Official Title: The Effect of Dorsolateral Prefrontal Cortex Theta Burst Stimulation on Alcohol Cue Reactivity and Cognitive Control: a Double-blind, Sham Controlled Study of Heavy Alcohol Drinkers With a History of Alcohol Related Injury.

NCT04223154

IRB-Approved Date: 8/25/20

Study Title: The effect of dorsolateral prefrontal cortex theta burst stimulation on alcohol cue reactivity and cognitive control: a double-blind, sham controlled study of heavy alcohol drinkers with a history of alcohol related injury.

Principal Investigator, Co-investigator(s): Colleen Hanlon, PhD; Laura Veach, PhD

Sponsor or funding source: Internal

Background, Rationale and Context

Background: Theta Burst Stimulation (TBS) is a patterned form of repetitive transcranial magnetic stimulation – a non-invasive technique which uses electromagnetic induction to discharge populations of neurons in the vicinity of the induced electrical field. Although the exact electrophysiologic mechanism of TBS is not understood on a cellular level, the induced E-field is strong enough to reliably result in motor evoked potentials in a somatotopic manner. The focality of stimulation is related to the shape of the coil, wherein a typical figure-of-8 coil (as used in the proposed pilot project) affects approximately 10cm2 of cortical surface and has a 1-2cm2 penetration depth (Deng et al 2010). When this depolarizing current is strong enough however, it is possible to induce activity in monosynaptic targets of the neurons directly affected by the field. In this manner, cortical pulses of TMS can be used to investigate frontal-striatal connectivity. Although the effects of TBS on dopamine binding have not yet been assessed [Note: a project the PI would also like to do at Wake Forest in the near future], traditional fixed frequency 10Hz stimulation to the left dLPFC appears to increase dopamine binding in the caudate (Strafella et al 2001), and dorsal medial PFC TMS increases dopamine binding in the cingulate and orbitofrontal cortex (Cho et al 2005). In the first sham-controlled evaluation of single pulse TMS in the MRI scanner, we recently demonstrated that TMS pulses lead to a causal increase in BOLD signal specific to the caudate and the anterior cingulate cortex (Dowdle et al 2019).

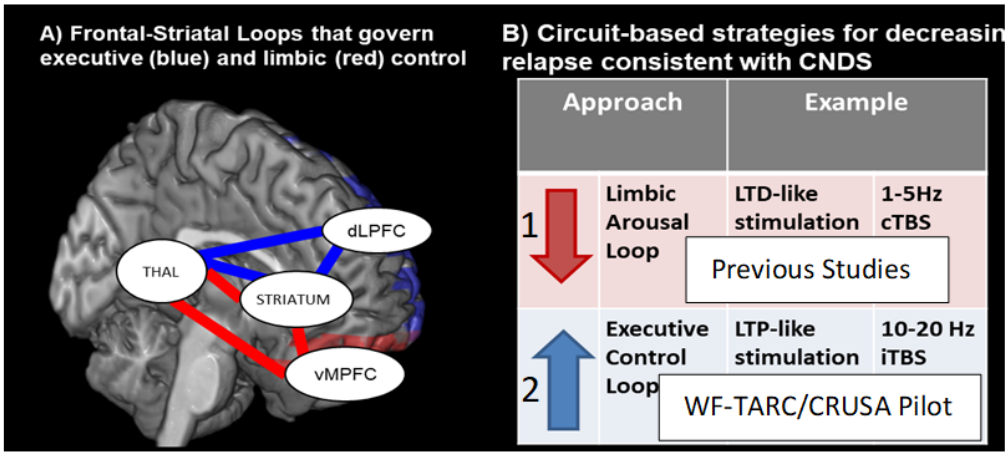


Figure 1. (Adapted from Hanlon et al 2018, Pharm. Reviews (34)). A) The competing neurobehavioral decision systems (CNDS) theory posits that in addiction, *choice* results from imbalance between 2 decision systems (impulsive and executive), which are functionally linked to limbic and executive control circuits in the brain (Bickel et al 2016 (35)). B) It follows then, by modulating these competing neural circuits with TBS (e.g. either dampening the limbic/impulsive system or amplifying the executive control system), we may be able to induce a sustainable change in alcohol use.

Intermittent TBS was FDA approved treatment for depression in 2018 – after an FDA-pivotal statement demonstrated that it was equipotent to traditional 10Hz stimulation which had been FDA-approved for over a decade (Blumberger et al 2018). For depression treatment it is now used in over 650 clinics in all 50 states and covered by Medicare in 48 states (Centers for Medicare and Medicaid Services, Local Coverage Determinations). The evolving availability of clinical devices and trained staff represents a latent public health resource.

Application to AUD and Conceptual Model (Figure 1). Through this network of devices, evidence based TMS protocols for substance use disorders, including AUD, could be swiftly distributed to the public. Currently however, the alcohol research field lacks sufficient data to make a well-informed decision regarding the TMS strategy that is best suited for improving treatment outcomes. **Developing a neural circuit based treatment tool for AUD is exciting and based in preclinical neuroscience research, the published data using TMS in AUD patients is highly variable.** As of January 2019, there were 12 studies published on the use of rTMS for alcohol addiction. The majority (9 of 12) have targeted the dLPFC, but have small sample sizes (less than 20 individuals) with limited sham-controls, and no neuroimaging biomarkers. We have spent the last 7 years evaluating Strategy 1 – dampening alcohol craving and brain reactivity to alcohol cues among heavy alcohol drinkers at risk for AUD or relapse to alcohol use (Hanlon et al 2015, Kearney-Ramos, Lench et al 2018, Kearney-Ramos et at. 2018, Hanlon et al 2019). These studies led to a formal double-blind sham-controlled clinical trial of mPFC cTBS in treatment-seeking alcohol users (NIAAA supported R01). Unfortunately, however, this approach is associated with more pain at the stimulation site (forehead) which undermines its promise as a tool to be readily scaled to a larger population, and it is not clear that this improves the attentional bias towards alcohol cues among these individuals. Our goal is to try to advance this field by evaluating iTBS to the dLPFC as a novel, potent form of brain stimulation which may be able to attenuate limbic reactivity to alcohol cues, improve cognitive control in the presence of an alcohol cue, and be less painful than cTBS delivered to the vmPFC.

Objectives

Alcohol Use Disorder (AUD) is prevalent, devastating, and difficult to treat. The intransigence of AUD is readily apparent in the Trauma Unit of Wake Forest University Baptist Hospital, wherein 23% of trauma related admissions are associated with alcohol - higher than the national average of 16% (Nunn et al 2016). Of these trauma related admissions, over 70% are estimated to have AUD and 41% will be likely be admitted to the trauma unit again within 5 years (Nunn et al 2016). While Dr. Veach (Co-I) and her team in the Department of Surgery have demonstrated that a brief counseling intervention on the inpatient trauma unit can decrease morbidity and recidivism (Veach et al 2018), the rates of AUD and relapse to drinking among these individuals remains very high (Veach et al 2000). With a growing knowledge of the neural circuits that contribute to relapse in AUD, there is an emerging interest in developing a novel, neural-circuit specific therapeutic tool to enhance AUD treatment outcomes. The long term goal of our multidisciplinary research team (Hanlon & Veach) is to develop an evidence-based brain stimulation treatment which can ultimately be prescribed to individuals that present to the Trauma Unit with AUD – decreasing their drinking and hospital recidivism (Future R01 topic).

The **competing neurobehavioral decision systems** (CNDS) theory posits that in addiction, *choice* results from a regulatory imbalance between two decision-making systems (impulsive and executive). These behavioral systems are functionally linked to two functional connectivity networks which regulate the incentive salience of the alcohol cue (Salience Network) and cognitive flexibility required for a vulnerable individual to shift attention away from the alcohol cue (Central Executive Network) (Bickel et al 2016). **Modulating these competing neural circuits (e.g. either dampening the incentive salience associated with alcohol cues (Strategy 1) or amplifying cognitive control in the presence of a cue (Strategy 2) may render alcohol users less vulnerable to relapse (Figure 1).** Over the past 7 years, Dr. Hanlon's human brain stimulation research group has been focused on focused on Strategy 1 – dampening alcohol craving and brain reactivity to alcohol cues among heavy alcohol drinkers at risk for AUD or relapse to alcohol use (Hanlon et al 2015, Kearney-Ramos, Lench et al 2018, Kearney-Ramos et at. 2018, Hanlon et al 2019). These studies led to a formal double-blind sham-controlled clinical trial of mPFC cTBS in treatment-seeking alcohol users (NIAAA supported R01). Unfortunately, however, this approach is associated with more pain at the stimulation site (forehead) which undermines its promise as a tool to be readily scaled to a larger population, and it is not clear that this improves the attentional bias towards alcohol cues among these individuals.

Hence, the goal of this proposal is to evaluate Strategy 2 of the CNDS theory- increasing activity in executive control circuitry- as an innovative approach to dampening alcohol cue-reactivity (Aim 1) and improving cognitive control in the presence of an alcohol cue (Aim 2). This will be achieved through a double-blind, sham-controlled cohort study in 48 heavy alcohol drinkers with a history of alcohol-related injury. The brain reactivity to alcohol cues (Incentive Salience) and cognitive performance in the presence of an alcoholic beverage cue (Cognitive Control) will be measured immediately before and after participants receive real or sham intermittent theta burst stimulation (iTBS- a potentiating form of transcranial magnetic stimulation) to the dorsolateral prefrontal cortex (dLPFC iTBS). iTBS is a high-potency form of brain stimulation wherein two minutes of iTBS (600 pulses) leads to an increase in cortical excitability that lasts for approximately 30 minutes (Huang et al. 2005). In 2018, dLPFC iTBS was FDA-cleared as a treatment for major depressive disorder (wherein 30 sessions over 6 weeks lead to a sustained decrease in depressive symptoms for 6 months; Blumberger et al. 2018). In 2019, the first 2 manuscripts were published demonstrating that iTBS decreases cue-reactivity to cocaine (Steele et al 2019, Sanna et al 2019). **The goals of this pilot study are to quantify the acute effect of a single session of real or sham dLPFC iTBS on brain response to alcohol cues (Aim 1) and cognitive flexibility in the presence of an alcohol cue (Aim 2) among risky drinkers ("target engagement").**

Aim 1: Evaluate the effect of dLPFC iTBS on <u>alcohol cue-reactivity</u>. The blood-oxygen level dependent (BOLD) signal associated with exposure to alcohol cues will be measured before and after sham and real iTBS using a validated, patient-tailored alcohol/non-alcoholic beverage cue task. Hypothesis: cue-evoked functional connectivity in the dLPFC, ACC, amygdala, and ventral striatum will be attenuated after real but not sham iTBS.

Aim 2: Evaluate the effect of dLPFC iTBS on <u>cognitive performance in the presence of an alcohol cue</u>. Following the alcohol cue reactivity task all individuals will perform the well-known alcohol Stroop task (downloaded from the NIH toolbox) on a Tablet PC while a glass of the participant's preferred alcoholic beverage (beer, wine, liquor) is placed within 5 feet of the participant (but out of arms length). This will occur before and after TBS. The participant will not be allowed to consume the drink. Hypothesis: Stroop accuracy and reaction time will be impaired at baseline, but this difference will be attenuated by real (but not sham) iTBS to the dLPFC (three way mixed model ANOVA, correcting for multiple comparisons).

<u>Methods and Measures</u>

<u>Design</u>

Our primary goal is to determine the extent to which one session of dLPFC iTBS can attenuate limbic circuitry involved in alcohol cue-reactivity (Aim 1) and cognitive control in the presence of an alcohol cue (Aim 2) among heavy alcohol users with a history of risky drinking behavior. This will be tested in a cohort of 48 heavy alcohol users, recruited through the resources of the Wake Forest Trauma Unit Registry and from the community at large through advertisements. This double-blind, sham-controlled study will involve 1 Screening visit and 1 TBS/MRI Scanning Visits. At the scanning/stimulation visit, functional MRI data will be collected before and after exposure to a session of real or sham theta burst stimulation (Figure 1). TBS will be applied over the left dorsolateral prefrontal cortex (landmark based on EEG 10-20 system: F3). A series of clinical assessments of drinking behavior and other relevant psychosocial and demographic measurements will also be collected (Table 1). We will test the hypotheses that TBS over the dLPFC will attenuate the neural response to alcohol cues (Aim 1) and improve cognitive performance in the presence of an alcoholic beverage cue (Aim 2). The results of these aims will be further evaluated in terms of their relationship to alcohol drinking severity and demographic factors. These data will be preliminary data for a subsequent R01 focused on the sustained effects

of multiple sessions of TBS as a tool to decrease drinking among individuals with AUD and lowering morbidity and hospital recidivism among these patients.

Setting

Interdisciplinary Research Team: The Principal Investigator, Dr. Colleen Hanlon is a professor in the Department of Cancer Biology leading a new human brain stimulation research group at Wake Forest. She has expertise in neuroscience, human neuroimaging and brain stimulation in substance dependent individuals. Dr. Laura Veach is an associate professor in the Department of Surgery wherein she leads a comprehensive screening and brief intervention research program designed to identify and decrease alcohol use among individuals that present to the Inpatient Trauma Unit.

All study activities will take place at Wake Forest University of Health Sciences.

Dr. Hanlon's primary office and research laboratory is located in the Clinical Neuromodulation Laboratory in the Department of Cancer Biology at Biotech Place. Dr. Hanlon's lab space will include a room dedicated for all research related activities including a space for screening participants and a space dedicated for TMS stimulation.

The majority of the contents of this study, however, will take place at the MRI center located on Medical Center Boulevard on the main campus of Wake Forest Baptist Health. This will utilize the 3T scanner in the MRI center and will have an outfitted setup including a laptop computer and desk for participant interviewing, as well as a TMS device.

Finally, recruitment efforts will come from associated clinics at Wake Forest University of Health Sciences, including the Department of Psychiatry and the Inpatient Trauma Unit. Collaborative efforts will be maximized in order to recruit subjects from the associated Wake Forest University Trauma Unit Registry and from the community at large.

In response to COVID-19: During COVID-19, interactions with study subjects will take place through videoconferencing. Prior to any remote consent/screening videoconference visit, the participant will be sent a copy of the ICF via mail/email to sign while the virtual meeting is taking place. Once this is signed, the participant will mail/email this back to the study staff to sign before proceeding with any research related activities.

Subjects selection criteria

Forty eight heavy alcohol users between 21 and 70 years old will be recruited through the resources of the Trauma Registry and the Piedmont Triad area. Participants will be prescreened by phone for eligibility. Potentially eligible participants will be invited for an in-person screening visit where, after signing informed consent they will receive a detailed evaluation and urine toxicology screen for illicit drugs. Individuals that remain eligible will then undergo the Stimulation/Scanning (see below).

Inclusion Criteria

1. Ages 21-70.
2. Alcohol use disorder identification test (AUDIT) score >7 or a clinician-determined risk score of Moderate to Severe on the Screening, Brief Intervention, and Referral to Treatment (SBIRT).
3. Drink at least 15 standard sized alcohol beverage servings per week sometime in the past month or have had a blood alcohol level of 140+ on admission to the trauma unit following injury.

Exclusion Criteria

1. Current use of prescription or illicit psychoactive drugs (except marijuana or nicotine) known to decrease seizure threshold by self-report in the last 30 days.
2. Currently meets DSM-V criteria for substance use disorder for a substance other than alcohol, marijuana, or nicotine.
3. Has current suicidal or homicidal ideation.
4. Not currently in or at risk for withdrawal, as indicated by CIWA-Ar >5.
5. History of seizures and/or seizure disorder(s).
6. Females of childbearing potential who are pregnant (by urine HCG), planning to become pregnant, nursing, or who are not using a reliable form of birth control.
7. Any other violation of MRI/TMS safety measures.
8. Unable to read and understand questionnaires, assessments, and the informed consent.
9. No presence of metal objects in the head/neck.
10. History of traumatic brain injury resulting in hospitalization, loss of consciousness for more than 10 minutes, and/or having ever been informed he/she has an epidural, subdural, or subarachnoid hemorrhage.

Sample Size

To determine the minimum number of participants necessary we performed a power calculation for the experiment based on our prior (Kearney-Ramos et al 2018). Based on the mean and standard deviation of mPFC activity in that study, Aim 1 will require 22 participants in both the real iTBS group and the sham iTBS group (95% power using two sided $p < 0.05$ level of significance). Assuming some loss of functional MRI data to movement artifacts (10%) we are proposing to enroll 48 participants (24 per group (real vs sham; 16 women (33%), 32 men (66%) based on prevalence of AUD in the US population. Integrity of the sham-control. The integrity of the blind will be assessed at the end of each visit with a standardized questionnaire regularly used in clinical trials of rTMS treatments. The randomization scheme for the study will be developed and monitored by a biostatistician associated with the Comprehensive Cancer Center's Biostatistical Shared Resource (to be named), and will be given to a member of the study team that has no contact with the participant. This person will set the MagVenture sham-controlled TMS system up before the PI, Co-I or research assistant enter the room with the patient. The data will be analyzed by the PI, Co-I and research assistant who will remain blinded until the end of the study.

Based on recruitment history from similar intervention studies in these individuals at Wake Forest Baptist hospital we anticipate that we will be able to recruit 3-4 participants per month (12-16 months = 48 participants). We have planned for 2 months of initial implementation and quality control assessment of the MRI scanning paradigm. Recruitment will commence in month 3 and likely continue through month 19. Data analysis (blinded) for Aim 1 (preprocessing, functional connectivity assessment) and Aim 2 (analysis of quality, rigor, and basic signal detection) will be ongoing. Months 20-24 will be spent performing final analyses, unblinding, preparing data for an R01 application and integrating outcomes with the clinical and preclinical projects within the WF-TARC in order to plan for future translational collaborations.

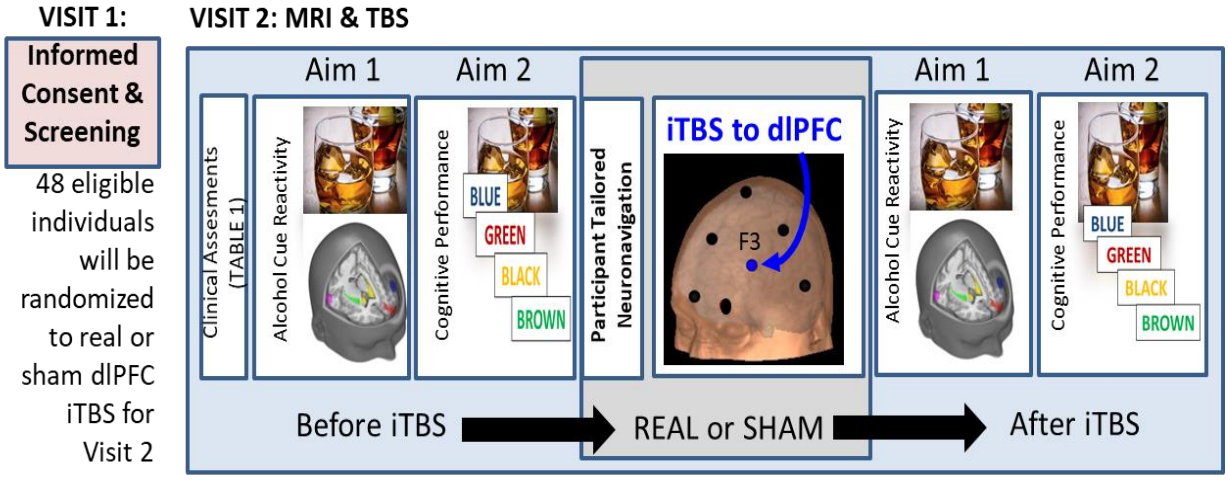
Interventions and Interactions

Visit 1. Informed Consent and Screening Assessments: All informed consent and Privacy procedures are done in accordance with Good Clinical Practice Guidelines and all study procedures will be approved by the Wake Forest Institutional Review Board before they are executed. Study personnel will review the consent and HIPAA documents with the participant and obtain a signature. Following this procedure

several assessments related to drug use history, past medical history will be administered at Visit 1. Several rating scales assessing alcohol use severity, craving, and past month drinking history will be administered at the screening visit and updated at each subsequent visit.

As typically done in cue-induced craving studies for both Visit 1 and Visit 2, study personnel will ensure that craving levels are at or below baseline before the participant finishes the visit.

Visit 2: Stimulation/Scanning Visit T1 MPRAGE: Participants will be scanned using a Siemens 3.0T Skyra (Siemens Medical, Erlangen, Germany) MRI scanner with a 32-channel head coil. High-resolution T1-weighted structural images will acquired using a magnetization prepared gradient echo (MPRAGE) sequence [TR/TE=1900ms/2.34ms; FOV=220mm; matrix=256x256 voxels; 192 slices; slice thickness=1.0mm with no gap; final resolution=1mm3 voxels]. This sequence will be acquired before and after TBS in order to maximize coregistration at each scanning session.



Alcohol Cue-reactivity task: The alcohol cue reactivity task which has been used by our group in the past (Schacht et al 2013, Kearney-Ramos et al 2018) will be administered in the MRI scanner as a block design using E-Prime software (Psychology Software Tools, Inc.). The total task time was 12 mins and consisted of six 120second epochs. Each epoch includes alternating 24-second blocks of four task conditions: Alcohol Cue, Neutral Beverage Cue, Blur, and Rest. Respectively, these task conditions included images of alcohol-related stimuli customized for each group (e.g. liquor bottle); neutral stimuli (e.g. water bottle); blurred stimuli acting as visual controls matched by color and hue; and a fixation cross for alert rest periods. T2* multiband EPI Acquisition. Functional images will be acquired with a multislice multiband gradient-echo echo planar imaging (EPI) sequence [TR/TE=1200ms/35ms; FOV=192mm; matrix=64x64 voxels; 36 slices; slice thickness=3mm with no gap; final resolution=3mm3 voxels]. Each functional run will consist of 656 time points.

Cognitive Interference in the presence of an alcoholic beverage cue task: An abnormally high attentional biases towards alcohol-associated cues have been observed in alcohol-dependent patients and is related to poor treatment outcomes (review: Field & Cox 2008). This bias towards alcohol cues impairs an individual's ability to withhold responding for alcohol, narrows their behavioral repertoire, and slows performance on cognitive tasks. One of the most well-established tasks for measuring cognitive performance and interference is the Stroop Color-Word Naming Task. During the Stroop task, 100 words will be presented are presented on a computer screen in a serial manner. Participants are asked to name the color of each word presented while ignoring the meaning of the word itself. Error rates and reaction times are the primary dependent measures. Previous studies have shown that heavy alcohol users

drinkers respond more slowly after exposure to alcohol-related priming conditions (Cox et al 1999, Cox et al 2003). Consequently, after the fMRI alcohol cue reactivity task and before the Stroop task, a glass of the participant's preferred alcoholic beverage (beer, wine, liquor) will be placed within 5 feet (but out of arm's length) of the participant. It will remain there for the length of the task, but the participants will not be allowed to drink it and the beverage will be discarded at the end of the study visit. This paradigm will be repeated before and after iTBS.

iTBS administration with neuronavigation: For TBS targeting the Cartesian position of the coil (X,Y,Z) will be determined by standardized positions from the EEG 10-20 system: F3 will be used for the left dlPFC targeting. The angular position of the coil (pitch, yaw, roll) will be determined by the individual's cortical geography beneath F3 using the individual's T1 scan for guidance. The locations and coil orientation will be indicated on a nylon cap which will be worn during the TMS sessions. We will then determine the participant's resting motor threshold (RMT, the minimal amount of stimulation required over the hand area of the primary motor cortex to induce contraction of the APB muscle of the hand 50% of the time) via the standardized PEST procedure. During each TMS session, we will utilize a Brainsight Neuronavigation suite to ensure that the coil is placed in the same position at each session at that the participant's head does not move away from the coil during stimulation. The procedures for motor threshold, performing cortical localization, standardized procedures, blinding, and training regimens for all staff, as well as safety are consistent with our prior publications. We will also publish a Standard Operating Procedure and video file as with any publications that arise from this project. The decision to utilize probabilistic as opposed to anatomical or functional MRI scans was made for consistency with our promising preliminary data. Additionally, targeting based on the 10-20 system is easily scalable in the clinic. Nonetheless, we will be examining the deviation of this target from those identified with individualized network parcellation, and the association to treatment outcome.

For intermittent theta burst stimulation (iTBS), participants will receive stimulation over the left dLPFC (each train: 3 pulse bursts presented at 5Hz, 15 pulses/sec for 2 sec, 8 sec rest, 600 pulses/session; 110% RMT, MagPro; 30 min inter session interval) using a figure 8 coil (Coil Cool-B65 A/P). During each real and sham TBS session the amplifier output will be escalated ("ramping" in 5% increments over 30 seconds) from 80% to 110% RMT to enhance tolerability. To further ensure feasibility for AUD participants, sessions will be made available on nights and weekends and all visits will be associated with compensation for travel/parking and time.

ACTIVE SHAM system: The MagVenture MagPro system has an integrated active sham that passes current through two surface electrodes placed on the scalp. The electrodes are placed on the left frontalis muscle under the coil for both the real and sham stimulation sessions. To assess the integrity of the blind (active sham) a questionnaire will be given to both the patients and to the research staff to evaluate their opinion on whether they received real or sham, their level of confidence (Likert scale 1-10), and their rationale (text entry). Pooled accuracy from prior work in our collaborator's laboratory was 47.6% suggesting that individuals were not aware of the stimulation being received.

Drug Screens: At the scanning/stimulation visits (Visit 1 and 2) a multidrug urine panel will be given to all participants (Quickvue 5-panel urine drug screen, Quidel, San Diego, CA). Individuals with a positive urine drug screen for opiates, stimulants, or benzodiazepines will be rescheduled for another visit and no treatment will be given on that day. If they test positive for these substances at the rescheduled visit, they will then be excluded from the study.

Remuneration: Total compensation is up to $125 per participant. Individuals will receive $25 for the Screening and $100 for TBS/MRI Visit. Partial compensation will be given to individuals that complete a portion of the TBS/MRI Visit. Additionally, while complimentary parking is provided at the MRI Center, money is budgeted to provide bus passes or ridesharing service fees for participants in need of transportation.

Payment will be made using a pre-paid debit card called Greenphire ClinCard. It works like a bank debit card. Participants will be given a debit card and each time they receive a payment for participation in this study, the money will be added to the card after each completed visit.

The card may be used at any store that accepts MasterCard or cash can be removed at a bank machine. However, there may be fees drawn against the balance of the card for cash withdrawals (ATM use) and inactivity (no use for 6 months). Participants will be given the ClinCard Frequently Asked Questions information sheet that answers common questions about the debit card. Participants will also receive letters with additional information on how to use this card and who to call if there's any questions.

The debit card system is administered by an outside company in conjunction with the Wake Forest Office of Clinical Research (OCR) who will distribute the cards in sealed envelopes to study staff prior to a participant's screening visit. The company, Greenphire, will be given the participant's name and social security number. They will use this information only as part of the payment system. The information will not be used for any other purposes and will not be given or sold to any other company. Greenphire will not receive any information about the participant's health status or the study in which they are participating.

Outcome Measure(s)/Analytical Plan

Cognitive Interference in the presence of an alcohol beverage cue task: It is hypothesized that individuals will have slower color-naming responses for alcohol words compared to neutral words at baseline, but this effect size will be lower following real versus sham iTBS (mixed model analysis of variance, error rate and reaction time, before and after TBS, 2 groups: real iTBS and sham iTBS).

Neuroimaging Preprocessing: MRI data will be preprocessed using SPM12 (Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab 7.14 (MathWorks, Inc., Natick, MA). MR Images will be first converted from DICOM format to 4D NIfTI files and motion corrected (Realign: 6 parameter rigid-body realignment to first image in each timeseries using a least-squares approach). Normalization parameters, bias correction and anatomical tissue maps will be determined simultaneously, using the Segment toolbox. Individual anatomical images will be stripped of their skulls by masking the bias-corrected image with the combined tissue masks of grey matter, white matter, and CSF. The functional images derived from realignment will be coregistered, through the mean image, to the skull-stripped anatomical image (Coregister: Estimate, using normalized mutual information). Coregistered images will be then normalized (Normalize: Write) to MNI template space with the nonlinear warps derived from the Segment tool. Finally, functional images will be masked (to remove the skull) and smoothed (8mm FWHM Gaussian kernel) to facilitate subsequent between-subject analysis.

Generalized Psychophysiological Interaction (gPPI): gPPI will be used to investigate task-modulated patterns of functional connectivity (FC) during the alcohol cue reactivity task. Regions-of-interest (ROIs) comprising frontal-striatal circuitry as well as elements of the Saleince Network and Central Executive Network will be identified from the standard Automated Anatomical Labeling (AAL) Atlas. These included the vmPFC (AAL: left and right Frontal_Med_Orb), left caudate (AAL: Caudate_L), right caudate (AAL: Caudate_R), left putamen (AAL: Putamen_L), right putamen (AAL: Putamen_R), left insula (AAL: Insula_L), right insula (AAL: Insula_R), and anterior cingulate cortex (AAL: left and right Cingulum_Ant). These ROI masks will then be used in CONN Toolbox to extract ROI timecourses from

the fMRI data for subsequent gPPI computation. The Drug/Alcohol vs. Neutral contrast βs from the Pre- and Post-Real cTBS and Pre- and Post-Sham cTBS were entered into a twoway ANOVA and subsequent *t*-tests to determine the effect of treatment on changes in drug cue-evoked FC. More details on the analysis can be found in prior publications from our group (Kearney-Ramos et al 2018).

Results will be analyzed initially using descriptive statistics. Comparison between groups will be done using chi square tests for proportions, and t-tests or ANOVA procedures for continuous variables. Regression analysis will be performed to identify independent outcome predictors. Other inferential statistical analysis will be conducted as appropriate.

Relationship with the WF-TARC Goals:

Alcohol dependence is a chronically progressing and relapsing disorder that is associated with harm for the users, their families, the communities, the justice system, and the health care system. Continued progression from casual use through high and dependent use is likely due to a combination of factors that contribute to uncontrolled drinking in the presence of an alcohol cue. While several pharmacotherapies have been developed for alcoholism, for many individuals these approaches are not sufficient. Consequently, of the thousands of alcohol-related admissions to emergency departments and trauma units nationwide each year, most of whom are chronic heavy drinkers, up to 41% will return to the hospital again within 5 years. For these individuals, it may be necessary to take a more powerful and targeted treatment approach to break the strong, sensitized, and potentiated response that they have to alcohol-related cues.

Functional neuroimaging studies in alcoholics have demonstrated that cue-reactivity and craving is associated with elevated activity in a network of limbic regions including the mPFC, ACC, and ventral striatum, but that activity in these areas can be attenuated by 'top-down' cognitive control networks, such as the dorsolateral prefrontal cortex node of the Central Executive Network. Despite a wealth of rodent and non-human primate literature demonstrating a causal link between activity in these cortical and subcortical brain regions and heavy alcohol consumption, there are no neural-circuit-based interventions available to treat drinking in our patients. Transcranial magnetic stimulation has some promise – especially theta burst stimulation which is a highly potent form of TMS- very little work has been done to apply this technique to heavy alcohol drinkers. These individuals, especially those that have engaged in risky drinking behavior that led to injury are very vulnerable to relapse, recidivism, and poor health outcomes overall. Consistent with the translational research emphasis of the WFTARC and the theme of vulnerability throughout the Center projects, this pilot project seeks to evaluate the acute effects of iTBS to the dLPFC as a tool to decrease alcohol cue reactivity and increase cognitive performance in the presence of alcohol cues among heavy alcohol users at high risk for negative health consequences of drinking.

Public Health Significance

Repetitive TMS is already an FDA approved treatment for depression and is growing in clinical use and acceptance, with machines located throughout the US and emerging insurance reimbursement. Non-invasive brain stimulation may prove to be a valuable adjuvant to behavioral and pharmacotherapy therapy for alcohol abuse as it is the only non-pharmacological non-invasive way we have to directly target the regions of the brain that are involved in craving and cognitive control over drinking. Before moving forward with slow and expensive clinical trials however, it is important to have an understanding of the effects of a single session of TBS on alcohol cue reactivity (Aim 1) and cognitive control in the presence of alcohol cues – a situation that recovering alcoholics face every day as they navigate their communities and form social bonds with others who may engage in social drinking (Aim 2).

Human Subjects Protection

Risks to subjects:

The risks fall into four categories: risks associated with psychological assessment, risks associated with repetitive TMS, risks associated with MRI scanning, and risks associated with randomization and alcohol related cues.

Risks of Psychiatric Interviewing (minimal risk): Some participants may get emotionally distraught when disclosing sensitive personal information. Some participants may feel anxiety about disclosing abundance use histories of alcohol and reporting some aspects of their demographics.

Risks Associated with MRI Scanning (minimal risk): The major potential risks for MRI are all subsumed under the risks for TMS and primarily include risks to individuals who have metallic implants, pacemakers, or pregnant women. These individuals will be excluded from the study. In addition, participants may feel restless or uncomfortable when lying in the MRI scanner.

Risks Associated with Repetitive TMS (FDA-designated minimal risk): Potential risks of TMS: Repetitive TMS has been considered "non-significant risk" by the FDA (2007) when applied at similar intensities, durations, and frequencies to those being used in this proposed protocol. Additionally motor cortex and dorsolateral prefrontal continuous theta burst stimulation in a manner identical to this protocol has been designated minimal risk by the MUSC IRB for healthy adults as well as individuals with opiate dependence.

Potential risk of a seizure: In designing this experiment, we have followed the latest safety guidelines for TMS. Despite these precautions, there is a chance of a seizure as a result of rTMS. Eight seizures have been noted in previous studies, with six of them occurring in healthy volunteers without any history of seizures, brain tumors or traumatic brain injuries. All of these seizures have occurred during rTMS with the participant in the treatment chair and a trained operator on hand. All seizures have stopped by themselves without any medication. No participants have had any problems after the seizures WFUHS has a plan for dealing with fainting and seizures, and **every TMS researcher involved in providing TMS treatment for this protocol (Key Personnel) will have extensive TMS training from the PI on the study as well as a skills test associated with collecting an accurate motor threshold (which is one of the largest factors that promotes safety).**. Additionally, if a participant has a seizure an emergency response team will be called. Most seizures, including those caused by rTMS, last less than 60 seconds and do not require any medication. Participants will be evaluated by a physician associated with the Wake Forest Brain Stimulation Laboratory following recovery from the seizure. Any participant who has a seizure cannot continue with the study.

Other potential risks:

1. Potential for scalp discomfort and headaches: Some people report mild discomfort when the magnetic pulses are applied over the scalp. A small number of people (~5%) report headache following rTMS. However, the headaches are temporary and manageable with common over-the-counter pain remedies.
2. Potential hearing loss: The TMS coil generates a high-energy click that may cause hearing damage. Humans exposed to TMS have shown temporary increases in auditory threshold (especially at high frequencies) lasting at least 5 minutes and less than 4 hours.
3. Safety in case of pregnancy: This protocol will exclude pregnant women. The risks of using TMS with pregnant women are currently unknown. Please inform the research team if you are pregnant or think that you might have become pregnant during the study. A pregnancy test will be performed before the experiment begins.
4. Potential for reflex syncopal event: Syncope is defined as a momentary loss of awareness and postural tone. It typically has a rapid onset, short duration, and spontaneous recovery. Although syncopal episodes are very rare with TMS (less than 1%), they typically occur during the motor

threshold procedure before the rTMS treatment has begun. Individuals that are sleep deprived and have low or unstable blood pressure are at greater risk.

5. Interaction with electrical or metal implants: Electrically, magnetically or mechanically activated implants (such as cardiac pacemakers), as well as clips on blood vessels in the brain may be affected by rTMS (as well as MRI) and cause pain or abnormal signal propagation. Although the pain has not reported to be significant protocol-approved research study members will conduct a thorough TMS safety questionnaire. This questionnaire will be checked and updated throughout the course of the study. Individuals that have these implants and devices or suspect that they may have pieces of metal in their eyes, head, or body (e.g. bullets, shrapnel, and fragments from metallurgy) will be excluded from the study in order to minimize any discomfort and abnormal signal propagation.

Risks regarding Randomization and Alcohol Related Cues:

Given that participants will be exposed to alcoholic beverages, there may be an added risk of induced cravings. However, it should be noted that the alcohol cues that participants will be exposed to are not as powerful as the daily cues that participant's encounter in their normal living environment. In addition, participants that will be randomized receive the placebo treatment may prove to be less effective than real study treatment(s) or other available treatments.

Risks regarding Confidentiality:

Despite efforts to maintain subjects' anonymity and confidentiality, there is always some minimal risk of people other than the study investigators gaining access to your health information. Every effort will be made to ensure that your health information will be collected and stored in a manner that ensures the highest level of protection of confidentiality.

Protocol for participants expressing suicidal ideation: All study team members performing the Becks Depression Inventory will have received online training from the Suicide Prevention Resource Center (https://training.sprc.org). Completion documentation will be saved on the laboratory drive. In the event that a participant expresses a desire to kill themselves (selects answer #2 or #3 on question #9 of the Becks Depression Inventory), the trained study team member will ask them about the level of detail of their thoughts. If the participant has a suicide plan to kill himself/herself, the study staff will recommend he/she speaks with the suicide hotline and initiate contact with the suicide prevention hotline (Cardinal Innovations at 1-800-939-5911) while the individual is in their presence. If the participant refuses to talk to the hotline and leaves, the study staff will call 911. A member of the study team will initiate contact with a local, licensed clinician while the individual is in their presence. If the licensed clinician deems necessary, they will dispatch a mobile crisis unit to the location to further assess and transport the participant to the hospital for a full mental health assessment and involuntary 72-hour hold, if needed. The study staff member will also contact the PI via phone, email, or text as soon as possible to inform them of the situation.

Subject Recruitment Methods

Participants will be identified and recruited through members of the study team and the trained counselors and staff of the Wake Forest Department of Surgery's inpatient trauma unit in an appropriate manner with particular sensitivity surrounding their admission and PHI. If the potential participant is interest, they will screened and consented during their admission, serving as Visit 1. Additionally, heavy alcohol users with a history of risky drinking behavior will be recruited through the resources of the Wake Forest Trauma Unit Registry and community advertising. The MRI scans and TMS sessions during Visit 2 will both be performed at the MRI center on the WFUBMC main hospital campus. The study team will try to coordinate study visits on the same day as outpatient clinic follow up in Janeway Tower from their recent inpatient admission, as to make it easier on the participant. A meal voucher of $10 will be provided for the participant to eat in the hospital cafeteria, should they so choose.

Additionally, a chart review will be conducted for research purposes. Potentially eligible patients will be identified. The potentially eligible patients in the PIs practice will be informed about the study as the PI feels is appropriate. Then potential patients who have agreed to be contacted for future research by logging their WFU Research Permissions preferences in MyChart will be contacted by phone and invited to participate. All other patients will be contacted through their providers to be informed of the study if the provider feels it is appropriate.

Informed consent will be reviewed with the potential participant by a member of the key personnel on this visit. The consent will be signed by the participant as well as one of the Key Personnel on the proposal. A copy of the consent will be given to the subject and the original placed in the research record. The consent and HIPAA process will be done in Dr. Hanlon's research laboratory and facility.

Informed Consent

Individuals that have previously consented to be contacted about future research studies will be contacted and phone screened to determine preliminary eligibility. They will be scheduled for their screening visit, which will take place in a private, quiet screening room in the Clinical Neuromodulation Laboratory space in Dr. Hanlon's research suite. Informed consent will be reviewed with the potential participant by a member of the key personnel on this proposal. The consent will be signed by the participant as well as one of the Key Personnel on the proposal. A copy of the consent will be given to the subject and the original placed in the research record. All records will be stored in locked departmental files. Section 301(d) of the Public Health Service Act of November 4, 1988 also protects a layer of protection for the privacy of health information for individuals that engage in federally funded medical research.

Confidentiality and Privacy

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a linkage file, store separately from the data. The linkage file will be kept secure, with access limited to designated study personnel. Following data collection subject identifying information will be destroyed three years after closure of the study, consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Data and Safety Monitoring

The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff.

Data and Safety Monitoring

The principal investigator (PI) will be the primary party responsible for data management, oversight, and accountability in terms of participant safety and consent. Quality control will include regular data verification (Integrity of the Consent and HIPAA, scores on assessments), study progress, subject status, adverse events, and protocol deviations. Protocol adherence will be monitored by the Wake Forest IRB, who will also be given access to the reports from the PI to the ME.

Plans for Interim Analysis of Efficacy Data: Data from this study will be analyzed when a 50% recruitment goal is obtained. Final analysis will occur when all TMS visits have been completed.

Responsibility for Data and Safety Monitoring: The PI and protocol-approved research team are all responsible for data and safety monitoring. The PI will be most involved in data and safety oversight. The PI will discuss data integrity and inquire about safety/patient tolerance in weekly meetings with the research team.

Data Entry Methods: Data will be collected using REDCap™, which is a secure web application for building and managing online surveys and databases. REDcap™ supports online or offline data capture for research studies and operations. Participants and protocol-approved study personnel will enter data directly into the online portal to ensure security and prevent data loss.

Data Analysis Plan: Data for this study (behavioral assessments) will be acquired by protocol-approved members of the research team, including graduate students and research specialists. These individuals will also perform data management and analysis under the guidance of the PI. Manuscript composition will be led by the PI and Co-Is, with the assistance of the research team.

Quality Assurance Plan: Weekly meetings will be held between the PIs and research team to discuss any data-related problems as well as qualitative comments received during data collection. Initial data analyses will examine distributions of variable scores, and comparability of baseline characteristics across conditions, any necessary adjustments to analyses will be made. Confidentiality protections are outlined below.

Statistical review of the study will be conducted annually by a Wake Forest biostatistician (including enrollment, retention, assessment inventories).

Definition and Reporting of AEs/SAEs to the IRB/NIH: An adverse event (AE) is defined as any untoward medical occurrence in a study subject who was administered rTMS but does not necessarily have a causal relationship with this treatment. Any unwanted change, physically, psychologically or behaviorally, that occurs in a study participant during the course of the trial is an adverse event. A Serious Adverse Event (SAE) is defined as an adverse event that has one of the following outcomes: death, life-threatening, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, a congenital anomaly/birth defect.

All unexpected AEs will be reported to the Wake Forest Institutional Review Board (IRB) and Committee on Human Research within 48-business hours. Serious AEs will also be reported within 24-business hours. Follow-up of all unexpected and serious AEs will also be reported to these agencies. AEs/SAEs are documented and reported as per IRB requirements. Research staff will identify AEs and obtain all available information to assess severity, seriousness, study relatedness, expectedness, outcome, and the need for change or discontinuation in the study intervention. AEs are documented on AE Logs and AE Case Report Forms. Additional relevant AE information, if available, will be documented in a progress note and stored in the research record as appropriate to allow monitoring and further evaluation. If the AE meets the definition for serious, appropriate SAE protocol specific reporting forms are completed and disseminated to the appropriate persons and within the designated timeframes as indicated above. For each AE/SAE recorded, the research staff will follow the AE/SAE until resolution, stabilization, or until the participant is no longer in the study as stated in the protocol. We will report adverse events to the Medical Wake Forest IRB online per the IRB's guidelines.

Collection and Reporting of AEs and SAEs: As mentioned above, all AEs/SAEs are documented and reported as per IRB requirements. Research staff will identify AEs, verify event with the participant, and

obtain all available information to assess severity, seriousness, study relatedness, expectedness, outcome, and the need for change or discontinuation in the study intervention. AEs are documented on AE Logs and AE Case Report Forms. Additional relevant AE information, if available, will be documented in a progress note and stored in the research record as appropriate to allow monitoring and further evaluation. If the AE meets the definition for serious, appropriate SAE protocol specific reporting forms are completed and disseminated to the appropriate persons and within the designated timeframes as indicated above. If applicable, copies of medical records and injury reports will be retrieved and safely stored in the subjects file. De-identified copies of reports will be sent to the Wake Forest IRB and ME/DSBM. For each AE/SAE recorded, the research staff will follow the AE/SAE until resolution, stabilization, or until the participant is no longer in the study as stated in the protocol.

Reporting of Unanticipated Problems, Adverse Events or Deviations: Any unanticipated problems, serious, and/or unexpected AEs, deviations or protocol changes will be reported within 24-72 business hours, depending on severity, by the principal investigator or designated member of the research team to the Wake Forest IRB, ME/DSMB and to the sponsor, NIH.

Management of SAEs or Other Study Risks: As described above, SAEs will be immediately reported, within 24 business hours, to the ME/DSBM, sponsor and Wake Forest IRB. For each SAE recorded, the research staff will follow the SAE until resolution, stabilization, or until the participant is no longer in the study as stated in the protocol. If applicable, copies of medical records and injury reports will be retrieved and safely stored in the subjects file. De-identified copies of reports will be sent to the Wake Forest IRB, ME/DSBM, and NIH.

Reporting of IRB Actions and ME/DSMB Reports to NIH: Any IRB actions and ME/DSMB reports will be reported to both the Wake Forest IRB and the NIH Institute supporting the study following the sponsor's report submission guidelines, should this study be awarded.

Report of Changes or Amendments to the Protocol: Any changes to the proposal/protocol must be approved by the NIH Institute supporting the study. Any amendments to the IRB protocol associated with the proposed work will be reported to NIH should this proposal be awarded funding.

Trial Stopping Rules: The protocol will immediately be paused following notification of a SAE. Per IRB policy, the IRB and ME/DSMB will be notified within 24 business hours following the SAE notification. SAEs will be reported to NIH within 72 hours. Should the reported SAE be confirmed as directly related to the protocol, the trial will be terminated. The device manufacturer will be notified within 72 business hours. Of note, according to the literature associated with the MagVenture device, there have been no clinical trials stopped or SAEs reported.

Conflict of Interest: Neither the PI, nor members of the research team have any Conflicts of Interest directly related to this protocol. The rTMS device used for the proposed study is manufactured by MagVenture.

Reporting of Unanticipated Problems, Adverse Events or Deviations

Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the principal investigator or designated member of the research team to the IRB.

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