Pilot and Feasibility Studies

STUDY PROTOCOL

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A pilot randomized controlled double-blind trial of intermittent theta burst stimulation (iTBS) repetitive transcranial magnetic stimulation (rTMS) to improve memory in mild cognitive impairment (MCI): a study protocol

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Abstract

Background Mild cognitive impairment (MCI), prevalent among older adults, often precedes Alzheimer's disease (AD) or Alzheimer's disease-related dementias (ADRD), emphasizing the need for effective interventions. Early intervention in MCI is crucial, not only to alleviate symptoms but to potentially delay the progression of cognitive decline. The lack of definitive treatments for MCI has prompted the exploration into alternative non-pharmacological therapeutic approaches. Specifically, noninvasive brain stimulation using repetitive transcranial magnetic stimulation (rTMS) has demonstrated promise in improving cognition in MCI and AD.

Objectives Our study will test the feasibility of using intermittent theta burst stimulation (iTBS) technique of rTMS in MCI, pilot test the study design, and collect pilot data on the effect of iTBS over three different brain regions on working memory, new learning, and executive function in MCI. Exploratory objectives are to assess the feasibility and usefulness of functional magnetic resonance imaging (fMRI), high-density electroencephalography (HD-EEG), and sleep architecture as potential biomarkers in response to iTBS.

Methods A pilot randomized double-blind controlled cross-over trial of iTBS on 20 MCI participants randomized to 10 days of active iTBS (left dorsolateral prefrontal cortex or left lateral parietal cortex) or control (vertex). After 4–6-week washout period, they cross over to the alternative treatment arm for another 10 days. Each participant will undergo a total of 20 iTBS sessions. Pre- and post-iTBS assessments include neuropsychological tests, fMRI, HD-EEG, and sleep architecture.

Discussion This innovative study aims to test the feasibility of iTBS as a cognitive enhancement strategy in MCI. If our study is feasible, it could lead to a future larger trial to further test whether iTBS can modulate underlying

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neurobiology and offer a therapeutic avenue to remediate cognitive decline in MCI or ultimately delay progression to dementia.

Trial registration ClinicalTrials.gov, NCT05327257. Registered 04 April 2022.

Keywords Noninvasive brain stimulation, Neuromodulation, Cognitive enhancement, Memory disorder, Cognitive decline, Dementia, Alzheimer's, Brain disorder, Neurology, Geriatrics

Introduction

Background and rationale

Mild cognitive impairment (MCI) is widely recognized as a risk for developing Alzheimer's disease (AD) and AD-related dementias (ADRD), but there are no established or effective treatments. MCI refers to circumscribed cognitive dysfunction without significant impairment in activities of daily living [1], and it often emerges as a transitional state between normal aging and mild dementia [2]. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, DSM-5 [3] criteria for mild neurocognitive disorder parallels those of MCI: (A) cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition), (B) cognitive deficits that do not interfere with capacity for independence in everyday activities, (C) cognitive deficits that are not due to delirium, and (D) cognitive deficits not due to another mental disorder. The prevalence of MCI is relatively high in older individuals, estimated at 12–18% of adults aged 60 or older [4] and 16% of community-dwelling persons 70 years and older [5]. The number of people with MCI increases with age, with 1 in 4 in the 80–84 age group having MCI [4]. Persons with MCI have high rates of progression to dementia at rates of 10–15% in the clinic and 8–10% in the community annually [5]. In another study, 38% of individuals with MCI developed dementia within 5 years [4, 6].

The frequency of MCI, increasing prevalence with increasing age, and the high rates of progression from MCI to dementia over a short period of time is a substantial public health problem that necessitates development of interventions to slow or prevent progression to dementia. The Alzheimer's Association report "Changing the Trajectory of Alzheimer's Disease: How a Treatment by 2025 Saves Lives and Dollars" [7] estimates that if by 2025 there can be a treatment that delays the onset of Alzheimer's by 5 years, the number of people with AD is projected to decrease from 8.2 million to 5.8 million by 2030. On the other hand, if by 2025 there can be a treatment slows the progression of AD, the number of people with AD is projected to increase shortly after it became available. Even though the trend will continue as people with AD live longer with the disease, slowing the progression may slow the rate of functional decline and reduce healthcare costs. It is therefore critical to intervene early in the disease process in order to reduce the overall burden of the disease.

Cholinesterase inhibitors are typically considered the standard of care for MCI given the commonly associated underlying AD pathology. While cholinesterase inhibitors stabilize certain dementia symptoms, the effectiveness in reducing incident dementia is still being investigated [8–11]. High-quality evidence to support its use in MCI is lacking [5, 12]. Recently, the FDA approved lecanemab for MCI or mild AD although the clinical impact of these drugs remains to be seen [13, 14]. Nonpharmacological interventions for MCI that focus on risk reduction such as cognitive training, psychosocial interventions, and nutraceuticals need further studies [8]. While the search continues for therapies that can prevent onset or slow or stop the progression of AD, there is growing interest in novel nonpharmacological interventions that may influence the trajectory of AD.

It is in this context that noninvasive brain stimulation using repetitive transcranial magnetic stimulation (rTMS) has emerged as a promising treatment option. TMS uses electromagnetic fields to stimulate specific regions of the brain to induce electrical currents in the underlying brain tissue, influencing neuronal activity. rTMS differs from standard TMS by delivering rapid successive magnetic pulses that can produce more sustained and consistent changes in brain activity [15]. This technique, FDA-approved for treatment resistant depression, offers promise in cognitive disorders based on preliminary evidence demonstrating its potential to enhance cognitive performance and neuroplasticity.

Evidence from systematic reviews and meta-analyses points to notable cognitive improvements using rTMS for MCI and AD patients. Specifically, significant enhancement in global cognition metrics, such as Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), and Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), was observed, especially when targeting the left DLPFC [16]. Findings from various reviews indicate beneficial effects, ranging from large effect sizes (standardized mean difference ≥ 0.8) to moderate and small improvements across diverse brain disorders, emphasizing the influence of

stimulation sites and treatment frequency [17–19]. Our own meta-analysis of 25 randomized controlled trials (RCTs) of rTMS on MCI and AD echoes these large effect sizes in global cognition, albeit with notable heterogeneity [20]. While numerous rTMS studies have explored cognitive enhancement in MCI and AD, methodologies and metrics have varied across studies [21–24]. Many focus on clinical diagnosis and neuropsychological evaluations, with a select few incorporating disease-confirming biomarkers and functional neuroimaging. This existing body of research has set the foundation, but also highlights the diverse approaches to treatment parameters and limited studies on optimal stimulation parameters, underlying mechanisms, and reliable biomarkers to track neural changes in response to rTMS.

Building on evidence that rTMS can enhance cognitive function in MCI and AD, we aim to further this understanding and fill existing knowledge gaps. We propose a feasibility and pilot randomized double-blind trial to assess rTMS in older adults with MCI. A key feature of our study is the application of intermittent theta burst stimulation (iTBS), a novel rTMS technique that rapidly delivers magnetic stimulation in the theta frequency, thought to mimic the brain's neural firing patterns, making it an intriguing research option.

Objectives

The overall objectives of this study are to test the feasibility of using iTBS in MCI, pilot test the study protocol to assess study design, and collect pilot data on the effect of stimulations over three different brain regions (left dorsolateral prefrontal cortex (DLPFC) vs. left parietal cortex (LPC) vs. vertex on working memory, new learning, and executive function in MCI. Exploratory objectives are to assess the feasibility and usefulness of functional magnetic resonance imaging (fMRI), high-density electroencephalography (HD-EEG), and sleep architecture as potential biomarkers in response to iTBS.

The primary objective is to test the feasibility of conducting a 10-day iTBS rTMS protocol in individuals with MCI, determined by the question "Can this study be done?" We hypothesize that the study can be feasibly implemented as designed, with acceptable levels of participant recruitment, adherence and retention, and without significant adverse events or logistical issues.

A secondary objective is to pilot test the study protocol to assess study components and key uncertainties of the study design, including randomized controlled double-blind cross-over design, recruitment of target population, treatment parameters on target areas of stimulation and neurostimulation techniques, data availability, and data collection methods. We hypothesize that the study components, including study design, intervention delivery, participant interactions, and data collection tools, will function as intended, with minimal modifications required, and will provide reliable and valid data for the intended outcomes.

Another secondary objective is to evaluate the efficacy of iTBS over the left DLPFC, left LPC, and the vertex (control condition) on the working memory, new learning, and executive cognitive function among individuals with MCI. We hypothesize that active iTBS on left DLPFC and/or left LPC will enhance working memory, new learning, and executive function compared to iTBS applied to the vertex.

The exploratory objective is to assess the feasibility and usefulness of fMRI, HD-EEG, and sleep architecture as biomarkers. We will assess whether these biomarkers are feasible and useful in measuring neurophysiologic responses and explain anticipated cognitive effects of iTBS. We will investigate iTBS-related changes in functional connectivity with resting fMRI, EEG synchrony during wakefulness and sleep, and evaluate whether sleep architecture is influenced by iTBS. We hypothesize that there will be observable changes of altered functional connectivity on fMRI, oscillatory and synchrony changes in EEG, and increase in slow wave sleep with active iTBS on left DLPFC and/or left LPC compared to iTBS applied to the vertex. We further hypothesize that these observable changes will correlate with improvements in cognitive functioning (working memory, new learning, and executive function) post-iTBS.

Trial design

General design

This is a feasibility and pilot randomized 3-arm double blind cross-over trial to investigate the use of iTBS in older adults with MCI. Before the randomized 3-arm double blind cross-over trial commences, 5 participants who are cognitively normal will serve as healthy controls and undergo iTBS treatments to the vertex (control condition) only. The study with 5 healthy controls will be conducted in order to assess the recruitment process, study procedures and workflow, opportunities for improving quality and efficiency for the main study and providing experience for the study team to implement the study protocol.

Methods: participants, interventions, and outcomes

Study setting

Older adults ($N=20$) with MCI will be recruited from outpatient clinics in Psychiatry, Psychology, Neurology, Internal Medicine, Family Medicine, Sleep Medicine, and Primary Care. Research participants in the Mayo Clinic Alzheimer's Disease Research Center (ADRC) may be

eligible for the study. The electronic medical records of potential participants will be reviewed, and those who may be eligible will be invited for further screening to determine eligibility. The research study is posted on clinicaltrials.gov and the Mayo Clinic research website.

Eligibility criteria

MCI participants

Inclusion criteria

1. Age range 55–90 years.
2. Must speak English fluently.
3. Diagnosis of MCI as defined by:
    a. Clinical diagnosis by a neurologist
    b. Neuropsychological testing support of MCI
    c. Meet criteria for MCI [1]
        i. Subjective cognitive decline reported by participant and/or an informant
        ii. Objective impairment in one or more cognitive domains for age
        iii. Essentially preserved general cognitive function
        iv. Largely intact functional activities
        v. Does not meet criteria for dementia as judged by a clinician
4. Eligible for transcranial magnetic stimulation (TMS) based on safety criteria.
5. Clinical Dementia Rating equal to 0.5
6. Geriatric Depression Scale score less than 6.
7. Medically stable and in good general health.
8. Stable medication regimen for at least 4 weeks prior to baseline visit.
9. Adequate visual and auditory abilities to complete neuropsychological testing.
10. Ability to provide informed consent.
11. Have a care partner who is available to accompany the participant to study visits for the duration of the protocol.

Exclusion criteria

1. Inability to communicate in the English language.
2. Meet criteria for dementia.
3. Contraindications to TMS or MRI, including patients who have.
    a. Conductive, ferromagnetic ,or other magnetic-sensitive metals implanted in their head or within 30 cm of the treatment coil (e.g., cochlear implants, implanted electrodes/stimulators, aneurysm clips or coils, stents, bullet fragments, or jewelry)
    b. Active or inactive implants, including deep brain stimulators, cochlear implants, vagus nerve stimulators, or implanted device leads
4. Any true positive findings on the TMS safety screening form.
5. Prior exposure to TMS, electroconvulsive therapy, or any neurostimulation within the past 12 months.
6. History of epilepsy or seizures.
7. Medical conditions or use of medications that increase risk of seizures.
    a. History of traumatic brain injury
    b. History of intracranial mass or lesion
    c. History of stroke, including hemorrhagic stroke and ischemic stroke
8. Psychiatric disorders
    a. Primary psychotic disorder (schizophrenia, schizoaffective, or schizophreniform disorder), any history
    b. Primary mood disorder (major depressive disorder, bipolar disorder) within the past 12 months
    c. Substance use disorder (except caffeine and nicotine) within the past 12 months
9. Active symptoms of depression, anxiety, mania, psychosis, or substance use (except caffeine and nicotine) within the past year
    a. Active symptoms of depression will be identified based on Geriatric Depression Scale ≥6
    b. Other active symptoms of psychiatric conditions to be determined by study investigators
10. Sleep disorders that are considered clinically significant and not sufficiently treated by the investigative team, including untreated obstructive sleep apnea, untreated/suboptimally treated rapid eye movement (REM) sleep behavior disorder, and untreated/suboptimally treated restless legs syndrome.
11. Pregnancy or suspected pregnancy
12. Participation in another concurrent interventional clinical trial
13. Any unstable medical condition (refers to any acute or chronic medical condition that is not adequately controlled, with significant fluctuations in severity,

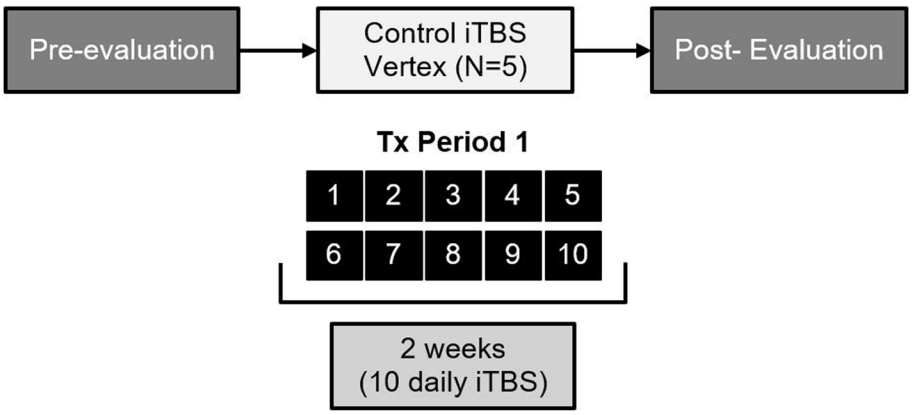

Fig. 1 Schema for cognitively normal healthy controls (HC)

and requires active medical intervention. Examples include conditions affecting the cardiovascular system, such as unstable angina or recent myocardial infarction; neurological system, such as poorly controlled epilepsy or recent cerebrovascular accident; respiratory system disorders, such as severe asthma or chronic obstructive pulmonary disease (COPD) with frequent exacerbations; metabolic system disorders, such as uncontrolled diabetes mellitus with labile blood glucose levels; and psychiatric conditions, such as active psychosis or severe depression requiring immediate psychiatric interventions).

14. Inability to provide informed consent
15. Inability to adhere to the protocol

Healthy control (HC) participants

Cognitively normal and healthy controls will be selected using the same inclusion and exclusion criteria as MCI cohort, except for diagnosis of MCI and Clinical Dementia Rating = 0.5.

Interventions

Healthy control (HC) participants

Before the pilot randomized 3-arm double blind crossover trial commences, 5 participants who are cognitively normal and healthy controls will undergo a 10-day iTBS treatment to the vertex only (our selected control condition) and complete pre- and post-iTBS evaluations (Fig. 1). This process is designed to test feasibility with recruitment, validate study procedures, ensure TMS equipment integrity, monitor potential adverse effects, and refine our RCT research design.

MCI participants

Experimental design: This is a feasibility and pilot trial that will utilize a randomized 3-arm double-blind crossover design.

iTBS treatment protocol

Stimulation sites: Three brain regions have been selected for stimulation: (1) left dorsolateral prefrontal cortex (DLPFC) or (2) left lateral parietal cortex (LPC) for active iTBS, and (3) vertex (serving as a control condition similar to sham). The choice of iTBS stimulation parameters in our study is based on a comprehensive review of extant literature on rTMS in MCI and AD [20], published safety data [25], and expert consensus of our co-investigators. We elected to probe three distinct stimulation sites, aiming to determine whether iTBS has differential effects and gain insights into the contributions of these regions to cognitive functions in MCI. Left DLPFC: The left DLPFC has consistently emerged as a focal target in prior rTMS research, particularly due to observed cognitive benefits in MCI and AD populations. By focusing on the left DLPFC, our study aligns with established TMS protocols. This approach facilitates a robust comparison with existing literature, while concurrently probing the efficacy for cognitive enhancement in MCI. Left LPC: The left LPC is integral to the Default Mode Network (DMN), which is active during rest and encompasses vital cognitive operations, including memory, attention, language, and problem-solving [26]. Literature underscores the pivotal role of the left LPC in episodic memory, with compelling findings highlighting its functional connectivity to hippocampal regions [27]. One seminal study demonstrated enhanced memory performance in 16 healthy adults following targeted high frequency rTMS over the left LPC, demonstrating its potential for memory modulation [28]. Ground-breaking research has intricately partitioned the

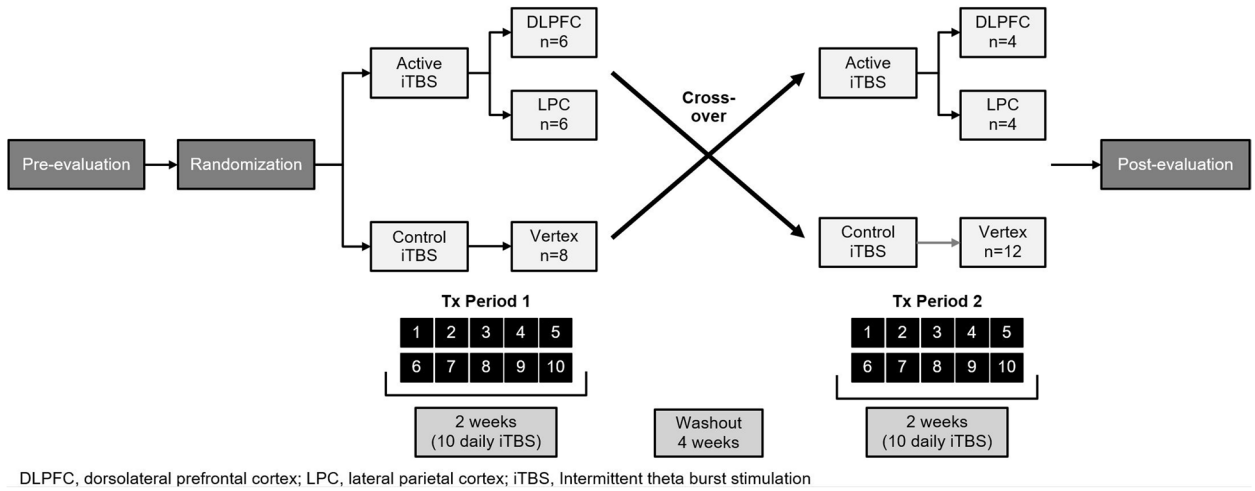

Fig. 2 Schema for MCI. DLPFC, dorsolateral prefrontal cortex; LPC, lateral parietal cortex; iTBS, intermittent theta burst stimulation

left LPC by using a combined resting-state functional connectivity MRI (rs-fcMRI) and task-based fMRI, elucidating its specific roles in cognition, attention, and memory [29, 30]. Our focus on the left LPC hinges on its centrality to memory and other cognitive functions. Outcomes from our study may provide evidence that the left LPC is an important target for iTBS in MCI, offering insights for the development of future interventions. Vertex (control): The vertex has emerged as a traditional control in TMS studies for its anatomic location and not being directly associated with specific cognitive or primary motor functions, ensuring that any observed effects can be attributed to active stimulation and not placebo effects. Vertex stimulation has little or no effect on brain activation or DMN functional connectivity [31]. This ensures an authentic control condition, critical for the validity of our findings.

Stimulation pattern: The iTBS pattern of rTMS is the chosen treatment intervention. During each iTBS session, the FDA-approved iTBS parameters will be followed: 600 pulses delivered intermittently in bursts of 2 s of stimulation followed by an 8-s pause for a total duration of 3.17 min. We selected iTBS due to neurophysiologic alignment with the brain's natural theta rhythms, central to cognitive processes and neural plasticity [32–34]. Studies suggest iTBS might be as effective, if not more so, than standard rTMS in modulating cortical excitability, suggesting superior therapeutic potential [32, 33, 35]. iTBS sessions last approximately 3.5 min, which is 10 times shorter than standard rTMS, enhancing efficiency and patient convenience [32–34]. With fewer pulses (600 vs. 3000), iTBS is more tolerable with fewer side effects [36]. The pulse intensity, ranging from 80 to 120% of motor threshold, is adaptable for patient comfort.

Sessions: MCI participants will undergo two distinct treatment periods, as detailed in Fig. 2. Each treatment period consists of a single iTBS session administered daily for 10 days (5 days per week). Participants receive a total of 20 iTBS sessions over 2 treatment periods. Based on literature review, we chose 20 sessions split into two 10-session treatment periods separated by a 4–6-week washout period. Most MCI TMS treatments range from 1 to 30, with 10 and 20 sessions being the most common regimen and deemed safe, feasible, and practical for patients [20].

Neuropsychological assessment protocol

For neuropsychological testing, the participant will meet with a psychometrist who will administer the instruments. The testing will occur with the participant alone in a quiet room. Both the participant and the psychometrist will be seated at a table during the testing. The tests will comprise paper-and-pencil instruments. They will be completed in one visit, and testing will last up to 1 h. Individuals with MCI are apt to demonstrate deficient new learning, executive function, and working memory [37, 38]. To assess new learning, measures of verbal and visual memory will be included. Selection of tests was guided by a preference for instruments that included alternate forms to control for potential bias associated with repeated testing. Additionally, a preference was given to instruments that are brief and would not excessively tax participants. To assess change in cognitive outcomes, measures of executive function, working memory, and new learning will be administered. Instruments will be administered within 6 weeks before commencing iTBS to establish a baseline estimate of function. Within 1 week of completing the last iTBS session, the battery of

tests will be re-administered to capture immediate post-treatment effects. To evaluate whether cognitive effects have been sustained, measures will be administered within 4 to 6 weeks after the last iTBS session.

fMRI protocol

Prior to MRI, all participants will complete a screening form that is standard for any patient undergoing MRI scans. Participants will be instructed to remove any facial or eye makeup which may contain metal. Prior to the iTBS intervention, brain imaging will be acquired on the compact 3.0 MRI scanner with a 32-channel head coil. A 3D T1 magnetization-prepared rapid acquisition with gradient echo (MPRAGE) pulse sequence of the brain will be acquired. This will be used for anatomic guidance and for anatomic registration of the resting-state functional connectivity scan. Afterward, resting-state fMRI images will be acquired with the participant's eyes open using gradient-recalled echo echo-planar imaging (GRE-EPI)-based functional sequences. A distortion-free diffusion scan based on a clinically used sequence "DIADEM" (Digital Reconstruction of Axonal and Dendritic Morphology project) will also be obtained. After data collection, we also use commonly used publicly available fMRI processing software including FSL and AFNI software for image segmentation, motion correction, and statistical analysis to generate the functional connectivity maps. The same imaging protocol will be repeated after the iTBS intervention is complete.

HD-EEG protocol

An electroencephalogram (EEG) is a test to evaluate the electrical activity in the brain using sensors (electrodes) attached to the scalp. High-density EEG (HD-EEG) uses a larger number of sensors than traditional EEG to provide high temporal and spatial resolution and a more detailed, 3 dimensional picture of brain activity. In a high-density EEG, the electrodes are closely spaced together, fitted in an elastic cap worn by the participant over the head. The electrodes are connected to the EEG machine with wires. The participant will be asked to relax or sleep in a comfortable position and remain still throughout the recording. The HD-EEG procedure will take up to 4 h to complete, including 1–3 h of EEG recording with video recording if able to sleep or as tolerated, and up to 30 min before and after recording for set up and removal of cap.

Sleep data collection protocol

The Sleep Profiler™ (SP, Advanced Brain Monitoring, Carlsbad, CA) is a portable, self-applied, multichannel electroencephalography (EEG) recorder to assess sleep electrophysiology and architecture. It is commercially available, non-invasive, lightweight and wireless, worn over the forehead like a headband, and provides data similar to laboratory polysomnography [39, 40].

The Sleep Profiler™ will be provided to the participant. Prior to use, the participant will be trained on how to properly use the device [40]. At baseline, the device will be worn on the forehead while sleeping for 3 nights before the first iTBS, i.e., treatment session #1. The device will be worn again for three nights after completion of ten iTBS treatment sessions for treatment periods 1 and 2, and again for two nights at the 4–6-week follow-up after the last iTBS session. The Sleep Profiler™ records EEG and other sleep data that are transmitted wirelessly to a tablet or computer for collection and interpretation.

Treatment allocation

Treatment period 1: Participants will be randomized to either active iTBS (targeting the left DLPFC or left LPC) or the control (vertex) for 10 days. Washout: This is followed by a 4–6-week washout period. Treatment period 2: Participants then crossover to the alternative active iTBS intervention or control for another 10 days. Assessments: Neuropsychological cognitive measures and exploratory biomarkers (including fMRI, HD-EEG, and sleep measures) will be evaluated at 5 distinct timepoints: (1) baseline, (2) post-treatment period 1, (3) post-washout period, (4) post-treatment period 2, and (5) 4-week follow-up (Fig. 2).

Assignment of interventions

Allocation

Randomization: Once study criteria are met and all pre-study procedures completed, participants will be randomized using permuted block-randomization in REDCap by the study biostatistician.

Blinding: Participants can be assigned to one of the three stimulation sites for each treatment period: left DLPFC, left LPC, or vertex (control). Participants, investigators, technicians, and raters will be unaware of the stimulation site. A limited unblinded team will consist of study coordinators, TMS operators, and MRI and EEG data scientists.

Criteria for discontinuing allocated interventions

Participants may withdraw from the study at any time. Because iTBS is clinically well tolerated in patients with major depressive disorder [41], we do not anticipate a large drop-out rate due to adverse effects. Possible conditions for withdrawing participants include:

Inability to tolerate iTBS treatments
Inability to adhere to at least 3 treatments per week (out of 10 treatments)

Development of any new psychiatric condition during the study
Unanticipated severe adverse event requiring cessation of treatment protocol

Outcomes

Primary outcomes

Feasibility

The primary objective is to test the feasibility of conducting a 10-day iTBS protocol twice using a cross-over design in individuals with MCI, with a primary study endpoint determined by the question "Can this study be done?".

Feasibility will be assessed using predefined feasibility parameters, including:

- Screening rate: Number of eligible participants identified per month
- Recruitment rate: Number of participants enrolled per month and proportion of eligible participants who consent to participate
- Clinician engagement: Willingness of clinicians to refer and assist in recruitment efforts
- Randomization feasibility: Proportion of enrolled participants successfully randomized
- Tolerability and adherence: Participant-reported tolerability of treatments, adherence to the treatment schedule, and completion rates of the 10-day iTBS protocol
- Retention rate: Percentage of participants completing post-treatment assessments
- Outcome measure acceptability: Completeness, variability, and responsiveness of proposed primary and secondary outcome measures

Rather than applying a strict Go/No-Go framework [42], we will evaluate these feasibility measures to refine study procedures for future trials. Feasibility benchmarks will be assessed based on descriptive statistics, and deviations from protocol adherence will be documented to inform study modifications. This approach aligns with recommendations from Eldridge et al. [43] which emphasizes that feasibility data should guide trial optimization rather than enforce rigid stop/go criteria.

Primary safety endpoints

The primary safety endpoints of this protocol consist of the side effects of rTMS in our patient population. The safety profile of rTMS in the general clinical population of patients with MDD has already been demonstrated through clinical trials, FDA approval in 2008, and post-FDA approval clinical practice. The side effects collected for each patient will be in the same categories as those used in the Blumberger study: headache, nausea, dizziness, fatigue, insomnia, anxiety or agitation, back or neck pain, vomiting, tinnitus, migraine aura, abnormal sensations, unrelated medical problem, unrelated accidents [33]. The frequency and rates of these adverse events will be reported, with the investigator assessment of the relationship of the adverse event to the device. Incidence of all serious adverse events including unanticipated adverse device effects and incidence of all device failures and malfunctions will also be collected.

Secondary outcomes

Cognitive measures

Neuropsychological assessments

1. Working memory
    - Symbol Digit Modalities Test—brief measure that presents a series of geometric figures that are uniquely associated with numbers. Subsequently, a list of geometric shapes is presented, and participants write down the numbers associated with each shape over a 90-s interval. This is followed by a second administration in which participants say the number associated with each shape over a 90-s interval. This instrument is highly sensitive to detecting impaired working memory and possesses satisfactory test–retest reliability and minimal bias associated with repeated testing.
2. New learning
    - Hopkins Verbal Learning Test-Revised (HVLT-R)—measure includes a 12-item word list that is presented three times. Recall is measured upon each learning trial, and this is followed by measurement of delayed recall and recognition memory.
    - Brief Visual Spatial Memory Test-Revised presents a series of six geometric shapes over three learning trials. Recall is measured over each of the trials, and this is followed by assessment of delayed recall and recognition memory.

These measures are sensitive to detecting memory impairment and possess satisfactory internal consistency and alternate form reliability.

3. Executive function

- Verbal fluency—assesses phonemic and semantic fluencies, with participants generating words that begin with specified letters or belong to designated semantic categories over 1-min intervals.
- Design fluency—assesses ability to generate unique geometric designs over 1-min intervals.
- Trail making—includes several facets that assess speed of information processing and mental flexibility. Among the key components, participants will draw lines connecting circles in either numeric or alphabetical order, and their accuracy and speed in completing the sequences are assessed. Subsequently, participants will draw lines that connect numbers and letters in alternating sequences (i.e., 1-A-2-B-3-C), and accuracy and speed in completing the sequence is measured.

These three tests are subtests of the Delis Kaplan Executive Function System possess satisfactory sensitivity to detect executive function deficits, and they are relatively robust to potential bias associated with repeated testing.

Functional measures

1. Functional Activities Questionnaire (FAQ)
    - The Functional Activities Questionnaire (FAQ) [44] consists of 10 questions to assess functional performance of instrumental activities of daily living, including writing checks, paying bills, balancing checkbook; assembling tax records, business affairs, or papers; shopping alone for clothes, household necessities, or groceries; playing a game of skill, working on a hobby; heating water, making a cup of coffee, turning off stove after use; preparing a balanced meal; keeping track of current events; paying attention to, understanding, discussing television, book, magazine; remembering appointments, family occasions, holidays, medications; traveling out of neighborhood, driving, arranging to take busses. Each of the 10 items is scored as 0 = normal, 1 = has difficulty but does by self, 2 = requires assistance, and 3 = dependent. Scores range from 0 to 30, with higher scores representing increased functional impairment.
2. Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale (ADCS-ADL)
    - The Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale (ADCS-ADL) [45, 46] is a 24-item questionnaire adapted for MCI. The first 18 questions assess functional abilities, and the remaining 6 questions assess for MCI. The 18 questions reflecting functional abilities include finding personal belongings; select clothes; getting dressed; clean house; balance checkbook or credit card statement; write anything down; clean a load of laundry; keep appointments with other people; use a telephone; prepare a meal/snack for self; get around outside home; talk about current events; read a book, magazine, or newspaper for more than 5 min at a time; watch television; go shopping at a store; was alone at home or away; use a household appliance to complete chores; and perform a pastime/hobby or game. They are scored from 0 to 53, with a higher score reflective of more functional independence compared to a lower score.

Quality of life (QOL) measure

1. Linear Analog Self Assessment (LASA)
    - The Linear Analog Self Assessment (LASA) consists of 5 items to assess quality of life (QOL), including overall QOL and 4 specific QOL domains of physical well-being, emotional well-being, spiritual well-being, and intellectual well-being. Each item is scored on a Likert scales from 0 (as bad as it can be) to 10 (as good as it can be). Higher ratings indicate higher QOL [47–50]. Participants and their care partners will be asked to complete the LASA at 2 timepoints—baseline and 4-week follow-up.

Participant timeline

Schedule of assessments

Screening occurs up to 4–6 weeks before the baseline, which is 1 week prior to the first iTBS session. Only those who pass screening and consent will have a baseline visit and enter the study. The intervention comprises two distinct treatment periods of 10-day iTBS sessions each, separated by a 4–6-week washout period. Assessments are done at 5 distinct timepoints: (1) baseline, (2) post-treatment period 1, (3) post-washout period, (4) post-treatment period 2, and (5) 4-week follow-up (Fig. 3).

At screening, participants undergo physical, neurologic, and psychiatric examinations, medication reviews, and complete assessments including TMS Adult Safety

	STUDY PERIOD							
	Enrolment	Baseline	Post-allocation					Close-out
TIMEPOINT	$-t_1$	0	t_1	t_2		t_3	t_4	t_5
			Tx Period 1 iTBS #1-10	Post Tx Period 1	Washout and cross-over	Tx Period 2 iTBS #11-20	Post Tx Period 2	4-week Follow-up
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							
Allocation		X						
INTERVENTIONS:								
Active (left DLPFC or left LPC) or control iTBS (vertex)			—					
Washout and cross-over					—			
Active (left DLPFC or left LPC) or control iTBS (vertex)						—		
ASSESSMENTS:								
History, PNPE	X							
Concurrent medications	X							
Neuropsychological assessment	X			X			X	X
TASS	X	X	X	X		X	X	
CDR	X							
GDS	X							
ESS	X							
MSQ	X							
PSQI		X		X			X	X
Brain MRI/fMRI		X		X			X	X
High density EEG		X		X			X	X
Sleep Profiler		X		X			X	X
FAQ		X						
ADCS-ADL		X						X
Adverse events			X	X	X	X	X	X
LASA (px/care partner)		X						X

Fig. 3 Schedule of assessments. PNPE, physical, neurologic, and psychiatric examination; DLPFC, dorsolateral prefrontal cortex; LPC, lateral parietal cortex; iTBS, intermittent theta burst stimulation; TMS, transcranial magnetic stimulation; TASS, TMS Adult Safety Screen; CDR, Clinical Dementia Rating; GDS, Geriatric Depression Scale; ESS, Epworth Sleepiness Scale; MSQ, Mayo Sleep Questionnaire; PSQI, Pittsburgh Sleep Quality Index; MRI, magnetic resonance imaging; fMRI, functional magnetic resonance imaging; EEG, electroencephalography; FAQ, Functional Activities Questionnaire; ADCS-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living; LASA, Linear Analog Self Assessment

Screen (TASS), MRI screening, Geriatric Depression Scale (GDS), Epworth Sleepiness Scale (ESS), Mayo Sleep Questionnaire (MSQ), Pittsburgh Sleep Quality Index (PSQI), and a neuropsychological assessment. The study physician conducts a Clinical Dementia Rating (CDR).

At baseline, participants undergo fMRI, HD-EEG, and home sleep study with the Sleep Profiler™ device. Care partners fill out the Functional Activities Questionnaire (FAQ) and Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale MCI (ADCS-ADL-MCI).

After each 10-day iTBS treatment period and at 4-week follow-up, participants repeat neuropsychological tests, fMRI, HD-EEG, and home sleep studies. Medications and adverse events are noted at every visit.

Data collection, management, and processing

In this single-site study, the PI and study team are responsible for all data collection, management, and processing. All data are entered by the study coordinator into an electronic database, password-protected and only accessible to research personnel. The PI and study coordinator will review data on an ongoing basis at regularly scheduled study team meetings. The PI and study coordinator will meet with statisticians every 3 months during the active data collection period to conduct a formal review of the accumulating data, data quality, and any data integrity issues.

Information about adverse events will be collected at each visit. Any potentially serious problem will be brought immediately to the attention of the PI and/or other study physicians.

Data integrity

Data monitoring is conducted to assure data are accurate and complete. Monitoring of data assures adherence to the Institutional Review Board (IRB)-approved protocol. The PIs and study team members will be responsible for data integrity. The PI ensures subject inclusion criteria are being met. The PI provides oversight of entry of study data by data managers to ensure accuracy, and work with data managers in resolving any discrepancies in recorded or missing data.

Data quality assurance

To enhance data quality, range checks and total scores that are automatically computed will be used in REDCap and reviewed by the biostatisticians.

Statistical methods

Sample size determination

Given this study is a pilot study for feasibility, sample sizes have been determined based on the timeframe of enrollment and the volume of eligible patients seen through our clinic during the recruitment period. Based on our clinical practice, we anticipate enrolling 20 MCI participants over 2 years. Similar studies have included sample sizes of fewer than 30 participants [51]. As recommended in feasibility study literature, sample size determination in pilot studies is typically based on practical considerations, study logistics, and precedent rather than statistical power calculations [52, 53]. Furthermore, Julious [54] suggests that 12 participants per group is a reasonable rule of thumb for pilot studies when prior data is unavailable. Similarly, Teare et al. [55] emphasize that pilot study sizes should be large enough to estimate key feasibility parameters with reasonable precision while remaining practical given resource constraints.

Feasibility studies using transcranial magnetic stimulation (TMS) in mild cognitive impairment (MCI) and Alzheimer's disease (AD) have employed small sample sizes. For example, Padala et al. [56] conducted a sham-controlled rTMS feasibility trial in AD with 20 participants, and Nguyen et al. [57] tested rTMS combined with cognitive training in AD in a feasibility study with 20–30 participants. Similarly, Senczyszyn et al. [58] conducted a randomized controlled pilot study on rTMS for working memory in MCI with 38 participants, where each experimental group included 13, 13, and 12 participants. These studies collectively support the feasibility of our chosen sample size and align with early-phase TMS research.

Sample sizes of 6, 6, and 8 in the DLPFC, LPC, and vertex groups, respectively, were selected accordingly. While we did not define an expected retention rate a priori, feasibility studies in TMS research have reported retention rates above 70%, with some exceeding 80% [59, 60]. With a target sample size of 20 participants, an anticipated retention rate of 70% can be estimated with a 95% confidence interval of approximately ± 21% (49 to 91%). This reflects the inherent variability of small samples, but feasibility data remain valuable for informing future trial design, recruitment strategies, and adherence estimates, consistent with feasibility study recommendations from Cocks and Torgerson [61].

Rather than using effect sizes from this study, the standard deviation (SD) of key outcomes will be estimated to inform sample size calculations for future larger trials, as recommended in feasibility study methodology [62]. By using a cross-over design, our protocol allows each group to serve as their own comparison, enabling the use of paired statistical tests if the washout period proves to be appropriate. The unbalanced sample sizes are intended to maximize power in the first phase of the cross-over design.

Data analysis

Primary outcome (feasibility) measures will be summarized using descriptive statistics to evaluate study feasibility. These feasibility measures will include screening rates (number of eligible participants identified per month), recruitment rates (number of participants enrolled per month and proportion of

eligible participants who consent to participate), clinician engagement (willingness of clinicians to refer and assist in recruitment efforts), randomization feasibility (proportion of enrolled participants successfully randomized), and retention rates (percentage of participants completing post-treatment assessments). Adherence to the treatment schedule, treatment tolerability, and completion rates for the 10-day iTBS protocol will be analyzed using descriptive statistics, with corresponding 90% confidence intervals to assess precision. The acceptability of primary and secondary outcome measures will be evaluated based on completeness, variability, and responsiveness. Side effect and adverse event (AE) total rates will also be calculated to evaluate treatment safety.

Rather than applying a strict Go/No-Go framework [42], feasibility outcomes will be systematically evaluated to assess recruitment, adherence, retention, and study procedures to identify study modifications needed for the development of a larger trial. This approach follows best practices in feasibility research, ensuring that feasibility assessment is data-driven and iterative, as recommended by Eldridge et al. [43] and Avery et al. [42].

Baseline values for demographic, clinical, and outcome variables will be tabulated across the treatment groups for future study consideration. These analyses will help identify potential confounding variables to be used as covariates in sensitivity analyses and further research.

All secondary measures including neuropsychological measures, PSQI, fMRI, EEG, and sleep study measures will be considered for exploratory analysis across 2-treatment locations (DLPFC and LPC vs. vertex) at two distinct timepoints: (1) baseline and (2) post-treatment period 2. Kruskal–Wallis tests will be used to compare treatment groups at these time points. Exploratory analysis will examine mixed effects longitudinal models incorporating all available data across all time points [63]. Effect size estimates will assess the magnitude of treatment across time.

Handling of missing data

Longitudinal mixed models will include all available data from all participants enrolled, regardless of drop out of loss to follow-up.

Multiplicity

No adjustment for multiple comparisons will be made as the primary outcome is feasibility. Effect sizes with confidence intervals and the sample size from which they are based will be thoroughly explained and labeled for each outcome measure, without conclusion of statistical significance.

Subject population(s) for analysis

All-treated population: Any subject randomized into the study that received at least one exposure (treatment) from the study device.

Monitoring

The principal investigator will conduct weekly meetings with study coordinators and monthly meetings with study team to review status of participants, safety issues, protocol adherence, and conduct of study. The PI will report any adverse events, serious adverse events, unanticipated events, deviations, and continuing reviews or progress report to the IRB and FDA in accordance with regulations.

Ethics and dissemination

Research ethics approval

This study is to be conducted according to US government regulations and institutional research policies and procedures. The study protocol was reviewed and approved by the Mayo Clinic Institutional Review Committee, with study ID 21–010661. This approval confirms that the study adheres to the ethical guidelines and standards for research involving human participants. Additionally, the study has been granted an Investigational Device Exemption (IDE) by the US Food and Drug Administration (FDA), with approval number G220016. This IDE allows us to use the investigational device in our research, ensuring that the study is being conducted in accordance with FDA regulations.

Protocol amendments

Any protocol amendments will be submitted to the Mayo Clinic IRB, and the US FDA as appropriate, for formal approval.

Consent or assent

All participants for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form was reviewed and approved by the Mayo Clinic by the IRB for the study. The formal consent of a subject, using the approved IRB consent form, will be obtained before that subject undergoes any study procedure. The consent form will be signed and dated by the subject and the individual obtaining the informed consent.

Confidentiality

An identification code will be assigned by the study staff to each participant. To protect the participant's identity, only the identification code will be used for any data, forms, reports, recordings, and other records.

All paper records containing individually identifiable information and protected health information (PHI) such as signed consent forms and testing results will be maintained in a secure room, and in locked file cabinets when not in use, accessible only to research personnel. Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from participants in this study.
- Who will have access to that information and why.
- Who will use or disclose that information.
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For participants that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long-term survival status that the subject is alive) at the end of their scheduled study period.

Discussion

The potential implications of this research are multifaceted. Scientifically, this study aims to provide deeper insights into how iTBS affects MCI by utilizing exploratory biomarkers, offering a clearer understanding of the neurobiological mechanisms involved. Technically, the pilot seeks to refine the practical applications of iTBS, identifying optimal stimulation parameters and target brain regions essential for MCI. From a clinical perspective, the outcomes might guide MCI care protocols, suggesting a more systematic and evidence-based approach to rTMS application. The exploratory findings from models of biomarkers and mechanisms may be underpowered with the caveat that null findings should not be overinterpreted as a result. The small sample size of the groups may limit the significant findings both in prediction or correlation of changes from the iTBS treatments, but will aid future study planning by establishing effect sizes, data for retention, and study washout periods.

Limitations

This study has several limitations inherent to feasibility trials. As a pilot study, it is not designed to test efficacy but to evaluate trial feasibility, including recruitment, retention, adherence, intervention implementation, and study procedures. While we are secondarily exploring intervention effects, the primary focus is on refining trial methodology and feasibility outcomes that may inform a future larger trial.

One limitation is the lack of predefined Go/No-Go progression criteria, which are sometimes used in feasibility studies to determine whether to proceed with a full-scale trial. While some studies use structured traffic light systems (e.g., Go/Amend/Stop decisions), our approach follows recommendations from Eldridge et al. [43] and Avery et al. [42], which emphasize that feasibility data should guide trial refinement rather than enforce rigid stop/go thresholds. This allows for a more flexible and adaptive feasibility assessment, ensuring that study modifications are based on real-world trial processes rather than arbitrary benchmarks.

Rather than applying a strict Go/No-Go framework, we will systematically evaluate feasibility outcomes such as screening and recruitment rates, randomization feasibility, adherence to the intervention schedule, treatment tolerability, retention, and outcome measure acceptability. Feasibility benchmarks will be analyzed descriptively rather than using statistical tests to determine significance, as this study is not powered for hypothesis testing. While this approach allows a structured yet adaptable feasibility assessment, the absence of predefined progression criteria can be considered a limitation, as some feasibility studies incorporate structured decision-making frameworks to guide trial progression.

Finally, because this study includes cognitive outcome analyses and exploratory biomarker, future results should be interpreted with caution, as feasibility studies are primarily designed to inform future research rather than establish definitive conclusions. Any observed findings may help generate mechanistic hypotheses but will require further validation in larger-scale studies.

Expanding the application of rTMS outside of psychiatric indications and investigating its potential to enhance cognitive functioning in those with MCI has the potential to shift current research and clinical practice paradigms in caring for patients with MCI. This novel noninvasive brain stimulation approach might offer alternative or adjunctive treatment options for cognitive impairment, facilitating more personalized, brain-targeted interventions, allowing for better treatment outcomes compared to traditional methods. If iTBS can indeed enhance cognitive functions in MCI or even ultimately delay progression to dementia, the clinical implications include

reducing rate of functional decline, better quality of life, and decreased healthcare costs from a societal perspective. Results from our study could lead to the wider use of rTMS in the field of cognitive neuroscience and could open up new avenues of research into the treatment of cognitive disorders.

Future directions

Findings from this feasibility study will help shape the design of a larger randomized controlled trial (RCT) evaluating the efficacy of iTBS in MCI. Specifically, feasibility outcomes—including recruitment, retention, adherence, and treatment tolerability—will guide decisions on key aspects of trial methodology, such as sample size estimation, eligibility criteria, study procedures, and follow-up duration.

Pending successful feasibility outcomes, NIH funding will be sought to support a larger trial evaluating iTBS in MCI. The insights gained from this study will be critical in refining study design and ensuring that a future RCT is well-structured, adequately powered, and methodologically rigorous.

Abbreviations

AD	Alzheimer's disease
ADAS-Cog	Alzheimer's Disease Assessment Scale-Cognitive Subscale
ADCS-ADL	Alzheimer's Disease Cooperative Study-Activities of Daily Living
ADRC	Alzheimer's Disease Research Center
ADRD	Alzheimer's disease-related dementias
AE	Adverse event
ANOVA	Analysis of variance
CDR	Clinical Dementia Rating
DLPFC	Dorsolateral prefrontal cortex
DMN	Default Mode Network
DSM	Diagnostic and Statistical Manual of Mental Disorders
EEG	Electroencephalography
ESS	Epworth Sleepiness Scale
FAQ	Functional Activities Questionnaire
FDA	Food and Drug Administration
fMRI	Functional magnetic resonance imaging
GDS	Geriatric Depression Scale
HD-EEG	High-density electroencephalography
HC	Healthy control
HVLT-R	Hopkins Verbal Learning Test-Revised
HIPAA	Health Insurance Portability and Accountability Act
IDE	Investigational Device Exemption
IRB	Institutional Review Board
iTBS	Intermittent theta burst stimulation
LASA	Linear Analog Self Assessment
LPC	Lateral parietal cortex
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
MSQ	Mayo Sleep Questionnaire
MT	Motor threshold
NIBS	Noninvasive brain stimulation
PHI	Protected health information
PI	Principal investigator
PSQI	Pittsburgh Sleep Quality Index
QOL	Quality of life
RCT	Randomized controlled trial
REM	Rapid eye movement
rTMS	Repetitive transcranial magnetic stimulation
SAE	Serious adverse event
TASS	Transcranial Magnetic Simulation Adult Safety Screen
TMS	Transcranial magnetic stimulation
US	United States

Supplementary Information

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Additional file 1. SPIRIT checklist.

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Authors' contributions

Study protocol conceptualization and trial design (MIL, SRP, MRB, PEC, JRG, JH, KI, BJ, WWK, SK, AML, BNL, RCP, EKS, MKW, KMW, GAW, BFB); writing original draft (MIL, SRP); critically reviewing and editing manuscript for intellectual content and approving final version to be published (MIL, SRP, MRB, PEC, JRG, JH, KI, BJ, WWK, SK, AML, BNL, RCP, EKS, MKW, KMW, GAW, BFB).

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Mayo Clinic

Data availability

Not applicable.

Declarations

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that influenced the work reported in this protocol paper. Dr. Maria I. Lapid serves as the sponsor-investigator and holder of Investigational Device Exemption (IDE) G220016.

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