# Continuation of a Study of Bilateral Prefrontal Transcranial Magnetic Stimulation (TMS) to Treat the Symptoms of Mild TBI (mTBI) and PTSD: Research Methods, Demographics, and Tolerability

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## Introduction

**Background:** Traumatic Brain Injuries (TBIs) have affected more than 320,000 service members (SM) since 2000.[1] Posttraumatic Stress Disorder (PTSD) may result from, complicate, or exacerbate other related cognitive, psychiatric, or physical sequelae of mild TBI (mTBI). Conventional treatments for mTBI/PTSD symptoms have limited efficacy and are associated with undesirable side effects.[2] Transcranial Magnetic Stimulation (TMS) alters cortical activity through non-invasive neuronal stimulation by pulsed magnetic fields.[3]

**Purpose:** This ongoing study examines the efficacy/tolerability of repetitive TMS (rTMS) as a treatment for mTBI with comorbid symptoms of PTSD.

## Methods

**Primary objectives:**

- Assess change in mTBI and PTSD symptoms over 7 weeks of active treatment/sham (T/S) TMS
- Evaluate tolerability and side effects of rTMS

**Secondary objectives:**

- Measure changes in mood pre- and post-rTMS T/S, both acutely and over the course of the protocol
- Assess durability of improvements over 3-month period following completion of the last T/S session
- Assess structural neuronal changes from initiation to conclusion of T/S TMS via functional imaging
- Measure metabolic neuronal changes during T/S TMS
- Examine mechanisms of action of rTMS

**Assessments:** administered to participants pre-treatment, biweekly during treatment (Week 2, 4, 6), and monthly for 3 months following treatment.

- Rivermead Post-Concussion Questionnaire (RMPQ)
- Posttraumatic Checklist 5 (PCL-5)
- TMS Tolerability Worksheet
- Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR
- Mayo-Portland Adaptability Inventory- military (MPAI-m)
- Satisfaction with Life Scale (SWLS)
- Becks Scale for Suicidal Ideation (BSS)

**Biomeasures:**

- FDG-PET imaging obtained prior to T/S, during Week 2 of T/S, and at conclusion of T/S
- Structural MRI obtained prior to T/S and at conclusion of T/S
- Blood serum/saliva samples collected 30 days after the first session of rTMS T/S, at conclusion of T/S, and at acute 3-month follow-up visit.

**Treatment:**

- Double-blinded, prospective randomized sham-controlled trial
- 30 sessions: 5 sessions per week for 5 consecutive weeks followed by 3 sessions during Week 6 and 2 sessions during Week 7 (tapering) using the Neurostar Advanced Therapy machine
- Each session: 3500 pulses administered to the left DLPFC at 10 Hz and 1500 pulses administered to the right DLPFC at 1 Hz over approx. 1 hour

## Demographics

Up to n=80; n=27 have been enrolled and n=13 have completed 30 T/S sessions.

**Gender:** Male (89%), Female (11%)

**Branch of Service:** Army (29.6%), Navy (25.9%), No response (26%), Marine Corps (14.8%), Air Force (3.7%)

**Highest education level attained:** No response (8.7%), Master's degree (29.6%), Bachelor's degree (25.9%), Associate's degree (13.6%), High school/GED (18.5%), Vocational training (3.7%)

## Figure 1: Demographics

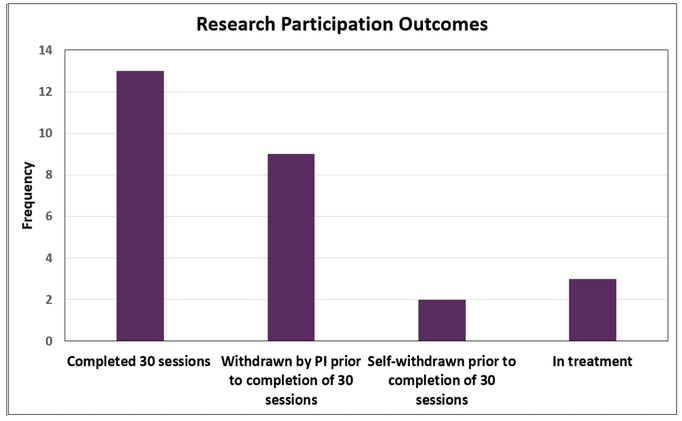


**Figure 1.** Breakdown of participant enrollment, completion, and withdrawal.

## Figure 2: Highest Pain

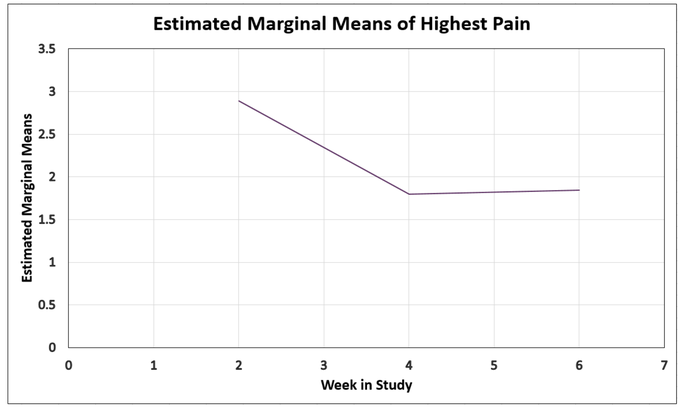


**Figure 2.** Repeated measures ANOVA of participants' mean perception of pain experienced during a T/S session. While nonsignificant ($F$ (2, 16) = 1.84, $p$ = 0.19), average patient pain ratings are still indicative of high tolerability.

## Figure 3: Reported Side Effects

| Reported Status Post-Treatment | Percentage of Participants |
|---|---|
| Tolerated | 100% |
| Rested/slept | 92.30% |
| Sore neck/back | 46.20% |
| Headache/sore head | 46.20% |
| Facial pain | 38.50% |

**Figure 3.** Self-reported side effects and participant statuses during TMS sessions.

## Preliminary Results

As of January 2019, n=27 participants with diagnoses of mTBI and presentation of significant PTS symptoms have been enrolled. Data analysis is currently limited to blinded descriptive analyses and analyses of tolerability (both T/S).

**Participant Complaints Prior to Treatment:**

- **Common comorbidities:** depressive symptomology (77.8%), migraine headaches (74.1%), anxiety (74.1%), sleep disorders (74.1%)
- **Work/life deficits:** unable to return to other activities at pre-injury level (85.2%), unable to return to work or school at pre-injury level (77.8%)
- **Social deficits:** moderate to severe problems within social relationships (74.1%)

**Mean Participant Baseline Scores Indicative of Symptomology/Cognitive Functioning:**

- **PCL-5:** 50.13/80 (suggestive of an increased need for PTSD treatment)[4]
- **ANAM:** 1.83 SD below age-matched cohorts in cognitive functioning
- **RMPQ:** 42.63/64 (severe mTBI symptomology)
- **QIDS-SR:** 16.47/27 (moderate to severe depressive symptomology)
- **MPAI-m:** 27.90/42 (moderate chronic mTBI symptomology)
- **SWLS:** 19.1/35 (slightly below average life satisfaction)

## Limitations & Future Directions

**Limitations:**

- **Recruitment:** recruitment challenges and high rate of attrition (see Figure 1)
- **Tolerability:** specific, daily tolerability data not collected for first 22 subjects
- **Efficacy:** Do current methods appropriately target dlPFC?

**Future Directions:**

- **Recruitment:** transition to multi-site study; decrease duration of involvement, number of visits, and/or intensity of involvement
- **Tolerability:** addition of tolerability worksheet a promising start to collecting tolerability and side effect data; expand tolerability assessments and probe more side effects
- **Efficacy:** integrate new technologies, such as image-guided rTMS, to properly target dlPFC

## Discussion

- All participants reported experiencing only minimal pain related to T/S during their sessions.
- Self-withdrawal rate is low—3/12. Most participants who meet all criteria for enrollment and initiate the study complete the T/S sessions.
- Study sample reflects a population that has a complex, polysymptom presentation and may require a more complex, multifaceted treatment approach than what is currently widely available as standard of care.
- Tolerability assessments should be expanded and new technology utilized for maximum efficacy.

## References

1. Snell FI, Halter MJ. A SIGNATURE WOUND OF WAR: Mild Traumatic Brain Injury. *J Psychiatr Ment Health Nurs*. 2010;48(2):22-28.
2. Hoge CW. Mild traumatic brain injury in U.S. Soldiers returning from Iraq. *N Engl J Med*. 2008;358(5):453-463.
3. Davidson JR. Pharmacotherapy of posttraumatic stress disorder: treatment options, long-term follow-up, and predictions of outcome. *J Clin Psychiatr*. 2000;61(5):52-59.
4. Bovin MJ, Marx BP, Weathers, FW, Gallagher MW, Rodriguez P, Schnurr PP, Keane TM. Psychometric properties of the PTSD checklist for Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (PCL-5) in veterans. *Psychol Assess.* 2016;28(11):1379-1391.