EEG-Guided Transcranial Magnetic Stimulation for the Treatment of Mild Traumatic Brain Injury: A Retrospective Chart Review of Special Operations Veterans with Post-Traumatic Stress Disorder and Traumatic Brain Injury

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Introduction

Traumatic Brain Injury (TBI) and related post-concussive symptoms affect a large proportion of military and veteran populations. Amongst military personnel and veterans, there have been more than 350,000 diagnoses of TBI; an estimated 98,000 of these will also be diagnosed with PTSD. Nearly a quarter of all military personnel will, at some point, be diagnosed with TBI and/or PTSD at some point in their lives. Diagnosis of TBI comes with a high likelihood of co-morbid indications and subtle, impactful cognitive impairments, including:

- PTSD
- Depression
- Suicidal Ideation
- Sleep Disruption
- Substance Abuse
- Slowed brain activity
- Drowsiness
- Cognitive difficulties
- Decreased Quality of Life

Many post-concussive symptoms are resistant to standard treatment and continue affect TBI patients far beyond the initial 6 months of recommended downtime. Following traumatic brain injury, brain networks are commonly injured; healthy 8-13Hz alpha activity transitions to slower, 4-8Hz theta activity. These disruptions in resting state cortical connectivity and function occur concomitantly with many cognitive impairments, and is often left unaddressed by traditional treatment methods[1]. Targeted neuromodulation may assist in repairing injured networks and relieving the long-lasting cognitive impairments of TBI and PTSD.

EEG alpha-guided transcranial magnetic stimulation (TMS), known as MeRT (Magnetic EEG-guided Resonance Therapy), provides a personalized, targeted form of neuromodulation. This neuromodulation entrains networks potentially injured in TBI[2]. Previous studies of this unique treatment, deployed in various populations and settings, have demonstrated that alpha-guided neuromodulation offers improved clinical outcomes over standard approaches in rTMS[3]. This retrospective chart review specifically investigated the effectiveness of MeRT on veterans with TBI and/or PTSD.

Materials + Methods

Thirty-six Special Operations Forces (SOF) veterans suffering from symptoms of TBI, PTSD, or a comorbid combination of the two underwent an average of 33 sessions of MeRT while clinicians tracked symptoms. Patients had either a previous diagnoses of PTSD, TBI, both, or no history of diagnosis. Research was conducted under IRB approval, no. 1286978.

The Rivermead Post-Concussion Questionnaire (RPQ) and the Post-Traumatic Checklist for DSM-5 (PCL-5) were the main clinical endpoints, for measuring severity of TBI and PTSD symptoms. Additional measures included the World Health Organization Disability Assessment Schedule (WHODAS) and the Brief Pain Inventory (BPI), for Pain Severity and Pain Interference. EEG regional power measures tracked network function.

MeRT treatment was administered 5 days/week. Clinical scales were assessed at the beginning and end of intervention. EEGs were analyzed prior to first treatment session and thereafter bi-weekly to assess each participant's individual alpha frequency (IAF). Treatment stimulation was set at patient-specific alpha frequency to 0.1Hz resolution within the 8-13Hz alpha band. Stimulation frequency was updated following each EEG administration.

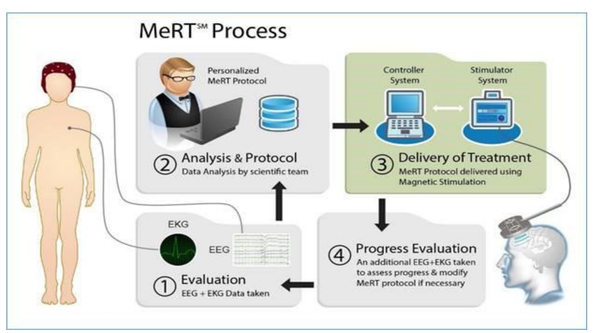

Figure 1. Visualization of MeRT analysis and treatment flow.

Results

Results were stratified on demographic, military, and clinical characteristics; main analysis groups were separated by diagnosis and treatment history. Paired two-tail t-tests were conducted on baseline and follow-up total scale scores for each measure. Independent samples t-tests and ANOVAs analyzed relationships between demographic, military factors, and symptom severity of TBI and PTSD.

Table 1. Previous Diagnoses

Population Size	Diagnosis
12	TBI + PTSD
10	TBI
4	PTSD
7	No prior diagnosis
3	No history provided

Table 2. Treatment history

Population Size	Treatment History
28	Treatment Naïve (TN)
8	Returning Patient (RP)

- There was a 54.0% reduction in mean RPQ score (*P<.01*) and a 37.6% reduction in mean PCL-5 score (*P<.01*). Patients reported a 35.4% mean reduction in WHODAS scores (*P=.02*), a 44.4% mean reduction in pain severity (*P<.01*), and a 60.6% mean reduction in pain interference (*P<.01*).
- Fifteen patients had a baseline PCL-5 score greater than 33, the PTSD cutoff threshold, and 10 of these patients achieved remission by end of therapy.
- All diagnoses groups saw significant reduction from baseline RPQ and PCL-5 scores.
- Treatment Naïve (TN) and Returning Patients (RP) were stratified and analyzed separately; both groups saw a significant drop from baseline RPQ and PCL-5 scores (*P<.05*) with MeRT.

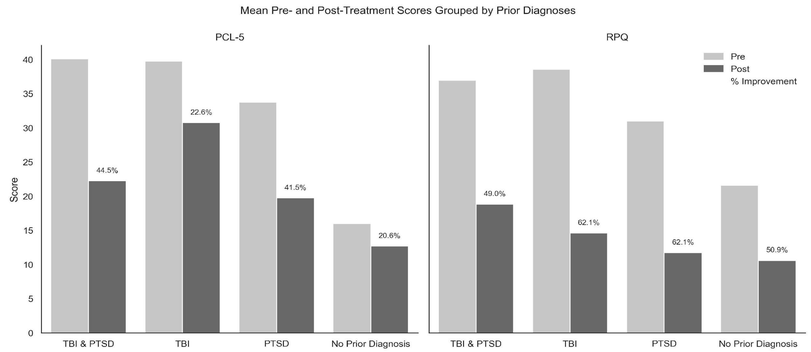

Figure 2. Change from baseline to end of treatment in primary scales, stratified by diagnosis history.

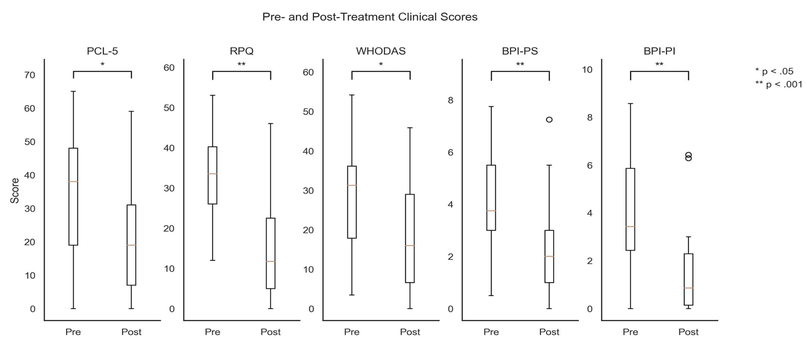

Figure 3. Mean scores on all clinical scales, baseline and end of treatment.

- Theta power was not different across groups at baseline (*P<.05);* following MeRT, patients with previous diagnosis of PTSD maintained elevated frontal theta relative power in comparison to the no diagnosis group (*P=.02*).
- The PTSD diagnosis group had higher beta relative power as compared to other groups at baseline (*P<.05*). There was a statistically significant reduction in relative beta in the posterior cluster following treatment for all diagnostic groups (*P<.01*).
- Beta relative power was more significantly reduced in PTSD as compared to all other groups (*P<.05*).

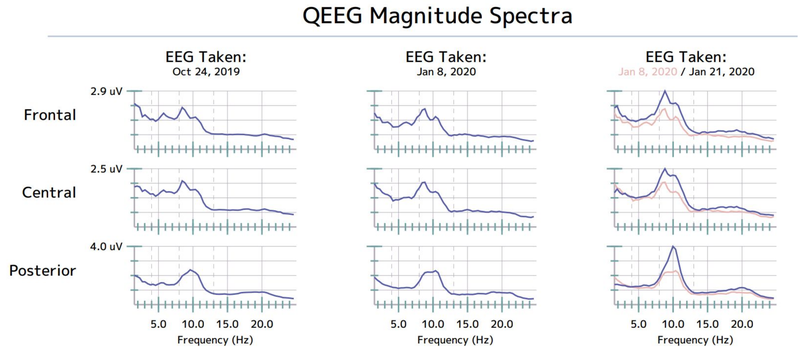

Figure 4. Fourier Transform of EEG spectra from baseline to end of treatment; the final column overlays a previous EEG to highlight improvement in activity. Note increase in global alpha band density and synchronization of posterior alpha rhythm.

- Side effects were mild and consistent with similar applications and clinical use of rTMS: 61% of patients reported mild headaches. Additional side effects included fatigue, increased irritability, poor sleep patterns, and mild discomfort.
- For the majority of patients, side effects resolved within two weeks. No patients discontinued treatment due to side effects.

Conclusions + Discussion

Results from this chart review are consistent with results from prior studies suggesting EEG-guided neuromodulation interacts with disruptions of neural networks, which may address long-lasting symptoms of PTSD and TBI. Patients demonstrated meaningful therapeutic changes in all clinical domains. PTSD remission rate was 66%, whereas standard PTSD remission with rTMS is 46.1%[4].

Studies have indicated elevated beta as a biomarker for PTSD in veterans. Observed reduction in beta, and corresponding clinical improvement in the PTSD group, suggests changes in cortical oscillatory activity correspondent to therapeutic outcomes.

RPs only saw significant decreases in the main outcomes measures (PCL-5 and RPQ), while TNs saw improvement in all measures. This may indicate that only certain symptom domains have robust long-term changes after treatment.

Study limitations include low sample size, lack of subject homogeneity with respect to diagnosis and lack of prospective hypothesis testing. With a reasonable safety profile, EEG-guided neuromodulation revealed promising neurophysiologic and clinical results. Additional study via sham-controlled clinical trials, greater subject number and integration of more robust EEG measures are necessary to fully evaluate potential clinical response, especially within this population. This study aligns with previous studies that have indicated the possibility of rTMS therapies being more effective when customized to the patient's unique alpha frequency[5].

References

1. Clancy KJ, Andrzejewski JA, Simon J, Ding M, Schmidt NB, Li W. Posttraumatic Stress Disorder Is Associated with α Dysrhythmia across the Visual Cortex and the Default Mode Network. eNeuro 2020;7(4) doi: 10.1523/eneuro.0053-20.2020[published Online First: Epub Date]|.
2. Lin Y-J, Shukla L, Dugué L, Valero-Cabré A, Carrasco M. Transcranial magnetic stimulation entrains alpha oscillatory activity in occipital cortex. Scientific Reports 2021;11(1):18562 doi: 10.1038/s41598-021-96849-9[published Online First: Epub Date]|.
3. Taghva A, Silvetz R, Ring A, et al. Magnetic Resonance Therapy Improves Clinical Phenotype and EEG Alpha Power in Posttraumatic Stress Disorder. Trauma Mon 2015;20(4) doi: 10.5812/traumamon.27360[published Online First: Epub Date]|.
4. Madore MR, Kozel FA, Williams LM, et al. Prefrontal transcranial magnetic stimulation for depression in US military veterans – A naturalistic cohort study in the veterans health administration. Journal of Affective Disorders 2022;297:671-78 doi: https://doi.org/10.1016/j.jad.2021.10.025[published Online First: Epub Date]|
5. Roelofs CL, Krepel N, Corlier J, et al. Individual alpha frequency proximity associated with repetitive transcranial magnetic stimulation outcome: An independent replication study from the ICON-DB consortium. Clinical Neurophysiology 2020 doi: https://doi.org/10.1016/j.clinph.2020.10.017[published Online First: Epub Date]|.