Protocol

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High-dose Accelerated rTMS to Cognitive Control Neurocircuitry in MCI: A Safety and Feasibility study

Short Title:
Plasticity Using Stimulation and Habit:
A Pilot Open-label rTMS Study for MCI (PUSH-Pilot)

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PROTOCOL TITLE:

High-dose Accelerated rTMS to Cognitive Control Neurocircuitry in MCI: A Safety and Feasibility study

PRINCIPAL INVESTIGATOR:

- Andreana Benitez, Ph.D.

1.0 OBJECTIVES / SPECIFIC AIMS

The objective of this study is to establish the safety, feasibility, tolerability, and acceptability of high-dose accelerated intermittent theta burst (iTBS) repetitive transcranial magnetic stimulation (rTMS) to the left dorsolateral prefrontal cortex (dlPFC) in patients with amnestic Mild Cognitive Impairment (aMCI). We also seek to obtain preliminary efficacy data as well as feasibility / acceptability data of computerized cognitive training as an adjunct to iTBS rTMS. The long-term goal of this project is to obtain preliminary data to support future empirical studies of iTBS rTMS for aMCI, including future randomized controlled trials to devise the optimum rTMS therapeutic delivery (with variations in dosing parameters, cortical targeting, and MCI syndrome indications), with the ultimate goal of dementia prevention. *The scientific merit of this pilot study has been peer-reviewed and subsequently recommended for funding through the National Center of Neuromodulation for Rehabilitation (NC NM4R).*

AIM 1: Establish the safety of an accelerated rTMS protocol for neurocognitive rehabilitation in aMCI. We hypothesize that accelerated rTMS will be safe as indexed by 1) no clinically significant structural brain changes; 2) no decrements in neurocognitive function; 3) no significant adverse events.

AIM 2: Establish the feasibility, tolerability, and acceptability of an accelerated rTMS protocol for neurocognitive rehabilitation in aMCI. We hypothesize that 1) aMCI patients will consider the treatment acceptable and that 2) recruitment and retention will be feasible (> 80% retention).

EXPLORATORY AIM: Establish the preliminary efficacy of an accelerated rTMS protocol for neurocognitive rehabilitation in aMCI. We hypothesize that aMCI patients will demonstrate modest improvements on neurocognitive testing and self-reported affective symptoms and quality of life from pre- to post-treatment.

EXPLORATORY AIM: Establish the feasibility, acceptability of computerized cognitive training as an adjunct to accelerated rTMS in MCI. We hypothesize that aMCI patients will complete a range of exercises between sessions and at home (feasibility) and will rate the intervention as productive (acceptability).

2.0 BACKGROUND

Mild Cognitive Impairment (MCI) is the pre-dementia stage in which individuals remain functionally intact yet demonstrate the early cognitive and behavioral changes of neurodegenerative diseases. Over half of those with MCI develop dementia within 10 years[1], but an intervention that can delay dementia onset by 5 years may cut dementia prevalence by a third and decrease healthcare costs[2]. However, the diagnosis and treatment of MCI is hampered by its variability in underlying etiology and clinical presentation. That is, the neuropathology of MCI is markedly heterogeneous[3,4], and neuropsychiatric symptoms are also highly comorbid, including depression, anxiety, apathy, and sleep dysfunction[5–7]. Thus, *the ideal MCI intervention must suit a pathologically and behaviorally heterogeneous condition and have a high potential to be disseminated for dementia prevention*.

Repetitive transcranial magnetic stimulation (rTMS) to left dorsolateral prefrontal cortex (dlPFC) is one such potential intervention. One hypothesized mechanism of action of this approach is the enhancement of cognitive control by targeting the neurocircuit substrates, leading to improved

affect regulation[8]. If so, then rTMS should be a powerful transdiagnostic intervention for both affective and cognitive symptoms. Indeed, rTMS has been shown to reduce these symptoms in various neuropsychiatric syndromes[9] including geriatric depression[10], with the specific literature on rTMS for MCI currently nascent yet promising[11].

Conventionally, a course of rTMS is 30-40 minutes of treatment each weekday for 4-6 weeks. To lessen burden while leveraging established outcomes, newer *high-dose accelerated intermittent theta burst (iTBS) rTMS* protocols increase the number of sessions per day, reducing the treatment course by >50% and yielding more rapid response and remission[12,13] while retaining safety, feasibility, acceptability, and effectiveness[14–18]. However, the safety and feasibility of this delivery schedule has yet to be established for MCI.

In this open-label, safety and feasibility trial, we will recruit 40 amnestic MCI (aMCI) patients (target completers N=30) through memory disorders and neuropsychology clinics, as overseen by PI and neuropsychologist Dr. Benitez. We will recruit clinically well-defined participants who will meet stringent actuarial neuropsychological criteria for aMCI[19]. **This study will employ identical procedures to an ongoing IRB-I approved NC NM4R pilot, *Neuromodulation and Plasticity in Cognitive Control Neurocircuitry in Chronic Stroke* (PI: McTeague; Pro 83136).** Specifically, neuronavigation-based targeting of the left dorsolateral prefrontal node of the cognitive control network will be performed. This study will utilize accelerated rTMS using a MagVenture MagPro TMS System. All participants will receive treatment for eight, 3-min sessions of iTBS on each of three days within an eight-day span. Each session would be separated by 10 mins or more per participant comfort and convenience. To collect preliminary feasibility and acceptability data for a planned follow-up combinatorial intervention study, participants will complete computerized cognitive exercises in the intervening periods between same-day rTMS sessions. At pre- and post-treatment, participants will undergo brain MRI (FLAIR, diffusion, T2*/gradient, volumetric scans, resting state) and computerized neurocognitive testing. As an open-label pilot study, there is no sham control group.

3.0 INTERVENTIONS TO BE STUDIED

Accelerated rTMS. We will utilize an LTP-like accelerated iTBS rTMS targeted to left dlPFC in aMCI using a MagVenture MagPro TMS System. All participants will receive treatment for eight, 3-minute sessions on each of three days within an eight-day span. Each session will be separated by 10 minutes, according to participant comfort and preference. As an open-label pilot investigation, there is no sham control group.

RATIONALE: Transcranial magnetic stimulation (TMS) is a means of non-invasively activating neuronal elements in the brain. Repetitive TMS (rTMS) in particular causally influences neural networks and produces acute neuroplastic periods that reliably persist after the termination of stimulation and promote cortical remodeling[22,23]. The evidence base for therapeutic rTMS has been most persuasive in the case of depression treatment. Proposed as a means of up-regulating prefrontal control over dysregulated limbic activation, high-frequency rTMS is most often applied to left dorsolateral prefrontal cortex[24] (dlPFC). Several meta-analyses have now shown that open-label effects sizes are large, while comparisons to sham stimulation are at least moderate to large among even patients highly resistant to pharmacotherapy[25,26]. In geriatric depression, the FDA-

approved course of rTMS has been found to be safe, tolerable, and yield commensurate response rates[10,27,28].

The proposed mechanism by which rTMS remediates depression implies that rTMS should also be a powerful transdiagnostic intervention for both cognitive and affective dysregulation. The left dlPFC site typically targeted with rTMS is seated in an area of cortex integral to intact higher order cognition[29] (i.e., executive function). Co-I Dr. McTeague has shown in a large meta-analytic study that this left dlPFC region (as well as the rest of the cognitive control or multiple demand network) is commonly hypo-activated during cognitive tasks across neuropsychiatric disorders[30]. While dementia was not included in this meta-analysis, a similar meta-analysis of task-based fMRI identifies prominent hypoactivation in MCI in the same frontoparietal network[31]. Thus, it is unsurprising that other meta-analyses and reviews of mild to moderate AD have shown that rTMS improves cognitive ability[32] and neuropsychiatric symptoms[33] with no adverse cognitive effects[34]. Although research into using rTMS as a treatment for MCI is in its infancy[11], it is an ideal disease stage for dementia prevention using rTMS particularly given that 25-40% of MCI patients have comorbid depression[35] which in turn increases risk of further cognitive decline and dementia[36]. Thus, *there is abundant preliminary data supporting our rationale to use rTMS of the dlPFC to target neurocircuitry integral to cognitive and affective dysfunction, although its delivery could be better optimized to support clinical application.*

A therapeutic course of rTMS typically consists of 30-40 minutes of high-frequency (i.e. 10 Hz) treatment on each weekday, for 4-6 weeks. This schedule can be burdensome and reduce adherence. To improve upon this conventional approach, Co-I Dr. George et al. pioneered accelerated rTMS, demonstrating that delivering 3 high-dose sessions per day (i.e. 10 Hz; 3,000 pulses for 30 mins; 18,000 pulses/day total) on three consecutive days was safe, feasible, and suggestive of rapid antidepressant effects[14]. More recently, a number of groups have demonstrated the feasibility, acceptability, and effectiveness of this form of delivery in which sessions are repeated daily, typically spaced by at least 30 minutes, to reduce total days of treatment. Safety has also been assessed with both structural and metabolic imaging as well as neurocognitive testing, which has shown no adverse effects and modest gains in cognition[13,17]. Furthermore, acceptability studies show that accelerated rTMS increases adherence and decreases interruptions to daily obligations while yielding faster response[15–18]. Importantly, critical to the success of this project is the fact that the procedures proposed in this study have already been approved by the MUSC Institutional Review Board for an NM4R pilot grant (PI: McTeague; Pro 83136). As such, all methods are already established and running, personnel trained, and, importantly, we will be able to compare the results in two prevalent and functionally impairing neurodegenerative disorders.

Computerized Cognitive Training. To collect preliminary feasibility/acceptability data for a planned follow-up combinatorial intervention study, participants will complete computerized cognitive exercises in the intervening periods between same-day rTMS sessions. Clinical trials using the online system Brain HQ (https://www.brainhq.com/world-class-science/science-team) have been shown to be associated with cognitive function in older adults[58,59]. Each exercise takes approximately 3-10 minutes and adapts to the individual's progress. The exercises fall under one of six categories: processing speed, memory, attention, people skills, cognitive flexibility and spatial navigation. During breaks between treatments, participants will complete exercises for a total of 20 minutes of exercises per day and 60 minutes of exercises over the

three days of treatment. Afterwards, participants will be asked to complete at least 20 minutes of these exercises per day at home during the 4 weeks following treatment completion.

RATIONALE: Because accumulating work suggests that the 10-60 minute window following excitatory rTMS is a window of particular neuroplasticity[37], the longer-term plan of this line of work is to utilize rTMS as an adjunct for multimodal interventions including computerized cognitive training and behavioral interventions to optimize neuroplasticity, cognitive remediation, and quality of life. Toward this goal, we will collect preliminary acceptability/feasibility data of computerized cognitive exercises, interleaved between rTMS sessions.

Team expertise for ensuring safety and integrity:

Dr. Benitez (PI) is a licensed clinical neuropsychologist who conducts patient-oriented research using neuropsychological and MRI methods. She is also an attending clinical faculty member in the Neuropsychology Clinic within the MUSC Department of Neurology and the research director of the newly formed Rapid Access Memory Clinic. She is ideally suited to ensuring that stringent study inclusion/exclusion criteria are met and to monitor the safety of participants during and following participation.

Dr. McTeague (Co-I) is a licensed clinical psychologist and an expert in the functional architecture of the cognitive control network and its relationship to deficits in neuropsychiatric populations, as well as the application of accelerated, high-dose rTMS in neuropsychiatric and neurodegenerative disorders. She will ensure that all rTMS procedures are implemented according to best-practice safety guidelines, replicability, and rigor.

Dr. Revuelta (Co-I) is an expert in utilizing rTMS in neuropsychiatric disorders, with a special emphasis in Parkinson's Disease. He is also an associate professor in the MUSC Department of Neurology and the director of the Deep Brain Stimulation Program.

Dr. Liu (Co-I) is a Professor of Neuroscience at MUSC and over the last 10 years has pioneered techniques for personalized mapping of functional networks. His techniques will be utilized to complement structural imaging data in assessing safety, while also providing preliminary evidence of the potential to modify the cognitive control and related networks in aMCI.

Dr. Antonucci (Co-I) is an associate professor in neuroradiology at MUSC. He will be responsible for providing clinical neuroradiological reads of structural imaging scans, to assess and changes pre- to post-treatment.

4.0 STUDY ENDPOINTS

AIM 1: Establish the safety of an accelerated rTMS protocol for neurocognitive rehabilitation in aMCI.

Primary Outcomes: Clinically significant structural brain changes; Neurocognitive performance changes; Adverse events

Secondary Outcomes: Psychopathology symptom changes

AIM 2: Establish the feasibility, tolerability, and acceptability of an accelerated rTMS protocol for neurocognitive rehabilitation in aMCI.

Primary Outcomes: Patient perception of treatment acceptability; Recruitment rates; Retention rates

EXPLORATORY AIM: Establish the preliminary efficacy of an accelerated rTMS protocol for neurocognitive rehabilitation in aMCI.

Primary Outcomes: Neurocognitive performance changes

Secondary Outcomes: Subjective psychopathology symptom/Quality of Life changes

EXPLORATORY AIM: Establish the feasibility, acceptability of computerized cognitive training as an adjunct to accelerated rTMS in MCI. We hypothesize that aMCI patients will complete a range of exercises between sessions and at home (feasibility) and will rate the intervention as productive (acceptability).

Primary Outcomes: Rate of usage

Secondary Outcomes: Game performance change; subjective acceptability

5.0 INCLUSION AND EXCLUSION CRITERIA/STUDY POPULATION

Participants will be recruited through outpatient memory disorders and neuropsychology clinics staffed by neurologists and neuropsychologists at MUSC/DVA. (No procedures will be performed at the DVA; only recruitment materials will be provided.) Clinic providers will be trained on study criteria and procedures and will be provided with recruitment materials. Dr. Benitez will oversee recruitment and will ensure that participants meet the following eligibility criteria:

Inclusion Criteria:

i. Age 60-85
ii. English as a first/primary language
iii. Has been diagnosed with MCI by a healthcare provider within the past two years per NIA-AA criteria[40]: (1) Concern regarding cognitive decline reported by patient, informant, or clinician, (2) Objective evidence of impairment for age in 1+ cognitive domains, typically memory, (3) Preserved independent function, (4) no dementia.
iv. Has met actuarial neuropsychological criteria for aMCI: (1) ≥2 impaired scores (i.e. ≤16th %ile) within one cognitive domain, or (2) ≥1 impaired scores (i.e. ≤16th %ile) in ≥3 cognitive domains, using demographically-corrected normative data[41–43]. (1) and (2) must include the Memory domain.
v. The primary suspected etiology of aMCI must be neurodegenerative, with competing differential diagnoses (e.g. psychiatric disorder, movement disorder, reversible causes, substance use) ruled out as the primary etiology/ies following a clinical evaluation by a healthcare provider.
vi. Ability to provide independent informed consent, consistent with the MCI diagnostic criterion of preserved independent function.

Exclusion Criteria:

i. Dementia diagnosis per DSM-5 or NIA-AA[44] criteria.
ii. Daily/weekly use of anticholinergics, neuroleptics, sedatives, or bupropion. Stimulant use may be allowed pending investigator review. Cholinesterase inhibitors, NMDA receptor

antagonists, and antidepressants are allowed if on a stable regimen of four weeks prior to enrollment.

iii. History of significant or unstable condition/s that may impact cognition such as significant cardiac, cerebrovascular, or metabolic disease, severe mental illness (e.g. bipolar disorder, psychoses), alcohol or substance use disorder, developmental disorder, or other neurologic disease (e.g. severe brain injury, seizures).

iv. MRI and TMS contraindications (e.g., implants, claustrophobia, conditions/treatments that lower seizure threshold, taking medications that have short half-lives, no quantifiable motor threshold, active substance use disorder, bipolar disorder).

v. Is enrolled in a clinical trial and/or has received an investigational medication within the last 30 days.

6.0 NUMBER OF SUBJECTS

The target completion is 30 participants. To contend with attrition, we propose to enroll 40 participants.

7.0 SETTING

All procedures will take place in private assessment and rTMS treatment rooms at the MUSC Center for Biomedical Imaging at 30 Bee Street. The MRI scanning will also occur at the Center for Biomedical Imaging at 30 Bee Street on the MUSC campus. Certain procedures, such as consenting and questionnaire completion may be completed virtually through telehealth using an MUSC approved electronic platform (e.g. musc.doxy.me or REDCap).

8.0 RECRUITMENT METHODS

Recruitment

Participants will primarily be recruited through outpatient memory disorders and neuropsychology clinics staffed by neurologists and neuropsychologists at MUSC/DVA. Clinic providers will be trained on study criteria and procedures and will be provided with recruitment materials. A study coordinator will be on-call to facilitate rapid recruitment should a potential participant indicate his/her interest to the recruiting provider. Dr. Benitez will oversee recruitment and will ensure that participants meet eligibility criteria.

Participant recruitment will also include flyers, handouts, electronic and physical bulletin board postings, social media/message boards (i.e., Craigslist, MUSC Broadcast Research studies section of Yammer, Instagram, Facebook), web-based recruitment tools (e.g., ResearchMatch, Trial Match), newsletter/newspaper/media advertisements, and recruitment talks at local community events/organizations and surrounding community. All approvals will be obtained prior to displaying flyers at the VA, and approvals will be obtained in other community locations if/as needed.

This project will also use an Epic-based tool that allows investigators to query clinical data for recruitment. The study team will receive a recruitment report from the Biomedical Informatics group containing a list of patients who potentially meet eligibility criteria. Study staff will then perform a chart review on these patients to further assess inclusion/exclusion criteria. Patients who appear to meet eligibility criteria and have opted in to being contacted about research will be contacted by the study team via phone, postal mail, and/or email.

Participants who make contact based on recruitment efforts will be given a description of the study purpose, procedures, and potential risks and benefits of the study by phone. The potential participant will be invited to ask questions until they are satisfied and can make a decision to proceed or not with the eligibility phone screen. If the potential participant agrees to continue, a phone screen will be conducted to determine eligibility for the next phase of the study.

Eligibility Phone Screening

Trained study staff will review the eligibility criteria with potential participants. The potential participants' aMCI diagnosis will be verified by Epic chart review (if he/she is an MUSC patient) or by a formal request for medical records initiated by the patient and provided to study staff. PI and neuropsychologist Dr. Benitez will personally review all potential participants' medical records to ensure that each MCI patient will meet the detailed inclusion/exclusion criteria, which necessitates that the patient has a comprehensive clinical history and neuropsychological test results on file. Should a potential participant not have an established MCI diagnosis, or have incomplete data in support of this diagnosis to the extent that his/her eligibility cannot be readily ascertained, study staff will recommend that he/she complete a clinical evaluation with a clinical neuropsychologist at MUSC or elsewhere, as convenient to him/her.

9.0 CONSENT PROCESS

Following recruitment and screening, the potential participant will be given a copy of the informed consent form (ICF) in-person, via postal mail, or e-mail for review. There is no required timeline between their receipt of the ICF and deciding whether or not to participate. Participants will be encouraged to take their time to decide.

Informed consent will take place on the MUSC campus or through telehealth by trained research staff (eConsent). If consenting through telehealth using an IRB-approved electronic/online platform (i.e. REDCap or musc.doxy.me; all future references to an "electronic/ online platform" hereafter refer to these), the study staff will first confirm that participants have the appropriate technology to complete the electronic consent process. In the case of eConsent, the participant will be asked to locate a private and interruption-free environment in order to complete the appointment. The participant will receive a copy of the signed e-consent by email from the research personnel. If consenting in-person, the visit will take place in laboratory or Center for Biomedical Imaging space at 30 Bee Street.

To ensure ongoing consent, participants will be queried at the start of any procedure about their comfort and willingness to continue.

10.0 STUDY DESIGN AND METHODS

A summary and timeline of all procedures are outlined and described below.

Session Number	Task Description	Location	Approximate Time Commitment
0	**Screening** Epic and/or medical record review Keel TMS Safety Screen	Telephone	30 minutes
1	**Pre-treatment Neurocognitive/Neuropsychiatric Assessment** ***Consent/Safety*** Consent* Keel TMS Safety Screen* TMS Motor Threshold Test Credibility/Expectancy Questionnaire (Pre-treatment) ***Cognition*** Montreal Cognitive Assessment (MoCA) NIH Cognition Toolbox NINDS-CSN 30-Minute Neuropsychological Protocol (Hachinski et al., 2006, which includes Semantic and phonemic fluency, Digit Symbol-Coding, Digit Span, Hopkins Verbal Learning Test-Revised, Trail Making Test) WASI-II (Vocabulary, Matrix Reasoning)* ***Affective Function/Quality of Life*** Lawton Instrumental Activities of Daily Living Scale (IADL)* Mini-International Neuropsychiatric Interview (M.I.N.I)* Columbia Suicide Severity Rating Scale (CSSRS) Geriatric Depression Scale (GDS)* Hamilton Depression Rating Scale (HAM-D)* Young Mania Rating Scale (YMRS)* PROMIS Measures: Anxiety, Depression, Applied Cognitive Abilities, Social Participation, General Life Satisfaction, and Fatigue*	Center for Biomedical Imaging	3 – 3.5 hours
2	**Pre-treatment MRI Scans** FLAIR, diffusion, T2*/gradient, volumetric scans, resting-state fMRI	Center for Biomedical Imaging	1 – 2 hours
3-5	**rTMS Treatment Sessions** Review of systems adverse events questionnaire (Yaejee et al., 2015) Momentary Assessment of TMS 8, 3 min sessions rTMS, interspersed with BrainHQ exercises	Center for Biomedical Imaging	2 – 3 hours per day, for 3 days within a 8-day span
6	**Post-treatment Neurocognitive/Neuropsychiatric Assessment** ***Cognition*** NIH Cognition Toolbox Montreal Cognitive Assessment (MoCA) NINDS-CSN 30-Minute Neuropsychological Protocol (Hachinski et al., 2006) ***Affective Function/Quality of Life*** Lawton Instrumental Activities of Daily Living Scale (IADL)* Mini-International Neuropsychiatric Interview (M.I.N.I)* Columbia Suicide Severity Rating Scale (CSSRS) Geriatric Depression Scale (GDS)* Hamilton Depression Rating Scale (HAM-D)* Young Mania Rating Scale (YMRS)* PROMIS Measures: Anxiety, Depression, Applied Cognitive Abilities, Social Participation, General Life Satisfaction, and Fatigue*	Center for Biomedical Imaging	2 - 3 hours

	Credibility/Expectancy Questionnaire (Post-treatment)* TMS Experience Questionnaire* BrainHQ Experience Questionnaire* Review of systems adverse events questionnaire (Yaejee et al., 2015)		
7	**Post-treatment MRI Scans** FLAIR, diffusion, T2*/gradient, volumetric scans, resting-state fMRI	Center for Biomedical Imaging	1 - 2 hours
8	**1 – 3 weeks post-treatment completion** Review of systems adverse events questionnaire (Yaejee et al., 2015) PROMIS Measures: Anxiety, Depression, Applied Cognitive Abilities, Social Participation, General Life Satisfaction, and Fatigue* BrainHQ exercises	REDCap Online	10 – 20 minutes >20 minutes per day
9	**4 weeks post-treatment completion** PROMIS Measures: Anxiety, Depression, Applied Cognitive Abilities, Social Participation, General Life Satisfaction, and Fatigue* Montreal Cognitive Assessment (MoCA)* TMS Experience Questionnaire* BrainHQ Experience Questionnaire*	REDCap Video Conference	30 min – 1 hour

*Option to complete remotely, such as due to COVID-19 precautions. Components of sessions 1&2 and 6&7 may be combined..

Session 1: In-person Pre-treatment Neurocognitive/Neuropsychiatric Assessment (2 - 3 hours). Participants will complete computerized cognitive tests from the NIH Toolbox[32] (30-40 minutes). Each of these tests has been extensively normed, compared to traditional neuropsychological measures. Tests from different batteries will be utilized in this study for optimizing a comprehensive but efficient, reliable, and minimally burdensome subset of tests for MCI patients.

For further sample characterization with more traditional and more extensively normed neuropsychological measures, participants will complete the Montreal Cognitive Assessment (MoCA)[47] and the 30-minute battery recommended by the National Institute of Neurological Disorders and Stroke-Canadian Stroke Network (NINDS-CSN) Vascular Cognitive Impairment Harmonization Standards[49]: Semantic and phonemic fluency, Digit Symbol-Coding, Digit Span, Trail Making Test A & B, and Hopkins Verbal Learning Test-Revised. Full scale IQ will be assessed with the Vocabulary and Matrix Reasoning subtests of the WASI-II[56].

During this session, the Lawton Instrumental Activities of Daily Living Scale (IADL)[57] will be administered in order to verify the participants' functional independence per MCI criteria.

To assess neuropsychiatric symptoms and conditions often concomittant with aMCI, participants will then complete the Mini-International Neuropsychiatric Interview (M.I.N.I)[50]. The Columbia Suicide Severity Rating Scale (CSSRS) [52] will be administered in order to assess suicide risk. The Geriatric Depression Scale (GDS) Hamilton Depression Rating Scale (HAM-D), and Young Mania Rating Scale (YMRS) will be administered. The computer adaptive test versions of the Anxiety, Depression[51], Applied Cognitive Abilities[53], Social Participation[55] and Fatigue[54] PROMIS Measures will also be administered. The PROMIS measures have been selected, specifically for the low-burden nature of the computerized adaptive form and the extensive normative data. Neuropsychiatric conditions other than psychotic disorders and substance use disorders will not

result in exclusion. The Edinburgh Handedness Inventory will be administered to assess hand preference on several forms of manual activity[51].

The option to remotely complete the M.I.N.I, MoCA, WASI-II, Demographics, Keel TMS Safety Screen, IADL questionnaire, GDS, HAM-D, YMRS, and the PROMIS measures will be given to participants if they are unable to physically come to the Center for Biomedical Imaging for the time being, such as due to COVID19 precautions. Phone calls or video conferencing through musc.doxy.me will be utilized in order to administer and oversee the completion of these assessments.

Comfort and reliability considerations: During the administration of some of the neuropsychological assessments, the participants' verbal responses will be audio recorded for quality control purposes. During all in-person sessions, snacks and water will be offered between testing administrations in order to improve energy, limit fatigue, and promote comfort. Furthermore, multiple breaks will be offered. Finally, participants will be given the option to schedule sessions on the same day, with a break, if additional visits/travel would be burdensome.

Session 2: MRI Scanning (1 - 2 hours). At pre- and post-treatment participants will complete FLAIR, diffusion, T2*/gradient, perfusion and volumetric scans for assessment of structural changes. Participants will also complete a resting-state fMRI scan.

Sessions 3-5: rTMS (2 – 3 hours). A MagVenture MagPro TMS System will be utilized. All participants will receive open-label treatment for approximately eight, 3-minute sessions of intermittent theta burst rTMS on each of three days within an eight-day span. A single session=600 pulses at 120% rMT, iTBS triplets at 50 Hz for 2 s and repeated every 10 s for a total of 190 s to left dlPFC. Total pulses=14,400. To enable adherence and retention, the days do not need to be contiguous. Same day sessions will be separated by 10-15 minutes, but more accounting for participant comfort. After each day of treatment, participants will be asked to complete an rTMS acceptability questionnaire. During treatment breaks participants will complete Momentary Assessment of TMS and 10-15 minutes of Brain HQ exercises between each session and will also have the option of completing tasks at home on intervening days during the treatment schedule. At the end of the final treatment session, participants will be asked to rate the exercises based on difficulty and enjoyment.

Session 6: In-person Post-treatment Neurocognitive/Neuropsychiatric Assessment (2 - 3 hours). Within one week following treatment, participants will repeat the pre-treatment neuropsychiatric and neurocognitive assessment for assessment of pre/post treatment changes.

Session 7: Post-treatment MRI Scans (1 - 2 hours). Within one week following treatment, participants will repeat the pre-treatment MRI scans for assessment of pre/post treatment changes.

Session 8: 1 – 3 weeks post-treatment completion. During the intervening weeks after Sessions 6/7 and before Session 9, the participants will be asked to remotely complete surveys using REDCap. Participants will also be provided with a research account for BrainHQ and asked to engage in at least 20 minutes of brain exercises daily until Session 9.

Session 9: 4 weeks post-treatment completion. Participants will again be asked to complete surveys using REDCap. Particiants will also be asked to complete the MoCA remotely, as well as acceptability/satisfaction questionnaires regarding the rTMS and BrianHQ interventions.

Participant Compensation. Participants will be compensated as follows:

Consent & Session 1:	$40 for screening and pre-treatment assessments
Session 2:	$50 for the pre-treatment MRI
Sessions 3 to 5:	$120 for rTMS treatment (i.e. $40/day)
Sessions 6 and 7:	$100 for post-treatment assessments and MRI
Session 8:	$42 for post-treatment questionnaires (i.e. $14/wk over 3 weeks)
Computerized Exercises:	$4.5/completed 20-minute session (up to $126)
Session 9:	$22 for post-treatment questionnaires at 4 weeks follow-up
Total:	$500 per participant upon the completion of all procedures.

You will receive payments after completion of each Session and after 3 days of TMS. Payment for study visits will be made using a pre-paid debit card, called a ClinCard. It works like a bank debit card and participants may use the card to purchase goods or services everywhere Debit MasterCard is accepted. Participants will be given a ClinCard at the beginning of the study. Each time they receive payment for participation in this study, the money will be added to the card, as outlined in the payment schedule above. In the event that any portion of the study is completed remotely, the ClinCard will be mailed to the participant.

11.0 SPECIMEN COLLECTION AND BANKING (Not Applicable)

12.0 DATA MANAGEMENT

Analysis

Aim 1. FLAIR, diffusion, T2*/gradient, perfusion and volumetric scans will be reviewed by Dr. Antonucci for any new signal abnormality. Adverse events will be surveyed and summarized.

Aim 2. Retention (i.e., defined as completion of all study sessions) will be determined. Participants will also complete a survey regarding acceptability, including qualitative responses for treatment modification.

Exploratory Aim 3. Neurocognitive performance and affective symptoms/quality of life will be analyzed with repeated-measures mixed models.

Exploratory Aim 4. BrainHQ usage/retention, performance, and acceptability will be analyzed with repeated-measures mixed models.

Power Considerations. The aims of this study are to determine safety and feasibility. The retention rate of 80% was determined to ensure that recruitment in the planned follow-up studies would be feasible in the longer time span allowed by future grants. Although these results will not be as compelling in the absence of a sham control, these data will give us an estimate of the

potential effect sizes and response variability that we can anticipate in future randomized controlled trials.

13.0 PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF SUBJECTS

The PI will be responsible for the overall monitoring of the data and safety of study participants. The PI's plan for ensuring safety and data integrity follows.

Quality Control. QC will include regular data verification at weekly meetings with the PI, Co-Is and study personnel. This will include verification of the documentation (Integrity of the Consent and HIPPA, scores on the assessments, MRI scanning information), study progress and participant status, any adverse events, and any protocol deviations. Events determined by the PI to be unanticipated problems involving risks to subjects or others (UPIRTSOs) will be reported by the PI to the IRB as soon as possible and no more than 10 working days per policy.

Safety Training. Before any investigator or assistant is allowed to enter the scanner room, they are required to take an extensive MRI safety course (with annual refresher courses) that cover powering down (or quenching) the magnet for patient safety and with established procedures for expediting participant contact with emergency medical personnel, should the need arise. These courses are run by the MUSC Center for Biomedical Imaging and are a prerequisite for obtaining privileges to book and use scanner time. Prior to administering TMS all personnel must be trained and certified by Drs. McTeague (Co-I) and Revuelta (Co-I).

Medical Emergencies:

1. Emergency responding in the scanner is facilitated by having two research staff running a scan. In the event of an emergency, one of these individuals remains with the participant and undocks the scanner bed from the magnet bore. This bed can easily be wheeled out of the scan room to facilitate speedy access to arriving emergency medical personnel. The second researcher calls 9-1-1 from the scanner suite and gives details of the participant's level of medical distress and location. Next, this person goes out to the front of the scanner building to flag down arriving emergency personnel and to direct them to the participant.

2. Drs. Revuelta and Antonucci are licensed physicians and will be on call during all sessions and rTMS sessions (or a similarly trained physician) to respond to any subtler potential medical situations.

3. These guidelines are in full agreement with the Center for Biomedical Imaging safety protocols and with published guidelines by a panel of experts in conducting TMS/rTMS and TMS/neuroimaging work for both research and clinical purposes (Rossi et al., 2009).

Suicidal Intent. Participants who have made a suicide attempt in the past year will be excluded. Also, suicidal intent will be assessed at the initial assessment phase of the study (during MINI Depression module) and with the Columbia Suicide Severity Rating Scale-Screen Version with Triage Points. At the initial assessment, the "Lifetime/Recent" version will be used. Consistent with the triage points determined by the scale authors, any positive endorsement to items 3 – 6 will necessitate immediate consultation with the PI. Any positive endorsement of items 4 – 6 and

participation will be discontinued. Depending upon the follow-up to endorsement of item 3 (passive ideation), participation may also be discontinued. Any participant endorsing these items will be referred to immediate consultation with the PI and provided appropriate referrals and follow-up contact to ensure engagement in care. For imminent suicidal intent, an emergency outpatient appointment or an in-house psychiatric consult will be arranged. MUSC police will be called directly in the event that the clinician deems the participant to be imminently of risk of harming him/herself and refuses to cooperate with a plan to report to the emergency psychiatric consult.

Ethical Research Practices. Ethical guidelines for clinical research will be followed strictly and all information obtained in the study will be kept strictly confidential. Data will be assigned coded identifiers and all names will be removed from study assessment and outcome data. Files linking participant names or identifying information to the coded identifier will be stored in a password-protected file, on a password protected desktop computer in a locked laboratory. Demographic and other identifying information will be stored separately from consent forms to eliminate the possibility of participant identification; signed consent forms will be locked in secure cabinets separate from data files. The files linking names to IDs will be deleted at the conclusion of the research project. De-identified data will be stored indefinitely following the conclusion of the project. Only the PI and active research staff will have access to the de-identified data. The PI and all research staff and mentors will be responsible for and will comply with mandated reporting rules. All researchers will be obligated to demonstrate that they have remained abreast of all guidelines and rules related to the Health Insurance Portability and Accountability Act (HIPAA). Each member of the research staff will complete focused training on each task for which they are responsible and will perform ongoing quality control for others performing similar work. The PI and/or study coordinator will produce quarterly administrative reports describing study progress including accrual, demographics, and participants' status. Reports will describe adherence to inclusion/exclusion criteria and the study protocol in addition to any unanticipated problems in the category of risks to participants or others as well as any adverse events. All collected data will be obtained for research (and participant safety) purposes only.

*Confidentiality***.** Any discussion of identifying sensitive and information will occur in private rooms at MUSC. Regarding documentation, participants' names will appear only on the IRB-approved Consent, HIPAA, and payment forms, initial screening form, and in a separate key file that links individual participant names and contact information to a random participant identification code. The participant identification code will be assigned to the individual during Visit 1 and all subsequent data collection will reference this code. The key linking individual identifying information to the participation code will be maintained in an electronic database accessible only to the PI and their designees in a password-protected file on an encrypted and password protected network (MUSC LAN). The questionnaire data collected through REDCap will be referenced by participant ID only and collected via a HIPAA compliant interface and downloaded to the MUSC server once a participant has completed participantion. If a participant consents to participate at the interview, the initial screening form will be entered into a secure electronic database according to the assigned participation code and then locked a secure office, separate from payment and consent forms including heath information. If a participant declines consent or is lost to follow-up (i.e., defined as not appearing for intake within 1 month of screen), the screening form will be securely shredded. The consent, HIPAA, and payment forms will be kept in a locked cabinet in a locked office. All other collected paper (e.g., interview responses) and electronic (e.g., questionnaire, neurocognitive, MRI data) files, including audio recording files, will be identifiable

only by participant code and stored in locked file cabinets or on the secure MUSC LAN at the Institute of Psychiatry (non-MRI data) and Center for Biomedical Imaging (MRI data). The key file linking names to IDs will be deleted after data collection is complete.

Consent and HIPAA forms will be kept on file for 6 years. Contact information is kept on file for 6 years if the participant consents to allowing their information to remain active in our files, or the contact information is destroyed immediately after the study is completed if participants chose that option on the consent form. Although individual-subject analyses may be written up in publications, the individual subjects producing that data will never identified by name or initials, or any other identifying information.

Other protections against risk. In designing this trial, the research team sought to maximize data collection within the overall priority of maintaining participant comfort and safety. As was discovered in the pilot study by George and colleagues[19], the proposed design is feasible, does not impose unreasonable expectations of time or effort, or expose patients to risks or limit them from the best available care. In the very unlikely event that a subject endorses transient alcohol or substance abuse during the course of this study, the coordinator will confer with a physician co-investigator prior to proceeding with any treatment.

Adverse Events & Trial Safety. Potential conflicts of interest will be reported using the NIH rules for disclosure. Adverse Events (AEs)/Serious Adverse Events (SAEs) occurring during the course of the project will be collected, documented, and reported in accordance with protocol and IRB reporting requirements. All research staff involved with adverse event reporting will receive general and protocol specific AE/SAE training including identification, assessment and evaluation, and documentation and reporting. Any potential adverse events will be identified during the course of the study from participant self-report and administration of the visit assessments and procedures. Research staff will identify adverse events and obtain all available information to assess severity, seriousness, study relatedness, expectedness, outcome and the need for change or discontinuation in the study intervention.

An Adverse Event (AE) is defined as any unwanted change, physically, psychologically or behaviorally, that occurs in a study participant during the course of the trial is an adverse event. A Serious Adverse Event (SAE) is defined as an adverse event that has one of the following outcomes:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, OR
- Requires intervention to prevent one of the above outcomes.

Adverse events are generally documented on AE Logs and AE Case Report Forms (CRFs). Additional relevant AE information if available should be documented in a progress note in the research record as appropriate to allow monitoring and evaluating of the AE.

When a reportable SAE is identified, the research staff will notify the MUSC Institutional Review Board (IRB) and DSMB within 24 hours and complete the AE report form in conjunction with the PI. The MUSC IRB meets monthly and is located at 1 South Park Circle, Bldg 1, Suite 401, Charleston, SC 29407. Communication with the IRB is through email, memos, official IRB forms, and online reporting.

If complete information is not available when the initial 24-hour SAE report is disseminated, follow-up information will be gathered to enable a complete assessment and outcome of the event. This information may include hospital discharge records, autopsy reports, clinic records, etc. The research staff will attach copies of source documents to the SAE report for review by the PI.

We will report adverse events to the Medical University of South Carolina (MUSC) Institutional Review Board (IRB) as soon as possible, but no later than 10 working days after the investigator first learns of the event. The MUSC IRB AE reporting requirements are as follows: All deaths that occur during the study or 30 days post termination from the study are required to be reported as adverse events even if they are expected or unrelated. Other adverse events are reportable to the MUSC IRB if the AE is 1) unexpected AND 2) related or possibly related AND 3) serious or more prevalent than expected. All three criteria must be met for an AE to be reported to the MUSC IRB. The IRB definition of unexpected is that the AE is not identified in nature, severity or frequency in the current protocol, informed consent, investigator brochure or with other current risk information. The definition of related is that there is a reasonable possibility that the adverse event may have been caused by the drug, device or intervention. Reportable AEs are reviewed by the IRB Chair and reported to the IRB Board at the next meeting.

The potential risks and benefits and methods to minimize these risks are outlined above. The research staff will report any unexpected AEs or any scores of “severe” on the side-effect symptom rating form or any FDA-defined serious AEs to the PI within 24 hours so that the PI can decide on the appropriate action. All unexpected AEs will be monitored while they are active to determine if treatment is needed. Study procedures will follow the FDA’s Good Clinical Practice Guidelines (www.fda.gov/oc/gcp).

Data and Safety Monitoring Procedures.

The PI will choose a group of faculty at MUSC to monitor the data on a bi-annual basis with respect to subject safety issues throughout the award period. The data and safety monitoring plan will include an internal Data Safety Monitoring Committee (DSMC), an external Data and Safety Monitoring Board (DSMB), and the Institutional IRB. The purpose of the DSMC, DSMB, and IRB are to ensure the safety of participants and the validity and integrity of the data.

Data Safety Monitoring Committee (DSMC). The internal DSMC will consist of the PI and co-investigators/consultants on the proposal. The functions of the DSMC will include: 1) providing scientific oversight; 2) reviewing all adverse effects or complications related to the study; 3) monitoring enrollment; 4) reviewing summary reports relating to compliance with protocol requirements; and 5) providing advice on resource allocation. The DSMC will meet quarterly, remotely or in-person. The recommendations of the DSMC will be reviewed and the PI will take appropriate corrective actions as needed.

Data and Safety Monitoring Board (DSMB). A DSMB will be established and will consist of professionals with appropriate expertise, who are willing to participate and who do not have any conflicts of interest. The DSMB will include: 1) two experts in the area of TMS, 2) a biostatistician with expertise in the conduct of clinical trials, and 3) two members with expertise in the treatment of MCI patients. The DSMB will meet on a bi-annual basis. The DSMB will perform the following activities:

- Review the research protocol and plans for data and safety monitoring.
- Evaluate the progress of the intervention, including periodic assessments of data quality and timeliness, participant recruitment, enrollment, and retention, participant risk versus benefit, integrity of the intervention, and other factors that can affect study outcome.
- Consider factors external to the study when interpreting the data, such as scientific or clinical developments that may impact the safety of study participants or the ethics of the study.
- Make recommendations to the internal DSMC and MUSC IRB for continuation or termination of the trial.
- Protect the confidentiality of study data and monitoring.

The DSMB will have the authority to temporarily or permanently discontinue the trial if it perceives that harm is occurring due to the intervention. The DSMB will meet with the internal DSMC yearly to review adverse event reports, patient complaints if any, and enrollment rates. Data will be provided at these meetings by the investigators on key variables that may indicate harm. The DSMB biostatistician will evaluate the confidentiality and integrity of the database and the procedures for recording and storing confidential files. The DSMB will also review the elements of the plan to manage emergencies.

Institutional Review Board (IRB). The MUSC IRB will review and approve the funded protocol; review patient and provider consent forms, ensure protection of patient privacy and safety, and monitor the study on an ongoing basis. Adverse events will be reported to MUSC IRB as they occur. Annual reports to MUSC IRB will indicate enrollment rates, adverse events, new findings that may influence continuation of the study, and reports of the DSMB.

14.0 WITHDRAWAL OF SUBJECTS

Early withdrawal of study subjects. As stated on the Informed Consent, all subjects reserve the right to withdraw from the clinical investigation at any time. The PI for any of the following reasons may discontinue subjects from the study:

- Subject is found to have entered the study in violation of the protocol.
- Subject withdraws consent to participate in the study.
- Subject is unable to tolerate the pre-treatment MRI.
- Subject is noncompliant with procedures set forth in the protocol.
- Subject experiences an Adverse Event that warrants withdrawal from the study.
- It is in the PI's opinion that it is not in the subject's best interest to continue.

- Subject displays other abnormal laboratory, medical or clinical findings for which clinical intervention should take precedence over study participation including:
    a) Development of mania/hypomania
    b) Generalized seizure
    c) Inpatient hospitalization
    d) Unable to complete desired treatment in the designated time frame

If a participant is lost to follow up, three documented attempts will be made to contact the participant.

15.0 RISKS TO SUBJECTS

Challenges will include patient tolerability to TMS, the MRI scanner, and the study clinical and neurocognitive assessments. The primary safety concern, the same as that for conventional once-daily rTMS, is risk of seizure. However, all reported TMS-induced seizures during conventional or accelerated protocols have been self-limiting, and NONE required further intervention to stop the seizure; no post-seizure sequelae or recurrent seizures developed. Extensive precautions with regard to suicidal ideation/homicidal ideation risk will be followed.

Due to the novel nature of the proposed study, the following table is included to provide a representative range of the stimulation parameters and populations examined with accelerated rTMS. The dosing range of these studies covers the range proposed in this study. In these as well as other accelerated rTMS studies, the authors have demonstrated the safety, feasibility and acceptability of accelerated, high-dose studies of rTMS in neurologically intact samples. Of pertinence to the issue of safety as well as the conceptual model proposed here, Holtzheimer et al.[6] showed reliably enhanced neuropsychological performance on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) from baseline to six weeks after an accelerated, high-dose rTMS protocol in patients with major depression. Furthermore, Baeken et al.[18,30] as well as Herremans et al.[29] and Williams et al.[28] additionally collected structural and functional imaging and demonstrated no adverse changes pre- to post-accelerated rTMS. Taken together, these studies demonstrate that the potential risks of accelerated rTMS are likely similar to conventional once-daily rTMS.

Representative accelerated rTMS studies for neuropsychiatric conditions.

Study	Total Pulses	Days	Total # Sessions	Stimulation Intensity	Disorder	Frequency	N
Holtzheimer et al.[6]	15,000	2	15	100%	Major Depression	10 Hz; 5s train, 25s ITI	14
Baeken et al.[18]	31,200	4	20	110%	Major Depression	20 Hz; 1.9s train; 12s ITI	15
Herremans et al.[29]	31,200	3	15	110%	Alcohol Use Disorder	20 Hz; 1.9s train; 12s ITI	19
Desmyter et al.[39]	32,400	4	20	110%	Major Depression	54 bursts of three; 2s train; 8s ITI s	50
Duprat et al.[40]	32,400	4	20	110%	Major Depression	54 bursts of three; 2s train; 8s ITI s	50
George et al.[19]	54,000	3	9	120%	Suicidal ideation	10 Hz;	41

McGirr et al.[41]	60,000	10	20	120%	Major Depression	10 Hz; 5s train, 25s ITI	27
Modirrousta et al.[42]	90,000	3	30	110%	Major Depression	10 Hz; 5s train, 25s ITI	18
Williams et al.[28]	90,000	5	10	90%	Major Depression	54 bursts of three; 2s train; 10s ITI	7
Schulze et al.[43]	120,000-180,000	10-15	20-30	120%	Major Depression	20 Hz; 2.5s train; 10s ITI	65

Weighing potential risks related to TMS. Based on previous clinical applications of left prefrontal rTMS in depression and in various other psychiatric disorders, as well as risks published by researchers and communicated experiences, it is hypothesized that left prefrontal rTMS is likely to be effective in reducing psychosocial impairment. This study is an important necessary step to characterize the safety, feasibility, and tolerability of the proposed neurocognition enhancing effect.

Potential worsening of neuropsychiatric symptoms with TMS. Several studies have thus far demonstrated the feasibility of using rTMS in depression without any alarming indicators of exacerbation of symptoms. The research team will work closely with patients to familiarize them with the nature of this experimental setup. All staff will also be trained to be alert to any worsening of neuropsychiatric symptoms and/or psychosocial impairment. Bipolar patients have at times shown hypomanic or manic switches in the course of once-daily rTMS, as such patients with bipolar type I will be excluded. Additionally, all patients will be assessed throughout each day for worsening symptoms. Participants will similarly be queried for worsening suicidal ideation/intent. Drs. Benitez or McTeague will additionally assess each patient once per week in-person or via telephone during rTMS treatment and the one month study involvement to assess mood, functioning, and safety.

Potential risk of a seizure with TMS. There is a risk that TMS can cause a seizure; but it is rare. The risk of seizure induction is related to the intensity, duration, frequency and rest interval of stimulation. Following the adoption and widespread use of the safety guidelines from a National Institute of Neurological Disorders and Stroke (NINDS) workshop on TMS, only 20 seizures have been reported since 1997, and they usually involved parameters of "higher settings" than the "safe range". To our knowledge, stimulation with the parameters and settings proposed in this study should not cause seizures. Each subject's stimulus intensity is determined by his or her motor threshold and will be carefully calculated before beginning treatment. In this study participants will receive rTMS to the prefrontal cortex, a region far less prone to seizure. Nonetheless, we will watch participants closely for any signs of seizure throughout all procedures. Additionally, our study patients will be free from using known stimulants and medications that are known to increase the risk of seizure (e.g., theophylline).

Other potential effects of TMS on brain tissue. TMS is thought to be safe, with no brain damage, despite extensive use in humans and other animals. Dr. George and colleagues[35] have recently completed a case report of a maintenance treatment of rTMS for depression over a year, where a depressed patient received a total of [(16,000 x 2 trials) + (8,000 x 12 trials)] = 32,000 + 96,000 = 128,000 stimuli over a year period. The patient's MRI showed no structural changes at the end from baseline. The patient experienced no seizures and had tolerated the procedure equally throughout the successive trials. Dr. George and colleagues have also reported a safety study[44] looking at the MRI scans before and after 2 weeks of daily left prefrontal rTMS for depression.

Specifically, no structural changes were found in the left prefrontal lobe of patients who received active rTMS compared to placebo. More specific to the current study, Baeken et al.[18,30] as well as Herremans et al.[29] and Williams et al.[28] additionally collected structural and functional imaging and demonstrated no adverse changes pre- to post-accelerated rTMS. Taken together, these studies demonstrate that the potential risks of accelerated rTMS are likely similar to conventional once-daily rTMS.

Potential changes in cognitive function. There have been no reports of deleterious changes (more than a minute) in cognitive function (memory, attention, etc.) in rTMS studies. Safety studies specifically looking for these changes did not find any effects of rTMS. Holtzheimer et al.[6] showed reliably enhanced neuropsychological test performance from baseline to six weeks after an accelerated, high-dose rTMS protocol in patients with major depression. Similar effects have been observed in Alzheimer's Disease and schizophrenia[21]. This study will assess for potential changes in cognitive function with pre- and post-treatment cognitive batteries designed to look for potential TMS effects, if they exist.

Potential hearing loss. The discharge of the rTMS coil generates a high-energy click that may cause cochlear damage. Humans exposed to rTMS have shown temporary increases in auditory threshold (especially at high frequencies) lasting at least 5 minutes and less than 4 hours[37]. Foam earplugs can protect against these changes and will be worn by the patients and researchers present during TMS sessions. Due to high dosage delivery in this proposal, participants will be instructed to ensure proper fit of earplugs prior to each session.

Risk of facial twitching and skin irritation. The TMS coil can cause facial twitching, skin irritation, or both, which can be acutely unpleasant. This typically often reduces over the course of treatment. Additionally, all patients will have a foam insert placed between the coil and their scalp for comfort and this typically reduces this discomfort. Furthermore, facial twitching and skin irritation are typically only acute and subside with the end of stimulation.

Risk of a first-degree burn. The TMS coil can heat up during use. The machine used in this study has two major protective engineering features: (1) an external heat monitor that will shut down the system if the coil gets too warm; and (2) a liquid-coiled coil design that keeps the coil much cooler than previous models. Additionally, all patients will have a foam insert placed between the coil and their scalp for comfort and also to act as additional thermal protection. The TMS treater will periodically monitor coil temperature during each treatment.

Potential risks related to delaying other psychotropic treatments. The investigators are sensitive to the ethical concerns of withholding changes in antidepressant medication from depressed patients or withdrawing them from antidepressants in an acute crisis due to their participation in a clinical trial. Thus in this trial, patients are allowed to stay on medications and to have their physicians adjust doses or even start new medications. The rationale is that the effects of medication changes or new medications are rarely visible within the 'trial' of acute TMS. Thus, ethically treatment as usual will be allowed and also address our hypothesis, without subjecting patients to slower medication adjustments by participating in the trial.

MRI risks. Exposure to magnetic field strengths used in the present study is not shown to be a significant health risk. Risks to an unborn fetus from exposure to the MRI field strength used in the proposed research (3 Tesla) are unknown. Participants will be asked to lie still and awake for

50-60 minutes in the scanner and this can occasionally result in soreness, stiff back, etc. Participants will be queried approximately every 10 minutes about their comfort. The main risk associated with MR imaging is the possibility of introducing metal to the magnet or its close proximity. Participants are thoroughly screened to prevent metal being brought into the MR environment. Other potential hazards of MRI scanning include: collision hazards, noise, neurostimulation at rapid sampling rates (i.e., short TRs), body temperature changes, helium, and nitrogen hazards. The MRI facility is tested regularly by internal and external safety monitoring teams. These risks are minimal, and the facility is run within FDA guidelines. All investigators and research assistants running participants in the Center for Biomedical Imaging are thoroughly trained in MR safety as a requirement to run scans.

Confidentiality Risks. There is a risk of a loss of confidentiality of personal information as a result of participation in any study. This is why all study records and audio recordings will be placed in a locked, secure, limited access location. Participation in the study and the information provided will be treated as confidential. The information we collect will contain a code number and not a name to protect confidentiality. Codes linking numbers and names will be kept in a locked secure location and will not be accessible to anyone outside the research team. Despite these efforts to maintain subjects' anonymity and confidentiality, there is always some minimal risk of people other than the study investigators gaining access to health information. Every effort will be made to ensure that health information will be collected and stored in a manner that ensures the highest level of protection of confidentiality.

16.0 POTENTIAL BENEFITS TO SUBJECTS OR OTHERS

High frequency repetitive TMS (rTMS) is FDA-approved for the treatment of major depression. Work by the investigative team as well as others has shown that the left dorsolateral prefrontal (dlPFC) site targeted with rTMS to remediate depression is seated in an area of cortex integral to efficient and adaptive higher order cognition (i.e., executive function). Furthermore, Co-I Dr. McTeague has demonstrated that this left dlPFC region is commonly hypoactivated during cognitive tasks across disorders. Thus, it is not surprising that cognitive improvements have been reported as ancillary benefits to rTMS treatment for depression. We propose that because rTMS to dlPFC is targeting cognitive neurocircuitry integral to adaptive functioning, that promoting neuroplasticity in this network with rTMS could be optimized to improve neurocognitive impairment in MCI. At present there is no FDA-approved treatment for cognitive impairment in MCI; all clinically available interventions (e.g. medication, cognitive rehabilitation) specific to ameliorating cognitive decline are either provided off-label or have limited efficacy per the literature.

17.0 SHARING OF RESULTS WITH SUBJECTS

We will inform participants of any new or relevant information that might influence their desire to continue participating in the study. We will also provide participants with an oral summary of their clinical outcomes should it be desired by the participant.

18.0 DRUGS OR DEVICES

We will use a MagVenture MagProsystem with a Cool-B65 coil to deliver iTBS to subjects. Access to the device will be limited to those who are trained to deliver the treatment and have been certified by Mark George, M.D.

Prefrontal rTMS at this intensity, frequency and number of stimuli has been considered "non-significant risk" by the FDA and the MUSC IRB for well screened depressed patients or healthy adults. (See the uploaded letter from the FDA; FDA_George.pdf). It is also FDA approved (Oct 2008) for the treatment of depression.

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