Frontal-pole Neuromodulation for Impulsivity and Suicidality in Veterans with Mild Traumatic Brain Injury and Common Co-Occurring Mental Health Conditions: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Suicide remains a leading cause of death among Veterans, and mild traumatic brain injury (mTBI) increases the risk of suicidal ideation and suicide attempts (SI/SA). mTBI worsens impulsivity and contributes to poor social and occupational functioning, which further increasing the risk of SI/SA. Repetitive transcranial magnetic stimulation (TMS) is a neuromodulation treatment approach designed to mimic endogenous brain rhythms. Intermittent theta burst stimulation (iTBS) is a "second-generation" form of TMS that is safe, shorter in duration, displays a minimal side effect profile, and is a promising treatment approach for impulsivity in mTBI. Our novel treatment uses frontal pole stimulation to target the ventromedial prefrontal cortex (VMPFC) and may reduce impulsivity by strengthening functional connectivity between the limbic system and frontal cortex, potentially saving lives.

Objective: The objectives of this study are to (1) develop an iTBS intervention for individuals with mTBI and SI, (2) assess the feasibility and tolerability of the intervention, and (3) gather preliminary clinical outcome data on SI, impulsivity, and functioning that will guide future studies.

Methods: This is a pilot, double-blinded, randomized controlled trial. In developing this protocol, we referenced SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials). We will enroll 50 subjects (25 active iTBS and 25 sham iTBS). The iTBS intervention will be performed daily, five days a week, for two weeks. We will collect quantitative outcome measures before and after the intervention. Measures included will assess functioning (Social and Occupational Functioning Assessment Scale (SOFAS), Veteran RAND-36), impulsivity (Urgency, Premeditation (lack of), Preservation (lack of), Sensation Seeking, Positive Urgency Impulsive Behavior Scale – Negative Urgency subscale (UPPS-P)), SI (Beck Suicide Scale (BSS), Columbia Suicide Severity Rating Scale (C-SSRS)), PTSD symptoms (PTSD Checklist for DSM-5 (CAPS-5) (PCL-5)), and depressive symptoms (Patient Health Questionnaire-9 (PHQ-9), Inventory for Depressive Symptoms – Self-Report (IDSSR)). We will collect qualitative data through semi-structured interviews to elicit feedback on the subject's experience and symptoms.

Results: This study protocol was approved by the Edward Hines Jr Veterans Administration Hospital Institutional Review Board (Hines IRB#14-003) and registered on ClinicalTrials.gov (NCT05647044). This novel treatment is a 5-year research project (04/01/2023 – 03/31/2028) funded by the VA Rehabilitation Research & Development (RR&D) service (CDA2 grant IK2

RX002938). Study results will be disseminated at or before the project's end date in March 2028.

Conclusions: We will provide preliminary evidence of the safety, feasibility, and acceptability of a novel frontal pole iTBS treatment for mTBI, impulsivity, SI/SA, and functional deficits. Clinical Trial: ClinicalTrials.gov (NCT05647044); https://clinicaltrials.gov/study/NCT05647044

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Conclusions: We will provide preliminary evidence of the safety, feasibility, and acceptability of a novel frontal pole iTBS treatment for mTBI, impulsivity, SI/SA, and functional deficits.

Trial Registration: ClinicalTrials.gov (NCT05647044);

https://clinicaltrials.gov/study/NCT05647044

Keywords: mild traumatic brain injury; transcranial magnetic stimulation; intermittent theta burst stimulation; suicidality; suicidal ideation; impulsivity; neuromodulation; functional deficits

Introduction

Background

The prevalence of suicide among Veterans is devastatingly high. Veterans die by suicide at almost double the rate of civilians [1]. The prevalence of suicide among Veterans with traumatic brain injury (TBI) is even higher. Veterans with TBI are 1.5 times more likely to die by suicide than Veterans without TBI, even when controlling for comorbid psychiatric conditions [1, 2]. These statistics are particularly concerning given that there have been over 400,000 new TBI diagnoses since the beginning of Operations Enduring Freedom, Iraqi Freedom, and New Dawn (OEF/OIF/OND), of which over 80% are mild traumatic brain injury (mTBI) [3]. Overall, between 16-20% of all OEF/OIF/OND Veterans have a history of mTBI, and among them, up to 22% report suicidal ideation [4].

Given the high suicide rate among Veterans, suicide prevention is a high-priority issue for the Veterans Administration (VA) nationwide [5]. The VA has assembled task forces that have created clinical practice guidelines for the assessment and management of Veterans at risk for suicide [6]. These guidelines establish significant risk factors to help providers identify which Veterans are at the highest risk. The guidelines specifically cite having a history of TBI, functional deficits, past suicidal ideation (SI), and a history of impulsivity [6] as independent risk factors for developing SI. TBI predisposes individuals to functional deficits [7, 8] and impulsivity [9], and those with impulsivity likely struggle with functional deficits [10]. Given these findings, our lab hypothesizes that these conditions may be interrelated and could serve as meaningful behavioral targets in the treatment of suicidal ideation.

The presented study aims to create a novel iTBS intervention delivered to the VMPFC to reduce impulsivity and SI among Veterans with mTBI while improving overall social and occupational functioning. We are interested in stimulating the ventromedial prefrontal cortex (VMPFC) with intermittent theta burst stimulation (iTBS) because the VMPFC appears to exhibit less functional connectivity with other brain regions in individuals with mTBI. This diminished connectivity is suspected to be responsible for developing impulsivity and SI within this population [11-13]. To our knowledge, however, no established treatment approach has used VMPFC iTBS to improve social and occupational functioning, SI, and negative urgency impulsivity among individuals with mTBI and comorbid mental illness.

Rationale

Suicidal Ideation

SI is a severe and prevalent condition among Veterans and civilians alike and can prove lethal. The Center for Disease Control and Prevention estimates that**,** during 2015-2019, 4.3% of the general adult US population had SI, and 5-10% of these individuals advanced to making a suicide attempt (SA) [14]. As such, focusing treatment on individuals with SI before they advance to making a suicide attempt gives providers an opportunity at suicide prevention.

Current evidence-based treatment options for SI include pharmacotherapy and psychotherapy.

Pharmacotherapeutic treatment (primarily antidepressants) can take 6-8 weeks or more to become effective. A recent meta-analysis suggested that only 2/3 of published studies demonstrated a reduction in SI with any pharmacotherapy compared to placebo [15]. Furthermore, many patients will require multiple medication trials [16], which may take months to experience any symptomatic improvement. Given the latency of these treatment options, individuals with SI require more suicide prevention options that are designed to exhibit better and faster resolutions toward promoting resilience.

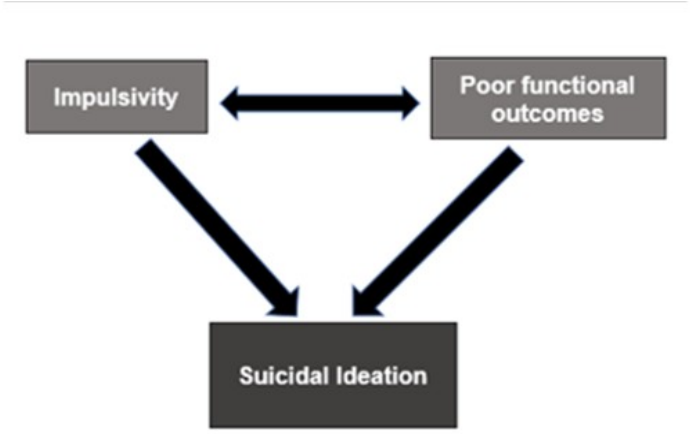
mTBI and suicide: the role of impulsivity

Impulsivity, broadly defined, is associated with TBI of all severities [9, 17, 18]. For the cohort of this study, we will focus on Veterans with mTBI. Veterans with mTBI make up most of the Veteran population with TBI [3]. A form of behavioral impulsivity, negative urgency impulsivity, is particularly prevalent in this population [18]. Negative urgency impulsivity refers to poor behavioral control in the setting of negative events or affect [19]. It is associated with excessive agitation, irritability, low moods, and a greater tendency for aggression toward oneself or others immediately following a negative event [20]. Unsurprisingly, negative urgency impulsivity increases the likelihood of SI [21] and is associated with significant risk factors for suicide, such as social and occupational functional deficits [22]. Our lab's previous work has built upon these findings and completed a chart review study that found negative urgency impulsivity most strongly mediated the relationship between a history of TBI and SI/SA [23].

Post-TBI negative urgency impulsivity is presumed to be secondary to disinhibition of the limbic system from damage to the prefrontal cortex (PFC), specifically the ventromedial prefrontal cortex (VMPFC) and/or medial orbitofrontal cortex (mOFC) [9]. The VMPFC, which serves as an inhibitory control center for the limbic system, is particularly vulnerable to damage in all severities of TBI as this region abuts the cranial floor and frontal cranial bone, making it susceptible to coup and contrecoup forces from nearly all directions [12, 24, 25]. Uninhibited limbic affect can manifest as poor frustration tolerance, fear, and aggression [26]. These characteristics of negative urgency impulsivity can reduce the quality of life and worsen community and social functioning, predisposing individuals to SI/SA (Figure 1) [26].

To our knowledge, no neuroimaging evidence implicates specific brain regions in mTBI-related impulsivity and SI. The presented study will help address this knowledge gap by using within-subject neuroimaging data to identify brain regions predisposed to these conditions.

Figure 1. Relationship between impulsivity, functionality outcomes, and suicidal ideation



mTBI and suicide: the role of functional deficits

TBI itself predisposes individuals to social and community functional deficits [27]. A meta-analysis of psychosocial factors found that difficulties in social and occupational functioning were strongly tied to increased levels of suicidal ideation, social isolation, and low socioeconomic status and are directly associated with increased incidences of suicidal ideation and completed suicides (Figure 1) [28]. Among individuals with TBI, those who were unemployed in the past year were at the highest risk for SI when compared to individuals who had been employed [10]. Given that TBI and impulsivity are both (1) independent risk factors for developing SI and (2) associated with impaired social and community functioning, it appears that TBI, SI, impulsivity, and functional deficits are intertwined and should be considered in tandem. The evidence is scarce, however, to directly support biological treatments for SI, impulsivity, and functional deficits following mTBI. The presented study aims to address this knowledge gap by providing further evidence to support the development of a novel neuromodulatory treatment to improve functioning for those with impulsivity, SI, and mTBI symptoms.

Transcranial Magnetic Stimulation (TMS) in Neuropsychiatry

Transcranial magnetic stimulation therapy (TMS) is a noninvasive neuromodulatory technique that involves placing an insulated electric coil on the scalp. This electrical current flowing through the coil produces alternating magnetic fields. These fields pass through the skull, inducing electric currents in the brain tissue beneath the coil. Multiple large, multisite, sham-controlled studies and meta-analyses have shown that TMS, generally to the left dorsolateral prefrontal cortex (DLPFC), effectively treats depression [29, 30]. TMS was FDA-approved for treatment-resistant depression in 2008 [31-33], and in 2020, a nationwide clinical TMS program was implemented in the VA after completing a multisite clinical trial. Thus, the VA healthcare system is well-poised to offer novel TMS treatment approaches for Veterans in need.

iTBS is a “second-generation” form of TMS designed to mimic endogenous brain rhythms with the added benefit of markedly reduced treatment time. Using this approach, iTBS can be administered in 3-10 minutes, compared to the standard 37.5-minute protocol for TMS. In a large, non-inferiority study comparing iTBS and TMS, patients with treatment-resistant depression show similar safety and adverse event profiles and exhibit improvements in their depressive symptoms to both interventions [34]. One of the most prevalent and widely known iTBS treatment protocols is based on Li et al. and delivers 1800 pulses of iTBS per day for ten days [35]. This amount of stimulation appears to be well tolerated and shows a good effect on depressive symptoms, even in a treatment-refractory group. The result of significant symptomatic improvement in a short period is particularly interesting and relevant in treating SI, where a shorter latency to treatment response is of the essence and could potentially be lifesaving.

TMS as a Treatment for TBI Sequelae

TMS has an established safety record as a treatment for individuals with mTBI [36], and there is accumulating evidence that TMS is a safe and effective treatment for the sequelae of mTBI. TMS has demonstrated efficacy in treating several post-mTBI sequelae and related neuropsychiatric conditions, including depression, posttraumatic stress disorder (PTSD), cognitive deficits, and chronic pain/headaches [36-39]. TMS also improves PTSD symptoms among those with co-occurring mTBI [40, 41]. Further, multiple studies and meta-analyses demonstrate that TMS, administered to a variety of anatomical brain locations, including the DLPFC [42], does not induce more significant numbers of adverse events among individuals with mTBI than among individuals without mTBI [36, 38, 43]. Specifically, in a National VA TMS study of 770 Veterans receiving TMS, nearly half had mTBI, and TMS was demonstrated to be equally as safe in Veterans with and without mTBI [44].

An overall estimate of 70% of individuals with mTBI struggle with at least one psychiatric comorbidity [45]. Thus, it is essential to consider TBI and comorbid mental illness simultaneously, as they frequently co-occur. Comorbid conditions include substance use disorders [46], PTSD, and depression [47, 48]. Moreover, neuroimaging studies of individuals diagnosed with PTSD and substance use disorder (two conditions also associated with impulsive behavior and SI) demonstrate diminished volume and hypoactivity in the VMPFC [49, 50]. Therefore, it is likely that when mental illness diagnoses such as PTSD and substance use disorders co-occur with mTBI, they have an additive effect on brain functioning in the VMPFC, further worsening negative urgency impulsivity [49, 50].

TMS as Treatment for Suicidality

Encouraging meta-analyses suggest TMS may also effectively treat suicidality [51, 52]. For example, a randomized controlled trial reported a 44% decrease in individuals experiencing "thoughts of suicide" after high-dose left-sided DLPFC TMS treatment [53]. Additionally, a study of pooled sham-controlled trials reported that bilateral TMS is associated with a decline in SI [54].

However, drawing overall conclusions from the existing literature on TMS for suicidality remains challenging due to the heterogeneity of the data. Studies often suffer from small sample sizes, inconsistencies in how suicidality is measured across studies, and contradictory findings [55, 56]. Interestingly, one analysis suggests that changes in suicidal ideation may be statistically independent of depression outcomes, underscoring the importance of studying SI separately from depression in contrast to many prior studies [57].

Post-TBI negative urgency impulsivity is presumed to arise from limbic system disinhibition due to damage to the VMPFC [9]. In mTBI, thinning of the right VMPFC is evident when compared to healthy controls [58], and individuals exhibiting this volume loss report increased aggression, anxiety, and depression following injury [59]. Uninhibited limbic affect can manifest as poor frustration tolerance and aggression, characteristics of negative urgency impulsivity [60]. Interestingly, individuals without a history of mTBI who attempted suicide or have a history of SI also show diminished VMPFC volume and reduced connectivity between the PFC and the limbic system, further supporting it as a potential therapeutic target [61, 62].

Frontal pole stimulation is a recent TMS/iTBS site of interest for reducing impulsive behaviors, including substance abuse [63] and compulsions in Obsessive Compulsive Disorder (OCD) [64]. iTBS can be applied to the frontal pole to target the VMPFC, and iTBS to the frontal pole is

tolerable, with no more subjective pain than TMS [42]. This approach allows for more direct stimulation of the VMPFC [42] and modulation of the limbic system [63].

The presented study proposes inducing neuroplasticity to the VMPFC by stimulating the frontal pole to treat suicidal ideation and impulsivity in Veterans with mTBI. We selected the frontal pole and associated right VMPFC as a treatment target as volumetric data demonstrates thinning of the right mOFC/VMPFC when compared to healthy controls [65], and individuals exhibiting this volume loss also report increased aggression, anxiety, and depression following injury [59]. The role of the VMPFC in negative urgency impulsivity is also supported by evidence that individuals with penetrating TBI to the VMPFC are significantly more likely to become aggressive than those with penetrating TBI elsewhere [24]. By inducing modulation and neuroplasticity to the VMPFC and limbic system, iTBS at the frontal pole offers a promising means of mitigating impulsive behaviors and decreasing SI through the opportunity of increasing connectivity and undoing limbic damage caused by mTBI. However, more research is essential to ensure this treatment approach's safety, tolerability, and efficacy.

Objectives

The objectives of this pilot study are to (1) determine the safety, feasibility, tolerability, and efficacy of frontal pole iTBS for Veterans with mTBI, negative urgency impulsivity, and SI, (2) collect advanced neuroimaging data from Veterans with mTBI, impulsivity, and suicidality to further our understanding of what neural changes are occurring when treatment is effective, and (3) gather preliminary clinical outcome data on impulsivity, SI, and social and occupational functioning of Veterans receiving iTBS. The results of these objectives will help to guide future studies on neuromodulation as a treatment for impulsivity and SI among patients with mTBI.

METHODS

Study design

The proposed study is a pilot, prospective, randomized, double-blinded, sham-controlled study to develop a frontal pole iTBS intervention. We will examine the safety, feasibility, tolerability, and efficacy of ten sessions of iTBS over two weeks. Preliminary impulsivity, SI, and social and occupational functioning data will be collected before and after receiving active or sham treatment. In developing this protocol, we referenced SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) [66].

Ethics Approval and Dissemination

The study protocol was approved by the Edward Hines Jr Veterans Administration Hospital Institutional Review Board (Hines IRB # 1716074) and registered on clinicaltrials.gov (NCT05647044). This research study is designed on a 5-year research plan.

Participants

We will enroll 55 Veterans between the ages of 22 and 65 with mTBI, impulsivity, and suicidal ideation within the previous three months. mTBI will be defined according to the VA Department of Defense guidelines [67] and utilize aspects of the mTBI symptom attribution and classification algorithm (SACA) [68] when determining eligibility. mTBI must have occurred at least one year prior to enrollment to ensure the injury has stabilized. Though it is not mandatory, Veterans may also have diagnoses of depression, posttraumatic stress disorder (PTSD), or bipolar spectrum illness

(without a history of psychosis). Recent SI will be defined as a score of >1 on the Columbia Suicide Severity Rating Scale (C-SSRS) [69] within the past three months. Impulsivity will be defined as having any mentions of impulsive behavior in the medical chart and any positive results on the Urgency, Premeditation (lack of), Preservation (lack of), Sensation Seeking, Positive Urgency Impulsive Behavior Scale – Negative Urgency subscale (UPPS-P) [21]. For safety, we will exclude persons with contraindications to TMS or MRI. We will also exclude subjects whose suicidal ideation is active, with intent and plan, as they require emergency psychiatric intervention. Both males and females will be included. We *will not exclude* participants based on gender, ethnicity, or race. To enhance generalizability, we will include Veterans regardless of previous combat or deployment experience. Since cannabis and alcohol use are prevalent among Veterans, intermittent or low amounts of cannabis or alcohol consumption will not be considered exclusionary if usage does not meet the criteria for a moderate substance use disorder. Detailed information on inclusion and exclusion criteria is listed below (Textbox 1).

Textbox 1. Participant inclusion and exclusion criteria.

Inclusion Criteria
• 22 - 65 years of age • Can read and speak English • mTBI Criteria: Symptom Attribution and Classification Algorithm (SACA) [68] criteria for mTBI (without the requirement of clinical neuropsychological impairment) • C-SSRS score of >1 within three months • History of impulsivity documented in the chart and exhibited on the UPPS-P (Urgency score >20) [21]
Exclusion Criteria
• Contraindications to iTBS/TMS (e.g., epilepsy) • Contraindications to MRI (e.g., claustrophobia, ferromagnetic metal implants) • Active substance use disorder per DSM-V criteria • Active suicidal ideation with intent and plan (these subjects will be brought to the ER for emergent psychiatric care) • History of moderate to severe TBI • History of non-traumatic neurological injury (e.g., stroke, neurosurgery, hemorrhage) • History of or current psychosis not due to an external cause (e.g., due to illicit drug use) • Pregnancy or breastfeeding • Within 12 weeks of a major surgery/operation • Active, unstable health condition (i.e., decompensated heart failure, recent severe heart attack) • Within one year of mTBI

Recruitment

We will recruit Veterans receiving care from the TBI/Polytrauma program, primary clinic, women's health clinic, and the Mental Health Service Line at Edward Hines Jr VA Hospital (Hines VA). Personnel at all mentioned clinics will be educated on the study and encouraged to give IRB-

approved flyers containing contact information to Veterans who may be a good fit for the study. We will be added as co-signers in the electronic medical records of Hines VA patients who may be deemed a good fit for this study. We will also mail informational letters to Veterans who have completed past TBI studies and permit us to contact them about future studies through a TBI Data Repository (Hines IRB#14-003), which currently includes over 300 Veterans. Research candidates at the Hines VA will also be identified using administrative electronic health record data available through the VA Informatics and Computing Infrastructure (VINCI). The VINCI database will search for TBI within the past ten years (FY2013-FY2023) according to appropriate ICD-9/10-CM codes reflecting study inclusion criteria. All potentially eligible Veterans will receive an informational letter and phone call to gauge interest and perform initial eligibility screens.

DATA COLLECTION AND MEASURES

MRI Data acquisition, neuronavigation, and motor thresholding

All participants will undergo an MRI of their brain pre- and post-iTBS administration. Prior to iTBS, a high-resolution, 3D, T1-weighted, multigradient-echo sagittal anatomical scan (voxel size=0.8 mm isotropic resolution) will be collected to allow for iTBS treatment site neuronavigation for each participant. Subjects will also complete a resting state fMRI and diffusion tensor imaging before and after iTBS administration to examine treatment-induced connectivity changes. Participants will be asked to complete a standardized MRI safety screening form before starting the study to ensure the MRI safety procedures are followed.

Each participant's T1 MRI will be loaded into a Localite TMS Neural Navigator system. Electrodes will be placed on the thumb over the abductor pollicis brevis (ABP) muscle and connected to an electromyography (MagVenture) to measure motor-evoked potentials (MEPs). To determine each participant's motor threshold (MT) for iTBS (to determine at which intensity the iTBS stimulation should be delivered), a MagVenture MagProX100 with MagOption stimulator and Magpro Cool Coil B65 A/P will be used. Single pulse TMS will be administered to the left motor cortex at the hand knob. The location of this part of the motor cortex will be estimated on the subject's MRI and then confirmed using TMS to identify the ABP muscle neural coordinates. The resting motor threshold is the lowest stimulus intensity necessary to produce MEPs of the peak-to-peak amplitude of ≥50μV in 5 of 10 trials. MEPs of the ABP will be recorded using surface electrodes on the right thumb.

Data Collection

Data collection is expected to take approximately 18-20 hours per participant over the intervention period of two weeks. Assessments will be collected at four-time points in the study: screening, baseline, midpoint, and endpoint (Table 1).

Table 1. Assessment timeline and purpose

Assessment Name	Assessment Purpose
Phone Screening Assessments:	
Ohio State TBI Identification Method [70]	mTBI eligibility criteria
Columbia Suicide Severity Rating Scale (C-SSRS) [69]	History of suicidality, eligibility determination – Secondary outcome
Urgency, Premeditation (lack of), Preservation (lack of), Sensation Seeking, Positive Urgency Impulsive Behavior Scale – Negative Urgency subscale (UPPS-P) [21]	Negative urgency impulsivity, eligibility determination – Secondary outcome
Demographics	Sample characterization
UIC CMRR MRI Safety Form	MRI safety compatibility

TMS Safety Form	TMS safety compatibility
In-Person Screening Assessments:	
Structured diagnostic interview [68]	mTBI symptoms
Neurobehavioral symptom inventory (NSI) [71]	mTBI symptoms
Clinically Administered PTSD Scale for DSM-5 (CAPS-5) [72]	PTSD diagnosis
Alcohol Use Disorder Identification Test (Audit-C) [73]	Active alcohol use disorder
Drug Use Disorders Identification Test (Dudit) [74]	Active substance abuse disorder
Structured Clinical Interview for DSM-5, Research Version (SCID-5-RV) [75]	Active mental illness diagnosis
Baseline, Midpoint, and Follow-Up Assessments:	
Social and Occupational Functioning Assessment Scale (SOFAS) [76]	Functioning in the community – Primary outcome
Columbia Suicide Severity Rating Scale (C-SSRS) [69]	History of suicidality – Secondary outcome
Urgency, Premeditation (lack of), Preservation (lack of), Sensation Seeking, Positive Urgency Impulsive Behavior Scale – Negative Urgency subscale (UPPS-P) [21]	Negative urgency impulsivity – Secondary outcome
Buss-Perry Aggressiveness Scale [77]	Aggression symptoms
Patient Health Questionnaire (PHQ-9) [78]	Depression symptoms
Veteran's RAND (VR-36) [79]	Perceived community functioning
Beck Suicide Scale (BSS) [80]	Suicidal ideation measurement
PTSD Checklist for DSM-5 (PCL-5) [81]	PTSD Symptoms
Inventory of Depressive Symptomatology, Self-Report (IDS-SR) [82]	Depression symptoms
Difficulties in Emotion Regulation Scale (DERS) [83]	Perceived struggles with emotion modulation
Delayed Discounting Task [84]	Impulsivity inhibition measure
Stroop Color & Word Test [85]	Impulsivity inhibition measure

Eligibility measures and information collected during the pre-enrollment phone screen include the Ohio State University TBI Identification Method [70], the Columbia-Suicide Severity Rating Scale (C-SSRS) [69], the Urgency, Premeditation (lack of), Perseverance (lack of), Sensation Seeking, Positive Urgency Impulsive Behavior Scale – Negative Urgency Subscale (UPPS-P) [21], self-reported age, the ability to read and speak English, the Center for Magnetic Resonance Research (CMRR) safety form, and TMS safety form. If deemed eligible, participants will be asked to complete an in-person screening.

The in-person screening will consist of completing several assessments incorporated into the mTBI SACA [68]. Measurements and interviews include the Structured Diagnostic Interview [68], the Neurobehavioral Symptom Inventory [71], the Clinician-Administered PTSD Scale for DMS-5 (CAPS-5) [72], the Alcohol Use Disorder Identification Test - Consumption Questions (AUDIT-C) [73], the Drug Use Disorders Identification Test (DUDIT) [74], and the Structured Clinical Interview for DSM-5 – Research Version (SCID-5, RV) [75].

Once the listed diagnostic and screening measures are completed and subjects meet eligibility criteria, participants will be asked to complete the following self-reported measures at their baseline, midpoint, and endpoint visits: Social and Occupational Functioning Assessment Scale (SOFAS) [76], Columbia-Suicide Severity Rating Scale (C-SSRS) [69], Urgency, Premeditation (lack of), Preservation (lack of), Sensation Seeking, Positive Urgency Impulsive Behavior Scale – Negative Urgency subscale (UPPS-P) [21], the Buss-Perry Aggressiveness Scale [77], Patient Health Questionnaire (PHQ-9) [78], Veteran's RAND (VR-36) [79], Beck Scale for Suicide Ideation (BSS) [82], PTSD Checklist for DSM-5 (PCL-5) [81], Inventory of Depressive Symptomatology, Self-Report (IDS-SR) [82], The Difficulties in Emotion Regulation Scale (DERS) [83], the Delayed Discounting Task [84], and the STROOP Color and Word test [85].

Feasibility completion rates will be described according to the reasons participants did not complete the two-week intervention and the rates of missed sessions. Study completion is defined as completing all ten sessions. Safety measures will follow procedures used in prior TMS studies [86] and will be scored using the Medical Dictionary for Regulatory Activities. Side effects, adverse events, and the TMS data safety sheet will assess change severity throughout the intervention. Tolerability will be measured through the number of patients who complete the treatment course and via self-report.

Safety and Adverse Event Monitoring

Subjects will participate in safety monitoring using the Data Safety Monitoring Scale (DSMS). This scale will rate changes from baseline vitals (temperature, blood pressure, heart rate, oxygen saturation levels), fatigue, tinnitus (ringing in the ears), sleep, dizziness, nausea, vomiting, confusion, seizure, syncope (fainting), headache, neck pain, skin integrity of the scalp, and substance use.

Subjects will be asked about adverse events (AEs) at each iTBS session, which will be logged to ensure safety throughout the intervention. These will be coded using the current version of the Medical Dictionary for Regulatory Activities, following procedures used in prior TMS studies [63]. The TMS safety sheet will be collected and scored regarding severity and change from baseline. Data on every side effect and AE will be collected, rated on a score of 0-5 to assess severity, and reported.

All iTBS sessions will be videotaped to monitor for safety and allow for review in case of an AE. Acknowledgment for pictures and videos will be completed as part of our informed consent procedure.

AEs can be non-serious and serious. A serious AE is when the changes are life-threatening and may be disabling, require hospitalization, or require intervention to prevent impairment. We will measure deleterious changes in (1) neurologic status and cognitive symptoms, (2) somatic and vestibular symptoms, (3) and depression. AE will be tracked using the AE log.

All unanticipated AEs related to this research study will be reported to the IRB, the study sponsor, and the research director within five business days. Serious AEs will be reported to these entities within 24 hours. If any unanticipated problem occurs, such as deviation from this protocol that involves risks or has the potential to recur, the investigator will report this information to the IRB. All AE information will be reported within two to five business days of the investigator or staff becoming aware of the event.

Participants will be clinically monitored for seizure by trained research staff. In the highly improbable event of a seizure, the research team member will activate the emergency code for the on-site Rapid Response Team (RRT) to provide emergent medical care to the participant. Trained research staff will assess the participant’s airway, breathing, and circulation until the RRT team arrives. RRT will then take over the participant’s care, including administering seizure-abating medications and airway protection, and transport the participant to the emergency department. Any seizure will result in stopping the intervention and withdrawal from the study.

EXPERIMENTAL INTERVENTION

iTBS intervention

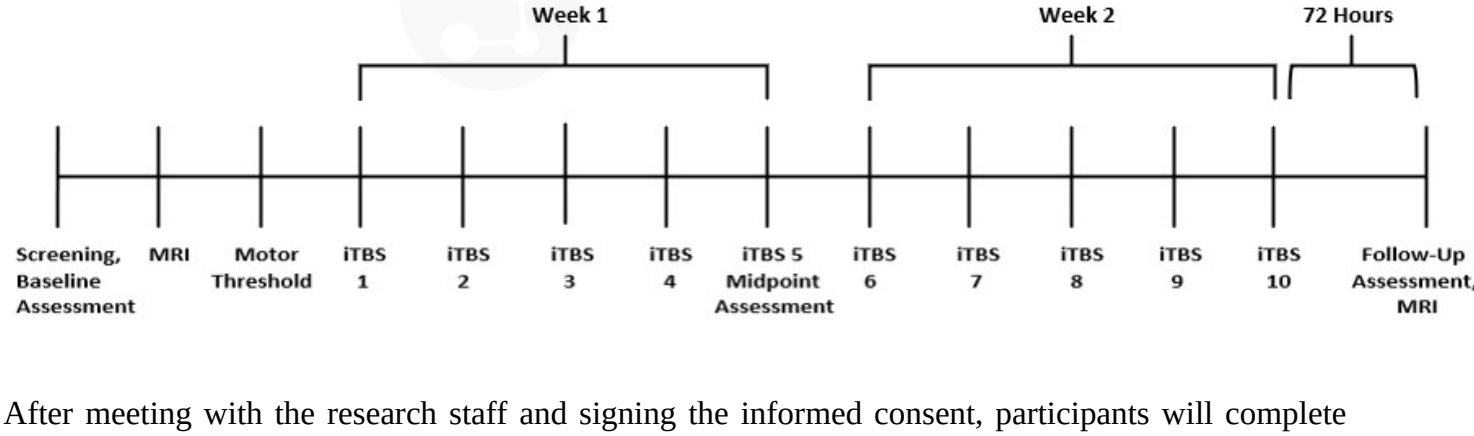
Each subject will be randomized to receive active or sham treatment throughout the protocol, with 50% receiving active treatment and 50% of subjects receiving placebo. We will use a T1 MRI to localize the frontal polar cortex (FP) stimulation site. This region will be easily located using anatomical landmarks [40, 63] and is correlated with electrode FP2 on an electroencephalogram (EEG), a region overlapping with the right VMPFC. To ensure precise and repeatable coil positioning over the frontal pole FP2 site, the Localite (neuronavigation) system and an MRI instrument marker will be used at every iTBS session.

Our 9-minute iTBS protocol will be delivered utilizing the MagVenture Mag-Pro X100 with the MagOption stimulator, including active and placebo coils (C-B60 Butterfly coils). The consensus in the literature is that iTBS can safely deliver 1800 pulses at 110% of the motor threshold to the frontal pole [63, 64]. iTBS parameters include 3 pulses of stimulation at 50 Hz, repeated every 200 ms. The interpulse interval is 20 ms. A 2-second train of TBS is repeated every 10 seconds for a total of 570 seconds, equaling a total of 1800 pulses delivered over 9 minutes. To ensure the subjects can tolerate the treatment, stimulation intensity will begin at 60-70% of the MT intensity and will slowly increase to 110% of the patient's tolerated intensity over the first 1-2 treatment sessions [42].

Study Procedures

A partial HIPAA waiver and waiver of informed consent for screening purposes will provide regulatory approval to screen potential candidates to determine study eligibility. Once identified as a potential research candidate, candidates will be contacted for an initial phone screening to determine eligibility criteria. Demographics, mental illness diagnosis, current medication use, and history of impulsive behaviors (e.g., history of fights, violence, anger, and irritability) will be cross verified in the patient's electronic medical record. A thorough chart review will be completed to cross-reference current medications with study eligibility criteria to identify anti-epileptics or medications that could lower the seizure threshold. If review findings indicate possible contraindications to TMS or MRI related to a metal implant, then the model and manufacturer of the implant will be obtained to determine whether it is safe to expose the implant to a strong magnet. Manufacturer recommendations regarding safety will be followed. Once identified as a potential research candidate, candidates will be contacted for an initial phone screening to determine eligibility criteria. If potential participants meet all eligibility criteria, they will be invited for their first research visit, an in-person screening (visit 1). There will be 14 visits for this research study (Figure 2).

Figure 2. Study Visit Diagram. iTBS: intermittent theta burst stimulation; MRI: magnetic resonance imaging.



After meeting with the research staff and signing the informed consent, participants will complete several baseline diagnostic and screening measures (Table 1). These measures will be used to track

changes in symptoms of impulsivity, suicidality, depression, anger, aggression, and social and occupational functioning throughout the study. If the participant is a woman of childbearing age, sexually active, and not on any form of physician-prescribed birth control, they will be asked to take a urine pregnancy test at this visit. Veterans who have completed baseline measures and have met eligibility criteria will be asked to complete a pre-treatment resting-state fMRI at the University of Illinois, Chicago, an institution partnering with us for this study (visit 2). After the pre-treatment MRI, participants will be invited back to the Hines VA to complete their motor threshold and brain mapping using the Localite TMS Neural Navigator system (visit 3).

Participants will be randomized to either active or sham treatment. Blinding procedures for active and sham iTBS will be delivered with the Magventure MagProX100 with MagOption stimulator and Magpro Cool Coil B65 A/P, which can be switched to active or sham (A/P). The coil is identical visually for the sham and active conditions. Veterans and researchers will wear headphones connected to the noise generator during treatment to hear active iTBS for both conditions, thereby maintaining the blind. The sham coil (P) and scalp electrodes will be placed in the same location for all participants and will mimic the sensation produced by the active coil (A) but will not alter brain physiology. Thus, the sham stimulation looks, sounds, and feels like active stimulation. A single unblinded study team member will determine which subjects are randomly placed in the active or sham group.

After the MRI and MT have been completed, subjects will be randomized, and the intervention will begin (visits 4-13). Intervention sessions will occur once daily for ten business days, with each session lasting 30 minutes to 1 hour. Research staff will complete a TMS safety rating scale before and after every iTBS session to assess for changes from baseline of vital signs, sleep duration, fatigue level, recent seizures, and tinnitus. Pain and tolerability measures will be completed at the end of every session to assess daily pain and session tolerability. After iTBS session 5 (visit 8), each subject will be asked to complete the self-report rating scales and neurocognitive testing they completed at baseline.

All Veterans who have completed the iTBS treatment course of ten sessions will be asked to return to UIC's CMRR to obtain a second resting-state fMRI for their final research visit. Post-treatment MRI data collection is expected to be completed 72 hours after the iTBS course. This time spacing between stimulation and imaging has been done in similar studies [86] and is thought to be a long enough gap post-iTBS completion not to represent the immediate effects of the most recent simulation.

Analytic Plan

Quantitative Analysis

A statistical significance level of 0.05 will be used to test hypotheses.

Descriptive statistics of feasibility, safety, and tolerability measures will be computed for all participants and compared between active- and sham-iTBS groups. We will calculate the categorical variables' frequencies and compare them using chi-square analyses for the descriptive statistics. For the continuous variables (i.e., daily pain ratings), we will compute mean, median, range, and standard deviations and compare using t-tests.

For functional outcome measures, we will estimate a mixed model ANOVA to measure differences

within-subjects (how the SOFAS changes over time), between-subjects (how the SOFAS differs between active and sham-iTBS), and whether there is a significant interaction between time and treatment.

For our neuroimaging analysis, to evaluate the VMPFC to the amygdala and anterior cingulate relationships and how they change before and after treatment, we will define regions of interest (ROIs) for the amygdala and anterior cingulate with clear anatomical boundaries identified using Freesurfer [87]. Average time series data will be extracted, and general linear modeling (GLM) will be used to quantify the relationship between the seeds and targets. The GLM results will yield individual r values (i.e., correlations), which will be normalized into Z scores using Fisher's R-to-Z transformation. The individual maps of Z scores will be the primary measure of connectivity between the seed and target ROIs. We will then implement an ROI-to-ROI analysis within the Connectivity toolbox [88] to evaluate resting-state functional connectivity (rsFC) between the amygdala, anterior cingulate, and VMPFC. Fisher's Z test will be used to compare active-iTBS and sham-iTBS groups, both pre- and post-treatment. We will adjust for a priori covariates, including age, sex, and baseline psychiatric diagnoses. All analyses will be corrected for multiple comparisons using false-discovery rate correction. We will use linear mixed models to test how connectivity changes correspond to functional and mental health outcome changes, with functional and behavioral measures included as the dependent variables.

To inform future research studies, we will estimate regression models that include additional covariates such as demographics, psychotropic medication use, comorbid psychiatric diagnoses, and scores on the IDS-SR and the PCL-5, in addition to testing our hypotheses for the primary and secondary outcomes.

RESULTS

This study is expected to begin enrolling participants in April 2024. Study results will be disseminated at or before the project's end date in March 2028.

DISCUSSION

Hypotheses

Our central hypotheses are that frontal pole iTBS will be safe, feasible, and tolerable among Veterans with mTBI based on existing literature that suggests frontal pole iTBS is no less safe or tolerable than iTBS performed elsewhere [36, 43, 89]. Similarly, iTBS, when administered to individuals with mTBI, is no less safe or tolerable than in individuals without mTBI [42]. Given that we are using an established iTBS protocol within the established TMS safety guidelines [90], we do not anticipate significant adverse events.

We further hypothesize that social and occupational functioning, negative urgency impulsivity, and SI will be improved for individuals who receive active-iTBS compared to those who receive sham-iTBS. Even if only a single domain improves, we consider this a positive finding.

Additionally, we hypothesize that resting-state functional connectivity between the VMPFC and the limbic system (especially the amygdala and anterior cingulate cortex) will be strengthened for the active-iTBS group compared to the sham-iTBS group. We also expect that Veterans with increased

connectivity between these regions of interest will likely show the most functional improvements.

Pending the results of this pilot trial, larger scale randomized controlled trials may be warranted to establish the efficacy of frontal pole iTBS for social and occupational functional deficits, negative urgency impulsivity, and suicidal ideation.

Strengths of the Study

The proposed study has several key strengths. First, the study uses an established FDA-approved device readily available in both VA and civilian healthcare systems throughout the United States. Compared to traditional pharmacological and behavioral approaches, iTBS has a reduced latency to treatment response, which could be lifesaving among individuals with SI. Our approach also differs from previous studies that primarily focused on improving SI via the treatment of depressive symptoms. We provide a novel framework for understanding and ultimately treating SI, which could be helpful for individuals who have yet to respond to past evidence-based treatments. Finally, by targeting the VMPFC and including pre- and post-treatment neuroimaging, this study has the potential to identify a novel target for iTBS, increase insight into the underlying neurological mechanisms of SI, and identify which individuals are more likely to respond to a neuromodulatory intervention.

Limitations of the Study

The limitations of this study could be as follows:

1. The small sample size reduces the study power, which may limit the detection of statistically significant outcome differences. However, this sample size reflects the pilot nature of the study and funding mechanism.
2. Variability in the baseline characteristics of the patient population (i.e., co-occurring psychiatric and somatic conditions, co-administration of other medications) that are being studied in detail in this project may impact our findings. Covariates will be explored; however, given the small sample size, only select covariates can be added to the final models.
3. The relatively short follow-up time of 72 hours after the final iTBS treatment will not provide insight into the long-term effects of our intervention. Future studies would benefit from additional follow-up outcomes assessments and imaging several months after the treatment to assess the intervention's durability.
4. Although prior studies used a dose of 110% MT and a time frame of ten sessions, we are still determining if these parameters are optimal. A future dosing study would help optimize the treatment parameters.
5. This study does not select targets based on resting-state data; however, in collecting these data in tandem with using neuronavigation, we can potentially target more specific sites in the future.

Acknowledgments

Authors’ Contributions

Conflicts of Interests

None Declared

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Abbreviations:

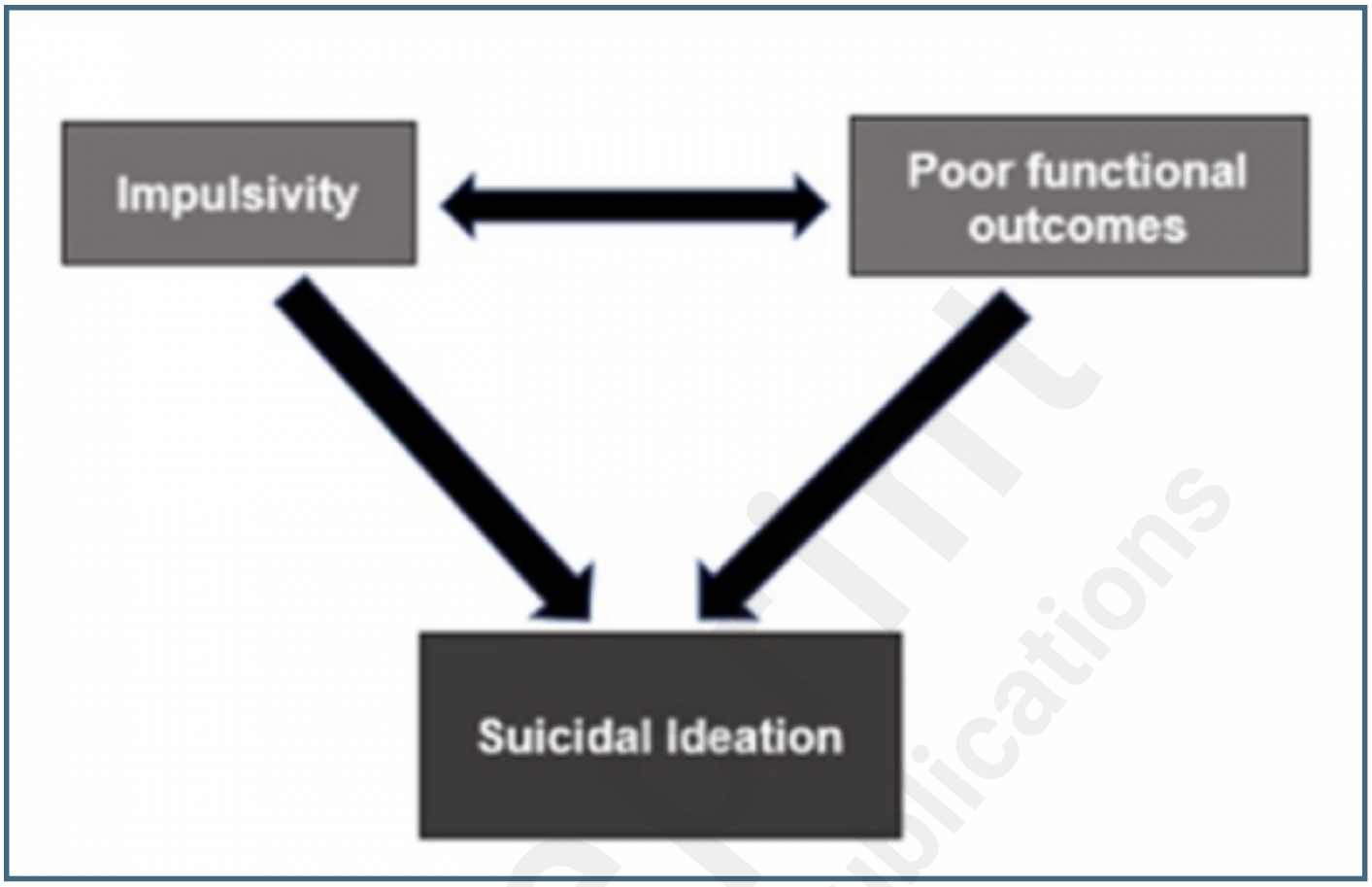
- ABP – abductor pollicis brevis
- AE – adverse event
- A/P – active/sham coil
- AUDIT-C – Alcohol Use Disorder Identification Test
- BSS – Beck Suicide Scale
- CAPS-5 – Clinically Administered PTSD Scale for DSM-5
- CMMR – Center for Magnetic Resonance Research
- CSSR-S – Columbia Suicide Severity Rating Scale
- DERS – Difficulties in Emotion Regulation Scale
- DLPFC – dorsolateral prefrontal cortex
- DSMS – Data Safety Monitoring Scale
- DUDIT-C – Drug Use Disorders Identification Test
- EEG – electroencephalogram
- EMG – electromyography
- FDA – Food and Drug Administration
- fMRI – functional MRI
- FP – frontal polar cortex
- GLM – general linear modeling
- HIPPA – Health Insurance Portability and Accountability Act
- IDS-SR – Inventory of Depressive Symptomatology, Self-Report
- IRB – Institutional Review Board
- iTBS – Intermittent theta burst stimulation
- MEPs – motor-evoked potentials
- mOFC – medial orbitofrontal cortex
- MRI – magnetic resonance imaging
- MT – motor threshold
- mTBI – mild traumatic brain injury
- NSI – Neurobehavioral symptom inventory
- OCD – obsessive compulsive disorder
- OEF/OIF/OND – Operations Enduring Freedom, Iraqi Freedom, and New Dawn
- PFC – prefrontal cortex
- PHQ-9 – Patient Health Questionnaire
- PTSD – posttraumatic stress disorder
- ROIs – Regions of interest
- RRT – Rapid Response Team

- rsFC – Resting-state functional connectivity
- SA – suicide attempt
- SACA – mTBI Symptom Attribution and Classification Algorithm
- SCID-5-RV – Structured Clinical Interview for DSM-5, Research Version
- SI – suicide ideation
- SOFAS – Social and Occupational Functioning Assessment Scale
- SPIRIT – Standard Protocol Items: Recommendations for Interventional Trials
- TBI – traumatic brain injury
- TMS – transcranial magnetic stimulation
- UIC – University of Illinois, Chicago
- UPPS-P – Urgency, Premeditation (lack of), Preservation (lack of), Sensation Seeking, Positive Urgency Impulsive Behavior Scale – Negative Urgency subscale
- VA – Veterans Administration
- VINCI – VA Informatics and Computing Infrastructure
- VMPFC – ventromedial prefrontal cortex
- VR-36 – Veteran's RAND

Supplementary Files

Figures

Relationship between impulsivity, functionality outcomes, and suicidal ideation.



Study Visit Diagram. iTBS: intermittent theta burst stimulation; MRI: magnetic resonance imaging.