Intermittent Theta Burst for the Treatment of Alcohol Use Disorders in Veterans

NCT03291431

08/01/2017

Study Protocol and Statistical Analysis Plan

Resources :

a) Qualified staff.

Please state and justify the number and qualifications of your study staff.

Qualification of PI:

Timothy C. Durazzo, PhD (PI/PD): He is a licensed Clinical Psychologist (in CA), with specialization in Clinical Neuropsychology and formal training in neuroscience and magnetic resonance neuroimaging. He is the attending Clinical Neuropsychologist for the War Related Injury and Illness Study Center (WRIISC) and Research Scientist for the Mental Illness Research and Education Clinical Center (MIRECC) at the VA Palo Alto Health Care System (HCS). He concurrently holds a faculty appointment as an Associate Professor in the Department of Psychiatry and Behavioral Sciences at Stanford University School of Medicine. He conducts psychoeducational/therapy groups at the VA Palo Alto Addiction Treatment Services. He has have served as PI, Co-PI, and Co-Investigator on multiple NIH and DoD grants. A major component of his research program focuses on the neurobiological and neurocognitive consequences of alcohol and substance use disorders, the factors that influence recovery from these conditions, and the mechanisms promoting the relapse/remit cycle in addictive disorders. He has extensive experience in the recruitment, screening, longitudinal cohort maintenance, fiduciary management, supervision of students, technicians and fellows, and the day-to-day administration of federally funded grants. He has expertise in the administration and interpretation of all proposed psychiatric, neuropsychological, and psychosocial measures, as well as in the acquisition and processing of data from all the magnetic resonance methods proposed in this project. The PI has received extensive training in TMS safety and administration, is certified to administer TMS in clinical and research settings, and will deliver all TMS procedures in conjunction with this study. He will direct the day-to-day conduct of the study, train and supervise project personnel, consult with Drs. Yesavage and Williams (as needed) to determine eligibility of prospective participants, oversee data collection, entry and management, and conduct or supervise all statistical analyses.

Qualifications of Other Personnel:

Claudia B. Padula, PhD (Co-PI/PD): Dr. Padula has experience with and continues her training in behavioral and cognitive testing, functional MRI, study design, execution and analysis via her VA Career Development Award. She is a Research Health Scientist Specialist at the VA Palo Alto HCS and Clinical Instructor at the Stanford University School of Medicine. Dr. Padula has extensive experience in the recruitment, screening, longitudinal cohort maintenance, fiduciary management, supervision of students, technicians and fellow's expertise in the administration and interpretation of all proposed psychiatric, neuropsychological, and psychosocial measures, as well as in the acquisition and processing of data from all the magnetic resonance methods proposed in this project.

Leanne Williams, PhD (OP): Dr. Williams is Director of PTSD Education at the VA Palo Alto HCS MIRECC and Professor in the Department of Psychiatry and Behavioral Sciences at Stanford University School of Medicine. She has extensive experience with behavioral and cognitive testing, functional MRI, study design, execution and analysis. She has have served as PI, Co-PI, and Co-Investigator on multiple NIH grants. She has expertise in the administration and interpretation of all proposed psychiatric, neuropsychological, and psychosocial measures, as well as in the acquisition and processing of data from all the magnetic resonance methods proposed in this project. Dr. Williams will also be involved in data interpretation, manuscript preparation, and dissemination of findings (via Posters or Presentations) at professional conferences.

Keith Humphreys, PhD (OP). Dr. Humphreys is a Career Research Scientist at the Center for Healthcare Evaluation, VA Palo Alto HCS and Professor in the Department of Psychiatry and Behavioral Sciences at Stanford University School of Medicine. Dr. Humphreys also co-directs the Neurochoice Initiative at Stanford Neuroscience Institute which among other projects is using fMRI and other MR technology to predict the outcome of alcohol and methamphetamine dependent Veterans in psychosocial addiction treatment. He will assist the PI in statistical analyses, manuscript preparation and provide additional guidance and advice on cohort maintenance and follow-up data collection. Dr. Humphreys will also be involved in data interpretation, manuscript preparation, and dissemination of findings (via Posters or Presentations) at professional conferences.

Jerome Yesavage, MD (OP): Dr. Yesavage is a Psychiatrist, ACOS Mental Health, and Director of VISN 21

MIRECC at the VA Palo Alto HCS and Professor in the Department of Psychiatry and Behavioral Sciences at Stanford University School of Medicine. Dr. Yesavage has extensive experience as PI and Co-Investigator in clinical trials of TMS treatment in multiple populations and in the diagnoses and treatment of mental disorders. Dr. Yesavage will serve as a study physician for the rTMS treatment component of this application (i.e., be available for medical emergencies and consultation) and will directly assist the PI on supervising rTMS safety, protocol adherence, and assessment for adverse events. Dr. Yesavage will also be involved in data interpretation, manuscript preparation, and dissemination of findings (via Posters or Presentations) at professional conferences.

Nolan Williams, MD (OP): Dr. Williams is a Psychiatrist and Neurologist, Clinical Instructor, and Director of the Brain Stimulation Laboratory at the Department of Psychiatry and Behavioral Sciences at Stanford University School of Medicine. Dr. Williams has extensive experience as PI and Co-Investigator in clinical trials of TMS treatment in multiple populations and in the diagnoses and treatment of mental disorders. He will serve as a study physician for the TMS treatment component of this application and will directly assist the PI on supervising TMS safety, protocol adherence, and assessment for adverse events. Dr. Yesavage will also be involved in data interpretation, manuscript preparation, and dissemination of findings (via Posters or Presentations) at professional conferences.

Margaret Windy McNerney, PhD (OP) is a postdoctoral scholar in the Stanford/VA WRIISC Fellowship and has a submitted application for a VA Career Development Award. She has extensive experience and current certification in the processing, genotyping and quantitation of genetic biomarkers associated with this study.

Art Noda, MS (OP). Mr. Noda is a MIRECC Data Manager and has 25 years of experience of research data management and analysis for clinical studies. He has developed advanced skills using SAS in database construction and management as well as proficiency in a variety of complex statistical analyses. He will assist the PI in creating a secure database and will be available for consultation, as needed.
Additional personnel will join the study as research assistants.

b) Training.

Describe the training you will provide to ensure that all persons assisting with the research are informed about the protocol and their research-related duties and functions.

All study personnel involved in this protocol, as well as those that may join at a later point, will be given all protocol materials, including background materials and the IRB proposal. The core study personnel [Drs. Durazzo, Padula, Yesavage and Research Assistants (RA)] will meet weekly to discuss the ongoing research and ensure that all personnel are appraised of any updates in the protocol. Study personnel will also communicate regularly with each other as to the progress of each person's roles and responsibilities within the protocol. Study personnel that will be performing magnetic resonance scans at the Stanford Center for Cognitive and Neurobiological Imaging will complete appropriate safety training courses required for users of those facilities prior to scanning participants. All core study personnel will also be trained on the necessary procedures and forms for informed consent form and participant compensation. Further, study personnel operating at the VA will be approved by the VA to conduct research on the premises.

c) Facilities.
Please describe and justify.

The facilities are available to support each component of the protocol:
Recruitment and screening: The VA Palo Alto HCS substance abuse treatment clinics and providers are available to support recruitment and screening of patient participants. These activities will be carried-out at the VA Palo Alto HCS MIRECC, Building 5, 4th floor or at participants substance abuse treatment clinic at the VA Palo Alto, depending on which location is most convenient for the participant. Private interview/exam rooms are available for this purpose at both locations.

Consent: Conducted at the VA Palo Alto HCS MIRECC, Building 5, 4th floor and/or at participants substance abuse treatment clinic at the VA Palo Alto, depending on which location is most convenient for the participant. Private interview/exam rooms are available for this purpose at both locations.

Clinical interview, neuropsychological and behavioral testing: Conducted at the VA Palo Alto HCS MIRECC, Building 5, 4th floor. Private interview rooms are available for this purpose. Neuropsychological and behavioral testing will be undertaken using computerized and paper-and-pencil measures.

Transcranial Magnetic Stimulation: Conducted at the VA Palo Alto HCS MIRECC, Building 5, 4th floor. Private treatment rooms are available for this purpose

Neuroimaging:

Magnetic resonance scans will be conducted at the Center for Cognitive and Neurobiological Imaging at Stanford University.

Blood draws and genetics: The MIRECC Genetics and Translational Laboratories are in Building 7. Blood samples will be taken and processed by trained nursing staff or trained phlebotomists in the VA Palo Alto HCS Center for Clinical Research (CCR), main hospital building 100.

d) Sufficient time.
Explain whether you will have sufficient time to conduct and complete the research. Include how much time is required.
We expect to begin participant recruiting participants in 07/2017 with an end date of 07/2019. We anticipate running 40 total participants over 2 years (20 active TMS, 20 sham TMS). With the addition of 2 RAs in August or September, we will have sufficient personnel to successfully execute all Aims of this protocol.

e) Access to target population.
Explain and justify whether you will have access to a population that will allow recruitment of the required number of participants.
Subjects for the study will be identified via the VA Palo Alto HCS Addiction Treatment Services (ATS) for recruitment of individuals with alcohol use disorder. Access to this population is provided via the support of the Director of ATS, Dr. John Nguyen (see attached letter of support). The records of ATS for the past 12 months demonstrate it is very feasible to meet the required target number of participants. The majority of participants will be recruited from residential
treatment programs; therefore, 24 hour monitoring for any adverse events will be in place as an additional layer of participant safety.

f) Access to resources if needed as a consequence of the research.
State whether you have medical or psychological resources available that participants might require as a consequence of the research when applicable. Please describe these resources.

If a medical adverse event should occur, study staff includes two physicians who are board-certified in psychiatry (Drs. Yesavage and Williams). Additional medical assistance will be available through the VA TMS clinical roll-out staff RN's and physicians trained in TMS safety and adverse event management, and VA Palo Alto HCS Emergency Department service is readily available, if needed. Immediate psychiatric/psychological consultation will available for participants if required (Dr. Durazzo: Licensed Clinical Psychologist and Dr. Yesavage: Board Certified Psychiatrist). Appropriate referrals will be made when necessary in the judgment of the PI/PD or study physician.

g) Lead Investigator or Coordinating Institution in Multi-site Study.
Please explain (i) your role in coordinating the studies, (ii) procedures for routine communication with other sites, (iii) documentation of routine communications with other sites, (iv) planned management of communication of adverse outcomes, unexpected problems involving risk to participants or others, protocol modifications or interim findings.

1. Purpose

a) In layperson's language state the purpose of the study in 3-5 sentences.
The purpose of this study is to evaluate the efficacy of intermittent theta burst (iTBS) transcranial magnetic stimulation (TMS) as a treatment for Veterans with an alcohol use disorder (AUD) to decrease the exceedingly high rate of relapse associated with this condition.

b) State what the Investigator(s) hope to learn from the study. Include an assessment of the importance of this new knowledge.

At least 60% of those with AUD will experience a major relapse period within 6 months of treatment, irrespective of the intervention (psychosocial and/or pharmacological) employed. Consequently, the high prevalence of AUD and relapse following treatment in Veterans is associated with substantial resource allocation and costs for the DVA Health Care System. Current pharmacological and psychosocial interventions demonstrate only a moderate level of efficacy, which is reflected in the high rate of relapse in AUD.

iTBS-TMS is a neurostimulation method that is at the forefront of innovative, non-invasive, and safe treatments for AUD, and the disorders that commonly co-occur with AUD. To reduce the high rate of relapse in Veterans with AUD, it is necessary for interventions to more effectively address the associated neurobiological dysfunction and salient co-occurring conditions. Accordingly, additional rigorously controlled studies are required to determine if iTBS-TMS is an effective treatment for Veterans with AUD.

This is double-blind placebo controlled project will deliver completely novel data on the efficacy of iTBS-TMS to promote sustained abstinence for Veterans with AUD during the first 6 months following treatment. Monthly monitoring over the entire first 6 months following treatment is crucial, given relapse within the first 6 months of treatment is robustly related to poor psychosocial functioning over the ensuing 1-3 years. The ultimate goal of this proposal is to provide treatment that more effectively promotes sustained abstinence in the Veteran with AUD, as extended abstinence is robustly associated with optimum biomedical, neuropsychological, psychiatric, and psychosocial recovery and functioning.

c) Explain why human subjects must be used for this project. (i.e. purpose of study is to test efficacy of investigational device in individuals with specific condition; purpose of study is to examine specific behavioral traits in humans in classroom or other environment)

The goal of this study evaluate the efficacy of iTBS-TMS as a treatment for Veterans with an AUD; therefore, humans must be studied.

2. Study Procedures

a) Please SUMMARIZE the research procedures, screening through closeout, which the human subject will undergo. Refer to sections in the protocol attached in section 16, BUT do not copy the clinical protocol. Be clear on what is to be done for research and what is part of standard of care.

PROTOCOL SUMMARY:

1. Recruitment and screening: Participants will be recruited via VA Palo Alto HCS Addiction Treatment Services.

2. Informed Consent: Prior to consent, The PI, or Co-PI or research assistant or qualified RA, will recheck inclusion/exclusion criteria.

3. Baseline/Pretreatment Assessment:
- Psychiatric Assessment
- Alcohol and Substance use
- Neurocognitive Assessment
- 3 Tesla Magnetic Resonance Neuroimaging
- Blood draw (as described in DETAILS OF RECRUITMENT, DESIGN AND TREATMENT below)

4. Treatment Phase: iTBS-TMS. Active iTBS-TMS Treatment Group – will receive a total of 20 treatments delivered 5 days/week, two treatments per day, over 2 consecutive weeks. Sham Treatment group will receive the same frequency and duration of treatment, without actual administration of iTBS-TMS. The majority of participants will be recruited from residential treatment programs; therefore, 24 hour monitoring for any adverse events will be in place as an additional layer of participant safety.

5. Post-Treatment Phase: Within 3-4 days of completion of the Treatment Phase, all participants will repeat neurocognitive assessment, select psychiatric assessment measures, select alcohol and substance questionnaires, 3 Tesla Magnetic Resonance Neuroimaging and blood draw. During this time, all participants will be receiving treatment-as-usual at the VA clinics, and scheduling of iTBS-TMS will be arranged as not to interfere with their daily curriculum.

6. Monthly Follow-ups: For the 6 months following completion of active/sham iTBS treatment, participants will be contacted monthly,
via telephone or in person, to complete brief standardized measures of alcohol and substance use, as well as craving to assess for changes in these variables over the preceding 30 days. These brief contacts will be 15-20 min in duration and tracking sobriety
is the primary outcome measure of this study..

DETAILS OF RECRUITMENT, DESIGN AND TREATMENT
Recruitment and screening: Potential participants from the VA Palo Alto treatment programs will be identified based on VA medical/clinical staff diagnoses of an alcohol use disorder without any comorbid condition any conditions that be contraindicated for study (e.g., taking medications that lower seizure threshold, magnetic resonance neuroimaging contraindications, medically confirmed seizure disorder). Specifically, medical/clinical staff of the programs listed above will identify potential participants who meet eligibility criteria and inform the patient that a research opportunity is available to them and offer contact information to study personnel or the participant may request that study personnel contact them. The study has been explained to clinicians via treatment team meetings, so they are familiar with eligibility criteria. The PI, Co-PI or qualified RA will check inclusion/exclusion criteria based on initial
eligibility and sociodemographic data via in person screen at the treatment program or at the MIRECC, Building 5, 4th floor. Private interview rooms are available for this purpose at both
locations.

Baseline/Pretreatment Assessment (see section 2.a.3.b. of grant
application):
a) Psychiatric Assessment: will use standardized measures employed in
clinical practice and research.
b) Alcohol and Substance use: will use standardized measures employed
in clinical practice and research.
c) Neurocognitive Assessment: will use standardized measures employed
in clinical practice and research
d) 3 Tesla Magnetic Resonance Neuroimaging: will be conducted at the
Stanford Center for Neuroimaging.
e) Blood draw A venipuncture of the arm be performed and maximum of 20 ml of blood will taken by trained nursing staff or trained phlebotomists in the VA Palo Alto Clinical Research (CCR), main hospital building 100. Dr. McNerney will obtain participants' blood
samples from the CCR and deliver them to the VA-MIRECC Genetics Laboratory for DNA extraction and genotyping and VA-MIRECC Translational Laboratory, where she will conduct biomarker analyses. These labs are located in Building 7 at VAPAHCS.

Design, Treatment Phase and Treatment Arms: This is a double-blind randomized group design, which will enroll 40 participants. After
screening and baseline procedures, participants will be randomized to active or sham iTBS-TMS conditions (20 active, 20 sham); thus
participants will have a 50% probability of receiving active treatment. Participants will receive 20 iTBS-TMS sessions over the course of 2 weeks. Participants will be required to be abstinent from alcohol and illicit substance for 7 days and demonstrate no clinically significant withdrawal symptoms prior to randomization.

Rationale for Brain Region Site: The left dorsolateral prefrontal cortex (DLPFC) was chosen as the iTBS stimulation site given excitatory transcranial magnetic stimulation to this region has been demonstrated to decrease cravings in non-Veterans with AUD. Additional stimulation of this site has been robustly shown to be associated with decreased unipolar depressive symptomatology; depressive disorders are highly comorbid in Veterans with AUD.

Duration of Treatment Phase: Active iTBS-TMS Treatment Group – will receive a total of 20 treatments delivered 5 days/week, two treatments per day (Monday-Friday), over 2 consecutive weeks. Sham Treatment group will receive the same frequency and duration of treatment, without actual administration of iTBS-TMS. iTBS-TMS sessions will be delivered prior to the beginning of participants' treatment day, and at lunch, as to not interfere with their treatment-as-usual in the VA substance treatment clinics. There have been no adverse events reported in the literature implementing two iTBS sessions per day in any population.

Procedures for Delivery of iTBS-TMS Sessions:
1) Anatomical localization of the left DLPFC for the stimulation coil will be individualized for each participant and achieved through standardized procedures for EEG electrode placement, optimized for transcranial magnetic stimulation. The localization of participant left DLPFC will be confirmed using the subject MRI data collected prior to the treatment phase.

2) Motor Threshold (MT) Elicitation: Inherent to the safe and accurate dosing of TBS stimulation, active MT elicitation will be performed according to established protocols, which have been in use since 1994. This protocol is well-established as an effective method for MT Elicitation, widely implemented within both sham-controlled transcranial magnetic stimulation research with demonstrated safety.MT will be calculated for all participants prior to randomization.

3) iTBS-TMS Dosing: Dosing of iTBS-TMS will = 100% of the active MT adjusted to the skull to cortex distance (via each participants structural MRI), as this is documented to modulate the desired cortical target, and is not associated with any adverse events. Six hundred (600) pulses of iTBS-TMS at 50 Hz will be utilized, consistent with standard parameters. There will be 10 trains of 3 pulses at 50Hz every 200ms (50Hz over 5Hz), which is 30 pulses per theta burst train. Twenty (20) trains will be delivered to achieve 600 pulses over approximately 3 minutes.

4) Sham Control and Blinding Methods: The sham-control and blinding methods will be the same as used in TMS trials in which investigator and participant blinding to group assignment was carefully documented and achieved in previous clinical trials conducted with Veterans at VA medical centers. These methods involve: (a) the Cool-B65-Active/Placebo Coil, which functions as both an active and sham coil; (b) scalp electrodes; and (c) a white-noise generator. The scalp electrodes are used to pass a low-voltage, low electric current (2–20mA at no more than 100V) to mimic the sensation of receiving actual iTBS. The white-noise generator is used to send low-volume white noise to the subject's ears when magnetic stimulation pulses are initiated to hide the click noise the iTBS-TMS produces.

Post-Treatment Phase: Within 3-4 days of completion of the Treatment Phase, all participants will repeat neurocognitive assessment, select psychiatric assessment measures, select alcohol and substance questionnaires, 3 Tesla Magnetic Resonance Neuroimaging and blood draw as described above in Baseline/Pretreatment Assessment. Monthly Follow-ups: For the 6 months following completion of the treatment phase, participants will be contacted monthly, via telephone or in person, to complete a brief standardized measures of alcohol and substance use, as well as craving to assess for changes in these variables over the preceding 30 days. These brief contacts will be 15-20 min in duration and tracking sobriety is the primary outcome measure of this study.

b) Explain how the above research procedures are the least risky that can be performed consistent with sound research design.

All procedures will be performed by staff trained specifically for the tasks for which they are responsible. All procedures, including the iTBS-TMS , and are considered low-risk procedures. iTBS-TMS is regarded as safe and without lasting side effects when established guidelines are followed. The primary serious adverse event associated with transcranial magnetic stimulation procedures are seizures, however, the estimated prevalence is very low at < 1%. In the case of transcranial magnetic stimulation-seizures, all have occurred during stimulation, there was no recurrence of seizures, and no incidences of status epilepticus. There have been no significant adverse cognitive, brain structural, neurologic or cardiovascular sequelae reported as a result of iTBS-TMS . Seizure risk will be minimized by careful patient selection (by rigorously screening and exclusion of participants with history

of seizure disorders or other conditions and medication use that increases risks of seizure). A seizure protocol is in place to avoid participant injury in the event that a seizure does occur (attached). Overall, the risks to participants in this proposal are reasonable in relation to anticipated benefits, if any, to
the participants, and the importance of the knowledge that may be expected to result.

c) State if deception will be used. If so, provide the rationale and describe debriefing procedures. Since you will not be fully informing the participant in your consent process and form, complete an alteration of consent (in section 13). Submit a debriefing script (in section 16).
N/A

d) State if audio or video recording will occur. Describe what will become of the recording after use, e.g., shown at scientific meetings, erased. Describe the final disposition of the recordings.
N/A

e) Describe alternative procedures or courses of treatment, if any, that might be advantageous to the participant. Describe potential risks and benefits associated with these. Any standard treatment that is being withheld must be disclosed in the consent process and form. (i.e. standard-of-care drug, different interventional procedure, no procedure or treatment, palliative care, other research studies).

The participants in this study will concurrently receive standard-of-care cognitive-behavioral and pharmacological interventions from the VA Palo Alto substance treatment clinics they are enrolled in. There are no potential risks to the participants who receive concurrent
cognitive-behavioral and any procedure associated with the proposed research protocol. No participant will enrolled who is taking a
medication that lowers seizure threshold. Risks to confidentiality will be minimized by following all procedures dictated by HIPAA and
NIDA/NIAAA Certificate of Confidentiality. Of course, potential participants may decline to be involved in the study and receive only
the available standard-of-care cognitive-behavioral and pharmacological interventions
Will it be possible to continue the more (most) appropriate therapy for the participant(s) after the conclusion of the study?

This study will not impose any restrictions on treatment/therapy after conclusion. At this point, the iTBS treatment under investigation will only be available during the treatment phase of the study.

g) Study Endpoint. What are the guidelines or end points by which you can evaluate the different treatments (i.e. study drug, device, procedure) during the study? If one proves to be clearly more effective than another (or others) during the course of a study, will the study be terminated before the projected total participant population has been enrolled? When will the study end if no important differences are detected?

In order to have sufficient power to evaluate the primary hypotheses of this study, it is expected to continue until all participants have
completed the procedures and follow-up assessments.

3. Background

a) Describe past experimental and/or clinical findings leading to the formulation of the study.
To date there have been nine transcranial magnetic stimulation studies for the treatment of AUD. Results suggest TMS may serve as a novel treatment intervention for AUD. However, the generalizability of the published clinical trials to Veterans is severely limited because of several design limitations:

- All were international studies with modest sample sizes, did not include Veterans, and consisted primarily of inpatients; AUD treatment at most VA and civilian facilities delivered via outpatient clinics
- Six of nine studies were single blind designs, only five utilized a true sham control condition; double blind, sham/placebo controlled
designs are the standard in evaluation of the efficacy of an intervention.
- Six studies excluded participants for conditions (e.g., MDD) that commonly co-occur with AUD, and the effects of concurrent smoking on TMS efficacy were not rigorously evaluated. Consequently, the results do not generalize to the typical Veteran seeking treatment for AUD.

• Two studies employed single TMS sessions and four had ≤ 10 total sessions; this number of treatments may have not been sufficient to promote sustained abstinence, particularly in Veterans.
• The primary outcome measure in most studies was craving. Higher baseline craving is moderately associated with relapse risk during the first few weeks of treatment, but is a poor predictor of relapse several months after treatment. Therefore, it is necessary to obtain
baseline measures of impulse control and risk taking, which are substantially more robust predictors of relapse after treatment.
• The primary follow-up period was ≤ 1 month; such a short follow-up interval did not permit evaluation of the long-term efficacy of TMS treatment. Regular monitoring over the entire first 6 months following treatment is imperative, given relapse during the first 6 months following treatment is strongly related to clinically significant impairments in psychosocial functioning
over the ensuing 1-3 years in Veterans and civilians with an AUD.
• Only one placebo controlled study employed biomarkers for the mechanism(s) of therapeutic action or treatment response, so objective biomarkers of TMS treatment response in AUD have yet to be firmly established. Identification of biomarkers of mechanism(s) and level of treatment response are necessary to more effectively tailor TMS treatment to the individual Veteran.
• No TMS study has employed the iTBS protocol proposed in this application.

The efficacy of iTBS-TMS for the treatment of Veterans with AUD is unknown until the foregoing limitations are addressed and a
representative sample of Veterans is studied. The proposed project will rigorously address the above limitations and provide completely
novel information on the efficacy of TMS to decrease the high rate of relapse in Veterans with AUD. It is imperative to conduct the proposed study over the next 4 years since TMS will be rolled-out as a clinical service to each VISN in 2017 (organized and lead by our VISN 21 MIRECC TMS treatment team) for treatment of major depression, and it will likely be applied to Veterans with AUD or comorbid AUD and depression without sufficient support and direction from clinical trials with Veterans. We believe this proposed work will provide preliminary data to allow VA clinicians to make decisions about the utility of iTBS-TMS treatment.

4. Radioisotopes or Radiation Machines

a) List all standard of care procedures using ionizing radiation (radiation dose received by a subject that is considered part of their normal medical care). List all research procedures using ionizing radiation (procedures performed due to participation in this study that is not considered part of their normal medical care). List each potential procedure in the sequence that it would normally occur during the entire study. http://www.stanford.edu/dept/EHS/prod/researchlab/radlaser/Human_use_guide.pdf
More Info
Identify Week/Month of study Name of Exam Identify if SOC or Research
b) For research radioisotope projects, provide the following radiation-related information:
Identify the radionuclide(s) and chemical form(s).
For the typical subject, provide the total number of times the radioisotope and activity will be administered (mCi) and the route of administration.
If not FDA approved provide dosimetry information and reference the source documents (package insert, MIRD calculation, peer reviewed literature).
c) For research radiation machine projects, provide the following diagnostic procedures:
For well-established radiographic procedures describe the exam.
For the typical subject, identify the total number of times each will be performed on a single research subject.
For each radiographic procedure, provide the setup and technique sufficient to permit research subject dose modeling. The chief technologist can usually provide this information.
For radiographic procedures not well-established, provide FDA status of the machine, and information sufficient to permit research subject dose modeling.
d) For research radiation machine projects, provide the following therapeutic procedures:
For a well-established therapeutic procedure, identify the area treated, dose per fraction and number of fractions. State whether the therapeutic procedure is being performed as a normal part of clinical management for the research participants' medical condition or whether it is being performed because the research participant is participating in this project.
For a therapeutic procedure that is not well-established, provide FDA status

5. Devices

a) Please list in the table below all Investigational Devices (including Commercial Devices used off-label) to

be used on participants.

5. 1 Device Name : MagPro X100 (with theta burst module)
Describe the device to be used.

The MagPro X100 and similar transcranial magnetic stimulation devices are FDA approved for treatment for major depressive disorder.

Manufacturer : MagVenture
Risk : Non-significant

Y I confirm the above are true.

Rationale for the device being non-significant risk:
Transcranial magnetic stimulation is an FDA approved treatment modality for major depressive disorder. Although the MagPro X100 and similar transcranial magnetic stimulation devices are not currently FDA approved for alcohol use disorders, the MagPro X100 to be used in the present study is an FDA-cleared device.

Sponsor of Project
Indicate who is responsible for submitting safety reports to the FDA:
Y The sponsor is the STANFORD (SU, SHC, LPCH, VA) investigator.

Please read the following:
Sponsor-Investigator Research Requirements

If you would like further information on this process and/or assistance prior to submitting your protocol contact: The Stanford Center for Clinical and Translational Education and Research (Spectrum) at clinicaltrials@med.stanford.edu or for cancer research contact: ccto-regulatory@stanford.edu

Y I have read and understand the above guidance.

Ordering, Storage and Control
To prevent the device being used by a person other than the investigator, and in someone other than a research participant: Confirm that the device will be handled according to the SHC/LPCH policy for Investigational New Devices or as appropriate. If no, please provide an explanation. :
Y Confirm?
b) Please list in the table below all IDE Exempt Devices (Commercial Device used according to label, Investigational In Vitro Device or Assay, or Consumer Preference/Modifications/Combinations of Approved Devices) to be used on participants.
6. Drugs, Reagents, or Chemicals
a) Please list in the table below all investigational drugs, reagents or chemicals to be administered to participants.
b) Please list in the table below all commercial drugs, reagents or chemicals to be administered to participants.
7. Medical Equipment for Human Subjects and Laboratory Animals
If medical equipment used for human patients/participants is also used on animals, describe such equipment and disinfection procedures.
N/A

8. Participant Population
a) State the following: (i) the number of participants expected to be enrolled at Stanford-affiliated site(s); (ii)the total number of participants expected to enroll at all sites; (iii) the type of participants (i.e. students, patients with certain cancer, patients with certain cardiac condition) and the reasons for using such participants.

(i)(ii) &(iii): Forty (40) participants are expected to be enrolled (20 active iTBS-TMS and 20 sham

iTBS-TMS) from all substance abuse clinics at the VA Palo Alto, but primarily from the Foundations of Recovery (FOR) 30 day residential program.

b) State the age range, gender, and ethnic background of the participant population being recruited.

The study will be open to males and females, regardless of race and ethnic origin, 21-65 years of age, who are in active treatment for an AUD at the VA Palo Alto. The 21-65 age range was chosen given the vast majority of information on iTBS-TMS efficacy and safety has been obtained from this range and this is the typical age range of Veterans seeking treatment for AUD at the VA Palo Alto.

c) State the number and rationale for involvement of potentially vulnerable subjects in the study (including children, pregnant women, economically and educationally disadvantaged, decisionally impaired, homeless people, employees and students). Specify the measures being taken to minimize the risks and the chance of harm to the potentially vulnerable subjects and the additional safeguards that have been included in the protocol to protect their rights and welfare.
Individuals with the following conditions that are associated with decisional impairment will be excluded: History of Schizophrenia Spectrum Disorders, Bipolar Disorders, neurodegenerative diseases (e.g., Alzheimer disease, Parkinson's disease) active current suicidal intent or plan (patients with a previous clinical flag for risk for suicide will be required to have an established safety plan involving their primary psychiatrist and the treatment team before entering the clinical trial). Individuals with a lack of fluency in English, Wechsler Adult Reading Test below the 7th percentile (i.e., moderate or greater impairment in estimated general intelligence), females who are pregnant or actively attempting pregnancy (conservative exclusion for magnetic resonance research) will also be excluded from the study. Children and homeless people will not be included. It is common for Veteran AUD and substance use samples to contain economically and educationally disadvantaged; however, no undue influence will be exerted on these individual and level of compensation for study participation will not be coercive. Additionally, the treatment phase of this study will occur while participants are receiving standard-of-care treatment at the VA Palo Alto, which will permit additional on-going monitoring for any adverse events.

d) If women, minorities, or children are not included, a clear compelling rationale must be provided (e.g., disease does not occur in children, drug or device would interfere with normal growth and development, etc.).
No children will be involved in this project as they are not in the age range of US Armed Services Veterans. The study will be open to male and females, regardless of race, ethnic origin, and sexual preference and identity, 21-65 years of age, who are in active treatment for an AUD at the VA Palo Alto HCS (VAPAHCS). Approximately 5% females and 30% racial and ethnic minorities were observed among the Veteran participants in PI's previous studies at the VA San Francisco HCS. Given the similar demographics
of Veterans at the VAPAHCS, we anticipate a similar distribution of females and racial and ethnic minorities.

e) State the number, if any, of participants who are laboratory personnel, employees, and/or students. They should render the same written informed consent. If payment is allowed, they should also receive it. Please see Stanford University policy.
It is possible that up to 15% of our participants may be current VA laboratory personnel or employees. We do not anticipate that any Veteran participants will be current Stanford employees or students.

f) State the number, if any, of participants who are healthy volunteers. Provide rationale for the inclusion of healthy volunteers in this study. Specify any risks to which participants may possibly be exposed. Specify the measures being taken to minimize the risks and the chance of harm to the volunteers and the additional safeguards that have been included in the protocol to protect their rights and welfare.
No healthy volunteers will be included in this study.

g) How will you identify participants for recruitment? (E.g., by: chart review; referral from treating physician; response to ad). Attach recruitment materials in Section #16 (Attachments). All Final or revised recruitment materials, flyers, etc. must be submitted to the IRB for review and approval before use. You may not contact potential participants prior to IRB approval. See Advertisements: Appropriate Language for Recruitment Material.

Potential participants from the VA Palo Alto treatment programs (Foundations of Recovery and ACT Intensive Outpatient programs) will be identified based on VA medical/clinical staff diagnoses of an alcohol

use disorder without any comorbid condition any conditions that be contraindicated for study (e.g., taking medications that lower seizure threshold, magnetic resonance neuroimaging contraindications, medically confirmed seizure disorder). Specifically, medical/clinical staff of the programs listed above will identify potential participants who meet eligibility criteria and briefly explain the study and offer contact information to study personnel or the participant may request that study personnel contact them. The study protocol has been explained to clinicians via treatment team meetings, and the clinical staff are fully cognizant of study procedures and eligibility criteria. The PI, Co-PI or qualified RA will check inclusion/exclusion criteria based on initial eligibility and sociodemographic data via in person screen at the treatment program or at the MIRECC, Building 5, 4th floor. Private interview rooms are available for this purpose at both locations.

h) Inclusion and Exclusion Criteria.
Identify inclusion criteria.
The study will be open to male and females, regardless of race and ethnic origin, 21-65 years of age, who are in active treatment for an AUD at the VA Palo Alto. The 21-65 age range was chosen given the vast majority of information on iTBS efficacy and safety has been obtained from this range and this is the typical age range of Veterans seeking treatment for AUD at the VA Palo Alto. At time of enrollment, 21-65 years of age, meet Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria for AUD, and alcohol is self-identified as primary substance of misuse. Actively in treatment at VA Palo Alto HCS Addiction Treatment Service, and able to read, verbalize understanding, and voluntarily sign the Informed Consent Form prior to participation in study procedures. Participants will be accepted if taking medications specifically for the treatment of MDD, cigarette smoking, or for other psychiatric conditions (as long as the medications are not documented to lower seizure threshold; must be stable on any psychotropic medication for at least 1 month prior to enrollment); it would be clinically contraindicated to require participants to discontinue such medications for research. iTBS is safely administered to individuals who are taking psychotropic medications that do not lower seizure threshold. Participants will be abstinent from alcohol and non-prescribed substances for at least 7 consecutive days prior to active or sham iTBS to ensure no participant is experiencing active acute withdrawal.

Identify exclusion criteria.
Psychiatric: History of Schizophrenia Spectrum Disorders, Bipolar Disorders, a current substance use disorder that exceeds the severity of the AUD (based on DSM-5 diagnostic criteria), active current suicidal intent or plan (patients with a previous clinical flag for risk for suicide will be required to have an established safety plan involving their primary psychiatrist and the treatment team before entering the clinical trial), any form of previous iTBS or electroconvulsive treatment. Biomedical: Including but not limited to uncontrolled thyroid disease, unstable congestive heart failure, angina, other severe cardiac illness as defined by treatment regimen changes in the prior 3 months, cerebrovascular accident, cancer if < 1 year since end of treatment; unstable diabetes, COPD requiring oxygen supplementation, Alzheimer's disease, Parkinson's disease, any biomedical implants with ferromagnetic content, neurostimulation devices, cardiac pacemakers or any magnetic resonance contraindications, traumatic brain injury with self-reported or observed loss of consciousness > 30 minutes, any primary or traumatically induced seizure disorder. General: Lack of fluency in English, Wechsler Adult Reading Test below the 7th percentile (i.e., moderate or greater impairment in estimated general intelligence), females who are pregnant or actively attempting pregnancy (conservative exclusion for magnetic resonance research), current use of any medication or substance that is documented to lower seizure threshold or has been identified as a contraindication for iTBS-TMS treatment.

i) Describe your screening procedures, including how qualifying laboratory values will be obtained. If you are collecting personal health information prior to enrollment (e.g., telephone screening), please request a waiver of authorization for recruitment (in section 15).
1) Initial screen for alcohol use disorder undertaken by clinical staff at intake, with the support of the director. The clinical staff will offer each incoming patient with a diagnosis of AUD the opportunity to participate in the study, and refer to the potential participant to the PI, Co-PI or trained RA's contact number; alternately, the participant can request to the clinical staff that PI, Co-PI or trained RA's contact them to further explain the study. study coordinator.
2) The PI, Co-PI or trained RA will then conduct an in-person or telephone screen for study specific inclusion and exclusion criteria (we are requesting a waiver of authorization for recruitment). Eligible participants will be invited to complete Informed Consent document and enroll in the study. Ineligible

participants will be immediately informed that they do not satisfy inclusion/exclusion criteria. Ineligible participants will not be given the specific reasons why they are not eligible in order to maintain the integrity and security of the study inclusion/exclusion criteria. Rather, ineligible participants will be informed that they have a current or past history of medical, physical or psychological conditions that does not permit safe application of the iTBS protocol used in this study.

j) Describe how you will be cognizant of other protocols in which participants might be enrolled. Please explain if participants will be enrolled in more than one study.
Subjects may be part of other protocols, including neuroimaging protocols, and this would not be expectedto interfere with our protocol. However, we plan to specifically inquire with subjects as to their involvement in other research protocols as to best safeguard the both the subject's welfare and the integrity of data collected by us and other research groups.

k) Payment. Explain the amount and schedule of payment, if any, that will be paid for participation in the study. Substantiate that proposed payments are reasonable and commensurate with the expected contributions of participants and that they do not constitute undue pressure on participants to volunteer for the research study. Include provisions for prorating payment. See payment considerations
Participants will not be compensated for study screening. Participants will receive $15/hour for all baseline and treatment phase and week 5 follow-up study procedures. Participants will receive $15 for each monthly contact from week 9 – 25. Those who complete all study phases will receive a $50 completion bonus. Total possible compensation over 6 months = $387. This rate of compensation is commensurate with other AUD research being conducted at the VA Palo Alto and VA San Francisco. Participants will be provided with a choice of an equivalent monetary amount in gift certificates to VA Palo Alto HCS Canteens, to an easily accessible department store chain (e.g., Ross), or Amazon. NO CASH or CHECKS WILL BE DISPENSED. The PI employed this procedure for 15 years at the VA San Francisco HCS to allow participants to purchase much needed fundamental clothing and other personal items, with no history of adverse events. The gift certificates are intended to facilitate participation without adding undue influence.

l) Costs. Please explain any costs that will be charged to the participant.
No costs will be incurred by any participant.

m) Estimate the probable duration of the entire study. Also estimate the total time per participant for: (i) screening of participant; (ii) active participation in study; (iii) analysis of participant data.
(i)Probable duration of study = 2 years.

(ii)Total time per participant:

Study Phase	Estimated Participation Time
Screening	20-30 min
Baseline	6.5 hours, 2 hours/day over 1 week.
Treatment	10 hours, 1 hour/day, over 2 weeks
Follow-up	Week 5 4 hours typically over 2 days
Follow-up Weeks 9 – 25	2 hours

Total Active Participation Time = approx. 22.5 hours over 6 months.
All procedures will be conducted before or after normal ATS clinic hours, or during lunch break, to not interfere with the patient's treatment schedule. The project will be conducted at the VAPAHCS MIRECC, which is on the same campus as the FOR program.

(iii) Analysis of participant data after breaking of blind will be conducted over the ensuing 6-9 months.

9. Risks

a) For the following categories include a scientific estimate of the frequency, severity, and reversibility of potential risks. Wherever possible, include statistical incidence of complications and the mortality rate of proposed procedures. Where there has been insufficient time to accumulate significant data on risk, a statement to this effect should be included. (In describing these risks in the consent form to the participant it is helpful to use comparisons which are meaningful to persons unfamiliar with medical terminology.)

Investigational devices.
iTBS-TMS device: iTBS-TMS is regarded as safe and without lasting side effects when established guidelines are followed. The primary safety concern associated with any form of transcranial magnetic stimulation procedures are seizures, however, the estimated prevalence is very low at < 1%. In the case of transcranial magnetic stimulation-seizures, all have occurred during stimulation, there was no recurrence of seizures, and no incidences of status epilepticus. All the reported seizures resolved promptly after removal of stimulation, without medical intervention and were not associated with lasting adverse effects.In those rare seizure cases, the motor cortex was typically being stimulated; in the proposed study a non-primary motor region of the cortex (left DLPFC) is the stimulation site. There have been no significant adverse cognitive, brain structural, neurologic or cardiovascular sequelae reported as a result of iTBS-TMS. Participants treated with iTBS-TMS may experience temporary discomfort at the site of stimulation due to depolarization of sensory and motor neurons in the scalp under the point of stimulation. Muscle tension headache may result in some participants (generally estimated at less than 10% of sessions), and can persist for 1-2 hours post stimulation. iTBS treatment can result in mild to moderate headaches in approximately 15% of participants. These headaches are never disabling or persistent and usually respond to ibuprofen or acetaminophen. The incidence of headaches in those with serial transcranial magnetic stimulation typically diminishes with increasing number of sessions. In some people, particularly those with a history of a history of Bipolar Disorder I or II, daily transcranial magnetic stimulation caused them to experience mania (increased energy, no need for sleep, and racing thoughts); this study will exclude for a history of Bipolar Disorders.

Magnetic Resonance Neuroimaging: The magnetic resonance scanning devices (3 Tesla, General Electric MR750) used in scanning at the Stanford Center for Cognitive (CNI) and Neurobiological Imaging poses a non-significant risk to subjects in line with the criteria for exception from an IDE, and routinely used by many other investigators at Stanford. There have been no serious adverse events incurred during scanning at the Stanford Center for Cognitive and Neurobiological Imaging.
Investigational drugs. Information about risks can often be found in the Investigator's brochure.
N/A
Commercially available drugs, reagents or chemicals. Information about risks can often be found in the package insert.
N/A

Procedures to be performed. Include all investigational, non-investigational and non-invasive procedures (e.g., surgery, blood draws, treadmill tests).

Venipuncture: There is mild local discomfort associated with venipuncture, along with a risk of bruising or bleeding. On very rare occasions there may be mild bleeding or bruising at the sampling site. Removal of blood by a needle and syringe poses a small risk of pain or bruising at the site of the needle stick, but this is temporary. Some people may experience fainting or dizziness, and there is also a slight risk of infection at the site of the needle stick.

Cognitive, Psychiatric and Alcohol/drug Assessments and Questionnaires. Memory and cognitive testing can cause anxiety or frustration. The level of psychological stress is similar to what might be be associated with a neuropsychological.

Genetic and Biomarker testing. Genetic testing will be conducted on the collected blood samples.
Samples will be brought to our research center's lab at VA Palo Alto HCS Dr. Windy McNerney, who will conduct all biomarker and genotyping analyses/assays,

iTBS-TMS. Risks are described above in 9.i. (Investigational devices). Magnetic Resonance Neuroimaging. Risks are described above in 9. i. (Investigational devices).

Radioisotopes/radiation-producing machines (e.g., X-rays, CT scans, fluoroscopy) and associated risks.
N/A

Physical well-being.
See above devices and procedures. No other risks to physical well-being are anticipated.
Psychological well-being.
Screening, neuropsychological, psychiatric interviews and questionnaires: The screening interview,

neuropsychological and psychiatric assessments, as well as self-report questionnaires may be fatiguing and/or distressing for some individuals. Study participants will be informed that they are free to decline to answer any questions or to stop the assessments at any time. Neurocognitive and psychiatric interview sessions will include breaks. In the event that a study participant appears to be under undue strain, the test or interview session will be discontinued.

Genetic Biomarker and Genetic testing: It is possible that biomarker and genetic testing could cause minor psychological stress in a some individuals. All participants will be informed that only members of the research staff will see results of the biomarker and genetic testing which will be in a coded format with no individual identification. The biomarker and genetic testing is strictly for research purposes only and results of the genetic testing will not be released to anyone outside of the research project (including participants, family, physician, or any other third party).

Economic well-being.

No risks to economic well-being are anticipated.

Social well-being.

No risks to social well-being are anticipated.

Overall evaluation of Risk.

Low - innocuous procedures such as phlebotomy, urine or stool collection, no therapeutic agent, or safe therapeutic agent such as the use of an FDA approved drug or device.

b) If you are conducting international research, describe the qualifications/preparations that enable you to both estimate and minimize risks to participants. Also complete the 'http://humansubjects.stanford.edu/research/documents/intl_rsch_APP-11.doc' International Research Form and attach it in the Attachments section. If not applicable, enter N/A.

N/A

c) Describe the planned procedures for protecting against and minimizing all potential risks. Include the means for monitoring to detect hazards to the participant (and/or to a potential fetus if applicable). Include steps to minimize risks to the confidentiality of identifiable information.

Screening, neuropsychological, psychiatric interviews and questionnaires: Participants will be informed that these procedures may be fatiguing and/or distressing for some individuals. Study participants will be informed that they are free to decline to answer any questions or to stop the assessments at any time. Neurocognitive and psychiatric interview sessions will include breaks. In the event that a study participant appears to be under undue strain, the test or interview session will be discontinued. Participants will be reminded that they are free to withdraw from participation at any time.

iTBS-TMS administration: The iTBS-TMS operator will be the PI (Dr. Durazzo) and he is fully trained and qualified to administer the procedure according to current safety practices and standards of care in research and clinical settings. Co-Investigators trained in iTBS-TMS will closely monitor the iTBS-TMS PIs adherence to safety protocols and administration for this proposal. This application employs all current established and standard iTBS-TMS treatment safety and monitoring for adverse events guidelines. The iTBS-TMS operator will monitor all participants for ear protection, coil placement, and seizure activity during all sessions. All participants will be required to have abstained from alcohol or non-prescribed medication for 7 consecutive days prior to the first rTMS session. Prior to the first rTMS session, participants will be administered the Clinical Institute Withdrawal Assessment for Alcohol-Revised and must score ≤ 8 (scores > 8 are indicative of potential autonomic instability); participants with a score > 8 will immediately be escorted to their VA Palo Alto Addiction Treatment Services clinic for further evaluation. Participants will be randomly screened x6 for alcohol (breath alcohol) and substance use (urine toxicology) prior to rTMS sessions during the 2 week treatment phase. If a participants test positive or report any alcohol or substance use during the 2 week iTBS-TMS treatment period, they will be immediately withdrawn from the study. Additionally, prior to each session, participants will complete a iTBS-TMS screen, which will include inquiring about any changes in medications or comorbid medical conditions, amount of sleep suicide screening questionnaire prior to each rTMS session to assess for current suicide risk. Although patients in the are regularly screened for alcohol and substance use and suicide risk while in treatment, we will conduct random alcohol/substance screening and pre-iTBS-TMS session suicide risk assessment to ensure participant welfare. Should a headache or site discomfort occur, these symptoms usually readily respond to acetaminophen or ibuprofen. Any reported painfulness typically improves over time or completely remits. To protect against possible hearing damage, participants will wear ear protection during rTMS sessions (foam ear plugs and noise attenuating headphones). This will greatly reduce the possibility of hearing loss. Hearing acuity testing pre-and-post rTMS is no longer a standard practice, given the remote likelihood of iTBS-TMS-related hearing loss.

Additional Procedures for the Monitoring of Seizures and Suicidal Ideation/Behavior:

Screening, Baseline and Treatment Phase: In the unlikely event that a seizure does occur, participants will be closely monitored and treated for any medical or psychological consequences. rTMS sessions will be conducted at the VA Palo Alto MIRECC, which fully equipped to safely handle a seizure. If at any point during study participation, a participant has a seizure, the participant will be withdrawn from the study immediately (although they will still be followed for protocol assessments). All seizures will be considered serious adverse events (SAE) and as such, will be reported to the study PI. We will immediately suspend enrollment if 10 participants experience a seizure during study participation, and request that the Data Monitoring Committee (DMC) evaluate the SAE data, to determine if enrollment of new participants should be resumed without protocol changes, if protocol modifications should be made before resuming enrollment, or if the study should be terminated. We recognize that study termination or modification based on SAEs, such as seizures, ultimately rests with the DMC and the study PI.
If a participant expresses suicidal ideation/intent, and is determined to be a risk to self, a clinical evaluation will be immediately conducted by the PI (a licensed clinical psychologist), Co-Is (a licensed clinical psychologist or board certified psychiatrist), by the participant's individual mental health provider, and/or a mental health emergency clinician. The participant will remain with qualified study personnel or a MIRECC clinician until the evaluation has been completed and a decision made about disposition in conjunction with the Chief of Mental Health Outpatient Clinic or the emergency mental health clinician.

Follow-up Phase: If a participant discloses active suicidal or homicidal ideation or other clinically significant psychiatric symptomatology during the follow-up phase of the study, they will provided with the number and encouraged to call Veterans Crisis Hotline or present to a local hospital emergency department. In the event of a seizure (or other medical issues possibly secondary to rTMS), the participant will be requested to immediate contact their primary health care provider. In the event of disclosure of the above psychiatric emergencies or a seizure, the PI or psychiatrist Co-Investigator will also be immediately notified and will contact the participant for further assessment and determine the appropriate intervention. If a participant discloses that they relapsed during the follow-up period, they will be encouraged to recontact VAPAHCS Addiction Treatment Services for re-evaluation and possible re-engagement in treatment.

Magnetic Resonance (MR) Studies
Participants will be informed of risks, using the text provided and required by Stanford University's Institutional Review Board. Our research team has been trained by MR Technologists at VAPAHCS and at Stanford to carefully pre-screen each participant for MRI safety before the MRI appointment. On-site neuroradiologists will be available for consultation. A certified MR Technologist will conduct all scans and perform a separate MR safety screen immediately prior to the scan. The scan will take place in the Diagnostic Radiology Center (DRC) at the VAPAHCS. The emergency room is nearby, in the wing next to the DRC. Minimal risks are associated with MR scanning and 3T MR scanners are now routinely used in clinical practice. Study participants who have metal implants, cardiac pacemakers, metal fragments or a known tendency for claustrophobia will not be admitted to the study. Study participants will be scanned with a metal detector before entering the 3T scanner room, and all metal objects will be removed.
There is a remote possibility that the magnet will attract a metal object, producing physical injury. To make certain such event do not occur, the door to the magnet room is closed and there is a metal detector outside the door to ensure no ferromagnetic metals are allowed into the scanner. One theoretical hazard of the experiments is heating of the body due to radio waves, but the machine has several safety devices to prevent such an occurrence. There is also a slight risk of nerve stimulation during a portion of the procedure. While there are safety devices that prevent such events, this can occur in rare cases. To reduce this risk, volunteers will be instructed to avoid skin-to-skin contact between their extremities, such as clasping their bare hands or crossing their bare feet. In any case, such sensation is temporary and harmless. Fatigue, boredom, feelings of claustrophobia, or discomfort due to loud banging sounds of gradient coils may accompany the MR procedures. Earplugs and supplied MR-safe headphones will be used during MR scanning. A communication system is set up inside each scanner so that study participants can contact the researchers at any time, and will be immediately removed from the scanner upon request. In case of adverse effects, medical intervention can be provided by Stanford Emergency Department staff. Study physicians will be available in the case of an adverse event to debrief with the participant.
Identification of clinically significant psychiatric symptomatology (other than suicidal ideation or plan), or neurocognitive abnormalities: Although unlikely, it is possible that during the screening process, on the psychiatric interview and questionnaires or during other study procedures, participants may manifest or

disclose clinically significant psychiatric symptoms (e.g., homicidal ideation, hallucinations) or disorders that were not previously identified/diagnosed by VA Palo Alto Addiction Treatment Services staff. In this case, the participant will be immediately assessed by the PI (a licensed clinical psychologist/neuropsychologist), the participant's individual mental health provider, or a mental health emergency clinician. The participant will not be left alone until the evaluation has been completed and a decision made about disposition in conjunction with the Chief of Mental Health Outpatient Clinic, or the emergency mental health clinician. If any participant manifests grossly clinically significant neurocognitive impairment (> 2 standard deviations below mean performance of the normative reference group) on any domain of functioning, Dr. Durazzo will debrief the participant and inform his current mental health treatment providers, with the participant's explicit approval and written consent (obtained in the informed consent) for further assessment. If a participant discloses that they relapsed during the follow-up period, they will be encouraged to recontact VA Palo Alto Addiction Treatment Services for re-evaluation and possible re-engagement in treatment.

Loss of confidentiality: Every precaution will be taken to minimize loss of confidentiality. A triple lock system will be maintained: within a locked lab, locked office, and locked file cabinet. All electronic data will be secured on an encrypted, password-protected database behind a VA firewall. The rTMS USB drives are proprietary to the rTMS device and are configured to store the non-PHI data that is captured from the machine. These devices are stored in a locked container, in a locked cabinet, in a locked office. The participant's name will not be used in any reports or publications resulting from this study. The participant's name will not be recorded on test material or other research records. An identification code will be used instead. The participant's identification code will be kept in a secured database. The PI and trained and qualified research team members will have access to the participant's information. The coded, de-identified data for each participant, which has been stripped of any information that could be used to identify the participant, may be shared with consultants. However, the participant's personal health information cannot be used for additional research without additional approval from either the participant or a review committee.

Adverse Events (AEs) and Adverse Device Effects (ADEs)
1. Adverse Device Effect (ADE) and Adverse Event (AE)

Definitions:
An Adverse Device Effect (ADE) is defined by 21 CFR 812.3(s) as any adverse effect/event caused by or associated with the use of a device.

An Adverse Event (AE) is defined by the ICH for Clinical Safety Data as any untoward physical or psychological occurrence in a human subject participating in research. The AE does not necessarily have to have a causal relationship with the pharmacological product, study intervention, or assessment. An AE can, therefore, be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom or disease associated with the use of a medicinal (investigational) product.

Reporting: In this study, all ADEs and AEs that occur during the acute treatment and follow-up phases will be collected and followed until resolution or the individual's participation in the study ends. All events will be recorded on the appropriate case report form. "Relatedness" involves an assessment of the degree of causality between the study intervention and the event. PIs will be asked to provide an assessment of relatedness. The assessment provided by the PI is part of the information used by the sponsor to determine if the adverse event or effect presents a participant safety concern. An ADE is deemed to be associated with the use of the study device if there is a reasonable possibility that the experience may have been caused by the device or by participation in the trial. Thus, all adverse events or effects with a reasonable causal relationship to the rTMS treatment should be considered related. A definite relationship does not need to be established. The following levels of relatedness will be used in this study:
- Not attributed to the iTBS-TMS treatment
- Possibly attributed to the iTBS-TMS treatment
- Attributed to the iTBS-TMS treatment

Serious Adverse Events (SAEs) and Unanticipated Adverse Device Effects (UADEs)
Definitions:
Serious Adverse Events (SAEs) are a subset of adverse events and are defined by the ICH for Clinical

Safety Data Management as any untoward medical occurrence that:
- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect or
- Any other condition that, based upon medical judgment, may jeopardize the subject and require medical or surgical treatment to prevent one of the above outcomes.

An Unanticipated Adverse Device Effect (UADE) is defined as: Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of participants. For this study an UADE is considered a category of SAE, which will be reported on the same form.
Collection and Recording

For this study, all SAEs and UADEs will be recorded on the SAE form, regardless of cause. The PI will be asked to determine whether the serious adverse event is related to:
- iTBS-TMS device
- iTBS-TMS treatment
- Medications used to treat AUD and/or co-occurring conditions

Collecting and recording SAEs/UADEs will begin at randomization and will continue throughout the follow-up phase. For a participant who ends study participation prior to the study's completion date, unresolved SAEs will be monitored and reported for 30 days after the End of Study date for that participant. In addition, the investigator must collect all SAEs reported to them for a period of 30 days after the study's completion.

Expedited Reporting of Serious Adverse Events (SAEs) and Unanticipated Adverse Device Effects (UADEs)

Study personnel will be responsible for initially evaluating all serious adverse events for participant safety concerns and will confer with the PI as required during this evaluation process. After being reviewed by the PI, any event deemed to be related, serious and unexpected will be reported to study investigators.
Expedited Reporting by the Sponsor to the FDA: PI will review the SAE report to assess completeness of documentation and to determine whether the SAE requires expedited reporting to the FDA. Specifically, if an event meets the criteria for unexpectedness (i.e., not previously reported) and seriousness it will be reported as required by regulation to the FDA within 10 working days for UADEs and within 7 calendar days for unexpected SAEs (Safety Reports) of the sponsor receiving the report as required by regulation.
Data Monitoring Committee (DMC): Reporting of Adverse Events, Adverse Device Effects, Serious Adverse Events, and Unanticipated Adverse Device Effects. Study Personnel will generate tabulations of AEs and SAEs and present a summary of these to the DMC on a schedule set by the DMC. The DMC will also determine when they should be unblinded to treatment assignment for the reviewing of adverse event data. The DMC will advise the PI concerning whether the study should continue or be stopped for safety reasons. Note: We request that a DMC be assigned to us by our VA granting agency.
Communication among the Investigative Team: The PI will have a weekly group lab meeting with all Research Health Scientist Specialists, and there will be a monthly lab meeting with all Co-investigators and consultants (some via Skype). Additionally, the VA Palo Alto MIRECC has weekly PI meetings to discuss issues relevant to ongoing MIRECC research projects. All VA Co-investigators associated with this project attend these weekly meetings.

Explain the point at which the experiment will terminate. If appropriate, include the standards for the termination of the participation of the individual participant Also discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the participants.
The experiment will end at either the normal termination or whenever the subject decides to withdraw from

the study. Participants will be asked to complete the brief monthly in person or telephone assessments as described in the follow-up phase. In the event that an interim analysis demonstrates futility, the PI, Co-PI or Co-Is determines unacceptable level of risk, regulatory agencies mandate discontinuation of the study, or a product recall occurs that necessitates stopping the study, any planned iTBS-TMS treatments will be immediately discontinued.

e) Data Safety and Monitoring Plan (DSMP). See guidance on Data Safety and Monitoring.
A Data and Safety Monitoring Plan (DSMP) is required for studies that present Medium or High risk to participants. (See Overall Evaluation of Risk above). If Low Risk, a DSMP may not be necessary. Multi-site Phase III clinical trials funded by NIH require the DSM Plan to have a Data Safety Monitoring Board or Committee (DSMC or DSMB). The FDA recommends that all multi-site clinical trials that involve interventions that have potential for greater than minimal risk to study participants also have a DSMB or DSMC. The role of the DSMC or DSMB is to ensure the safety of participants by analyzing pooled data from all sites, and to oversee the validity and integrity of the data. Depending on the degree of risk and the complexity of the protocol, monitoring may be performed by an independent committee, a board(DSMC/DSMB), a sponsor's Data Safety Committee (DSC), a Medical Monitor, a sponsor's safety officer, or by the Protocol Director (PD).

Describe the following:
What type of data and/or events will be reviewed under the monitoring plan, e.g. adverse events, protocol deviations, aggregate data?
Although this study protocol is low risk, with a modest number of participants, we will create a DSMP as we believe this is consistent with best clinical practices. Types of data and events that will be reviewed are: 1) Aggregate Data Analysis Reports 2) Progress toward Study endpoint(s) 3) AEs, SAEs and unanticipated problems (UPs) 4) Protocol deviations.

Identify who will be responsible for Data and Safety Monitoring for this study, e.g. StanfordCancer Institute DSMC, an independent monitoring committee, the sponsor, Stanford investigators independent of the study, the PD, or other person(s).
The grant utilize a DSMB that will review the progress of the study. The IMC will monitor patient enrollment, aggregate outcomes, adverse events, and other issues related to patient safety. The safety monitoring plan reflects the low risk of the TBS intervention, the 2-week duration of intervention, the extra precautions taken (e.g. MRI safety screening and exclusions of individuals with a risk of seizure), the modest number of subjects involved, and the single-site nature of the study.

Provide the scope and composition of the monitoring board, committee, or safety monitor, e.g., information about each member's relevant experience or area of expertise. If the Monitor is the Stanford Cancer Center DSMC or the PD, enter N/A.
The composition will include a neurological surgeon and clinical psychologist, not affiliated with the study, with expertise in clinical trials and familiarity with transcranial magnetic stimulation.

Confirm that you will report Serious Adverse Events (SAEs), Suspected Unexpected Serious Adverse Reactions (SUSARs), or Unanticipated Problems (UPs) to the person or committee monitoring the study in accordance with Sponsor requirements and FDA regulations.
All SAEs will be reported within 24 hours of learning of the SAE. Unanticipated problems (UPs)involving risks to participants or others will be reported within 5 days.
If applicable, how frequently will the Monitoring Committee meet? Will the Monitoring Committee provide written recommendations about continuing the study to the Sponsor and IRB?
Given the modest number of participants studied per year (approximately 20), the DSMB will meet once per year to review data reports prepared by the PD's research team. Any member of the DSMB can ask for an emergency meeting of the group. The DSMB will issue written reports to the PD on the safety and progress of the trial. The report will include recommendations to the PD concerning continuation, termination or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study. The PD will provide of the DSMB reports to the IRB.

Specify triggers or stopping rules that will dictate when the study will end, or when some action is required. If you specified this in Section 2g [Study Endpoints], earlier in this application enter 'See 2g'.

See 2g.

Indicate to whom the data and safety monitoring person, board, or committee will disseminate the outcome of the review(s), e.g., to the IRB, the study sponsor, the investigator, or other officials, as appropriate.

The IMC will provide its written reports to the PD, who will submit them reports to the IRB.

Select One:
The Protocol Director will be the only monitoring entity for this study.
Y This protocol will utilize a board, committee, or safety monitor as identified in question #2 above.

10. Benefits

a) Describe the potential benefit(s) to be gained by the participants or by the acquisition of important knowledge which may benefit future participants, etc.
iTBS-TMS could potentially generate substantial health benefits for VHA patients. Repetitive iTBS-TMS may offer a viable and more efficacious treatment option for Veterans with AUD. Moreover, it could be disseminated and delivered to both urban as well as to rural facilities, and in VA Hospitals as well as Community Based Outpatient Clinics (CBOC's). In sum, iTBS-TMS has the potential to dramatically improve access to effective mental and cognitive health and rehabilitation for a large number of Veterans with AUD. For these reasons, the anticipated risks are reasonable in relation to the anticipated benefits to study participants. However, if shown safe and effective, the budgetary cost of iTBS-TMS will likely be an important consideration relating to its subsequent evaluation and implementation. If our hypotheses are confirmed, replicated in independent samples, and critically evaluated by peer review, the VA Palo Alto HCS (VAPAHCS) Mental Illness Research and Education Clinical Center (MIRECC) is well-suited to lead a nationwide roll-out of an iTBS-TMS treatment protocol for AUD. The VAPAHCS MIRECC has developed treatment protocols and led highly successful nationwide roll-outs of evidence-based practices (EBP) of cognitive-behavioral therapy for depression and insomnia to well over 2000 VA clinicians. VISN-21 MIRECC Education Core currently is funded for core resources for such tasks. The VISN-21 MIRECC has been funded a roll-out for TMS for depression concurrent with the conclusion of CSP 556 (The Effectiveness of rTMS in Depressed VA Patients). Thus, the findings and protocol for our iTBS-TMS intervention for AUD can be readily disseminated to VA (and non-VA) researchers, clinicians, and leadership through the MIRECC EBP program. In clinical research studies at VAs and universities throughout the nation, rTMS is currently routinely and safely administered by trained non-medical personnel, under the supervision of qualified medical professionals. As described in this proposal, iTBS-TMS is a very safe treatment when standard safety protocols are followed. Therefore, it is highly feasible that iTBS-TMS can be safely and effectively implemented at both VA medical centers and CBOCs to treat AUD by trained non-medical technicians under the supervision of qualified medical personnel. This will significantly increase Veteran access to the iTBS-TMS intervention throughout the VA system and substantially reduce the costs of treatment delivery.

Privacy Protections

a) Describe how the conditions under which interactions will occur are adequate to protect the privacy interests of participants (e.g., privacy of physical setting for interviews or data collection, protections for follow-up interactions such as telephone, email and mail communications).
During the consenting process, in-person screening, and the collection of other study data, participants will meet in a private interview room with a member of the study team at the study site (Bldg 5 at VA Palo Alto; CNI for Neuromaging). Blood samples will be obtained in a private setting at the study site (VA Palo Alto CCR, Bldg 100).

Confidentiality Protections

b) Specify PHI (Protected Health Information). PHI is health information linked to HIPAA identifiers (see above). List BOTH health information AND HIPAA identifiers. If you are using STRIDE, use the Clinical Data Work Sheet to ensure that your request will match your IRB-approved protocol. Be consistent with information entered in section 15a.

We will collect the following HIPAA identifiers, as mentioned on
the VA HIPAA form:
- Social security number (for participation compensation i.e., gift cards, and entry of required research notes into VA medical records);

- Name, address and telephone number (for follow-up assessments and to mail participation compensation); and to mail payment);
- Birth dates & visit dates.

We will collect the following PHI, as mentioned on the HIPAA:
- Demographic information including age and race/ethnicity;
- Results of past routine laboratory tests;
- Physical examinations and related past medical records;
- Magnetic resonance neuroimaging data, MRI digital images and clinical reads of MRIs;
- Research data, questionnaires, blood specimens, and study progress notes, which may include: cognitive test scores; questionnaires about mood and everyday function; current and past medical history; current and past medications; adverse effects during the study; and height and weight.

(laptops and desktops; OFFICE or HOME); smart phones; tablets; external hard disks, USB drives, etc. that may hold identifiable participant data will be password protected, backed up, and encrypted. See http://med.stanford.edu/datasecurity/ for more information on the Data Security Policy and links to encrypt your devices.
Provide any additional information on ALL data security measures you are taking. You must use secure databases such as RedCap https://clinicalinformatics.stanford.edu/services/redcap.html. If you are unsure of the security of the system, check with your Department IT representative. Please see http://med.stanford.edu/irt/security/ for more information on IRT Information Security Services and http://www.stanford.edu/group/security/securecomputing/mobile_devices.html for more information for securing mobile computing devices. Additionally,any PHI data on paper must be secured in an locked environment.
By checking this box, You affirm the aforementioned. Y
Paper data with PHI will be kept in locked file cabinets in locked offices. Data collected on paper forms and questionnaires will be
entered into encrypted, password-protected databases. Electronic files and databases are maintained on a secure VA network, on a server that is backed up and located in a secure server room accessible only by authorized personnel. Only staff listed for a given protocol are granted access to appropriate server folders. Staff's computers are password protected, encrypted, and backed
up. The VA prohibits removable drives. At the VA, REDCap data are transmitted from behind the VA firewall (on the VA intranet) and
REDCap servers are housed at the VA Informatics and Computing Infrastructure (VINCI). VINCI servers are physically located at
the VA Austin Information Technology Center (AITC), located in Austin, Texas. VA REDCap is only available to VA researchers through a web URL that requires a VA generated login and email address. Each subject will be assigned a participant ID number (PID). All computer-entered data will be coded using PIDs only. Biomarker/genetic information is stored in a separate password protecte file, which can only be accessed by the PI, Co-PI ,the data manager/analyst, and appropriately delegated staff. Only the data
manager/analyst can match genetic information with the participant ID number. The genetic data is only used for analysis of data
conducted by the PI or data manager in this study unless the subject or LAR consents to future use and sharing of genetic data and samples as documented on the informed consent form. All personnel involved in this study will have successfully completed applicable VA and Stanford training. All subject-level identifiable data will be treated as Protected Health Information (PHI) unless that
data does NOT contain any of the data elements that HIPAA considers protected. Any data, specimens, forms, reports, and other records that leave the site will be identified only by a PID to maintain confidentiality. Information will not be released without written
permission of the participant, except as necessary for monitoring by IRB,

d) Describe how data or specimens will be labeled (e.g. name, medical record number, study number, linked coding system) or de-identified. If you are de-identifying data or specimens, who will be responsible for the de-identification? If x-rays or other digital images are used, explain how and by whom the images will be de-identified.
Data, specimens and image files will be labeled by a participant ID number (PID). Information linking the PID code and PHI will be kept on a secure, password protected computer behind a firewall. The Data Manager is responsible for de-identification of data. The PI is ultimately responsible for de-identification of samples.

e) Indicate who will have access to the data or specimens (e.g., research team, sponsors, consultants) and describe levels of access control (e.g., restricted access for certain persons or groups, access to linked data or specimens).
Members of the research team will have access to all non-genetic data. The data manager has access to both non-genetic and genetic
data; however, the data manager has no access to subject names, SSNs, or contact information.
If the subject requests it explicitly (in writing), we will send information about neuropsychological assessments and clinical results to his/her personal physician. De-identified study data may be shared with collaborating researchers at Stanford University and at other institutions. Deidentified data may also be shared with collaborating researchers at other institutions in the future. No genetic data and biomarker specimens will be shared with anyone outside of this research study unless the subject or legally authorized representative consents future use and sharing of genetic data and samples as documented on the informed consent document.

f) If data or specimens will be coded, describe the method in which they will be coded so that study participants' identities cannot be readily ascertained from the code.
A participant ID number (PID) is assigned to a subject after they sign a consent form. This numeric code is independent of any identifying information.

g) If data or specimens will be coded, indicate who will maintain the key to the code and describe how it will be protected against unauthorized access.
The key to the code will be maintained by the PI and Co-PI; it will be available to appropriate members of the research team but kept in a locked file cabinet and on a physically secure, password-protected computer at VA Palo Alto that is separate from other study data or specimens.

h) If you will be sharing data with others, describe how data will be transferred (e.g., courier, mail) or transmitted (e.g., file transfer software, file sharing, email). If transmitted via electronic networks, describe how you will secure the data while in transit. See http://www.stanford.edu/group/security/securecomputing/ http://www.stanford.edu/group/security/securecomputing/. Additionally, if you will be using or sharing PHI see https://uit.stanford.edu/security/hipaa https://uit.stanford.edu/security/hipaa.
No PHI will be transferred to anyone outside of the established research team.

i) How will you educate research staff to ensure they take appropriate measures to protect the privacy of participants and the confidentiality of data or specimens collected (e.g. conscious of oral and written communications, conducting insurance billing, and maintaining paper and electronic data)?
All research staff will complete and remain current with all required VA and Stanford training prior to working with human subjects. The PI, along with VA Research Administration, also reinforce the importance of maintaining confidentiality.

12. Potential Conflict of Interest

Investigators are required to disclose any financial interests that reasonably appear to be related to this protocol.
You will be unable to submit this protocol until all financial interest tasks are completed. "javascript:void(0);" onClick="javascript:startResendOpacs();return false;" Click here to send reminder emails.

13. 1 Consent Consent for participants

Check if VA related Y

a) Describe the informed consent process. Include the following.
i) Who is obtaining consent? (The person obtaining consent must be knowledgeable about the study.)
ii) When and where will consent be obtained?
iii) How much time will be devoted to consent discussion?
iv) Will these periods provide sufficient opportunity for the participant to consider whether or not to participate and sign the written consent?
v) What steps are you taking to minimize the possibility of coercion and undue influence?
vi) If consent relates to children and if you have a reason for only one parent signing, provide that rationale for IRB consideration.
(i) Study personnel obtaining consent will be one of the investigators, or RA, who have been trained to give informed consents.
(ii) The consenting is always done after the potential research subject has been presented with a description of the study and indicated interest in
participating, and before any information is collected, or any questionnaires answered. The consenting will

typically takes place in one of the private interview rooms in the VA Palo Alto MIRECC (Bldg 5, 4th floor) or at the participants VAPAHCS Addition Treatment Program. (iii) Sufficient time will be allowed for the participant to read the consent and to ask any and all questions they may have and discuss the study with the study personnel obtaining consent. We estimate this will take approximately 30 minutes (iv) The potential participant may take the consent to review, and contact study personnel to ask further questions or sign it if they so desire. (v) Participants will be told that involvement in the study is completely voluntary, and that they can withdraw at any time, for any reason. Research personnel will also emphasize that any treatment they receive at VAPAHCS will not be affected by their choice to participate in the study. (vi) n/a

What is the Procedure to assess understanding of the information contained in the consent? How will the information be provided to participants if they do not understand English or if they have a hearing impairment? See /hrpp/Chapter12.html#ch12_2 HRPP Chapter12.2 for guidance.
Participants will be given an explanation of the consent form by trained research staff. In addition, they will be given ample time to read and review the consent forms and given the opportunity to ask questions or clarification. Given the nature of the study, individuals must be fluent in English and not have visual or auditory acuity impairment that would prevent them from completing the assessments, including the consent.

c) What steps are you taking to determine that potential participants are competent to participate in the decision-making process? If your study may enroll adults who are unable to consent, describe (i) how you will assess the capacity to consent, (ii) what provisions will be taken if the participant regains the capacity to consent,(iii) who will be used as a legally authorized representative, and (iv) what provisions will be made for the assent of the participant.
The study will not enroll individuals who are not able to give written, informed consent. If there is any question about a potential subject's capacity to give informed consent, they will be screened by the study PI/PD, who is a licensed clinical psychologist/neuropsychologist for the cognitive competency to provide written informed consent.

Additional VA questions:

i) List the people to whom you have formally delegated responsibility to obtain informed consent, and state whether they have the appropriate training to perform this activity.
Timothy Durazzo, Claudia Padula, Leanne Williams, Jerome Yesavage, Nolan Williams are all delegated responsible staff to obtain written informed consent. All have been trained in the study, and process for obtaining consent. To-be-hired research personnel will be trained in the consent processes and completed the required training in Human Subjects, Good Clinical Practice, and HIPAA prior to obtaining informed consent.

ii) Will legally effective informed consent be obtained from the participant or the participant's legally authorized representative (LAR) or both? If LAR, is it clear who can serve as LAR?
Individuals who are not able to competently provide independent written, informed consent for themselves will not be included in the study.

iii) Will the circumstances of the consent process minimize the possibility of coercion or undue influence and provide the prospective participant or their representative sufficient opportunity to consider whether to participate?
Participants will be given ample time to consider participation in the study and for signing the written consent form. Participants will also be told that their involvement in the study is completely voluntary, and that they can withdraw at any time, for any reason. Research staff will also emphasize that the treatment they receive at VA Palo Alto HCS will not be affected by whether they decline or participate in the study.

iv) Will the circumstances of the consent process minimize the possibility of coercion or undue influence?
Participants will be informed that participation in the study is completely voluntary, and that they can withdraw at any time, for any reason. Research staff will also emphasize that the treatment they receive at VA Palo Alto HCS will not be affected by whether they decline or participate in the study minimizing risk of coercion. The level of participant compensation is appropriate for the population being studied and no cash or checks will be dispensed.

v) Will the information being communicated to the participant or the representative during the consent process exclude any exculpatory language through which the participant or the representative is made to waive or appear to waive the participant's legal rights, or release or appear to release the investigator, the sponsor, the institution, or its agent from liability for negligence (e.g. I give up any

property rights I may have in bodily fluids or tissue samples obtained in the course of the research)?
All information presented to the participant, including anything they must sign, will be approved by the IRB.

vi) Please confirm the following:
a. A witness to the participant's signature or the participant's legally authorized representative's signature will sign and date the consent document.
b. If the sponsor or the IRB requires a witness to the consenting process in addition to the witness to the participant's signature and if the same person is needed to serve both capacities, a note to that effect is placed under the witness's signature line.
c. A copy of the signed and dated consent document will be given to the person signing the consent document.
d. The consent form is on the VA Form 10-1086.

13. 2 Waiver of Documentation Study Participant Screening Form

Check if VA related Y
a) Describe the informed consent process. Include the following.
i) Who is obtaining consent? (The person obtaining consent must be knowledgeable about the study.)
ii) When and where will consent be obtained?
iii) How much time will be devoted to consent discussion?
iv) Will these periods provide sufficient opportunity for the participant to consider whether or not to participate and sign the written consent?
v) What steps are you taking to minimize the possibility of coercion and undue influence?
vi) If consent relates to children and if you have a reason for only one parent signing, provide that rationale for IRB consideration.
The PI, Co-PI or qualified and trained research staff will conduct this screen to determine basic eligibility. We believe it is an excessive burden on the potential participant to require them to complete the entire informed consent to conduct this brief screen for study eligibility. It will be administered prior to obtaining written informed consent, but after the potential participants have already expressed interest and willingness to provide study personnel their contact information.
b) What is the Procedure to assess understanding of the information contained in the consent? How will the information be provided to participants if they do not understand English or if they have a hearing impairment? See /hrpp/Chapter12.html#ch12_2 HRPP Chapter12.2 for guidance.
The purpose of the screening interview is given in the script preceding screening. Participant oral consent/assent will be confirmed prior to screening. VA waiver of HIPAA authorization for recruitment has also been included in the protocol.
c) What steps are you taking to determine that potential participants are competent to participate in the decision-making process? If your study may enroll adults who are unable to consent, describe (i) how you will assess the capacity to consent, (ii) what provisions will be taken if the participant regains the capacity to consent,(iii) who will be used as a legally authorized representative, and (iv) what provisions will be made for the assent of the participant.
The clinical staff who refer patients to the study will be asked if the patient has capacity to consent for the study. In addition, if it appears that a patient does not understand the consent procedure or does not have the capacity to consent to screening, we will not screen or include them in the study.
Additional VA questions:
i) List the people to whom you have formally delegated responsibility to obtain informed consent, and state whether they have the appropriate training to perform this activity.
The PI, Co-PI or qualified research staff have responsibility of obtaining oral consent/assent prior to screening individuals for the study.
ii) Will legally effective informed consent be obtained from the participant or the participant's legally authorized representative (LAR) or both? If LAR, is it clear who can serve as LAR?
N/A
iii) Will the circumstances of the consent process minimize the possibility of coercion or undue influence and provide the prospective participant or their representative sufficient opportunity to consider whether to participate?
Potential participants will be given information about the study and it will be made clear that participating in the screening interview is completely voluntary and choice of participation will not affect their current or future VA treatment in any manner.
iv) Will the circumstances of the consent process minimize the possibility of coercion or undue influence?

Patients screened for participation will be explicitly informed that completing the screening interview is completely voluntary and there will be no compensation for the screen.

v) Will the information being communicated to the participant or the representative during the consent process exclude any exculpatory language through which the participant or the representative is made to waive or appear to waive the participant's legal rights, or release or appear to release the investigator, the sponsor, the institution, or its agent from liability for negligence (e.g. I give up any property rights I may have in bodily fluids or tissue samples obtained in the course of the research)?
No

vi) Please confirm the following:
a. A witness to the participant's signature or the participant's legally authorized representative's signature will sign and date the consent document.
b. If the sponsor or the IRB requires a witness to the consenting process in addition to the witness to the participant's signature and if the same person is needed to serve both capacities, a note to that effect is placed under the witness's signature line.
c. A copy of the signed and dated consent document will be given to the person signing the consent document.
d. The consent form is on the VA Form 10-1086.
Select one of the following regulatory criteria for a waiver of documentation (signature) and provide a protocol-specific justification:
1) 45 CFR 46.117(c)(1). For research that is not subject to FDA regulation, the only record linking the participants and the research would be the consent document,and the principal risk would be potential harm resulting from a breach of confidentiality; each participant will be asked whether he/she wants documentation linking the participant with the research, and the participant's wishes govern.
2) 45 CFR 46.117(c)(2). For research that is not subject to FDA regulation, presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside of the research context.
3) Y **21 CFR 56.109(c)(1). For research that is subject to FDA regulation, presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside of the research context.**
Rationale for above selection:
The screening interview is expressly to determine basic study eligibility, with an emphasis on rapidly excluding potential subjects with medical or psychiatric contraindications for participation. If the individual is deemed eligible, and is willing to participate, written informed consent will be provided prior they engage in any study procedure.

14. Assent Background (less than 18 years of age)
15. HIPAA Background
15. 1 Waiver of Authorization for Recruitment waiver for screen
health information linked to HIPAA identifiers. List BOTH health information AND HIPAA identifiers. If you are using STRIDE, use the Clinical Data Work Sheet to ensure that your request will match your IRB-approved protocol.
Patient name and phone number are collected during the screening to contact the individual in the case that eligibility cannot be determined at the time of screening. In addition, if deemed eligible, this information allows us to contact the individual for scheduling purposes study informed consent.

b) Please Answer:
Y **Do you certify that the use or disclosure of protected health information involves no more than a minimal risk to the privacy of individuals?**
Y **Do you certify that the research could not practically be conducted with out the waiver?**
Y **Do you certify that you have adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted?**
Y **Do you certify that the research could not practically be conducted with out access to and use of the protected health information?**

c) Please describe an adequate plan to protect any identifiers from improper use and disclosure.
Screening information will only be used to determine eligibility for the study and to facilitate contact for study informed consent and enrollment purposes. Completed screening forms will be kept in a locked file cabinet in a locked office at the Palo Alto VA.

d) Please describe an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law.

Per VA requirements, screening forms for participants deemed ineligible will stored in a secure, locked file cabinet in a locked office, and disposed of 6 years after the study ends. In addition, participants will be notified of their eligibility status by study staff.

IRB approval of any project is for a maximum period of one year. For continuing projects and activities, it is the responsibility of the investigator(s) to resubmit the project to the IRB for review and re-approval prior to the end of the approval period. A Notice to Renew Protocol is sent to the Protocol Director 7 weeks prior to the expiration date of the protocol.
Department Chair must approve faculty and staff research that is not part of a sponsored project. VA applicants must have Division Chief or Ward Supervisor approval. E-mail the Department Chair approval to IRBCoordinator@lists.stanford.edu.

Statistical Analyses Plan

Primary Hypothesis:

1a) Veterans who receive active iTBS-TMS treatment for AUD demonstrate a significantly lower frequency of relapse at 6 months following treatment than controls (i.e., Veterans with AUD who receive sham iTBS-TMS).

Statistical Approach: Primary Hypothesis 1a will be tested with binary logistic regression. The criterion/dependent measure is relapse status (abstained or relapsed during the 6 months after last iTBS-TMS session). Treatment group (active iTBS-TMS vs. control) is the target predictor, and covariates will include age and composite neurocognitive functioning (based on demographically adjusted RBANS total score) as these variables may account for both within and between subject group variance. PTSD severity (based on PCL-5 total score), substance use severity (based on NIDA Drug Survey composite score), depression severity (based on BDI total score), and/or smoking severity (based on pack-years) will be considered as covariates if, after random assignment, there are post-hoc differences between treatment groups on these variables following breaking of the blind.

1b) Veterans who receive active iTBS-TMS treatment for AUD will demonstrate a significantly greater duration of abstinence in the 6 months following treatment than controls.

Statistical Approach: Primary Hypothesis 1b will be tested with Cox regression. The criterion/dependent measure is duration of abstinence after final iTBS-TMS session, and covariates include those listed for Primary Hypothesis 1a.

Secondary Hypothesis:

In the active iTBS-TMS group, Veterans with: (a) lower Glu concentration, (b) lower perfusion (blood flow), and (c) smaller volume of the left DLPFC at baseline will demonstrate a longer duration of abstinence over 6 months post treatment. Confirmation of this hypothesis will indicate that participants who exhibit lower baseline Glu concentration, lower perfusion (blood flow), and/or smaller left DLPFC volume, and receive active iTBS-TMS, demonstrate the most robust iTBS-TMS treatment response because iTBS-TMS addresses these key neurobiological deficits that are associated with increased relapse risk. Confirmation of this hypothesis will advance our understanding of the neurobiological characteristics that predict the greatest benefit from iTBS-TMS at entry into treatment for AUD.

Statistical Approach: The Secondary Hypothesis will be tested with generalized linear mixed modeling or linear mixed modeling, depending on the distribution of the dependent measure. Duration of abstinence is the dependent measure. Neuroimaging measure (e.g., Glu level) and treatment group (active iTBS-TMS vs. control) are the target predictors, with age as a covariate because it will likely account for significant within and between subject variance. Smoking, PTSD and/or substance use severities will be used as covariates if there are post-hoc differences between treatment groups on these variables after random assignment. We predict an interaction between the specific neuroimaging measure (e.g., Glu level) and treatment group; follow-up simple effect tests will indicate that participants in the active iTBS-TMS group with lower Glu concentration,

lower perfusion (blood flow), and smaller volume of the left DLPFC at baseline will show the longest duration of abstinence. Separate models will be run for each neuroimaging predictor to minimize the risk of overfitting and corresponding inflated Type I error. To control significance levels of main effects and interactions for multiplicity of tests, we will employ a modified Bonferroni procedure described in our previous studies .

Exploratory Hypothesis 1

1a) Veterans with co-occurring MDD, who receive active iTBS-TMS, demonstrate a significantly lower frequency of relapse over 6 months following treatment than controls (i.e. Veterans with co-occurring MDD who receive sham iTBS-TMS).

Statistical Approach: Exploratory Hypothesis 1a will be tested with binary logistic regression. The criterion/dependent measure is relapse status (abstained or relapsed during the 6 months after last iTBS-TMS session). Treatment group (active iTBS-TMS vs. control) is the target predictor, with antidepressant use (binary, yes/no) as a covariate. Education and severity of PTSD, substance use, and/or depressive symptomatology will be considered as covariates if, after random assignment, there are post-hoc differences between treatment groups on these variables following breaking of the blind.

1b) Veterans with co-occurring MDD, who receive active iTBS-TMS, demonstrate significantly greater duration of abstinence in the 6 months following treatment than controls.

Statistical Approach: Exploratory Hypothesis 1b will be tested with Cox regression. The criterion/dependent measure is duration of abstinence after the final iTBS-TMS session. The target predictor and covariates include those for Exploratory Hypothesis 1a.

Exploratory Hypothesis 2

2a) Cigarette smokers, who receive active iTBS-TMS, demonstrate a significantly lower frequency of relapse over 6 months following treatment than controls (i.e., Veterans with co-occurring smoking who receive sham iTBS-TMS).

Statistical Approach: Exploratory Hypothesis 2a will be tested with binary logistic regression. The criterion/dependent measure is relapse status (abstained or relapsed during the 6 months after last iTBS-TMS session). Treatment group (active iTBS-TMS vs. control) is the target predictor and with current pharmacotherapy for smoking cessation use (binary, yes/no) as a covariate. Education and severity of PTSD, substance use, and/or smoking severity (based on pack-years) will be considered as covariates if, after random assignment, there are post-hoc differences between treatment groups on these variables following breaking of the blind.

2b) Smokers, who receive active iTBS-TMS, demonstrate a significantly greater duration of abstinence over the 6 months following psychosocial treatment than controls.

Statistical Approach: Exploratory Hypothesis 2b will be tested with Cox regression. The criterion/dependent measure is duration of abstinence after final iTBS-TMS session. Treatment group is the target predictor and covariates include those for Exploratory Hypothesis 2a.

Tertiary Analyses

We will concurrently examine the associations between treatment group, multiple neurobiological, neurocognitive and clinical variables (and their potential interactions) and relapse status via an advanced multivariate dynamic longitudinal latent variable modeling framework. However, we are mindful of the proposed sample size, and will avoid building models that risk overparameterization and overfitting.