Intermittent theta burst stimulation to relieve depression and concurrent executive function impairment in older adults: A Pilot Randomized Trial

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A Introduction

A1 Study Abstract

Executive function deficits are common in late life depression. They are associated with resistance to antidepressants, poor quality of life, considerable disability and increased risk for suicide. No optimal treatments exist for this problem. Selective serotonin reuptake antidepressants do not improve executive impairments and psychotherapy is less helpful with co-occurring executive deficits. Therefore, a safe and well-tolerated treatment is needed to improve executive function, depression burden and overall quality of life. This study will use a novel type of Transcranial Magnetic Stimulation called intermittent Theta Burst Stimulation (iTBS). iTBS uses very high frequency (50Hz) magnetic pulses delivered in "bursts" of 3 stimuli delivered at 50 Hz. It is posited that this intervention induces plasticity in the human cortex. Theoretical and empirical evidence from research studies informs that iTBS is can also improve depression and executive deficits. However such effects have not been examined in older adults.

This project examines iTBS's ability to improve depression and executive impairment in Late life depression (LLD). In addition the study tests the effects of iTBS on brain connectivity within the Cognitive Control Network (CCN). This study will enhance the understanding of LLD and will provide critical pilot data regarding feasibility to support the development of future randomized controlled clinical trial.

Both active and sham (placebo) interventions will be administered sequentially to the left and right dorso-lateral prefrontal cortex. The total time of stimulation or sham is less than 7 minutes. Active or sham intervention will be administered for 6 weeks (Monday to Friday). A total of 20 subjects will ben randomized. Changes in mood from baseline to the end of 6 weeks will be measured using The Montgomery-Asberg Depression scale. Executive function at baseline and end of study will be evaluated with the National Institutes of Health (NIH) Toolbox executive domain battery. Safety assessments will include: The 21 item Scale for suicidal ideation SSI. The frequency, intensity and burden of side effects rating (FIBSER) and the Altman Self Rating Mania scale (ASRM). Ancillary depression measures include the The self-reported Quick Inventory of Depressive Symptoms (QIDS) and the Clinical Global Impression of Improvement scale.

Subjects will undergo functional Magnetic Resonance Imaging (fMRI) before and after the study interventions to tests the effects of iTBS vs. placebo on brain's functional connectivity.

This research will provide meaningful information about the effects of the iTBS intervention on mood and executive function in older adults as well as information regarding the effects of the intervention on brain function. Results of this pilot study will inform a grant submission and allow us to calculate power for a definitive randomized controlled clinical trial to test the efficacy of of iTBS and placebo.

A2 Primary Hypothesis

Aim 1. To assess the efficacy of iTBS in improving mood and executive dysfunction in older adults with depression. H_1. Older adults randomized to iTBS will show significant

decreases in the Montgomery Asberg Depression Rating Scale consistent with improvement, and significant increases in scores on the NIH Toolbox executive domain measures[5-7] consistent with executive function improvement compared to those subjects randomized to placebo stimulation (sham).

Aim 2. To test the effects of iTBS on functional connectivity within the Cognitive Control Network (CCN) in depressed older adults using resting state fMRI. H_2 Depressed older adults randomized to iTBS versus sham will have a significant increase in functional connectivity within the CCN.

Aim 3. To examine the association between change in clinical symptoms and neurocognitive assessments and changes on brain connectivity within the CCN. H_3 Among older adults who receive iTBS, changes in connectivity within the CCN will correlate with changes in depression and executive function.

A3 Purpose of the Study Protocol

The purpose of this study protocol is to address the research question of whether intermittent TBS (iTBS) leads to improvement in depression and executive impairment in older adults when compared to placebo. In addition the study will test the effects of iTBS vs. sham (placebo) on functional connectivity within the Cognitive Control Network (CCN) in depressed older adults using resting state fMRI

B Background

B1 Prior Literature and Studies

Late Life depression is associated with executive impairment:

Major depression episodes occurring in older adults, known as Late Life Depression (LLD), are frequently associated with executive impairment. Executive functions are specialized cognitive processes integral to social and occupational success and overall quality of life. These functions involve planning, goal-directed activity, impulse inhibition and capacity for change and adaptation. Three main executive domains have been consistently described: 1. Inhibitory control; 2. working memory; and 3. cognitive flexibility.4 Brain regions within the Prefrontal Cortex (PFC), particularly the Dorso-Lateral Prefrontal Cortex (DLPFC) have been proposed to orchestrate executive control.5 Functional neuroimaging studies have shown recruitment of PFC regions when subjects perform tasks related to executive domains. Meta-analytic evidence supports the key involvement of a superordinate Cognitive Control Network (CCN) involving fronto-parietal brain regions including the DLPFC (Brodmann Area 9, 46), anterior cingulate (Brodmann Area 32) inferior (Brodmann Areas 39, 40) and superior (Brodmann Area 7) parietal lobe and pre-cuneus (Brodmann Area 19) subsuming executive function. The CCN is involved in “top-down” control and executive tasks. Besides, dysfunction of this network may be responsible for deficits in attention, working memory and slowed processing speed in LLD.

Executive function is reduced with normal aging, but much more so in LLD, a conclusion from neuropsychological studies and brain imaging studies which have characterized executive deficits, shown volume reduction and white matter tracks ischemic changes in frontal and limbic brain regions and more recently connectivity changes in key cortical networks including the Cognitive Control Network (CCN) and the Default Mode Network. The resultant LLD with co-occurring executive function deficits has devastating consequences including a protracted and treatment-resistant depression course, poor quality of life and increased risk for suicide. No optimal treatments exist for this problem. Selective serotonin reuptake antidepressants do not improve executive impairments and psychotherapy is less helpful with co-occurring executive deficits. Therefore, an effective and well-tolerated treatment is needed to improve executive function, depression burden and overall quality of life.

Theta Burst Stimulation (TBS) enhances neuroplasticity:

TBS is a highly efficient form of Transcranial Magnetic Stimulation (TMS). TMS is a standard FDA approved treatment for depression. In TBS, magnetic stimuli are delivered in "bursts" of 3 stimuli at 50 Hz (i.e. 20 ms between each stimulus) given every 200 milliseconds (i.e. 5 Hz). This pattern of stimulation has been used to probe synaptic efficiency of the motor cortex using in vivo slice preparations of animal tissue, but has been adapted for stimulation of the human brain using magnetic stimulators and has shown to induce faster effects on synaptic plasticity than conventional TMS. The excitability of the corticospinal system in humans has been probed before and after two main theta burst paradigms intermittent (iTBS) and continuous (cTBS). Although they both induce a mixture of excitatory and inhibitory effects, it is generally accepted that iTBS induces facilitation of the motor-evoked response indicating predominant excitatory, long-term potentiation (LTP) effects and cTBS decreases the motor evoked response indicating predominantly inhibitory, Long-Term Depression (LTD) effects. Both LTP and LTD mechanisms are triggered by an influx of Ca+ to the post-synaptic neuron. Since iTBS increases LTP indicating enhancement of the brain's plasticity, it is conceivable that iTBS may lead to increase synaptic efficiency and connectivity in key brain networks.

Rationale for the use of iTBS to relieve depression and executive impairment in older adults:

The following studies provide empirical evidence of the use of iTBS in depression and in the improvement of executive function.

Studies providing empirical evidence of rTMS and iTBS improvement of depression and/or executive function		
Study	**Effects of intervention**	**Study and paradigm**
Barr et al.[64]RCT in patients with schizophrenia (n= 27)	Improved working memory (measured by n-back task)	High Frequency – excitatory rTMS over bilateral DLPCF
Moser et al.[65] RCT in healthy middle age and elderly (n = 19)	Enhanced cognitive flexibility (measured by Trail-Making-Test B)	5 sessions of (High frequency) rTMS
Hoy et al.[66] RCT in healthy subjects (n = 20)	Improved working memory measured by n-back task. Increased EEG's theta connectivity.	One session of iTBS (600 pulses) over the DLPFC vs. sham
Cheng et al./ Li Ct et al.[67,68] RCT of iTBS in depressed subjects (n= 60) aged 21-70 years old.	Depression and executive function improvement (using the Wisconsin card sorting test)	Comparison or iTBS over the left DLPFC vs. cTBS over the right DLPFC vs. sham.

Plewnia C. et al.[69] RCT of TBS in depressed subjects (n- 32)	Improved depression	Bilateral TBS paradigm iTBS over the left and cTBS over the right.

These studies demonstrate depression improvement with high frequency rTMS and iTBS paradigms. Previous studies also demonstrate beneficial effects on executive function with these paradigms. These studies provide rational for the use of iTBS to relieve depression and executive function impairment in older adults.

Rationale to test the effects of iTBS on brain function using resting state functional connectivity measures:

Resting State Functional Connectivity (rsFC) has allowed a further understanding of brain systems in relationship to depression. rsFC is based on the principle that functionally related brain regions exhibit correlated activity in intrinsic very low frequency (<~ 0.1 Hz) Blood Oxygen Level Dependent (BOLD) signal.[34-36] Such low-frequency BOLD fluctuations constitute an indirect measure of spontaneous neural activity.[34,37,38] This approach proposes canonical resting state networks defined as neural systems exhibiting intrinsic brain activity which is temporarily correlated with widely distributed brain regions[39-41]. Networks relevant to LLD include the Cognitive Control Network (CCN) a fronto-parietal circuit involved in top down attention dependent executive control, the Default Mode network (DMN) which is involved in self-referential processes, and the affective fronto-limbic circuits, involved in emotion regulation.[42] The CCN is the key network of interest of this proposal given its control of executive function. This network involves fronto-parietal regions including the DLPFC (Bas 9,46), anterior cingulate (BA 32) inferior (BAs 39, 40) and superior (BA 7) parietal lobe and pre-cuneus (BA 19) subserving executive function[43]. Multiple lines of evidence indicate an association between altered CCN function and executive impairment in depression: 1) Dysfunction of CCN regions has been linked to executive impairment in depression[42,44,45] 2) Cognitive regulation of emotions is deficient in depression[46,47] 3) Middle aged and older adults with depression exhibited low rsfMRI connectivity within the CCN[48,49]; which was linked to dysexecutive behavior and antidepressant resistance[48] 4) A pattern of decreased activity in the DLPFC during cognitive tasks and decreased connectivity between the DLPFC and the Dorsal Anterior Cingulate[14] has been found in depression.

In summary, LLD with executive dysfunction is associated with poor outcomes. Such a "malignant" depression variant appears to be the end result of aberrant connectivity in the CCN. iTBS is a novel kind of magnetic stimulation treatment, which offers the potential to improve mood and executive function by enhancing connectivity within the CCN. This intervention has the potential to provide an effective treatment approach for LLD with executive dysfunction and the study will compare the effects of this intervention against sham (placebo).

B2 Rationale for this Study

C Study Objectives

C1 Primary Aim

Aim 1. To assess the efficacy of iTBS in improving mood and executive dysfunction in older

adults with depression. Hypothesis 1. Older adults randomized to iTBS will show significant decreases in the Montgomery Asberg Depression Rating Scale consistent with improvement, and significant increases in scores on the NIH Toolbox executive domain measures consistent with executive function improvement compared to those subjects randomized to placebo stimulation (sham).

C2 Secondary Aims

Aim 2. To test the effects of iTBS on functional connectivity within the Cognitive Control Network (CCN) in depressed older adults using resting state fMRI. H_2 Depressed older adults randomized to iTBS versus sham will have a significant increase in functional connectivity within the CCN.

Aim 3. To examine the association between change in clinical symptoms and neurocognitive assessments and changes on brain connectivity within the CCN. H_3 Among older adults who receive iTBS, changes in connectivity within the CCN will correlate with changes in depression and executive function.

C3 Rationale for the Selection of Outcome Measures

Depression Measure:
The Montgomery-Asberg Depression Rating Scale, is a standardized mood rating scale, widely used in depression studies. The scale is particularly sensitive to treatment effects, demonstrating greater sensitivity to change (between responders and non-responders) to antidepressant treatment than other scales such as the Hamilton Depression Rating Scale.

Executive function measures:
The flanker inhibitory control, the Dimensional Change Card sort test and the List Sorting Working memory test will measure executive function. These scales are state of the art scales and are recommended by the National Institutes of Health in their NIH Toolbox. NIH Toolbox measures are brief and standardized for assessing function from ages 3 to 85. The NIH toolbox monitors behavioral function over time and across developmental stages. This makes it possible to study changes across the lifespan, and evaluate the effectiveness of a treatment.

Brain's connectivity measure: Resting State Functional Connectivity (rsFC) is based on the principle that functionally related brain regions exhibit correlated activity in intrinsic very low frequency (<~ 0.1 Hz) Blood Oxygen Level Dependent (BOLD) signal. Such low-frequency BOLD fluctuations constitute an indirect measure of spontaneous neural activity. This approach has identified canonical resting state networks, defined as neural systems exhibiting intrinsic brain activity which is temporarily correlated with widely distributed brain regions. Using resting state fMRI we will measure functional connectivity within the Cognitive Control Network (CCN) in depressed older adults before and after study intervention. We will also explore functional connectivity within and between other networks that are relevant to depression including the Default Mode network and the cingulo-opercular networks.

D Study Design

D1 Overview or Design Summary

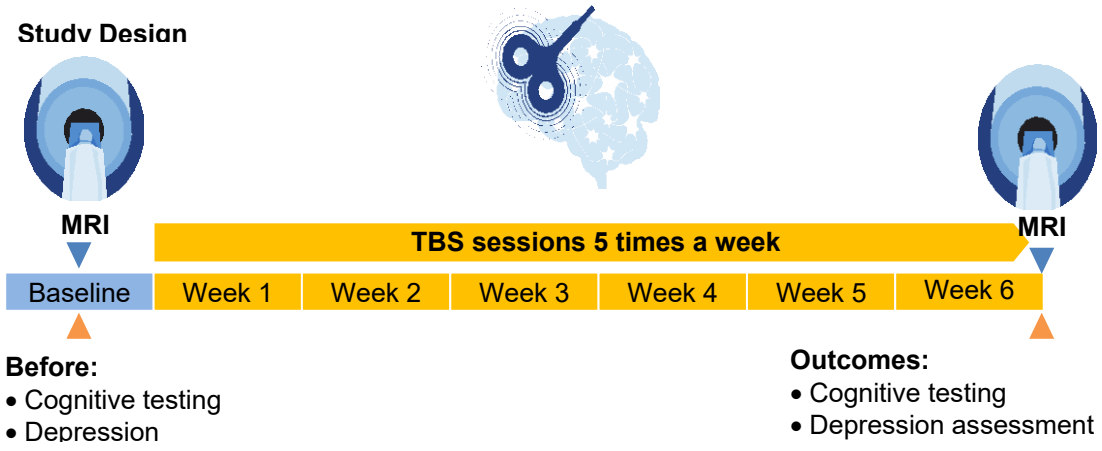

Figure 1. Study Design: Subjects will receive a total of 30 session of intervention (daily Monday – Friday) for 6 weeks. Executive function and mood assessments will be performed pre- and post-intervention.

D2 Subject Selection and Withdrawal

2.a Inclusion Criteria :

1) Age ≥ 60 – 85 years old
2) Diagnosis of major depressive disorder (MDD), single or recurrent, with a current Major depression episode as diagnosed by the Mini-international Neuropsychiatric Interview (MINI 6.0)
3) Montgomery Asberg Depression Scale score greater than or equal to 15 at baseline.
4) Evidence of decreased executive function as evidenced by either of the following conditions: a) scoring below the mean normative scaled score on the average of the NIH Toolbox executive function measures: Flanker inhibitory control and attention test and the Dimensional sort card test, approximate score 70 – 100 as per PI discretion. b) Discrepancy of at least 10 points between the average of the picture vocabulary score and the reading recognition test score and the average of the Flanker inhibitory control and dimensional card sort test score. c) Frontal Systems Behavior Scale (FRSBE) T scores above 60 (indicative of borderline to clinically significant impairment) and at least 10 points (1 Standard Deviation) above subject's premorbid (pre-depression) scores.

Exclusion Criteria

• Exclusion criteria: 1) Inability to complete NIH tool box cognitive testing; 2) Inability to provide informed consent; 3) <22 score on the Montreal Cognitive Assessment MoCA indicative of moderate to severe cognitive impairment per PI discretion;4) Lifetime diagnosis of bipolar I or II disorder or psychotic disorder as per the MINI interview; 5) current psychotic symptoms 6) alcohol or other substance use disorder per DSM V criteria in the past 6 months; 7) High risk for suicide (active suicidal ideation/intent or plan and patient is unsafe to be in the outpatient setting), an urgent psychiatric referral will be made in those cases; 8) Have a diagnosis of obsessive compulsive disorder, post-traumatic stress disorder (current or within the last year), anxiety disorder (generalized anxiety disorder, social anxiety disorder, panic disorder), assessed by a study investigator to be primary 9) Previous history of TMS 10) history of failure to an adequate course of electroconvulsive therapy (ECT) such as equal or more than 7-9 electroconvulsive therapy treatments, per PI discretion;11) Major unstable medical illness including advanced/uncontrolled diabetes, hypertension, renal disease or advanced cancer, per PI discretion 12) Psychotropic use other than antidepressants (e.g., Benzodiazepines [more than 2mg of lorazepam equivalent daily], anticonvulsants [except low dose of Neurontin approximately 600mg/day] or cognitive enhancers such as N-Methyl D – Aspartate (NDMA) receptor antagonists [Memantine HCL], psychostimulants [such as methylphenidate or modafinil]) per PI discretion; 13) Recent changes or initiation of antidepressant therapy approximately in the last 4 weeks prior to intervention delivery, per PI discretion 14) if participating in psychotherapy, must have been in stable treatment for at least 3 months prior to entry into the study, with no anticipation of change in the frequency of therapeutic sessions, or the therapeutic focus over the duration of the study 15) contraindications for TMS including the presence of metallic objects within 30 cm of the TMS coil, intracranial implants (e.g., aneurysm clips, shunts, stimulators, cochlear implants, or electrodes) or any other metal object within or near the head, excluding the mouth, that cannot be safely removed; presence of intracardiac lines, defibrillators or a cardiac pacemaker and unable to assess safety; presence of implanted electronic devices that control physiologic functions and unable to assess safety. 16) have a personal history of a primary seizure disorder or a seizure associated with an intracranial lesion. 17) History of severe head trauma or neurological disorders that substantially increase seizure risk, per PI discretion.18) non-correctable clinically significant sensory impairment (i.e., cannot hear well enough to cooperate with interview).

No exclusion criteria based on race, ethnicity, gender or HIV status.

2.b Ethical Considerations

No exclusion criteria based on race, ethnicity, gender or HIV status.

2.c Subject Recruitment Plans and Consent Process

Depression is common in older adults: up to 15% of older adults experience a major depressive episode. We will recruit Community-dwelling older adults with depression via advertisement as well as referring care providers. The Clinical Transcranial Magnetic Stimulation service directed by Dr. Cristancho as well as Dr. Lenze's outpatient geriatric practice at Washington University will also provide recruitment sources. Recruitment strategies for subjects will involve the use of IRB approved advertisements, in the print, advertisement via electronic media such as facebook, referrals by word of mouth,

referrals by clinicians in both primary care and specialty mental health sectors. Volunteers for health, and the formation of partnerships with community agencies and primary care networks. All these methods have provided ongoing access to older adults with depression.

Consent process:
The Pi designee will obtain participant's verbal consent prior to doing a phone screen to determine study eligibility. After completion of the phone screen if the subject is determined eligible, the PI designee will provide detailed information about the study and will review the consent form with them over the phone. The subject will be told that study participation is optional and it will not affect their care. Per subject's request a copy of the consent form will be mailed, faxed or e-mailed to the subject, so he/she has time prior to his/her visit to review and discuss with family/friends. A screening visit will be scheduled.

During the screening visit the PI designee will review the consent form with the subject, page by page and answer any questions the study subject has to their satisfaction. The subject will be told that study participation is optional and it will not affect their care. If subject agrees, his/ her signature will be obtained and both subject and PI designee will sign and date the consent form.

A note to file will be used to document the consent process.

2.d Randomization Method and Blinding:

Subjects who consent to study participation will be randomized to receive six weeks of either iTBS or sham. Each subject enrolled in the study will have equal probability to be randomized in each study arm and permuted blocks of randomly varying sizes (4, 6, and 8) will be used to generate the scheme. Each block will contain equal numbers of assignments to iTBS and sham providing a balanced design. Neuropsychological testing, mood assessments and fMRI scans will be performed pre- and post-interventions.

Blinding: To deliver the stimulation we will use One treatment coil (B-65 A/P) capable of delivering iTBS and sham. Subjects randomized to iTBS will receive iTBS and those randomized to sham will receive sham (placebo) stimulation. Sham stimulation is ensured by an Internal shielding mechanism in the delivery coil, which reduces the magnetic field strength to < 5% of active field which is biologically inactive. The coil's symmetric design and identical clicking noises during both active and sham. The coil has a built-in position sensor to ensure that the correct (active or sham) side of the coil faces toward the subject's head. We will use synchronized gentle electrical stimulation to the scalp via pre-gelled surface stimulation electrodes to simulate scalp sensations on the sham delivery, which will mimic the active stimulation. Subject's assignment to the intervention will be defined by the Maglink software according to the randomization schedule. Assignments are stored on individualized USB memory devices.

At intervention end, subjects will be queried about what they believed was their intervention assignment.

2.e Risks and Benefits

Risks associated with TBS intervention

Risk with theta burst delivery is assessed based on the risk associated with TMS therapy (FDA approved treatment for depression) and based on published clinical trials using TBS intervention.

Risk of common side effects: Most frequent side effects included headaches, dizziness, nausea, vertigo, pressure in the head, twitching in superficial muscles of the face while receiving stimulation, palpitations and tremor. These have been reported to be mild and moderate tolerability.
Stimulation may affect hearing due to the loud sound of the magnetic stimulator. As in clinical practice subjects are required to wear earplugs throughout the entire session.

Risk of serious side effects: Seizure during stimulation is a potential risk. No seizures have been reported in TBS literature in depression studies. The largest reported naturalistic study (N = 87) estimated an incidence rate range of seizure or other serious adverse effects at 0.011 per patient (95% CI, 0-0.362). We will comply with the International Safety guidelines for TMS administration, and we have a written protocol to handle seizures at the TMS suite.

Intervention emergent mania or hypomania: This is a theoretical concern, as such as reaction has not been reported with iTBS. The rTMS literature estimates the risk for intervention emergent mania or hypomania at 0.84% but this was not statistically different from sham 0.73%.

Risk of mood worsening: Due to the clinical course of depressive illness it is conceivable that subject's assigned to either iTBS or sham may experience worsening of mood during their participation in the trial.

Suicide risk: Patients who are identified, as being acutely suicidal will be excluded from the study. Nevertheless, since the rate of completed suicide in the USA remains high (i.e., about twice the rate of homicide) and most Americans who commit suicide suffer from depression, all subjects eligible to participate in this study are statistically at a relatively higher risk for suicide than the general population. Participation in the study does not create or increase the risk of completed suicide. Actually, most experts believe that one of the most efficient ways to decrease suicidal risk in older depressed individuals is to treat their depression. A Recent study by the PI indicated that intervention emergent suicidal ideation in older adults is likely to be related to the underlying illness rather than being an antidepressant treatment side effect.

Breach of confidentiality: this is a potential risk of clinical research due to the need to inquire about health related information.

For protections against risk see letter F subheading, below.

Risks associated with MRI

Likely risks: During scan and behavioral task procedures, patients may experience boredom or get tired.

Less likely risks: Because patients are asked to lie still during the scan they may experience mild muscle aches and pains. Participants are offered cushions to place at pressure points or beneath the knees to reduce discomfort. Participants will be exposed to the MRI scanner acoustic noise. They will be provided with earplugs to dampen the noise. Participants may feel anxious or even experience claustrophobia (fear of being in closed spaces) while in the scan. Participants are able to communicate with staff throughout the scan and are encouraged to tell the staff if they feel anxious and whether they want to interrupt or stop the scan.

Rare risks: Because the scanner uses a high strength magnet, subjects with ferro-magnetic metallic objects inside their bodies are at substantial risk. Metallic objects can be pulled by the magnetic field and cause physical harm. The following medical devices and body implants can be affected by the MRI field or be potentially hazardous in the MRI environment: cardiac pacemaker, implanted cardioverted defibrillator (ICD), aneurysm clip, implanted insulin/drug pump, neurostimulator (TENS unit), biostimulator/bone growth stimulator, hearing aid/cochlear implant, Gianturco coil (embolus coil), vascular clip, surgical clip or staples, heart valve prosthesis, Greenfield Vena Cava filter, middle ear implant, penile prosthesis, shrapnel or bullets, wire sutures, tattooed eye liner, body piercing jewelry, permanent contraceptive implants such as diaphragm/ UID and pessaries, intraventricular shunts, wire mesh, artificial limb or joint, any orthopedic item that is ferro-conductive (ei, pins, rods, screws, nails, clips, plates, wire etc) dentures, any type of dental item held in place by a magnet, dental braces or any type of removable dental item, any other implanted item not mentioned. There may be unknown risks to the unborn fetus during pregnancy. Prior to the MRI, each subject will be carefully screened for the presence of any of these devices or implants.

Benefits of study participation: Benefits to subjects include the possibility that their depression improves with this intervention. There are theoretical grounds and other research evidence indicating that TBS has potential beneficial effects on depression and executive dysfunction. The side effect profile for TBS is predicated on the side effect profile of repetitive Transcranial Magnetic Stimulation (rTMS). TMS was cleared as a depression treatment by the FDA in 2008. According to Dr. Cristancho Pimiento's clinical experience (Director of the TMS clinic at Washington University), patients often seek alternative treatments to medications, because medications have the potential for systemic side effects. TMS is generally an amenable treatment to patients.

Benefits to society: Depression in older adults with co-existing executive function impairment has devastating consequences including a protracted and treatment resistant depression course, poor quality of life and increased risk for suicide. Testing TBS intervention will inform research in this area of significant public health relevance.

2.f Early Withdrawal of Subjects

Subjects can terminate their participation at any time.

Subjects will be terminated by the PI if they experience a new event that will compromise their safety to receive the study intervention. For example, subject becomes sick and

her/his new condition precludes the use of the study intervention. Or, subject experiences a seizure during the intervention administration; this will preclude further study intervention sessions. Subjects can be withdrawn due to other medical or psychiatric events that in the judgment of the PI will compromise subject's safety to receive iTBS.

In addition, subjects may be terminated due to missing sessions. More than four consecutive missed sessions will cause withdrawal from study. Missed sessions will have to be made up, in this way the subject will still receive the entire 20-30 interventions, but over a longer time period (i.e. greater than 4-6 weeks). Missing more than six non-consecutive sessions (20% of the intervention), which cannot be made up will also lead to study withdrawal.

All missed intervention days will be recorded in a log for each participant.

2.g When and How to Withdraw Subjects

Subjects can withdraw their consent to participate at any time. Subjects should inform the study team about their wish to withdraw or sent a withdrawal letter.

Subject's termination from study by PI will be documented in Case report forms.

2.h Data Collection and Follow-up for Withdrawn Subjects

All data collected from subjects up to their withdrawal date will be used for analysis.

If a subject decides to withdraw, we will ask him/ her to come for a close out visit to complete the same mood and executive function assessments that were recorded at baseline.

D3 Study Device: rTMS device

3.a Description of the rTMS device used to deliver iTBS vs sham (placebo)

We will use the rTMS device currently available at our institution for clinical and research applications. The stimulator is a MagPro R 30 magnetic stimulator manufactured by MagVenture A/S (Farum, Denmark) and FDA approved for treatment of major depressive disorder. Equipment components include: 1) R30 magnetic stimulator 2) coil cooler unit 3) dedicated C-B60 butterfly coil for Motor threshold assessments only 4) Treatment chair with neck rest and cloth cover, subjects will recline in this comfortable motorized recliner during intervention delivery 5) Head Stabilizer System (Airtight Pillow and Evacuation Pump).

The intervention will be delivered using:

- A Coil- cool B65 A/P butterfly coil. This coil functions as both active and sham coil. The coil has a symmetrical design, one side of the coil delivers active treatment and the other side delivers sham. Both sides of the coil are identical.
- Theta burst delivery software
  Maglink software, this software interfaces with the B65 A/P coil to deliver the randomization assignment. The software provides codes assignments according to the randomization schedule to ensure double -blind conditions

The Magpro R30 is a non-significant risk device because:

- It is not an implant
- It is not for use in supporting or sustaining human life
- It does not present a potential for serious risk to the health, safety or welfare of study

3b. Other devices used:

MRI guided neuronavigation equipment: This frameless stereotactic system (Brainsight; Rogue Research, Quebec, Canada), co-registers the patient's head in a standardized magnetic resonance imaging (MRI) space. The equipment allows for accurate coil targeting of the Dorsolateral Prefrontal Cortex within and between Theta Burst stimulation sessions. The equipment is located at the Laboratory for Applied Brain Plasticity (LABP), which is also equipped with a Magstim Super Rapid and a **Magstim BiStim²** (The Magstim Company Ltd, Wales, UK) and various coil types for brain stimulation (TMS).

3T Prisma MRI Scanners

The newest-generation fMRI scanner from Siemens, the Prisma 3T Magnet Resonance Imaging Scanner, will be used for this project. Washington University (WU) has PrismaFit at the Mallinckrodt Institute of Radiology (MIR), operational since October 2015. A PrismaFit upgrade to a TRIO in the Center for Clinical Imaging Research (CCIR) is scheduled for December of 2017. These two Prismas will be running the same software version and will be equipped with identical equipment and resources for the structural and functional sequences proposed in this application. The Prisma scaners at the MIR and the CCIR are fully research dedicated scanners and available for use 24 hours a day. The Siemens Prisma is the most advanced, FDA-approved 3Tesla MR scanner one can buy today. This scanner is the first commercial scanner to offer 80 mT/m gradients with a slew rate of 200 T/m/s. These gradients are the product version of the research gradients used in the WU Human Connectome Project (HCP) Scanner. The key benefit to these gradients is the ability to achieve high diffusion sensitivity at shorter echo times than is possible with the previous generation of gradient system. The Prisma platform is also notable for 64 independent RF channels. Our scanners are (or will be) configured with both 32 and 64 element head coils to ensure protocol compatibility across multiple centers. These coils enable high acceleration factors during traditional parallel imaging approaches as well as the more modern techniques of simultaneous multislice and multiband acquisitions utilized in the HCP. Together, these technologies enable whole brain imaging with submillimeter structural MRI, sub-second BOLD fMRI and high angular resolution diffusion imaging with higher signal to noise than is possible on traditional, widely available 3T MR scanners. The new Prisma platform offers parallel RF transmission that enables uniform RF excitation and thus prospective signal homogeneity and inner volume imaging without aliasing. These state of the art

technologies built into the Prisma will ensure neuroimaging data of optimal quality and maximal compatibility with HCP data.

MRI Scanner Peripheral Equipment: The Prisma Suites will also contain the necessary equipment to present experimental stimuli and acquire responses including (1) a rear projection system; (2) an S14 fMRI Compatible Insert Earphones system (Sensimetrics Corporation, Malden, MA); and (3) ergonomic subject response devices.

Physiological Recording in the MRI Scanner: During bold EPI scans, recording of respiratory and pulse oximeter measurements can be conducted using the built-in Prisma Siemens Physiological Monitoring Unity (PMU).

3.b Intervention Regimen

iTBS delivery:
According to Huang et al, each burst consisting of three stimuli at 50 Hz, repeated every 200ms will be administered using a two-seconds train repeated every 10 seconds for a total of 190s (600 pulses). We chose this paradigm due to its excitatory effects and LTP properties and given the best available evidence for effects on depression and executive function. iTBS will be delivered over bilateral Dorso-Lateral Prefrontal Cortex (DLPFC) (600 pulses left/ 600 pulses right). TBS will be administered for a total of six weeks, one daily session, Monday thru Friday. The coil (B-65 A/P) will be used to deliver the iTBS intervention.

Sham (placebo) delivery: To deliver sham, we will use the same B-65 A/P coil. Sham stimulation is ensured by an Internal shielding mechanism in the delivery coil, which reduces the magnetic field strength to < 5% of active field which is biologically inactive. The coil's symmetric design and identical clicking noises during both active and sham. The coil has a built-in position sensor to ensure that the correct (active or sham) side of the coil faces toward the subject's head. We will use synchronized gentle electrical stimulation to the scalp via pre-gelled surface stimulation electrodes to simulate scalp sensations on the sham delivery, which will mimic the active stimulation. Subject's assignment to the intervention will be defined by the Maglink software according to the randomization schedule. Assignments are stored on individualized USB memory devices.

Localization of the Dorso-lateral prefrontal cortex (DLPFC) for iTBS and placebo interventions: Subjects assigned to either iTBS or sham intervention will receive stimulation on the DLPFC. We will target the DLPFC because it is a key prefrontal cortex structure involved in orchestration of executive function.[74] The DLPC is a main region of the CCN network which is also implicated in the pathophysiology of LLD.[43,76] We will stimulate bilaterally given evidence from our open label study. Subject's structural MRI scans will be used to localize the DLPFC stimulation target. The DLPFC target comprises an area between the center of Brodman area (BA) 9 and the border of BA9 and BA 46[77], the Tailarach coordinates for left DLPFC stimulation will be [x = -45 y=45, z = 35] and [x = +45 y=45, z = 35] for the right DLPFC.[78,79] This neuronavigated target has been successfully used in previous rTMS depression studies[78,79] and it is expected to reduce variability resulting from localization of the stimulation, which has been problematic with previous localization approaches such as the 5cm rule.[80,81]

Neuronavigation procedures: Following randomization and baseline MRI subjects will undergo neuronavigation, the target locations will be specified by reverse co-registration from a stereotaxic coordinate on the Tailarach template brain, onto each subject's anatomical MRI. Neuronavigation will proceed using the frameless stereotactic system Brainsight (Rogue Research, Quebec, Canada), to position the coil for maximal field strength at the left and right target regions of the DLPFC for each subject. Neuronavigated coordinates will be marked on a textile cap and subjects will wear this cap during each intervention session, ensuring delivery of stimulation on the DLPFC target. A picture of the subject will be taken with the stimulation coil on the head. This will help investigators get a better visualization of where the coil should be placed after the subject undergoes neuronavigation.

Motor Threshold Determination: Each subject's Motor Threshold (MT) will be assessed using a dedicated C-B60 butterfly coil before the first intervention session. The MT will be re-assessed at the beginning of intervention weeks 2, 4 and 6 and re-checked as needed according to PI instructions, for example if the subject has had any medication changes or other conditions that may cause fluctuations in the MT. MT is the lowest stimulation intensity required to induce a motor response of the Abductor Pollicis Brevis (APB) muscle in the contralateral hand. MT will be measured via the visualization method, by observing movement of the contralateral thumb or adjacent fingers. Because of our subjects' age range, we will "dose" iTBS at 120% of the resting MT. This dosing is necessary to adjust for prefrontal atrophy in the elderly. This dosing has been used in a large sample without serious adverse events.

In order to ease subjects into stimulation we will begin the first intervention at the level of MT and titrate up to 120% of the MT during the first week of intervention. Subjects will achieve 120% of MT by the end of the first week.

The TMS device to be used in this study for delivery of the interventions is currently employed in clinical operations and is housed at the West Pavilion, suite 15340, Outpatient Psychiatric Clinic at 1 Barnes-Jewish Hospital Plaza. The equipment will remain in place once study is finished. Therefore, there is not need for maintaining device shipment and receipt records.

The equipment used for neuronavigation procedures is located at the Laboratory for Applied Brain Plasticity (LABP) on the East Building located at 4525 Scott Ave., St. Louis, MO 63110 and it is currently used in research operations.

Scanning facilities :.

Scanning facilities: MRI scans will be performed at the following scanning facilities at Washington University:

- Center for Clinical Imaging Research (CCIR): The CCIR is located on the 10th floor of Barnes-Jewish Hospital West Pavilion. The CCIR possesses four dedicated research scanners, which include a 3T MRI Siemens scanner which will undergo PrismaFit upgrade.

- The MRI facility at the Mallinckrodt Institute of Radiology: located at 4525 Scott Avenue, Rm. 1109. This facility houses 2 PRISMA 3T Systems.

3.c Method for Assigning Subjects to Intervention Groups

A randomization scheme generated by the study statistician will be used. Subjects who consent to study participation will be randomized to receive six weeks of either iTBS or sham. Each subject enrolled in the study will have equal probability to be randomized in each study arm and permuted blocks of randomly varying sizes (4, 6, and 8) will be used to generate the scheme. Each block will contain equal numbers of assignments to iTBS and sham providing a balanced design. Neuropsychological testing, mood assessments and fMRI scans will be performed pre- and post-intervention.

3.d Subject Compliance Monitoring

Subjects will receive a total of 30 study intervention sessions, administered once daily, Monday thru Friday for six weeks. Single- day intervention sessions missed due to expected (holidays) or unexpected (eg. Inclement weather, illness, transportation difficulties) reasons will have to be made up, in this way the subject will still receive the entire 30 interventions, but over a longer time period (i.e. greater than 4-6 weeks). More than four consecutive missed sessions will cause withdrawal from study. Missing more than six non-consecutive sessions (20% of the interventions), which cannot be made up will also lead to study withdrawal.

All missed intervention days will be recorded in a log for each participant, and reviewed (weekly if no adherence is detected, so that study staff can intervene) by the PI.

3.e Prior and Concomitant Therapy

Subjects may continue existing antidepressant treatments (which are not part of excluded medications). However, subjects will be asked not to make changes on antidepressant doses in order to maintain a consistent regimen of medications during TBS intervention. Likewise, is a subject is receiving psychotherapy, this regimen should not be modified.

E Study Procedures

E1 Screening for Eligibility

A phone screen will be performed prior to the first study visit. Over the phone the participant will be given a detailed description of the study including risk/benefits. They will be asked to provide information to help determine eligibility. Questions include demographics and health questions related to subject's history of depression,

medications. Other questions include those to rule out contraindications to TMS such as metal in the head, a personal history of seizures or severe head trauma. Questions about contraindications to MRI will be asked as well. If participant meets eligibility criteria based on that information an appointment will be scheduled to review and discuss the informed consent in person.

E2 Schedule of Measurements

After providing informed consent the following procedures will begin.

Screening visit (Visit 0)
At this visit a psychiatric interview will be performed by PI or her designee, during the visit the diagnosis of major depressive disorder will be confirmed, and information about subject's health status and ongoing medications will be obtained. Also a safety assessment will be performed to rule out the presence of active suicidal ideation with plan and imminent danger which will preclude study participation.
Screening assessments include:
Montreal Cognitive Assessment (MoCA)
TMS Adult Safety Screen (TASS)
MINI
FrSBE
Montgomery Asberg Depression Rating Scale (MADRS) (Repeat it at Baseline Assessment Visit if screening visit is done more than a week prior to intervention)

National Institute of Mental Health Tool Box will be administered using an IPAD application. The tests include:
NIH Toolbox Picture Vocabulary Test (TPVT)
NIH Toolbox Flanker Inhibitory Control and Attention Test (Flanker)
NIH Toolbox Dimensional Change Card Sort Test (DCCS)
NIH Toolbox Picture Sequence Memory Test (PSMT)
NIH Toolbox List Sorting Working Memory Test (List Sorting)
NIH Toolbox Pattern Comparison Processing Speed Test (Pattern Comparison)
NIH Toolbox Oral Reading Recognition Test (Reading)
NIH Toolbox Oral Symbol Digit Test
NIH Toolbox General Life Satisfaction

Screen visit will take about 145 minutes to complete.

If subject qualifies for the study a baseline visit will be conducted.

Baseline Assessment Visit

At this visit the following assessments will be administered:
Trail Making Test
Semantic Fluency Test
The Revised Observed Tasks of Daily Living (OTDL-R)
Delis-Kaplan Excecutive Function System (D-KEFS): Color–word interference
Quick Inventory of Depressive Symptoms Self report
Anxiety Measure (self report)

Ruminative Response Scale (RRS) (self report)
NIH Toolbox – General Life Satisfaction CAT and Positive Affect CAT
Cumulative Illness Rating Scale-Geriatric (CIRS-G)
The Antidepressant Treatment History Form (ATHF)
California Verbal Learning Test – second edition (CVLT-II)
Line Orientation test from RBANS

Safety and side effects assessments:
21 item for suicidal ideation SSI
Frequency Intensity and Burden of side effects (FIBSER)
Altman Self Rating Mania Scale (ASRM)

Baseline Assessment will take about 3 hours to complete.

Pre-intervention MRI Scan Visit:
Neuroimaging Pre-Scan Questionnaire
Pre-intervention MRI scan (about 60 minutes)

This visit will take one hour and half to complete

Intervention visit 1
Motor Threshold determination: Each subject's Motor Threshold (MT) will be assessed using a dedicated C-B60 butterfly coil. Motor Threshold for the left and the right hemisphere will be determined. MT will be repeated every two weeks afterwards at the beginning of each intervention week. MT will be re-checked in situations such as recent medication changes, changes in sleep habits as determined necessary by the PI. MT is the lowest stimulation intensity required to induce a motor response of the Abductor Pollicis Brevis (APB) muscle in the contralateral hand. MT will be obtained by the observation method, by observing movements of the thumb and fingers on the contralateral hand. Motor Threshold determination takes about 20 minutes to complete.

Determination of stimulation site: Stimulation will be delivered over the scalp over the brain area corresponding to the dorsolateral prefrontal cortex (Brodmann areas 9 and 46). Stimulation will be bilateral, subsequent left and right. We will localize the DLPFC using subjects's structural scans and the following Tailarach coordinates: [x = -45 y=45, z = 35] for the left DLPFC and [x = +45 y=45, z = 35] for the right DLPFC.[74,75] Following randomization and baseline MRI subjects will undergo neuronavigation, the target locations will be specified by reverse co-registration from a stereotaxic coordinate on the Tailarach template brain, onto each subject's anatomical MRI. Neuronavigation will proceed using the frameless stereotactic system Brainsight (Rogue Research, Quebec, Canada), to position the coil for maximal field strength at the left and right target regions of the DLPFC for each subject.

Intervention delivery #1: will be delivered as follows:
Subjects assigned to iTBS: Burst of three stimuli at 50 Hz, repeated every 200ms using a two-seconds train repeated every 10 seconds for a total of 190s (600 pulses). TBS will be delivered over the scalp over the brain area corresponding to the dorsolateral prefrontal cortex. We will apply stimulation bilaterally with a total of 600 pulses on the left and 600 pulses on the right. This protocol takes about 8 minutes to complete.

Subjects assigned to Sham: Stimulation will be delivered mimicking the pulse

frequency, sound and sensation of the active stimulation but with not active magnetic pulse delivery.

Intervention delivery # 2- 30: Subsequent interventions will be scheduled daily Monday to Friday the theta burst stimulation paradigm as described above will be used.

Weekly assessments:
We will obtain the following assessments on a weekly basis, at the end of the intervention week.
Montgomery Asberg Depression Rating Scale (Week 2, Week 4, and Week 6 only*)
Quick Inventory of Depressive Symptoms Self report
21 item for suicidal ideation (SSI)
Frequency Intensity and Burden of side effects (FIBSER)
Altman Self Rating Mania Scale (ASRM)
NIH Toolbox – General Life Satisfaction CAT and Positive Affect CAT (Baseline, Week 2, Week 4, and Week 6 only*)
Anxiety Measure (self-report) (Baseline, Week 2, Week 4, and Week 6 only*)
Ruminative Response Scale (RRS) (self report) (Baseline, Week 2, Week 4, and Week 6 only*)

End of intervention assessments:
At the end of 6 weeks, or 30 interventions we will repeat the NIH Tool box battery, Semantic Fluency, Trail Making Test, FrSBE, the Revised Observed Tasks of Daily Living (OTDL-R), Delis-Kaplan Executive Function System (D-KEFS): Color–word interference, the California Verbal Learning Test – second edition (CVLT-II), and the Line Orientation test from RBANS in addition to the weekly assessments. This assessment session will take about three hours to complete.

Post-intervention MRI Scan Visit
Neuroimaging Pre-Scan Questionnaire
Post-intervention MRI scan (about 60 minutes)

This visit will take one hour and half to complete.

E3 Safety and Adverse Events

Interventions and precautions to minimize subject's risk during TBS intervention:

• Treating personnel is trained to act as first line responder, and will have cardiopulmonary resuscitation (CPR) training, in case of a seizure event.
• Intervention will be delivered in a suite equipped with necessary materials to assist the subject in case of a seizure (oxygen, pulsoxymetry monitor, etc.).
Besides the suite is located in house Barnes Jewish hospital and the emergency response team at Barnes Jewish hospital is readily available to assist. The TMS treater will call the emergency response team in case of a seizure or other event deemed an emergency.
• The TMS suite has a written protocol to handle a seizure occurrence
• Subjects with increased risk of seizure or history of head trauma that may increase seizure won't be eligible for intervention. Besides we will screen subjects with The TMS

Adult Safety Screen (TASS) prior to iTBS intervention.
• Cognitive function is monitored throughout the intervention.
• Side effects of the intervention will be monitored weekly with the Frequency, Intensity and Burden of Side Effects rating (FIBSER). If deemed clinically necessary side effects will be also monitored by the study physician. Besides, subjects will be asked about side effects and will be monitored on all intervention days by the staff member administering the interventions.
• Hearing will be protected by the use of earplugs during intervention sessions

Interventions to minimize risk of worsening of mood and suicide risk:
• Depressive symptoms will be monitored weekly and every day subjects will be asked about how is their mood. Standardized mood scales are administered pre and post intervention.
• Emergent suicidal ideation will be monitored daily during the intervention and suicidal ideation will be assessed weekly with the 21-item Scale for Suicidal Ideation SSI,
• During the course of the intervention if necessary, Dr. Cristancho Pimiento will perform a safety assessment. If clinically indicated, severely depressed patients will be advised hospitalization for close monitoring of their depressive symptoms. Hospitalization will be reported as a serious adverse event and the participant will be terminated from the study protocol.

Confidentiality: Subject's confidentiality will be assured through a multi-layered approach, entirely compliant with HIPAA regulations. We will have the following formal mechanisms limiting access to information that can link data to individual participants. Data forms that include identifying information will be kept in locked cabinets. Only the unique ID number, assigned by the research assistant at the time of initial contact will represent participants during data entry, data transfer, data analysis, or other file management procedures. To facilitate tracking, a password-protected computer file will be maintained containing the identity of participants, their ID numbers, and information about how they can be reached. This file, however, will contain no clinical data. Only members of the investigative group will have access to secured files or to master lists for participant code numbers and will be well informed regarding the protection of patients' rights to confidentiality. Identities of participants will not be revealed in the publication or presentation of any results from this project.

Interventions to Minimize Risk of MRI:
To minimize the risk of claustrophobia, participants could do a mock scan on fake scanner, which can help them ease this. In addition, during the scan, participants will be able to talk with the MRI staff through a speaker system and can tell them to stop the scan at any time.
To minimize the risk of injury caused by presence of metal and other MRI contraindications, participants will be asked a series of questions about metal exposure over the course of their lifetime from work experiences and medical procedures.
To minimize the risk of boredom, tiredness, muscle aches and anxiety, participants may take breaks as needed throughout the study. They will also be told they can take breaks. Participants are offered pillows and blankets to alleviate discomfort in the scanner. Participants will be able to communicate with study staff at all times during the scan and will be told they can stop the scan at any time for any reason. Earplugs will be offered to decrease the exposure to the scanner's acoustic noise.

Participants will be screened at the time of the phone screener and again before the MRI scan using the 3.0 T MRI Recruitment/Pre-entry Screening form and will not receive an MRI scan if the screen is positive. Individuals with fear of confined spaces may become anxious during an MRI. There are no known long-term risks or consequences of MRI scans. The length of scan will be about 60 mins.

3.a Safety and Compliance Monitoring

At each intervention session, the intervention administrator will monitor subjects for safety and compliance with study procedures.

Compliance monitoring: All missed intervention days will be recorded in a log for each participant, and reviewed (weekly if nonadherence is detected, so that study staff can intervene) by the PI.

3.b Medical Monitoring

At each intervention session, the intervention administrator or the PI designee, will monitor subjects' safety during study procedures.

Dr. Cristancho Pimiento is a board-certified psychiatrist with expertise in mood disorders and brain stimulation treatments (TMS). She will be overseeing all study procedures. Subjects will be provided with her office number and a 24-hour emergency contact number to cover subjects' concerns.

3.c Definitions of Adverse Events

A. **Definition**

An adverse event (AE) is any untoward medical occurrence in a subject temporally associated with participation in the clinical study or with use of the TMS device. An adverse finding can include a sign, symptom, abnormal assessment (laboratory test value, vital signs, electrocardiogram finding, etc.), or any combination of these.

A Serious Adverse Event (SAE) is any adverse event that results in one or more of the following outcomes:

- Death
- A life-threatening event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly or birth defect
- Important medical event based upon appropriate medical judgment

3.d Classification of Events

AEs will be labeled according to severity, which is based on their impact on the subject. An AE will be termed “mild” if it does not have a major impact on the subject, “moderate” if it causes the subject some minor inconvenience, and “severe” if it causes a substantial disruption to the subject’s well being.
Additionally they will be classified as expected or unexpected.

AE Attribution Scale

AEs will be categorized according to the likelihood that they are related to the study intervention or other study procedures. Specifically, they will be labeled definitely unrelated, definitely related, probably related, or possibly related to the study intervention or procedures.

3.e Data Collection Procedures for Adverse Events

We will systematically collect AEs and summarize them in a running table throughout the study, including date of onset/offset, type of AE, severity, and interventions if any. Per Washington University IRB policy, reportable AEs are those that are possibly, probably, or definitely related to the study intervention or procedures.

Throughout the study interventions, each subject will be queried about any adverse events since the last iTBS/ placebo session to date. The study research assistant or the blinded intervention administrator will do the questioning of AE’s.

After an adverse event occurrence, a detailed note will be generated. Note will include time, point in the intervention session, subject’s symptoms or complaints, and any steps taken. Steps taken may include physical examination, medical care delivered, etc.

3.f Reporting Procedures

The PI or a sub-PI will be notified of all unexpected AE’s, all severe expected AE’s, and all AE’s which meet the qualifications of serious (SAE’s). If an adverse event occurs then PI will be notified and an evaluation will be performed. Intervention (iTBS or placebo) - related events or any safety issue will be addressed by Dr. Cristancho.

A compilation on AE will be documented for the yearly HRPO renewal review.

SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported to the IRB, and NIH/NCATS in accordance with reporting guidelines.

D. Data and Safety Monitoring Plan (DSMP) :

<u>General considerations:</u>

The PI will have primary responsibility for the monitoring of participants throughout their participation, both with respect to their safety and the integrity of the research data. Likewise the PI will be responsible for reporting of adverse events to the IRB, FDA and or the National Institute of Health.
All participants will be reviewed by the PIs at baseline; exclusion criteria (e.g., suicidality, contraindications to study intervention) will reduce the risk to participants. Participants will be carefully monitored during the study. Additionally, the study will have a 24-hour answering service with physician coverage.

The PI Dr. Cristancho Pimiento and her designee will meet weekly for research meetings to focus on screening forms; inclusion/exclusion criteria; case report form review; adverse events and other Human Research Protection Office (HRPO) required monitoring and reporting activities. The PI or her designee will record each subject screened for study inclusion and maintain records of reasons for subject exclusions. This information will be included in yearly renewals with the HRPO.

Dr. Eric Lenze (Professor at the Department of Psychiatry) will be fully available to provide guidance regarding issues related to the safety of study participants and the integrity of the study. Dr. Lenze will participate in research meetings to review accuracy of screening, subject accrual, and all subjects who withdraw from the study. Likewise, he will be available to assess with issues regarding participant accrual, overall study progress, intervention efficacy, adverse events, ethical concerns, quality of monitoring, and protocol adherence. The entire investigative team with Dr. Cristancho , Dr. Lenze and the PI Designee will meet at least once per quarter.

We will follow procedures pertaining to adverse events and serious adverse events as specified in the DSMP document

E4 Study Outcome Measurements and Ascertainment

Primary outcome measures:
The effects of the study intervention depression will be measured using the Montgomery Asberg Depression Rating Scale.
The effects of the study intervention on executive function will be evaluated using the Flanker inhibitory control, the Dimensional change sort task and the
List Sorting Working memory test will measure executive function, from the NIH Tool box executive function domain.

Brain's connectivity measure: Using resting state fMRI we will measure functional connectivity within the Cognitive Control Network (CCN) in depressed older adults before and after study intervention. We will also explore functional connectivity within and between other networks that are relevant to depression including the Default Mode network and the cingulo-opercular networks.

F Statistical Plan

Statistical Analyses: We will use intention-to-treat principles. We will use t-test or its non-parametric equivalent to compare the distribution of continuous variables and the changes in the main outcome measures between active and sham groups. χ^2 tests will be used to compare categorical variables between groups. We will use a mixed general linear model (GLM) to accommodate data from our within- and between-participant study design to examine changes from baseline to post-intervention, and compare them between active vs. sham groups. The GLM explores estimated marginal means by taking into account within- and between-participant variability, adjusting for confounders and allowing exploration of significance of within-participant and between-group interaction effects. Differences between groups in behavioral outcome measures and network connection changes will be evaluated through 2-way interaction effect (time*group). Through the 2- way interaction iTBS*Fazekas score we will explore the modification effect of grade of white matter burden on the impact of iTBS in the observed network connectivity changes. Pearson's correlation will examine the correlation between changes in behavioral measures with changes in network connectivity. We will use Hayes' PROCESS[114] macro to evaluate the role of the difference in the strength of connections pre-intervention minus the strength of connection post intervention as mediator of change for iTBS and bootstrap and Monte Carlo confidence intervals will be calculated. All statistical tests will be two-sided and evaluated at the alpha level of 0.05. SAS 9.4 (SAS Institute, Cary, NC) and R 3.2.3 statistical software packages will be used for all analyses. Sample size justification: For this pilot study, I plan to enroll 20 elderly subjects and randomized them to iTBS arm or placebo arm (10 in each group). The sample size of 20 subjects is feasible for the time limit of the KL2 award. This pilot sample will provide meaningful data to estimate sample size and calculate power for a subsequent grant application to rigorously test the effects of theta burst stimulation on depressed older adults.

G Data Handling and Record Keeping Records retention:

Study data will be kept for potential future analysis. Records will be maintained for at least 7 years after completion of the study as per local HRPO requirements.

G1 Confidentiality and Security

Obtaining consent forms and interviews will be conducted in the private research offices suites of Dr. Cristancho or study staff. Intervention sessions will be conducted in a private office in the West pavilion 15th floor at BJH Psychiatry Department at the TMS clinic suite. Only the minimally necessary number of personnel will be present. MRI scans will be performed at scanning facilities at Washington University: The CCIR and the MRI facility at the Mallinckrodt Institute of Radiology.

G2 Training

All staff involved in TBS administration will be trained by Dr. Cristancho Pimiento (director of the TMS clinic).

G3 Case Report Forms and Source Documents

Confidentiality Subject confidentiality will be assured through a multi-layered approach, entirely compliant with HIPAA regulations. We will have the following formal mechanisms limiting access to information that can link data to individual participants: Data forms that include identifying information will be kept in locked cabinets. Only the unique ID number, assigned by the research assistant at the time of initial contact will represent participants during data entry, data transfer, data analysis, or other file management procedures.

Electronic case report forms will be created using the same confidentiality procedures described above. Data will be stored into a secure data base on the university network.

G4 Records Retention

Records will be maintained for at least 7 years after completion of the study as per local HRPO requirements.

H Study Administration

H1 Organization and Participating Centers

Washington University School of Medicine

H2 Funding Source and Conflicts of Interest

Support is from The National Institutes of Health and the National Center for Advancing translational Sciences, and the Department of Psychiatry, through the Center for Brain Research in Mood Disorders.

H3 Subject Stipends or Payments

Subjects will be compensated up to $125 for their participation in the study. Cards to cover the cost of parking will be provided for subjects.

H4 Study Timetable

Recruitment and data acquisition will take place from 2018 to 2020.

I Publication Plan

It is estimated that a primary publication will be produced reporting outcomes of this study. Depending on study results additional publications may result.

J Attachments

Please refer to IRBS submission for all attachments.

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