ACCELERATED ELECTROENCEPHALOGRAM (EEG) GUIDED TRANSCRANIAL MAGNETIC STIMULATION (ETMS) FOR POST-TRAUMATIC STRESS DISORDER (PTSD) IN VETERANS AND FIRST RESPONDERS

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INTRODUCTION

Military veterans and first responders experience higher rates of post-traumatic stress disorder (PTSD) than the general population. Despite the availability of evidence-based psychotherapies and pharmacological treatments, a substantial proportion of individuals continue to experience persistent symptoms, including hyperarousal, intrusive recollections, avoidance, and negative alterations in cognition and mood[1,2]. Treatment-resistant PTSD remains a significant clinical challenge, highlighting the need for novel therapeutic approaches that target underlying neurobiological mechanisms. Repetitive transcranial magnetic stimulation (rTMS) has emerged as a promising noninvasive neuromodulation intervention for many psychiatric disorders. However, most clinical protocols rely on standardized scalp-based targeting methods, which may not account for individual variability in brain organization and network dysfunction. PTSD has been increasingly conceptualized as a disorder of dysregulated large-scale brain networks, including alterations in connectivity between prefrontal, limbic, and salience systems[3], providing a rationale for targeted neuromodulation strategies. **EEG-informed or frequency-guided rTMS (eTMS) may enhance treatment efficacy** by aligning stimulation with patient-specific neural dynamics[4,5]. Although early studies have demonstrated the feasibility and potential efficacy of TMS in PTSD, there remains a need to evaluate personalized targeting approaches in clinically relevant populations. In the present open-label clinical trial, **we evaluated the effects of EEG-targeted rTMS in a sample of veterans and first responders with PTSD**. We hypothesized that eTMS would reduce PTSD symptom severity over the course of treatment. By focusing on a high-risk, trauma-exposed population and incorporating precision neuromodulation, this study aims to contribute to the growing literature on personalized interventions for PTSD.

METHODS

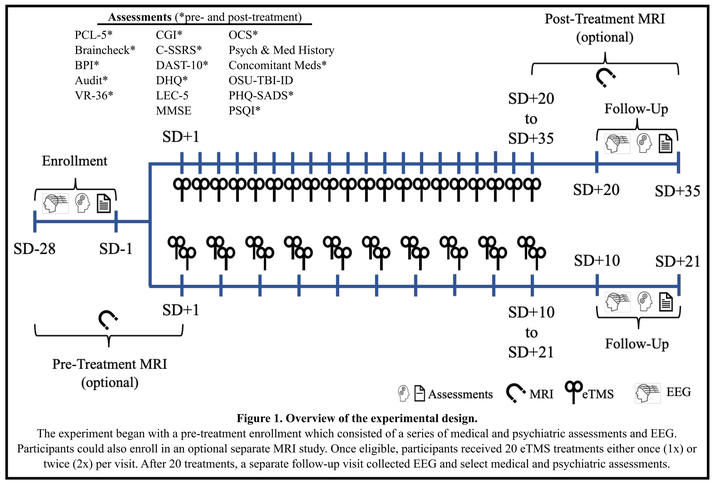

Figure 1. Overview of the experimental design.
The experiment began with a pre-treatment enrollment which consisted of a series of medical and psychiatric assessments and EEG. Participants could also enroll in an optional separate MRI study. Once eligible, participants received 20 eTMS treatments either once (1x) or twice (2x) per visit. After 20 treatments, a separate follow-up visit collected EEG and select medical and psychiatric assessments.

All participants were prescreened via telephone for potential eligibity prior to completing a pre-treatment eligibity assessment. At the eligibility assessment, voluntary informed consent was first collected followed by the collection of several assessments using standardized and non-standardized instruments, medical screening and an initial EEG. After eligibility was determined, participants then scheduled **20 eTMS treatments**. The first 16 participants received 1 treatment per visit (1x) completing 20 treatment visits within a maximum of 35 days. The last 14 participants received 2 treatments per visit (2x) completing 10 treatment visits in no more than 21 days. The frequency of rTMS was computed for each individual using a single frequency computed from the alpha band of their pre-treatment EEG derived via an automated proprietary algorithm. Each eTMS treatment lasted 13min providing **30-6s trains of stimulation** with an inter-train interval of 20s. **eTMS was provided to Fz at an intensity of 80% motor threshold** which was determined at the first treatment visit. Participants in the 2x group had at least 30min of rest between treatments. All participants completed 18 or more treatments. After all treatment visits, select assessments were repeated during a separate follow-up visit. The follow-up visit was completed within the 35-day (1x) or 21-day (2x) treatment window. Figure 1 provides a visual of the experimental design. Prior to treatment, participants could enroll in a separate MRI study which acquired MRI pre- and post-treatment. Neuroimaging was performed on a 3-Tesla MRI using a 32-channel phased array headcoil and several sequences including 3D psuedo-continuous arterial spin labeling (pcASL) to quantify cerebral perfusion.

RESULTS

Intent-to-Treat (ITT) Group (n=30)

Mean age: 42.7 years ± 9.5

Gender
6 Females, 24 Males
Race
1 American Indian or Alaska Native
25 White
3 more than one race
1 unknown/not reported
Ethnicity
2 Hispanic/Latino
28 Not Hispanic/Latino
Military/First Responder Status
22 Military (retiree or Veteran)
4 Firefighters
6 Police Officers

Overall, stimulation was tolerated well by all participants. A total of **31 adverse events** (AEs) were reported (Figure 2), with 2 being severe and 3 moderate. 17 AEs were determined to be not related to treatment, 5 suspected and 9 definitely related to treatment. 14 of the 30 participants in the ITT group reported at least 1 AE. Headache was the most common reported AE with 19 occurrances (10 of which were determined to be not related to treatment).

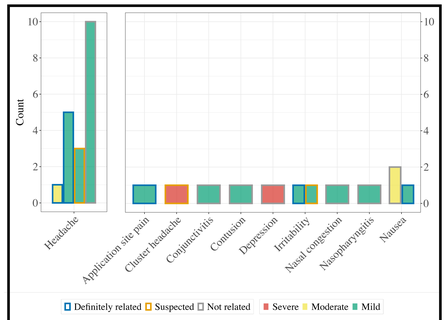

Figure 2. Adverse events from our per protocol (PP) group (n = 30).
The number of occurrences of each adverse event type are separated by relatedness to treatment and severity.

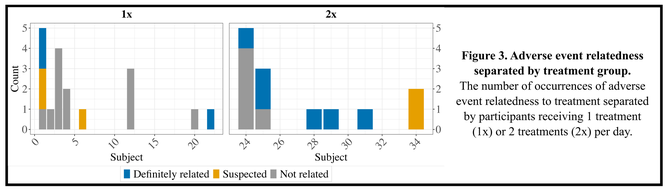

Figure 3. Adverse event relatedness separated by treatment group.
The number of occurrences of adverse event relatedness to treatment separated by participants receiving 1 treatment (1x) or 2 treatments (2x) per day.

Per Protocol (PP) Group (n=27)

27 participants completed 80% or more of treatments and the follow-up session within the protocol timeframes, 13 from the 1x group and 14 from the 2x group. A 2x2 (time by group) linear mixed-effects model was fitted using the lme4 package in R with a random intercept to account for within-subject repeated measures (Table 1). The two groups did not significantly vary in their response to treatment. A post-hoc pairwise comparison of time was conducted using estimated marginal means revealed a significant decrease in PCL-5 scores following treatment (Table 2), with an average reduction of 30.393 points.

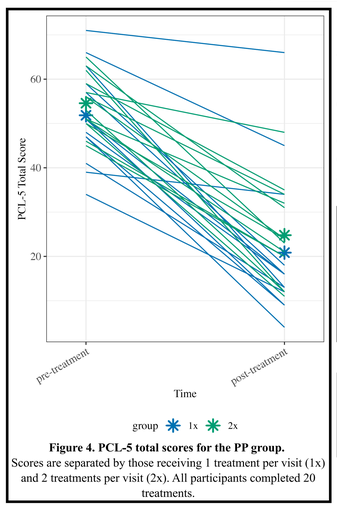

Figure 4. PCL-5 total scores for the PP group.
Scores are separated by those receiving 1 treatment per visit (1x) and 2 treatments per visit (2x). All participants completed 20 treatments.

Table 1. Linear mixed-effects model results for PCL-5 total score.
No significant effect of group or group-by-time interaction was observed.

	Summary Statistics			Linear Mixed-Effects Model		
Variable	Mean Pre-Treatment	Mean Post-Treatment	SE	F(df)	p	η^2
1x	51.8	20.8	3.28			
2x	54.6	24.8	3.16			
Main Effect: Time				159.4(1,25)	< 0.001	0.864
Main Effect: Group				0.746(1,25)	0.396	0.029
Interaction: Group x Time				0.064(1,25)	0.803	0.003

Table 2. Post-hoc pairwise comparison of pre- versus post-treatment.
PCL-5 total scores were found to significantly reduce by over 30 points.

	Summary Statistics			Pairwise Comparison	
	Mean Difference	SE	95% CI	t(df)	Sig (two-tailed)
PCL-5 Total Score	-30.393	2.407	[25.44, 35.35]	-12.625(25)	<.0001

MRI Sub-Group (n=16)

16 participants underwent the separate MRI study. Resting perfusion (CBF) was assessed from 3D pcASL pre- and post-treatment.

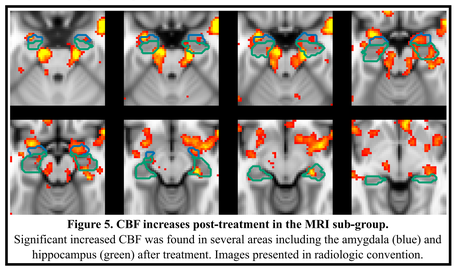

Figure 5. CBF increases post-treatment in the MRI sub-group.
Significant increased CBF was found in several areas including the amygdala (blue) and hippocampus (green) after treatment. Images presented in radiologic convention.

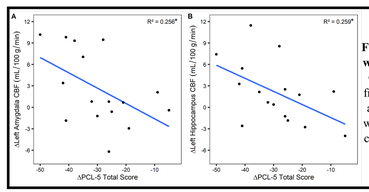

Figure 6. ΔCBF correlates with ΔPCL-5 total scores.
Changes in average CBF from the left amygdala (A) and left hippocampus (B) were found to significantly correlate with the decrease in PCL-5 total scores.

DISCUSSION

- The PCL-5 was used to assess PTSD symptom severity
- eTMS consisting of 30-6s trains with a 20s inter-train interval was provided at 80% motor threshold to Fz
- 30 participants formed our ITT group and completed **597 eTMS treatments**, 16 receiving 1 treatment per day and 14 receiving 2 treatments per day
- **31 Adverse Events were reported**
  - 14 of the 30 participants reported at least 1 AE (6 in the 1x group, 8 in the 2x group)
  - 9 definitely related to treatment, 5 were suspected to be related to treatment
  - Headache was the most frequent adverse event with 19 occurrances (10 determined to be not related to treatment) (see Figure 2)
- 27 participants formed our PP group all completing 20 treatments, (13 in the 1x group, 14 in the 2x group)
- The change in PTSD symptom severity after treatment was found to **not significantly vary between the 1x and 2x groups** (Table 1)
- Combining groups, PTSD symptom severity was found to **significantly decrease** following treatment (Table 2)
  - PCL-5 scores **decreased by 30.393 points** on average, 24 of the 27 in the PP group had a decrease of over 10 points (Figure 4)
  - A 10 point decrease is regarded as an indicator of response[6]
- 16 participants from the PP group completed the separate MRI study
  - **Resting perfusion increased** from pre- to post-treatment in several areas of the brain including the amygdala and hippocampus (Figure 5)
  - Amygdala and hippocampus perfusion was lower pre-treatment than that observed in a uncontrolled healthy group
  - Changes in perfusion from the left amygdala and left hippocampus were found to significantly correlate with changes in PCL-5 total scores (Figure 6)

Conclusion: eTMS was well tolerated and produced a clinically significant reduction in PTSD symptom severity. Neuroimaging found significant increases in resting perfusion including the amygdala and hippocampus, with larger the changes in resting perfusion observed in participants with a larger decrease in PTSD symptom severity suggesting dysregulation at rest may contribute to PTSD symptomology.

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Scan for more results and future updates

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