Examining the Effectiveness of Deep TMS in Veterans with Alcohol Use Disorder

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Brief Summary

The purpose of this study is to evaluate the efficacy of deep transcranial magnetic stimulation as a treatment for Veterans with an alcohol use disorder (AUD) to decrease the exceedingly high rate of relapse associated with this condition.

Objectives

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 VA 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. TMS is a neurostimulation method that is at the forefront of innovative, non-invasive, and safe treatments for AUD, and other psychiatric disorders. To reduce the high rate of relapse in Veterans with AUD, it is necessary for interventions to more effectively address the associated neurobiological dysfunction. Non-invasive neuromodulation techniques are showing promise toward the aim of modifying specific and selective neural targets related to AUD and relapse. However, device-based interventions to date for AUD have focused on cortical stimulation. In contrast, preclinical and clinical studies, including our research team's preliminary data, suggest that subcortical nodes within the salience network could be promising novel neuromodulation targets. The dorsal anterior cingulate cortex (dACC) is a core node of the salience network, and hence the target of this proposal. Deep repetitive transcranial magnetic stimulation (dTMS) is one type of neuromodulation technique, and utilizing an H7 coil design can reach the dACC. Monitoring periodically throughout the 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

Rationale for Research in Humans

The goal of this study is to evaluate the effectiveness of deep TMS applied through the established H7 coil protocol as a treatment for Veterans with an AUD; therefore, humans must be studied.

STUDY PROCEDURES

Procedures:

ALL RESEARCH ACTIVITIES WILL BE COMPLETED AT THE VA,
WITH THE EXCEPTION OF THE MRI, WHICH WILL BE DONE AT STANFORD:

Recruitment and screening: Participants will be recruited via the VA Palo Alto Addiction Treatment Services, Foundations of Recovery program.

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

Baseline/Pretreatment Assessment:
- Psychiatric Assessment
- Alcohol and Substance Use assessment
- 3 Tesla Magnetic Resonance Neuroimaging
- Breathalyzer, urine test, saliva collection

Treatment Phase: Participants will receive a total of 30 deep TMS treatments, delivered 3 times per day, over 10 consecutive business days, with minor schedule variability to allow for participants' regular program scheduling at the treatment centers. Since participants will be recruited from Palo Alto VA residential treatment programs, 24-hour monitoring for any adverse events will be in place as an additional layer of participant safety. During this time, all participants will be receiving treatment as usual at the VA clinics, and scheduling of TMS will be arranged so as not to interfere with their daily curriculum.

Post-Treatment Phase: Within 3-4 days of completion of the Treatment Phase, all participants will repeat select psychiatric assessment measures, select alcohol and substance questionnaires, and 3 Tesla Magnetic Resonance Neuroimaging.

Monthly Follow-ups: For the 6 months following completion of treatments, participants will be contacted at 2-, 4-, and 6- months post-participation, 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 10-15 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 VAPAHCS 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-Is, 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 Innovator Grant application:
a) Psychiatric Assessment: we will use standardized measures employed in clinical practice and research.
b) Alcohol and Substance use: we will use standardized measures employed in clinical practice and research. Participants will be asked to submit a urine sample to screen for illegal/non-prescribed drug use and/or complete a breathalyzer to screen for alcohol use.
c) 3 Tesla Magnetic Resonance Neuroimaging: will be conducted at Stanford University CNI.
d) Saliva collection: Participants will be asked to provide a saliva sample for genotyping.

Design, Treatment Phase, and Treatment Arms:
This study will enroll 10 participants to receive deep TMS. Participants will receive 30 dTMS sessions over the course of 2 weeks. Participants will be required to be abstinent from alcohol and illicit substances for 7 days and demonstrate no clinically significant withdrawal symptoms prior to the pre-assessment described above.

Rationale for Brain Region Site and Technique: Converging lines of evidence support the salience network as a promising future neuromodulation target to impact treatment outcomes for AUD. However, most TMS studies to date have focused on cortical stimulation. In contrast, preclinical and clinical studies,

including our research team's preliminary data, suggest that subcortical nodes within the salience network (SN) are promising novel neuromodulation targets. Based on this evidence, our study will utilize the H7 coil to administer deep TMS to core salience network nodes. See section 3A (paragraphs 1 and 2) for a more in-depth rationale for the brain region site.

Duration of Treatment Phase: Participants will receive a total of 30 treatments over 10 consecutive days, allowing for minor scheduling variability so as not to interfere with regular program scheduling in the treatment programs. Participants will typically receive 3 treatments per day (Monday- Friday), over 2 consecutive weeks; inter-treatment interval will be at least 2 hours. Sessions will typically be conducted prior to the beginning to the participants' treatment day, and at lunch, as to not interfere with their treatment-as-usual in the VA substance treatment clinics.

Procedures for Delivery of dTMS Sessions:

1. **Motor Threshold MT Elicitation:** Each subject will complete the motor determination procedure (MT) as outlined by the device specifications for the H7 coil.

2. **Anatomical localization to the medial PFC and the dACC:** After MT, the TMS helmet will be positioned to the treatment location by aligning the coil to the center of the head and then moved 4 cm anterior to the optimal MT location targeting the left and right prefrontal cortex with a preference to the left medial PFC extending to the ACC.

3. **Personalized Provocation Protocol:** Review of the literature suggest that in order to optimally modify neural networks associated with disease sites, priming prior to treatment is suggested. Current FDA cleared H7 coil protocol for OCD already implements this as standard clinical care. As such, the proposed study will develop a personalized provocation protocol for each participant that will be reviewed prior to the start of treatment in the study. During the baseline assessment, participants will meet with trained clinical study staff (i.e., clinical post-doctoral fellow or study PIs) and provided structured instruction on writing a half-page narrative describing the situation or circumstances that triggered their desire to quit. This narrative will be securely stored in order to be available for participants prior to each treatment session regardless of the treatment protocol they have been randomized. Before each dTMS treatment session, the subject will be instructed to review this personalized narrative, not to exceed 5 minutes. Once they have reached a distress level ranging from 4 - 7 on a visual analog scale, treatment pulses will be delivered.

4. **dTMS dosing:** To minimize subject discomfort, an adaptation train will be administered at the beginning of each treatment session followed by their personalized treatment parameters calculated during the MT session at the baseline visit. Device settings will be set for 100% of the subject's measured MT at a frequency of 20 Hz for 2 seconds at a time (train duration) with a 20-second intertrain interval. Each subject will) receive 50 trains for a total of 2000 pulses delivered per treatment session lasting approximately 18.5 minutes per session. Each participant will receive 30 sessions totaling 60,000 pulses over the course of treatment

Post-Treatment Phase: Within 3-4 days of completion of the Treatment Phase, all participants will repeat select psychiatric assessment measures, select alcohol and substance
questionnaires, random urine substance screen and alcohol breathalyzer,3 Tesla Magnetic Resonance Neuroimaging as described above in Baseline/Pretreatment Assessment.

Monthly Follow-ups: For the 6 months following completion of the treatment phase, participants will be contacted three times (2-, 4-, and
6-months post-participation), 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 and tracking sobriety is the primary outcome measure of this study.

Procedure Risks

All procedures will be performed by staff trained specifically for the tasks for which they are responsible. All procedures, including the rTMS, and are considered low-risk procedures. rTMS 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 rTMS. 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 unlikely event that a seizure does occur attached.

The study will use the 3T UHP system at CNI. The UHP shares a common software and hardware architecture to GE's FDA-approved Premier system but uses a higher-performance gradient coil and is not FDA approved for diagnostic

use and is subject to the 21 CFR 812 investigational device(IDE) regulations as well as 21 CFR 50 and 56. The system has been tested by GE according to UL606001-1 and also for compliance with IEC 60601-2-33 (ed 3.1) - meeting limits and guidelines for peripheral nerve stimulation, patient thermal, SAR limit, acoustic noise, flammability rating UL94-5VA for safety covers, hydrostatic pressure, electrical hazards, dielectric strength and pinch point. The MRI scans in this study will also utilize operational parameters within FDA guidelines for Nonsignificant Risk thus an Investigational Device Exemption (IDE) from FDA should not be necessary. The research conducted under this protocol is not to evaluate the safety or efficacy of this device. In support of this research study, some of the image acquisition pulse sequences and post-processing software will be developed in collaboration with GE Healthcare. Any such software will be considered investigational, will function as a non-significant risk device, and is subject to the 21 CFR 812 investigational device(IDE) regulations as well as 21 CFR 50 and 56. The investigational image acquisition software will conform to FDA guidelines for MR safety related to heating (SAR), peripheral nerve stimulation (dB/dt), and acoustic noise.
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.

a. Use of Deception in the Study- N/A

b. Use of Audio and Video Recordings-N/A

Alternative Procedures or Courses of Treatment

The participants in this study will concurrently receive standard-of care cognitive-behavioral and pharmacological interventions from the VAPAHCS substance treatment clinics they are enrolled in. There are no potential risks the participants who receive concurrent cognitive-behavioral and any procedure associated with the proposed research protocol. No participant will be enrolled who is taking a medication that lowers seizure threshold. Risks to confidentiality will be minimized by following all procedures dictated by HIPAA. 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.

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

Study Endpoint(s)

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.

BACKGROUND

Past Experimental and/or Clinical Findings

To date, TMS has emerged as a promising treatment avenue for AUD and is being tested in clinical trials with some encouraging results. The traditional target of the left dorsolateral prefrontal cortex (DLPFC) suggests that targeting the DLPFC alone may be insufficient, as treated individuals resume drinking shortly after treatment at similar rates as those receiving sham. One possible explanation is the well-documented atrophy of the PFC as a result of chronic heavy drinking. Therefore, targeting a structurally compromised brain region, may not yield the most robust effect. The literature describes how TMS treatment is associated with physiological changes in the brain at the treatment target area stimulated as well as in remote brain regions connected structurally or functionally. TMS has been associated with changes in long-term potentiation (LTP) or depression (LTD) to increase neuroplasticity through increases in brain-derived neurotrophic factor (BDNF) and is implicated in influencing the excitatory/inhibitory balance of GABAergic synapses. Given the demonstrated downstream impact, novel approaches for stimulation need to occur.

An emerging advancement is the use of coils that target deeper regions of the brain and have the potential of targeting multiple, interacting brain networks. The coil configuration in this technique (and proposed in this study) stimulates a broader area (volume of stimulation is 40.3 cm^3), as well as a deeper area (subdural depth is 3cm). Through the use of this less commonly used coil type (H7), we hypothesize that we will be able to modify core nodes within the salience network that are otherwise not reached through traditional figure-of-eight coil approaches. Notably, there are only two published studies to date that utilize these H-coils for AUD, and only one focusing on the H7 coil proposed in this study. Harel and colleagues (2022) recently reported that an H7 stimulation protocol similar to the one proposed here resulted in changes in functional connectivity AND lower heavy drinking days in the active condition compared to the sham condition. However, it remains unclear if the proposed stimulation strategies will have an objectively measurable impact on their respective brain targets.

The proposed project will begin to explore if deep TMS treatments will be associated with 1) changes in task-based activation to emotional stimuli and 2)

whether these changes are associated with a reduced risk of relapse after standard VA treatment.

We believe this proposed work will provide preliminary data for a larger grant submission that could allow for a more complex study design to fully answer gaps in current knowledge about deep TMS H7 coil as a possible treatment approach for AUD.

2. DEVICES USED IN THE STUDY

Investigational Devices (Including Commercial Devices Used Off-Label)

Investigational Device 1	
Name:	3T UHP
Description:	GE 3T Ultra High Performance (UHP) MRI scanner GE Healthcare
Significant Risk? (Y/N)	No
Rationale for Non-Significant Risk	The GE 3T Ultra High Performance (UHP) MRI scanner is an upgrade of an FDA-approved 3T MR750 scanner but is not itself FDA approved. The UHP scanner utilizes components from GE's 3T Signa Premier scanner (an FDA approved system) including gradient drivers, power supply, transmit and receive system, but uses a higher-performance gradient coil. The scanner has been tested by GE according to UL606001-1 and for compliance with IEC60601-2-33 (ed 3.1), meeting limits and guidelines for peripheral nerve stimulation, patient thermal, SAR limit, acoustic noise, flammability rating UL94-5VA for safety covers, hydrostatic pressure, electrical hazards, dielectric strength and pinch point. MRI research scans also frequently require specialized research software, but this will conform to FDA guidelines for MR safety related to heating (SAR), peripheral nerve stimulation (dB/dt), and acoustic noise. As a result, the 3T UHP system is considered a non-significant risk investigational device and is subject to 21 CFR 812 investigational device (IDE) regulations as well as 21 CFR 50 and 56. The MRI scans in this study using the UHP scanner will utilize operational parameters within FDA guidelines for Nonsignificant Risk thus an Investigational Device Exemption (IDE) from FDA should not be necessary. In addition to the GE receive coil components that are included with the UHP system, there are some non-GE coils. These devices are legally marketed components, used in accordance with their labelling, and are of non-significant risk. They include 32 channel and 16 channel receive-only brain RF coil arrays, manufactured by Nova Medical, Inc.
Investigational Device 2	
Name:	BrainsWay Deep TMS H7 coil
Description:	Deep TMS is FDA-cleared for other impulse control disorders and specifically the BrainsWay H7 Deep TMS coil was FDA-approved for OCD in September 2017 (DEN170078)101.
Significant Risk? (Y/N)	No
Rationale for Non-Significant Risk	Deep TMS is FDA-cleared for other impulse control disorders and specifically the BrainsWay H7 Deep TMS coil was FDA-approved for OCD in September 2017 (DEN170078)101. Review of the clinical summaries

	submitted to the FDA demonstrated that this technology is clinically efficacious and safe for individuals with these conditions. Although the Brainsway dTMS system is not FDA-approved for alcohol use disorder, the device presents non-significant risk since it is an FDA-approved device that is not intended as an implant, will be used in supporting or sustaining human life, is of substantial importance in treating AUD since participants will continue with standard of care, or otherwise presents a potential for serious risk to the health, safety or welfare of a subject.

IDE-Exempt Devices- N/A

DRUGS, BIOLOGICS, REAGENTS, OR CHEMICALS USED IN THE STUDY

Investigational Drugs, Biologics, Reagents, or Chemicals-N/A

Commercial Drugs, Biologics, Reagents, or Chemicals-N/A

DISINFECTION PROCEDURES FOR MEDICAL EQUIPMENT USED ON BOTH HUMANS AND ANIMALS-N/A

PARTICIPANT POPULATION

Planned Enrollment

10 Veteran participants are expected to be enrolled from the VAPAHCS Foundations of Recovery (FOR), a 28-day residential program.

Age, Gender, and Ethnic Background

The study will be open to males and females, regardless of race and ethnic origin, 21-70 years of age, who are in active treatment for an AUD at the VAPAHCS. The 21-70 age range was chosen given the vast majority of information on rTMS efficacy and safety has been obtained from this range and this is the typical age range of Veterans seeking treatment for AUD at the VAPAHCS.

Vulnerable Populations

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) 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. Anyone with active current suicidal intent or plan will be excluded. 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, using conservative exclusion for magnetic resonance research will also be excluded from the study. 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 VAPAHCS, which will permit additional on-going monitoring for any adverse events.

Rationale for Exclusion of Certain Populations

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, 21-70 years of age, who are in active treatment for an AUD at the VAPAHCS. Approximately 5% females and 40% racial and ethnic minorities were observed among the Veteran participants in PI's previous studies at the VA Palo Alto. Given the similar demographics of Veterans at the VAPAHCS, we anticipate a similar distribution of females and racial and ethnic minorities.

Stanford Populations

It is possible that up to 2 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.

Healthy Volunteers

No healthy volunteers will be included in this study.

Recruitment Details

Potential participants from the VAPAHCS treatment programs (Foundations of Recovery) 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. The study protocol has been explained to medical/clinical via treatment team meetings, and they are fully cognizant of study procedures and eligibility criteria. Medical/clinical staff of the programs listed above will identify potential participants who meet eligibility criteria and will verbally inform them that there is a VA-sponsored treatment they may be interested in; the medical/clinical staff offer contact information for study personnel or the participant may request to the medical/clinical staff that study personnel contact them. In this way, the participant is self-referred to the study. The PI, VA-based Co-Is 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.

Eligibility Criteria

Inclusion Criteria

The study will be open to male and females, regardless of race and ethnic origin, 21-70 years of age, who are in active treatment for an AUD at the VAPAHCS, Foundations of Recovery.

An age range of 21-70 at time of enrollment was chosen given the vast majority of information on rTMS efficacy and safety has been obtained from this range and this is the typical age range of Veterans seeking treatment for AUD at the VAPAHCS.

Participants must 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.

Able to read, verbalize understanding, and voluntarily sign the Informed Consent Form prior to participation in study procedures in English.

Participants will be accepted if taking medications specifically for the treatment of major depressive disorders, cigarette smoking, or for other psychiatric conditions as long as the medications are not documented to lower seizure threshold - it would be clinically contraindicated to require participants to discontinue such medications for research. rTMS 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 rTMS to ensure no participant is experiencing active acute withdrawal.

Exclusion Criteria

Psychiatric: Current diagnosis of Schizophrenia Spectrum Disorders and Bipolar Disorders; a current moderate-severe substance use disorder other than alcohol, tobacco, or marijuana, 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 rTMS 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, and alcohol-related seizure(s) in the past 30 days.

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 rTMS treatment.

Screening Procedures

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1) Initial screen for alcohol use disorder undertaken by the treatment program 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-I or trained RA's study contact number, and the PI, Co-I or trained RA's will answer/return the potential participant's call; alternately, the potential participant can request to the clinical staff that PI, Co-I or trained RA's contact in-person at the VAPAHCS treatment program them to further explain the study.

2) If the potential participant is interested in the study, the PI, Co-I, or trained RA will then conduct an in-person screen for study-specific inclusion and exclusion criteria. We are requesting a waiver of authorization for this recruitment process. Eligible participants will be invited to complete the 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 do not permit safe application of the rTMS protocol used in this study.

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a. Participation in Multiple Protocols

Subjects may be part of other protocols, including neuroimaging protocols, and this would not be expected to 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.

b. Payments to Participants

Participants will not be compensated for study screening. Participants will receive a maximum of $250 for all baseline and treatment phase and post-assessment study procedures. If participants do not complete all baseline or post-treatment visit procedures, they will receive a pro-rated amount based on how many procedures were completed. In addition, participants can receive up to $50 for completing all assessment phone calls during the follow-up phase of the study. In total, the maximum payment that can be received for all phases of the study is $300 ($75 for pre-assessment, $100 for the treatment phase, $75 for the post-assessment phase, and $50 for the follow-up phase).

The mechanism of payment will adhere to the VA mandated procedure: payment form, which the participant can obtain cash or check at the VA Palo Alto upon completion of Baseline and Post-treatment Visit. This rate of compensation is commensurate with other AUD research being conducted at the VAPAHCS and the payment mechanism is used by other alcohol/substance abuse research currently conducted at the VA Palo Alto. The total amount of payment is proportional to the participant's time and effort and is intended to facilitate participation without adding undue influence.

Costs to Participants

No costs will be incurred by any participant.

Planned Duration of the Study

(i) Probable duration of study = 2.5 years.

(ii)Total time per participant:
Screening: 15 min
Baseline: 6 hours, over 1-day.
Treatment: 15 hours (Over approx 10 business days: 30 dTMS sessions, approx. 30 min each, performed 3x/day)
Post-Tx Assessment: 4 hours, over 1-day.
Follow-up assessments: 45 min (15min 3 times at 2-, 4-, and 6-months post-study)

Total Active Participation Time = approx. 26 hours over 6 months.

All procedures will be conducted before or after normal ATS clinic hours, or during lunch break, so as not to interfere with the patient's treatment schedule. The project will be conducted at the VAPAHCS MIRECC Palo Alto Division, which is on the same campus as the FOR program.

(iii). Analysis of participant data will be ongoing.

RISKS

Potential Risks

i. Risks of the Investigational devices.

Transcranial magnetic stimulation (TMS) device: 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, dACC, is the stimulation site. There have been no significant adverse cognitive, brain structural, neurologic or cardiovascular sequelae reported because of TMS. Participants treated with rTMS 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 estimated to occur in less than 10% of sessions, and can persist for 1-2 hours post stimulation. rTMS 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 current cyclothymia and Bipolar Disorders.

Magnetic Resonance Neuroimaging: The magnetic resonance scanning devices (3T Ultra-High Performance (UHP) system) used in scanning at the Stanford Center for Cognitive and Neurobiological Imaging (CNI) 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 CNI.Source: eProtocol Section 9a (box 1)

ii. Investigational drugs-N/A

iii. Commercially available drugs, biologics, reagents or chemicals-N/A

iv. Procedures

Psychiatric and Alcohol/Drug Assessments and Questionnaires. Answering questions about one's psychiatric history can cause feelings of anxiety or mild psychological stress.

rTMS risks are described above in 9 .i. Investigational devices. Magnetic Resonance Neuroimaging risks are described above in 9. i. Investigational device.

v. Radioisotopes/radiation-producing machines-N/A

vi. Physical well-being

See above devices and procedures. No other risks to physical well-being are anticipated.

vii. Psychological well-being

Screening, psychiatric interviews, and questionnaires: The screening interview 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. 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.

viii. Economic well-being

No risks to economic well-being are anticipated.

ix. Social well-being

No risks to social well-being are anticipated.

x. 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.

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c. **International Research Risk Procedures-** N/A

d. Procedures to Minimize Risk

Screening, 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. 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.

rTMS administration: The rTMS operator will be fully trained and qualified to administer the procedure according to current safety practices and standards of care. Co-Is Dr. Madore and Dr. Durazzo have full rTMS training and, together with physician Co-Is also trained in rTMS, closely monitor the rTMS operator for adherence to safety protocols and rTMS administration for this proposal. Additionally, PI Padula will obtain full rTMS training and be available as an additional monitor and resource to the rTMS operator. The protocol employs all current established and standard rTMS treatment safety and monitoring for adverse events guidelines. The rTMS 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 CIWA- Ar and must score <8 (scores >8 are indicative of potential autonomic instability); participants with a score >8 will immediately be escorted to VAPAHCS ATS or 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 participant tests positive or reports any alcohol or substance use during the 2-week rTMS treatment period, they will be immediately withdrawn from the study. Additionally, participants will be given the C-SSRS prior to each rTMS session to assess for current suicide risk. Although patients in the VAPAHCS are regularly screened for alcohol and substance use and suicide risk while in treatment, we will conduct random alcohol/substance screening and pre-rTMS session suicide risk assessment to ensure participant welfare.
Should a headache or site of stimulation discomfort occur, these symptoms usually readily respond to acetaminophen or ibuprofen. Any reported painfulness typically improves over time or completely remits. If dental pain

occurs, study staff may be able to move the rTMS coil position or provide a bite block to reduce or eliminate this pain. To protect against possible hearing damage, participants will wear ear protection during rTMS sessions. This should 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 rTMS-related hearing loss.

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 VAPAHCS 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 any of the participants experience a seizure during study participation and request that the Data Monitoring Safety Board (DMSB) 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 DMSB 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 (two licensed clinical psychologists and a board-certified psychiatrist), or 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 be provided with a warm hand off to the Veterans Crisis Hotline or they will be encouraged to 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 the VA. Our Research Assistants (RA) have been trained by the PI, Co-Is carefully pre-screen each participant for MRI safety before the MRI appointment. RAs also have been certified to independently operate the CNI magnetic resonance scanner by qualified CNI personnel. 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: 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) that were not previously identified/diagnosed by VAPAHCS Addiction Treatment Services staff. In this case, the participant will be immediately assessed by the PI or Co-I or Foundations of Recovery treatment staff (licensed clinical psychologist), 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 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.

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 or Stanford RedCap firewall. 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):

Definitions:

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.

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

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 TMS treatment
- Possibly attributed to the TMS treatment
- Attributed to the 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:

- rTMS device
- rTMS 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 Safety Board (DMSB): 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 DMSB on a schedule set by the DMSB. The DMSB will also determine when they should be unblinded to treatment assignment for the reviewing of adverse event data. The DMSB will advise the PI concerning whether the study should continue or be stopped for safety reasons.

Communication among the Investigative Team: The PI will have a weekly group lab meeting with all RAs. Additionally, the VAPAHCS MIRECC has weekly PI meetings to discuss issues relevant to ongoing MIRECC research projects. All key VA Co-Is associated with this project attend these weekly meetings.

Study Conclusion

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, or Co-Is will determine unacceptable level of risk, regulatory agencies mandate discontinuation of the study, or a product recall occurs that necessitates stopping the study, any planned rTMS treatments will be immediately discontinued.

e. Data Safety Monitoring Plan (DSMC)

i. Data and/or events subject to review

ii. Although this study protocol is low risk, and will enroll a modest number of participants, we will create a DSMB 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 endpoints; 3)AEs, SAEs and unanticipated problems; 4) Protocol deviations.Person(s) responsible for Data and Safety Monitoring

The Protocol Director will be the only monitoring entity for this study.

iii. Frequency of DSMB meetings-N/A

iv. Specific triggers or stopping rules

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.

v. DSMB Reporting

All SAEs will be reported within 24 hours of learning of the SAE. Unanticipated problems involving risks to participants or others will be reported within 5 days.

vi. Will the Protocol Director be the only monitoring entity?

YES

vii. Will a board, committee, or safety monitor be responsible for study monitoring?

NO

f. Risks to Special Populations

N/A

3. BENEFITS

dTMS could potentially generate substantial health benefits for VHA patients. Deep TMS may offer a viable and more efficacious treatment option for Veterans with AUD. For these reasons, the anticipated risks are reasonable in relation to the anticipated benefits to study participants. If this preliminary study proves feasible, acceptable, and beneficial, then it will serve as the basis for a larger mechanistic study and subsequent clinical trial. The VISN-21 MIRECC has 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 deep

TMS intervention for AUD can be readily disseminated to VA and non-VA researchers, clinicians, and leadership through the MIRECC EBP program. As described in this proposal, TMS is a very safe treatment when standard safety protocols are followed.

4. PRIVACY AND CONFIDENTIALITY

All participant information and specimens are handled in compliance with the Health Insurance Portability and Accountability Act (HIPAA) and privacy policies of Stanford University, Stanford Health Care, and Stanford Children's Health.

Most medical research must comply with the Health Insurance Portability and Accountability Act (HIPAA) regulations if it uses *protected health information* (PHI). See more information on HIPAA.
PHI is health information with one or more of the following identifiers:

1. Names
2. Social Security numbers
3. Telephone numbers
4. All geographic subdivisions smaller than a State, including street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of a zip code, if, according to the current publicly available data from the Bureau of the Census: (1) The geographic unit formed by combing all zip codes with the same three initial digits contains more than 20,000 people; and (2) The initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000s
5. All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older
6. Fax numbers
7. Electronic mail addresses
8. Medical record numbers
9. Health plan beneficiary numbers
10. Account numbers
11. Certificate/license numbers
12. Vehicle identifiers and serial numbers, including license plate numbers
13. Device identifiers and serial numbers
14. Web Universal Resource Locations (URLs).
15. Internet Protocol (IP) address numbers
16. Biometric identifiers, including finger and voice prints
17. Full face photographic images and any comparable images; and
18. Any other unique identifying number, charactristic, or code (except the unique code assigned by the Investigator(s) to code the research data, unless the code was derived from other identifiable information, such as the SSN).

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 VAPAHCS).

We will collect the following HIPAA identifiers, as mentioned on the VA HIPAA form:
- Social security number for participation compensation i.e., participant payment, 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, 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.

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. 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 participant id number (PID) to maintain confidentiality. Information will not be released without written permission of the participant, except as necessary for monitoring by the IRB.

Data 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.

Members of the research team will have access to all data. If the participant requests explicitly in writing, we will send information about clinical results to his/her the medical or mental health care provider of their choice. De-identified study data may be shared with collaborating researchers at Stanford University and at other institutions. De-identified data may also be shared with collaborating researchers at other institutions in the future.

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.

No PHI will be transferred to any person/organization outside of the or VA research team.

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.