findings reported below.

NF learning: NF learning was assessed among completers using a repeated measures ANOVA examining overall learning effects over trials utilizing a 2(group)X2(cue)X9(NF session) design (cue refers to the type of intervention used, whether the auditory or the animation interface).

All analyses were conducted using SPSS version 27, Lisenced by IBM and its corporations, 1989, 2020.

RESULTS

Fifty participants passed the initial phone screening phase and began DRSP evaluation. Of these, 28 had a confirmed prospective diagnosis of PMDD. One dropped out prior to randomization and thus 27 participants underwent randomization on a 2:1 basis favoring Amyg-EFP. These patients included females aged 23 to 47, with no significant differences between groups (see Table 1 for demographics). Demographic results were descriptive and expressed as mean ± standard deviation of continuous variables and Chi-squared comparisons of proportions for categorical variables. In the Amyg- EFP group 4 participants received a SSRI or SNRI, as did one participant in the AAS group. Yet their treatment was initiated more than 3 months before enrollment and was stable throughout the trial.

Seven patients dropped out of the trial due to various reasons (1 due to family health issues, 2 started hormonal medication for health reasons, 1 dealt with a recurrence of cancer, and 4 did not adhere to the treatment timetable), resulting in 20 patients completing the full NF training course - 13 from the Amyg-EFP group and 7 from the AAS group. A follow up evaluation was obtained three months after the completion of training, to assess the lasting effect of treatment. Out of the 20 patients that completed training, 17 completed the clinical follow-up evaluation (out of the 13 Amyg-EFP group 3 patients did not show up for the follow-up evaluation, 2 did not wish to continue, and one conceived after the training), resulting in 10 patients in the Amyg-EFP group and 7 in the AAS group. For the full patient flow chart, see Figure 1.rCompleters and non-completers did not differ in any demographic or clinical variables, apart from a lower depression subscale score for the non-completing group (F=34.422, p<.001; see Table S2 for more information).

Clinical analyses

A significant main effect for time was observed on core PMTS-OR scale and subscales in ANOVA, and all apart from depression and mood lability in GLMM. A group effect was observed only in core symptoms and only in ANOVA, with higher baseline scores in the Amyg-EFP group driving the difference (Table 2, Figure 2; also see Table S1 in the supplement for specific time point group differences). Overall core PMTS-OR score showed a group by time effect, significantly so in ANOVA and trend-level in GLMM, favoring improvement in the Amyg-EFP group [$F(1,15)$=4.968, p=.042 for group by time linear effect in ANOVA, $F(4,88)$=2.36,

p=.059 for group by time interaction in GLMM]. Within core subscales, only anger showed a similar significant effect [*F(1,15)*=22.254, *p*<.001 for group by time linear effect in ANOVA, *F(4,88)*=4.07, *p*=.004 for group by time interaction in GLMM], with nonsignificant interaction effects on depression and anxiety, and a significant effect on mood lability in GLM [(*F(1,15)*=4.753, *p*=.046] that did not remain significant when GLMM was used [*F(4,88)*=1.529, *p*=.201]. Post-hoc tests showed that core symptoms, as well as anger and mood lability subscales, were higher in the Amyg-EFP group at baseline as compared to the AAS group, and that core symptoms, anger, and anxiety were lower in Amyg-EFP group as compared to AAS group at final follow up (see Table S1 in the supplement). Outlier examination using boxplots revealed only two instances of outliers at baseline: one outlier was in the AAS group, and reported no mood lability at baseline (0 on the subscale), and one was in the Amyg-EFP group, with very low anger at baseline (1 on the subscale). Therefore, these outliers were unlikely to drive group differences.

NF Learning analyses

The ANOVA revealed a significant effect for session (F=5.475$_{(8.10)}$, p=.008, η_p^2=.814) and significant interactions between cue and group (F=4.989$_{(1.17)}$, p=.039, η_p^2=.227), session by group (F=8.817$_{(8.10)}$, p=.001, η_p^2=.876), and cue by group by session (F=3.631$_{(8.10)}$, p=.030, η_p^2=.744) and therefore separate analyses were conducted by cue. No learning effect was found over sessions in the WR condition (F=1.724$_{(8.11)}$, p=.198, η_p^2=.556), nor was there a significant group by session effect (F=.465$_{(8.10)}$, p=.856, η_p^2=.253). A significant group effect favoring the Amyg-EFP condition (M=-1.580, SE=.222 vs. M=.025, SE=.291; F=19.162$_{(1.17)}$, p=<.001 η_p^2=.530), learning effect was found in the auditory condition (F=3.704$_{(8.10)}$, p=.028, η_p^2=.748), with a group by session interaction (F=5.063$_{(8.10)}$, p=.010, η_p^2=.802). To examine the relationship of transfer effects with change in symptoms, transfer was added as a covariate to the above analyses, with null results [F=.222$_{(1.14)}$ p=.645].

Association between learning and clinical improvement

In accordance with our exploratory hypothesis, a significant correlation was found between best composite learning score (i.e., the score composed of auditory and visual learning index scores during best NF session for the individual learner) and

overall improvement in core symptoms (r=.514, p=.042). This was in line with hypotheses, suggesting a specific association between mechanism of change and clinical improvement.

DISCUSSION

In this proof-of concept study we report that an EEG based neurofeedback technique aimed at downregulating the amygdala, helped alleviate core symptoms associated with PMDD, specifically anger and mood lability. The effect of this intervention on the clinical outcome was mainly evident three months after NF training ended. In contrast, participants who received NF training aimed at improving alpha asymmetry (AAS), did not retain their initial clinical improvement on a three-month follow-up. Previous studies have shown that some pharmacological agents, mainly SSRI's, help reduce symptoms of PMDD in similar magnitude in a portion of patients (10), yet this intervention was not specifically aimed at emotional regulation (ER) symptoms, mainly anger and mood lability, that are thought to be at the crux of PMDD (6–8). On a neural basis, ER is linked to the limbic system, a central hub of emotional response, which was therefore chosen as a target of our intervention. Our focus on limbic related modulation is also congruent with the general notion that the amygdala is considered the most common target for assessing emotion regulatory outcomes (15,39,40) and novel emotion regulation neurofeedback studies probe the modulation of limbic areas as the target for regulatory implementation (41–43). Our findings echo those described in clinical populations with mental disorders in which ER is a central symptom. For example, patients with post-traumatic stress disorder (PTSD) demonstrated successful amygdala down-regulation that corresponded to increased connectivity with emotion related prefrontal regions (44), and patients with borderline personality disorder learned to down-regulate their amygdala activity using rt-fMRI-NF (45).

The experience gained in our lab at providing EEG-based interventions that specifically target the amygdala, without having to use costly and less accessible fMRI techniques, enabled us to propose a relatively easy to use mechanism-based treatment option for PMDD, that focuses primarily on improving ER – Amyg-EFP-NF (17,18).

Our findings showed that patients in the Amyg-EFP group retained their improvement 3 months after the conclusion of training.. This finding is consistent with previous studies of clinical populations (OCD and Tourette syndrome), whose symptoms improved continuously up to 80 days post NF training (46). Similar patterns were evident at the behavioral, clinical and neural levels in previous NF studies focusing on attention bias and emotional regulation, among others (47–49). Two mechanisms are suggested to underlie these latent effects. The first is behavioral: much like other coping skills, such as those acquired by cognitive behavioral therapy (also demonstrated to have a latent effect (50)), NF can turn into a skill that is integrated into daily life. Hence, as time goes by, it is possible that trainees continued to

practice the new skill they acquired, and thus symptoms and neural regulation continued to improve. The second mechanism suggested relates to neural learning principles: over time, consolidation and reconsolidation processes that underlie learning paradigms such as NF are likely to take place. As these processes occur regardless of practice, synchronization, or desynchronization of the targeted brain process may increase over time (46).

Our findings suggest that significant learning over time was only apparent in the Amyg-EFP group, which was also the group that retained much of the clinical improvement observed upon follow-up. We do not have a full explanation as to why learning differed between the two groups but assume that the non-specific intervention (AAS) did not bring upon positive changes in neural circuits related to the participants clinical situation, and thus was not reinforced and learnt.

Symptoms of PMDD occur classically in the late luteal phase of the menstrual cycle, a time characterized by low estrogen levels and a drop in progesterone levels. The precise mechanism that precipitates symptoms is unknown, and neither is the mechanism underlying the alleviation of these symptoms through Amyg-EFP. Nevertheless, the localization of this effect to the limbic regions is not surprising as this area is rich with both progesterone and estrogen receptors (51,52). Ovarian hormones have been reported to influence emotional processing and the regions involved in these processes (e.g. the amygdala) are direct and indirect targets of these hormones (53,54).

In previous studies, the strong placebo effect of NF interventions was addressed (55,56). We did not use a sham control group, but rather an active control group receiving AAS-NF. This group of patients showed modest clinical improvement during the NF-training, an improvement that was not retained after cessation of treatment. A possible explanation to this observation is that the AAS-NF intervention might have had some soothing effect while applied, yet it did not modify basic ER capacities as did the Amyg-EFP intervention, and thus the effect did not last.

The strengths of our study include the meticulous screening and diagnosing processes, that rendered a group of symptomatic PMDD patients and enabled achievement of significant results in this small cohort. Our main study limitation was indeed the relatively small number of participants, due to the challenging recruitment procedure and the demanding training protocol. Future study directions may include a larger scale of patients, as well as considering using a placebo arm (sham-NF) or other active control arms. There was also a significant difference in symptom level at baseline between the groups. Yet. although people with severer

symptoms may improve to a greater degree – this improvement was manifest in lower symptoms at 6 months from baseline, suggesting treatment effect and not an artifact.

In conclusion, using a randomized, double blind, controlled design we showed that Amyg-EFP-NF may serve as an accessible non-pharmacological, non–invasive treatment option for women suffering from PMDD, a disorder that currently has limited treatment options. This preliminary study, that needs to be expanded, further serves to support the clinical potential of mechanism-based fMRI driven EEG-NF approaches that target specific neural processes relevant to different disease states, offering a highly accessible therapeutic tool, both in medical settings as well as in the patient's home environment.

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Supporting Information Legend

Table 1: Demographics by group

Table 2: Results of ANOVA and GLMM

Figure 1: Study flowchart

Figure 2: PMTS-OR core and subscale symptom levels (a-e) over time by treatment group

Supplement:

Table S1: Differences in group clinical measures throughout the study

Table S2: Completers vs. non completers

Table 1

Demographics by group

Variable	***Categories***	***Group***		***Statistics***	
		AAS	*Amyg-EFP*	X^2	*P*
Marital status	Married	3	4	0.35	0.95
	Single	4	8		
	Divorced	1	1		
	Widowed	2	4		
Education	No matriculation	1	1	0.78	0.98
	Matriculated	1	2		
	Some post-matriculation education	1	1		
	BA	2	6		

	Some graduate studies	3	5		
	Graduate degrees	1	2		
Religiosity	Traditional	1	6	0.15	0.16
	Secular	9	11		
Employed	Yes	5	14	3.34	0.19
	No	4	2		
	Other	1	1		
Family income	Very much above average	0	1	3.04	0.55
	Above average	3	7		
	Average	2	4		
	Below average	4	2		
	Very much below average	1	2		
Variable		***M (SD)***		***t***	***P***
Age		33.09 (6.02)	33.7 (5.40)	-0.277	0.784

Note: Amyg-EFP=Amygdala fingerprint; AAS= Alpha asymmetry

Table 2: Results of ANOVA and GLMM

		ANOVA			***GLMM***	
		F(1,15)	***p***	***Partial η²***	***F(4,88)***	***P***
Core Symptoms	Group	0.916	**0.001**	0.012	0.04	0.843
	Time	17.363	**0.001**	0.537	6.743	**<0.001**
	Time*Group	4.968	**0.042**	0.249	2.362	0.059
Anxiety	Group	4.146	0.06	0.217	4.007	**0.048**
	Time	5.697	**0.031**	0.275	4.65	**0.002**
	Time*Group	1.736	0.207	0.104	1.293	0.279
Depression	Group	1.1	0.311	0.068	0.045	0.832

	Time	7.948	**0.013**	0.346	0.709	0.587
	Time*Group	0.148	0.706	0.01	0.228	0.922
Mood Lability	Group	0.724	0.408	0.046	2.295	0.133
	Time	8.241	**0.012**	0.355	1.844	0.128
	Time*Group	4.753	0.046	0.241	1.529	0.201
Anger	Group	0.565	0.353	0.561	0.578	0.449
	Time	52.37	**<0.001**	0.78	8.058	**<0.001**
	Time*Group	22.254	**<0.001**	0.597	4.072	**0.004**

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CONTRIBUTIONS: M.B., T.H., O.T and M.B.C conceived of the presented idea. D.P, P.B. A.H, G.A.R and Z.B.Z were involved in the recruitment of patients and the management of the clinical trial. L.H, N.F and N.G performed the computations and aided with statistical analysis. O.T orchestrated the writing of the paper. All authors discussed the results and contributed to the final manuscript.

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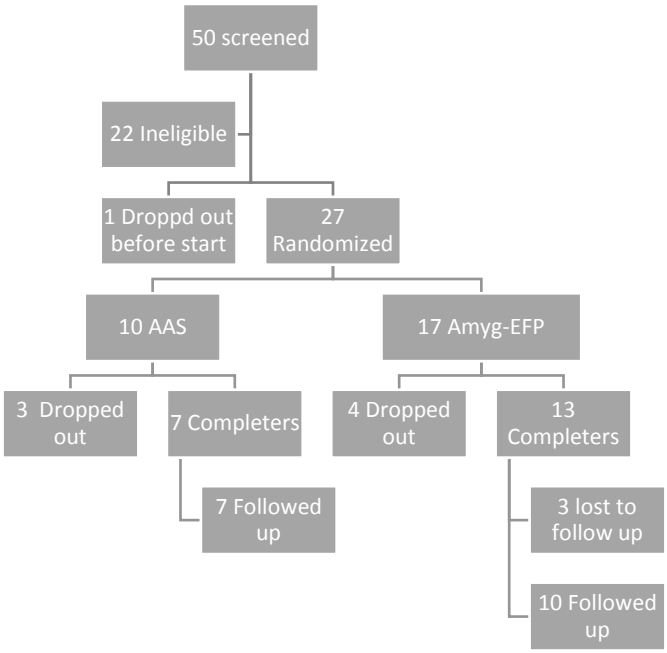
Figure 1: Study flowchart

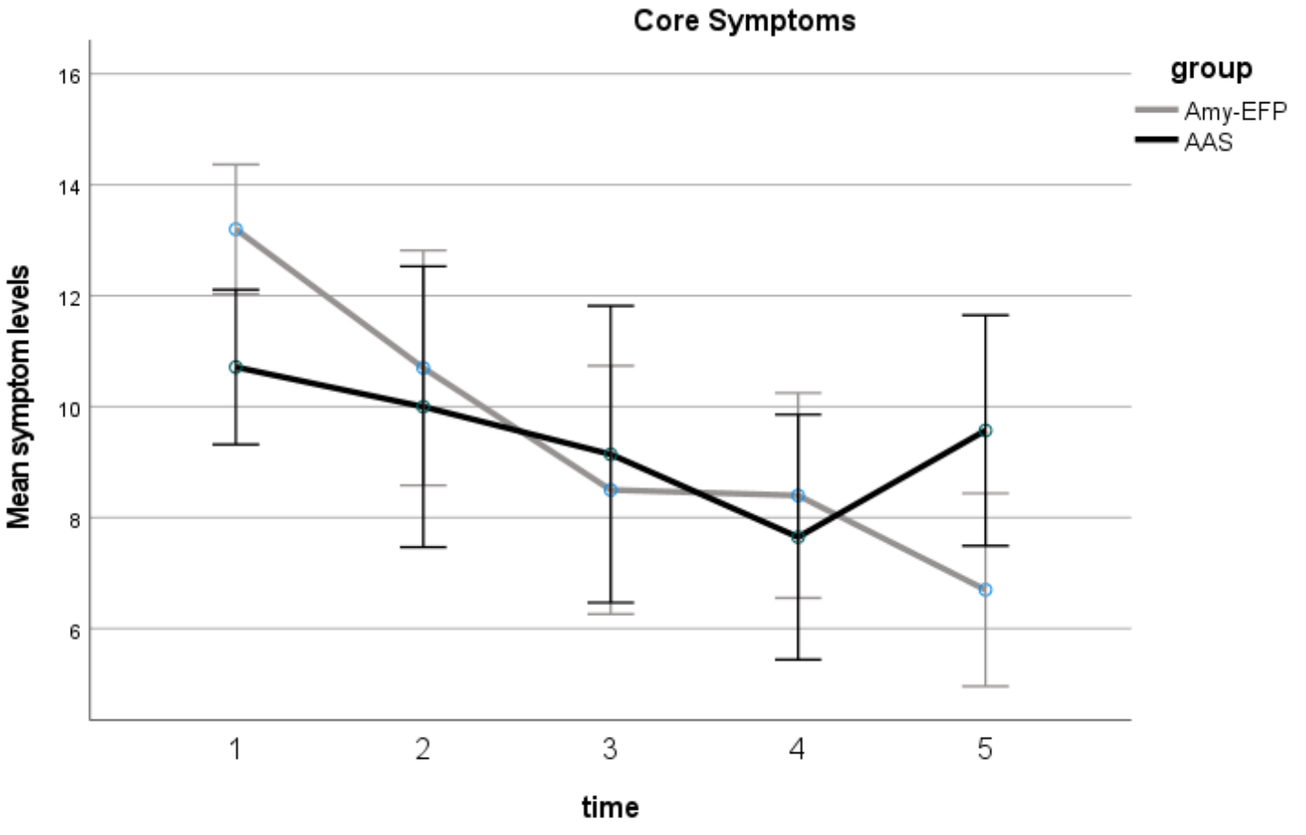


Amyg-EFP = Amygdala electrical fingerprint neurofeedback, AAS = alpha asymmetry neurofeedback

Figure 2

PMTS-OR Core and Subscale Symptom Levels (a-e) over Time by Treatment Group

a



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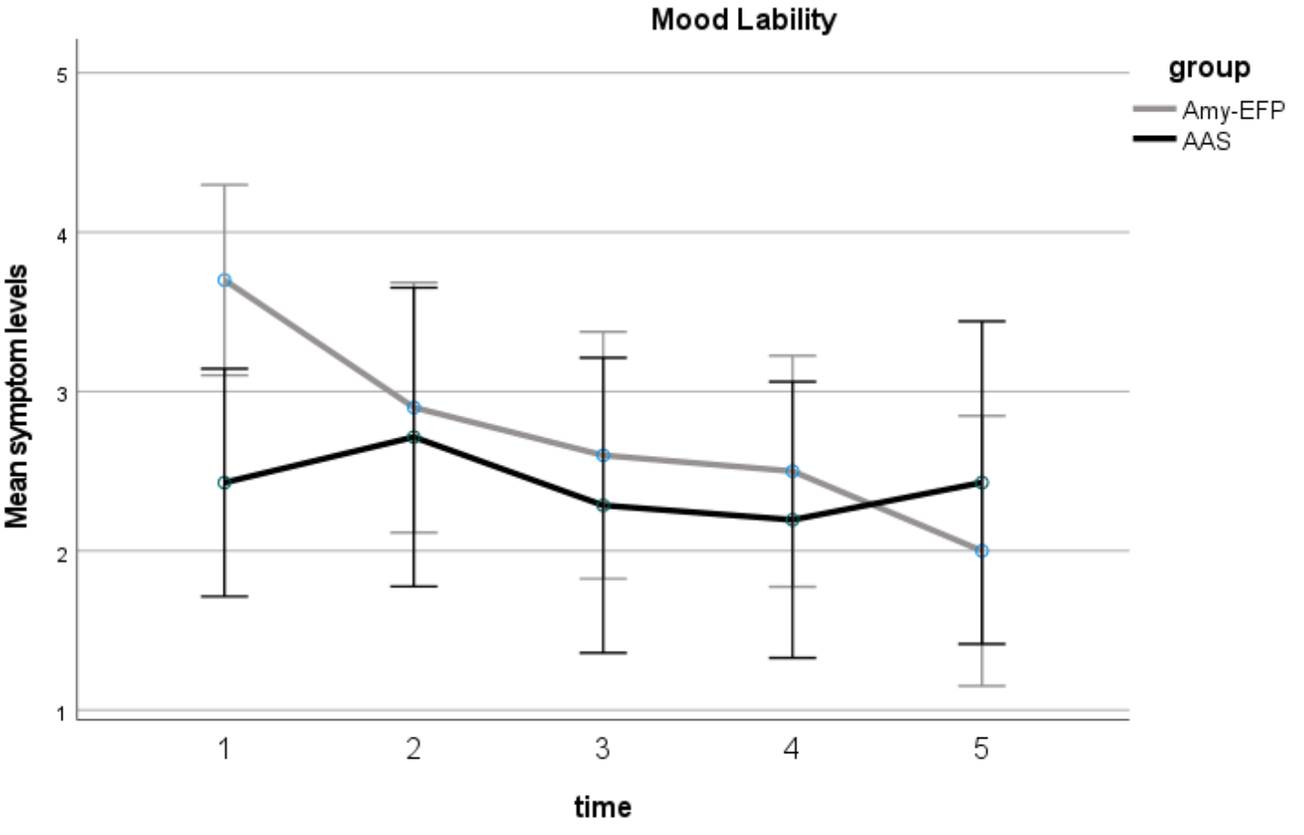

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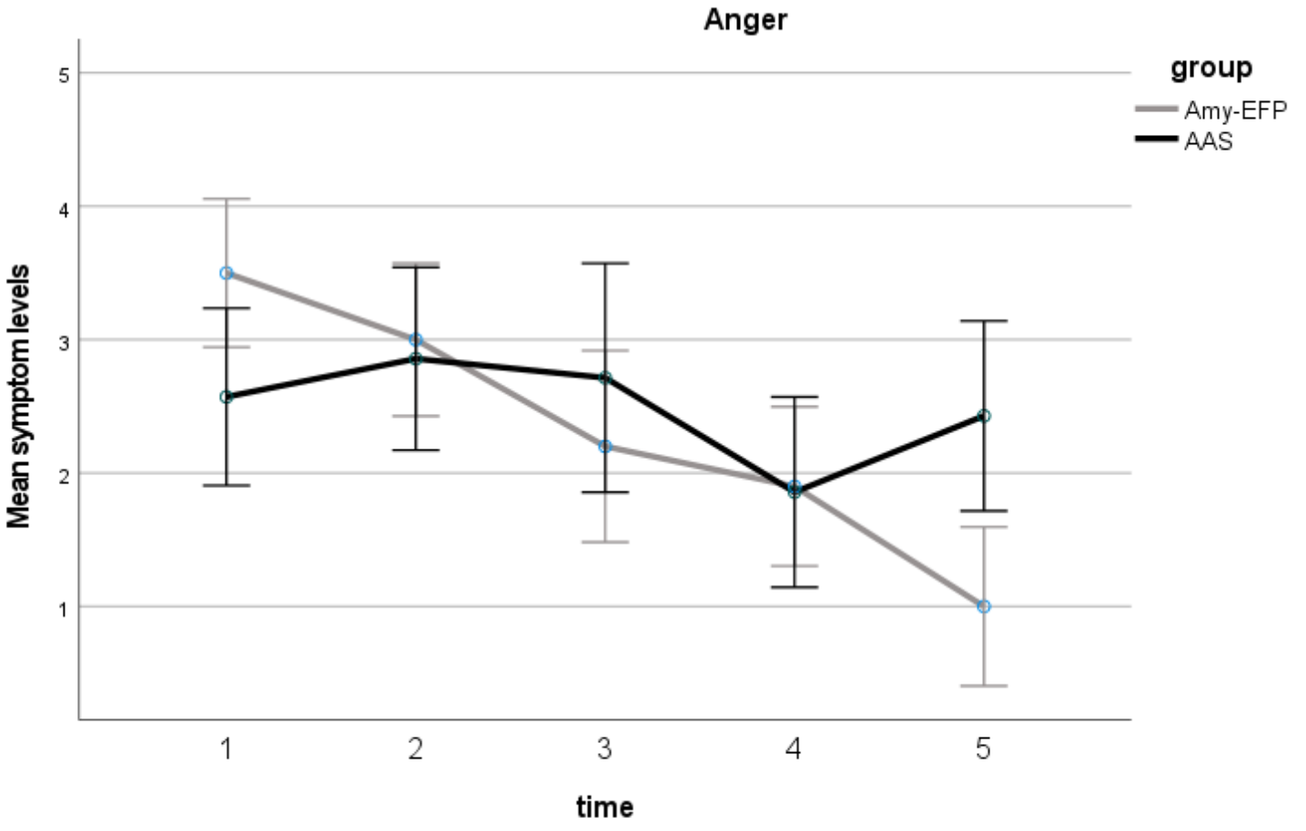

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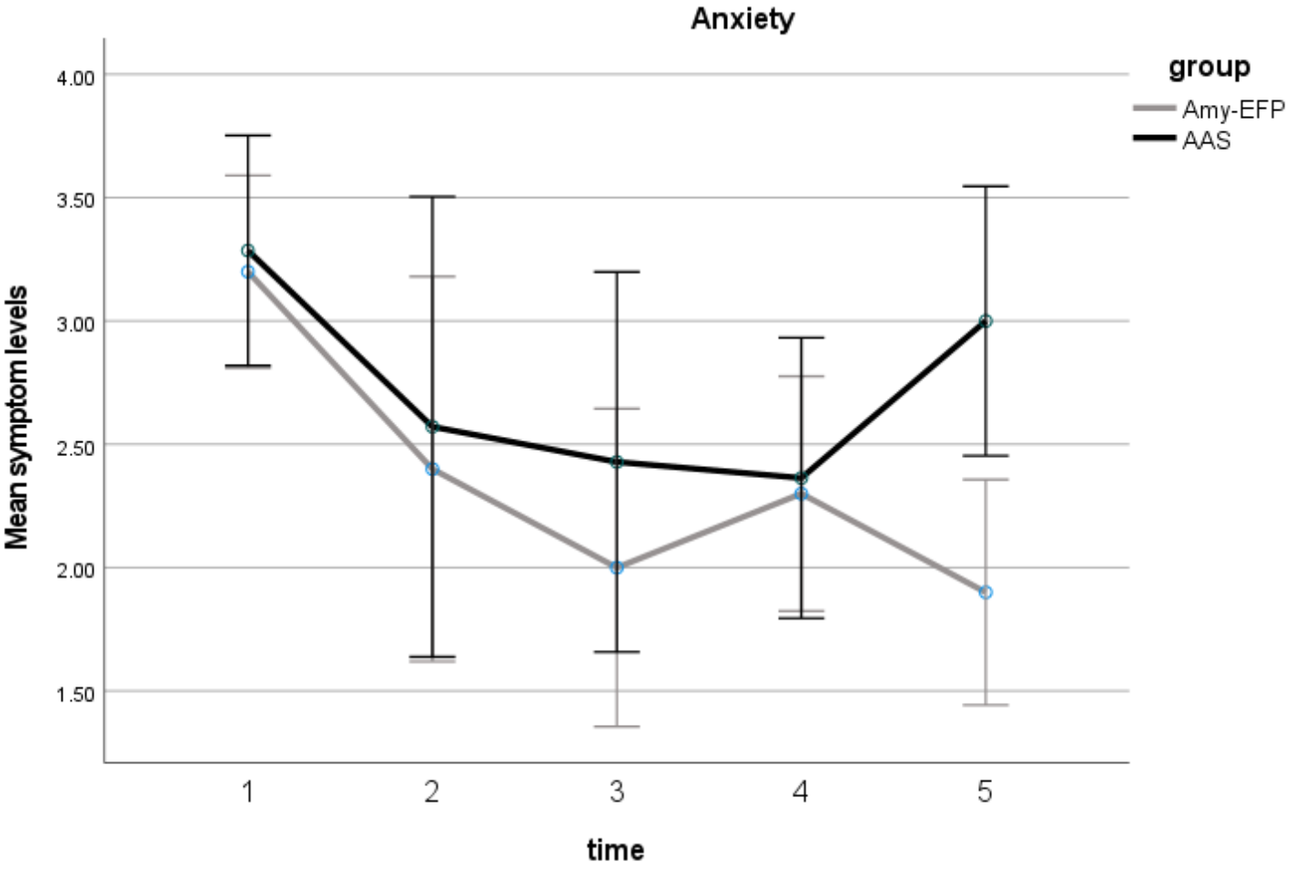

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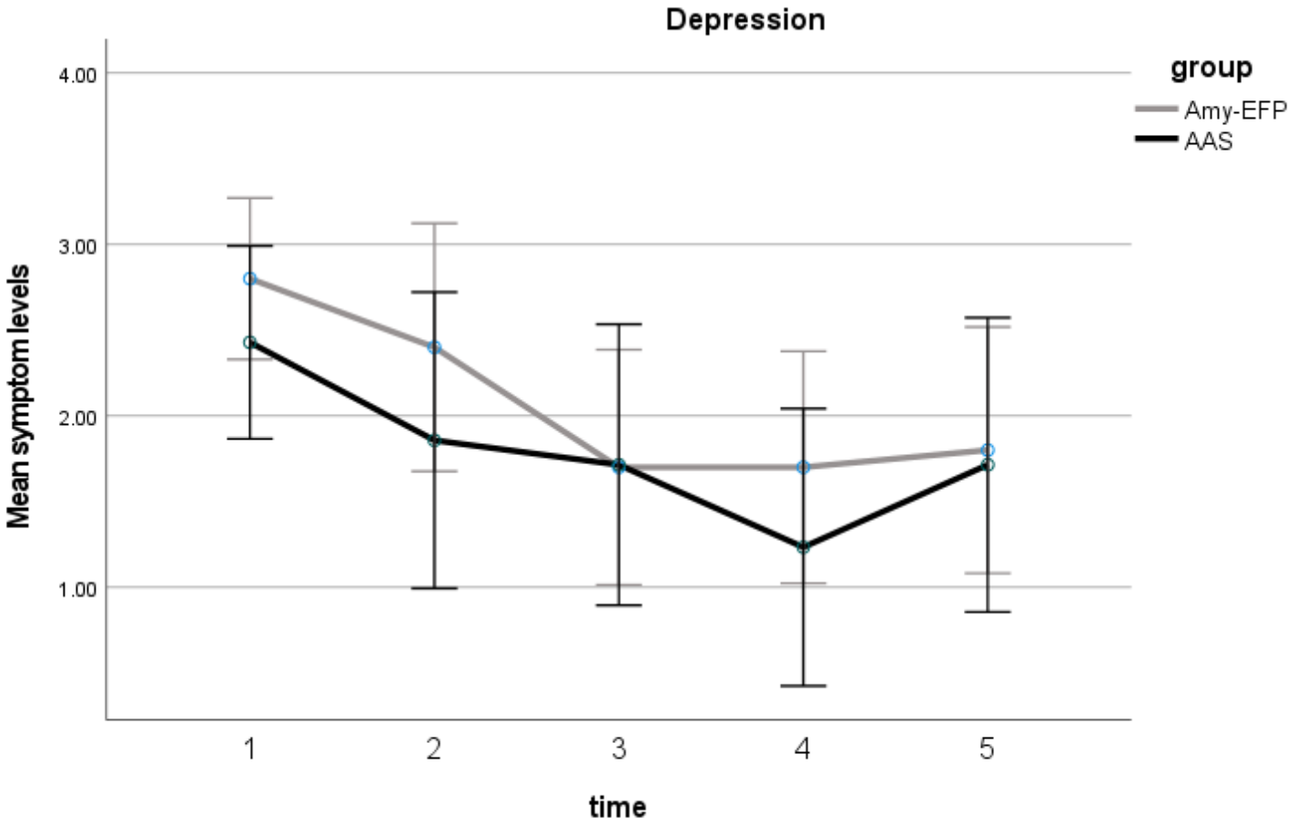

Note: PMTS-OR = Revised Observer Premenstrual symptom scale. Amyg-EFF = Amygdala electric fingerprint neurofeedback training. AAS = Alpha asymmetry neurofeedback training. Time = Timepoint of evaluation.

*Independent sample t-tests of group differences were conducted for time 6 PMTS, reflecting significant group differences in Core (t=-2.26, p=.04), Anger (t=-3.28, p=.005), and Anxiety (t=-3.29, p=.005), but not Mood Lability (t=-.69, p=.50) at follow up. Error bars: 95% CI.