Using network-guided TMS to ameliorate memory deficits in early Alzheimer's disease

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## Purpose of the Study

Objective 1. Testing network-based TMS method for Episodic Memory enhancement in MCI. Network-level dynamics have an important influence on a region's effectiveness as a stimulation site. To determine this effectiveness, we use the network science concept of controllability, a network property which refers to the ability of a single region to shift a global network into a target brain state. Our hypothesis is that by modeling the controllability of the semantic memory success network (MSN), network-based TMS will reliably improve memory performance compared to standard TMS targeting. Our approach is to apply intermittent theta-burst (iTBS) delivered to either an MSN site or a control site (vertex). We define memory success as memory accuracy change from baseline in active subjects compared with sham subjects. We predict that the TMS response in our semantic memory task will be greater at the network-targeted stimulation site compared to a control site. Thus, our method will directly compare our more novel network-based approach with standard cognitive neuroscience approaches for affecting memory networks.

Objective 2. Using network-based TMS to characterize the lasting behavioral and neural changes in MCI. The capacity for TMS to induce long-lasting changes is well established in the study of many neuropsychiatric disorders. However, the neural basis of even intermediate changes are not well understood. Given that AD-related syndromes are associated with a diverse set of structural, functional, and vascular alterations in neuropathology, it is therefore likely that neurostimulation may lead to qualitatively different changes in intact versus dysfunctional neural circuits. Our hypothesis is that network-based TMS induces widespread neuroplastic changes in both network structure and neurovascular coupling within even short treatment regimens. Our approach will be to model behavioral, structural and neurovascular (resting state fluctuations in amplitude, or RSFA) changes in each individual across 3 timepoints, in order to estimate the short-term neuroplastic change associated with network-based TMS. We predict that in regions structurally connected to the network-targeted site will show longitudinal structural and functional changes, and that these changes will be positively correlated with behavior for memory performance in subjects who receive MSN targeted TMS.

## Background & Significance

The scientific premise of the current project emerges from two complimentary literatures: the study of functional connectivity patterns underlying memory functioning in healthy and pathological aging, and the study of neurostimulation-based modifications of brain states. Since the introduction of functional and structural connectivity approaches, MRI has also been used to assess age-related differences on a brain network level. For example, older adults rely on greater frontotemporal connectivity than younger adults, and these patterns are deficient MCI groups. Data from our lab and others strongly support the idea that functional connectivity in healthy OAs is constrained by white matter (WM) connectivity, and that the organization of white matter architecture constrains these cognitive states. However, no TMS-based study has established a reliable framework for targeting of a network associated with a specific brain state.

To unite these two empirical frameworks, we draw on recent advances in network control theory to develop a biologically informed mathematical model of brain dynamics in response to exogenous neurostimulation. From this framework we can infer how the topology of white matter architecture constrains how neurostimulation to specific cortical sites may control transitions between brain states, leading to effective and mechanism-based forms of TMS therapy. Thus, our approach provides a balanced trade-off between complexity and plausibility for whole-brain functional connectivity, incorporating key anatomical constraints and modeling major dynamical elements captured by our neuroimaging techniques.

Recently, different forms of noninvasive brain stimulation techniques have been applied both to healthy older adults and to improve memory impairments in patients with AD. While most inferences on the cognitive benefit of TMS are based on healthy young adult populations, it is possible that the effects of noninvasive brain stimulation on cognitive function may be more prominent in older adults and in patients with AD because physiological and pathological aging show structural and functional alterations related to neural plasticity. A recent metanalysis of noninvasive brain stimulation in AD found a more pronounced, positive effect of TMS on cognitive function in patients with AD compared with that of healthy older adults. This suggests that TMS may lead to qualitatively different outcomes in intact versus dysfunctional neural circuits as studies have demonstrated diversity of structural, neurovascular, and functional alterations in brains with AD. Furthermore, these factors likely interact, as poor neurovascular health is known to impair white matter health, and influences dynamic factors affecting the controllability of a cortical network. To date, all studies using TMS in AD-related populations have ignored any distinct mechanisms of cortical dysfunction specific to this population, highlighting the timeliness of the proposed network-based TMS approach.

Studies applying the stimulation during the execution of the task demonstrated more pronounced effects compared with studies delivering the stimulation before the execution of the task. Since it will not be possible to deliver stimulation during our task, we will deliver a  rhythm TMS (theta-burst) that has been shown to have 30-60 minute impacts on cortical excitability. This stimulation will be consistent with studies showing that stimulation impacts before and during task have more pronounced effects. Also consistent with our project, most of these trials used rTMS applied to a standard left DLPFC target, to find small but reliable improvements in Mini-Mental performance or visual recognition memory in MCI. Nonetheless, considerable questions remain as to whether TMS has clinically relevant effects in these populations, as well as to what neuroscience-based mechanisms account for these effects. Neuromodulation approaches to date have not endeavored to engage networks thought to be involved in episodic memory on such an individualized basis—a necessary step for translating neuromodulation to effective therapies. Given the reliance of aging brains on compensatory frontal brain networks for maintaining healthy cognition, engineering a more individualized prefrontal TMS approach to applications in MCI promises to be a more direct path to effective treatment protocols for enhancing the memory processes in these populations.

Design & Procedures

The study comprises five sessions, the general format is outlined by the Figure below. In Day 1 (~3 hr session), participants fill forms, complete a neuropsychological test battery (NIH Toolbox, NACC UDS, BDI), and provide a saliva sample to be banked for future APOE genotype determination. On Day 2 (~2 hr session), subjects will perform an initial MRI scanning session. In this session, MRI, RSFA, DWI, and fMRI are collected so they can be used for network-based targeting. In Days 3-5(~2.5 hr session) a few days later participants will undergo combined TMS-fMRI sessions. Before the scan, participants undergo theta-burst TMS. The priming effects of TBS on cortical excitability have been shown to last 30 to 60 minutes. Participants are moved immediately into the scanner to complete an encoding task followed by a subsequent visual and semantic memory task for images and labels encoded in scanner. Participants will complete three days of TMS delivered to one of two participant specific sites that are derived from the baseline activation.

Episodic Memory task. In order to test TMS-related memory enhancements, we will rely on an episodic memory task that has shown (1) reliable SMEs in univariate activity and multivariate connectivity, and (2) reliable deficits in MCIs. During each block of the Encoding phase, participants read a list of 120 English words and perform a domain judgement (living/nonliving) during both network-based (Fig 6; active: red, sham: orange) and standard TMS targets (active: purple, sham: blue). Active and sham TMS trials are intermixed within a block, enabled by an advanced sham technique which employs cutaneous scalp stimulation mimicking the TMS effect. During the Retrieval phase (post-scan), participants perform a recognition memory task including a mix of old words and new words (grey), and memory is then subsequently assessed as a function of Targeting and TMS condition.

Screening: During the Screening Session, participants will be screened for the study with the TMS screening forms (demographics, health, etc.), BIAC screening form, the MINI, CDR, NACC, BDI, the MOCA and/or DUCE, a handedness questionnaire, and a urine test. If they pass the screening procedure, they will proceed to the to the TMS Service Center, where they will learn and practice the Picture Encoding tasks used in the study (about 0.5 hr) and to obtain right and left hand motor thresholds for future dosing of TMS. Occasionally participants are too fatigued to complete all screening forms (questionnaires and assessments) in one visit. When this happens they are asked to return on another day to complete remaining assessments. When the burden of an additional visit to Duke is prohibitive to their continued participation study staff will offer to complete remaining questionnaires via phone (questionnaires) or in the participant's home (cognitive assessments).

SALIVA SAMPLE: Volunteers can voluntarily provide the study team with a saliva sample that will be used to perform APOE genetic testing, a risk marker for Alzheimer's Disease. Study volunteers are not obligated to provide a saliva sample. Samples will be obtained by administration of saliva sample collection tube and stored in a locked and secured environment. Subject samples will be deidentified and labeled with the subject study number. Genetic testing will be performed at the Biofluids Shared Resource.

Motor Threshold Determination: All TMS procedures will occur in the Brain Imaging and Analysis Center located in the Radiology area of Duke North. Motor threshold (MT) is defined as the minimum magnetic

flux needed to elicit a threshold EMG response in a target muscle in 5 out of 10 trials. MT is the standard in the field for determining the intensity of TMS for each individual to reduce seizure risk. The motor evoked potentials (MEP) for the contralateral first dorsal interosseus (FDI) will be measured with EMG. The scalp region producing the largest amplitude MEP will be identified. At that scalp location, the lowest TMS intensity able to elicit 5 MEP's of ≥50μV in peak-to-peak amplitude in 10 trials at this site will be determined, using a descending method-of-limits procedure. MT will be determined for each hemisphere with the muscle at rest (verified by baseline EMG). Individual MT will be used to determine the intensity of stimulation for each individual, as recommended by safety guidelines.

Imaging acquisition and preprocessing. Three forms of structural images will be acquired: 1) full-brain high-resolution T1-weighted structural images (inversion recovery prepared 3D SPGR) with full coverage of the head and neck, (TR = 500ms; TE = 20ms; FoV = 24cm2; image matrix = 256x256; voxel size = 0.94 x 0.94 x 1mm), and 2) echo-planar (EPI) sensitivity encoding (SENSE) DWI images with the same orientation (TR = 2000 ms; FoV = 24 cm2; image matrix = 1282; voxel size 0.94 x 0.94 x 1 mm; b-value = 1000 s/mm2; 1 repetition; 36 diffusion-sensitizing directions), and 3) susceptibility-weighted images, which will be used to estimate VAD (TR = 49 ms, TE = 40 ms; FoV = 24 cm2; image matrix = 1282; voxel size 0.94 x 0.94 x 1 mm). In addition, two forms of functional images will be collected: 1) for resting state EPI functional imaging data, which will be used to estimate RSFA, we will acquire 24 slices parallel to the AC-PC plane using a BOLD-sensitive gradient-echo sequence with EPI k-space sampling, at TR of 2s (TE: 35ms; FOV: 25.6cm; voxel size: 63mm), and 2) event-related EPI, which uses the same scan parameters and will measure the global reactivity to our Episodic Memory Task.

Stimulation parameters for iTBS comprised 50-Hz triplets at 5 Hz applied for 2 seconds with an intertrain interval of 8 seconds; 40 trains were delivered, lasting a total of 4.5 minutes.

TMS methods. Coil targeting will be achieved using Brainsight. TMS is applied with an 8-shaped coil based on 80% resting motor threshold (rMT). TMS will be targeted to a participant-specific site that is determined through a functional analysis of the initial baseline scan. Two targets are derived from the baseline scan of each participant and the study team determined which target to use based on the best possible matching of participants based on age, sex, and cognitive performance. Since the participant population is quite limited, it is not possible to match on all characteristics. Coordinates for TMS targeting will also be informed by E-field modeling. TMS will be delivered using a MagVenture stimulator immediately prior to encoding task in the MRI scanner. Stimulation parameters comprised 50-Hz triplets at 5 Hz applied for 2 seconds, with an entertain interval of 8 seconds; 40 trains were delivered, lasting a total of 4.5 minutes. Targets for stimulation will always be participant specific and will be derived using two methods.

Selection of Subjects

For Healthy Older Adult Controls

This study will enroll a small number of healthy older adult controls in order to test the task acceptability and efficacy at eliciting desired performance. Inclusion criteria for health controls include:

- Age 60-82
- No history of psychiatric disorders other than depression and generalized anxiety disorder.
- Stable dose (unchanged for 3+ months) or no use of psychoactive medications.
- Normal cognition as measured by the MoCA, NACC, NIH Toolbox, and Rey

For Subjects with amnestic Mild Cognitive Impairment (MCI-AD)

All diagnostic assignments for the MCI-AD diagnosis is decided through a clinical consensus by the clinicians, a process that considers all sources of information including an individual's premorbid function, medical conditions, and neuropsychological testing, including the Mini-Mental State Exam (MMSE), and Clinical Dementia Rating (CDR). Subjects must either be free of psychotropic medications, or continue on stable doses of psychotropic medications with dosage unchanged for at least four weeks prior to study entry. The final decision to recruit a given MCI-AD patient into the current project will be made by Dr. O'Brien in his memory clinic. Subjects who receive the clinical diagnosis of MCI-AD, and meet other eligibility criteria for the study, including no contraindications to MR scanning and TMS, will be invited to participate.

Study Inclusion Criteria:

1. Age restrictions
    a. Age 60-82
2. Willing to provide informed consent
3. English speaking
4. Signed HIPAA authorization
5. Use of effective method of birth control for women of childbearing capacity
6. Concern regarding a change in cognition (obtained from the patient)
7. Preservation of independence in functional abilities and maintenance of their independence of function in daily life with minimal aids or assistance (e.g., paying bills, preparing a meal, shopping).
8. Not demented, including a CDR score of (but not exceeding) 0.5
9. Subjects must stay on the same dose of psychiatric medication (if any) throughout the study

Study Exclusion Criteria (ascertainment when appropriate):

1. Current history of substance abuse or dependence (excluding nicotine)
2. Women who are pregnant or breast feeding
3. Current significant laboratory abnormality or serious medical illness (physician evaluation, medical history)
4. Diagnosed but untreated Axis I DSM-IV disorder (MINI, DSM-IV) including depression and anxiety
5.Diagnosed with any of the following conditions (current unless otherwise stated):
    a. Psychotic symptoms
    b. Bipolar I disorder (current or lifetime)
    c. Life-threatening anorexia or any other disorder requiring immediate hospitalization

d. High-risk for suicidal behavior, including current suicidal ideation with a method and plan, or hospitalization for suicidal behavior within 1 year before the study.

e. Schizophrenia

f. PTSD

6. Increased risk of seizure for any reason, including:

a. Prior diagnosis of epilepsy;

b. Seizure disorder;

c. Increased intracranial pressure, or;

d. History of significant head trauma, including with loss of consciousness for ≥ 30 minutes, alteration of consciousness for up to 24 hours following the event, or post-traumatic amnesia

7. Symptoms of dementia or severe cognitive impairment (a score > 135 on the Mattis Dementia Rating Scale)

8. Neurological disorder including, but not limited to:

a. Any condition likely to be associated with increased intracranial pressure;

b. Space occupying brain lesion;

c. History of stroke;

d. Personal history of seizures;

e. First-order family history of seizures;

f. History of cerebrovascular accident;

g. Fainting;

h. Transient ischemic attack within two years;

i. Cerebral aneurysm;

j. Dementia;

k. Huntington chorea;

l. Parkinson's disease;

m. Multiple sclerosis

n. trigeminal neuralgia

9. Intracranial implants, such as:

a. Cochlear implants;

b. Aneurysms clips;

c. Shunts;

d. Stimulators;

e. Electrodes;

f. Cardiac pacemakers;

g. Vagus Nerve stimulation devices.

10.Current use of medications known to lower the seizure threshold

11. Currently on psychotropic medications with dosage unchanged for less than four weeks prior to study entry OR plan to make changes in medication within 2 months after starting the study

Subject's Capacity to Give Legally Effective Consent

N/A: Study involves participants with MCI, who are not decisionally impaired. Only individuals capable of consent will be enrolled in the consent process.

Risk/Benefit Assessment

There are no known long-term health risks to the use of MRI when operated within FDA guidelines. However, there are safety concerns posed by the strong magnetic fields used to make images collected with MRI. All scans conducted under this protocol meet the FDA's guidelines for non-significant risk for static field strength, specific absorption rate (SAR), time varying magnetic fields (dB/dt), and acoustic noise.

There are no known long-term health risks to the use of TMS per se when operated within consensus safety guidelines (Rossi et al., 2009). The Duke Medical Center Institutional Review Board recently classified two similar research applications of TMS proposed by the PI as a "non-significant risk" (Protocols 65334 and 24349). In 2008, the FDA approved the use of high frequency TMS in the treatment of depression. Also in 2008, an international consensus conference on safety guidelines for TMS met, including a representative from our own lab . Their report (Rossi et al., 2009) systematically reviewed the thousands of healthy subjects and patients who have undergone TMS in order to allow for a better assessment of relative risks. The relative infrequency of adverse events using TMS was noted. They concluded that in the case of Class 3 studies (studies involving indirect benefit and low risk in normal subjects and patients that are expected to yield important data on brain physiology or safety, but have no immediate relevance to clinical problems), normal volunteers should be permitted to participate in TMS research when it is likely to produce data that are of outstanding scientific or clinical value. They also concluded that this research can be performed in a non-medical setting (i.e., psychology labs, robotics labs, research institutions, etc. as opposed to a hospital or appropriately equipped outpatient clinic). The Rossi et al. consensus report went on to suggest safety guidelines based on the now rather extensive international experience with TMS. These guidelines include the TMS intensity and timing parameters considered safe, training, and planning for and managing emergencies. We will follow these guidelines, and have incorporated them into our screening and session procedures. The consensus safety guidelines (Rossi et al., 2009a) are included as a Study Documents attachment with this IRB application.

Participation is voluntary, and there will be no pressure or time constraints regarding the decision to participate. There are no direct benefits to the participants except for the monetary reward or compensation, as well as the good will of helping the progress of scientific research. The information learned from this study may aid our understanding of the mechanisms of action underlying TMS and the dose-response relationships between stimulation and neural activity.

MRI Adverse Events Plan:

An MRI procedure is considered to be "minimal risk" according to federal definitions. To date, no after effects have been revealed and the FDA has classified the MR procedure as possessing a "non significant risk" for the subject of study. To minimize risks, all subjects will be screened for metallic devices, implants and other contraindications to scanning. Women of child-bearing capacity will be evaluated for pregnancy using a urine pregnancy test prior to scanning. Those unlikely to tolerate the sense of confinement during scanning will also be excluded.

Adequate safety monitoring and observation during scanning will be provided, as will measures to enhance the subject's physical and emotional comfort during the scan. It is possible that some subjects might experience minor distress by the confined and noisy conditions in the scanner. This possibility will be minimized by earplugs and headphones, and experienced technicians who will monitor all subjects for distress. In the event that a subject becomes anxious during a scan, the study will be halted. Subjects will be able to communicate with the investigators at all times using the intercom system should they wish to request that a study be terminated or have concerns or questions during the procedure. The subject is in full view of the operator at all times.

The probability of an incidental finding that might lead to the diagnosis of an unknown abnormality is greater than zero. All subjects will be alerted to this possibility during the consent process. In that event, subjects or their designated physician will be provided copies of their anatomical scans and advised to seek further evaluation if they have concerns.

TMS Adverse Events Plan:

Seizure is a theoretical risk with TMS. In the Rossi et al. report it was stated that "The occurrence of seizures has been extremely rare, with most of the few new cases receiving TMS protocols exceeding previous guidelines, often in patients under treatment with drugs which potentially lowered the seizure threshold." As Rossi et al. delineate, "rare" means that 16 cases (out of tens of thousands of TMS sessions over the last two decades) of seizure related to TMS have been reported. Eight occurred before safety parameters were established in 1997. Of the other eight reports, six occurred either when the safe TMS parameters were exceeded or other safety guidelines ignored, and the actual occurrence of a seizure has been questioned in the other two (i.e., convulsive syncope or pseudoseizure may have occurred). In a workshop convened by the National Institute for Neurological Disorders and Stroke (NINDS) in 1996, researchers in the field agreed upon a set of TMS consensus safety guidelines, including recommended stimulation parameters and contra-indications (Wassermann, 1998), and these consensus guidelines have been recently updated (Rossi et al., 2009). Widespread adherence to the 1996 guidelines has resulted in the virtual elimination of inadvertent seizures in TMS studies (Rossi et al., 2009). The levels of stimulation used in this protocol are well within safety guidelines (Rossi et al., 2009; Wassermann et al. 1998).

We will screen subjects for known risk factors for seizure with TMS (medical screening and medical history). Personnel who administer TMS are trained to recognize a potential seizure event and to act as "first responders" in order to administer appropriate initial care. All study personnel have undergone Basic Life Saving training, and seizure-specific training. The major physical signs the study personnel will look out for in detecting a potential seizure include chewing movements, convulsions/tremor/shaking, difficulty talking, a blank stare, eyes rolling up, and profuse sweating. If any of these signs are observed, study personnel will stop the research procedure and inquire whether the subject feels okay. If the subject is unresponsive (and therefore likely experiencing a seizure), first-aid will be supplied. The first-aid response consists of making sure the subject is physically safe for the duration of the seizure. This involves moving the subjects out of the TMS chair and onto the floor lying down on his or her left side. The subject will be kept lying down on his or her left side, while the staff call emergency medical help, via a 911 call. Resources available in the laboratory include a first-aid kit and immediate phone access. A

seizure constitutes a reportable adverse event, and will thus be immediately reported to the IRB via the Safety Events Form mechanism.

The most commonly reported side effect of TMS is headache. This headache is typically of a muscle-tension type. It usually develops during or immediately after the stimulation and may last for minutes to hours following the end of the stimulation. It is typically limited to the day of stimulation, and usually responds promptly to single doses of over–the-counter pain medications. Neck pain or scalp pain may also occur. Both are usually managed easily with over-the-counter analgesics.

As noted in Rossi et al. (2009), Loo and colleagues reported mild and transient changes in auditory threshold in two depressed patients following a 2-4 week TMS course of TMS(Loo et al., 2001). Cases of tinnitus have been reported after TMS treatments. In addition, in a recent study investigating the effects of TMS on symptoms of depression, a patient experienced moderate to severe tinnitus after an TMS session in which earplugs were not used. Rossi et al. recommended that hearing protection always should be worn during TMS application, and that individuals with cochlear implants not receive TMS. In the current study, earplugs will be worn by all subjects during TMS procedures. Individuals with cochlear implants will be excluded from participation.

Risks to the unborn children of pregnant women receiving MRI and TMS are unknown. Pregnant women will be excluded as per IRB policy. Female subjects are tested once with a urine pregnancy test prior to their first MRI session as per IRB-approved BIAC policy. These female subjects agree not to become pregnant while remaining within the subject pool, and to notify the experimenter or subject coordinator if they become pregnant. If sexually active, the subject must agree to use appropriate contraceptive measures for the duration of the study. Medically acceptable contraceptives include: (1) surgical sterilization (such as a tubal ligation or hysterectomy), (2) approved hormonal contraceptives (such as birth control pills, patches, implants or injections), (3) barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). Contraceptive measures such as Plan B (TM), sold for emergency use after unprotected sex, are not acceptable methods for routine use. If the subject has any uncertainty about whether they could be pregnant, another urine pregnancy test will be performed before they can participate in this protocol. The person(s) who will perform the urine pregnancy test will have successfully completed training as directed by the Chair of Obstetric and Gynecology of the Duke University School of Medicine. The urine pregnancy test kits used for this research study will be those commercially available test kit specified by the Chair of Obstetric and Gynecology and in routine use at DUHS.

Safety of TMS in the elderly: There have been no reports of serious adverse events with the use of TMS in elderly subjects in all of the clinical studies reported to date.

Risks associated with the MCI cohort As with any clinical population in disease, age-related neurodegenerative conditions are often associated with psychiatric comorbidity, including post-traumatic stress disorder, anxiety disorders, and disorders of compulsion. Difficulty with recruiting subjects with a lack of comorbidities is anticipated but we will nonetheless filter available subject pools to avoid patients with such exclusion criteria.

Genetic Data: It is possible that when analyzing certain regions of the genome we may discover information concerning whether or not that person has or may develop a particular disease. Due to the candidate genes we will be analyzing, the most likely examples of this are: discovery that the volunteer has a mutation leading to a form of Parkinson's when examining genes such as alpha-synuclein or leucine-rich repeat kinase 1, discovery that a volunteer carries a mutation conferring a Mendelian form of Alzheimer's disease (AD) when examining presenilin or APP genes, or discovery that the individual has increased likelihood of developing AD due to the presence of a particular ApoE allele. Such information regarding disease status would not be given to the volunteer, and will be stored separately from personally identifying information. The volunteer is informed at the time of consent that this is the case, and that they should consult their physician if they have medical concerns. All genetic testing takes place in a non-clinical laboratory.

Data Management, Analysis and Statistical Considerations

For external collaborators/personnel who are NOT ENGAGED in the research but are handling de-identified or a limited data set of Duke data, include their name, role and a description of the data. DWI fiber tracking. Our DWI tractography methods have been reported (Davis et al., 2009). For a priori tracts connecting the MT cortex, we use TrackVis (trackvis.org) to identify MT and all connecting regions (FEF, IPS)(Kier et al., 2004b, a). FA values are extracted and analyzed using standard statistics.

Power analysis. This R21 mechanism supports exploratory studies, and there are no direct data to inform power estimates for our specific manipulations. Nonetheless, we do have estimates of the support for controllability in supporting behavioral enhancements due to TMS, summarized above52. Power calculations were therefore conducted in R statistical software (R Development Core Team, 2016).

The first primary outcome measure is the difference in memory accuracy between TMS conditions (active vs. sham, network-targeted vs. traditional targets); to estimate likely effect sizes we use data from our NIA-funded K01, which used the same behavioral task. Here we observed an effect size of 0.7 [ (MTMS – MSham) /σpooled]. This moderate effect size is due largely to a low sigma (~0.05), which we attribute to extensive piloting for a memory paradigm that reduces the variations in performance across individuals. Thus, a power analysis was performed using the two-tailed t-test, Sidak corrected for 3 comparisons (based on a mixed-effects design consisting of 4 repeated measurements per subject (2 memory conditions [successful, unsuccessful] x 2 TMS targeting [network-based, traditional targeting)], with an alpha of 0.05 and a power of 0.7. This analysis found that an n = 37 would be required; accounting for a 29% dropout rate, we therefore recruit 55 MCIs.

The second primary outcome measure comprises longitudinal changes in the same measures; as such a different approach is not only the sample size, but also how many sessions are necessary to detect an effect? For the behavioral estimates, we analyze the TMS Condition x Session interaction, which comprised 4 sessions of TMS with longitudinal estimates of behavior in 30 older adults. Here we observed an effects size of 0.8, due largely to lower sigma values, reflecting consistent changes over time within TMS conditions. As such, we can expect a reasonable power with 3 sessions of the same

task, using 20% larger sample, and remain resilient to the moderate dropout we see in our MCI patient population.

Data & Safety Monitoring

The subjects will be fully informed of the nature of the study requirements prior to enrollment and periodically throughout the study. The subject's wellbeing will be continuously monitored by the experimenter, and the Principal Investigator will report all serious adverse events in an expedited manner to the Duke University Health System (DUHS) Institutional Review Board (IRB) office and all applicable regulatory authorities in accordance with the Center's standard operating procedures.

The study monitor will be Dr. Andrew Liu. Dr. Liu will ensure the quality of the study and establish that each co-investigator is complying with the investigational plan and IRB regulations. Monitoring of this protocol is simplified by the fact that this study involves a small number of investigators and a single facility in which the study is being conducted.

Throughout the investigation, the monitor will ensure that the facilities being used continue to be acceptable for the purposes of the study, that the investigational plan is being followed, that any changes to the protocol have received IRB approval and have been reported to the sponsor, that accurate, complete, and current records are maintained, that accurate, complete, and timely reports are made to the IRB. This will be accomplished through quarterly meetings during which the status of the protocol, investigators, and IRB compliance are reviewed. The monitor will review each research chart for completeness and accuracy. He will confirm that inclusion and exclusion criteria have been met for each subject enrolled, and compliance with all other aspects of the investigational plan are met.

Occasionally, participants in this study will later be recruited into a related research study that has overlapping components of cognitive evaluation or structural imaging. To reduce the burden of the study on the participant and remove the confounding influence of re-testing cognitive evaluations this study uses limited data sharing. Only for participants enrolled in both studies within the validity window of the applicable measures (typically 6-12 months) this study will share overlapping collected data with: Pro00085432 (Bilateral), Pro00079534 (CONNECT), Pro00107503 (SchemRep).