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Amygdala-derived-EEG-fMRI-pattern neurofeedback for the treatment of chronic post-traumatic stress disorder. A prospective, multicenter, multinational study evaluating clinical efficacy

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ABSTRACT

We conducted a prospective, single arm, multisite, multinational, open label trial assessing the safety and efficacy of a novel amygdala derived neurofeedback treatment, designated Amygdala-Derived-EFP, for chronic PTSD. Participants, including veterans and civilians, underwent screening, training, 15 neurofeedback sessions over 8 weeks and; baseline, termination (8 weeks) and 3 month post treatment assessments with validated measures. The primary endpoint was more than 50 % of the participants demonstrating a Minimally Clinically Important Difference (MCID) defined as a 6-point reduction, on the Clinician Administered PTSD Scale (CAPS-5) total score at 3 months. Secondary measures included the PCL-5, ERQ, PHQ-9, and CGI. Statistical analyses were performed using SAS®V9.4. The primary endpoint was met, with a CAPS-5 MCID response rate of 66.7 %. The average reduction in CAPS-5 total scores at 3 month follow up was 13.5 points, more than twice the MCID. Changes from baseline in CAPS-5, PCL-5, PHQ-9 scores at 8 weeks and the 3 month follow-up demonstrated statistically significant improvements in response and; demonstrated effect sizes ranging from 0.46 to 1.07. Adverse events were mild and resolved after treatment. This study builds on prior research demonstrating similar outcomes using amygdala-derived neurofeedback. Positive attributes of this therapy include monitoring by non-physician personnel, affordability, accessibility, and tolerability.

1. Introduction

More than 70 % of adults worldwide experience a traumatic event at some time in their lives (Frans et al., 2005). Depending upon the nature of the trauma, approximately 5–9 % of people exposed to a traumatic event will go on to develop post-traumatic stress disorder (PTSD) (Frans et al., 2005). PTSD symptomatology includes intrusive thoughts, hyperarousal, flashbacks, nightmares, sleep disturbances, changes in memory and concentration, and startle responses (Peitrzak et al., 2014). Chronic PTSD can be a severe, debilitating and treatment refractory psychiatric disorder.

Recovery can naturally occur in PTSD (Galatzer-Levy et al., 2013) during the first 3–24 months from the index trauma. It has been noted that upwards of 50 % of trauma survivors will recover within 24 months (Rosellini et al., 2018). The long term effects of untreated PTSD can include co-morbidities such as: depression, substance abuse, suicidal

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ideation, chronic musculoskeletal pain, hypertension, hyperlipidemia, obesity, and cardiovascular disease (McFarlane 2010). Thus, effective treatments to address PTSD are crucial to mitigating its effects, including societal costs.

Current US guidelines consider psychotherapeutic and pharmacologic therapies as first line treatments for PTSD (Martin et al., 2021). Psychotherapies include variations of cognitive behavioral therapy (CBT) including prolonged exposure therapy (PE), cognitive processing therapy (CPT) as well as eye movement desensitization and reprocessing (EMDR). However, meta-analytic reviews show that only 30 % to 60 % of patients receiving evidence based psychotherapy achieve remission with a significant proportion who improve continuing to have substantial residual symptoms (Shalev et al., 2017). Additionally, psychotherapy can be demanding, emotionally taxing on patients or unavailable (CBT, 2023), with some therapies (e.g. trauma-focused CBT) requiring patients to re-experience their trauma (CBT, 2023) which can lead to high patient attrition rates (Fernandez et al., 2015) or to reluctance in initiating CBT. In particular, CBT relies on a patient focusing on the trauma to facilitate fear extinction and cognitive reappraisal allowing for context updating, including the understanding that the danger from the trauma is over (Shearing et al., 2011). As it relates to the use of pharmacologic therapies for PTSD, patients can have a higher reluctance to initiating pharmacologic therapy vs. psychotherapy (Swift et al., 2017) and higher dropout rates vs. psychotherapy (Swift et al., 2017) based on unwanted side effects from the drugs (Williams et al., 2022). Evidence for the effectiveness of selective serotonin reuptake inhibitors (SSRIs) is mixed, independent of duration of PTSD (Lewis et al., 2020). Other pharmacologic agents including antipsychotics have limited benefits and unfavorable side effect profiles for treating PTSD (Bremner et al., 1995). Thus the limitations of psychotherapy and pharmacotherapy, together with the stressful nature of exposure based treatments and the substantial attrition rates raise the importance of alternative complementary adjunctive therapies.

Areas of the deeper brain that are considered to play an important role in PTSD include anterior cingulate cortex, amygdala, and medial pre-frontal cortex (Paradiso et al., 1999). The amygdala in particular appears to be hyper-reactive to trauma related stimuli (Nutt and Malizia, 2004). During episodes of trauma related arousal, there is an increase in cerebral blood flow to the amygdala and greater activation (Paradiso et al., 1999). It has been found that down-regulating amygdala activity via the pre-frontal cortex and anterior cingulate cortex reduces stress related psychopathologies (Johnstone et al., 2007).

Neurofeedback (NF) therapy is a form of brain training utilizing operant conditioning through real time displays of brain activity to teach individuals how to self-regulate their brain function. Brain function is commonly captured via electroencephalogram (EEG), an accessible, low cost technology. The major drawback of existing EEG neurofeedback methods lies in the fact that EEG signals have low spatial resolution (Babiloni et al., 2001) and do not capture neural activity from the deeper portions of the brain associated with processes affecting PTSD symptoms. Functional Magnetic Resonance Imaging (fMRI) studies on the other hand have identified areas of the brain involved in emotional dysregulation –including the amygdala and can accurately measure its activity (Keynan et al., 2016). The drawbacks of using fMRI in assessing amygdala activity include expense, low accessibility and portability, and it may generate stress and anxiety from claustrophobia. A recently developed, innovative technology integrates simultaneous EEG and fMRI recordings designated Amygdala-derived- EEG-fMRI--Pattern (EFP). By utilizing machine learning for predicting fMRI activity in specific brain regions of the limbic system including the amygdala from simultaneously acquired EEG data, a set of coefficients (named EFP – EEG-fMRI-Pattern) were derived (Keynan et al., 2016). The EFP can be viewed as a mathematical derivative of EEG and fMRI, that can be used to process real time EEG data during NF, thus enabling an fMRI-informed processing of the EEG signal. The Amygdala-derived-EFP represents a pattern associating EEG and fMRI signals of specific regions of the limbic system. Using the Amygdala-derived-EFP in a NF system, the effect of NF training on the PTSD patient's response to non-traumatic stimuli can be measured (Madhusoodanan, 2021). Amygdala-derived-EFP NF is intended to be used as an adjunctive intervention in conjunction with evidence based treatments for PTSD (Fruchtman-Steinbok et al., 2021) in order to improve clinical outcomes. The advantages of the Amygdala-derived EFP approach include cost effective, widely available, office based real time NF training in PTSD patients (Nature, 2023).

Based on the shortcomings of psychotherapy and pharmacotherapy for PTSD as outlined above, there is a clear need to develop alternative and adjunctive therapies in order to improve outcomes for individuals suffering from PTSD. Prior randomized controlled trials have demonstrated the feasibility and clinical potential of the Amygdala-derived-EFP NF intervention for stress resilience (Keynan et al., 2019). However, those studies were small in nature (Noohi et al., 2017; Kelson, 2013), short term (Kelson, 2013), examined only men (Noohi et al., 2017), and did not perform follow-up assessments post treatment (Kelson, 2013). The current trial was designed to evaluate Amygdala-derived-EFP NF (termed Prism; GrayMatters Health Ltd., Haifa, Israel) safety and effectiveness in a larger longer term trial, including men and women, with post treatment follow-up assessment, as an adjunct to standard of care (SOC) treatments in chronic PTSD patients. Of note, the chronic PTSD patients included a cohort of treatment resistant combat veterans with PTSD.

2. Methods

Participants and recruitment: Inclusion and exclusion criteria can be found in Appendix 1. Patients were recruited from centers in Israel (Rambam Medical Center, Sheba Medical Center, Be'er Ya'akov Mental Health Center, Barzilai Medical Center) and the United States (New York University Langone Health).

The research protocol was approved by the ethics committees at each participating clinical site and the trial was registered on Clinical Trial.gov (NCT04891614). The study took place from November 1, 2020 to May 20, 2022.

The Consensus on the Reporting and Experimental Design of clinical and cognitive-behavioral Neurofeedback studies (CRED-nf) best practices checklist was used (Appendix 2).

2.1. Study design, device description, and procedure

The study was a prospective, single arm, open label trial, to assess the safety and efficacy of NF using Amygdala-Derived-EFP neurofeedback as an adjunct to SOC, with PTSD SOC provided to patients for at least one month prior to use of Amygdala-Derived-EFP NF). Participants were to complete 15 NF training sessions delivered twice per week, on non-consecutive days, over 8 consecutive weeks. Each session lasted approximately 25 min. Neurofeedback sessions were delivered using Prism, a software device intended for NF training (i.e., operant conditioning based on Amygdala-Derived- EFP signals), used in combination with a standard computer and supported EEG hardware. Prism provides visual/auditory signals that respond to the patient's Amygdala-Derived-EFP signal. Subjects underwent screening, baseline, then 15 training sessions over 2 months, immediate post training assessment (referred to as 8 week assessment), and then another assessment 3 months later (after training conclusion). Training session device description, screening, and baseline assessments can be found in Appendix 3. The protocol has been used in prior studies and demonstrated clinical efficacy. Further the protocol was established based on conversations with mental health professionals.

2.1.1. Outcome measures

The primary endpoint was the proportion of subjects who demonstrated a response in terms of a clinically meaningful improvement in

the Clinician Administered PTSD Scale (CAPS-5) score from baseline to the 3 months follow-up visit. Clinically meaningful improvement was defined as a 6-point or greater reduction in the CAPS-5 score (termed response rate) (Stefanovics et al., 2017). The null hypothesis being evaluated was that <50 % of patients would not meet the response rate of $a \geq 6$ point reduction in the CAPS-5 score. [Note: A Minimally Clinically Important Difference (MCID) is calculated via CAPS-4 to be 10 points. The CAPS-4 ranges from 0 to 136, while CAPS-5 ranges from 0 to 80. Therefore translating CAPS-4 to CAPS-5 equates to $80/136 \times 10 = 5.88$ points, or 6 which was used as the MCID in this study (NCT 04891614 https://clinicaltrials.gov/) (NCT, 2023).]

Secondary endpoints included a response on the PTSD Checklist for DSM-5 (PCL-5); Change from baseline to the 3-month follow-up in: (a) Clinician Administered PTSD Scale (CAPS–5); (b) PTSD Checklist for DSM-5 (PCL-5); (c) Emotion Regulation Questionnaire (ERQ; Cognitive Reappraisal and Expressive Suppression Moore at al., 2008; Gross and John, 2003); (d) Patient Health Questionnaire (PHQ-9) and; (e) Clinical Global Impression (CGI); 3) Safety as measured by the incidence of adverse events. Specifics can be found in Appendix 4.

A post hoc analyses was carried out on remission rates defined as a CAPS-5 score of <25 points plus no longer meeting the clinical symptoms criteria at 8 weeks and 3 month follow-up visit. Further a post hoc CAPS-5 percent response rate with increasing thresholds of response was calculated.

2.1.2. Sample size calculation

The prospectively specified null hypothesis was $P_{PRISM} \leq 50$ % versus the alternative hypothesis of $P_{PRISM} > 50$ %, where P_{PRISM} represents the proportion of subjects who demonstrated a clinically meaningful improvement in the CAPS-5 score from baseline to the 3 months follow-up visit. Assuming a P_{PRISM} of 64 % a sample size of 53 subjects was calculated (using SAS® proc power) such that the lower limit of the two-sided 95 % exact binomial confidence interval is greater than 50 % with at least 90 % power (in this context power is the probability (conditional method) of obtaining a confidence interval half-width less than or equal to the hypothesized value). At least 70 subjects were to be recruited to account for a potential ~25 % drop-out rate. This drop-out rate was based on an analysis of rates from prior published studies.

2.1.3. Statistical methods

Statistical analyses were performed using SAS®V9.4 (SAS Institute, Cary NC, USA). Three analysis sets were prespecified in the protocol full analysis sets (all subjects enrolled; FA); effectiveness analysis set (FA patients who had 15 ± 3 completed sessions as well as the post-training assessment; EF); per protocol set (all subjects from the EF set who finished the study without major protocol deviation; had at least 12 completed sessions; and completed the 3 month follow up assessment; PP). For presentation purposes, the EF set is reported on in the main body of the manuscript and the FA and PP analyses appear in Appendix 4. Continuous variables are summarized by the mean and standard deviation and categorical variables by a count and percent. A hierarchy approach was adopted for the secondary endpoints to control type I error due to multiple endpoint testing. Thus, the primary endpoint was analyzed and; only if the null hypothesis was rejected, were the secondary endpoints tested. Nominal p-values ($P < 0.05$ for significance) and/or non-adjusted two-sided 95 % confidence intervals are presented. Response rates were summarized by a count and percent and presented with two-sided exact binomial 95 % confidence intervals, the lower bound of the CI was used to test the null hypothesis. A linear mixed repeated measures ANCOVA model was used to assess the clinical improvement for CAPS-5, PCL-5, EQR, and PHQ-9 between the different assessment times. Each modeled the change from baseline as a function of visits (categorical) with the baseline value entered as a covariate. The model estimated means (LS means) with 95 % confidence intervals and; the level of significance of the change from baseline to each visit were presented for each outcome measure. Further, standardized mean differences (which Cohen's d was derived from) were calculated to evaluate the effect size (Farone, 2008). Pooling across centers comparing US to non-US, for the primary endpoint, was assessed using a Fisher's exact test at a significance level of 10 %. If found significant, the reason for the significance was further explored and rationalized. In sensitivity analysis, the primary endpoint was also analyzed for the FA set using several methods of imputation, the best case scenario - where each subject with missing primary endpoint data is considered as having a response; the worst case scenario - where each subject with missing primary endpoint data is considered as not having a response, and multiple imputation (20,000 data sets) using site, sex, race, marital status, latitude, age, baseline CAPS-5, time from traumatic event, time from 1st symptoms as predictors of the binary response.

3. Results

Fig. 1 shows the disposition of patients.

3.1. Demographic & baseline characteristics (FA set)

Table 1 shows the baseline characteristics of those enrolled in the trial. There were 35.4 % of the subjects who completed 1 full course of trauma focused psychotherapy prior to the current study. PTSD symptoms developed due to combat/military service in 46.8 % of the patients. Note: Since this is a within subjects' design, there is no possibility for there to be differences in Table 1 below between groups.

3.2. Clinical outcomes (EF set)

The CAPS-5 response rate at 3 months was 66.7 % [95 % *CI*:53.99 % to 77.8 %] (Table 2). Based on the primary outcome results for CAPS-5, the null hypothesis (H_0: $P_{PRISM} \leq 50$ %) was rejected.

The changes from baseline in CAPS-5, PCL, and PHQ-9 scores to 8 weeks (post treatment and the 3 month follow-up later on for the EF set were found to show statistically significant improvement based on the linear mixed model repeated measures ANCOVA except for the ERQ (Table 3).

The effect sizes evaluated from baseline in CAPS-5, PCL, and PHQ-9 scores to 8 weeks (post treatment and the 3 month follow-up later on for the EF set were found to show statistically significant improvements and; demonstrated large effect sizes (effect size >0.8) on CAPS-5 (8 weeks and 3 months) and on PCL-5 (3 months) suggesting a strong effect of Prism on PTSD symptomatology (Table 4 - which notes the change from baseline CAPS-5, PCL, ERQ, and PHQ-9 - EF set [standardized mean difference]). The effect size for ERQ CR at 3 months follow up of 0.31 was statistically significant as well.

Also see Fig. 2 for the effect size change from baseline to post treatment (8 weeks) and at 3 months post treatment.

At both 8 weeks and 3 months, >80 % of patients exhibited an improvement in the CGI.

3.3. Pooling of US and non-US sites

There was a statistically significant difference between the US and non-US sites with respect to the CAPS-5 response at 3 months but not at 8 weeks (Table 6). This result was further explored by comparing demographic and other baseline data.

In the OUS centers there were significantly more male subjects, and most were married. In the US site there were significantly more subjects who had no prior trauma focused psychotherapy and none of the subjects had combat/military exposure as the index trauma. When the results were stratified by trauma type, for non-military trauma there was no statistically significant difference between the US and OUS response rates (Table 7).

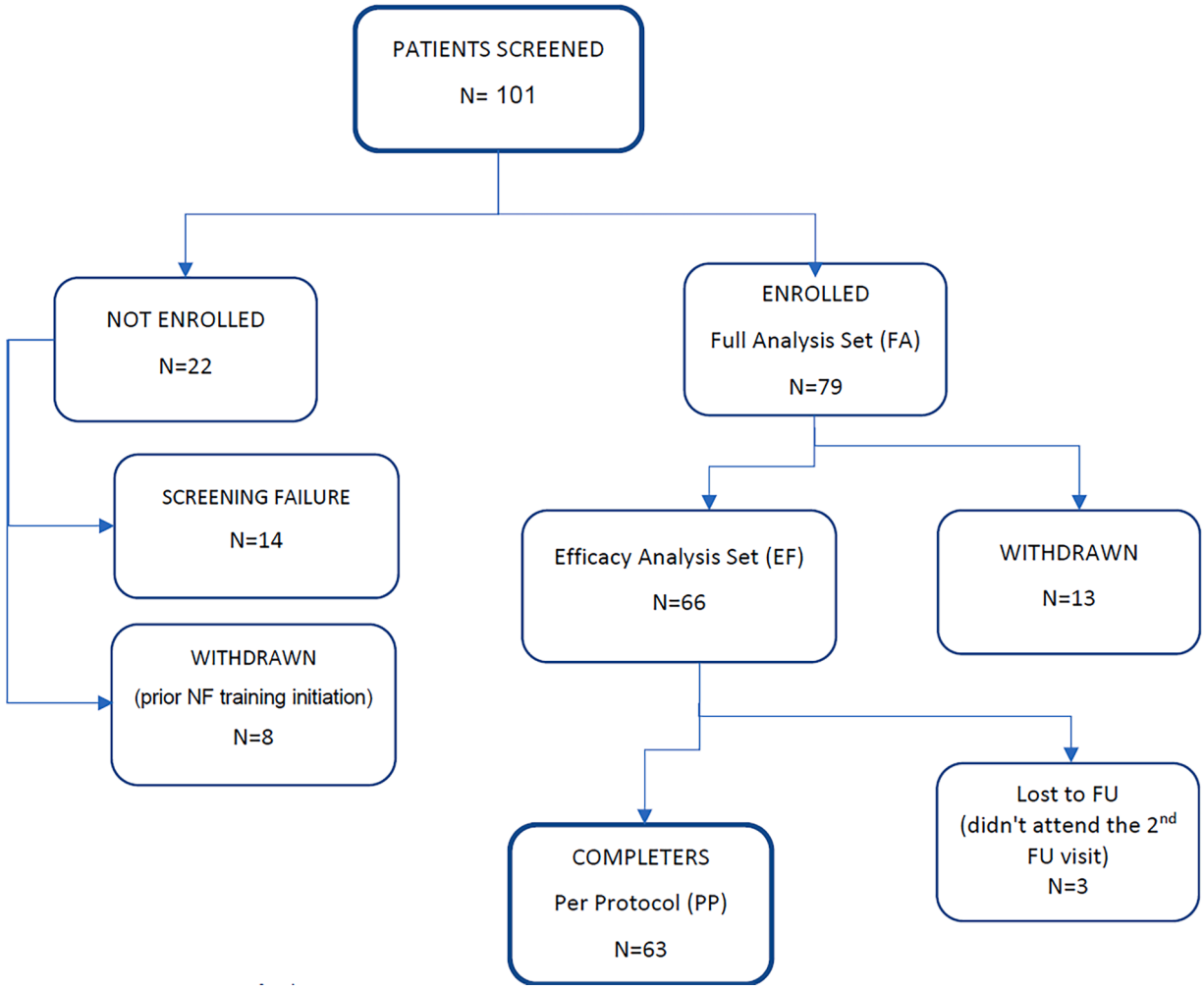

Fig. 1. Disposition of patients in trial.

3.4. Sensitivity analysis

We performed sensitivity analyses of the primary endpoint to assess the CAPS-5 response rate. In using sensitivity analyses for the missing 13 outcomes (based on the methods section), it was found that in the best case and multiple imputation sensitivity analysis methods, the null hypothesis of (H0: PPrism $\leq$ 50 %) was rejected (Appendix 4).

3.5. Safety analysis

There were 2 serious adverse events (SAEs) [2.53 %] identified. These included a psychiatric hospitalization and acute pharyngitis with hospitalization. None of the SAEs were related to the software or to the EEG device. The psychiatric hospitalization was due to alcohol abuse, suicidal thoughts, a suicide attempt two weeks prior to the hospitalization and, worsening depressive symptoms. This patient was terminated early from the trial. While 50.6 % of the subjects experienced AE's, the majority were mild in nature (e.g. fatigue, headache, anxiety, fever, impatience, runny nose) and recovery occurred right after the training sessions.

Remission: CAPS-5 remission rate (score of <25 points plus no longer meeting the clinical symptoms criteria) (Table 8).

As seen in Table 8, there was a 31.8 % remission rate at 3 month follow up and; an increase over the 8 week assessment.

As seen in Table 9, 3 at 3 month follow-up, 54.6 % of the patients had $a \geq 10$ point reduction in CAPS-5 and; 50 % of the patients had $a \geq 13$ point reduction. Overall it appears there is an increased response over time.

4. Discussion

The primary clinical endpoint of the trial that >50 % of the patients would experience $a \geq 6$ point reduction in the CAPS-5 score from baseline to 3 month follow-up visit was met. Mean CAPS-5 reduction at 3 month follow-up visits was 13.2 suggesting the change was clinically significant, and is more than twice the MCID. Change in PTSD symptom severity of $\geq$13 on CAPS-5 is indicative of change beyond what would be attributable to measurement error (i.e. termed reliable change) (Marx et al., 2022). Additionally CAPS-5 reductions using Prism, demonstrated large effect sizes ($P > 0.8$) on lowering PTSD symptomatology as measured by CAPS-5 and PCL-5. In other words, the effect of Prism on CAPS-5 scores (baseline, 8 weeks, and 3 months) and PCL-5 (baseline and 3 months) were meaningfully different from each other - i.e. Prism has a large and significant effect on CAPS-5 and PCL-5 reductions. Notably, the effect size increased over time. Further, other secondary outcomes evaluated namely PCL-5 and PHQ-9 also demonstrated statistically and clinically significant improvement from baseline to 8 weeks and 3 months. The reductions in the PHQ-9 scores moved a number of patients to less severe depression categories as defined by the PHQ-9 instrument (PHQ, 2023). Evidence for the PCL-5 for DSM-IV suggests that a 10–20 point change represents clinically significant change (CSC) (PTSD, 2023).

The mean change in this study for PCL-5 was 12.7. CSC translates into significantly better psychosocial functioning (Marx et al., 2022). As

Table 1
Demographics & Baseline characteristics - FA set ($N = 79$).

Characteristics	*n* (%)
Age, mean(SD), years	39.0 (10.6)
Sex	37 (46.8)
Female	
Male	42 (53.2)
Race	3 (3.9)
Hispanic or Latino	
White Caucasian	70 (88.6)
Black-African	2 (2.5)
Asian	2 (2.5)
Other	2 (2.5)
Level of education	22 (27.9)
High school diploma or equivalent	
Some college, no degree	6 (7.6)
Associate degree (for example: AA, AS)	5 (6.3)
Vocational/Trade training	8 (10.2)
Bachelor's degree (for example: BA, BS)	24 (30.4)
Master's degree (For example: MA, MS, Meng, Med, MBA	13 (16.5)
Professional degree (for example: MD, DDS, DVM)	1 (1.3)
Marital status	32 (40.5)
Married	
Divorced	8 (10.1)
Separated	2 (2.5)
Single	37 (46.8)
Laterality	
Left	6 (7.6)
Right	69 (87.3)
Ambidextrous	4 (5.1)
Time from traumatic event, mean(SD), years	10.0 (5.7)
Time from first symptoms, mean(SD), years	8.8 (5.3)
Concurrent medications	
SSRI/SNRI	56 (70.1)
Cannabis	38 (48.1)
The EFP model is the result of applying various machine learning regression models on EEG and amygdala fMRI voxel data	35 (44.3)
Other medications (for other comorbidities)	50 (63.3)

Table 2
Primary and first secondary endpoint results: response** rates with exact binomial 95 % confidence interval.

Instrument	8 weeks (post treatment) assessment		3 months after the 8 weeks assessment	
	Rate (*n*/*N*)	95 % *CI**	Rate (*n*/*N*)	95 % *CI**
CAPS-5 (primary endpoint)	69.7 % (46/66)	57.2 % to 80.4 %	**66.7 % (44/66)**	**54 % to 77.8 %**
PCL-5 (secondary endpoint)	36.4 % (24/66)	24.9 % to 49.1 %	51.5 % (34/66)	38.9 % to 64 %

*Exact binomial confidence interval.
**Response defined as ≥6 point reduction in score with CAPS-5 and ≥10 points with PCL-5.

Table 3
Change from baseline CAPS-5, PCL, ERQ, and PHQ-9 – EF set (mean difference).

Instrument	Baseline to 8 weeks assessment		Baseline to 3 months after the 8 weeks assessment	
	Least Squares Means (95 % *CI*)	*p*-value*	Least Squares Means (95 % *CI*)	*p*-value*
CAPS-5	−11.7 (−14.8 to −8.6)	<0.0001	−13.2 (−16.4 to −10.0)	<0.0001
PCL-5	−9.8 (−13.5 to −6.0)	<0.0001	−12.7 (−16.8 to −8.5)	<0.0001
ERQ CR	−1.06 (−2.77 to 0.65)	0.219	−2.13 (−3.8 to −0.5)	0.01
ERQ ES	0.74 (−0.33 to 1.85)	0.171	0.7 (−0.64 to 2.04)	0.31
PHQ-9	−3.5 (−5.1 to −2.0)	<0.0001	−4.5 (−6.0 to −3.1)	<0.0001

Abbreviations: *CI*, confidence interval; EF, Effectiveness analysis set; CR, Cognitive Reappraisal; ES, Expressive Suppression.
*Linear mixed model repeated measures *ANCOVA*.

Table 4
Change from baseline CAPS-5, PCL, ERQ, and PHQ-9 – EF set (standardized mean difference).

Instrument	Baseline to 8 weeks assessment		Baseline to 3 months after the 8 weeks assessment	
	Std. mean difference (95 % *CI*)	*p*-value*	Std. mean difference (95 % *CI*)	*p*-value*
CAPS-5	−0.95 (−1.31 to −0.59)	<0.0001	−1.07 (−1.44 to −0.71	<0.0001
PCL-5	−0.68 (−1.03 to −0.33)	<0.0001	−0.83 (−1.19 to −0.47)	<0.0001
ERQ CR	−0.15 (−0.395 to 0.09)	0.219	−0.33 (−0.58 to −0.07)	0.01
ERQ ES	−0.12 (−0.46 to 0.22)	0.171	−0.2 (−0.46 to 0.23)	0.31
PHQ-9	−0.46 (−0.81 to −0.12)	<0.0001	−0.61 (−0.96 to −0.26)	<0.0001

statistically significant and clinically significant results for CAPS-5 score in the chronic PTSD study population were demonstrated, it is anticipated that the same or potentially better results in acute PTSD patients would be realized based on the added clinical outcome of natural recovery (for acute PTSD). Lastly, 84 % of patients were improved as identified via the CGI instrument (Appendix 4, Table 13). This is a promising finding considering the types of patients (many combat veterans) and conditions encountered during the trial (i.e. COVID pandemic) might mitigate it.

During the 2 months of treatment, 13 out of 79 participants or 16.5 % (post hoc analysis) dropped out of the trial. Prior studies using Amygdala-Derived-EFP with NF have shown similar low dropout rates to this (Fruchtman-Steinbok et al., 2021). One explanation could be that The Prism therapy does not expose the patient to the initial trauma and/or the stigma of pharmacological treatment and; these may be reasons for such low dropout rates. This is in contrast to trauma exposure based treatments which can result in dropout rates of up to 40 % (Imel et al., 2013). Thus, its adjunctive use in this trial with other first line therapies and the outcomes obtained should be viewed positively for this indication (adjunctive treatment).

A meta-analysis of amygdala targeting NF (using fMRI or fMRI-informed EEG) on behavioral indices of emotional processing, have demonstrated that amygdala-NF facilitates learned modulation (down regulation of the amygdala) (Goldway et al., 2022). Further, prior RCTs examining fMRI NF with EEG vs. control for PTSD [of unknown duration] have demonstrated statistically significant and clinically meaningful reductions in CAPS-4 scores (≥10 points) in the NF/EEG group vs. baseline with 20 sessions over successive weeks; with no such change in the control group (see Note in outcome measures in the methods section above) (Zotev et al., 2018; Nicholson et al., 2020). It is thus encouraging to see similar clinically meaningful changes in CAPS-5 with the current study, further supporting the clinical usefulness of Amygdala-Derived-EFP NF.

An interesting finding is that while there was no statistically significant difference in the response rates between the US and non-US at the 8 weeks (post treatment) assessment, there was one in the follow up assessment 3 months later. This difference (as can be seen in Table 5) is explained by the differences in the rates of military and non-military trauma in the two populations, as shown in Table 6 stratifying for trauma type. Psychotherapy as first line treatment for PTSD has been shown to be less effective in military vs. non-military patients (Straud et al., 2019). Forty four percent of non-US patients (with the vast majority of these patients experiencing military/combat related PTSD)

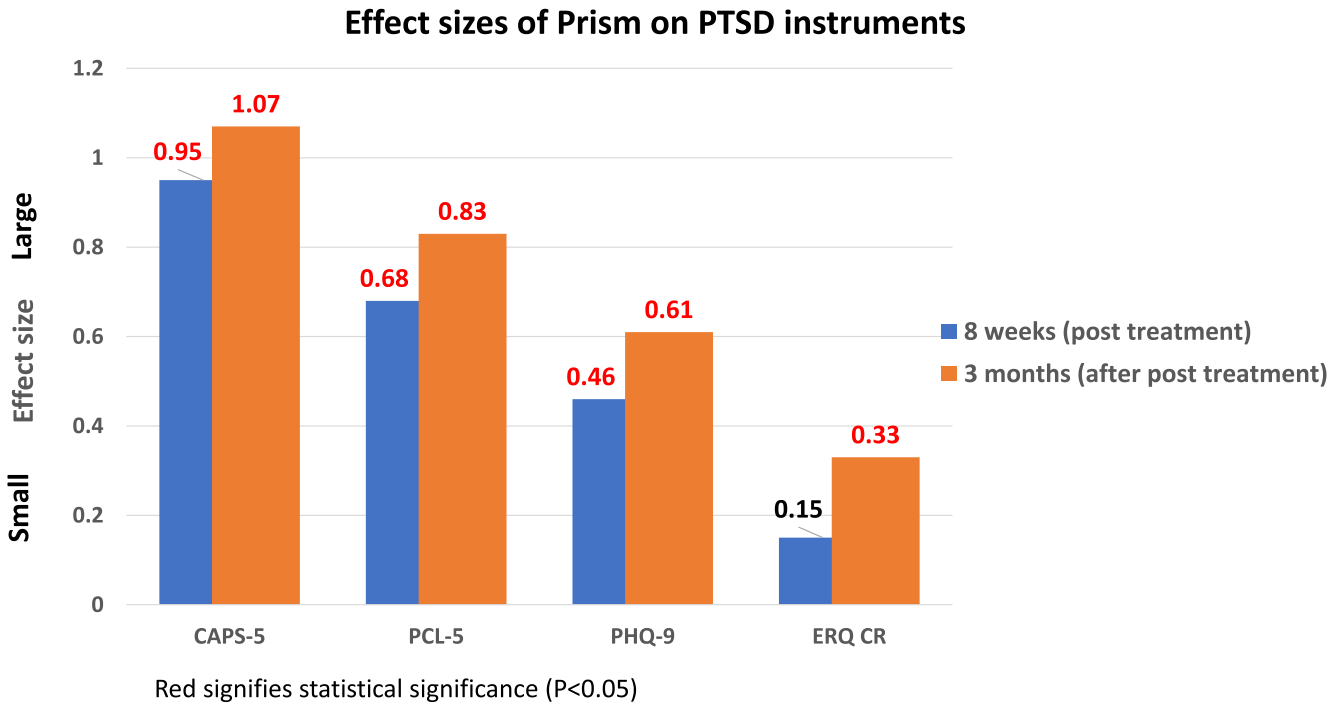

Fig. 2. Effect sizes of prism on various PTSD instruments.

Table 5
CGI results at 8 week (post treatment) and 3 months follow up:.

Clinical Global Impression (CGI)	8 weeks (post treatment) assessment		3 months after the 8 weeks assessment	
	n	%	*n*	%
Very much improved	6	9.1 %	8	12.7 %
Much improved	29	43.9 %	18	28.6 %
Minimally improved	20	30.3 %	27	42.9 %
No change	8	12.1 %	5	7.9 %
Minimally worse	3	4.6 %	2	3.2 %
Much worse	–	–	3	4.8 %

Table 6
Response rate US vs. OUS.

Follow up	US/ OUS	Response rate reduction of ≥6 points CAPS-5		*p* value (Fisher's exact test)
		% (*n*/*N*)	Exact Binomial 95 % *CI*	
8 weeks assessment	US	77.8 % (14/18)	52.4 % to 93.6 %	0.5494
	OUS	66.7 % (32/48)	51.6 % to 79.6 %	
3 months after the 8 weeks assessment	US	88.9 % (16/18)	65.3 % to 98.6 %	0.0211
	OUS	58.3 % (28/48)	43.2 % to 72.4 %	

underwent psychotherapy. There was however a degradation of improvement as measured by CAPS-5 from week 8 to 3 month follow up in military/combat patients (although not statistically different from the non-military patients at the 8 week assessment; see Table 5). A possible reason for declining improvement at follow-up could have been from terror and rocket attacks on Israel that occurred during this timeframe – which may have resulted in an exacerbation of PTSD symptoms and re-traumatization. It has been found that re-traumatization on pre-existing PTSD, resulted in a significantly higher increase in symptoms (Schock et al., 2016). As it relates to psychotherapy, recommendations of a recent meta-analysis were that greater emphasis should be placed on enhancing PTSD psychotherapies for military populations and on treatment retention across populations (Straud et al., 2019). It is possible that Amygdala-Derived-EFP NF booster sessions during the 3 months follow up period could have prevented this degraded improvement. Perhaps adjunctive Amygdala-Derived-EFP NF could enhance psychotherapy for this population and lead to better retention rates as seen in this trial. This patient subset is to be studied in a follow-on analysis on these and other issues.

Despite the trial being a single arm trial, the findings herein mirror what was found in a randomized controlled trial using the same technology in PTSD patients – an on average >10 point or more reduction in CAPS-5 vs. a 1 point reduction in the control group over a similar number of treatment sessions (Fruchtman-Steinbok et al., 2021). Secondly, the average response rate for CAPS-5 was a decrease of 13.2 points in the CAPS-5 score, and a decrease of 12.7 points on the PCL-5 representing more than a MCID. Third, it should be emphasized that all of the patients in the current study were chronic PTSD (average duration from time of traumatic event of 10 years) and had not responded to SOC therapy. Additionally, what is encouraging is the remission rate of 31.8 % at 3 months follow up in this chronic PTSD cohort when using Amygdala-Derived-EFP NF. Remission rates of chronic PTSD patients systematic review and meta-analysis (using other than Amygdala-Derived-EFP NF) has been demonstrated to be 36.9 %. However this well after a 40 month observation period (Morina et al., 2014). It appears that Amygdala-Derived-EFP NF may be able to achieve similar remission rates in a shorter time period than other more traditional therapies.

There is a learning curve associated with the Prism therapy which takes a limited number of Prism sessions for uptake and understanding by a patient. A future study will address this issue.

Limitations: The primary limitation is that this study was a single arm open clinical trial. Thus the positive clinical effect finding may be limited by the lack of a placebo arm or sham-NF (e.g. exposure to a busy and noisy waiting room without receiving contingent feedback via Amygdala-Derived-EFP). However, there are possible confounding

Table 7
Trauma reason (Combat/Military vs. Non-military):.

		Response reduction ≥6 points CAPS-5					
		8 weeks (post treatment) assessment			3 months after the 8 weeks assessment		
		% (*n*/*N*)	95 % exact binomial *CI*	*p* value	% (*n*/*N*)	95 % exact binomial *CI*	*p* value
Combat/Military	OUS	62.1 % (18/29)	42.3 % to 79.3 %	0.7748	44.8 % (13/29)	26.5 % to 64.3 %	0.4186
Non-military	OUS	73.7 % (14/19)	48.8 % to 90.9 %		78.9 % (15/19)	54.4 % to 93.9 %	
	US	77.8 % (14/18)	52.4 % to 93.6 %		88.9 % (16/18)	65.3 % to 98.6 %	

p value: Mantel-Haenszel test.

Table 8
CAPS-5 remission rates.

Follow up	% (*n*/*N*)	Exact Binomial 95 % *CI*
8 weeks assessment	28.8 % (19/66)	[18.3 %; 41.3 %]
3 months after the 8 weeks assessment	31.8 % (21/26)	[20.9 %; 44.4 %]

Table 9
CAPS-5 response rate with increasing thresholds of response reduction definition:.

Follow up	≥6 points	≥10 points	≥13 points	≥16 points	≥21 points
8 weeks assessment	69.7 %	50 %	45.5 %	33.3 %	22.7 %
3 months after the 8 weeks assessment	66.7 %	54.6 %	50 %	40.9 %	27.3 %

effects using sham-NF such as not receiving feedback for NF learning which can lead to reduced motivation, task engagement, and positive expectations (Schabus et al., 2017), further biasing outcomes obtained in control arms of NF studies.

The positive attributes of Prism, are its ability to be monitored and evaluated by non-physician behavioral health personnel; its affordability and accessibility; and minimal training/oversight. Further, self-regulation through operant conditioning learning provides PTSD patients with a sense of control or agency over their own lives (Zweerings et al., 2018). These attributes may help those PTSD patients who do not have ready access to psychotherapy, such as with smaller clinics and in rural areas.

In conclusion, this study supports Amygdala-Derived-EFP NF in modulating activity and in alleviating PTSD symptoms through operant conditioning. This response is captured via various PTSD instruments (CAPS-5, PCL-5, PHQ-9) demonstrating improved clinical outcomes 3 months after terminating therapy. The study further builds on prior studies demonstrating similar positive outcomes when using Amygdala-Derived-EFP NF. Consideration should be made by specialty societies and by payers in supporting and covering services for this type of adjunctive therapy. Additional studies are planned for PTSD with Amygdala-Derived-EFP NF including designs with sham controls.

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CRediT authorship contribution statement

Eyal Fruchter: Writing – review & editing, Investigation, Data curation, Conceptualization. **Nadav Goldenthal:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Lenard A. Adler:** Writing – review & editing, Resources, Investigation, Data curation. **Raz Gross:** Writing – review & editing, Investigation, Data curation. **Eiran V. Harel:** Writing – review & editing, Investigation, Data curation. **Lisa Deutsch:** Writing – review & editing, Methodology, Formal analysis. **Nitsa Nacasch:** . **Shulamit Grinapol:** Writing – review & editing, Investigation, Data curation. **Daniela Amital:** Writing – review & editing, Investigation, Data curation. **Jeffrey D. Voigt:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis. **Charles R. Marmar:** Writing – review & editing, Resources, Investigation, Formal analysis, Data curation.

Declaration of competing interest

Jeffrey Voigt is a reimbursement consultant for GrayMatters, the developer and manufacturer of the Prism technology. Charles Marmar has received support from: National Institute on Alcohol Abuse and Alcoholism, National Institute of Mental Health, Department of Defense-CDMRP * US Army Research Office * DARPA, Bank of America Foundation, Brockman Foundation, Cohen Veterans Bioscience, Cohen Veterans Network, McCormick Foundation, Home Depot Foundation, New York City Council, New York State Health, Mother Cabrini Foundation, Tilray Pharmaceuticals, and Ananda Scientific. Lenard Adler has received support from: Supernus Pharmaceuticals, Otsuka Pharmaceuticals, Bracket/Signant, SUNY and, Takeda Pharmaceuticals. Len Adler also receives royalties as an inventor from licensing agreements with the NYU Grossman School of Medicine. Lisa Deutsch is a statistician for hire and received compensation from GrayMatters for statistical analysis. Nadav Goldenthal and Raz Gross receive research support from GrayMatters. Eyal Fruchter, Shulamit Grinapol, Amital Daniela, Nitsa Nacasch, and Eiran Harel, have nothing to disclose.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2023.115711.

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