A Single Arm Study of Resting State Functional Magnetic Resonance Imaging (rs-fMRI)-Guided Theta Burst Stimulation (TBS) in Early-Stage Alzheimer's Disease (AD)

SHORT TITLE: TMS PILOT IN EARLY AD

Protocol Number: Version 3.0

National Clinical Trial (NCT) Identified Number: 05292222

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Sponsor: HealthPartners Neuroscience Research

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CONFIDENTIALITY STATEMENT

This document is confidential communication. Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior approval of the Principal Investigator or other participating study leadership and as consistent with the terms of the award.

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STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Council for Harmonisation guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46) All personnel involved in the conduct of this study have completed human subjects protection training.

INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines, as described in the *Statement of Compliance* above.

Principal Investigator or Clinical Site Investigator:

Signed: _____ Date: _____

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: A Single Arm Study of Resting State Functional Magnetic Resonance Imaging (rs-fMRI)-Guided Theta Burst Stimulation (TBS) in Early-Stage Alzheimer's Disease (AD)

IRB Number:

Study Description: Alzheimer's disease (AD) is a progressive neurodegenerative condition affecting 6.2 million individuals in the United States, resulting in an annual cost of care of $305 billion. AD is functionally characterized by progressive degeneration of large-scale brain networks (LSBNs), including the default mode network (DMN) presumably from the deposition of amyloid plaques and neurofibrillary tangles. Available FDA-approved medications for AD such as donepezil and memantine offer limited benefit and modest impact on quality of life. In combination with resting state functional MRI (rs-fMRI), transcranial magnetic stimulation (TMS) with intermittent theta burst stimulation (iTBS) offers a non-invasive alternative to pharmacotherapy in persons with AD. We propose a pilot trial using rs-fMRI to target dysfunctional LSBNs in early stage AD.

Objectives: Primary Aim: To estimate the effect of rs-fMRI-guided TBS on connectivity dysfunction within the temporal area G dorsal (TGd) in persons with early stage AD.

Exploratory Aim 1: To estimate the effect of rs-fMRI-guided TBS on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) score in persons with early stage AD.

Exploratory Aim 2: To estimate the effect of rs-fMRI-guided TBS on the Geriatric Depression Score (GDS) in persons with early stage AD.

Exploratory Aim 3: To identify and estimate the effect of rs-fMRI-guided TBS on two additional dysfunctional parcellations within the default modal network (DMN), central executive network (CEN), and salience network (SN) in persons with early stage AD.

Endpoints: Primary Endpoint: Connectivity Measures of the TGd parcellations at baseline and post-treatment

Exploratory Endpoints:

- RBANS at baseline and post-treatment
- GDS at baseline and post-treatment
- Connectivity levels of other parcellations that are anomalous

Study Population: The study will enroll 10 subjects with a diagnosis of early stage AD (mild cognitive impairment or mild AD).

Inclusion criteria:

1. Established diagnosis of MCI/mild AD
2. Evidence for CNS amyloidosis (e.g., Amyloid PET or CSF biomarkers consistent with AD)
3. Prior brain imaging performed
4. MMSE >24
5. CDR 0.5-1

6. Stable dose of cholinesterase inhibitors and memantine for at least one month
7. Subjects are between 40-90 years of age

Exclusion Criteria:

1. Non-AD dementia including, but not limited to, Lewy body dementia, frontotemporal dementia, vascular dementia, Jakob-Creutzfeldt disease, etc.
2. Inability to tolerate rs-fMRI
3. Contraindication of rs-fMRI due to implants or metal
4. Seizure disorder
5. Alcoholism

Description of Sites/Facilities Enrolling Participants:	Participants will be enrolled at HealthPartners Neuroscience Center, located at 295 Phalen Blvd., St. Paul, MN 55130.
Description of Study Intervention:	All subjects will receive treatment with intermittent theta burst stimulation (iTBS), There will be a total of 5 iTBS sessions per treatment visit, and a total of 5 treatment visits distributed over a two-week period (#3 during week 1 and #2 during week 2). All patients will receive iTBS to the right TGd region. In addition, we will further provide TBS treatment for two additional sites within the LSBNs that is found to contain the greatest number of connectivity anomalies. Data from the Infinitome program will be exported to the Localite TMS Navigator; the navigator is a device that visualizes brain regions to facilitate correct positioning of patient and coil based on the coordinates from the Infinitome analysis.
Study Duration:	The duration of this study is 1.5 years.
Participant Duration:	10-12 weeks

1.2 SCHEMA

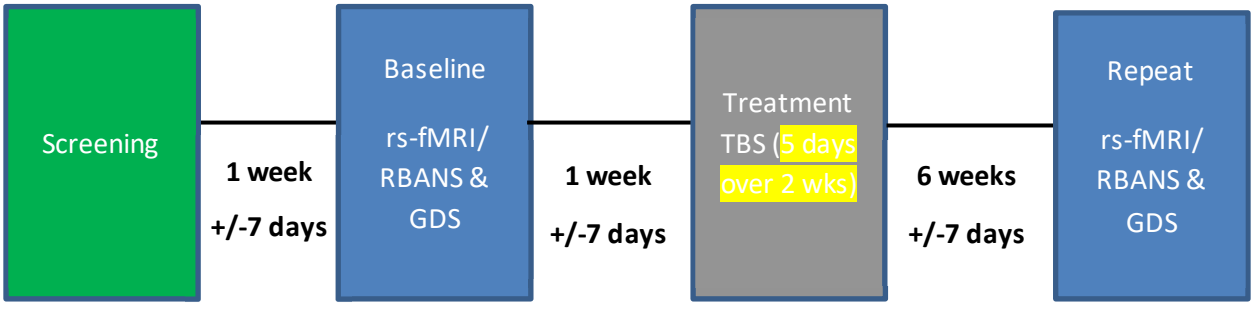


Figure 1: Study Visit/Workflow

1.3 SCHEDULE OF ACTIVITIES (SOA)

Table 1: Study Visit Schedule

Procedure	Screening	Baseline	Treatment	Follow-up	Early Withdrawal
Visit #	Visit 1	Visit 2	Visits 3-7	Visit 8	
	Day 0	Week 1	Weeks 2-4	Week 10	
Window		± 7 Days	± 7 Days	± 7 Days	
Informed consent	X				
Medical History	X				
Demographics	X				
MRI Contraindications	X	X	X		
Concomitant Medications	X	X	X	X	X
Inclusion/Exclusion Criteria	X	X	X		
MMSE	X				
CDR	X				
TMS Safety Questionnaire	X	X			
Physical Exam	X				X
RBANS		X		X	
GDS		X		X	
iTBS Treatment			X		
MRI Imaging		X		X	
Adverse Events/Serious Adverse Events	X	X	X	X	X

2 INTRODUCTION

2.1 STUDY RATIONALE AND BACKGROUND

Alzheimer's disease is the most common cause of dementia, the 6th leading cause of death, and the only illness among the top ten that cannot be slowed, prevented, or cured (cite All Association Facts and Figures). The condition affects 6.2 million Americans and results in $305 billion in annual costs ("2021 Alzheimer's disease facts and figures," 2021). The pathological signature of AD is the presence of cerebral amyloid plaques and neurofibrillary tangles resulting

in disrupted connectivity of large-scale brain networks (LSBN), including, but not limited to the default mode network (DMN). Available FDA approved treatments for AD temporary alleviate symptoms but have no bearing on overall disease progression (Mielke et al., 2012). Furthermore, cholinesterase inhibitors, the most commonly prescribed drugs for AD, cause dose-limiting gastrointestinal side effects in 20% of patients. Therefore, the current limitations of cognitively enhancing medications suggest a role for a more targeted treatment in AD.

Transcranial magnetic stimulation (TMS) is a therapeutic tool, consisting of magnet and coil that utilizes Faraday's principle to induce electric currents in specific brain regions, leading to cortical excitability or suppression (Janicak & Dokucu, 2015). The treatment is relatively safe with the most common side effect being tension headache (to which patients frequently acclimate over time) and is FDA-approved for the treatment of depression (Janicak & Dokucu, 2015). The device is routinely used in outpatient psychiatry clinics including HealthPartners and Park Nicollet behavioral health. Repetitive TMS (rTMS) has been shown to induce changes in cortical excitability and modulate neural network activity beyond the duration of the stimulus itself (Pascual-Leone et al., 2011). Intermittent theta burst stimulation (iTBS) is a more recent variation of TMS that delivers longer lasting change in brain activity with less stimulation and has likewise been found to be safe and well-tolerated by patients (Blumberger et al., 2018; Gonsalvez, Baror, Fried, Santarnecchi, & Pascual-Leone, 2017). Whereas, rTMS applied to the dorsolateral prefrontal cortex is an FDA approved treatment for refractory depression, TMS has significant potential as a targeted treatment for cognitive disorders. A proposed mechanism is that persistent enhancement of cortical excitability results in long-term potentiation (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005) and increased expression of brain derived neurotrophic factors (Phillips et al., 1991).

In addition to improving mood, TMS has demonstrated positive effects on cognitive performance. TMS has been shown to improve memory in young and healthy elderly individuals (Manenti, Cotelli, Robertson, & Miniussi, 2012) as well as in memory impaired adults (Gonsalvez et al., 2017). In mild-moderate AD, rTMS at 20 Hz applied over the DLPFC resulted in improvement of object naming at 8 weeks (Cotelli et al., 2011). In addition, this frequency and anatomical location has improved performance in mild AD on the MMSE, the instrumental activities of daily living (IADL) scales, and global deterioration scale at 3 months, but no such benefits were noted in severe stage dementia (Ahmed, Darwish, Khedr, El Serogy, & Ali, 2012). An investigation targeting the precuneus, a hub within the DMN, with 20 Hz stimulation lead to improved episodic memory performance compared to sham (Koch et al., 2018). In addition, this study was remarkable in showing that iTBS, a more efficient approach to non-invasive neurostimulation, was well-tolerated in prodromal AD (Koch et al., 2018) In addition to AD, rTMS applied to the DLPFC at 10 Hz in MCI has resulted in cognitive benefits (Marra et al., 2015). The use of rTMS in conjunction with concurrent cognitive training has further improved

outcomes relative to placebo on the ADAS-Cog, MMSE, and CGIC lasting up to 4.5 months (Bentwich et al., 2011; Lee, Choi, Oh, Sohn, & Lee, 2016; Jose Martin Rabey & Dobronevsky, 2016; Jose M Rabey et al., 2013). Prior areas that have been targeted by TMS treatments for memory impairment in AD include the left/right dorsal prefrontal cortex, left inferior frontal gyrus, left middle temporal gyrus, left/right temporal parietal junction, precuneus, and left/right superior parietal lobule (Gonsalvez et al., 2017).

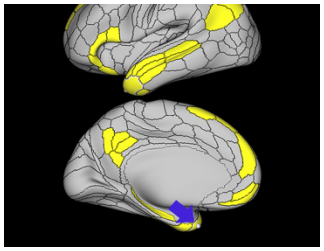
Investigation of the role of TMS in AD has been guided by anatomical landmarks, prolonged EEG, and structural imaging, but has yet to leverage resting state fMRI (rs-fMRI) imaging of LSBNs. rs-fMRI clinical tool relies on the low-frequency fluctuation in the blood-oxygen-level-dependent contrast (BOLD) signal to interrogate LSBNs (Joo, Lim, & Lee, 2016). In the behavioral health literature, rs-fMRI has been employed to better target key brain regions and networks responsible for mood regulation and have shown improvements in mood compared to standard approaches to treatment (Cole et al., 2019). Thus, the combination of rs-fMRI with TMS has the potential to enhance outcomes in targeted interventions for cognitive dysfunction.

*Omniscient (*Forbes Startup -30 Million*),* a for-profit, Sydney, Australia-based company, has designed the Infinitome program, which utilizes data from the Human Connectome Project (HCP) together with machine learning to analyze diffusion tensor and resting-state fMRI imaging data from remote sites. The HCP commenced one of the most ambitious neuroscientific initiatives to "map the brain(Glasser et al., 2016)," identified 379 functional areas of the cerebrum, and discovered 97 new brain regions that had not been previously described. The foundation for this imaging tool is based upon the HCP atlas, which has also informed prior publications from our group, including the Connectomic Atlas of the Human Cerebrum (Baker et al., 2018). The Infinitome program creates a subject specific version of the Human Connectome Project Multimodal Parcellation (HCP-MMP1) atlas using diffusion tractography (DT). Analytics are performed on both diffusion tensor imaging (DTI) and rs-fMRI (see appendix *Guide to Planning an Infinitome Study*). Outlier detection using a tangent space connectivity matrix is performed by comparing results with a subset of 300 normal HCP subject fMRI samples to determine the range of normal correlations for each regions of interest in a LSBN. Abnormal connectivity is determined as a 3-sigma outlier for that correlation. The program includes a 15-minute imaging protocol that can readily be added on to structural MRI sequences and provides automated support for image analysis, thus simplifying the process of accessing clinically applicable imaging data. Preliminary work has shown that connectomic analysis in AD subjects using this software is feasible and can detect functional anomalies involving regions of interest described by the HCP (Ren et al., 2020).

Our preliminary research at HealthPartners using Infinitome in AD (n=4) and dementia with Lewy bodies (n=6) has shown temporal area G dorsal (TGd) (**Figure 2**) within the default mode network to have connectivity anomalies in persons with dementia. We suspect this area to be

important in the clinical presentation of various dementia, and therefore, these regions may be targeted with transcranial magnetic stimulation to improve symptoms.

Figure 2: Temporal Area Gd



2.2 RISK/BENEFIT ASSESSMENT

2.2.1 KNOWN POTENTIAL RISKS

Transcranial Magnetic Stimulation (TMS)

The TMS device to be used in this study is the MagVenture TMS Therapy® with theta Burst stimulation. MagVenture is a computerized, electromechanical medical device that produces and delivers non-invasive, magnetic fields to induce electrical currents targeting specific regions of the brain. In 2018, MagVenture received FDA clearance for the 3 minute protocol which we market under the trademarked name Express TMS®. The Lancet: "THREE-D: a randomized non-inferiority trial"), comparing the standard, 37 minute TMS protocol to the newer, 3 minute Theta Burst protocol (TBS) (Blumberger et al., 2018). The study concluded that the Theta Burst protocol is just as safe and effective for the treatment of major depressive disorder as standard TMS. Recent safety review of TMS summarizes the Theta Burst studies and concludes that TBS in the range of 80-100% of motor threshold is safe (Supplementary Table 5, (Rossi et al., 2020)). In this study, the planned motor threshold is 80%.

The TMS devices are non-significant risk devices, in line with the criteria for exception from an IDE. Transcranial magnetic stimulation (TMS) is a therapeutic tool, consisting of magnet and coil that utilizes Faraday's principle to induce electric currents in specific brain regions, leading to cortical excitability or suppression (Janicak & Dokucu, 2015) . The treatment is relatively safe with the most common side effect being tension headache (to which patients frequently acclimate over time) and is FDA-approved for the treatment of depression (Janicak & Dokucu, 2015). The device is routinely used in outpatient psychiatry clinics including HealthPartners and Park Nicollet behavioral health. Patients are generally able to drive home or return to work immediately after an TMS session. Rare side effects include dizziness, memory trouble, trouble concentrating and sudden mood changes. The long-term effects of TMS are not known.

Magnetic Resonance Imaging (MRI)

Structural MRI is a routine diagnostic procedure at HealthPartners, and the resting state portion merely requires 15 minutes of scan time. The patient may experience claustrophobia with the narrow imaging space and hearing loud noises while inside the machine. An MRI scan does not involve radiation like conventional X-rays. Instead, images are generated using a magnetic field and radio signals. Because an MRI scanner uses strong magnets, subjects will be screened by the NSC Imaging staff – as for a routine MRI. People with artificial heart valve, metal plate, pin, or other metallic objects in their body (including gun shot or shrapnel) will not be eligible for this study.

Neuropsychological Testing

Neuropsychological testing may result in frustration on the part of the patient but does not have any other significant risks.

Loss of Confidentiality

There may be a slight possibility of breach of confidential information that was collected. However, the following procedures will be implemented to reduce this risk:

- Data collection and reporting tools will be developed and stored internally.
- Data collected and stored electronically will remain confidential and secure (e.g. secured server and password protected files [REDCap]).
- Study binders will be stored in a locked file cabinet within a locked office.
- After the study is closed, all subject identifiers will be destroyed.

2.2.2 KNOWN POTENTIAL BENEFITS

Benefits for the patient include the ability to review imaging of their rs-fMRI imaging studies. In addition, patients may experience improvements in mood or cognition with the TMS although this has not been well-established at this time.

This research will be important to better investigate the role of non-invasive neurostimulation for symptoms in AD in a larger cohort and will support a future application for an NIH-sponsored grant.

2.2.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

We believe the potential risks to the participants in this study are minimal.

The following measures will be taken to protect patients from risk of TMS

- Transcranial magnetic stimulation is associated with a 50% risk of self-limiting headache and a 1/10,000 risk of seizures. All patients will undergo the TMS Adult Safety Screen (TASS), which will ensure that the risk of seizure is negligible for each subject participating in the study. In the event of adverse events during TMS treatment, specific procedures will be outlined (aligned with HealthPartners Behavioral Health) and staff will be trained and on-site for any assistance. In addition, all research staff will be

trained on the operation of device (Fried et al., 2020). Repeated exposure to TMS may result in sensorineural hearing loss, which is prevented by routine use of ear plugs.

- Relative to most oral medications used in treatment of dementia, TMS has a very favorable side effect profile.

The following measures will be taken to protect providers and patients from the risk of breach of confidentiality:

- A unique study ID code unrelated to the medical record number or other study subject-specific information will be assigned to each patient and used to link data from various sources and needed for analysis. The study number will be used on the RedCap database and Infinitome Program. All imaging data uploaded from the NSC research site will be de-identified and uploaded to the Infinitome cloud-based server.
- Infinitome program uses an industrial grade cyber security that is superior to what is offered at the leading medical device companies. No personal health information is stored on servers and only de-identified scans are stored on a dedicated edge node on encrypted MinIO instances. Patient data is only accessed through authenticated calls form Kubernetes pods contained in the VPC. The web service requires user authentication. Only the data related to a specific facility can be retrieved through authenticated calls and are restricted to their use.

3 OBJECTIVES AND ENDPOINTS

Table 2: Objectives and Endpoints

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To estimate the effect of rs-fMRI-guided TBS on connectivity dysfunction within the temporal area temporal area G dorsal (TGd) in persons with early stage AD.	*Connectivity measures of the TGd parcellations at baseline and post-treatment*	*Infinitome processed rs-fMRI data that is targeted with TMS*
Exploratory		
1. *To estimate the effect of rs-fMRI-guided TBS on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) score in persons with early stage AD.* 2. *To estimate the effect of rs-fMRI-guided TBS on the Geriatric Depression Score (GDS) in persons with early stage AD*	1. *RBANS at baseline and post-treatment* 2. *GDS at baseline and post-treatment*	*Provide pilot data for larger trials.*

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
3. *To identify and estimate the effect of rs-fMRI-guided TBS on two additional dysfunctional parcellations within the default modal network (DMN), central executive network (CEN), and salience network (SN) in persons with early stage AD.*	3. *Connectivity levels of other parcellations that are anomalous*	

4 STUDY DESIGN

4.1 OVERALL DESIGN

This investigation is a prospective single arm treatment trial in early stage AD (MCI and mild AD).

Primary Aim

To estimate the effect of rs-fMRI-guided TBS on connectivity dysfunction within the temporal area temporal area G dorsal (TGd) in persons with early stage AD.

Exploratory Aims

1. To estimate the effect of rs-fMRI-guided TBS on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) score in persons with early stage AD.
2. To estimate the effect of rs-fMRI-guided TBS on the Geriatric Depression Score (GDS) in persons with early stage AD.
3. To identify and estimate the effect of rs-fMRI-guided TBS on two additional dysfunctional parcellations within the default modal network (DMN), central executive network (CEN), and salience network (SN) in persons with early stage AD.

4.2 OVERVIEW – STUDY PROCEDURES/DATA COLLECTION

Early AD (MCI and Mild AD) patients will be recruited from a multidisciplinary dementia clinic. Patients will receive TMS treatment and data will be obtained for cognitive measures and imaging. This research investigation will take place at the Center for Memory and Aging at the HealthPartners Neuroscience Center (multidisciplinary dementia clinic).

4.3 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed study visits and assessments.

5 STUDY POPULATION

The study will enroll 10 subjects with a diagnosis of early stage AD (mild cognitive impairment or mild AD). Those patients where fMRI is contraindicated (e.g. implantable device, pacemaker, metallic implants, etc.) or who are unable to tolerate sitting for a one-hour fMRI will be excluded from the study.

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Established diagnosis of MCI/mild AD
2. Evidence for CNS amyloidosis (e.g., Amyloid PET or CSF biomarkers consistent with AD)
3. Prior brain imaging performed
4. MMSE >24
5. CDR 0.5-1
6. Stable dose of cholinesterase inhibitors and memantine for at least one month
7. Subjects are between 40-90 years of age

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Non-AD dementia including, but not limited to, Lewy body dementia, frontotemporal dementia, vascular dementia, Jakob-Creutzfeldt disease, etc.
2. Inability to tolerate rs-fMRI
3. Contraindication of rs-fMRI due to implants or metal
4. Seizure disorder

5.3 LIFESTYLE CONSIDERATIONS

N/A

5.4 SCREEN FAILURES

Research Referral Form: This will be filled out by PI or qualified designee to assess the appropriateness of TMS in these patients. Patients will be considered ineligible and not screened if they do not meet one or more of the criteria.

Pre-screening Phone Call: All potential participants will undergo a pre-screening phone or a video call to determine whether they meet the inclusion/exclusion criteria. Patients will be considered ineligible if they do not meet one or more of the inclusion/exclusion criteria during pre-screening.

We will collect information on why participants are ineligible or decide not to move forward with the trial.

Screen failures are defined as participants who are considered eligible during the pre-screening phone call, but it was subsequently determined that they do not meet one or more of the inclusion/exclusion criteria. We will collect information on why participants screen fail or decide not to move forward with the trial.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

All subjects will be recruited from the Center for Memory and Aging clinic. An Epic-based list has been created with subjects having either an MCI or early AD diagnosis. Patients and their caregivers will be presented with the option of participating in the study by the PI including providing a brochure at the clinic visits. Participants with clinic visits will meet with research staff. Other patients will be mailed/e-mailed a letter and flyer/brochure. An informed consent form will be provided to those individuals expressing interest in the study. A video or phone encounter will be arranged to provide additional details of the study and informed consent

To reach our target enrollment, we anticipate that we will need to screen 40 people.

Remuneration: Participants will be provided gift cards totaling $100 per subject. The gift cards will be provided at the end of the study for completing all the study visits.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

All subjects will receive TMS treatment with intermittent theta burst stimulation (iTBS). The TMS devices are non-significant risk devices, in line with the criteria for exception from an IDE.

The TMS device to be used in this study is the MagVenture TMS Therapy® (MagPror30/Theta Burst option) with theta Burst stimulation (See User Guide). A B65-coil – FDA cleared figure 8 coil will be utilized for iTBS treatment. In 2018, MagVenture received FDA clearance for the 3 minute protocol which we market under the trademarked name Express TMS® for Major depressive disorder (Blumberger et al., 2018), but TMS is not approved by the FDA for symptoms in Alzheimer's disease.

Localite Neuro Navigator will utilized to stimulate brain regions identified by the Infinitome software and allows correct positioning of the patient and coil (https://www.magventure.com/tms-research/localite-neuronavigation).

6.1.2 DOSING AND ADMINISTRATION

There will be a total of 25 intermittent theta burst sessions (iTBS) spread evenly across 5 treatment visits (5 sessions per treatment visit), all distributed over a two-week period (#3 treatment visits during week 1 and #2 during week 2). Intermittent theta burst sessions will be administered at the following settings, which have been used in a standardized manner by our collaborators in their TMS clinic:

Table 3: TMS Treatment Parameters

Resting Motor Threshold	80%
# of Pulses/Session	1200 pulses (40 cycles x 10 burst pulses x 3 pulses per burst pulse)
Inter-Train Interval	8 sec
Pulse Frequency in Burst	50 Hz
Session Length	15-30 min
Time between Sessions	45 min to Hour
Number of Targets	3
Number of Sessions per Day	5
Treatment Days	5
Total Pulses per Day	18,000
Total Pulses for Treatment	90,000

The treatment regime above will be applied to a total of three regions of interest or parcellations (right TGd + two other sites found to have greatest # of anomalies). The interval between treatment of separate regions of interest (target) will be 2 minutes. The interval between iTBS sessions within the same treatment visit will be 45-60 minutes. Details of the operations of TMS and intervention will be included in a SOP or User guide that will be kept on site.

During the treatment, the TMS operator will be in the room and trained to activate the seizure protocol (*https://healthpartnersconnect.sharepoint.com/:b:/r/sites/bhc/TMS%20Library/Safety/Emergency%20Management%20of%20Seizures%20Standing%20Order.pdf?csf=1&web=1&e=p5h4Gg*. All patients will be screened with the TASS screening questions. Vital signs will be monitored prior to and after treatment in participants.

6.2 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

N/A

6.3 STUDY INTERVENTION COMPLIANCE

Each treatment will be recorded on CRFs developed internally and will be based on HealthPartners Behavioral Health Clinic workflow and documents.

6.4 CONCOMITANT THERAPY

Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications and supplements. Specifically, any medication with that increases the risk of seizure will be documented in CRF and judged by the PI if it is allowed in the study.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

If the patient develops a seizure, the PI may discontinue the TMS treatment and early withdrawal procedures will be performed.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may withdraw a participant from the study if:

- Any medical condition, event or situation occurs such that continued participation in the study would not be in the best interest of the subject.
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- Significant study procedure non-compliance
- Lost-to-follow up; unable to contact subject

7.3 LOST TO FOLLOW-UP

The reason for participant discontinuation or withdrawal from the study will be recorded on the relevant CRFs. Subjects who sign the informed consent form and undergo only cognitive measures, and not imaging or TMS will not have completed participation and may be replaced.

A participant will be considered lost to follow-up if he or she fails to attend any scheduled study visit and study staff are unable to contact the participant after at least 5 attempts.

The following actions must be taken if a participant fails to attend any required study visit:

- Study staff will attempt to contact the participant, reschedule the missed visit, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, telephone calls or e-mail – if no answer leave a voicemail on the first and last attempt). These contact attempts will be documented.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 STUDY SCHEDULE

See Figure 1 under protocol summary.

8.1.1 SCREENING VISIT (VISIT 1) DAY 0

- This visit may be virtual or in-person at NSC
- This visit will last about 90 minutes
- Review, obtain and document consent from subject and caregiver (e-consent)
- Administer MMSE, CDR
- Review medical history, demographics to determine eligibility to participate
- Review history regarding any contraindications for MRI imaging
- Schedule study visits for individuals who are eligible and available for the duration of the study.

8.1.2 BASELINE VISIT (VISIT 2) -WEEK 1 (± 7 DAYS)

- Verify inclusion/exclusion criteria
- Neuropsychological battery as mentioned in Section 8.2.
- This visit is at the clinic (HealthPartners Neuroscience Center [NSC]), is about 2 hours. This may be extended depending on availability of Imaging slot.

- Subject will undergo MRI imaging as mentioned in section 8.2
- Subject will be screened for TMS safety
- Review concomitant medications
- Record any adverse or serious adverse events

8.1.3 TREATMENT VISIT (VISTS 3-5 AND VISITS 6,7) (5 DAYS OVER 2 WEEKS, ± 7 DAYS AFTER VISIT 2)

- Verify inclusion/exclusion criteria
- Motor threshold mapping in Visit 3. Visit 3 will be 5 -7 hours. Visits 4-7 will be 4-6 hours each.
- All visits will be at NSC
- Subject will receive 5 theta burst stimulation sessions at each of the treatment visits
- Visits will be on alternating days (weekdays)
- Review concomitant medications at each visit
- Record any adverse or serious adverse events at each visit

8.1.4 FOLLOW-UP/REPEAT VISIT (VISIT 8)(WEEK 10, 6 WEEKS AFTER VISIT 7 ± 7 DAYS)

- Verify inclusion/exclusion criteria
- Neuropsychological battery as mentioned in Section 8.2.
- This visit is at the clinic (HealthPartners Neuroscience Center [NSC]), is about 2 hours. This may be extended depending on availability of Imaging slot.
- Subject will undergo MRI imaging as mentioned in section 8.2
- Review concomitant medications
- Record any adverse or serious adverse events

8.2 EFFICACY ASSESSMENTS

8.2.1 DEMOGRAPHICS AND MEDICAL HISTORY

Demographic information will be collected, including: gender, age, race, ethnicity, height, weight, BMI, education, dementia diagnosis, co-morbidities (such as Diabetes, Hypertension) and e-mail address for consent.

8.2.2 MMSE (MINI-MENTAL STATUS EXAMINATION)

Originally developed in 1976 by Folstein, the MMSE is a paper-based test commonly used in clinical and research settings (Folstein, Folstein, & McHugh, 1975). A 30 point cognitive screening tool that assesses orientation, working memory, short term memory, visuospatial construction, and language. This will be used in the screening visit for eligibility of participants in the study

8.2.3 CLINICAL DEMENTIA RATING (CDR)

The CDR is a 5-point scale used to characterize six domains of cognitive and functional performance applicable to Alzheimer disease and related dementias: Memory, Orientation, Judgment & Problem Solving, Community Affairs, Home & Hobbies, and Personal Care *http://alzheimer.wustl.edu/cdr/aboutcdr.htm*. The necessary information to make each rating is obtained through a semi-structured interview of the patient and a reliable informant or collateral source (e.g., family member). The CDR table (*http://knightadrc.wustl.edu/cdr/PDFs/CDR_Table.pdf*) provides descriptive anchors that guide the clinician in making appropriate ratings based on interview data and clinical judgment. In addition to ratings for each domain, an overall CDR score may be calculated through the use of an algorithm. This score is useful for characterizing and tracking a patient's level of impairment/dementia:

CDR-0.5 = very mild dementia

CDR-1 = mild

CDR-2 = moderate

CDR-3 = severe

In addition, the total CDR ratings for each of the six cognitive/functional domains can be added to create a CDR sum of boxes (SOB). This will be used in the screening visit for eligibility of participants in the study

8.2.4 NEUROPSYCHOLOGICAL ASSESSMENTS

All enrolled subjects will undergo the following cognitive scales. These will be administered by the research staff trained in these assessments using instructions specific for tests under the guidance/ supervision of the study neuropsychologist.

8.2.4.1 REPEATABLE BATTERY FOR THE ASSESSMENT OF NEUROPSYCHOLOGICAL STATE (RBANS)

The RBANS is a brief, individually administered neurocognitive battery measuring immediate and delayed memory, attention, language, and visuospatial skills. The RBANS is a "pencil-and-paper" test and requires only a stimulus booklet and record form for administration and scoring. It is specially designed for repeat evaluations and includes alternate forms to control for practice effects related to content. The measure is broadly used for clinical diagnostic purposes and has also been increasingly employed as an endpoint in clinical trial investigations of medications believed to impact neurocognitive status. The RBANS will be administered by a research staff member to early stage AD subjects at baseline and 6 weeks after treatment to assess for response to TBS intervention

8.2.5 MOOD ASSESSMENTS

8.2.5.1 GERIATRIC DEPRESSION SCALE (GDS)

The GDS is a screening measure for depression in older patients (http://neurosciencecme.com/library/rating_scales/depression_geriatric_ long.pdf). The scale will be administered by research staff at baseline and 6 weeks after TBS treatment.

8.2.6 MRI IMAGING

Subjects will undergo MRI imaging at HealthPartners Neuroscience Center. Subjects will be screened for any contraindications for MRI. Subjects will undergo a protocol based on recommendation by Omniscent (o8t MR Acquisition Recommendations). We anticipate 15 minutes of scan run time using a 3T Siemens Skyra scanner and the following images will be obtained.

1) High-resolution multi-scan directional diffusion scan, which is most similar to a diffusion tensor image (DTI) acquisition - Specifically, diffusion weighted imaging with the following acquisition parameters will be used: *2 mm x 2 mm x 2 mm voxels, FOV = 25.6 cm, matrix = 128 mm x 128 mm, slice thickness = 2.0 mm, one non-zero b-value of b = 1000, 40 directions, and gap = 0.0 mm.*
2) EPI BOLD rs-fMRI - *A resting-state fMRI as a T2-star EPI sequence, with 3 x 3 x 3-mm voxels, 128 volumes/run, a TE = 27ms, a TR = 2.8s, a field of view – 256mm, a flip angle = 90°*
3) Anatomical Scan –T1 Weighting

All images will be de-identified and uploaded to the infintome cloud-based server to be analyzed. Internal guidelines/best practices based on infinitome user manual will be developed for transfer, obtaining accounts, uploading of raw images and downloading of analyzed data.

This will be transferred to the Localite Neuro Navigator to help with target areas for TMS Treatment

8.2.7 CONNECTOMIC ANALYSIS

All subject images will be processed using the infinitome tool. This will be used to conduct a connectomic analysis to identify large scale brain networks.

The Infinitome tool creates a machine learning-based, subject specific version of the Human Connectome Project-Multimodal Parcellation (HCP-MMP1) atlas based upon diffusion tractography structural connectivity (Figure 3). All data uploaded to the cloud is de-identified. This novel method was created by training a machine learning model on 200 normal subjects by first processing T1 and DT images. An HCP-MMP1 atlas in NIFTI MNI space is then warped onto

each brain and the structural connectivity calculated between every pair of this atlas and a set of ROI containing 8 subcortical structures per hemisphere and the brainstem based on the streamlines which terminated within an ROI. To ensure this atlas is applicable to pathologically distorted brains, a machine-learning tool takes the individual's DTI or CSD tractography and locates every voxel and reassigns them to an area that fits more accurately with the structural connection to create a personalized adjusted atlas. The personalized patient atlas is used to subset the resting-state and CSD tractography data to create Structural and Functional connectivity matrices. When these matrices are compared to other individuals using machine-learning, an output of structural and functional anomaly matrices demonstrates the abnormal connectivity in this subject's brain (Figure 4). Abnormal connectivity is determined as a 3-sigma outlier for that correlation, after excluding the highest variance 1/3 of pairs, to further reduce the false discovery rate. Assignment of parcellations to various large-scale brain networks is based on several previous coordinate based meta-analysis and matching the HCP-MMP1 parcellations to the coordinates of the ALE in MNI space, which has been previously published (or in review presently) by our group.

Figure 4: Connectomic Analysis

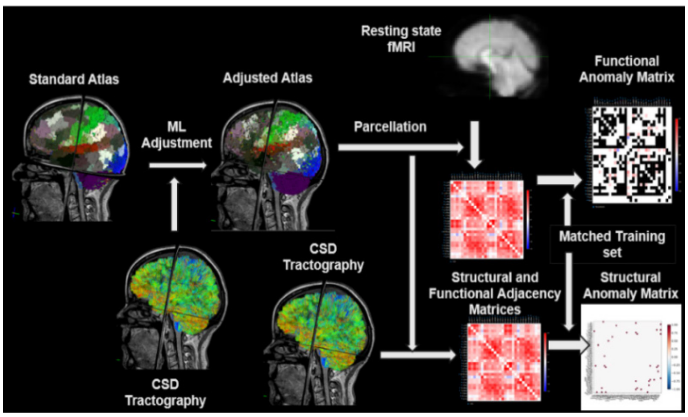
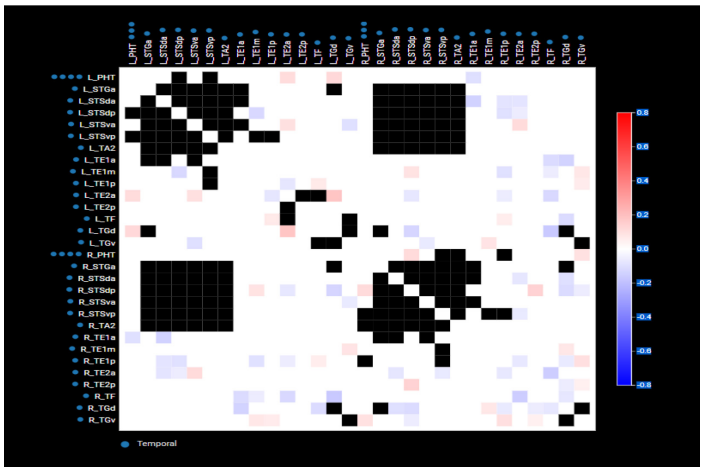


Figure 3: Anomaly Matrix for LSBNs in Temporal Lobe



8.3 SAFETY AND OTHER ASSESSMENTS

8.3.1 TRANCRANIAL MAGNETIC STIMULATION ADULT SAFETY SCREEN (TASS)

Screening questionnaire to assess the safety of TMS prior to treatment. This will be conducted at visits 1 and 2.

8.4 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.4.1 DEFINITION OF ADVERSE EVENTS (AE)

An adverse event is any symptom, sign, illness or experience which develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- Results in study withdrawal.
- Is associated with clinical signs or symptoms.
- Leads to treatment or to further diagnostic tests.
- Is considered by the investigator to be of clinical significance.

8.4.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Adverse events are classified as either serious or non-serious. A serious adverse event is any event that results in:

- Death.
- Life-threatening situation.
- Hospitalization or prolongation of hospitalization.
- Disability or incapacitation.
- Other events determined by investigator to be medically significant in which subject's well-being is jeopardized (e.g. events that have high likelihood of escalating to the point of meeting criteria outlined above)

8.4.3 EXPECTEDNESS

PI will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.4.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

Upon consenting, a subject is considered to be a participant in the study, and until that person either withdraws or completes study, AEs and SAEs will be recorded. The investigational team will promptly report any AE/SAE as required per federal guidelines.

8.5 UNANTICIPATED PROBLEMS

8.5.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

This protocol uses the definition of Unanticipated Problems as defined by the Office for Human Research Protections (OHRP). OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;

2. Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.5.2 UNANTICIPATED PROBLEMS REPORTING

The PI will report unanticipated problems (UPs) to the reviewing IRB. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number
- A detailed description of the event, incident, experience, or outcome
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs will be reported to the IRB as soon as possible, but no later than 10 working days after the investigator first learns of the event

9 STATISTICAL CONSIDERATIONS

9.1.1 STATSTICAL PLAN OVERVIEW

The study population demographics (age, race, etc.) will be described using appropriate summary measures (i.e. means, standard deviations, or medians for continuous variables and counts or percentages for discrete variables). Disease characteristics (MMSE and CDR) will also be summarized to describe our population.

The primary aim will be assessed by calculating the difference and corresponding 95% confidence interval between follow-up and baseline connectivity measures of the TGd parcellations. We will conduct a t-test to statistically test if that difference is greater than 0, which would indicate a non-null effect of the TBS intervention on those areas of the brain.

Exploratory aims 1 and 2 will be analyzed similarly to the primary aim.

For exploratory aim 3, parcellations within the DMN, CEN, or SN associated with ≧4 anomalies on the baseline matrix will be considered for the third TBS treatment. We will descriptively note whether there are shared anomalous parcellations between study patients. If one area of the

brain is anomalous in at least half of the subjects, we will target that area with the third TBS treatment for all patients and analyze it similarly the primary aim. If no such area rises to this level, we will simply describe changes from baseline for the individual areas treated for each patient.

9.1.2 POWER ANALYSIS

From our 4-person pilot study of persons with Alzheimer's Disease, we calculated the average HCP-standardized functional connectivity levels of right TGd with all areas that had non-zero functional connectivity. The mean was 0.096 with a pooled standard deviation of 0.033. Given this limited preliminary data, we will consider a one standard deviation (0.033) change from baseline to be meaningful. With 10 subjects, we have 80% power to detect a 0.033 change from baseline if the pooled standard deviation remains similar to our preliminary findings.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

All research study staff will maintain certification in human subject's protection. All study investigators and staff will take an active role in developing procedures to protect against or minimize potential risks to the safety and well-being of enrolled participants. Potential research subjects will be informed that participation in this study is voluntary and will not be discriminated against if they choose not to participate. Written informed or electronic consent and assent will be obtained from participants, and family member/caregivers or legally authorized representatives (LAR). Participants will be asked to describe in their own words the study's expectations. Subjects will be informed that they can withdraw from the study at any time and will be given a copy of the consent form. Subjects will have written assurance that while de-identified individual subject data may be available to other researchers for research purposes, or used to improve the software program, only a summary of the results will ever be published or otherwise publicly released. Subjects will be assured that participation in the study will be strictly confidential, that any identifying information will be available to the study staff only, and that no identifying information concerning the data and results will be made known.

Potential research subjects will be informed that participation in this study is voluntary and that their decision to participate will not reflect upon their relationships with the Center for Memory and Aging, Regions Hospital, or HealthPartners. Subjects will be informed that they can withdraw from the study at any time and will be given a copy of the consent form.

With the electronic consent via REDCap the patient/caregiver providing consent will be able to review the consent form themselves and sign electronically with a stylus, touch screen, or cursor

using a signature field in REDCap. After the individual has received the link and can view the consent form, the research staff member will go through the consent form with the individual as would be typical in person. Following the consent conversation, the staff member will sign and e-mail the consent and HIPPA electronically to the patient. The patient will electronically sign, certify, and submit the consent and HIPPA in REDCap. A fully executed PDF copy of the consent and HIPPA will be provided electronically to the patient for their records as well as saved via the auto-archiver function in REDCap.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB). Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

Study may resume once concerns about safety, protocol compliance, and data quality are addressed.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor(s). This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally-identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency.

All research activities will be conducted in as private a setting as possible.

All study regulatory binders will be stored in a locked file cabinet within a secure office. The internal study monitor, representatives of the IRB, or regulatory agencies, may inspect all documents and records required to be maintained by the investigator, for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor/funding agency requirements.

A unique study ID code unrelated to the medical record number or other study subject-specific information will be assigned to each patient and used to link data from various sources and needed for analysis. The study number will be used on the RedCap database and Infinitome Program. All imaging data uploaded from the NSC research site will be de-identified and uploaded to the Infinitome cloud-based server.

Infinitome program uses an industrial grade cyber security that is superior to what is offered at the leading medical device companies. No personal health information is stored on servers and only de-identified scans are stored on a dedicated edge node on encrypted MinIO instances. Patient data is only accessed through authenticated calls form Kubernetes pods contained in the VPC. The web service requires user authentication. Only the data related to a specific facility can be retrieved through authenticated calls and are restricted to their use

The PI will ensure all mechanisms used to share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

10.1.4 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator
Michael Rosenbloom, MD
HealthPartners Neuroscience Center
295 Phalen Blvd. St. Paul, MN 55130

10.1.5 SAFETY OVERSIGHT

There is no Data Safety Monitoring Board for this study, as the risks are minimal. We plan to have a data safety officer (DSO), who will be an independent individual and is not participating in the trial and have no direct affiliation with the research team. The DSO responsibilities include but are not limited to the following:

- Monitoring the study for compliance to the protocol.
- Stopping the study if the rate of SAE's raises safety concerns.

Frequency of the DSO meetings, responsibilities, and procedures will be documented prior to initiation of the study.

10.1.6 CLINICAL MONITORING

N/A, refer to next section

10.1.7 QUALITY ASSURANCE AND QUALITY CONTROL

Study staff will perform internal quality management of study conduct, data collection, documentation and completion.

Quality control (QC) procedures will be implemented as follows:

Informed consent --- Study staff will review both the documentation of the consenting process and 10% of the completed consent documents. Feedback will be provided to study staff to ensure proper consenting procedures are followed.

Protocol Deviations – The study team will review documented protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.

Should independent monitoring become necessary, the PI will provide direct access to all study related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/funding agency, and inspection by local and regulatory authorities.

10.1.8 DATA HANDLING AND RECORD KEEPING

10.1.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of the research study staff under the supervision of the PI. The PI will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Data collection/reporting tools will be developed internally (i.e. CRFs or eCRFs (RedCap Database) and source documents). Data collected and stored electronically will remain confidential and secure (e.g. secured server, encrypted data, password protected file).

10.1.8.2 STUDY RECORDS RETENTION

Investigator records will be retained in accordance with regulatory, organizational and sponsor or grantor requirements. All records will be maintained securely with limited access. Disposal of investigator records will be done in such a manner that no identifying information can be linked to research data.

10.1.9 PROTOCOL DEVIATIONS

Plans for detecting, reviewing, and reporting deviations from the protocol should be described. A This protocol defines a protocol deviation as any noncompliance with the study protocol. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

10.1.10 PUBLICATION AND DATA SHARING POLICY

This study will be registered at ClinicalTrials.gov, and results information from this study will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

Data from the de-identified images may be utilized by Omniscent for improvement of Infinitome program and potential future imaging research studies.

10.1.11 CONFLICT OF INTEREST POLICY

The study leadership in conjunction with HealthPartners Institute has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

N/A

10.3 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
1.0	Sep 2 2021		Initial Version
2.0	March 30 2022	Clarification of Number of Treatment sessions per day	In order for subjects to receive the goal 6000 pulses per target per treatment day, they will require a total of **5 sessions per treatment day**
2.1	April 26 2022	Clarification of treatment visits over two weeks	The TMS treatment visits have been updated to reflect alternating days. This is to provide flexibility for scheduling visits for patients and easy viewing on the consent. No change in the number of treatment visits
3	May 18 2023	Change in PI -from Dr. Rosenbloom to Dr. Kashyap	Dr. Rosenbloom is leaving HP

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