Addressing Intensive PTSD Treatment Non-Response Via Transcranial Magnetic Stimulation: A Pilot Study

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Addressing Intensive PTSD Treatment Non-Response Via Transcranial Magnetic Stimulation: A Pilot Study

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Abstract:

The 2- and 3-week Cognitive Processing Therapy-based intensive treatment program for veterans with PTSD at Rush University Medical Center's Road Home Program (RHP) has been shown to be highly effective (Zalta et al., 2018; Held et al., 2020). Close to 60% of all veterans who complete the program no longer meet the diagnostic criteria for PTSD upon treatment completion and over 75% experience significant symptom reductions (Held et al., 2020). Despite its demonstrated effectiveness, not all veterans benefit equally from treatment.

Although the rate of treatment non-responders in the Intensive Outpatient Program (IOP) at the Road Home Program at Rush (~25%) compares favorably to traditional PTSD treatment (30-51%; Steenkamp et al., 2015), it is important to explore alternatives to our regular programing in which can help the ~25% who do not experience a meaningful reduction in PTSD or symptoms. The goal of this study is to determine whether complementing regular intensive PTSD treatment with intermittent theta burst stimulation (iTBS) applied to the right dorsolateral prefrontal cortex (DLPFC) can improve treatment response for individuals who are likely non-responders. Specifically, the present study will evaluate iTBS during the second week of the 2-week IOP for veterans and service members who have not experienced PTSD symptom reductions over the course of the first week of the Road Home Program intensive PTSD treatment program.

Scientific Review:

Despite the efficacy of many evidence-based treatments for psychiatric disorders, a large percentage of treatment completers maintain their diagnosis and symptoms after treatment (e.g., Nemeroff, 2012; Schottenbauer et al., 2008; Larsen et al., 2019). For veterans with PTSD, approximately 66% of all individuals who successfully complete an evidence-based treatment retain their PTSD diagnosis (Steenkamp et al., 2015).

An intervention that has been shown to be effective for non-response to first-line psychotherapies is transcranial magnetic stimulation (TMS). TMS is a safe, noninvasive intervention that uses a magnetic field to modulate cortical activity in brain areas linked to an overactive stress response. When compared to sham conditions which resemble the TMS condition but do not utilize any magnetic fields (i.e., proposed active ingredient), TMS has been associated with reduced depressive symptoms in treatment non-responders (e.g., Somani & Kar, 2019). Although the bulk of research examines TMS as a treatment for major depressive disorder, TMS has also shown promise in reducing symptoms of other psychiatric disorders such as PTSD (Kan et al., 2020).

In prior research TMS was associated with medium to large reductions in core PTSD symptoms when compared to sham conditions. Symptom reductions achieved via TMS have been

demonstrated to persist (Kan et al., 2020). A recent study compared Cognitive Processing Therapy (CPT) combined with TMS to CPT with a sham condition and found that CPT combined with TMS was associated with greater PTSD symptom reductions during treatment and at six-month follow-up than CPT combined with a sham condition (Kozel et al., 2018). This finding suggests that TMS may be beneficial as an augmentation to CPT. However, to our knowledge, previous literature has not yet examined whether TMS improves outcomes for individuals who are likely to not respond to CPT treatment.

Due to the demand for briefer TMS protocols, theta burst stimulation (iTBS) is a variation on TMS. Studies have found iTBS to be more efficient than standard TMS but still associated with significant improvements and low side effects in both depression and PTSD (Philip et.al., 2019; Chu, et. al., 2020). The present study will utilize the more efficient iTBS protocol applied to the right dorsolateral prefrontal cortex (DLPFC) in order to reduce the length of stay for the participants.

Roughly one in four participants who complete Cognitive Processing Therapy (CPT) in the 2-week intensive outpatient program (IOP) at the Road Home Program at Rush do not report a meaningful reduction in PTSD symptoms and can be classified as non-responders. The present study seeks to determine whether adding iTBS to standard IOP programming reduces PTSD symptoms among participants who have not reported reduced symptoms by the end of the first week of treatment (i.e., likely non-responders).

Research Plan:

We plan to evaluate the incremental impact adding iTBS to the IOP has on overall PTSD and depression symptom reductions among likely non-responders. Using our established machine learning algorithms, we plan to identify individuals who are predicted to be likely non-responders by the end of the first IOP week. Identified individuals will then be offered to participate in a study on PTSD and iTBS for the remainder of their treatment (last six days of the IOP). Interested individuals will be consented by study staff . On the Friday of the first week and throughout the second week of the IOP, individuals receive a dose of TMS prior to each of their two CPT sessions per day.

To better evaluate the results of TMS, we will do propensity score matching using demographic (i.e., gender, age) and clinical characteristics (i.e., PCL-5 at intake and IOP Day 5). This data will be pulled from the Road Home Data Repository (ORA#14011508) for analysis.

Inclusion and Exclusion Criteria:

Inclusion Criteria:

- Veterans or service members between the ages of 18 and 65 who are attending the 2-week Intensive Outpatient Program at the Road Home Program and have not had significant PTSD symptom change based on the PCL-5 during the first week of treatment.
- Participants with an HDRS-21 score ≤ 26 at screening visit
- Negative pregnancy test in women of childbearing age

- Subject is able to adhere to the treatment schedule

Exclusion Criteria:

- Individuals with implants and non-removable metals which prevent them from safely receiving TMS, including:
    - Aneurysm clips or coils
    - Stents in the head, neck, or brain
    - Deep brain stimulators
    - Metallic implants in the head, neck, or brain (braces and dental implants do not interfere and are safe for TMS)
    - Shrapnel or bullet fragments in or near the head
    - Facial tattoos with metallic or magnetic-sensitive ink
    - Other metal devices or ferromagnetic objects implanted in or near the head
    - Pacemakers, intra-cardiac lines, or implanted medical pumps
- Individuals with a history of seizures or epilepsy (except those therapeutically induced by ECT)
- Individuals diagnosed with major, chronic mental health illnesses such as Psychotic Disorders, Bipolar Disorders, and Obsessive Compulsive Disorder
- Individuals with a history of substance abuse within the past six months
- Individuals with a history of significant head trauma with a loss of consciousness for longer than 5 minutes
- Individuals with severe or frequent headaches
- Individuals with significant hearing loss
- Individuals with significant neurological disorders such as Parkinson's disease, Huntington's chorea, and Multiple sclerosis
- Individuals with unstable physical disease, such as unstable cardiac diseases
- Individuals currently on Benzodiazepine at a dose higher than 3mg or Lorazepam or equivalent.
- Women who are breastfeeding
- Individuals with previous TMS treatment

Study Population:
We plan to enroll a total of 15 likely non-responders and will evaluate PTSD and depression symptom reductions from pre-to post-treatment and pre- to 1- and 3-month follow-ups.

Study Activities:

Screening/Baseline Assessment:
On day 5 of IOP treatment, participants who have not had significant PTSD symptom change based on the PCL-5 will be approached to participate in the study.

Acute Treatment Phase:
The present study uses the FDA cleared NeuroStar TMS Therapy System. Participants will receive two iTBS treatments daily for 5 days. At each iTBS session the study personnel will collect and record any adverse events reported.

Prior to the initiation of iTBS on the first day, each participant's motor threshold (MT) will be established with an active coil. The MT will be determined by the stimulator output sufficient to induce movement in the contralateral hand >50% of the time.

Treatment Parameters:

- Total Number of pulses: 1800
- Orientation: right dorsolateral prefrontal cortex (DLPFC)
- Pulses: 3
- Interpulse interval: 20 seconds
- Bursts per second: 5
- Stimulation time: 2 seconds
- Interval: 10 seconds
- Intensity: 90% active motor threshold
- Total treatment time: 12 minutes

1- and 3-Month Follow-Ups:
Participants will be contacted to complete assessments.

Measures:
Study participants will complete the same validated measures as individuals enrolled in the Road Home Program IOP at treatment endpoint and at the 1- and 3-month follow-up timepoints. In addition to these measures completed by all IOP participants, participants in this study will complete the HAM-D to measure depressive symptoms, respectively, at the time of enrollment on Friday of the first week of treatment, 1-month follow-up, and at 3-month follow-up.

Measure	Focus	Timing
PTSD Checklist for DSM-5	PTSD Symptoms	IOP Baseline*, Endpoint*, 1-month*, 3-month*
Patient Health Questionnaire	Depression Symptoms	IOP Baseline*, Endpoint*, 1-month*, 3-month*
Hamilton Depression Rating Scale	Depression Symptoms	End of first week, 1-month, 3-month
PROMIS SF8a	Satisfaction with Social Roles and Functioning	IOP Baseline*, Endpoint*, 3-month*
Veteran RAND-12	Mental and physical functioning	IOP Baseline*, 3-month*
Neurobehavioral Symptom Inventory	Neurobehavioral symptoms	IOP Baseline*, Endpoint*

* Part of the standard Road Home Program IOP assessment schedule.

Risks:
TMS is well-tolerated and associated with few side-effects. The most common side-effect, which is reported in less than half of individuals, is mild headache. Some individuals report feeling sensations on the scalp or facial twitching which should not be painful or and should diminish rapidly. Due to the noise the TMS machine produces, earplugs are given to individuals to mitigate any discomfort. The most serious risk of TMS is seizures, however, the risk of experiencing a seizure during TMS is exceedingly low. Qualified medical staff will be present during the TMS administration and would be able to intervene immediately and ensure patient safety in the event of an adverse event. Qualified medical staff is also present during business hours as part of the Road Home Program IOP. Participants will be advised to call 911 or go to their nearest emergency room in case of emergencies.

Describe the procedures that will be in place to minimize any risks:
Prior to beginning TMS treatments, a medical history asking about possible implants or other metals in the body will be completed. Participants will be thoroughly screened for any magnetic-sensitive objects prior to each treatment session. Participants will be asked to remove any magnetic-sensitive objects from their person (e.g., jewelry, credit cards). Participants will be given earplugs during treatment for their comfort and hearing protection. TMS treatments will be administered and supervised by qualified medical staff trained in TMS. The participant can stop treatment at any time. Qualified medical staff will be present during the TMS administration and would be able to intervene immediately and ensure patient safety in the event of an adverse event. Qualified medical staff is also present during business hours as part of the Road Home Program IOP. Participants will be advised to call 911 or go to their nearest emergency room in case of emergencies.

To minimize the risk of loss of confidentiality, all study staff will work very hard to ensure that all data is stored securely so that only members of the study staff will have access to identifiable data. No identifiable data will ever be disclosed to any outside parties. Participants' identities will not be revealed on any report, publication, or at scientific meetings.

Benefits:
Participants may experience direct benefits as a result of participating in this study. If iTBS is effective at improving outcomes for likely non-responders, as hypothesized, these individuals may experience meaningful PTSD and depression symptom reductions.

Assuming the proposed project is successful and veterans who are likely non-responders report substantially larger PTSD and depression symptom reductions following TMS compared to no additional intervention, iTBS could become part of the routine clinical programming that is offered to likely non-responders. As a result, overall program outcomes, including satisfaction, should further improve.

If successful, the proposed project may also have broader implications for the future of IOP programming. Whereas IOP programming is currently relatively static, the successful project would suggest that modifying and personalizing the care veterans receive based on their observed treatment response can further improve care. As such, this project would lay the

foundation for future studies that examine various program modification that can help tailor treatment to each warrior based on their symptoms prior to and during treatment.

Informed Consent:
Informed consent will be obtained prior to any study procedures. Potential participants will be informed that their decision about participation will in no way affect the care that they receive at the Road Home Program or at RUMC.

Are you applying for a waiver of consent or assent? (*Waiver of consent implies you will not obtain written or signed consent.***)**
No.

Will a Certificate of Confidentiality be obtained for this study?
No.

Data Storage:
Specify the site at which the data will be stored and how it will be stored:
Sources of data that will be included in this study are captured in the IRB-approved data repository (ORA# 14011508). All survey data are collected using online surveys (REDCap), which are regularly used for Department of Psychiatry procedures. All electronic data that is collected through self-reported questionnaires will be password protected and stored on the RUMC secure server. A request for de-identified data will be submitted to Sarah Pridgen, the data repository manager, who will manage all access to data from the data repository. Only individuals that have been IRB approved will have access to any data collected. The information that is collected in this study will not be disclosed to any outside parties. All the findings in this study will be reported at a group level will no risk of identifying individual participants.

Given the clinical nature of this study, study participants' MRN will be obtained to link their study data to their Electronic Medical Record in Epic, REDCap, and any data that is stored on the secure Rush network server. Medical record data will be stored in Epic in accordance with RUMC policy.

How long will the data be maintained and/or stored?
This project will examine whether ITBS can aid veterans at risk of treatment non-response. Results will be evaluated, in part, via the same measures given as part of the routine care in the Road Home Program IOP. Because much of the outcome data is connected to routine care, all study-related data will be maintained and stored securely indefinitely.

Who, other than the specified study team, will have access to the study records or data? Specify their name, role, and affiliation.
No one outside of the specified study team will have access to the study data or records.

If coded or identified data will be released, specify the persons/agencies to whom the information will be released. Please also indicate the provisions that will be taken to assure that the transmission of the data will maintain confidentiality:

Results from analyses of group level limited use datasets may be presented in grants, manuscripts, or professional presentation in the future.

Describe what will happen to the data or dataset (including photographs and/or audio/video recordings) when the study is completed. Please indicate your plans for the destruction of identifiers at the earliest opportunity consistent with the conduct of the research and/or clinical needs, if applicable:
Because much of the outcome data is connected to routine care (ORA# 14011508), all study-related data will be maintained and stored securely indefinitely.

What process will be in place to assure that all investigators seeking access to the data bank have received IRB approval or exemption for their studies?
The individuals listed on this IRB or first approved in the future specifically on this IRB protocol will have access to the data set for research activities. In addition, individuals who obtain IRB approval to use the data set established by this study will be given access to a de-identified data set containing only the approved variables of interest following a formal request for a data set submitted to the principal investigator. All such research activities will be conducted with a de-identified data set and will be reported at the group level with no risk of identifying individual patients.

Justify your needs to collect PHI in this study:
PHI will be collected to access Epic and REDCap in order to characterize the participant sample. Treatment dates are collected as part of routine clinical care to document treatment progress.

Describe how and where PHI will be destroyed following the completion of the study:
Not applicable. PHI exists in Epic and REDCap or in a restricted folder on the RUMC secure server; data will remain here secure and indefinitely. No identifiable data will ever be shared with personnel outside of the approved study staff.

Will subjects be able to request that their information be removed from the data bank?
No.

If no, please explain why not:
The data collected are necessary clinic procedures that are conducted to ensure proper care. As is true with all clinical care, patients have the right to refuse care procedures. Thus, patients could refuse to complete the questionnaires which are used to determine PTSD symptom severity. However, once the questionnaires have been collected, these data become part of the patient's clinical record and cannot be removed.

Costs:
There will be no cost to participants to participate in this study.

Compensation:

Participants will be compensated for their time if they complete the additional surveys: $20 at the end of the first week of treatment, $20 for 1-month post-treatment, and $40 for 3-month follow-up surveys.