Study Protocol

Noninvasive Cortical Stimulation to Improve Memory in Mild Cognitive Impairment (MCI)

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Principal Investigator:
Joy L. Taylor, PhD

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Note: Any modification to the final, approved protocol will be annotated in an appendix. The annotation will note the exact words that are changed, the location in the protocol, the date the modification was approved by the DSMB and NIH Program Official, and the date it became effective.

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PRÉCIS

Study Title

Noninvasive Cortical Stimulation to Improve Memory in Mild Cognitive Impairment (MCI)

(IRB Title of Study: Noninvasive Brain Stimulation for Mild Cognitive Impairment)

Objectives

The purpose of this study is to test the efficacy of repetitive transcranial magnetic stimulation (rTMS) as a treatment for mild cognitive impairment (MCI). There are currently no effective treatments for MCI.

Primary Objective: Test the hypothesis that participants receiving active ("real") rTMS will show more improvement in memory at the immediate post-treatment assessment than the placebo (sham) control group.

Secondary Objectives (aims):

(2a) Assess the durability of rTMS effects on memory over a 6-month follow-up period, which is longer than assessed in previous studies;

(2b) Examine effects of rTMS on behavior and brain function related to the site of stimulation, which is a novel approach in the Alzheimer's disease (AD) spectrum;

(2c) Explore patient characteristics that could be useful in identifying who responds preferentially to rTMS or to a particular stimulation site.

Design and Primary Outcome

The study will use a double-blind, placebo (sham)-controlled, randomized 3-arm design.

Different cortical stimulation-sites will be studied in the two Active arms:

Active group 1: Bilateral dorsolateral prefrontal cortex (DLPFC);
Active group 2: Bilateral Lateral Parietal cortex (LPC)

Primary Outcome is the California Verbal Learning Test (CVLT-II) Trials 1-5 Total raw score

Interventions and Duration

Participants will be randomly assigned to one of **three treatment groups**: Group 1: DLPFC Active rTMS; Group 2: LPC Active rTMS; and Group 3: Placebo (sham) control (evenly split between each coil location). Thus, a participant has a 2/3 chance of receiving active rTMS.

Each participant will participate in the study for approximately 7 ½ months—including a daily rTMS treatment phase (20 sessions in all), and post-intervention follow-up lasting 6-months.

Sample Size and Population

Sample Size: 99 men and women between the ages of 55 and 90 inclusive (n=33 per group).
Target population: Individuals with a clinical diagnosis of single- or multi-domain amnestic MCI (aMCI). MCI is an intermediate state between normal aging and dementia due to conditions such as Alzheimer's disease (AD).

STUDY TEAM ROSTER

Principal Investigator: **Joy L. Taylor, Ph.D.**

VA Palo Alto Health Care System (151Y)
3801 Miranda Avenue
Palo Alto, CA 94304
Voice: (650) 493-5000 extension 63102
FAX: (650) 852-3297
email: joyt@stanford.edu and Joy.Taylor@va.gov

Co-Investigators: **J. Wesson Ashford MD, PhD (Psychiatry; Alzheimer's Disease)**

VA Palo Alto Health Care System (151Y)
3801 Miranda Avenue
Palo Alto, CA 94304
Voice: (650) 493-5000 extension 64059
FAX: (650) 852-3297
e-mail: ashford@stanford.edu and Wes.Ashford@va.gov

Margaret Windy McNerney, PhD (Mechanisms of TMS)

VA Palo Alto Health Care System (151Y)
3801 Miranda Avenue
Palo Alto, CA 94304
Voice: (650) 493-5000 extension 64901
FAX: (650) 852-3297
email: windymc@stanford.edu

Laura C. Lazzeroni, PhD (Biostatistician)

Department of Psychiatry & Behavioral Sciences
Stanford University School of Medicine
401 Quarry Road, 3305
Stanford, CA 94305
Voice: (650) 723-0947
FAX: (650) 723-4655
email: lazzeroni@stanford.edu

Maheen Adamson, PhD (rTMS Brain Injury Rehabilitation)

VA Palo Alto Health Care System (PSC/117)
3801 Miranda Avenue
Palo Alto, CA 94304
Voice: (650) 493-5000 extension 62179
FAX: (650) 650-849-0130
email: madamson@stanford.edu and maheen.adamson@va.gov

Other Significant Contributors

(Jauhtai) Joseph Cheng, MD, PhD (rTMS-Dementia)
VA Palo Alto Health Care System (151Y)
3801 Miranda Avenue
Palo Alto, CA 94304
email: Jauhtai.Cheng2@va.gov

Michael D. Greicius, MD, MS (fMRI)
Department of Neurology & Neurological Sciences
Stanford University School of Medicine
300 Pasteur Drive
Palo Alto, CA 94304
email: greicius@stanford.edu

Mark George, MD (rTMS)
Brain Stimulation Laboratory
Medical University of South Carolina
67 President Street, Room 502 North MSC 861
Charleston, SC 29425
email: georgem@musc.edu

Joachim Hallmayer, MD (Genetics)
Department of Psychiatry & Behavioral Sciences
Stanford University School of Medicine
401 Quarry Road
Stanford, CA 94305-5717
email: joachimh@stanford.edu

Ruth O'Hara, PhD (Neurocognitive /Neuropsychiatric Disorders)
VA Palo Alto Health Care System (151Y)
3801 Miranda Avenue
Palo Alto, CA 94304
email: roh@stanford.edu

Ahmad Salehi, MD, PhD (BDNF)
VA Palo Alto Health Care System (151Y)
3801 Miranda Avenue
Palo Alto, CA 94304
email: Ahmad.Salehi2@va.gov

Jerome A. Yesavage, MD (Geriatric Psychiatry; rTMS Clinical Development)
VA Palo Alto Health Care System (151Y)
3801 Miranda Avenue
Palo Alto, CA 94304
email: yesavage@stanford.edu and Jerome.Yesavage@va.gov

Other Personnel

Nicole Strossman, BS Biochem & Molecular Biology (Study Coordinator)
VA Palo Alto Health Care System (151Y)
3801 Miranda Avenue
Palo Alto, CA 94304
email: Nicole.Strossman@va.gov

Beatriz Hernandez, BS (Data Manager)
VA Palo Alto Health Care System (151Y)
3801 Miranda Avenue
Palo Alto, CA 94304
email: Beatriz.Hernandez@va.gov and bhernandez@stanford.edu

Art Noda, MS Statistics (Back-up Data Manager)
VA Palo Alto Health Care System (151Y)
3801 Miranda Avenue
Palo Alto, CA 94304
email: Arthur.Noda@va.gov and artnoda@stanford.edu

Priyanka Bhatt, MS Biomedical Engineering (Neuroimaging Data Analyst)
VA Palo Alto Health Care System (151Y)
3801 Miranda Avenue
Palo Alto, CA 94304
email: PBhatt@pavir.org

ABBREVIATIONS

AD Alzheimer's Disease

ADE Adverse Device Effects

ADNI Alzheimer's Disease Neuroimaging Initiative

ADRC Alzheimer's Disease Research Center

AE Adverse Event

ALE Activation Likelihood Estimation

aMCI amnestic Mild Cognitive Impairment

ANCOVA Analysis of Covariance

ANT Attentional Network Task

APOE Apolipoprotein E

ASL Arterial Spin Labeling

BA Brodmann Area

BDNF Brain-derived Neurotropic Factor

BNT Boston Naming Test

BVMT-R Brief Visuospatial Memory Test-Revised

CDR Clinical Dementia Rating

CEN Central Executive Network

CNS Central Nervous System

COMT Catechol-O-Methyltransferase

CVLT-II California Verbal Learning Test, second edition

DAN Dorsal Attention Network

DLPFC Dorsolateral Prefrontal Cortex

DMN Default Mode Network

DSMB Data Safety Monitoring Board

DSM-IV Fourth Edition of Diagnostic and Statistical Manual of Mental Disorders

ECog Everyday Cognition Scale

EDTA Ethylenediamine Tetraacetic Acid

ELISA Enzyme-Linked Immunosorbent Assay

EMG Electromyographic measurement

ETOH Ethanol

FAQ Functional Assessment Questionnaire

FC Functional Connectivity

FLAIR Fluid-Attenuated Inversion Recovery

fMRI	functional Magnetic Resonance Imaging
GDS	Geriatric Depression Scale
GRE	Gradient Recalled Echo
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICNs	Intrinsically Connected Networks
III	Individually Identifiable Information
IRB	Institutional Review Board
ITI	Inter-Train Interval
ITT	Intention-To-Treat
LPC	Lateral Parietal Cortex
LTP	Long-Term Potentiation
MCI	Mild Cognitive Impairment
MIRECC	Mental Illness Research, Education, and Clinical Center
MLS-PEST	Maximum-Likelihood Strategy using Parameter Estimation by Sequential Testing
MNI	Montreal Neurological Institute
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
MT	Motor Threshold
MTL	Medial-temporal Lobe
NIBS	Noninvasive Brain Stimulation
PCC	Posterior Cingulate Cortex
PE/NE	Physical/Neurological Examination
PFC	Prefrontal Cortex
PHI	Protected Health Information
ROIs	Regions of Interest
ROCF	Rey-Osterrieth Complex Figure
rs-fMRI	resting state functional Magnetic Resonance Imaging
RSNs	Resting State Networks
RT	Reaction Time
rTMS	repetitive Transcranial Magnetic Stimulation
SAE	Serious Adverse Event

SAS	Statistical Analysis System
sgACC	subgenual Anterior Cingulate Cortex
SMD	Standardized Mean Difference
SMS	Simultaneous Multi-Slice
SNP	Single Nucleotide Polymorphism
SP	Study Partner
TBI	Traumatic Brain Injury
TMS	Transcranial Magnetic Stimulation
TRMDD	Treatment-Resistant Major Depressive Disorder
UADE	Unanticipated Adverse Device Effect
VAPAHCS	VA Palo Alto Health Care System

1 STUDY OBJECTIVES

1.1 Primary Objective

Test the hypothesis that participants who receive active ("real") rTMS will show more improvement in memory at the immediate post-treatment assessment than the placebo (sham) control group.

1.2 Secondary Objectives

(2a) **Assess the durability** of rTMS effects. To address Objective 2a, we will assess the extent to which rTMS-related improvements in memory are sustained at the 3- and 6-month follow-up points

(2b) **Examine effects related to the site of stimulation** (DLPFC vs LPC).
To quantify effects of rTMS treatment, MCI-relevant behavioral measures and resting-state functional MRI (rs-fMRI, aka task-free fMRI) data will be collected.
2.b.1. One set of analyses will be done to examine differences in behavioral outcomes related to the site of rTMS stimulation.
2.b.2. The second set of analyses will focus on indices of improved brain functional connectivity (derived from rs-fMRI) and plasticity (assessed by levels of BDNF).

(2c) **Explore patient characteristics** that could be useful in identifying who responds preferentially to rTMS or to a particular stimulation site. To address Objective 2c, regarding heterogeneity of response to rTMS, baseline functional connectivity, genetic, and selected clinico-demographic variables will be explored as potential moderators of response to rTMS.

2 BACKGROUND AND RATIONALE

2.1 Background on Mild Cognitive Impairment

The goal of this study is to test the efficacy of repetitive Transcranial Magnetic Stimulation (rTMS) as a treatment for Mild Cognitive Impairment (MCI). MCI an important public health concern due to its prevalence and risk of progression to dementia. Alzheimer's Disease is the most common underlying cause of dementia.

There are currently no effective treatments for MCI, aside from general health recommendations. As discussed in the NIH/NIA R01 application, the low efficacy of cholinesterase inhibitors is outweighed by their adverse effects (Cooper, Li, Lyketsos, & Livingston, 2013; Fitzpatrick-Lewis, Warren, Ali, Sherifali, & Raina, 2015; Raschetti, Albanese, Vanacore, & Maggini, 2007; Russ & Morling, 2012; Tricco et al., 2013). Systematic reviews of other interventions for MCI (Cooper et al., 2013; Fitzpatrick-Lewis et al., 2015; Rodakowski, Saghafi, Butters, & Skidmore, 2015) indicated that the treatment investigated was ineffective; or if the treatment showed promise of efficacy, the finding still needs to be independently replicated; or the clinical trial was underpowered (Cooper et al., 2013).

This clinical interventional study, originally proposed in response to NIH/NIA PAR-16-365 "Pilot Clinical Trials for the Spectrum of Alzheimer's Disease and Age-related Cognitive

Decline (R01)," is designed to provide key cognitive and other outcome data as to whether rTMS is a viable nonpharmacological intervention for treatment of MCI.

2.2 Study Rationale

Cognitive Efficacy of rTMS

rTMS has shown promise in improving cognitive function in patients with Alzheimer's disease (AD) dementia (Ahmed, Darwish, Khedr, El Serogy, & Ali, 2012; Cotelli et al., 2011; Cotelli et al., 2006; Cotelli, Manenti, Cappa, Zanetti, & Miniussi, 2008; Rabey et al., 2013; Rutherford, Lithgow, & Moussavi, 2015). As discussed in the NIH R01 application, these studies had limitations including small sample sizes, non-blinded control treatments, and collected limited outcome data. The limited follow-up data published so far suggests that five or more sessions of rTMS can produce significant benefits lasting up to 4 months (Ahmed et al., 2012; Cotelli et al., 2011; Rabey et al., 2013). Two meta-analyses have been conducted. One meta-analysis reported a Standardized Mean Difference (SMD) = 1.00, which is a relatively large effect size (based on seven rTMS studies with a total of 94 AD patients) (Liao et al., 2015). The second meta-analysis reported a SMD = 1.35 (Two NIBS methods were pooled based on six rTMS and five transcranial direct current stimulation studies) (Hsu, Ku, Zanto, & Gazzaley, 2015). After adjusting for potential publication bias, the mean effect size was 0.78, still a large and clinically meaningful effect (Cohen, 1977; Kraemer, 1992).

For MCI, we found only one rTMS experiment (Turriziani et al., 2012), one rTMS clinical trial (Drumond Marra et al., 2015), and one case report (Cotelli et al., 2012). In the clinical trial, which was sham-controlled and involved 34 MCI patients, half the patients received 10 Hz rTMS, applied over the left DLPFC for 10 weekday sessions (Drumond Marra et al., 2015). This rTMS treatment protocol significantly improved performance on the primary efficacy measure, the Rivermead Everyday Memory Test (Drumond Marra et al., 2015). The improvement in memory was sustained at the 1-month follow-up ($p = .03$; SMD = 0.78).

Together, these scant preliminary findings suggest that rTMS may enhance cognition in MCI patients. As in the case of AD dementia, it is unknown how long the effects of rTMS last. A rigorous pilot trial using sensitive methods is needed to evaluate the short-term efficacy of rTMS and duration of effects.

Therapeutic Rationale for rTMS as a treatment for MCI and AD spectrum disorders

AD leads to regionally specific synaptic loss due to a neurodegenerative cascade of processes involving "amyloid-β facilitated tauopathy" (LaFerla, Green, & Oddo, 2007; Nisbet, Polanco, Ittner, & Gotz, 2015; Sadigh-Eteghad et al., 2015). In patients with MCI, structural MRI studies reveal gray-matter volume loss in AD-vulnerable regions, in particular medial and posterior regions of the limbic lobe, and middle and inferior regions of the temporal lobe (Bakkour, Morris, & Dickerson, 2009; Convit et al., 2000; Desikan et al., 2008; deToledo-Morrell et al., 2004; Driscoll et al., 2009; Fennema-Notestine et al., 2009; Greene & Killiany, 2010; Kaye et al., 1997; Whitwell et al., 2008). Synaptic dysfunction or loss in AD-vulnerable regions plausibly underlies functional MRI abnormalities seen in resting-state networks (RSNs; aka intrinsically connected networks or ICNs).

According to a meta-analysis of rs-fMRI studies comparing aMCI to healthy controls, the most consistently significant regions that show loss of functional connectivity in aMCI are the posterior cingulate cortex (PCC: medial and right), the right angular gyrus, right

parahippocampal gyrus, and left fusiform gyrus (Lau, Leung, Lee, & Law, 2016), regions that are canonically accepted to be part of posterior Default Mode Network (DMN). As described in the NIH R01 application, an experiment in healthy younger adults provided proof of concept that rTMS can induce greater functional connectivity within the DMN (J. X. Wang et al., 2014) when delivered to the LPC over an area encompassing the angular gyrus.

While much remains to be learned regarding the mechanism of action of rTMS, rTMS has evidence of modulating brain networks in a relatively selective fashion depending on the site of stimulation. Thus, rTMS offers a neurocircuit-driven strategy for stimulating and targeting neural networks that likely underpin core deficits of amnestic MCI. rTMS may also have restorative effects, owing to the hypothesized effects of rTMS on long-term potentiation (LTP) and synaptic modification.

Pre-clinical animal and cell culture studies hold the most promising keys to understanding the mechanisms of action of neuromodulation. Pre-clinical studies of transcranial EMF treatment, another neuromodulatory intervention for cognitive decline due to AD, have been conducted by Arendash and colleagues (Arendash, 2016). These studies, using AD transgenic mice that overproduce Aβ, were able to show positive effects of EMF on measures of learning and memory, on Aβ plaque burden, as well as more general positive effects on brain function—mitochondrial function and neuronal activity measures (Arendash, 2016).

Evidence of disease-modifying actions of neuromodulation via noninvasive brain stimulation in human research would be a major step forward in the clinical development these noninvasive brain stimulation as a nonpharmacological treatment for MCI due to AD (Albert et al., 2011). If the current study provides a signal that rTMS favorably modulates brain networks affected in MCI, the next step in clinical development would the inclusion of AD-neuropathological biomarkers of treatment response in a longer clinical trial.

Scientific Motivation for studying effects of rTMS at two different cortical sites

Only two of the controlled rTMS trials in AD dementia and MCI targeted a site that is functionally part of the DMN. The majority of trials--without an explicit disease-relevant rationale--stimulated the DLPFC, the target site for treating major depression and likely to be a "node" withiin the Central Executive Network (CEN). It is not known whether the stimulation site used for treatment of depression—the DLFPC—is truly the ideal stimulation site for MCI / AD patients.

In younger and non-AD populations, there is experimental and clinical evidence that rTMS delivered to the right or left DLPFC region can improve network interactions between the CEN and DMN regions (Chen et al., 2013; Liston et al., 2014). Importantly, rs-fMRI studies of aging and the AD spectrum have revealed altered network interactions between the DMN and attention-related networks such as the CEN, which in turn correlate with lower cognitive performance (Grady, Sarraf, Saverino, & Campbell, 2016; Ng, Lo, Lim, Chee, & Zhou, 2016; K. Wang et al., 2007; P. Wang et al., 2015). Thus, stimulating the DLPFC using rTMS has potential to improve CEN:DMN interactions in AD and MCI.

By manipulating what cortical site is stimulated, this pilot project aims to gain novel insights as to how rTMS could improve brain network function in aMCI patients, laying the ground work for later-stage clinical trials. Ultimately, stimulating both cortical regions might provide superior clinical outcomes given the profound effects of AD on widespread interconnected brain regions. However, clearer understanding of how rTMS over a cortical

site leads to changes in behavior and brain function would be important in deciding whether one site is ideal and sufficient, or whether stimulating multiple sites could be superior.

As described below, this project is designed to provide data on the short-term efficacy of rTMS and its potential to improve memory, cognition and brain functioning in MCI. Ultimately, if rTMS treatment can be delivered optimally in a way that improves clinical outcomes in a sustained manner, this will be a significant advance for the treatment of MCI.

Empirical Basis for the Stimulation Parameters and Delivery Schedule

In this study, each participant will receive a total of 20 sessions of rTMS bilateral 10 Hz rTMS lasting 25 minutes per session. The stimulation parameters of this study were selected on the basis of a meta-analyses of rTMS studies targeting the AD dementia population (Liao et al., 2015), publications that presented safety and tolerability data (Nahas et al., 2004), and the clinical interventional research experience of our co-investigators and consultants to ameliorate the core symptoms of treatment-resistant major depressive disorder (TRMDD), mild AD dementia, and mild traumatic brain injury (mTBI). The empirical basis is summarized below:

Stimulation Frequency and Intensity. The decisions to use10 Hz rTMS and to stimulate both hemispheres is based on a recent meta-analysis of AD trials, which reported that the cognitive efficacy of rTMS was larger when high frequency (≥ 10 Hz) rTMS was used, and when stimulation was bilateral or to the right hemisphere (Liao et al., 2015). The decision to use an intensity of 120% magnetic field intensity relative to the participant's resting motor threshold (MT) is also based on a strategy to achieve efficacy in the older population without compromising safety. Early studies used lower intensity stimulation because of safety concerns at the time, which have now been alleviated with greater experience. This intensity is safe, tolerable, and has been necessary and sufficient to overcome the effect of age-related cortical atrophy (Nahas et al., 2004). Recent rTMS studies of cognitive enhancement that targeted the older population used intensity levels ranging from 90% MT to 120% MT, depending on the site selected for treatment stimulation (Hsu et al., 2015). 120% is the intensity used in the AD, mild TBI, and depression clinical trials, directed by our Co-Investigators, Drs. Jauhtai Joseph Cheng, Maheen Adamson, and Jerome Yesavage.

Stimulation Pattern and Session Duration: The 10 Hz pulse frequency will be patterned as a 4-second train (40 pulses) with an 11-second interval between trains, which is repeated over a period of 25 minutes (i.e. a total of 4,000 pulses per session: 40 pulses per train x 4 trains per minute x 25 minutes). Prior studies generally used 1,900 pulses or less per session, in line with 2009 safety recommendations (Rossi, Hallett, Rossini, Pascual-Leone, & Safety of TMS Consensus Group, 2009). The lack of serious adverse effects seen with 1,900 pulses has motivated clinical investigators focused on the target population of treatment-resistant major depressive disorder (TRMDD) to deliver an efficacious course of treatment safely, but in a shorter period of time. We note that MagVenture received 510(k) FDA clearance in June 2017 to use "... a range of inter-train intervals from 11 to 26 seconds" in delivering the 10 Hz / 3000 pulse, FDA cleared protocol for treatment of adults with TRMDD.

A 10 Hz 4-sec train, 10-sec ITI protocol that delivered a total of 4,000 pulses during a 23-minute session was used in the VA 9-site depression trial (VA CSP #556; PI: Yesavage), which completed data collection in 2016. Although detailed safety and efficacy data are not available as of August 2017, the CSP #556 PI and Co-Chair Mark George, MD state that no seizures occurred in CSP #556 (per email communicated to the PI and DSMB members). Study co-investigators, Drs. Cheng and Adamson, have adopted a 10 Hz 5-sec train, 10-sec ITI protocol for use in their currently ongoing rTMS clinical trials for treatment of cognitive impairment due to mild AD and mild TBI. The DSMB of the present trial has advised stricter adherence to the published safety table (Rossi et al., 2009). In summary, we have selected a 10 Hz 4-sec train, which is within the safety table, and an 11-sec ITI, which is 1 sec longer than that used in CSP #556.

Delivery schedule. Delivery of the study intervention will be scheduled as two rTMS sessions per treatment visit, with 10 treatment visits scheduled M-F during two consecutive weeks. This delivery schedule was documented to be safe and effective in a depression-treatment trial (Loo, Mitchell, McFarquhar, Malhi, & Sachdev, 2007) (10 Hz, 110% intensity, 1,500 stimuli per session). This "twice-daily" procedure is being used at our site by Co-Investigators Drs. Adamson and Cheng in two ongoing clinical interventional studies (10 Hz, 120% intensity, 4000 stimuli per session). From a patient's perspective, a twice-daily intervention that requires a 2-week commitment is likely to be more convenient than coming to a clinic M-F for 4 weeks, particularly if there is some flexibility for "make-up" sessions, e.g. when the participant needs to fulfill other commitments.

In summary, the 10 Hz stimulation protocol to be used in this study will consist of delivering up to 8,000 magnetic pulses per day, with a total of 80,000 pulses over 2 to 2.5 weeks. This is within the range of 60 to 90,000 total pulses that is delivered in FDA-approved rTMS treatment of TRMDD (e.g. 3,000 magnetic pulses per day, 5 days per week, for 4 to 6 weeks) and more than the 39,000 pulses delivered by the NeuroAD ™ Therapy System protocol (Rabey & Dobronevsky, 2016; Rabey et al., 2013). Our experience, based upon clinical research involving more than 60 AD and mTBI study volunteers, is that the stimulation protocol to be used in this study will be a safe, tolerable, and efficient means of providing noninvasive brain stimulation, provided that safety screening and other precautions are taken to minimize the risks of rTMS.

Summary of the known and potential risks of the rTMS study intervention:

The serious known and potential risks of rTMS are:

- Inadvertent induction of a seizure (less than 1 in 1000 patient exposures);
- In the absence of careful screening, ferromagnetic implants, objects or electromechanical devices such as pacemakers are serious risks

Other known and potential risks of rTMS are:

- Discomfort at the site of rTMS stimulation (15% of patients);
- Mild to moderate headaches (up to 30% patients), and the
- Possibility of temporary hearing loss if ear protection is inadequate.

For detailed information on risks of rTMS, see Study Protocol Section 7 "SAFETY ASSESSMENTS." See also, the original IRB protocol submission and informed consent form, approved by the Stanford IRB Panel 3, March 14, 2017.

3 STUDY DESIGN

Our hypotheses regarding the effect of rTMS on memory in persons with aMCI will be tested in a randomized, 2-stimulation-site, double-blind sham-controlled, 3 parallel-arm design, in which bilateral rTMS is delivered as: (1) real rTMS of the DLPFC, (2) real rTMS of the LPC, or (3) sham rTMS (evenly split between each coil location).

Note: All IRB-approved materials refer to the treatment groups as active "real" rTMS and inactive/placebo rTMS. In the study protocol, we use the more conventional terms, "active" and "sham" rTMS.

Overview of Measures. As shown in Table 1, behavioral and cognitive outcome measures will be collected at 4 timepoints: Baseline, Immediate post-treatment, and at two subsequent Follow-up visits at 3 and 6 months. Resting-state fMRI (rs-fMRI, aka task-free fMRI) scans will be acquired at Baseline and repeated Immediate post-treatment to examine the effects of rTMS on functional connectivity. BDNF levels will be measured twice, prior to the first treatment session and again during the last treatment visit. Genomic DNA will be collected at the first treatment session to examine heterogeneity of response to rTMS.

Table 1. Study Design

	Phase				
Screening	Baseline	Randomization	Treatment	Immediate Post-Treatment	Follow-up
6-week window	Day 0		Days 7 -37 (20 sessions)	7 ± 3 days after Session 20	3 & 6 mos post
In-person Visit	fMRI Behavioral & cognitive outcomes	[3 Arms]	DLPFC LPC Sham	fMRI Behavioral & cognitive outcomes	Behavioral & cognitive outcomes

Primary Outcome:

Memory performance at the end of the treatment phase, as assessed by the California Verbal Learning Test (CVLT-II; (Delis, Kramer, Kaplan, & Ober, 2000)) Trials 1-5 Total raw score.

Secondary Behavioral Outcomes:

Memory performance at the 3- and 6-month follow-up visits, as assessed by the CVLT-II Trials 1-5 Total raw score.

Depressive symptoms, assessed using the 15-item Geriatric Depression Scale (GDS; (Yesavage, Brink, & Rose, 1982)).

Everyday function, assessed using the Everyday Cognition Scale (ECog; (Farias et al., 2008)).

Other aspects of cognitive function will be assessed using: (a) a measure of global cognitive function, (b) subscores on the CVLT-II, and (c) objective indices of the major cognitive domains-- visuospatial episodic memory, language, visuoconstructional ability, speed of processing, executive function, visual-spatial orienting of attention, specifically:

- Montreal Cognitive Assessment (MoCA; (Nasreddine et al., 2005));
- CVLT-II; (Delis et al., 2000) selected subscores: semantic clustering, short-delay free recall; long-delay free recall, and recognition discriminability
- Brief Visuospatial Memory Test–Revised (BVMT-R) (Benedict, Schretlen, Groninger, Dobraski, & Sphritz, 1996)

- Rey-Osterrieth Complex Figure (ROCF). Copy task only (2 stimulus forms: original ROCF form and modified Taylor figure (Hubley, 2010; Hubley & Jassal, 2006);
- Category Fluency (Strauss, Sherman, & Spreen, 2006)
- Boston Naming Test (BNT) (Huff et al. (1986) two-equivalent forms version)
- Trail Making (Partington & Leiter, 1949; Reitan, 1958)
- Attentional Network Task (ANT) (Fan, McCandliss, Sommer, Raz, & Posner, 2002; Posner, 2012; Y.-F. Wang et al., 2015),

  (Note: Except for Fluency and Trail Making tests, all tests have validated alternate stimulus forms, in order to reduce the magnitude of practice effects. Fluency and Trails are included because they are widely used tests, and their brevity should not add substantial participant burden.)

Secondary fMRI and BDNF measures relevant to improved functional connectivity and plasticity. Resting-state fMRI (rs-fMRI, aka task-free fMRI) scans will be acquired at the Baseline and Immediate post-treatment visits to examine effects of rTMS on functional connectivity. Additionally, plasma levels of brain-derived neurotrophic factor (BDNF) will be measured before and at completion of treatment as a strategy to gain more information about mechanisms of action. BDNF expression in the brain plays a role in synaptic remodeling (McAllister, Katz, & Lo, 1999). It has been suggested that the longer-lasting effects of rTMS involve long-term potentiation-like (LTP-like) mechanisms (Hoogendam, Ramakers, & Di Lazzaro, 2010). Although a direct link between neuromodulatory stimulation, such as rTMS, and synaptic plasticity remains to be demonstrated, an rTMS-related rise in BDNF plasma levels would be consistent with an effect on brain plasticity.

Secondary measures relevant to heterogeneity of therapeutic response. Genomic DNA will be collected to examine heterogeneity of response to rTMS. For this project, three genotypes will be determined--Apolipoprotein E (APOE) ε4 ε3 ε2, *BDNF val66met*, and catechol-*O*-methyltransferase (*COMT*) *val158met* genotypes--and used in exploratory analyses of heterogeneity of response to rTMS. In addition, selected Baseline clinico-demographic variables and summary measures of functional connectivity, will be used in these exploratory analyses (See Section 9.5.2).

Study Location and Duration

The study will be conducted in an outpatient clinic setting at the VA Palo Alto Health Care System. The total duration of the study will be 5 years, with a 46-month enrollment period. During the first half of Year 5, follow-up visits of the last enrollees are to be completed. Each participant will be in the trial for a total of approximately 7 ½ months, which includes 4 to 6 weeks to undergo screening and baseline assessments, and 2 to 2.5 weeks to receive 20 treatment sessions. Each participant will be followed for 26 weeks post-treatment.

The study database will ultimately include data from 99 aMCI participants (33 per arm), with measures of cognitive efficacy, change in brain function, and predictors of response to rTMS, which will be analyzed as described in Section 9.5.

4 SELECTION AND ENROLLMENT OF PARTICIPANTS

Participants will be eligible to enroll in the rTMS study if, based on screening assessments, they have a clinical diagnosis of amnestic Mild Cognitive Impairment (aMCI) (Albert et al., 2011; R. C. Petersen, 2004) and they meet all of the following inclusion and exclusion criteria:

4.1 Inclusion Criteria

1. Age 55 – 90 years inclusive;
2. Diagnosed with amnestic Mild Cognitive Impairment (aMCI);
3. Stable medications (including any dementia-related meds) for at least 4 weeks prior to Baseline;
4. Geriatric Depression Scale score less than 6;
5. Ability to obtain a motor threshold, determined during the screening process;
6. Study partner available; living situation enables attendance at clinic visits;
7. Visual and auditory acuity adequate for neuropsychological testing;
8. Good general health with no diseases expected to interfere with the study, as determined by the referring Memory Clinic Physician or the rTMS Study Physician;
9. Participant is not pregnant or of childbearing potential (i.e. women must be 2 years post-menopausal or surgically sterile);
10. Modified Hachinski Ischemic score less than or equal to 4;
11. Agree to DNA extraction for single nucleotide polymorphism (SNP) genotyping;
12. Able to understand study procedures and comply with them for the entire length of the study.

4.2 Exclusion Criteria

A candidate will be excluded from the study if he or she meets any of the following exclusion criteria at Screening or Baseline:

1. Prior exposure to rTMS within the past 12 months;
2. Magnetic field safety concern such as a cardiac pacemaker, cochlear implant, implanted device in the brain (deep brain stimulation), or metal fragments or foreign objects in the eyes, skin or body;
3. Any significant neurological disease other than suspected incipient Alzheimer's disease;
4. Unstable cardiac disease or recent (< 3 months previous) myocardial infarction. Any significant systemic illness or unstable medical condition that could lead to difficulty with protocol adherence;
5. History of epilepsy or repetitive seizures, as determined by patient report or chart review;
6. History of a medical condition or current use/abuse of medications and substances that increase the risk of a seizure, specifically:

- Traumatic brain injury within 2 months that would increase the risk for seizure;
- Unable to safely withdraw, at least 4 weeks prior to Baseline, from medications that substantially increase the risk of having seizures (for example, theophylline, clozapine, and methylphenidate). See Appendix III. "List of Exclusionary Medications."
- Current or past history of a mass lesion, cerebral infarct, or other non-cognitive active neurological disease that would increase the risk for seizure.
- Stimulant abuse within the previous 90 days. Cocaine and abuse of amphetamine and methylphenidate are associated with an increased risk of seizures;

7. Major depression or bipolar disorder (DSM-IV) within the past 1 year, or psychotic features within the last 3 months that could lead to difficulty w/protocol adherence;
8. Taking sedative hypnotics or medications with anti-cholinergic properties and unable to withdraw at least 4 weeks prior to Baseline;
9. Current alcohol or substance abuse (not including caffeine or nicotine) within the past 1 year, as determined by chart review, participant or study partner report, or greater than "moderate" alcohol use defined by the Quantity-Frequency-Variability Index (Cahalan, Cisin, & Crossley, 1969);
10. Any contraindications for MRI studies, e.g. severe claustrophobia, weight above 350 lb maximum allowed by MRI scanner, pregnancy;
11. Participation in another concurrent clinical trial;
12. Inability or unwillingness of individual or legal representative to give written informed consent;

4.3 Study Enrollment Procedures

Recruitment strategies. (1) We will recruit participant in collaboration with the NIA-funded Stanford Alzheimer's Disease Research Center (ADRC) and the California-funded Stanford-VA AD Center. The two centers will enable us to minimize screen fails by referring participants who are likely to meet the study's eligibility criteria. The ADRC and California AD center both have ongoing outreach efforts in place to recruit participants of diverse ethnic and racial backgrounds. (2) Participants will also be recruited from local clinics and physicians. We estimate that the Study Coordinator will conduct 3 screens for every 1 that is eligible for randomization.

To augment the AD Centers' outreach efforts to older, ethnically diverse individuals, we have budgeted for direct-mail advertising that will be targeted to older ethnically diverse residents. Local area marketing companies have lists of individuals by age, by minority status, and by geographical area. Our collaborators at both Centers have found that these IRB-approved postcards are one of the most effective outreach strategies. More general advertising will include IRB-approved flyers posted throughout the Stanford campus, VAPAHCS and AD Center newsletters. Interested respondents will learn more about the study during a telephone interview. If the respondent has never had a MCI/dementia work-up, they will be invited to undergo the rTMS study's screening evaluation at the NIA

ADRC or the California AD Center to obtain a consensus diagnosis and provide educational services to the participant and family.

Overview of consent procedures. Our IRB approval includes a waiver of individual HIPAA authorization for recruitment and a waiver of documentation of consent for telephone pre-screening. Before any in-person screening procedure is performed, written informed consent will be obtained. A single consent form describes both the screening and study procedures.

Enough time will be allowed for the potential participant to make an informed decision, including time to discuss the study with the researchers and ask any questions they may have. If the prospective participant lacks adequate decision-making capacity, a designated legal representative will need to sign the form prior to the participant undergoing screening or other study procedures. Prospective participants will need to co-sign the consent form to indicate assent. Consent procedures are described more fully in Sections 11.1 and 11.2.

Documentation of eligibility and decision to enroll. A Phone Screening Log will be used to record information on each candidate who is pre-screened by telephone prior to scheduling Visit 1, the in-person screening visit. For each candidate screened in person, two forms will be completed to document eligibility and the participant's decision to enroll:

- The **Inclusion-Exclusion Form** will document study eligibility and reasons for ineligibility.
- The **Enrollment and Randomization Form** will document eligibility as a binary Y/N outcome. The form will also have a check-box variable for recording why an eligible candidate was not enrolled.

Randomization. Participants who meet all criteria for enrollment will be randomized in a 2:1 ratio to double-blind active treatment or sham at Baseline. Within the active and sham groups, subjects will be randomized in a 1:1 ratio to the two unmasked cortical sites. The method of random assignment to treatment (active vs. sham) and to cortical site (DLPFC vs LPC) will be determined by a computer-generated random sequence as explained in "Treatment Assignment Procedures 9.2.1."

For the purposes of the Data Analyses, there are 3 equally sized treatment groups of interest in this randomized trial:
(1) one-third of subjects will receive active DLPFC;
(2) one-third of subjects will receive active LPC; and
(3) one-third of subjects will receive sham (sham DLPFC and sham LPC are combined).

5 STUDY INTERVENTIONS

5.1 Intervention Device

Briefly, the TMS device system used in this study is comprised of the following components: MagPro X100 magnetic stimulator, the C-B60 coil (for MT determination), Coil Cooler unit, and motorized treatment chair. These are the major components of the MagVita TMS Therapy system, which is FDA cleared to market for the treatment of drug resistant Major Depressive Disorder.

For this double-blind controlled trial, the TMS Therapy System will be configured with three additional research components: a Coil Cool-B65 A/P (Active & Sham figure-of-eight coil), a TMS Sham Noise generator (for masking any difference in sound between real and sham), and a Localite TMS Navigator Spectra Edition system (for fMRI-guided placement of the rTMS coil).

5.2 Schedule and Procedures for Administering the Study Intervention

Schedule. The intervention will be administered as 20 weekday sessions during a period of 2 to 4 weeks, depending on scheduling constraints. Typically, a participant will have a morning session and an afternoon session. At the study physician's discretion and if the participant requests, up to three rTMS sessions can be scheduled per day with at least a one-hour interval between sessions.

Intervention sessions are scheduled as a 1-hour blocks, to allow time for late arrivals, for assessments of adverse effects, and for the 25-minute rTMS intervention. The intervention will be administered in outpatient clinic setting. In all, the participant will receive a total of 20 rTMS sessions.

Procedures for administering the rTMS Intervention

1. Motor Threshold Determination. Prior to administering the intervention, the participant's right and left motor threshold (MT) will be measured to standardize the stimulation intensity to be 120% of resting MT, i.e. 1.2 x MT). The 120% intensity will be specific to the MT of each hemisphere. The TMS Operator will determine the left MT at the end the screening visit, and the right MT at the beginning of Session 1 of the Intervention Phase. The TMS Operator will record the right and left MTs—and the corresponding stimulation intensities equal to 120% of right and left MT—on the participant's TMS Intervention Log (described in Section 6.2.3). The participant's right MT will also be recorded within the TMS system in association with the participant's randomization treatment number. (The device software allows for one MT to be saved per participant.)

Left and right hemisphere MT will be determined using electromyographic measurement (EMG) of the resting contralateral thumb (abductor pollicus brevis) using a mathematical algorithm (Maximum-Likelihood Strategy using Parameter Estimation by Sequential Testing; MLS-PEST) that efficiently and reproducibly arrives at the participant's MTs. As explained in the appended TMS Operator manual (Appendix IV. "TMS Quick Guide and TMS Operator's Manual of Procedures"), adapted from the CSP #556 Study Protocol (Yesavage, Fairchild, & George, 2015, November), the EMG and MLS-PEST features are incorporated within the TMS device and software. If the screening MT is so high that the TMS system lacks capability to deliver rTMS at an intensity of 120% MT, the participant will not be eligible to enroll in the study. Fewer than five percent of participants are expected to be ineligible due to an excessively high MT (see Table 2 of George et al., (2010) for a large-sample distribution of MT values). The remainder of this section gives an outline of the basic procedures for administering rTMS:

2. Neuronavigation to guide placement of the coil. The placement of the coil will be individualized to each subject, using the subject's MRI data collected at the Baseline visit. By using neuronavigation, we aim to optimize subjects' clinical responses (Bashir, Edwards, & Pascual-Leone, 2011; Fox, Buckner, White, Greicius, & Pascual-Leone, 2012; Fox, Liu, & Pascual-Leone, 2013), irrespective of whether the subject is assigned to DLPFC or LPC stimulation.

As discussed in the grant application, multiple sessions of rTMS, when applied to the DLPFC or LPC, can ultimately change DLPFC:PPC connectivity and LPC:PPC connectivity, respectively in TMRDD (Liston et al., 2014) and healthy young adults (J. X. Wang et al., 2014). Regarding aMCI, the most significant *x, y, z* coordinates of abnormal functional connectivity appear to be located near MNI coordinate: x = 6, y= -52, z=16, located in the PCC bilaterally. This coordinate was derived through an ALE meta-analysis of 21 rs-fMRI studies comparing aMCI participants to healthy older control participants (Lau et al., 2016). Therefore, in the present study, each subject's MRI data and a frameless stereotactic neuronavigation system will be used to position the coil where it is most likely to ultimately target the medial PCC, given evidence that this hub-like region of the brain is most consistently abnormal in aMCI.

The present study's procedures for neuronavigation will be performed in consultation with Dr. Michael Greicius and Dr. Keith Sudheimer of Stanford University School of Medicine. The general methods, which are based on prior work (J. X. Wang & Voss, 2015), are outlined in the grant submission, Section C.2.d.4 and in Appendix VIII. "Resting-state functional MRI Methods"). Briefly, the first step is to generate a seed-based connectivity map for each subject, using the subject's rs-fMRI Baseline data. In this step, the fMRI timeseries of the bilateral PCC region will be extracted as the seeds. Next, timeseries analyses will be used to locate bilateral LPC or bilateral DLPFC cortical targets, depending which of the two cortical site the subject has been randomly assigned to. If the fMRI data are too noisy due to excessive head motion, large framewise displacement, and/or low temporal signal-to-noise ratio, then the T1-weighted anatomical image will be used as a fallback. Review of data quality and selection of stimulation locations for individual subjects will be done in collaboration with Dr. Sudheimer. Dr. Sudheimer's image-processing pipeline and connectivity mapping procedures are currently being used in four ongoing rTMS projects at Stanford, each involving unique diagnoses or unique targets.

LPC: To locate the left and right LPC cortical stimulation sites, we will locate the clusters of voxels located within the left and right angular gyri (and near Brodmann Area (BA) 39/40) that show local maximum connectivity (i.e. are positively correlated) with the PCC seeds. The left cluster should also lie within a 15-mm radius of MNI coordinate: x= -47, y= -68, z=36; this coordinate is the peak location, across subjects, in the rTMS experiment that stimulated the left LPC to improve memory (J. X. Wang et al., 2014).

DLPFC: To locate the left and right DLPFC sites for stimulation, we will locate the clusters of voxels within left and right prefrontal gyri (near the juncture of BAs 9 and 46) that show local maximum negative connectivity (i.e. are inversely correlated) with the PCC seeds. The left cluster within the DLPFC should also lie within a 15-mm radius of the peak MNI coordinate (x= -38, y=44, z=26), which was found to be predictive of how effective rTMS was in treating clinical depression (Fox et al., 2012). This coordinate is also near the peak active cluster in fMRI studies of working memory in MDD (Fitzgerald et al., 2006), and shows significant inverse correlations with the PCC in resting-state fMRI (Greicius, Krasnow, Reiss, & Menon, 2003).

Following localization of the stimulation site (LPC or DLPFC), the bilateral locations for that subject will be marked in stereotactic space, transformed into original MRI space, and overlaid onto the structural MRI to aid in positioning the coil for the intervention. These locations will be marked on the subject's cap. Once the locations are marked, a coil template will be placed over each location to mark the location on the cap where the edge of the coil should be. As described in the TMS Operator manual (Appendix IV), cap fitting

and marking provides a way of reproducibly delivering rTMS across multiple intervention sessions.

3. Procedures for each intervention session. Except for positioning the rTMS coil over the assigned cortical site, the intervention procedures are identical for all treatment groups. The TMS Operator manual (Appendix IV) lists, step by step, the procedures for safety screening, for operating the rTMS device, placing scalp electrodes (see also Section 5.3 below), cap repositioning, positioning the participant for comfort and stable head position, delivering the treatment and monitoring for safety and tolerance to the procedure. The TMS Operator will manually set the amplitude to equal 1.2 times the MT of the to-be-stimulated hemisphere. For example, if the right MT = 65 and the left MT= 70, then the TMS Operator will manually set the amplitude to 78 (1.2 x 65) to stimulate the right, and to 84 (1.2 x 70) to stimulate the left.

As in Ahmed et al (Ahmed et al., 2012), rTMS will be applied over the right hemisphere first, immediately followed by rTMS over the left hemisphere. Rabey et al. (2013) also used a R, L order for the two bilateral regions. In both studies, all participants will receive the same order. It is beyond the scope of this study to investigate order effects. Given the absence of *a priori* data on this point, this study will follow the methods of the two prior studies (Ahmed et al., 2012; Rabey et al., 2013) and stimulate the right, immediately followed by the left.

TMS Stimulation Parameters for the active DLPFC and active LPC rTMS intervention groups will be: 10 Hz, 4-second train duration and 11-second inter-train interval. During each session, 2,000 pulses will be applied for each hemisphere (for a total of 4,000 pulses per session). These parameters will be pre-programmed in the device at the outset of the clinical trial, before the TMS operator begins administering the intervention.

Modifications and supportive care in case of difficulty tolerating the intervention. As noted previously, headache, scalp discomfort at the site of stimulation are relatively common, although tolerance to these adverse effects generally develops over the first 5 to 10 sessions of TMS therapy (Perera et al., 2016). Should a headache or site discomfort occur, these symptoms are expected to be self-treated, e.g. with ibuprofen. Discomfort can vary depending on intensity and location. For better tolerability, intensity can be ramped up from 80% to 120% during the first two sessions, and study staff may be able to move the coil position slightly if dental pain occurs.

5.3 Mechanisms for Masking (i.e., blinding) Study Interventions

The mechanisms used to create matched sensations for active and sham rTMS are the same as those used in currently ongoing VA-funded rTMS trials at this site and are very similar to those used in an NIMH-funded randomized rTMS trial for patients with depression (George et al., 2010).

The masking system is comprised of three components: (1) the Cool-B65-Active/Placebo Coil, which functions as both a real and sham coil; (2) scalp electrodes; and (3) a white-noise generator. The Active/Placebo coil has a symmetrical mechanical design and no labeling identifying the active and the sham side of the coil. Second, the subject wears scalp electrodes through which, in the case of sham assignment, a low voltage, low electric current (2–20mA at no more than 100V) is passed to mimic the sensation of receiving actual rTMS. Third, a white-noise generator is used to hide the click noise produced by

rTMS, by sending low-volume white noise to the subject's and the TMS Operator's headphones when magnetic stimulation pulses are initiated.

5.4 Concomitant Interventions

Currently there are no medications or interventions that have been FDA-approved or have proven effectiveness in MCI. Even so, some of the participants might be taking one or more medications for cognition. As listed below, FDA-approved medications for cognition will be permitted, as will certain types of antidepressants and other medications frequently prescribed to older adults.

5.4.1 Allowed Medications

Permitted medications* include:

FDA-approved medications for cognition (e.g. donepezil);

Estrogen replacement therapy

Stable doses of antidepressants lacking significant anticholinergic side effects will be allow if the participant's treatment for depressive symptoms is adequate and the participant does not have a history of major depression within the past 1 year;

*Medication dosing should be stable for at least 4 weeks prior to the Baseline visit.

5.4.2 Required Interventions

None

5.4.3 Prohibited Medications

Safety is the determining factor. Any medication that substantially increases the risk of having epileptic seizures will not be allowed while the participant is on study. Therefore, the herbal medicine gingko biloba, sometimes used as a supplement to for memory function, will be prohibited (Granger, 2001; Kupiec & Raj, 2005). Other medications that substantially increase the risk of seizures are: amphetamines, clozapine, modafinil, olanzapine, phenothiazines, pseudoephedrine and theophylline. See Appendix III. "List of Exclusionary Medications."

The washout period for all prohibited medications is ≥4 weeks prior to the Baseline visit.

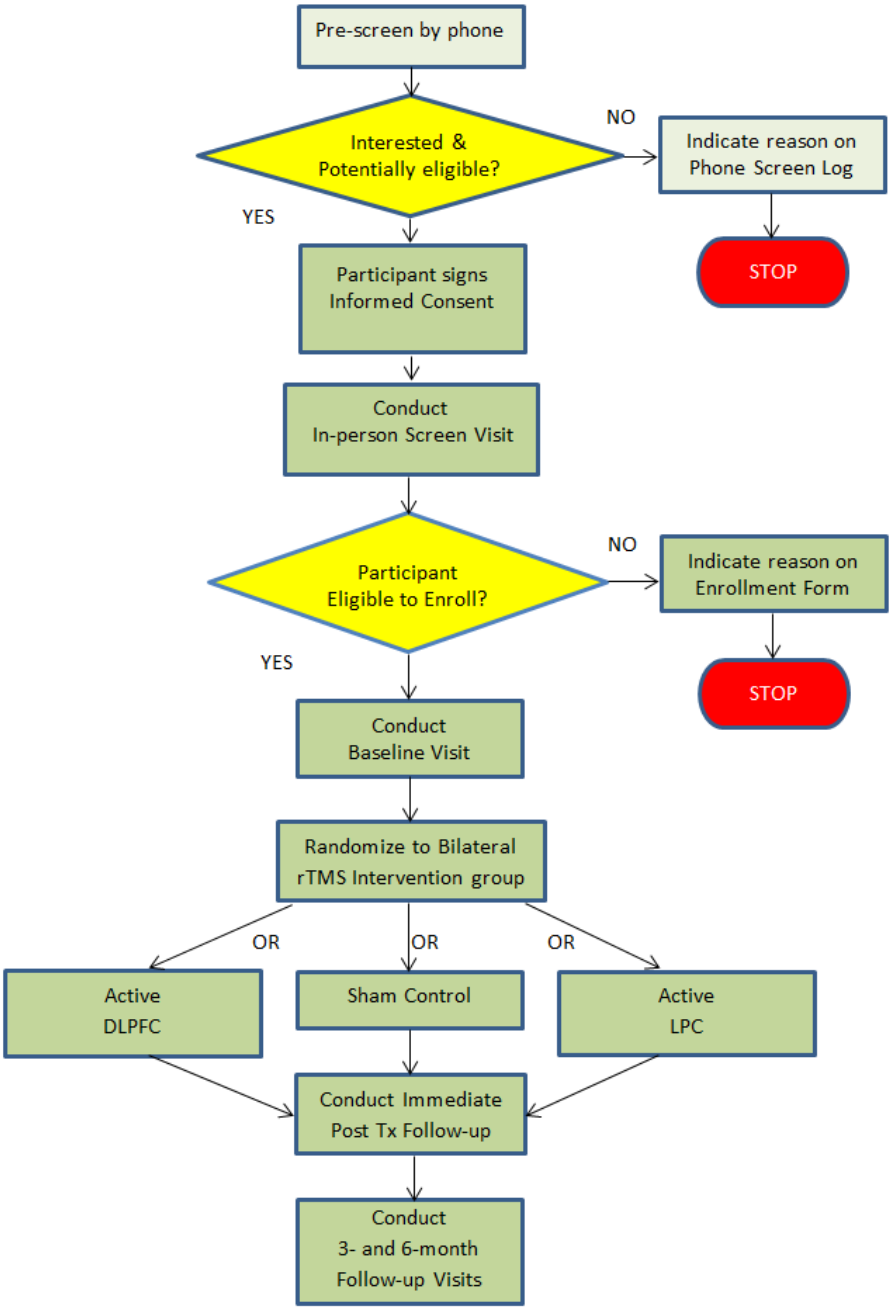
5.5 Adherence Assessment

Adherence will be defined as attending at least 80% of the twenty 25-min rTMS sessions (completed at least 16/20 sessions, or received at least 400/500 minutes of stimulation)

6 STUDY PROCEDURES

Figure 1 provides an overview of the flow of study procedures, from the initial phone pre-screen to a participant's completion of the study when the 6-month Follow-up is completed.

Figure 1. Study Flow Diagram



6.1 Schedule of Assessments

On the following page, **Table 2** lists the study assessments and their timing during the Pre-Treatment, Treatment, and Follow-up phases of the study. Following Table 2, we list each assessment that will be performed during these phases.

Table 2. Schedule of Assessments

	Pre-Treatment Phase		Treatment Phase			Follow-up Phase		
Visit Description	In-person Screening	Randomization & Baseline	Sessions 1-10	Sessions 11-20	Make-up sessions allowed through Day 37	Immediate Post-Tx	3-Month Post-Tx	6-Month Post-Tx
Visit Number	*1*	*2*	*3-7*	*8-12*		*13*	*14*	*15*
Timeline	Days -42 to -35	Day 0	Days 7-11	Days 14-18	Days 21-37	7 ± 3 days after S20	90 ± 14 days after S20	180 ± 14 days after S20
Informed Consent Form	**X**							
Demographics	**X**							
Vital Signs	**X**		**X**	**X**	**X**		**X**	**X**
Cognitive Change Index; MMSE, Logical Memory I	**X**							
CDR (Subject and SP)	**X**							
GDS, ETOH Questionnaire, Logical Memory II	**X**							
Medical, Psychiatric & Seizure Hx; Hach; PE/NE; Diagnostic Summary	**X**							
Concomitant Medications	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
MRI and rTMS Safety forms; Motor Threshold (MT)	Safety & Left MT	Safety	Safety & Right MT	Safety	Safety	Safety		
Inclusion/Exclusion Criteria	**X**							
Enrollment/Randomization		**X**						
MRI scan		**X**				**X**		
CVLT-II and Secondary Behavioral Assessments		**X**				**X**	**X**	**X**
Blood Sample (Genomic DNA and BDNF Biomarkers)			Session 1 DNA & BDNF		Session 20 BDNF only			
rTMS Intervention Log			**X**	**X**	**X**	**X**	**X**	
Adverse Events		**X**	**X**	**X**	**X**	**X**	**X**	**X**

6.2 Description of Assessments and Procedures

6.2.1 In-Person Screening Visit

Consenting Procedure

Before any in-person screening procedure is performed, informed consent will be obtained. A single informed consent form describes both the screening and study procedures. See Appendix II. "Informed Consent Forms."

The Study Coordinator or PI, in consultation with the Study Physician will conduct the consent process. The process will be implemented as described in Section 11.2 "Informed Consent Forms." To document that informed consent was obtained, a progress note will be entered in the participant's binder of study documents that contain PHI. The original signed consent form will be filed in a single Study Consent Binder to facilitate the annual audit of consent forms that are conducted by VA Research Administration. The participant will receive a copy of the signed consent form.

Note: If a change in the study procedures is required, a revised consent form will be submitted to the local IRB for review and approval. At their next clinic visit, study participants will be reconsented using the revised, approved consent form.

Screening Evaluation (Visit 1)

All screening evaluations to determine eligibility must be completed within 42 days (6 weeks) of the Baseline visit. Typically, the screening evaluation will be completed at a single clinic visit and eligibility will be determined within the next 2 weeks. The next 4 weeks is a waiting period to obtain a time slot for the Baseline MRI.

To assess whether an individual meets enrollment eligibility criteria, the following assessments will be performed:

The **Participant** will complete the following questionnaires

- Cognitive Change Index
- Geriatric Depression Scale (GDS 15-item)
- ETOH Use Questionnaire (note ETOH use will also be assessed during MD interview with SP)

The **Study Coordinator** will complete:

- Vitals Signs (Safety Measure)
- MMSE (Mini-Mental State Examination)
- Logical Memory I and II

The **CDR Rater** will complete:

- Clinical Dementia Rating (CDR) Scale

The referring **Memory Clinic Physician** or the **rTMS Study Physician** will perform the following medical evaluations

- Medical history form /Initial Health Assessment
- Physical, neurological examination
  (PE and NE within the past 12 months will be acceptable)

- Modified Hachinski Ischemic Score
- Concomitant Medications & Key Background Medications
- MCI Diagnostic Worksheet (normal, MCI and subtype, or dementia)
- Inclusion / Exclusion Criteria Form

The **TMS Operator** will administer the following:

- MRI (and rTMS) Safety Screening
- Motor Threshold (Left Hemisphere)

If the MMSE is less than 24, the Study Coordinator will alert the PI, who will decide whether the remaining screening evaluations should proceed, or whether to end the screening visit early and inform the individual that the study is not a good fit for them.

6.2.2 Enrollment, Randomization, and Baseline Assessments

Enrollment

Enrollment is defined in this study as the date when *all* of the screening criteria have been met *and* the previously consented individual agrees to participate. Typically, eligibility will be determined within 2 weeks of completing the screening evaluation; enrollment will occur as soon as the individual expresses willingness to participate.

The Study Coordinator will record the participant's eligibility status, willingness to enroll, and the enrollment date on the Enrollment and Randomization Form.

Randomization

The Data Manager/SAS Analyst will receive the Study Coordinator's emailed copy of the **Enrollment and Randomization Form**. The Data Manager will randomize the participant using the randomization method described in Section 9.2.1 "Treatment Assignment Procedures." Once the participant is assigned, the Data Manager will record the date of randomization on the form and return the form to the Study Coordinator for data entry. The Data Manager emails the following information to the TMS Operator and the MRI Data Analyst:

1. TMS Operator: receives the participant ID, the randomly assigned 6-digit treatment code, and the randomly assigned cortical site (DLPFC or LPC). The 6-digit code masks whether the assigned treatment is active or sham. (This code maps to the TMS device's pre-programmed table of treatment codes.) The site assignment is unmasked.
2. MRI Data Analyst: receives the participant ID and the randomly assigned cortical site assignment for use in subject-specific fMRI-guided neuronavigation of coil placement.

Randomization will occur at least 14 days before the initiation of study intervention.

As noted above, the time window from the beginning of Screening to the completion of Baseline Assessments is 42 days; the time window from the completion of Baseline to the initiation of the intervention is 7 $\pm$3 days. A 7-day interval between Baseline and initiation of the intervention is needed to allow time for subject-specific fMRI-guided neuronavigation of coil placement.

Baseline Assessments (Visit 2)

Baseline assessments are only performed for consented participants who have completed screening, have met all eligibility criteria, are willing, and have enrolled into the study.

All Baseline imaging and medical/cognitive assessments must take place within a 1-week timeframe. These Baseline assessments must be completed at least 7 days before initiation of the intervention. Typically, the Baseline assessments will be completed during a single visit, lasting 4 to 5 hours.

The following assessments will be performed at the Baseline Visit:

The **Study Coordinator** will complete:

- Concomitant Medications (update of previously recorded medications)
- Adverse Event Monitoring (to capture a new or a worsening ongoing condition)
- Repeat of MRI (and rTMS) Safety form
- MRI scan: 40 minutes of scan-time, which includes:
  - Scout and calibration scans
  - 3D T1-weighted anatomical scan
  - T2-weighted FLAIR (Fluid-Attenuated Inversion Recovery) T2 GRE (Gradient Recalled Echo)
  - ASL (Arterial Spin Labeling) perfusion MRI
  - Task-free/resting-state functional MRI (rs-fMRI) using Simultaneous Multi-Slice (SMS) acquisition)
  - DTI (Diffusion Tensor Imaging; 25 directions)

    <Rest Break>
- Cognitive Assessments - Order of Testing
  - Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005);
  - California Verbal Learning Test (CVLT-II) (Delis et al., 2000);
  - Brief Visuospatial Memory Test–Revised (BVMT-R) (Benedict et al., 1996)
  - Trail Making (Partington & Leiter, 1949; Reitan, 1958)
  - CVLT-II Long-Delay Free Recall and Recognition
  - BVMT-R Delayed Recall and Recognition

    <Rest Break: Snack or Lunch>
  - Boston Naming Test (BNT; Huff et al. (1986) 42 items, two equivalent forms)
  - Rey-Osterrieth Complex Figure copy task only (ROCF copy) (Hubley, 2010; Hubley & Jassal, 2006)
  - Category Fluency (boys' names; girls' names) (Strauss et al., 2006)
  - Attentional Network Task (ANT) (Fan et al., 2002; Posner, 2012; Y.-F. Wang et al., 2015)

The **Participant and Study Partner** will independently complete the Everyday Cognition (ECog) questionnaire (Farias et al., 2008).

The **Study Partner** will complete the Functional Assessment Questionnaire (FAQ) (Pfeffer, Kurosaki, Harrah, Chance, & Filos, 1982).

Brief Descriptions of Behavioral Assessments

Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005). The Montreal Cognitive Assessment test (MoCA) is, similar to the MMSE, a brief, 30-point cognitive assessment designed to detect participants at the MCI stage of cognitive dysfunction. This instrument has been shown to have adequate sensitivity and specificity in clinical settings to detect suspected MCI. The MoCA provides a brief assessment of global cognitive function.

California Verbal Learning Test-II (CVLT-II) (Delis et al., 2000), primary efficacy measure). The CVLT is a list-learning task that assesses multiple aspects of verbal learning and verbal episodic memory. List A of the CVLT-II contains 16 concrete words; four words each from four categories (animals, vegetables, ways of traveling, and furniture). List A is presented for 5 learning trials. After presentation and recall of another List (B), a short-delay free recall and cued recall of list A is performed. After a 20-minute delay filled with nonverbal testing, long-delay free recall and cued recall are assessed, followed by yes/no recognition of list A.

Brief Visuospatial Memory Test–Revised (BVMT-R) (Benedict et al., 1996)). The BVMT-R assesses visual memory. The BVMT-R has six alternate, equivalent forms. Each test form consists of a) 6 sets of geometric figures, each set arranged as a 2x3 array and printed on a page of the Recall Stimulus Booklet; and b) 12 recognition stimuli, each printed on a page in the Recognition Stimulus Booklet.

Trail Making Test, Parts A & B (Partington & Leiter, 1949; Reitan, 1958). These two tests progress from a numerical connect-the-dots puzzle to a more challenging alternation between alpha- and numerical order. Although both Parts A and B depend on visuomotor and perceptual-scanning skills, Part B also requires cognitive flexibility in shifting from number to letter sets under time pressure.

Boston Naming Test (BNT) Huff et al. (1986) 42-items, two-equivalent forms. The BNT assesses the ability to verbally name pictured objects. The subject is shown a series of line drawings and asked to name the object. If the correct name of the object is not produced within 20 seconds, then a semantic cue (e.g., "kind of a building" for "house") is offered. If the correct name of the object is not produced within the next 20 seconds, then a phonemic cue is provided. The test items become progressively more difficult (items are presented in order of decreasing frequency of the target word).

Rey-Osterrieth Complex Figure (ROCF) (Hubley, 2010; Hubley & Jassal, 2006); copy task only). The complete Rey-Osterrieth Complex Figure Test is designed to measure visuospatial constructional ability and visual memory. In this clinical trial, the Brief Visuospatial Memory Test–Revised (described below) has been selected for assessment of visual memory, and the ROCF copy task will be used to assess visuospatial constructional ability. The participant will be presented with the complex figure and asked to copy it.

Category Fluency (Strauss et al., 2006). This is a measure of verbal fluency in which the participant is asked to generate examples from a semantic category during a one-minute period.

Attentional Network Task (ANT) (Fan et al., 2002; Posner, 2012; Y.-F. Wang et al., 2015) (Y.-F. Wang et al., 2015). The ANT was developed by Posner and colleagues to provide reaction-time measures of the efficiency of alerting, orienting and executive attention. Posner has proposed that each attentional function is subserved by anatomically distinct networks in the brain (S. E. Petersen & Posner, 2012; Posner, 2012). The ANT requires

participants to determine whether a central arrow in a set of 5 arrows points left or right. The basic design of the ANT incorporates a combination of Posner's cued reaction time (RT) task (Posner, 1980) and the flanker task (Eriksen & Eriksen, 1974). Efficiency of orienting, alerting, and executive attention is assessed by measuring how response times are influenced by alerting cues, spatial cues, and congruent or incongruent flankers. Overall, the task has been deliberately kept short and simple so that it can be used with adults, children, monkeys, and patients with mild abnormalities of attention, and so that reliable estimates of the three attentional networks can be obtained within a half hour.

Everyday Cognition (ECog) (Farias et al., 2008). This instrument assesses for very mild functional impairment as may occur in MCI. The ECog is an informant-rated questionnaire, but participants will also be asked to complete a self-reported version of the same questionnaire. It looks at everyday function in seven key cognitive domains: memory, language, semantic (factual) knowledge, visuospatial abilities, planning, organization and divided attention. ECog correlates well with well-known established measures of functional status and global cognition. ECog can differentiate between individuals diagnosed with mild impairment in memory only and those mild impairment in several cognitive domains. ECog correlates weakly with age and education.

Functional Assessment Questionnaire (FAQ) (Pfeffer et al., 1982). The FAQ consists of 10 questions to ascertain the level of performance of daily function activities, including: paying bills; assembling tax records or other papers; shopping alone; playing a game or working on a hobby; keeping track of current events; understanding a TV program, book, or magazine; remembering appointments, family occasions, and medications; and driving or arranging to take public transportation. The four levels ranging from dependence or preparing meals. Each of the 10 items is scored as one of four levels of independence (normal=0, has difficulty=1, requires assistance=2, and dependent=3).

Geriatric Depression Scale Short Form (GDS) (Sheikh & Yesavage, 1986). The GDS Short Form is a self-report scale designed to screen for symptoms of depression in the elderly. Note: the GDS is collected at the Screening Visit and at all three post-intervention Follow-up Visits.

Clinical Dementia Rating Scale (CDR) (Morris, 1993). The CDR is a 5-point scale used to characterize level of functioning in six domains of cognitive and functional performance applicable to Alzheimer disease and related dementias. The six domains are: Memory, Orientation, Judgment & Problem Solving, Community Affairs, Home & Hobbies, and Personal Care. The information to make each rating is obtained through a semi-structured interview of the participant and a reliable collateral source, the Study Partner. In addition to ratings for each domain, an overall CDR score is calculated through the use of an algorithm; the overall scores are: 0 = Normal; 0.5 = Questionable Dementia; 1 = Mild Dementia; 2 = Moderate Dementia; 3 = Severe Dementia. As in ADNI, a clinical diagnosis of MCI requires an overall CDR score = 0.5. Note: the CDR is rated at the Screening Visit only.

6.2.3 Intervention Visits (Visits 3 – 12)

A participant will receive a total of 20 rTMS intervention sessions within a period of 2 to 2.5 weeks, depending on scheduling constraints. Typically, a participant will have a morning session and an afternoon session during a one-day clinical visit. Accordingly, 2

intervention sessions are recorded as a single "visit" and the visits are numbered from Visits 3 through Visit 12.

The first intervention session (Visit 3) needs to take place during a window of 7 ±3 days after the completion of the Baseline assessments. An Intervention session is scheduled as a 1-hour block to allow time for late arrivals, assessment of adverse effects, and for the 20-minute rTMS intervention. At the study physician's discretion and if the participant requests, up to three rTMS sessions can be scheduled per day with at least one hour between sessions.

To be fully adherent, the participant should complete 20 sessions within 30 calendar days.

The following assessments and procedures will be performed at the Intervention Visits:

First Intervention Session (am, Visit 3: *Overnight fasting is necessary*)

- Concomitant Medications (update of previously recorded medications)
- Adverse Events (to capture a new or a worsening pre-existing condition)
- Vital Signs
- Fasting Blood Sample (Genetic and BDNF Biomarkers), followed by breakfast
- rTMS Safety Questionnaire
- Motor Threshold Determination (Right Hemisphere), as described in Section 5.2*
- rTMS Intervention Log
- Administration of study intervention, as described in Section 5.2

  ** Motor thresholds will be rechecked at the study physician's direction at subsequent intervention sessions in the event a change in medication or a change in sleep pattern is reported by the participant and/or study partner. If a participant's subsequent MT is greater than the capacity of the TMS device, the subject will be treated at the maximum device capacity and tracked as such.*

Second Intervention Session (pm, Visit 3)

- Concomitant Medications
- Adverse Events
- rTMS Safety Questionnaire if more than 24 hours since the previous
- rTMS Intervention Log
- Administration of the study intervention

Intervention Sessions 3-18 (Visits 4 – 11)

- Concomitant Medications
- Adverse Events
- Vital Signs
- rTMS Safety Questionnaire
- rTMS Intervention Log
- Administration of the study intervention

Intervention Session 19 (am, Visit 12: *Overnight fasting is necessary*)

- Concomitant Medications
- Adverse Events

- Vital Signs
- Fasting Blood Sample (Genetic and BDNF Biomarkers), followed by breakfast
- rTMS Safety Questionnaire
- rTMS Intervention Log
- Administration of study intervention

Final Intervention Session 20 (pm, Visit 12)

- Concomitant Medications
- Adverse Events
- rTMS Safety Questionnaire if more than 24 hours since the previous
- rTMS Intervention Log
- Administration of the study intervention

Brief Descriptions of Assessments During the Intervention Phase

Concomitant medications and AE monitoring. Concomitant medication use (prescription, natural food products, and "over the counter") will be updated at each morning intervention session. During the intervention phase, medication use is recorded by the TMS Operator. The Study Physician will be apprised of changes in medications.

rTMS Safety Questionnaire. The items of the Safety Questionnaire cover changes in mental and physical health, sleep patterns, changes in prescribed medications, recent alcohol consumption, and recent use of non-prescribed drugs. The questionnaire is completed by the participant, in collaboration with the participant's study partner. See Section 7.1.4 "rTMS: Safety and AE Monitoring during the rTMS Study Treatment Sessions 1-20," for additional information on study staff responsibilities.

rTMS Intervention Log (adapted from VA CSP 556). The rTMS Intervention Log has 20 rows corresponding to 20 intervention sessions. Across the log sheet are a total of 13 columns. Columns 4-8 serve the purpose of prompting the TMS Operator to elicit medication changes, adverse events, hours of sleep, and use of alcohol and other recreational drugs *and* to notify the Study Physician in the event of a change in medication, change in sleep pattern, recent consumption of more than 1 alcoholic beverage, or use of street drug. Column 10 is used to record all MTs, ie., the right and left MTs determined at Visits 1 and 3, and all MTs determined thereafter, Column 11 is used to record the corresponding stimulation intensity. Columns 12-14 are used to record adherence-related information (Treatment Completed (Y/N), # of minutes of treatment completed, and comments as to why treatment was not completed or what adjustments were made to improve tolerability). These intervention-related data will be entered in the study database. See also Section 7.1.4 "rTMS: Safety and AE Monitoring during the rTMS Study Treatment Sessions 1-20."

Vital Signs. Vital signs, including temperature and weight, will be measured at all morning intervention sessions. Blood pressure, respiration, and pulse will be measured in the sitting position.

Fasting Blood Samples. Blood samples for genotyping, plasma-, and serum-derived biomarkers and will be collected at Intervention Session 1. Blood for plasma and serum biomarkers will be collected again at Intervention Session 19.

Procedures for Sample Collection. FASTING OVERNIGHT (MINIMUM 6 HOURS) IS REQUIRED. Only water is permitted until blood draws are completed. The study visit schedule includes time for breakfast after the fasting blood sample is drawn.

CONSENT TO DRAW BLOOD: When samples are collected, the Study Coordinator will confirm the subject consented to biomarker collection per prior written informed consent. If the participant consented to biomarker collection, but is unable to provide a blood sample, a saliva sample can be collected for the genetic research.

Table 3 summarizes the timing and sequence of sample collection, and the instructions for the immediate handling of samples.

Table 3. Biological Samples: Overview of Collection Procedures

IS 1 Tube Order	IS 19 Tube Order	Sample Uses	Tube Type	# Tubes x Volume (mL)	Total Amount (mL)	Instructions and
1	1	Whole blood: Genomic DNA banking Plasma: Analysis of pre-post levels of BDNF at Intervention Sess 1 &19 Buffy coat: Analysis of BDNF, APOE, COMT genotypes (Intervention Sess 1 only)	Purple top EDTA	1 x 10	10	Gently mix each tube by inversion, 10 -12 times;
2	2	Serum: Tissue Banking	Red top serum	1 x 10	10	Keep vertical and allow the blood to clot

* IS = intervention session

Blood samples will be centrifuged within 1 hour of collection. Samples of saliva, if collected in lieu of blood, need to be delivered within 1 week of collection.

Genetic and plasma-derived biomarkers. Genomic DNA will be extracted from the participant's sample for genotype determination of three genetic variants: *APOE* e2/e3/e4, *BDNF* Val^{66}Met (rs6265) and *COMT* Val^{158}Met polymorphism (rs4680) and for genetic tissue banking. APOE, BDNF and COMT genotypes will be used in exploratory analyses of heterogeneity of response to rTMS. The amounts of BDNF in plasma will be quantified from the participant's two samples that are collected at Intervention Sessions 1 and 19. Appendix V. "Sample Collection, Processing, Storage and Laboratory Protocols" further describes the procedures for obtaining, processing, and storing the samples, including details on required temperatures, location of storage, and labeling.

6.2.4 Follow-up Visits (Visits 13, 14 and 15)

Immediate Post-Treatment (Visit 13)

The Immediate Post-Treatment Visit 13 needs to occur 7 ± 3 days after the 20th and final intervention session.

- Each of the assessments and procedures performed at the Baseline Visit will be repeated at this visit. See Section 6.2.2.

- In addition, the participant and study partner will be asked to complete a brief questionnaire regarding their views on the acceptability of rTMS as a treatment.

Follow-up at 3-Month (Visit 14)

Visit 14 can be completed ± 2 weeks of the target date.

- Vital Signs
- Concomitant Medications
- Adverse Events
- Cognitive Assessment Battery, administered by the Study Coordinator
- ECog and FAQ Functional Outcome Questionnaires completed by Participant and/or Study Partner

6-Month Follow-up (Visit 15)

Visit 15 can be completed ± 2 weeks of the target date.

- Each of the assessments performed at the 3-Month Follow-up will be repeated.
- The Study Completion/Participant Withdrawal Form will be filled out to document the participant's completion of the study.

6.2.5 Study Completions, Withdrawals, Early Discontinuations and Terminations

Study Completions and Withdrawals

Visit 15 serves as the participant's final evaluation. If a participant withdraws from the study before Visit 15, every attempt will be made to collect the reason for the withdrawal of consent. If the withdrawal from the study is due to a Serious Adverse Event (SAE) or Unanticipated Adverse Device Effect (UADE), the participant will be followed by telephone at least every 30 days to monitor recovery or other outcome, until the SAE is resolved. If the SAE or UADE is not resolved, the participant will continue to be followed until 30 days after the End of Study date for that participant. The SAE form will be updated at each contact. Adverse Events (AEs), SAEs, and Adverse Device Effects (ADEs) are defined and discussed in more detail in Section 7.3.

Early Discontinuation of the Study Intervention

If a participant has a seizure during the intervention phase, the intervention will be discontinued immediately and completely. A VA Outpatient Neurology Outpatient Consult evaluation will be requested to provide an understanding of precipitating factors involved in the seizure, and whether follow-up care is needed. Study staff will then follow the participant by telephone to monitor recovery or other outcome, and report this SAE promptly per the appended protocol Appendix VI. "Seizure Protocol."

If it is determined that a participant is using medications or abusing substances that increase risk of having a seizure, the PI and study physician will evaluate the situation and determine if it is appropriate for the participant to continue the intervention. If the study physician or PI feels that it is in the participant's best interest to discontinue intervention because clinical judgment is that the intervention is not safe or tolerable for the participant, the intervention will be discontinued.

In each of these situations that lead to early discontinuation of the intervention, the participant will be asked to undergo the assessments that are normally administered during the Follow-up Phase (i.e. all assessments for Visits 13, 14, and 15).

Early Termination of Participation

Study enrollees are unlikely to be terminated from the study per se, unless an SAE occurs prior to the first rTMS session; or, if after enrollment, the investigators determine that the participant is ineligible.

Documentation of Study Status

Whenever a participant withdraws, is terminated, or completes Visit 15, the **Study Completion/Participant Withdrawal Form** will be filled out to formally document and track the enrollees' study status.

7 SAFETY ASSESSMENTS

7.1 Expected AEs; Safety screening; Modifications and management if an AE occurs

Expected adverse experiences, monitoring of participant safety, and modifications or management in case an AE occurs are described below for each study intervention, in order of procedural flow, starting with the Baseline MRI:

7.1.1 MRI

MRI has potential risks and discomforts but with careful screening of patients and adherence to manufacturer's operation instructions, many adverse events can be prevented (Shellock, 2001; Shellock, 2002).

MRI Safety Screening (Telephone pre-screening; Visits 1, 2, and 13)

Serious adverse events (SAEs) occur if ferromagnetic objects (particularly when implanted) or electromechanical devices such as pacemakers enter the MRI. To assess for MRI Safety, all subjects will be rigorously screened by MR personnel to be certain that they do not have any medical contraindications for MRI which include metallic foreign bodies in the brain or eye, or cardiac pacemaker. This safety screening is part of routine clinical practice at MRI centers and is performed before any subject is permitted to enter the scanning room.

The MRI Safety Form provides screening for factors that might affect the participant's comfort in the MRI environment. These factors include claustrophobia and back pain that interferes with their ability to lie supine for a prolonged period. Individuals who know they are severely claustrophobic would be excluded from participating in the study. People with weight or size above the size allowable by the manufacturer will not be scanned. While it is unlikely that women in this study will be of childbearing age, the formal, written screening form lists pregnancy as exclusion.

Safety Procedures and Modifications during an MRI Scan Session (Visits 2 and 13)

Anxiety. Any participant who experiences anxiety when placed into the MR scanner will be pulled out of the scanner, offered reassurance by the MR tech doing the scan, and offered the option of continuing or terminating the scan. There will be no attempt to

persuade participants to complete a scan that they are uncomfortable with. No sedative or anxiolytic agents will be given, as this is a voluntary research protocol.

Ear Protection. As with a routine clinical MRI, participants will wear MR compatible ear protection.

Incidental findings. The scans performed in this study are not optimized to find abnormalities. However, a Stanford radiologist will provide clinical reads of the anatomical scans and will also notify the PI whether an abnormal finding merits follow-up. In that case, the study physician will contact the participant regarding follow-up with the participant's physician. Image data collected in the course of the research project will not be made available for diagnostic purposes because they do not comprise a full clinical MRI series.

Investigational MRI. Some of the imaging software are not FDA approved, but have been tested for safety and are very similar to what is used regularly in clinical MR examinations. The MR personnel are highly trained in the set-up, monitoring, and use of this software.

Metal. There is a slight risk that someone will accidently bring metal into the MRI scanner room, which might be pulled into the MRI magnet and injure the participant. MR personnel work with the participant to make sure such objects are removed and stored in a locker before entering the magnet room.

Medical emergency. In the unlikely event of a medical emergency, the Stanford University Hospital's Emergency Department is a nearby, where medical intervention can be provided by Stanford Health Care Emergency Department staff. See Appendix VII. "MRI Emergency Protocol".

7.1.2 Neuropsychological testing and Questionnaires

The risks posed by neuropsychological testing are temporary fatigue and mild frustration.
Fatigue. Participants will be reminded that they are free to take a break if feeling tired.

Frustration. If the participant appears to be excessively frustrated, they may discontinue that test and be offered an easier one. If a participant is unwilling to continue a testing session, they will be given the option of continuing at a later time, ending the current session, or ending all participation.

7.1.3 Blood draws for analysis of biomarkers and genetics

Blood draw discomforts. There is a small risk of pain with a blood draw when the needle enters the skin. Bruising at the site of the needle stick may occur, but this is temporary. Some people may experience fainting or dizziness. To minimize these risks, experienced personnel at the VA Outpatient Surgical Center will handle all the blood drawing procedures.

Blood draw infection risk. Sterile conditions are maintained at the VA Outpatient Surgical Center. In the unlikely event of infection at the site of the needle stick, the participant will be treated at the study site.

Genetic testing concerns. It is possible that biomarker and genetic testing could cause some psychological stress in a few individuals. All participants will be informed that tissue samples and results of the biomarker and genetic testing will be labeled using a code that has no individual identification. Participants will be informed that we will not release

results of the genetic testing to them, to members of their family, physician, or other third party.

7.1.4 rTMS

TMS Safety Screening (Telephone pre-screen and Visit 1 in-person screen)

To minimize risks and AEs related to rTMS, the same ferromagnetic safety policies and procedures described above for MRI will be applied to rTMS safety screening. During the consenting and history taking process, we emphasize to participants that giving false information about their medical history, including past and present drug use, could have serious consequences for their health and well-being.

Individuals who might be prone to seizures (e.g. have had a recent traumatic brain injury, have history of a seizure disorder, need to be on medications that substantially increase the risk of having seizures, or abuse medications or use illegal substances that can increase the chance of having a seizure) will be excluded from this study, as documented on the Medical History and the Inclusion/Exclusion Forms.

Even though psychotic symptoms and suicidal ideation have been never described in normal subjects during or after rTMS, there is a report of one patient with major depressive disorder who developed delusions during rTMS treatment (Zwanzger, Ella, Keck, Rupprecht, & Padberg, 2002). In the present MCI rTMS study, participants with a Geriatric Depression Scale score ≥ 6 will not be eligible to enroll. (They will be referred for evaluation and treatment of their depressive symptoms.)

Safety and AE Monitoring during the rTMS Study Treatment Sessions 1-20

Eligible participants will be closely monitored by the study physician and the certified TMS operator during the intervention phase to minimize the risks associated with the rTMS intervention/device and to document adverse effects.

At the beginning of every morning treatment session, the participant will be asked about changes in mental and physical health, sleep patterns, changes in prescribed medications, recent alcohol consumption, and recent use of non-prescribed drugs, using the TMS Session Safety Questionnaire. This questionnaire will be used by the TMS Operator to probe an AE further. All AEs will be documented on the Adverse Event form.

In case of a safety concern, the Study Coordinator or TMS Operator will alert the Study Physician before proceeding with rTMS. If the participant reports having had less than one hour of sleep the previous night, the rTMS session will postponed until the participant's sleep pattern improves. During every session, the rTMS Operator will monitor the participant's ear protection, coil placement, and possible seizure activity. The log sheet explicitly reminds the Operator to notify the Study Physician in the event of a change in medication, change in sleep pattern, recent consumption of more than 1 alcoholic beverage, or use of street drug. Motor thresholds (MTs) will be rechecked at the Study Physician's direction. Rechecked MTs and power outputs will be documented in the participant's intervention log.

If an AE occurs: Risk management, modifications, and assessments

Discomfort. Should a headache or site discomfort occur, these symptoms are expected to be self-treated (e.g. with ibuprofen). Reported levels of discomfort often diminish in later sessions in the absence of over the counter (OTC) pain medications. If dental pain occurs,

study staff may be able to move the rTMS coil position slightly or provide a bite block to reduce or prevent the pain.

Ear Protection. To protect against possible hearing damage, participants will wear ear protection during rTMS sessions.

Syncope. Occasionally, syncope occurs with TMS, particularly in initial sessions. Staff will provide reassurance and monitor the participant for level of anxiety and psycho-physical discomfort. Premonitory complaints are: "I need to lie down", or "I need air" "I think I'm going to black out." Visceral distress, nausea, dizziness, pallor, and diaphoresis are other symptoms. Upward eye deviation, which is common in circulatory syncope, is rare in partial seizures unless there is progression to generalized convulsions. Because participants will be reclined in a chair during the stimulation procedure, the risk of syncope and a fall-related injury are lower. Study staff will be trained to be first responders to these unlikely events, and will know to call the VAPAHCS facility's E-Team as a proactive measure. Uncomplicated syncope *not* requiring hospitalization is normally considered an adverse event; the seriousness of the AE is a clinical judgement of the study physician.

Seizure. The VAPAHCS facility where the rTMS treatment sessions are performed is fully equipped to safely handle a seizure. The initial management of syncope and seizure is identical. Clinically, the cardinal feature that distinguishes syncope from seizure is rapid recovery of consciousness within seconds and not minutes. Delayed recovery of normal consciousness beyond 30 seconds mandates further evaluation and a neurological work-up. The participant will be treated at the study site for any medical or psychological consequences. Procedures for medical care, for documenting this study-specific SAE, and for monitoring the outcome of a seizure-related SAE are described separately in seizure safety protocol (see Appendix VI. "Seizure Protocol").

7.2 Summary of Safety Assessments

Safety will be measured based on the occurrence of serious adverse events, such as seizures, and syncope that results in hospitalization. Tolerability of rTMS will be based on the number of adverse events reported (grouped per side effect type) and number of dropouts due to AEs and other reasons during the intervention phase of the study.

All AEs will be documented on the Adverse Event form. If the AE is serious, then the SAE will be further documented on the SAE Form. Briefly, the forms contain the event description, severity, outcome, recovery date, and other follow-up information.

7.3 Adverse Events and Serious Adverse Events

Definitions for Adverse Events (AEs)

An **Adverse Event (AE)** is any untoward medical occurrence, including any abnormal sign, symptom, or disease *temporally* associated with study participation, whether or not considered related to participation in the research.

- An AE is deemed to be associated with the use of the study device if there is "a reasonable possibility that the experience may have been caused by the device."
- Chronic problems which are unchanged from baseline are not considered AEs. However, worsening of an ongoing condition would be considered an AE.

A **Serious Adverse Event (SAE**) is an adverse event that

- results in death

- is life-threatening, or places the participant at immediate risk of death from the event as it occurred
- requires or prolongs hospitalization
- leads to persistent or significant disability or incapacity
- is a seizure (Note: intervention-specific SAE definition)
- Is another condition which investigators judge to represent significant hazards.

An **Unanticipated Adverse Device Effect (UADE)** is an SAE caused by or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients.

Time span of collecting AEs and SAEs

Collection of all adverse events will begin at the time the participant signs the informed consent form and will continue throughout the 6-month post-intervention follow-up phase:

- At the Baseline visit, the participant and study partner (SP) will be asked about changes in medications, any other health or behavior changes, and any medical care received since the Screening visit;
- At each Intervention session, the participant will be asked about any side effects experienced. At each morning Intervention session, the participant will additionally be asked about any changes in medications, any other health or behavior changes, and any medical care received;
- At the Immediate Post-Intervention Follow-up visit, the participant will be asked about any side effects experienced since last seen, and any changes in medications, any or other health or behavior changes since the previous visit or phone follow-up, and any medical care received;
- At the 3- and 6-Month Follow-up visits, the participant will be asked about any changes in medications, medical care received, or other health or behavior changes since the previous visit or phone follow-up.

In summary, study staff will screen for new AEs/SAEs and review any unresolved AEs/SAEs at each encounter with the participant.

7.4 Reporting Procedures

Time lines for reporting AEs and SAEs

The PI and research team will notify the DSMB and the NIA Program Official of all SAEs (regardless of intervention vs. follow-up phase) by group email within 24 hours of study staff's knowledge of the event.

- The emailed, expedited report will be followed by a detailed, written initial SAE report as soon as possible.
- The PI is responsible for verifying that the report has been submitted and that that the DSMB Chair and NIA Program Official acknowledge receipt.

The PI and research team will report SAEs to the local IRB per Stanford University's HRPP Policy Guidance "Events and Information that Require Prompt Reporting to the IRB" GUI-P13 1/3 (see Appendix X).

All adverse events will be reported annually or more often to the DSMB, Stanford IRB, and NIA staff.

- The study's Data Manager will generate tabulations of all AEs (including SAEs and non-serious AEs) and present a summary of these to the DSMB and NIA staff on a schedule set by the DSMB.
- Aggregate summaries of SAEs and non-serious AEs will also be reported annually to the Stanford IRB.

Procedures and forms for recording AEs

Any new condition, recurrence of a previously resolved condition, or worsening of a pre-existing condition will be reported as an AE. (The Screening Visit Medical History Form provides a list of all pre-existing conditions and whether each condition is resolved or ongoing.)

All adverse events (including adverse device effects) will be recorded on the AE report form (based on NIH Template AE form 9a) and, if severe, on the SAE form (based on NIH Template SAE form 9b). Both SAEs and UADEs will be recorded using SAE form 9b. All adverse events will be assessed as "Not related," "Possibly related," or "Definitely Related" to the intervention or to other study procedures.

Decisions regarding AE relatedness and severity

The Study Physician will be responsible for decisions regarding relatedness and severity.

Assessment of study relatedness. Relatedness involves an assessment of the degree of causality between the study intervention and the event. Relatedness can be assessed by considering the following criteria:

- Previously reported with this treatment,
- Occurred after treatment began,
- Improved when treatment is withdrawn or a specific antagonist administered,
- Reappearance upon re-challenge,
- No alternative causes for the reaction,
- Increased severity when dose increased or lessened when dose decreased,
- Patient previously had similar reaction when exposed to the treatment, and
- Reaction confirmed by objective evidence.

Study-relatedness criteria.

- All adverse events or effects with a clear causal relationship to the intervention or to the procedures involved in the research should be considered "**Definitely related**".
- All adverse events or effects with a possible causal relationship to the intervention or to the procedures involved in the research should be considered "**Possibly related**".
- In general, if event is determined to be caused solely by an underlying disease, disorder, or condition of the subject, or due to other circumstances unrelated to either the research or any underlying disease, disorder, or condition of the subject, it would be considered "**Unrelated"** to participation in the research.

Study Staff Responsibilities

- During the pre- and post-intervention phase of the study, the Study Coordinator will be responsible for collection of initial AEs, follow-up of AEs (see Section 7.5) and completion of AE forms.
- The TMS Operator will be responsible for initial AE collection, follow-up, and form completion during the intervention phase.
- The Study Physician will be responsible for reviewing all AEs and for making decisions regarding relatedness and severity.
- The PI will be responsible for reviewing the AE forms for completeness and accuracy, for monitoring the AE data to avoid double capture of AEs, and for monitoring charts and CRFs for documentation of the physician's review of AEs.

7.5 Follow-up of Adverse Events

All AEs will be followed until resolution, or until the patient's participation in the study ends. For a participant who ends study participation prior to the 3-month follow-up visit (Visit 14), unresolved SAEs/UADEs will be monitored and reported for 30 days after the date the participant was last-seen.

An AE will be considered "**resolved**" when one of the following criteria are met:

- Health has returned to baseline status or applicable variables have returned to normal.
- The event has stabilized and the study staff expect no further improvement or worsening of the event.

If the Adverse Event does not resolve and it has been determined that the condition is stable or chronic, then the event can be considered "resolved with sequelae".

The study staff are also responsible for following up on AE/SAE information that was initially incomplete. Whenever new information about an SAE is obtained, the staff is responsible for reporting the follow-up information as soon as it becomes available. Examples of incomplete AE/SAE information that may require follow up:

- An event for which complete information was not available at the time of reporting to the DSMB or NIA Program Official.
- Update or new information related to an event that was previously reported (e.g. receipt of hospitalization records, clarity from study participant on event details).

7.6 Safety Monitoring and other DSMB Reporting

The PI will be responsible for ensuring participants' safety on a daily basis. The Data and Safety Monitoring Board (DSMB) will act in an advisory capacity to the NIA Director to monitor participant safety, evaluate the progress of the study, to review procedures for maintaining the confidentiality of data, the quality of data collection, management, and analyses. The DSMB will also determine when they should be un-blinded to treatment assignment for the reviewing of AE data and evaluating whether the aggregate AE information may also qualify as a UP. The DSMB will advise the PI concerning whether the study should continue or be stopped for safety reasons.

DSMB will meet twice annually, typically by teleconference call to review study progress, data quality, and participants' safety. The DSMB may decide to meet less frequently (such

as annually) and may receive a data report for their review in-between meetings. The DSMB will discharge itself from its duties when the last participant completes the study.

Open-Session Reports to the DSMB will include information on: (1) recruitment and overall study status; (2) participants descriptive information; (3) safety information, and (4) information on study quality. The contents of the report will be based on the NIH Single-site Open DSMB Reports Templates. Appendix IX "Data and Safety Monitoring" provides an outline of the various tables and charts that the PI proposes to provide to the DSMB. For example, a recruitment-related table will show the reasons for screen failures, including any refusals to donate blood or saliva for DNA extraction.

For Closed-Session reports, the Study's Data manager will generate AE reports using modified NIA templates with information reported by blinded treatment group (A, B, C). The final content and format of the reports for both the open and closed sessions will be determined by the DSMB. Throughout the trial, the DSMB may request changes in the content or format of the reports.

Special Procedures for the Monitoring of Seizures

As addressed in the rTMS Safety Section 7.1.1, participants will be closely monitored by the study physician and the certified TMS operator during the intervention phase to minimize the risks associated with the rTMS intervention/device. In the unlikely event that a seizure occurs, the hospital where this rTMS study will be conducted is fully equipped and staffed to respond to a seizure. The study staff will be trained as first responders, and trained to carry out the "Seizure Protocol" previously developed by the CSP 556 investigators (see Appendix VI). Procedures for medical care, for documenting and reporting this study-specific SAE, and for monitoring the outcome of a seizure-related SAE are described separately in the seizure safety protocol.

8 INTERVENTION DISCONTINUATION

8.1 Permanent discontinuation of the study intervention

The study intervention will be discontinued if:

- A participant has a seizure;
- There are signs or reports of inability to tolerate the intervention. Specifically, the participant will no longer continue with the intervention if the participant either reports or indicates upon questioning that a side effect (such as a headache) is not well tolerated despite self-treatment (e.g. severe in intensity and persists beyond the first week of treatment), or if the study physician feels it is in the participant's best interest to discontinue with the intervention.
- Or, any other health or safety concern that contraindicates continuation, based on the judgment of the study physician.

Continued follow-up will occur in each of these cases. The participant will be closely monitored and treated for any medical or psychological consequences. The Study Coordinator will be responsible for phone follow-ups to check on the participant's well-being and to collect follow-up AE information.

Such participants will be encouraged to return for all three post-intervention follow-up evaluations (Visits 13, 14, and 15). Except for the MRI scan (Visit 13), all other outcome

measures, safety assessments, and AE information would be collected at the three follow-up visits.

8.2 Temporary discontinuation of the study intervention

The intervention will be temporarily discontinued in case of a concern regarding safety or intolerability to rTMS.

Recognized safety concerns for eligible participants during intervention are:

- Insufficient sleep;
- Use of substances or medications that increase seizure risk.

Tolerability concerns include:

- In case of headache or site application discomfort or other AE, the intervention can be temporarily discontinued either at the request of the participant or based on a physician's recommendation.

Modifications to the intervention schedule. In the event of a safety concern, the Study Coordinator or TMS Operator will alert the Study Physician before proceeding with rTMS. If the participant reports having had less than one hour of sleep the previous night, the rTMS session will postponed until the participant's sleep pattern improves. If it is determined that a participant is using or abusing substances or medications that increase risk of having a seizure, the Study Physician and PI will evaluate the situation and determine if it is appropriate for the participant to continue.

While a participant is temporarily discontinued from receiving the intervention, the Study Coordinator will be responsible for phone follow-ups to check on the participant's well-being and, if applicable, to collect information regarding resolution and/or occurrence of adverse events.

8.3 Replacement Subjects and Voluntary Withdrawals

Replacements. In the event of an SAE prior to the Baseline Visit or a medical emergency during a Baseline MRI, (i.e. prior to randomization), the intervention and study assessments will be canceled. Such a participant would continue to be followed to monitor recovery; however, active participation in the study would end for the participant's safety, and because of unstable or uncertain health status. (See also Appendix VII. "MRI Emergency Protocol" and Section 7 above.) Another subject will be enrolled to replace that participant.

Voluntary withdrawals. Subjects may withdraw voluntarily from participation in the study at any time and for any reason. If voluntary withdrawal occurs during the intervention phase, the participant will be encouraged to return for all three post-intervention follow-up evaluations (Visits 13, 14, and 15). Except for the MRI scan (Visit 13), all other outcome measures, safety assessments, and AE information would be collected at the three follow-up visits. If an AE or SAE begins during the intervention phase and the participant decides to withdraw, the Study Coordinator will continue to do phone follow-ups to check on the participant's well-being and to collect follow-up AE information.

9 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

This is a double-blind, randomized, 2-stimulation-site, sham-controlled parallel group design of rTMS treatment to either bilateral DLPFC or LPC. The parallel groups design avoids potential carryover effects of active rTMS treatment to other treatment conditions within the same subject. The length of an appropriate washout period for rTMS has not been established for this rTMS intervention protocol in this population.

Primary Hypothesis

The primary hypothesis is that participants receiving active ("real") rTMS will show more improvement in memory at the immediate post-treatment assessment than the placebo (sham) control group. The sham group is comprised of all subjects assigned to the sham group, regardless of the position of the sham coil.

Testing the primary hypothesis involves two statistical tests: Test 1 will compare Active DLPFC to sham; Test 2 will compare Active LPC to sham.

For these tests, memory is measured by the CVLT-II Trials 1-5 Total raw score. This outcome measure has excellent retest reliability (Total and Delayed: $r > .75$), diagnostic validity (Rabin et al., 2009) (Silva et al., 2012), and normative data on a representative sample. The CVLT, which is comprised of 16 concrete words presented for 5 learning trials, helps achieve a wide range of scores that are neither at floor nor at ceiling level (Ellis et al., 2009; Karrasch, Sinerva, Gronholm, Rinne, & Laine, 2005; Ribeiro, de Mendonca, & Guerreiro, 2006). An additional advantage of the CVLT-II is the availability of alternate test forms.

Secondary Analyses

This study, was originally proposed in response to NIH/NIA PAR-16-365 "Pilot Clinical Trials for the Spectrum of Alzheimer's Disease and Age-related Cognitive Decline (R01)." In addition to testing the primary hypothesis to learn whether rTMS is a viable nonpharmacological intervention for treatment of MCI, this study was designed to address essential questions of durability, choice of site, and prediction of response. Information gained from this study will inform efforts to optimize rTMS effectiveness and pave the way for further clinical development. From this perspective, we plan to examine durability of rTMS over the 6-month follow-up, and to describe effects of rTMS on secondary cognitive and behavioral outcomes, as described below:

(Grant Aim 2a) Assess the durability of rTMS effects: The primary efficacy measure, the CVLT-II Trials 1-5 Total raw score will be analyzed for effects of rTMS on memory at 3- and 6-month post-intervention. Our working hypothesis is that an effect of rTMS on memory will be sustained up to 3 months.

(Grant Aim 2b.1) Examine behavioral differences related to the site of brain stimulation: The secondary behavioral outcomes will be analyzed in longitudinal data analyses with respect to the site of active stimulation (DLPFC or LPC). The secondary behavioral outcomes of most interest are selected sub-scores of the CVLT-II.

- Because the DLPFC and LPC have distinct roles in memory encoding and delayed recall (Long, Oztekin, & Badre, 2010), our working hypothesis is that DLPFC stimulation could result in a higher level of semantic clustering compared to LPC

stimulation. By contrast, LPC stimulation could result in higher recall, assessed by CVLT-II short- and long-delayed recall scores. An rTMS-induced increase in semantic clustering would be a positive outcome in MCI because older adults who showed more semantic clustering on the CVLT-II were more cognitively stable over time (McLaughlin et al., 2014). An rTMS induced increase in delayed recall would also be clinically important.

As part of addressing secondary Aim 2b.1, effects of rTMS on other secondary outcomes will be described. These outcomes include depressive symptoms, objective assessments of global cognitive function, visuospatial episodic memory, language, visuo-constructional ability, orienting of attention, information processing speed, executive function, and self-/partner-reported assessments of everyday cognitive functioning. All measures have demonstrated re-test reliability and construct validity. These secondary outcomes (which are described in Section 6.2.2) are listed in Section 9.4.2 below.

(Grant Aim 2b.2) Changes in brain function related to the site of brain stimulation. This study is designed to provide novel information about the therapeutic mechanisms of rTMS in the target population. Resting-state fMRI scans will be acquired at the Baseline visit and the Immediate Post-Treatment visit to examine effects of rTMS on brain functional connectivity. Additionally, plasma levels of brain-derived neurotrophic factor (BDNF) will be measured before and at completion of the rTMS intervention.

- Our working hypothesis is that BDNF levels will increase more in either active rTMS group, compared to that in the sham group.
- Our working hypothesis is that rTMS will beneficially modulate functional connectivity within and between large-scale networks that are abnormal in MCI. Two analyses will be performed: (1) The aim of one set of analyses is to learn the extent to which rTMS can restore connectivity within regions of the Default-Mode Network (DMN), especially to the hypo-connected PCC; (2) The aim of the second set of analyses relates to between-network connectivity. We will examine if rTMS reduces abnormally strong functional connectivity between the Central Executive, and Default-Mode Networks (CEN and DMN), as has been found preliminarily in rTMS studies on ameliorating depressive symptoms in TRMDD and executive dysfunction in mild TBI. Functional connectivity metrics are outlined in Section 9.4.2 "Secondary neuroimaging outcomes." Analyses are outlined in Section 9.5.2 "Secondary Analyses."
- As part of addressing secondary Aim 2b.2, we will explore the extent to which rTMS-induced changes in functional connectivity correlate with changes in selected behavioral variables, e.g., is the amount of reduction in functional connectivity between the CEN and DMN associated with improvement in executive function?

(Grant Aim 2c) Heterogeneity of response to rTMS. We expect that baseline clinico-demographic characteristics, baseline connectivity, and genetic variants may help explain individual differences in responsiveness to rTMS, either generally, or to a particular rTMS site. Selected baseline variables relevant to explaining heterogeneity of response are outlined in Data Analysis Sections 9.5.2.

9.2 Sample Size and Randomization

Power to test the primary hypothesis. We have powered the proposed study to detect a moderately large effect size (Cohen's d = 0.80) of either rTMS treatment on the primary outcome. Moderately large effect sizes of 1.0, 0.80, and 0.80 were reported in two meta-analyses of rTMS studies in AD (Liao et al., 2015) (Hsu et al., 2015) and one rTMS trial in MCI (which used unilateral rTMS (Drumond Marra et al., 2015), deemed suboptimal by (Liao et al., 2015)). Our proposed design is estimated to have 80% power to detect an effect size of 0.8, for a 5% two-tailed test., with a multiple testing penalty for 2 tests.

Attrition and the test of the primary hypothesis. The attrition rate in Dr. Adamson's rTMS TBI trial at our site has been 0% so far. The rate of attrition in the rTMS MCI trial (Drumond Marra et al., 2015) due to all reasons was 6%. Based on these rates of attrition, we do not expect attrition to substantially reduce power or the interpretation of results. If a participant in the present study discontinues the intervention early, we will encourage the participant to undergo all post-intervention assessments that are normally administered during the Follow-up Phase (Visits 13, 14, and 15). If there are baselined participants who have missing outcome data, we will perform and report sensitivity analyses that include participants with missing data, and make plausible assumptions about their outcomes based on the observed data. Additionally, the total minutes of rTMS received by each participant can be used as a covariate in the data analyses.

Attrition and secondary data analysis of behavioral outcomes. For the durability analysis of rTMS effects, mixed-effect growth curve analyses will be used, which enables full utilization of repeatedly measured outcomes and minimizes bias if subjects drop out during the extended follow-up period of the study (Singer & Willett, 2003).

Likelihood of obtaining other useful secondary results. In these secondary analyses, the proposed sample size will provide 80% power to detect a large difference (d = 1.00) related to the site of stimulation. For all analyses, we will convey practical significance by reporting effect sizes and confidence intervals, in addition to reporting statistical significance.

9.2.1 Treatment Assignment Procedures

Participants will be randomized to one of three treatment groups: (1) active rTMS of the DLPFC, (2) active rTMS of the LPC, or (3) sham rTMS (evenly split between each coil location). An adaptive randomization scheme will be used so that equal numbers of participants will be randomized to each of the 3 treatment groups within blocks of every 6 participants. For each block, 4 active and 2 sham treatment numbers will be randomly assigned. To ensure proper allocation of participants, a block of 6 participants will consist of: 2 active DLPFC, 2 active LPC, 1 sham DLPFC and 1 sham LPC.

The treatment numbers are non-sequential, and a 6-digit number is assigned to each participant. This unique 6-digit number will be key entered into the TMS device interface, whose programming enables the device to deliver the appropriate treatment (active or sham) to that participant.

Masking. To ensure appropriate masking for the study, the Database Manager/SAS Programmer performs the randomization of each participant to treatment and maintains the randomization codes. The Database Manager will store the randomization codes in an encrypted restricted-access file on the server. Only the Database Manager will know the link for randomization. To prevent unplanned breaking of randomization codes, the

Database Manager will utilize codes to refer to treatment groups, and maintain the link of these codes to the actual treatment groups in a separate file.

Unmasking. If a participant were to experience an SAE during the intervention phase, unmasking of that participant's treatment is permitted only if knowledge of the participant's treatment assignment is necessary to protect patient safety. The DSMB will determine when they should be unmasked to treatment assignment for the reviewing of adverse event data.

9.3 Interim analyses and Stopping Rules

There is no planned interim analysis for this single-site project. The DMSB or NIA will determine if a planned interim analysis should be conducted. If the DSMB requests a detailed safety review of SAEs or severe AEs by group, then based on that review, the DSMB or NIA Officer will determine what steps will be taken.

9.4 Outcomes

Outcome measures will be collected by blinded staff (study coordinator, imaging analyst, laboratory staff), and analyzed at study completion by the Database Manager under the supervision of the Ph.D. biostatistician.

9.4.1 Primary outcome

Primary outcome is the California Verbal Learning Test (CVLT-II) Trials 1-5 Total raw score (possible range 0-80), assessed at Visit 13 (immediate post-treatment).

The CVLT-II is also assessed at Visit 2 (Baseline) and at Visits 14 and 15. As described in Sections 9.4.2 and 9.5. these scores will be used as the baseline covariates and secondary outcomes.

9.4.2 Secondary outcomes

a) Secondary behavioral outcomes (assessed at Visits 2*, 13, 14 & 15)

- Depressive symptoms: 15-item Geriatric Depression Scale (GDS), Total score (0-15)
- Everyday functional outcomes: Everyday Cognition Scale Total score (39-156) and Functional Activities Questionnaire Total score (0-30)
- Global cognition: Montreal Cognitive Assessment Total score (0 to 30)
- Verbal episodic memory: CVLT-II Semantic clustering (chance-adjusted) Trials 1-5 (0-80) and CVLT-II Short-delay free recall correct (0-16)
- Visuospatial episodic memory: Brief Visuospatial Memory Test–Revised (BVRT) Trials 1-3 Total raw score (0-36)
- Language: Category Fluency Total score & 42-item Boston Naming Test Total score (0-42)
- Visuoconstructional function: Rey-Osterrieth Complex Figure, Copy score (0-36)
- Speed of processing: Trail Making Test, Part B, number of seconds to complete and the Attentional Network Task (Alerting) correct reaction time (RT) (msec)
- Executive function: Attentional Network Task (Executive) correct RT (msec)
- Visuospatial orienting: Attentional Network Task (Orienting) correct RT (msec)

*GDS is assessed at the time of screening (Visit 1) because the GDS is an eligibility criterion. The visit 1 GDS score will also be treated as a Baseline score.

b) Secondary neuroimaging outcomes (assessed at Visits 2 and 13)

- Functional connectivity metrics (derived from the pre- and the post-intervention rs-fMRI scans) will be computed with respect to:
  - Connectivity within the DMN, and
  - Connectivity between the DMN and the CEN.
- Analyses are outlined in Section 9.5.2 "Secondary Analyses."

c) Secondary biomarker outcome (assessed at Visits 3 and 12)

- Plasma levels of BDNF will be measured from fasting blood samples that are collected at the first and last morning intervention sessions of Visits 3 and 12.

9.5 Data Analyses

9.5.1. Primary Hypothesis Testing

- Analysis: Test the hypothesis that active rTMS (to either stimulation site) is superior to sham in improving memory performance, as observed at the immediate post-treatment visit.
- Method: Analysis of Covariance (ANCOVA)
- Population: Intention-to-treat (ITT), defined as all randomized patients who started at least 1 treatment session.
- Independent variable: rTMS Treatment group
  - ANCOVA 1: active DLPFC vs sham
  - ANCOVA 2: active LPC vs sham
- Dependent variable: Primary outcome, i.e. CVLT-II Trials 1-5 Total raw score at Visit 13
- Covariate: CVLT-II Trials 1-5 Total raw score at Baseline, i.e. Visit 2
- Results will be presented as n, mean and standard deviation of CVLT-II (Total Trials 1-5) scores at baseline and post-treatment. ANCOVA model parameters with estimates will be provided.
- The two tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, adjusted for two tests; 2-sided confidence intervals will be displayed with a 95% confidence level.

9.5.2. Secondary Analyses

Durability of rTMS effects (Aim 2a)

- Analysis: Longitudinal analysis of primary efficacy measure (memory performance) over the entire trial period in relation to treatment group
- Method: Mixed-effects growth curve modeling
- Population: ITT
- Dependent variable: CVLT-II Trials 1-5 Total raw score (Visits 2, 13, 14,15)
- Independent variable: rTMS Treatment group
  - Model 1: active DLPFC vs sham
  - Model 2: active LPC vs sham
- Results: Mixed model parameters with estimates will be provided.

- Contrasts: To convey the durability of the effect of each type of rTMS stimulation on the primary efficacy measure, the magnitude of treatment effects at the 3-mos and 6-mos time points will be reported.

Analysis of behavioral differences related to stimulation site (Aim 2b.1)

- Analysis: Longitudinal analysis of behavioral changes over the entire trial period in relation to treatment group.
- Method: Method: Mixed-effects growth curve modeling.
- Population: ITT.
- Dependent variables: Behavioral measures listed in Section 9.4.2.a (Visits 2, 13, 14 & 15). Semantic clustering and delayed recall sub-scores of the CVLT-II are of most interest.
- Independent variable: Active rTMS Treatment group (DLPFC vs LPC).
- Results: Mixed model parameters with estimates will be provided.

Analysis of effects on brain function related to stimulation site (Aim 2b.2)

As noted above, rs-fMRI data will be acquired at baseline (Visit 2) and post-intervention (Visit 13) to examine effects of rTMS on brain function. Secondly, plasma levels of brain-derived neurotrophic factor (BDNF) will be measured at the first and last intervention sessions to gain information about mechanisms of action of rTMS with respect to brain plasticity.

<u>BDNF levels analysis</u> (two time-points). As in the primary analysis, ANCOVA will be used.

<u>Functional connectivity</u> (two time-points).

- To define the DMN and CEN networks, we will perform seed-based whole brain analysis of the baseline fMRI data, using the methods of Greicius (for the DMN) and Vincent (for the CEN). The networks will be broadly defined *(p*<.01) from the group data to generate inclusive masks of the DMN and CEN.
- 1) Analysis of rTMS effects on PCC connectivity within the DMN. As described in more detail in Appendix VIII, connectivity maps will be calculated by the correlating subject's timeseries of the PCC seed-ROI with those of non-seed voxels in the DMN group mask, followed by Fisher' *r* to *z* transform of the values. Contrasts of the connectivity maps will be made (Pre- vs. Post-Tx, for each active rTMS vs. sham, and for active LPC vs. DLPFC). The aim of these analyses is to discover the extent to which rTMS restores connectivity of the PCC within regions of the DMN. rTMS-induced increases in PCC:hippocampal, PCC:parahippocampal, PCC:LPC, and/or PCC:mPFC connectivity would provide indications of therapeutic response (J. X. Wang et al., 2014; J. X. Wang & Voss, 2015; Ward et al., 2014).
- Analysis of rTMS effects on between-network connectivity. As explained in Appendix VIII, we will define 6 *a priori* ROIs: bilateral PCC (posterior DMN), and DLPFC (key node of the CEN) and medial PFC (anterior DMN). For each subject and scan session, a correlation matrix of ROI-pairwise timeseries correlations will be computed; next, each participant's z-score matrix (using Fisher's *r*-to-*z* transform) will be used to compute Pre-minus-Post changes in z values. These will be used in group-level analyses to compare each active rTMS to sham-control and

to compare active LPC to DLPFC. The aim of these analyses is to examine the extent to which rTMS reduces functional connectivity between the DMN and CEN. Decreases in PCC:DLPFC and mPFC:DLPFC between-network connectivity would provide indications of therapeutic response.

- Finally, we will explore the extent to which rTMS-induced changes in functional connectivity correlate with changes in selected behavioral variables (delayed recall, semantic clustering, executive function, and depression).

Heterogeneity of response to rTMS (Moderators: Aim 2c).

To explore the extent to which one treatment is superior over another as a function of a moderator variable, we will fit regression models with interactions between the treatment group variable and a selected moderator variable, yielding estimates of the regression line for each group. In addition to reporting the magnitude of the interaction as a p value, we will obtain predicted values of the regression lines corresponding to each group. (From these, we can estimate the superiority of one treatment over another as a function of the moderator; confidence intervals and p-values can be readily reported). As these are exploratory analyses, we would analyze individual moderators separately to avoid over-fitting the models.

Based on limited data from previous TMS studies, the following classes of moderators are most likely to account for heterogeneity of response to rTMS in patients with MCI:

- Profiles of baseline cognitive deficits, as defined by CVLT-II clustering and delayed recall scores;
- Brain endophenotypes, as defined by a baseline functional connectivity metric for the Language, Central Executive, and Default-mode Networks;
- BDNF met carrier status (in other clinical populations, val/val genotype has predicted a better response to rTMS (Chang et al., 2014; Cheeran et al., 2008)).

In addition, gender and racial/ethnic categorical variables will be examined to gauge the magnitude of any potential differences in response to rTMS in patients with MCI.

Descriptive analyses of safety and tolerability

Adverse events will be coded according to established Medical Dictionary for Regulatory Activities (MedDRA) terms and summarized by MedDRA System Organ Class and Preferred Term. In most cases, aggregate safety and tolerability data (see Section 7.2) will be summarized with descriptive statistics (counts, percentages, mean and standard deviation) for all participants, by treatment group and by study phase (i.e., intervention and follow-up). Summaries will indicate whether events were determined to be related to the study device and whether the AE led to treatment discontinuation. Inferential comparisons may include t-tests or chi-square tests as appropriate. The time course of incidence of common treatment-related adverse effects will be examined to characterize the extent to which participants accommodated to the treatment.

10 DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Management

In this single-site study, the PI and study team are responsible for all data collection and management. The Database Manager will monitor all data entered into the database by the Study Coordinator. The PI will review data on an ongoing basis at regularly scheduled staff meetings. A formal review of the accumulating data and any data integrity issues will be conducted at a meeting of the PI and the Data Manager every 3 months during the active data collection period.

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 the Study Physician.

Biomarker/genetic information will be stored in a separate password-protected file, in a separate database, which can only be accessed by the Study Data Manager and MIRECC Senior Data Manager. Only the Data Managers can match genetic information with the participant ID (PID); the Data Managers are blinded as to which PID is associated with which study participant. The genetic data will only be used for analysis of data conducted by the Data Manager.

The Participant ID (PID) will be recorded on all data collection forms and entered into encrypted, password-protected databases located on physically secure VA servers behind a firewall.

10.2 Data Collection Forms

Data collection forms include:

- Original copyrighted test forms (e.g. CVLT-II);
- Standard questionnaires (e.g. ECog form and GDS like those used in the Alzheimer's Disease Neuroimaging Initiative [ADNI]);
- Case report forms adapted from the NIH Clinical Trial Toolkit (e.g. Participant Demographic form, Enrollment & Randomization form, Vital Signs form, and Adverse Event Forms).
- Forms developed specifically for this study, many of which were adapted from VA CSP #556 (e.g. Inclusion-Exclusion Form, and rTMS Intervention Log sheet).

No data collection forms will show an individual participant's identifiers, such as name or initials. For additional steps taken to maintain participants' confidentiality, please see Section 11.3. For information regarding which members of the study team will fill out the about forms, please see Section 6.2.

10.3 Quality Assurance

10.3.1 Training

General Training. All staff will have completed all VA- and Stanford-required online training in Human Subjects, Good Clinical Practice (GCP), Privacy, and HIPAA before engaging in any study-related activities. Each member of the study staff will have completed training specific to their scope of practice and specific to their roles before performing study procedures. These types of training include:

TMS Training. Didactic and practical hands-on training will be provided onsite to the study staff at VA-Palo using the training model of the VA-funded, Mental Illness Research, Education, and Clinical Center (MIRECC)-led "TMS Clinical Roll-out" training program. The trainers will be rTMS-certified physicians and nurses. The didactic materials include the MagVita TMS Therapy User Guide for use with MagVenture MagPro devices, software version 7.1.

Study Staff TMS Safety training. Multiple study personnel, including the Study Coordinator and TMS Operator, will be trained comprehensively in TMS safety procedures, including: pre-session safety screening, solicitation and recognition of AEs, and training as first responders per the seizure protocol. Knowledge will be demonstrated by taking a written examination that includes questions on what to do if there is a TMS-induced seizure. Annual drills simulating a TMS emergency will be conducted to maintain staff preparedness.

TMS Operator training. The TMS Operator will be trained to reach proficiency in all aspects of the rTMS intervention procedure, including: device operation, motor thresholding, coil placement for cortical targeting, and delivery of rTMS. Proficiency will be demonstrated by both a written test and by observation-based testing of all aspects of the rTMS intervention procedure. Once the TMS Operator is certified as proficient by the trainers, the TMS Operator's research scope of practice will allow the operator to independently administer rTMS under the supervision of an rTMS-certified physician. This aspect of training is the "Core" component of TMS Certification. Following completion of the Core training, the TMS Operator will be trained to proficiency in the specific stimulation protocol of this study, and certified by the PI.

Assessments Training. The Study Coordinator will be trained in the administration and scoring of the behavioral assessments by the PI. Training will take place in three phases: self-study of the test manuals; practice in administering and scoring the assessments with a trained study coordinator (e.g. the ADNI 3 coordinator), and finally observation by PI to check for adherence to the test manuals. The PI and other staff at the study site who will provide training are experienced in administering these same assessments.

Training of Specific Assessments: CDR. The CDR rater in this study will be another researcher at the study site, so that the CDR—which is part of the screening visit diagnostic evaluation—will be collected independently of the outcome measures. The CDR rater will be certified through Washington University. If the rater has never been CDR certified, full certification will be required. The training includes nine (9) reliability tapes. The ratings/scores are compared to the Gold Standard and, if the rater passes, Washington University will issue a certificate. CDR Certification and Refresher Course can be found online at url: http://alzheimer.wustl.edu/cdr/application/step1.htm

Experienced MIRECC personnel associated with the Study Protocol. The following long-time study staff have worked on NIH- and VA-funded protocols that involve similar populations, assessments, biomarkers, and/or interventions (e.g. rTMS clinical trials, older adults, and cognitive outcomes):

Beatriz Hernandez, Database Manager and SAS Programmer (15% FTE). Ms. Hernandez is presently studying for a Master's in Statistics and has used SAS professionally for over 9 years. She and the PI have worked together 6+ years on cognitive and MRI datasets. She has performed complex analyses, including multiple linear regression modeling and mixed-effects growth curve modeling under the supervision of Dr. Lazzeroni.

She has substantial experience in database management, gained under the direction of Art Noda, the MIRECC Senior Data Manager. Ms. Hernandez will perform randomization of the subjects to treatment arms, to ensure that all other research staff are blinded. Ms. Hernandez will be responsible for setting up REDCap study database for the Study Coordinator to enter screening and other behavioral data. She will also be responsible for dataset merges in SAS and coding the data analyses and models involving the primary and secondary outcome measures.

Phoebe (Chun-Ping) Liao, Laboratory Technician (effort as needed). Ms. Liao and the PI have worked together 10 years. Ms. Liao, who has Bachelor's Degree from UC Davis, has over 10 years of laboratory experience. She has performed complex protocols, including DNA extraction, genotyping assays, microarray genotyping, sequencing, and measurements of gene expression both genome-wide and targeted. She consistently meets a high level of reproducibility, as demonstrated by implementing robust procedures and protocols that resulted in multiple publications over the past decade. Quality control measures of her work have consistently shown that her results are reliable. Ms. Liao will be responsible for DNA extraction and tissue banking, and for performing the laboratory protocols for determining BDNF, COMT, and APOE genotypes that will be used in the data analyses relevant to heterogeneity of response to rTMS.

New Staff. Any new staff who join the project will undergo all required training before beginning work on the project, and will be carefully trained on all necessary aspects of the protocol by rTMS-certified physicians, nurses, and the PI.

10.3.2 Quality Control Metrics

Outcome measures will be entered using the procedures outlined in Section 10.2 "Data Management" above. Range checks and automatically computed total scores will be utilized in RedCAP to enhance data quality. Double data entry will be performed on randomly selected records using RedCAP's double data entry feature. The percentage of errors detected will be captured and tabulated for review by the study's biostatistician and members of the DSMB.

10.3.3 Protocol Deviations

Protocol deviations will be captured using a Protocol Deviation Log that is very similar to the NIH Clinical Trial Toolbox form.

- Any serious protocol deviation (that meets the definition of an SAE or compromises the safety, welfare or rights of subjects or others) will be reported to the DSMB Chair, NIA Program Official, and IRB as soon as possible, not more than 7 days after the PI first learns of the deviation.
- The report will describe what steps have been taken and what steps are planned as a result of the event.

The DSMB will receive a tabulation of all protocol deviations (e.g. visits out of window; missed assessments) at each meeting or reporting interval.

10.3.4 Monitoring

The Research Compliance Officer of the VA Palo Alto Health Care System conducts annual audits of the participants' informed consent documents.

11 PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

An IRB-required protocol and informed consent documents for study participants and their study partners were approved on March 14, 2017. This IRB approval includes a waiver of individual HIPAA authorization for recruitment and a waiver of documentation of consent for telephone pre-screening using an approved telephone script.

This study protocol, as well as any subsequent modifications, the informed consent documents, and other information for participants--will be reviewed and approved by the IRB.

11.2 Informed Consent Forms

The consent form describes the purpose of the study, the procedures to be followed, and the risks and benefits of participation. See Appendix II. "Informed Consent Forms." A separate consent form will be presented to the study partner (SP). The SP's consent form informs the SP of their role in the study including the kinds of information the partner will be asked to provide during the study.

Procedures for obtaining informed consent. During the consenting process, each prospective participant and a study partner will meet in a private interview room at the study site with the PI or the Study Coordinator. The information contained in the Informed Consent Form (ICF) is initially described orally to the prospective participant. Care is taken to inform prospective participants repeatedly that participation is entirely voluntary and that they may withdraw at any time and for any reason. Any questions will be answered. The prospective participant is then asked to read the consent form carefully. The prospective participant is asked to summarize the consent form, including the discomforts, risks, and confidentiality sections.

Enough time will be allowed for the potential participant to make an informed decision, including time to discuss the study with the researchers and ask any questions they may have. We estimate the consenting process will take between 30 minutes and one hour. The potential participant may take the consent home to discuss with others, and return later to sign it if they desire.

Procedures for documenting informed consent. Only after the prospective participant demonstrates by stating in their own words that they understand the purposes, risks, and potential benefits of the study and they are willing to volunteer, will the participant be asked to sign and date the consent form. If the prospective participant lacks adequate decision-making capacity, a designated legal representative will need to sign the ICF prior to the participant undergoing screening or other study procedures. Prospective participants will need to co-sign the ICF to indicate assent.

A copy of the ICF will be given to each participant and study partner or legally authorized representative. This fact will be documented in the participant's record. All original signed consent forms will be stored in the Study Consent Binder in a locked file when not in use.

Provisions for vulnerable populations. Most participants with aMCI are expected to be demonstrate adequate decision-making capacity by stating in their own words that they understand the purposes, risks, and potential benefits of the study and they are willing to volunteer. As noted above, each prospective participant is asked to summarize the consent form, including the discomforts, risks, and confidentiality sections. Participants will be

given ample time to discuss the study and ask the researchers questions. Participants will be given time to discuss the study with the study partner, or with any family member, friend, or primary care provider.

It is possible that a volunteer who comes for an in-person screening visit may be more impaired than we expected, based on the phone pre-screening interview. If the prospective participant lacks adequate decision-making capacity at any in-person visit, then a legally authorized representative will need to sign the ICF and the volunteer will need to co-sign to indicate assent prior to participating in screening or any other study procedures.

We will follow the recommendations set out in the Alzheimer's Assn position paper, "Research Consent for Cognitively Impaired Individuals" (AD & Associated Disorders 2004, 18:171-175), which puts forth that cognitive impairment is not always associated with the lack of capacity for informed consent to research. Nevertheless, potential participants will be evaluated by a Stanford/VA California Alzheimer's Center physician, a Stanford Neurology ADRC physician, or a VA physician for competency. In case a person lacks capacity, a proxy (legally authorized representative) will need to sign the consent form. The subject's assent will be obtained & documented by also including their signature on the ICF. Using these procedures for obtaining consent, we aim to protect the rights of any decisionally-challenged subjects.

We note that anyone who scores less than 24 on the MMSE at the Screening Visit will be a screen-fail and will not be enrolled in the study because the inclusion /exclusion criteria select for participants with MCI, who by definition do not meet criteria for dementia. Given the low risks of the proposed procedures and study's exclusion criteria, we feel that the risks and chance of harm to potentially vulnerable subjects are minimized.

11.3 Participant Confidentiality

An identification code (Participant ID, PID) will be assigned by the study staff to each participant. The PID will be used in lieu of the participant's name in order to protect the participant's identity:

- All computer entry will be done using participant identification numbers (Participant ID, PID) only;
- Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by PID to maintain confidentiality;
- The PID will be used when reporting AEs and/or other trial-related data;
- No research reports will identify any individual participant or otherwise disclose identifiers.

Privacy. All paper records containing individually identifiable information (III), including Identifiable Protected Health Information (PHI)--such as original signed consent forms, telephone pre-screening and study visit progress notes--will be maintained in a secure room, and in locked file cabinet when not in use.

HIPAA compliance. Information will not be shared or disclosed without written permission of the participant, except as necessary for monitoring by IRB, the FDA, the NIA, and the OHRP.

Data security requirements. All portable IT equipment (i.e., laptops, USB thumb drives, and other removable storage media) used in the research project must be encrypted. Access to

electronic versions of data will be limited to authorized researchers who need access to conduct the research.

Record retention. Paper data collected under the HIPAA waiver for recruitment will be shredded when the research has been completed and all required waiting periods have elapsed. Per the VA record control schedule, research records must be maintained for 6 years after study closure.

11.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the NIA, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research participants are protected.

12 ETHICAL CONSIDERATIONS

The research conducted in this study will follow the guiding ethical principles of the *Declaration of Helsinki* and *The Belmont Report* (Office of the Secretary, Ethical Principles and Guidelines for the Protection of Human Subjects of Research, The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1979]).

13 PUBLICATION OF RESEARCH FINDINGS

Any presentation, abstract, or manuscript will be made available for review prior to submission, at the written request of the NIA Program Official.

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15 APPENDICES

Appendix I - X. Consent forms, detailed study procedures, and study manuals are available from the Study Investigative Team. Contact: Joy Taylor at joyt@stanford.edu

Appendix XI. Protocol Amendment

Appendix XI

Protocol Amendment / Modification:

Attention Network Task Dropped

Noninvasive Cortical Stimulation to Improve Memory in Mild Cognitive Impairment (MCI)

NCT03331796

Amendment: The Attention Network task (ANT) was dropped from the study protocol on September 19, 2019 by approval of the Data Safety and Monitoring Board (DSMB).

DSMB meeting minutes summary: "Other assessments already require 2 hours to complete. Members agreed that the protocol already included enough assessments to answer the research question. The possibility of study drop-outs due to participant burden was more concerning than administering the ANT task and collecting data on this secondary outcome. Consensus was to drop the ANT from cognitive battery.

Date of approval by the DSMB and NIH Program Official: September 19, 2019

Effective date: Immediate

The following pages document approval of this protocol modification by the DSMB and the Stanford University Administrative Panel on Human Subjects in Medical Research.

DSMB Meeting, Teleconference, Thursday, September 19, 2019
Study: Noninvasive Cortical Stimulation to Improve Memory in Mild Cognitive Impairment
Grant Number: 1 R01 AG055526-02

Meeting attendees

Board Members – F. Andy Kozel MD (Chair), Prasad Padala MD**,** Ping Luo PhD, Noah Philip MD

NIA – Kristina McLinden PhD, Alvin McKelvy PhD

Blinded Study Staff: Joy Taylor PhD (PI), **not present**: Joshua Teso (Research Coordinator)

Unblinded study staff: Beatriz Hernandez (Data Manager)

I. Open Session

Opening Remarks: PI summarized the open report.

Summary of Discussion

1. Study Progress:
    a. **Enrollment**: 26 participants screened, 17 enrolled, 15 completed baseline evaluation, 14 completed post-treatment measures, and 6 completed the study. **Committee discussion:** Board members discussed the importance of meeting recruitment milestones for the study to continue. From an NIA perspective, insufficient statistical power due to low recruitment raises ethical concerns about continuing the study; Dr. McLinden outlined a milestone of 33 participants by the next NIA progress report on March 15, 2020. Given that this is an under-represented population, the committee would like the study team to provide a realistic recruitment rate with assessment of its impact on the study timeline. Consensus was to continue the study and reassess in 6 months. **PI Actions**: 1) Aim to screen 4-6 participants per month; 2) provide the board with a realistic recruitment rate and its impact on the study timeline.
2. Protocol:
    a. **Inclusion criteria:** PI requested guidance about allowing exceptions to the current age range of 55 to 90 years. **Committee discussion**: Board members agreed there are no safety concerns but discussed data integrity issues that may result from exceptions. Consensus was to recommend keeping the age range unchanged.
    b. **Excluded medications:** PI had question about safety of dextroamphetamine while receiving TMS. **Committee discussion:** board members pointed out this medication is excluded based on a theoretical concern, and that the motor threshold value may provide a favorable level of safety. That said, there is no solid evidence for contra-indication of rTMS or for safety of rTMS. Given the research protocol context, recommended participant be tapered off medication before starting rTMS (achieve a washout period of at least 4 times the drug half-life). **PI Actions**: proceed with screening if participant is willing to discontinue dextroamphetamine during the rTMS Intervention phase.

c. **Secondary outcomes:** PI raised possibility of dropping the Attention Network Task (ANT) as other assessments already require 2 hours to complete. **Committee discussion**: members agreed that protocol already includes enough assessments to answer the research question. The possibility of drop-outs is more concerning given recruitment issues. Consensus is to drop the ANT from cognitive battery. **PI Actions**: submit a protocol modification to drop the ANT.

3. Safety Assessments: Chair verified that board members had no safety assessment concerns before ending the open session.

II. Closed Session

Meeting attendees

F. Andy Kozel MD (Chair), Prasad Padala MD**,** Kristina McLinden PhD, Alvin McKelvy PhD, Ping Luo PhD, Noah Philip MD, Beatriz Hernandez (unmasked, Data Manager); **not present**: Joy Taylor PhD (PI)**,** Joshua Teso (Research Coordinator)

Summary of Discussion

1. Board members would like greater clarification about the degree of medical instability permitted before denying further participation. Study team should make clear the criteria and procedures to evaluate medical instability during study participation (post-randomization).
2. Board chair would like to know how often beam F3 is used instead of sole reliance on the Localite method.
3. There were no safety concerns raised during the closed session.

III. DSMB Recommendations

1. Continue the study with recruitment goal of at least 33 participants by the next DSMB meeting in March 2020. Consider the possibility of adding a 2nd site to boost recruitment.
2. Submit a protocol modification to drop the Attention Network Task from assessments.
3. Clarify criteria and procedures to determine whether medical instability warrants discontinued participation.
4. Next meeting will be held in 6 months (NIA requires DSMB meeting every 6 months).

DEPARTMENT OF VETERANS AFFAIRS
James A. Haley Veterans' Hospital
13000 Bruce B. Downs Blvd
Tampa, FL 33612

8 October 2019

Regarding: DSMB Meeting # 4
Noninvasive Cortical Stimulation to Improve Memory in Mild Cognitive Impairment

To Whom it may concern:

The fourth Data Safety and Monitoring Board (DSMB) meeting for Dr. Joy Taylor's Noninvasive Cortical Stimulation to Improve Memory in Mild Cognitive Impairment study was held Tuesday, 19 September 2019. In attendance were DSMB Board Members: F. Andy Kozel MD (Chair); Prasad Padala MD; Ping Luo PhD; and Noah Philip MD. All reviewed the study information and concurred with below assessment and recommendations. In addition, the NIA program staff including Kristina McLinden PhD (Program Official) and Alvin McKelvy PhD (Program Analyst) as well as the study team Joy Taylor PhD (PI) and Beatriz Hernandez (Database Manager- unmasked) were present.

The data for open (all investigators and board members) and closed sessions (board members and unmasked study personnel) were reviewed. The study protocol was reviewed with the board members and questions addressed. Study procedures, subject enrollment, protocol deviations, adverse events, and protocol changes were discussed.

Presently there have been 17 subjects enrolled in the study. There were no serious adverse events reported. The protocol deviations since last review did not put the participants at increased risk.

Low recruitment number was identified. The study staff has already implementing changes to increase recruitment, and they are starting to demonstrate improvement.

The board recommended continuing the study with agreement on the discussed changes to include: recruitment goal of at least 33 participants by the next DSMB meeting in approximately March 2020; submitting a protocol modification to drop the Attention Network Task from assessments; and clarify criteria and procedures to determine whether medical instability warrants discontinued participation. The study is safe to continue.

The next meeting will be in approximately 6 months. All events requiring a special report to the IRB will be passed on to Board Members via email.

If there are any further questions, please do not hesitate to contact me.

Sincerely,

F. Andrew Kozel

F. Andrew Kozel, M.D., M.S.C.R.

Director of TMS Clinic & Staff Psychiatrist in Mental Health and Behavioral Sciences
James A. Haley Veterans' Administration Hospital and Clinics

Professor,
Department of Psychiatry and Behavioral Sciences
University of South Florida

STANFORD UNIVERSITY

Stanford, CA 94305 [Mail Code 5579]

David Spiegel, M.D. (650) 724-9815
CHAIR, PANEL ON MEDICAL HUMAN SUBJECTS (650) 725-6766

Certification of Human Subjects Approvals

Date: March 10, 2020

To: Joy Taylor, PhD, Psychiatry and Behavioral Sciences
Joshua Teso B.A., Alesha Maree Heath PhD, Arthur Noda, John Wesson Ashford M.D., Ph.D. (VA), Beatriz Hernandez, Harlene Grewal, Jauhtai Joseph Cheng MD, PhD, Joachim Franz Hallmayer MD, PhD., Laura Lazzeroni Ph.D, Logan Douglas Schneider, Maheen Mausoof Adamson, Monica Mercedes Nable B.S., Priyanka Manojkumar Bhatt M.B.E., Ruth O'Hara Ph.D., Allyson Rosen Ph.D., Steven Chao M.D., Ph.D., Timothy Durazzo Ph.D., Vivian Quyah Nbu Chu B.A., Margaret Windy Mcnerney Ph.D., Jerome A Yesavage M.D.

From: David Spiegel, M.D., Administrative Panel on Human Subjects in Medical Research

eProtocol Non-Invasive Brain Stimulation for Mild Cognitive Impairment

eProtocol #: 39859 **IRB 3 (Registration** 350)

The IRB approved human subjects involvement in your research project on 03/10/2020. **'Prior to subject recruitment and enrollment, if this is: a Cancer-related study, you must obtain Cancer Center Scientific Review Committee (SRC) approval;** a CTRU study, you must obtain CTRU approval; a VA study, you must obtain VA R and D Committee approval; and **if a contract is involved, it must be signed.'**

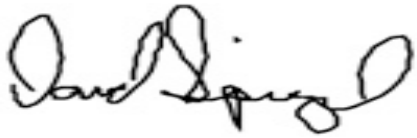
The expiration date of this approval is 03/10/2021 at Midnight. If this research is to continue beyond that date, it is your responsibility to submit a Continuing Review application in eProtocol. Research activities must be reviewed and re-approved on or before midnight of the expiration date. The approval period may be less than one year if so determined by the IRB. Proposed changes to approved research must be reviewed and approved prospectively by the IRB. No changes may be initiated without prior approval by the IRB, except where necessary to eliminate apparent immediate hazards to subjects. (Any such exceptions must be reported to the IRB within 10 working days.) Unanticipated problems involving risks to participants or others and other events or information, as defined and listed in the Report Form, must be submitted promptly to the IRB. (See Events and Information that Require Prompt Reporting to the IRB at http://humansubjects.stanford.edu.) Upon completion, you must report to the IRB within 30 days.

Please remember that all data, including all signed consent form documents, must be retained for a minimum of three years past the completion of this research. Additional requirements may be imposed by your funding agency, your department, HIPAA, or other entities. (See Policy 1.9 on Retention of and Access to Research Data at http://doresearch.stanford.edu/policies/research-policy-handbook)

This institution is in compliance with requirements for protection of human subjects, including 45 CFR 46, 21 CFR 50 and 56, and 38 CFR 16.

Includes: Attention Network Task dropped.
Documents related to DSMB Meetings 3 and 4 were submitted.
copy of Notifications to DSMB of SAEs 1 & 2 were submitted.

Waiver of Individual Authorization for recruitment under 45 CFR 164.512(i)(2)(ii)(A),(B),(C), pursuant to information provided in the HIPAA section of the protocol application.



David Spiegel, M.D., Chair

Approval Period: 03/10/2020 - 03/10/2021
Review Type: REGULAR - CONTINUING REVIEW
Funding: NIH - Grant: R01 AG055526-01

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