PROTOCOL TITLE:

Effects of Neuromodulation and Cognitive Training on Brain Networks Associated with Relapse in Alcohol Use Disorder

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VERSION NUMBER/DATE:

10-25-2021 version

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	10/03/2017	detailing recruitment methods, consent process, inclusion/protection of vulnerable populations	No
2	05/14/2018	Adding new recruitment site: Boynton Health Services	Yes
3	08/02/2018	Changing title, new K01 funding	Yes
4	08/30/2018	Adding sample size to 50	No
5	12/10/2018	Adding assessment tasks, hotline information cards, and expanding inclusion	Yes
6	05/01/2019	More detailed plan in case of acute mental health. Compensation no longer mentioned under benefits section.	No
7	04/09/2019 Re-submitted 05/14/2019	Recruitment changes under the CAR Recruitment Registry, increasing sample size to 70, adding an acceptable time window for completion of follow-up visits, and indicating participants will be compensated with ClinCard.	No
8	06/06/2019	Addition of an MRI scan at ~1-month follow-up with updated compensation. Addition of optional saliva collection for genotyping. Exclusion criteria regarding psychiatric diagnosis changed to only exclude those with psychosis. Modify definition of follow-up visits with more flexible timepoints. Indication of how data will be collected for missed visits. Removal of Boynton as a recruiting site. Addition of optional informed consent to communicate through unencrypted email and/or	Yes

9	08/05/2019	Addition of form to assess and record more detailed understanding of informed consent	Yes
10	02/19/2020	Increase number of consented participants to 100. Test for alcohol use at in-person follow-up visit on an as-needed basis.	Yes
11	04/08/2020	COVID19: Only during the COVID19 crisis, research staff will take subject material home.	No
12	05/08/2020	Addition of optional decision-making computerized task; Option to complete follow-up assessments remotely; Updated Set Shifting task stimuli.	Yes
13	09/10/2020	Modifications related to COVID19 crisis, statement saying study will follow Sunrise Plan; Addition of research-dedicated room in Lodging Plus treatment program.	Yes
14	03/09/2021	Modifications related to routine audit. Modifications related to optional ecological momentary assessment (EMA) survey.	Yes
15	06/03/2021	Parking reimbursement for participants	Yes
16	08/31/2021	Modification related to maintaining COVID19 changes permanently, for having the option of either in-person or remote visits.	Yes, only change is new lab phone number

17	10/25/2021	To directly collect EMA data on factors that can mediate clinical outcomes (influencing Aims 2 and 3), participants will be given the option of using a wearable device that passively tracks stress and sleep when they leave the addiction treatment program. Passive data collected from the wearable device will be useful to complement and compare with the self-report EMA data collected through surveys.	Yes

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ABBREVIATIONS/DEFINITIONS

- DLPFC - Dorsolateral Prefrontal Cortex
- NAcc - Nucleus accumbens
- FC - Functional connectivity
- AUD - Alcohol use disorder
- fMRI - Functional magnetic resonance imaging
- tDCS - Transcranial direct current stimulation
- CMRR - Center for magnetic resonance research
- HCP - Human Connectome Project

STUDY SUMMARY

Study Title	*Effects of Neuromodulation and Cognitive Training on Brain Networks Associated with Relapse in Alcohol Use Disorder*
Study Design	Double-blind, within subject, and sham-controlled
Primary Objective	The overall objective of this proposal is to enhance FC between DLPFC and NAcc as a therapeutic intervention to enhance cognitive flexibility.
Secondary Objective(s)	Reduce craving in addiction.
Exploratory Objective(s)	Explore associations between genotype/epigenetic changes and intervention response.
Research Intervention(s)/ Investigational Agents	Transcranial direct current stimulation and magnetic resonance imaging.
IND/IDE # (if applicable)	N/A
Investigational Drug Services # (if applicable)	N/A
Study Population	Individuals with alcohol use disorder
Sample Size (number of participants)	**100 consented**
Study Duration for Individual Participants	8 months, up to 4-month extension available depending on participant availability for follow-ups

1. **Objectives**
    2. The overarching goal of this project is to expand the traditional expertise in non-invasive neuromodulation at the University of Minnesota towards developing novel paired-neuromodulation approaches using tDCS for new addiction treatments that support long-term abstinence. This study will allow us to investigate whether the pairing of DLPFC stimulation and cognitive flexibility training can enhance FC between DLPFC and NAcc. We have identified higher FC between DLPFC and NAcc in alcoholics that have successfully maintained abstinence for extended periods of time (7 years). This paired-neuromodulation approach can potentially be used as a therapeutic intervention to decrease relapse probability in addiction. The long term goal is to develop new addiction treatments that support long-term abstinence. The overall objective of this proposal is to enhance FC between DLPFC and NAcc as a therapeutic intervention to enhance cognitive flexibility and reduce craving in addiction.
    3. Exploratory objectives: To associate genotypes and epigenetic changes with variations in intervention response and clinical outcome.

2. **Background**
    1. Significance of Research Question/Purpose: The relapsing nature of alcoholism is a major obstacle to successful treatment. About 60% of those entering treatment will relapse within one year. To improve treatment outcome, new interventions targeting the underlying brain biomarkers of relapse vulnerability hold significant promise in reducing this critical public health problem.
    2. Preliminary Data: Using resting functional magnetic resonance imaging (fMRI) we have identified brain biomarkers that support long-term abstinence. Our cross-sectional and longitudinal findings provide evidence that higher functional connectivity (FC), particularly between nucleus accumbens (NAcc) and dorsolateral prefrontal cortex (DLPFC), is a potential brain biomarker that supports abstinence. Long-term abstinent alcoholics (7 years of abstinence) have higher resting FC between NAcc and DLPFC when compared to controls. Short-term abstinent alcoholics (11 weeks of abstinence) have intermediate FC (lower than long-term abstinent alcoholics and higher than controls) (Camchong, Stenger, and Fein 2013c, [a] 2013). Further, lower FC between NAcc and DLPFC at 11 weeks of abstinence can be a predictor of subsequent relapse (with 74% accuracy) (Camchong,

Stenger, and Fein 2013b). Moreover, in a pilot longitudinal FC study examining resting FC of NAcc at 5 and 13 weeks of abstinence in individuals with substance use disorder, we found that FC between NAcc and DLPFC decreased from 5 to 13 weeks of abstinence in subsequent relapsers, while it increased in subsequent abstainers (Camchong et al. 2014). Based on the above, we believe that long-term abstinence is supported by a compensatory mechanism that mediates proper executive function over reward (mediated by DLPFC-NAcc FC), a potential brain biomarker that could be an intervention target. These findings provide a compelling case to explore whether this brain biomarker can be modulated to enhance patients' ability to remain abstinent. There is a need to investigate methods that can be used to increase FC between DLPFC and NAcc.

3. Existing Literature: Cognitive flexibility, the ability to change maladaptive behavior, depends on DLPFC input to NAcc (Gruber, Hussain, and O'Donnell 2009). DLPFC transmits reward representations to NAcc through glutamatergic projections that guide goal-directed behavior (Ballard and Knutson 2009). If DLPFC fails to activate when required, a common observation in substance use disorder, target neurons in the NAcc core do not receive critical information needed to select the appropriate outcome, causing acquired maladaptive response patterns to persist (e.g. drug consumption) (Gruber, Hussain, and O'Donnell 2009). Higher FC between DLPFC and NAcc may be achieved by stimulating DLPFC while subjects perform a task that requires cognitive flexibility, the reversal learning task. Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique that can modulate brain connectivity. DLPFC stimulation may increase input to NAcc to facilitate proper selection of goal-directed behavior and may also decrease craving in individuals with substance use disorder (Boggio et al. 2008). Genetics and treatment response: A source of treatment response variability could stem from differences between participants in baseline genetic profiles or epigenetic changes over the course of treatment. Genetic polymorphisms, especially in genes important for neuroplasticity, may also mediate neuroplastic changes underlying the effects of tDCS (Chhabra et al., 2016), as has been demonstrated with gene BDNF (Antal et al., 2010; Fritsch et al., 2010). In light of these genetic influences on key tenants of our study - i.e. treatment response in alcohol use disorder and physiological effects of tDCS - we will collect genetic samples from participants to determine whether genetic or epigenetic variations may affect

response to the cognitive training and tDCS intervention. This information may help inform the development of more individually-tailored treatment protocols in the future. As this is a secondary aim, participants will be given the choice in the consent form to opt in or out of the genetic sampling procedure.

4. There is preclinical data suggesting that sleep alterations are associated with increased alcohol consumption (Garcia-Garcia et al 2021). We have preliminary clinical data showing that sleep alterations are associated with vulnerability to relapse. The nature of these associations may be specific to an individual, so that not enough sleep or too much sleep can be associated with relapse vulnerability depending on the individual. Moreover, sleep alterations, which are common in alcohol use disorder are associated with brain alterations (Zhang et al 2021). It is important to determine whether sleep disturbances are a factor that affects treatment outcome in alcohol use disorder.

3. Study Endpoints/Events/Outcomes

1. Primary Endpoint/Event/Outcome: In a double-blind randomized design, 100 abstinent (~2 weeks abstinent) individuals with alcohol use disorder (AUD) recruited from Lodging Plus Program will receive 10 sessions (2 sessions per day for 5 days) of either (i) transcranial direct current stimulation (tDCS) to the PFC or (ii) sham-tDCS. All subjects will perform the reversal learning task during tDCS intervention (active or sham) to prime the engagement of the NAcc-PFC brain circuit that mediates cognitive flexibility. Rest fMRI and craving measures will be collected before the first and after the last day of tDCS sessions, and about one month after the last fMRI (timepoint depending on participant availability). Monthly follow-up interviews will be conducted for approximately 8 months after intervention completion to query relapse status. Dependent variables will be (i) change in NAcc-PFC FC between 2,3 weeks of abstinence and one month later, (ii) change in craving scores between 2 and 3 weeks of abstinence and (iii) relapse status ~8 months after study participation. Aim 1: To investigate whether NAcc-PFC FC can be modulated, we will compare magnitude and durability of change in NAcc-PFC FC between active-tDCS and sham-tDCS groups. Aim 2: To determine if PFC stimulation has a short-term effect on behavior related to clinical outcome, we will compare change in craving scores (difference in craving scores between 2 and 3 weeks of abstinence) between active-tDCS and sham-

tDCS groups. Aim 3: To correlate neuromodulation intervention with long-term clinical outcome, we will record craving and relapse status during the ~8 months following treatment discharge. We will examine the relationship between change in NAcc-PFC FC between 2 and 3 weeks of abstinence and subsequent (i) monthly craving scores and (ii) relapse status. Aim 4: Examine relationships between genetic variants, epigenetic changes and treatment outcome (e.g. durability, functional connectivity).

4. **Study Intervention(s)/Investigational Agent(s)**
    1. Description: As in previous clinical studies that achieved treatment response and reduction of relapse probability (Klauss et al. 2014), patients will receive two 13 minute daily sessions with a rest interval (no stimulation) of 20 minutes in between (13:20:13 schedule; as in (Klauss et al. 2014; Monte-Silva et al. 2013)) of either active (2-mA) or sham transcranial direct current stimulation (tDCS) every day for five consecutive days. This study will add to the literature by having patients practice the reversal learning task (D'Cruz et al. 2011) during tDCS intervention, to enhance paired neuromodulation. While patients practice the reversal learning task, half of the patients will receive active tDCS stimulation to the left DLPFC to enhance top-down control and improve the tuning or gating of the extraneous information and the other half will receive sham tDCS.
    2. The tDCS will be performed with Neuroelectrics Starstim Enobio 20 (Neuroelectrics Barcelona, Spain). This device has been approved for use in research without an investigational device exemption due to meeting criteria for non-significant risk. In addition, the device has built in safety mechanisms which allow for the immediate cessation of stimulation should the subject become uncomfortable or impedance levels too high. The current will be administered via two saline soaked electrode sponges (approximately 25cm²) for two 13 minute blocks. The current strength during each administration will be 2 mA. These administration procedures are in line with other protocols that have outlined safe administration (Nitsche et al. 2008, 2007). Across more than 2000 subjects no side-effects have been reported with the exception of slight itching under the electrode and occasional occurrence of headache, fatigue, or nausea (Poreisz et al. 2007). The anodal electrode will be placed over left DLPFC and the cathodal electrode will be placed over right DLPFC.
    3. Drug/Device Handling: We will use transcranial direct current stimulation (tDCS) to stimulate dorsolateral prefrontal cortex (DLPFC). TDCS is a non-

invasive brain stimulation technique that can modulate brain connectivity. TDCS involves applying a weak electrical current (2mA or less) to the scalp via anodal and cathodal electrode sponges, causing either increases or decreases in cortical excitability, respectively. Research has shown in both healthy subjects and patients (e.g. Alzheimer's disease, Parkinson's disease, stroke, and depression) that tDCS has the potential to modulate synaptic strengthening and neurotransmitter-dependent plasticity underlying changes in behavior and learning (Lang et al. 2005).

4. IND/IDE: *N/A*
5. Biosafety: *N/A*
6. Stem cell research: *N/A*

1. Procedures Involved

1. Study Design: This study is double-blind, within subject, and sham-controlled. The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design includes: In a double-blind randomized design, 100 abstinent (approximately 2 weeks abstinent) individuals with alcohol use disorder (AUD) recruited from Lodging Plus Program will receive 10 sessions (2 sessions per day for 5 days) of either (i) active transcranial direct current stimulation (tDCS) to DLPFC or (ii) sham-tDCS. All subjects will perform the reversal learning task during tDCS intervention (active or sham) to prime the engagement of the NAcc-PFC brain circuit that mediates cognitive flexibility (D'Cruz et al., 2011). Rest fMRI and craving measures will be collected before the first and after the last day of tDCS sessions. Follow-up interviews will be scheduled for each month, but may not happen exactly every month, depending on the participant's availability. Follow-ups will be conducted for approximately 8 months after study completion to query relapse status. Dependent variables will be (i) change in NAcc-DLPFC FC between 2 and 3 weeks of abstinence, (ii) change in craving scores between 2 and 3 weeks of abstinence and (iii) monthly queries on relapse status for the next 6 months after intervention completion. Aim 1: To investigate whether NAcc-DLPFC FC can be modulated, we will compare magnitude of change in NAcc-DLPFC FC between active-tDCS and sham-tDCS groups. Aim 2: To determine if DLPFC stimulation has a short-term effect on behavior related to clinical outcome, we will compare change in craving scores (difference in craving scores between 2 and 3 weeks of

abstinence) between active-tDCS and sham-tDCS groups. Aim 3: To correlate neuromodulation intervention with long-term clinical outcome, we will record monthly craving and relapse status ~8 months after intervention completion. We will examine the relationship between change in NAcc-DLPFC FC between 2 and 3 weeks of abstinence and subsequent (i) monthly craving scores and (ii) relapse status. Patients will be asked to complete these scales monthly for ~8 months after intervention completion to examine long-term effects. Patients will be asked to come back for 3 in-person (or remote) visits scheduled approximately 1, 4 and 8 months later, with the actual date of each visit varying depending on participant availability. On a case-by-case basis, follow-ups may be scheduled up to 3 months after each timepoint (1, 4, and 8 month timepoints) depending on participant availability. In these in-person (or remote) visits the participants will complete the same assessments and fill out questionnaires assessing behavior, personality and substance use metrics as in the baseline appointment. At the ~1-month follow-up timepoint, the participant will also complete a third MRI session, which could be on the same day of the assessments and questionnaires or on a different day, depending on participant availability.

2. Study Procedures: Randomization: Participants will be randomly assigned to either active or sham tDCS. Blinding: Participants will not be informed on their assigned protocol. During consent, they will be informed that there is a 50% chance of receiving active tDCS or sham tDCS every day for five consecutive days. Study appointments will be conducted either in-person, or remotely.

3. Participants who consent to the study and meet study criteria as per the screening evaluation will be asked to participate in an 8-day session study, be available for monthly phone follow-up measures after study completion to query relapse status and for 3 in-person (or remote) follow-up visits. At any of the in-person follow-up visits, research staff may test participants for recent alcohol use using a Breathalyzer (will not be administered if assessments are remote). Participants will be informed of alcohol level, but will not be excluded from the study if test shows recent alcohol use. If Breathalyzer shows alcohol level of > 0.08%, participant will be asked to reschedule visit. While the target will be to conduct follow-up phone calls every month, plus in-person/remote assessments at 1, 4 and 8 months

timepoints, the actual date for these follow-up sessions will vary depending on participant availability.

The participants who are referred to our study by the Consortium of Addiction Research (CAR; approved under IRB protocol #STUDY00005170) will be asked if they are interested in participating. Participants will be informed about the study via the "1406M51241 Invite," which informs them that they need to be available for 8 appointments during their stay at the treatment program. They also need to be available for monthly (depending on subject availability) phone follow-up measures after study completion to query relapse status and for the 3 in-person (or remote) follow-up visits.

Baseline Interview: A research staff member will meet the participant either in person or through a virtual video conference to complete the informed consent process with the participant and administer surveys assessing behavior, personality and substance use, and alcohol craving levels. Understanding of informed consent will be assessed with the "Assessment of Informed Consent" form. Participants will also complete a screening questionnaire for contraindications of MRI scanning. Females who could potentially be pregnant will be tested for pregnancy and, if positive, will not be allowed to participate. If testing is refused, participation will not be allowed. Baseline assessments will take about 1.5 hours total.

MRI #1: The participant will undergo an MRI scan (3T), which takes about 75 to 80 minutes. MRI involves taking pictures of the participant's brain, from which the properties of certain brain tissues can be measured. While sometimes MRI scans are done for clinical purposes, the scans the participant will receive are being done for research purposes. Since these scans are not designed for clinical or medical reading, the participant's scans will not receive a clinical or medical interpretation. For the scan, the participant will be asked to lie down quietly on a bed, and the bed will slide into the scanner. Once the participant is inside the scanner, it will start to take the pictures. During the scan, the participant will simply lie quietly in the scanner with eyes closed while the scanner takes images of the participant's brain. The MRI scan will be performed at the University of Minnesota's Center for Magnetic Resonance Research. Day 2 assessments will take about 1.5 hours total.

Interventions Days 1-5: Will involve reversal learning task training and two

tDCS interventions. We will first explain to the participant what the reversal learning task is, and the participant will perform one trial/practice run. During the reversal learning task the participant will be presented with four identical stimuli. The participant will be required to choose the stimulus that is in the correct location (correct location is randomly determined and changes across trials). Before and after completion of all tDCS interventions (pre-intervention and post-intervention), the participant will perform the following two tasks:

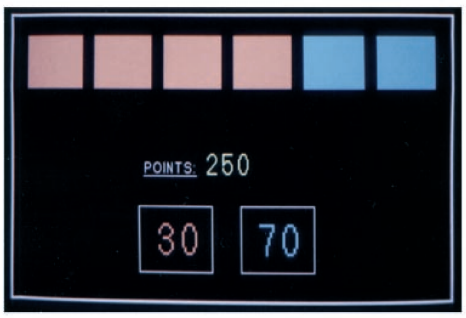
Before and after completion of all tDCS interventions (pre-intervention and post-intervention), the participant will perform the following two tasks:

1. **Computerized dimensional set shifting task** (available in jspsych https://expfactory.github.io/experiments/): this will measure whether changes in cognitive flexibility generalize to a task similar to the task that is practiced (reversal learning task, IRB approved) jspsych https://expfactory.github.io/experiments/ (additional 7 minutes).

   The Computerized Dimensional Set Shift task is a test of rule acquisition and reversal. It involves visual discrimination and attentional set formation maintenance, shifting and flexibility of attention. This test is sensitive to changes in the fronto-striatal areas of the brain and is a computerized analogue of the Wisconsin Card Sorting test.

   Task Description: In this task, participants must use feedback to work out a rule that determines which stimulus is correct. After a variable number of correct responses, the stimuli and/or rule changes. Initially the task will involve simple stimuli which are made up of just one of the dimensions, i.e. different geometric shape or line. Later on in the task, compound stimuli are used: different types of geometric shapes and different types of lines. The shifts in rule are initially intra-dimensional (i.e. shape remain the only relevant dimension) and then later extra-dimensional (i.e. line become the relevant dimension).

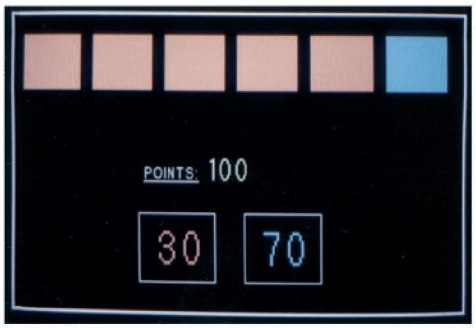
A



2.**Risk Task** (Gilmore et al. 2018; Rogers et al. 1999): To evaluate whether there is a generalization effect, the Risk task will be administered before and after the complete course of intervention.

The Risk Task is a computerized behavioral measure of the propensity for risk-taking within a decision-making task, wherein participants must make a choice between high- and low-risk options determined by the ratio of blue or red colored boxes potentially hiding a single token; the higher-risk option being associated with the higher value reward.

B



Two typical displays from the decision-making task are shown below, Figures A and B. The subject is told that the computer has hidden a yellow token inside one of the red or blue boxes arrayed at the top of the screen and that he has to decide whether this token is hidden inside a red box or a blue box. However, this decision involves gambling a certain number of points associated with each choice. In the Figure A and B examples, if the subject chooses red, then he/she gains 30 points if the yellow token is indeed hidden inside a red box, but he/she loses 30 points if the token is hidden inside a blue box. On the other hand, if the subject chooses blue, then he/she gains 70 points if the token is hidden inside a blue box, but loses 70 points if it is hidden inside a red box. The subject is told that there is an equal probability that the token would be hidden inside any of the six boxes.

The subject indicates his decision by touching one of the two square response panels, located at the bottom of the display, containing the associated "stake" written in either red or blue ink. Immediately after a selection, one of the boxes opens to reveal the location of the token, accompanied by either a "You win!" or a "You lose!" message written in large yellow font. If the subject chooses the correct color, the stake associated with that color is added to the total points score; if the subject chooses the wrong color, the same stake is subtracted. No monetary significance is attached to the points accumulated by the end of the task. At the start of each sequence, the subject is given 100 points and instructed to make whatever choices thought necessary to increase this score by as much as possible. It is emphasized that these choices might involve either conservative or risk-taking behavior. The ratio of colored boxes (5:1, 4:2, and 3:3) and the balance between the associated rewards

(10 vs 90, 20 vs 80, 30 vs 70, 40 vs 60, and 50 vs 50) vary independently from trial to trial according to a fixed pseudorandom sequence. This sequence ensures that each balance of reward and each ratio of colored boxes co-occurs an equal number of times, with the restriction that on all trials with an unequal ratio of red and blue boxes (i.e., 5:1 or 4:2), the larger reward is always associated with the least likely outcome (i.e., the color with the fewest number of boxes; see Figures A and B), thus capturing the conflict inherent in risk-taking situations.

After the last tDCS day, the participant will be given the same behavior, personality, craving and substance use questionnaires as baseline.

MRI #2: Follow-up MRI scan with the same procedures as baseline will be collected. Total participation time for MRI #2 will be about 3 hours.

4. Optional Procedures

Optional Ecological Momentary Assessment (EMA) self-report surveys. We will gather information related to whether or not the participant has experienced: craving, mood states, stressful events, or has used any alcohol or drugs. The purpose of adding optional daily EMA surveys is to obtain a more granular picture of the timing of events leading to a return to alcohol or drug use following treatment. Participants will have the option to fill out the EMA survey both (i) at each visit with research staff while they are in the treatment program if time allows (once for each visit) and (ii) for the 30 days following their residential addiction treatment completion (up to three daily surveys spaced out throughout the day). Surveys will take about five minutes to complete and will be completed via a secure internet enabled REDCap survey. Only participants who will have a cell phone that receives text messages after discharge from the addiction treatment program will be able to opt in the EMA procedure.

During visits with our research staff while staying in the Lodging Plus treatment program. EMA surveys (up to one per day) will be completed on a computer via REDCap. REDCap version of the paper survey in ETHOS may appear different because of formatting within REDCap. Study staff will be available at each of these appointments to answer questions participants have about the EMA survey. Participants will be compensated $1 for each

EMA completed. Participants will only complete the EMA surveys if time allows while in the treatment program.

After discharge from Lodging Plus, participants will receive text messages for 30 days with an embedded link to complete a REDCap survey assessing mood, substance use/urges, and use of coping skills. Participants will receive a text message at 9am, 2pm, and 7pm including the embedded link to the REDCap survey. The survey will be open until midnight that day and participants will receive reminders every 1.5 hours or until it is complete. Daily reminders will stop at 8:30pm in the evening (or earlier if completed). Participants will be compensated $1 for each survey completed. Payment will be given weekly and these payments will be processed on the business day following each 7-day window. At each weekly payment, participants will get a $5 bonus if they have completed at least 2 EMA assessments per day in the past week.

Text messages will be generated through the REDCap and Twilio integration with all data stored in REDCap's secure server. Data will be entered directly into the REDCap survey and REDCap ensures that SMS transcriptions are not stored in Twilio servers, but are shortly removed after completing for security reasons. REDCap version of the paper survey in ETHOS may appear different because of formatting within REDCap.

During the first week of the EMA procedure, study staff will monitor completion rates and may contact a participant if two days in a row are missed. Participants will be informed that EMA data is not being monitored and will be provided mental health resources at the end of every survey. Once a participant completes a survey, they will not be able to open it again.

Optional Wearable Device. To collect objective data about sleep, activity and other physiology information that may affect treatment outcome, we will use a consumer wearable device, the Garmin VivoSmart4 device. This device is worn on the wrist and is equipped with an accelerometer, an optical heart rate monitor, barometric altimeter, ambient light sensor, and a blood oxygenation saturation monitor. The device provides measures on sleep, physical activity, heart rate (every sec), and stress level. If the participant agrees to this optional portion, they will install the Garmin Connect App on their mobile device with a Garmin Connect account and then the **participant authorizes Garmin to transfer data directly to our**

secured HST-maintained UMN server. Garmin Connect App will connect with the VivoSmart4 device at least once a day to pull data to the GarminConnect server. Garmin then pushes the data to the UMN server. This will allow us to monitor that data is being received and that the device is being charged. Participants who agree to this optional portion will wear the device after recruitment and during the complete 8-month follow-up period of this study. The participant will be paid $80 for wearing the device during the 8-month follow-up period. Besides the upfront App installation and authorizing data sharing, there is no additional burden to the participant. All data stored in the HST-maintained UMN server will be secured, will only be accessible to IRB-approved research staff via password, and will be kept for a total of 6 years. At the end of the 8-month follow-up period the participant will have the choice of returning the wearable device or keeping it for personal use. Research staff will no longer access information collected from the wearable device after the 8-month follow-up period is over.

Optional Genetic Sampling Procedure. All participants will be given the option to provide one saliva sample for genetic analyses. This sample may be collected at any point during participation of the study. A study staff member will provide the participant with written step-by-step instructions for the collection of a saliva sample using the Oragene DISCOVER saliva self-collection kit (DNA Genotek, Ottawa, ON, Canada, Catalog number OGR-500) and ask the participant to not eat, drink, smoke or chew gum for 30 minutes before giving a saliva sample. The total amount of saliva collected is approximately 2 milliliters (about half a teaspoon) and will take approximately 5 minutes to complete.

Nucleic Acid (DNA) Extraction:

Collected samples will be stored in the laboratory of Dr. Jeffrey R. Bishop at the University of Minnesota (516 Delaware Street S.E. Phillips-Wangensteen Building room B150 Minneapolis, MN 55455). Saliva samples will be processed for DNA using the prepIT extraction kit following the manufacturer's standard protocol (DNA Genotek, Ottawa, ON, Canada, catalog number PT-L2P-5). Extracted DNA will be quantified by the Quant-iT™ PicoGreen™ dsDNA Assay Kit (Invitrogen, Waltham, MA USA, Catalog number P7589) using the Synergy HTX multi-mode plate reader (BioTek Instruments, Winooski, VT, USA).

Genetic analyses:

DNA extracted from saliva specimens will be standardized to a working concentration of 10-25ng/l prior to analyses. Targeted gene variants will be genotyped using TaqMan SNP Genotyping assays and the Applied Biosystems 7500 Real Time PCR system (Applied Biosystems, Foster City, CA, USA), Restriction Fragment Length Polymorphism (RFLP) performed by fragment analysis on the 3730 Genetic Analyzer (Applied Biosystems), or multiplexed genotyping assays performed on the MassARRAY System (Agena Bioscience) at the University of Minnesota Genomics Core facility (UMGC). Genome-wide scale genotyping will be performed using microarray or sequencing techniques in consultation with the University of Minnesota Genomics Core (UMGC) For methylation detection studies, DNA extracted from saliva specimens will be bisulfite-converted using the EZ DNA Methylation Kit (Zymo Research, Irvine, CA, USA). Bisulfite-modified DNA will be PCR-amplified using primers designed to cover target gene regions for CpG site DNA methylation detection, and sequenced using the Illumina MiSeq system following a standardized protocol at the University of Minnesota Genomics Core facility (UMGC). Genome-wide methylation assessments will be performed using the Infinium MethylationEPIC BeadChip Kit (Illumina) (or comparable alternative) which interrogates over 850,000 methylation sites quantitatively across the genome at single-nucleotide resolution.

Optional computerized decision-making task. Participants will be given the option of completing a novel computerized task that measures decision-making in the context of the neuroeconomics of addiction, the Websurf task. The Web-Surf Task provides a rich behavioral economics data space to explore complex variables that capture multiple aspects of reward valuation and decision-making processes (Sweis et al 2018; Abram et al 2016; Abram et al 2019a; Abram et al 2019b). During this task, participants will be asked to make a series of economic choices on a computer for ~ 30 minutes simulating the experience of surfing the web for entertaining video clips. The participant will be paid $20 for completing this task. The task can be completed at any visit (remote or in-person) while in Lodging Plus, and/or at any in-person follow-up timepoint. This data may be collected at any point (as many as 3 times) during participation of the study. All data collected using this task will be encrypted and stored on box.umn.edu or on an AHC-

IS maintained server (cnc2.med.umn.edu) that is secured and accessible only via password to research staff.

5. Follow-Up: TELEPHONE FOLLOW-UP: Monthly follow-up phone interviews, for which timing may vary depending on subject availability, will be conducted until the 3rd in-person (or remote) follow-up visit is completed to query relapse status. We will ask the participant to provide the phone number of a good friend or relative who will know the participant's whereabouts to help us re-contact the participant if needed. IN PERSON (OR REMOTE) FOLLOW-UP: The participant will be asked to complete follow-up assessments about 1, 4 and 8 months later (in person or remotely), with the actual date of each timepoint varying depending on participant availability. The participant will be given the option to complete these follow-up assessments over the phone and follow-up questionnaires through RedCap. Follow-up timepoints may be conducted up to 3 months after each timepoint to maximize scheduling flexibility. At the first follow-up timepoint, the participant will undergo a follow-up MRI scan with the same procedures as the baseline scan. At all 3 in-person (or remote) follow-up visits, the participant will complete the same assessments and fill out the same behavior, personality and substance use questionnaires as baseline. At any of the in-person follow-up visits, research staff may test participants for recent alcohol use using a Breathalyzer. Participants will be informed of alcohol level, but will not be excluded from the study if test shows recent alcohol use. If Breathalyzer shows alcohol level of > 0.08%, participant will be asked to reschedule visit. At the first in-person timepoint, which will happen approximately 1 month after the post-intervention MRI, will be about 3 hours. Because of the length, participants will have the choice to complete the scan and questionnaire/assessments on separate days. The second and third follow-up timepoints will be about 1.5 hours each. MISSED VISITS: In the case that a participant misses a telephone or in-person follow-up assessment, research staff will attempt to collect as much missing data as possible at the next contact with the participant.

6. Individually Identifiable Health Information: Participants will be probed for personal information during the interviewing process. As noted in the consent form, participants will be told that all diagnostic and other sensitive raw data will be kept in a locked file and available only to authorized investigators involved in this study.

Trained research staff will be instructed to keep the content of the records confidential. During the initial consent process subjects will be told that they have the right to refuse to answer questions; however, this may affect whether they continue in the study. At all points in the study subjects will be warned at the beginning of procedures which involve the disclosure of personal and sensitive information. These warnings will occur in the introductory comments of interviews or in the instructions of questionnaires and surveys.

Only research staff will have access to subject information. Data contained on paper records and computer files will not include names or other identifying information of subjects. Records containing identifying information will be stored in a private research office in a locked file cabinet and be accessible only by the principal investigator and the study coordinator. The study coordinator or the principal investigator will review and remind research staff of this guideline on a regular basis. Paper and electronic records will be kept for 3 years or longer. Paper records not under use will be stored in locked file cabinets in a private research space. Any identifying information on magnetic or optical media will be stored in a similar manner or be password protected. The password for accessing this information will be available to only select staff that need access to the information to conduct their research duties. All other data will not contain identifying information. All other data will be stored on encrypted magnetic or optical media that is secured or on computer systems accessible only by research staff and computer system administrators via password. There is a slight possibility that data (without identifiers) will be requested by reviewers and other scientists when study data is presented to the scientific community.

Individuals will complete a screening questionnaire for contraindications of MRI scanning. Any affirmative responses on the questionnaire will result in an interview regarding the possible contraindication. An attempt will be made to secure any records of the nature of the possible contraindication and this information will be reviewed by the PI and CMRR staff at the University of Minnesota. A determination will be made regarding the level of risk to the subject and whether they are approved for scanning. If approved for scanning by professionals, all risks to the subject

will be conveyed to him or her so they can deliberate as to whether or not they want to complete the procedure. Any concerns from the review committee will be conveyed to the participant at that time. If the subject has certain problematic iron or steel implants in their body that cannot be removed, the subject may not have the scan and will be excluded from that part of the study.

There are no known risks to humans due to the static magnetic field. Since the risks to fetuses are unknown, pregnant women are excluded from the study. Female subjects in child-bearing years will be informed that their consent to participate indicates that they are willing to complete a urine pregnancy test to demonstrate that they are not pregnant. Subjects, operators, and guests are carefully screened prior to entering the magnetic environment, and frequently reminded of the potential danger of introducing magnetic objects to the controlled area. Subjects are carefully screened and excluded from the study if they have any implanted devices. Subjects are always accompanied when near the magnet, and reminded to move slowly and carefully as they enter and leave the magnet.

The risk of tissue damage by energy emitted by the MRI device is controlled by compliance with FDA guidelines for commercial MRI devices. Safety devices are in place so that the magnet will cease to operate should any parameters begin to exceed their preset safety limits. The risk of peripheral nerve stimulation by dB/dt is limited by safety devices. The noise levels generated by each scan are monitored to ensure adherence to guidelines. In addition, subjects are provided with earplugs and secondary protection (foam covering or headphones) to increase comfort during the scan.

All information obtained from the subject will be strictly for research purposes. Our procedures for obtaining this information will conform to HIPAA policies.

7. Use of radiation*: N/A*
8. Use of Center for Magnetic Resonance Research*:* This study has CMRR (PARS) Project Application Review System (application # 4528)

1. Data and Specimen Banking

1. Storage and Access: Only research staff will have access to subject information. Records containing identifying information will be stored in a private research office in a locked file cabinet and be accessible only by the principal investigator and the study coordinator. The study coordinator or the principal investigator will review and remind research staff of this guideline on a regular basis. Paper and electronic records will be kept for 3 years or longer. Paper records not under use will be stored in locked file cabinets in a private research space. Any identifying information on magnetic or optical media will be stored in a similar manner or be password protected. The password for accessing this information will be available to only select staff that need access to the information to conduct their research duties. All other data will not contain identifying information. All other data will be stored on encrypted magnetic or optical media that is secured or on computer systems accessible only by research staff and computer system administrators via password. There is a slight possibility that data (without identifiers) will be requested by reviewers and other scientists when study data is presented to the scientific community.

   To comply with retention requirements, records including HIPAA and consent forms will be retained for at least six years after completion of the research.

   All biological specimens for genetic analyses collected through this protocol will be stored in the laboratory of Dr. Jeffrey R. Bishop at the University of Minnesota (516 Delaware Street S.E. Phillips-Wangensteen Building room B150 Minneapolis, MN 55455). All specimens will be labeled and stored with a study specimen number, not with any personal or protected health information.

- Data: All diagnostic and other sensitive data will be kept in a locked file and be available only to authorized investigators involved in this study. Identifiers will include name, birthdate, address, and telephone numbers. The PI will keep the data file containing the link between subject number and identity. This will be kept in a password-protected computer file and also in printed form in a locked file cabinet. Research staff will have access to the identifiers only after a subject has agreed to participate in the study. They will use this information only for making contact to schedule visits, etc.

COVID19: To be able to work remotely during the COVID19 crisis, research staff will take subject material home.

- *Subject material will be kept behind two locked doors.*

- *When transporting equipment and documents, employees will take the same precautions as they would when transporting any kind of extremely valuable item. The items should be kept out of sight in a closed bag and will not be left unattended at any time. The research staff will go straight home without any stops, during transportation, the items will be locked securely and out of sight in the trunk of their car before they stop.*
- *While the work items are in the research staff's home, research staff will take care that other people in their home are not able to view any confidential information. Papers with confidential or sensitive information will be kept out of sight of other people in their home.*
- *Items will be returned to the University worksite when employees are able to return. Items will not be left at home indefinitely or destroyed/discarded at home.*
- *Any loss or theft of PHI or University owned devices will be reported immediately to the employee's supervisor and privacy@umn.edu.*

2. Genetic data may be banked for future studies. Participants will choose on the consent form whether or not they wish for their specimens to be banked for future studies.

3. If a participant is found to be eligible for this study and completes the consent process for this study, all information provided at the CAR screening appointment will be made available to us via REDCap access.

4. Release/Sharing: The data collected may represent a unique resource for some investigators. Following HHS/CDC (Department of Health and Human Services/Centers for Disease Control and Prevention) policy, we will make the de-identified data available to interested investigators who contact us for access to the data. As the proposed work is a clinical trial, the most appropriate database for our collected data appears to be clinicaltrials.gov. The investigator, co-investigator, and research staff will permit trial-related monitoring, audits, IRB/IEC(s) review and regulatory inspection(s) by providing direct access to source data/documentation.

7. Sharing of Results with Participants

1. The consent form states that the benefits to the participants as: "There is no direct benefit to you to participate in this study. Learning more about brain function in psychiatric disorders could aid in directing patient treatment in the future". No results are shared with participants.
2. Should participants be interested in up to three screenshots of their MRI images for souvenir purposes, they must sign a release of information authorizing us to send these photos by mail or through the University of Minnesota's preferred encrypted email service. No identifying details will be in the subject line or other non-encrypted text areas.

8. Study Duration

1. *Describe:*
    1. The anticipated duration an individual participant's participation in the study is ~8 months since recruitment with up to 4-month later depending on participant availability for follow-ups.
    2. The duration anticipated to enroll all study participants: Anticipated end date Fall 2022.
    3. The duration anticipated to complete all study procedures and data analysis: Anticipated end date Winter 2022.

1. Study Population

1. Inclusion Criteria: Abstinent individuals (18-65 years old; ~2 weeks of abstinence) who meet DSM-V criteria for alcohol use disorder (AUD) will be recruited from the Lodging Plus Program, part of the University of Minnesota Medical Center. This 28-day program provides a supervised environment to treat alcoholism in which patients receive random drug/ alcohol screenings daily. Lodging Plus has 50 beds and admits an average of 20 patients per week and 59% of patients admitted have a diagnosis of alcohol use disorder. Inclusion criteria: (i) ability to provide written consent and comply with study procedures; (ii) meet the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) diagnostic criteria for AUD. Subjects may have current comorbid drug use, but their primary substance use disorder diagnosis needs to be based on alcohol use. Subjects must have the intention to remain in the Lodging Plus program until the end of the intervention portion of the study. Vulnerable populations will not be included.
2. Exclusion Criteria: (i) Any medical condition or treatment with neurological sequelae (i.e. stroke, tumor, loss of consciousness>30 min, HIV); (ii) a head

injury resulting in a skull fracture or a loss of consciousness exceeding 30 minutes (i.e., moderate or severe TBI); (iii) any contraindications for tDCS or MRI scanning (tDCS contraindication: history of seizures; MRI contraindications; metal implants, pacemakers or any other implanted electrical device, injury with metal, braces, dental implants, non-removable body piercings, pregnancy, breathing or moving disorder); (iv) any primary psychotic disorder (e.g. schizophrenia, schizoaffective disorder). Participants with other treated and stable psychiatric disorders will be included ; (v) presence of a condition that would render study measures difficult or impossible to administer or interpret; (vi) age outside the range of 18 to 65; (vii) primary current substance use disorder diagnosis on a substance other than alcohol except for caffeine or nicotine; (viii) clinical evidence for Wernicke-Korsakoff syndrome; (ix) left handedness, (x) entrance to the treatment program under a court mandate. Nicotine use will be recorded.

The study staff person will thoroughly describe the study at the baseline appointment, either in-person or remotely. Then the patient will be given time to read the consent form and ask questions of study staff. If the patient agrees they will sign the consent with the study staff person looking on. Part of the consent involves asking questions of the patient and having him or her record their responses in the Assessment of Informed Consent to ensure they understand the study and that they can terminate participation at any point. To **protect vulnerable populations**, if the patient does not seem to fully understand the nature of the study (including procedures, risks, confidentiality, voluntary nature), they will not be included in the study. They are also informed that study staff may terminate study participation at any point if they are concerned about the patient's welfare or behavior.

3. Screening: Individuals recruited under the CAR registry have undergone a combined screening process, approved as IRB protocol #STUDY00005170. Participants referred to our study are asked if they are still interested in participating. If they agree, the informed consent process starts. After informed consent, individuals will complete a screening questionnaire for contraindications of MRI scanning. Any affirmative responses on the questionnaire will result in an interview regarding the possible contraindication. CMRR staff will need to approve any affirmative response before participant can undergo MRI scanning.

1. Vulnerable Populations

1. Vulnerable Populations:

   ☐ Children
   ☐ Pregnant women/Fetuses/Neonates
   ☐ Prisoners
   X☐ Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, **psychiatric disorders**, neurologic disorders, developmental disorders, and behavioral disorders
   ☐ Approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc.
   ☐ Disadvantaged in the distribution of social goods and services such as income, housing, or healthcare
   ☐ Serious health condition for which there are no satisfactory standard treatments
   ☐ Fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior)
   ☐ Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research
   ☐ Undervalued or disenfranchised social group
   ☐ Members of the military
   ☐ Non-English speakers
   ☐ Those unable to read (illiterate)
   ☐ Employees of the researcher
   ☐ Students of the researcher
   ☐ None of the above

2. *Adults lacking capacity to consent and/or adults with diminished capacity to consent*

   1. Study will recruit abstinent individuals (18-65 years old; ~2 weeks of abstinence) who meet DSM-V criteria for alcohol use disorder (AUD; a psychiatric disorder) will be recruited from the Lodging Plus Program, part of University of Minnesota Medical Center. Potential

participants will self-identify based on response to a flyers posted on IRB approved boards within the treatment program distributed to all incoming patients.

2. Alcohol use disorder is considered a psychiatric disorder (listed in 10.1), capacity to consent will be evaluated thoroughly by research staff as detailed below.

3. Part of the **consent** involves asking questions of the subject and having him or her record their responses in the Assessment of Informed Consent form to ensure they understand the study and that they can terminate participation at any point. Participants are explained the study in detail before giving informed consent and evaluated on their capacity to consent with a form that contains the following items:

    - Participant was given time to review the consent form
    - The Consent document was explained, discussed, and reviewed
    - Study explanation and discussion was completed (check all that apply)
    - The participant's comprehension was assessed to ensure that he/she understands the research and the risks and benefits involved in the study
    - Participant's questions were answered satisfactorily and concerns were addressed
    - Upon completion of conversation participant did Not have any additional questions or concerns
    - The participant has agreed to participate in the study, and has signed and /dated the most current, IRB-approved consent form prior to the start of any study procedures.
    - Written consent was obtained with most recent IRB approved consent form
    - Participant was given a copy of the consent form
    - The original signed and dated consent form was placed in the research record or participant study binder

4. To **protect vulnerable populations**, if the patient does not seem to fully understand the nature of the study (including procedures, risks, confidentiality, voluntary nature), they will not be included

in the study. They are also informed that study staff may terminate study participation at any point if they are concerned about the patient's welfare or behavior.

5. **Importance of knowledge to be gained:** There are increasing data supporting specific cognitive and brain functional connectivity abnormalities in alcohol use disorder. An understanding of whether these specific abnormalities can be modulated with cognitive training and non-invasive brain stimulation interventions will hold significant promise in designing new targeted interventions that can reduce vulnerability to relapse and improve treatment outcome. The knowledge derived from this research will allow us to gather crucial evidence supporting the therapeutic use of interventions targeting both cognitive and underlying neural mechanisms that support alcohol abstinence. The knowledge gained from this study may eventually help guide further research in the area and future studies to improve addiction treatment programs.
6. **Protection against risk:** Trained research staff will be instructed to keep the content of the records confidential. During the initial consent process subjects will be told that they have the right to refuse to answer questions; however, this may affect whether they continue in the study. At all points in the study subjects will be warned at the beginning of procedures which involve the disclosure of personal and sensitive information. These warnings will occur in the introductory comments of interviews or in the instructions of questionnaires and surveys.
7. **Additional safeguards:**
   i. **To protect vulnerable populations**, if the patient does not seem to fully understand the nature of the study (including procedures, risks, confidentiality, voluntary nature), they will not be included in the study. They are also informed that study staff may terminate study participation at any point if they are concerned about the patient's welfare or behavior.
   ii. No neonates, prisoners, individuals who have not attained legal age for consent.

1. Local Number of Participants

1. Local Number of Participants to be Consented: 100

1. Local Recruitment Methods

1. Recruitment Process: Participants recruited under the Consortium of Addiction Research (CAR) registry and referred to this study will be recruited. CAR research staff will give qualifying participants the "1406M51241 Invite," which provides a brief study description, a study appointment time, and a Consent Form to review before their appointment if they are interested in completing the study.
2. If participants cannot make it to the appointment but do wish to learn more about the study, they are instructed to return the note requesting another appointment date. If participants do not show up at the appointment time and no note is returned, research staff will assume they are not interested in the study and will not try to look for them.
3. If participants do show up to their appointment, research staff will give them detailed information about the study. If participants are still interested in participating in the study after learning all details of the study, research staff will ask them if they would like to answer confidential questions to confirm that they qualify to be in the study.
4. If participants do not qualify to be in the study, research staff will thank them for their time. . If participants do qualify to be in the study, research staff will let them know that they do qualify to be in the study and ask them if they are still interested to be in the study. If so, research staff will proceed (e.g. consent, HIPAA, etc).
5. When a subject arrives for their first study appointment they will complete a consent process. A trained and IRB-approved study staff person will carry out the process. The study staff person will describe the study, consent form, and the required signatures if the individual agrees to commence with the study. Then the subject will be given time to read the consent form and ask questions of study staff. If the subject agrees they will sign the consent form with the study staff person looking on. Part of the consent involves asking questions of the subject and having him or her record their responses to ensure they understand the study and that they can terminate participation at any point. They are also informed that study staff may terminate study participation at any point if they are concerned about the subject's welfare or behavior.

6. **Source of Participants**: Only participants recruited under the Consortium of Addiction Research (CAR) will be recruited.
7. Identification of Potential Participants: Only participants recruited under the Consortium of Addiction Research (CAR) and referred to our study by the CAR will be recruited. Participants will **not** be recruited based on information contained in private/protected records (e.g., medical records, student records; note that this also includes participants who will be recruited from the PI's or Co-PI's patient or student population.)
    1. No private/protected records will be used.
    2. Potential participants will self-identify and express their interest after learning about the study through the CAR registry.
    3. No **MEDICAL** records will be used.
    4. HIPAA form states that the participant does agree to have research staff communicate with treatment program staff that they are participating in research so that they know their whereabouts during their break time.
8. Recruitment Materials: Only participants recruited under the Consortium of Addiction Research (CAR) and referred to our study by the CAR will be recruited.
9. Payment: There is no cost for the participant to be in the study. Participant will be compensated at the end of each of each day of participation (8 potential days plus three follow-up timepoints). Participants will be compensated $25 for Baseline questionnaires completed; $25 at the end of the second MRI scan; $10 for tDCS interventions days 1-5; $25 on MRI #2 for questionnaires completed; and $25 for the scan. For the first follow-up timepoint the participant will be compensated with $100 ($50 for the questionnaires/assessment session and $50 for the MRI scan). For the second and third follow-up timepoints, the participant will be compensated with $100. To summarize, if a participant completes all participation days, they can receive up to $450 for participating in this study. Additionally, if participants choose to complete the optional Websurf task (~30 minutes), they will be compensated with $20 for each task completion (Participants can complete this task up to three times during their participation in this study). If participants choose to complete the daily optional Ecological Momentary Assessment survey during their visits while they are in the treatment program, they will receive $1 per completed EMA assessment. (*EMA payment will be given weekly and these payments will be processed*

on the business day following each 7-day window. At each weekly EMA payment during the follow-up period, participants will get a $5 bonus if they have completed at least 2 EMA assessments per day in the past week). If participants choose to complete the wearable device optional portion of the study, they will receive $80. All compensation will be awarded through a reloadable Greenphire ClinCard.
Parking expenses up to $7 will be reimbursed to the participant if they need to pay parking at each in-person follow-up visit.

No Research Experience Points will be awarded.

1. **Withdrawal of Participants**

    1. Withdrawal Circumstances: The prospective participants will be able to discontinue study participation at any time. The participants may choose to discontinue stimulation at any time during the session if experiencing excessive discomfort or side effects. Criteria for discontinuation related to intervention: i) sores at the tDCS administration site; ii) headaches that impair global functioning. If subjects choose to stop their participation, they will be released from the study. To **protect vulnerable populations**, if a patient that was deemed capable of providing consent goes through unforeseeable situations that may affect their capacity to consent, their capacity will be reassessed, and if not deemed capable, they will not be withdrawn from the study. Participants are also informed that study staff may terminate study participation at any point if they are concerned about the patient's welfare or behavior.
    2. Withdrawal Procedures: If participants withdraw from procedures, all their data collected until the withdrawal data will be retained. No new data will be collected from any private/protected record.
    3. Termination Procedures: If at any point research staff is concerned about participant's welfare or behavior, they will notify the participant that their participation in the study needs to terminate because of safety reasons. The participant will be paid for their time as per 12.5 until their last active participation day. Data collected until the termination date will be used and considered incomplete.

1. Risks to Participants

1. Foreseeable Risks: tDCS is considered to be a non-invasive investigational device that involves applying a weak electrical current to the scalp. This device has been labeled as a non-significant risk device by the FDA for investigational purposes. There is currently no evidence of serious side-effects. Mild side-effects that typically resolve upon discontinuing tDCS include light itching under the electrode at the beginning of administration, headache, fatigue, and nausea. The subject may choose to discontinue stimulation at any time during the session if experiencing excessive discomfort or side effects. Although seizures are not a known risk of tDCS intervention (Fregni et al., 2006), anyone with a history or a risk for seizures will be excluded from the study. No other risks related to tDCS are anticipated. To minimize risks regarding tDCS, study staff will be using standards of administration that have been shown as safe in numerous other studies using transcranial direct current stimulation. The length of administration of the current, size of electrode sponges used, and method of applying stimulation are the same as methods of administration that have been demonstrated as safe.

2. The other potential risks pertain to the maintenance of <u>confidentiality</u>. Participants will be probed for personal information during the interviewing process. As noted in the consent form, participants will be told that all diagnostic and other sensitive raw data will be kept in a locked file and available only to authorized investigators involved in this study. To minimize confidentiality risks, as noted in the consent form, all diagnostic and other sensitive raw data will be kept in a locked file and be available only to authorized investigators involved in this study. Genetic and epigenetic information will be for research purposes only and will not be included in participants' medical records. Genetic specimens and data will be labeled with the participant's study ID number and will not contain personally identifying information. Confidentiality is not absolute. Research staff are mandated reporters and are legally required to report suspicion of child or vulnerable adult abuse or neglect to the relevant authorities.

3. <u>MRI risks.</u> Individuals will complete a screening questionnaire for contraindications of MRI scanning. Any affirmative responses on the questionnaire will result in an interview regarding the possible contraindication. An attempt will be made to secure any records of the nature of the possible contraindication and this information will be reviewed by the PI and CMRR staff at the University of Minnesota. A determination

will be made regarding the level of risk to the subject and whether they are approved for scanning. If approved for scanning by professionals, all risks to the subject will be conveyed to him or her so they can deliberate as to whether or not they want to complete the procedure. Any concerns from the review committee will be conveyed to the participant at that time. If the subject has certain problematic iron or steel implants in their body that cannot be removed, the subject may not have the scan and will be excluded from that part of the study.

1. There are no known risks to humans due to the static magnetic field. Subjects, operators, and guests are carefully screened prior to entering the magnetic environment, and frequently reminded of the potential danger of introducing magnetic objects to the controlled area. Subjects are carefully screened and excluded from the study if they have any implanted devices. Subjects are always accompanied when near the magnet, and reminded to move slowly and carefully as they enter and leave the magnet.
2. The risk of tissue damage by energy emitted by the MRI device is controlled by compliance with FDA guidelines for commercial MRI devices. Safety devices are in place so that the magnet will cease to operate should any parameters begin to exceed their preset safety limits. The risk of peripheral nerve stimulation by dB/dt is limited by safety devices. The noise levels generated by each scan are monitored to ensure adherence to guidelines. In addition, subjects are provided with earplugs and secondary protection (foam covering or headphones) to increase comfort during the scan.
3. Reproduction Risks: Since the MRI risks to fetuses are unknown, pregnant women are excluded from the study. Female subjects in child-bearing years will be informed that their consent to participate indicates that they are willing to complete a urine pregnancy test to demonstrate that they are not pregnant.

4. Risks to Others: N/A.

15. Potential Benefits to Participants

1. Potential Benefits: There is no direct benefit to you to participate in this study. Learning more about brain function in psychiatric disorders could aid in directing patient treatment in the future.

16. Data Management

1. Data Analysis Plan: A mixed model analysis of variance will be conducted with between-group measures (sham vs active tDCS) and within-group measures (FC and craving reports before and after cognitive flexibility training and tDCS intervention). This mixed model analysis will examine main effects and interaction effects. To examine the long-term effects of cognitive flexibility training and tDCS, we will conduct a repeated measures analysis using longitudinal data collected monthly for 6 months after intervention completion. A Log-rank (Mantel-Cox) Test (used in Klaus et al 2014) will be conducted to establish the efficacy of cognitive flexibility training and active tDCS vs. cognitive flexibility training and sham tDCS in the time domain.
2. Power Analysis: The study in reference is a pilot study for which a power analysis is not applicable.
3. Data Integrity: The principal investigator and co-investigator will monitor data quality for this study. They will ensure that data are generated, documented (recorded), and reported, in compliance with this protocol, with Good Clinical Practice, and any other applicable regulatory requirements.

17. Confidentiality

1. Data Security: Trained research staff will be instructed to keep the content of the records confidential. During the initial consent process subjects will be told that they have the right to refuse to answer questions; however, this may affect whether they continue in the study. At all points in the study subjects will be warned at the beginning of procedures which involve the disclosure of personal and sensitive information. These warnings will occur in the introductory comments of interviews or in the instructions of questionnaires and surveys.

   Only research staff will have access to subject information. Data contained on paper records and computer files will not include names or other identifying information of subjects. Records containing identifying information will be stored in a private research office in a locked file cabinet and be accessible only by the principal investigator and staff. The study

coordinator or the principal investigator will review and remind research staff of this guideline on a regular basis. Paper and electronic records will be kept for 3 years or longer. Paper records not under use will be stored in locked file cabinets in a private research space. Any identifying information on magnetic or optical media will be stored in a similar manner or be password protected. The password for accessing this information will be available to only select staff that need access to the information to conduct their research duties. All other data will not contain identifying information. All other data will be stored on encrypted magnetic or optical media that is secured or on computer systems accessible only by research staff and computer system administrators via password.

No copy of the consent form or other research study information will be placed in the participants' medical, employment, or educational records.

1. Optional Unencrypted Digital Communication With Participants: Participants have the option to provide informed consent for the study team to contact them using unencrypted email and/or unencrypted text message. This communication would primarily be used for appointment scheduling purposes. Souvenir MRI screenshots will not be sent using unencrypted communication means.

18. Provisions to Monitor the Data to Ensure the Safety of Participants

N/A

19. Provisions to Protect the Privacy Interests of Participants

1. Protecting Privacy: Only research staff will have access to subject information. Data contained on paper records and computer files will not include names or other identifying information of subjects. Records containing identifying information will be stored in a private research office in a locked file cabinet and be accessible only by the principal investigator and the study coordinator. The study coordinator or the principal investigator will review and remind research staff of this guideline on a regular basis. Paper and electronic records will be kept for 3 years or longer. Paper records not under use will be stored in locked file cabinets in a private research space. Any identifying information on magnetic or optical media will be stored in a similar manner or be password protected. The password for accessing this information will be available to only select staff that need

access to the information to conduct their research duties. All other data will not contain identifying information. All other data will be stored on encrypted magnetic or optical media that is secured or on computer systems accessible only by research staff and computer system administrators via password.

2. As part of study interviews, questions may be asked which touch on sensitive or private issues which the subject may feel uncomfortable discussing. Although there is a potential for disclosure of sensitive personal information, every effort will be made to lessen the risk. The subject may refuse to answer any questions they do not wish to answer at any time; however, this may lead to their discontinuation from the study protocol.

3. Access to Participants: Research team will not access any medical records from participants.

1. Compensation for Research-Related Injury

1. Compensation for Research-Related Injury: There is no compensation in the event of research-related injury. The consent form states: "In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner, to you or the participant's insurance company. If you think that you have suffered a research-related injury, please let us know right away."

2. Contract Language: N/A

21.0 In Case of Acute Mental Health

1. If a participant endorses thoughts of suicide (SCID-IV screening), the action(s) taken will depend on the level of risk.

   For low risk, research staff will encourage the participant to speak with their treatment program (e.g. Lodging Plus) therapist and give an IRB approved resource card with the following information:

   - Thoughts of suicide: National Suicide Prevention Lifeline, 1-800-273-8255
   - Feeling like a threat to yourself or others: 911
   - Addiction and mental health services referral: Substance Abuse and Mental Health Services Administration, 1-800-662-4357

For medium risk, research staff will consult with the PI and/or the study clinicians prior to the participant leaving the appointment to determine best steps to take. Recommended steps include continued monitoring, encouraging use of the suicide hotline as needed, and consulting the participant's therapist.

For high risk, research staff will immediately alert the PI and/or study clinicians to ensure proper steps are taken. Research staff will inform treatment staff (e.g. Lodging Plus) directly. If neither is available, research staff will bring the participant to the Fairview-Riverside UMMC Emergency Department for care.

2. If a participant is suffering from active and/or unstable Axis I disorders, suicidal ideation, and/or homicidal ideation mid-study, their participation will be discontinued.

1. Consent Process

1. Consent Process (when consent will be obtained): Consent will take place either in a private room in the Ambulatory Research Center housed in the Department of Psychiatry at the University of Minnesota (in person) or in a private research-designated area within the Lodging Plus addiction treatment program (remotely). Depending on location, consent will be completed in person or remotely (through a video conference). If consent is completed remotely, an eConsent form will be completed in RedCap while using Zoom or a phone call.

   COVID-19 Adaptations: The following modifications to consent procedures may be used to mitigate pandemic-related risks while participating in this study. These modifications may stay in place even after the pandemic-related risks are considered to have diminished:

   - Consent procedures will be completed remotely using REDCap, while also using Zoom or a phone call to communicate to the participant who will be in a private research-designated area within the Lodging Plus addiction treatment program. The physical consent form will be available to the participant at the Lodging Plus addiction treatment program and then a copy with all required emailed to them.
   - The electronic versions of forms in REDCap may be formatted slightly different than the paper versions, due to limited formatting options in REDCap. The content will be the same.

The study research staff will thoroughly describe the study and read the consent form. Then the patient will be given time to read the consent form and ask questions of study staff. If the patient agrees, they will sign the consent with the study staff person looking on. Part of the consent involves asking questions of the patient and having him or her record their responses in the Assessment of Informed Consent form to ensure they understand the study and that they can terminate participation at any point. To **protect vulnerable populations**, if the patient does not seem to fully understand the nature of the study (including procedures, risks, confidentiality, voluntary nature), they will not be included in the study. They are also informed that study staff may terminate study participation at any point if they are concerned about the patient's welfare or behavior.

2. To ensure ongoing consent: After consent is provided and at each intervention day, participants are monitored for any concerns they have about the intervention with the Treatment Side Effect Questionnaire. Participants who agree to continue in the study will sign this questionnaire daily.

3. Waiver or Alteration of Consent Process (when consent will not be obtained): N/A

4. Non-English Speaking Participants: We will not enroll participants who do not speak English.

5. Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age): We will not recruit participants under 18 years of age.

6. Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent: We will record the informed consent process in the "Documentation of the Informed Consent Process" to ensure full understanding of study procedures and voluntary nature. In addition to the informed consent assessment, participants will complete the Montreal Cognitive Assessment (MoCA), which has been modified to be administered remotely (Blind – Version 8.1). This will be administered at the baseline visit after Informed Consent. If a participant has a score of 14 or below (out of 22 possible points), they will not be included in the study because of potential cognitive impairment.

7. Adults Unable to Consent: We will not recruit any individual unable to consent for themselves.

1. Setting

1. Research Sites:
    1. This study has been approved by Fairview after following research approval procedures. Participants will be recruited from Lodging Plus treatment program for addiction, part of the University of Minnesota Medical Center.
    2. Screening, consent, interview, assessments and tDCS intervention will take place either at the Ambulatory Research Center in the Psychiatry Department (2nd floor, same building as Lodging Plus treatment program) *or at a research-dedicated room within the Lodging Plus treatment program*. *These procedures will be done in person or remotely.*
    3. Only brain scans will be conducted at the Center for Magnetic Resonance Research (CMRR).
    4. Biological samples for genetic analyses will be stored and processed at the laboratory of Dr. Jeffrey R. Bishop at the University of Minnesota (516 Delaware Street S.E. Phillips-Wangensteen Building room B150 Minneapolis, MN 55455).

24. Multi-Site Research

N/A

25. Resources Available

1. Resources Available:
    1. To collect complete data for 70 participants, we expect to screen and consent approximately 100 participants with alcohol use disorder. We estimate to have a 25% attrition rate which will yield data collection from 70 participants.
    2. 30% of PIs effort will be dedicated to completing the research.
    3. Facilities:
        i. **Laboratory of Neuropsychiatric Imaging (LNPI; led by Dr. Lim).** Dr. Camchong is part of the LNPI, a multidisciplinary research group that studies the biological underpinnings of neuropsychiatric disorders by combining imaging techniques with neurocognitive assessments and genetics. The facility is a fully equipped and secure research laboratory supported by the UMN Medical with private offices and conference rooms, full computer and telecommunication systems and support, secure entrance and file storage, private research testing rooms, a reception desk and

waiting area for research subjects, and physical space to house multiple research staff and support graduate student research efforts. All of these resources are currently and will continue to be available to the P.I.

ii. **Center for Magnetic Resonance Research (CMRR).** The CMRR is located on the UMN campus. This imaging center was established in 1991 as a result of the rapidly growing and successful in vivo magnetic resonance imaging (MRI). CMRR is an interdepartmental and interdisciplinary research laboratory that provides state-of-the-art instrumentation, expertise, and infrastructure to carry out biomedical research utilizing the unique capabilities provided by high field MRI and MRS methodology. The central aim of the research conducted in CMRR is to non-invasively obtain functional, physiological, and biochemical information in intact biological systems, and use this capability to probe biological processes in health and disease. The CMRR is currently equipped with nine high field magnets for humans with magnetic field strength of 3 Tesla and greater, with the most notable being a 10.5 Tesla/89cm. MRI data (resting, task-evoked and high-resolution structural scans) will be collected using a 32-channel head coil on a Siemens Prisma FIT 3T scanner (Siemens Medical Solutions, Erlangen, Germany). The Prisma was inspired by the success of the Connectome 3T systems, in particular the one-of-a-kind modified Siemens Skyra system that was built specifically for the WU-Minn Human Connectome Project (HCP) consortium (Connectome Skyra). The HCP is from the 16 NIH Institutes and Centers that support the NIH Blueprint for Neuroscience Research. The consortium led by Washington University, University of Minnesota, and Oxford University (the WU-Minn HCP consortium) is comprehensively mapping human brain circuitry in a target number of 1200 healthy adults using cutting-edge methods of non-invasive neuroimaging. The unique features of the Prisma system are based on an integrated system that combines a high strength gradient system with capability of 80 mT/m @ 200 T/m/s (FDA approved mode, but capable of 100 mT/m in research mode), an advanced RF receiver system that provide better signal-to-noise performance, 64 channel receive capability.

Accelerated data collection provides improved signal in resting state networks (Griffanti et al 2014). HCP has developed and supports multiband acquisition sequences for the Prisma, which accelerate data acquisition by a factor of up to 12. These fMRI sequences use MB factor of 8, allowing us to collect 32 slices in 1/8 TR, which is 8 simultaneous slices in one TR.

iii. Biological samples for genetic analyses will be stored and processed at the laboratory of Dr. Jeffrey R. Bishop at the University of Minnesota (516 Delaware Street S.E. Phillips-Wangensteen Building room B150 Minneapolis, MN 55455).

iv. Kelvin O. Lim, MD will be available in case of unanticipated issues.

v. All research staff will undergo protocol training. Only trained research staff will obtain consent.

1. References

Abram S. V., Hanke M., Redish A. D., MacDonald A. W. (2019) Neural signatures underlying deliberation in human foraging decisions. Cognitive, Affective, & Behavioral Neuroscience, 19(6):1492-1508.

Abram S. V., Redish A. D., MacDonald A. W. (2019) "Learning from loss after risk: Dissociating reward pursuit and reward valuation in a naturalistic foraging task" Frontiers in Psychiatry

Abram S. V., Breton Y. A., Schmidt B., Redish A. D., MacDonald III A. W. (2016) "The Web-Surf Task: A translational model of human decision-making" Cognitive, Affective, and Behavioral Neuroscience 16(1):37-50.

Ballard, Kacey, and Brian Knutson. 2009. "Dissociable Neural Representations of Future Reward Magnitude and Delay during Temporal Discounting." *NeuroImage* 45 (1): 143–50.

Boggio, Paulo S., Natasha Sultani, Shirley Fecteau, Lotfi Merabet, Tatiana Mecca, Alvaro Pascual-Leone, Aline Basaglia, and Felipe Fregni. 2008. "Prefrontal Cortex Modulation Using Transcranial DC Stimulation Reduces Alcohol Craving: A Double-Blind, Sham-Controlled Study." *Drug and Alcohol Dependence* 92 (1-3): 55–60.

Camchong, Jazmin, Angus W. Macdonald 3rd, Bryon A. Mueller, Brent Nelson, Sheila Specker, Valerie Slaymaker, and Kelvin O. Lim. 2014. "Changes in Resting Functional Connectivity during Abstinence in Stimulant Use Disorder: A Preliminary Comparison of Relapsers and Abstainers." *Drug and Alcohol*

Dependence 139 (June): 145–51.

Camchong, Jazmin, Andy Stenger, and George Fein. 2013a. "Resting-State Synchrony in Long-Term Abstinent Alcoholics." *Alcoholism, Clinical and Experimental Research* 37 (1): 75–85.

———. 2013b. "Resting-State Synchrony during Early Alcohol Abstinence Can Predict Subsequent Relapse." *Cerebral Cortex* 23 (9): 2086–99.

Camchong, Jazmin, Victor Andrew Stenger, and George Fein. 2013c. "Resting-State Synchrony in Short-Term versus Long-Term Abstinent Alcoholics." *Alcoholism, Clinical and Experimental Research* 37 (5): 794–803.

D'Cruz, A. M., M. E. Ragozzino, M. W. Mosconi, M. N. Pavuluri, and J. A. Sweeney. 2011. "Human Reversal Learning under Conditions of Certain versus Uncertain Outcomes." *NeuroImage* 56 (1): 315–22.

García-García F, Priego-Fernández S, López-Muciño LA, Acosta-Hernández ME, Peña-Escudero C. Increased alcohol consumption in sleep-restricted rats is mediated by delta FosB induction. Alcohol. 2021 Jun;93:63-70. doi: 10.1016/j.alcohol.2021.02.004. Epub 2021 Mar 1. PMID: 33662520.

Gruber, Aaron J., Rifat J. Hussain, and Patricio O'Donnell. 2009. "The Nucleus Accumbens: A Switchboard for Goal-Directed Behaviors." *PloS One* 4 (4): e5062.

Klauss, Jaisa, Leon Cleres Penido Pinheiro, Bruna Lima Silva Merlo, Gerson de Almeida Correia Santos, Felipe Fregni, Michael A. Nitsche, and Ester Miyuki Nakamura-Palacios. 2014. "A Randomized Controlled Trial of Targeted Prefrontal Cortex Modulation with tDCS in Patients with Alcohol Dependence." *The International Journal of Neuropsychopharmacology / Official Scientific Journal of the Collegium Internationale Neuropsychopharmacologicum* 17 (11): 1793–1803.

Lang, N., H. R. Siebner, N. S. Ward, L. Lee, M. A. Nitsche, W. Paulus, J. C. Rothwell, R. N. Lemon, and R. S. Frackowiak. 2005. "How Does Transcranial DC Stimulation of the Primary Motor Cortex Alter Regional Neuronal Activity in the Human Brain?" *The European Journal of Neuroscience* 22 (2): 495–504.

Monte-Silva, Katia, Min-Fang Kuo, Silvia Hessenthaler, Shane Fresnoza, David Liebetanz, Walter Paulus, and Michael A. Nitsche. 2013. "Induction of Late LTP-like Plasticity in the Human Motor Cortex by Repeated Non-Invasive Brain Stimulation." *Brain Stimulation* 6 (3): 424–32.

Nitsche, M. A., L. G. Cohen, E. M. Wassermann, A. Priori, N. Lang, A. Antal, W. Paulus, et al. 2008. "Transcranial Direct Current Stimulation: State of the Art 2008." *Brain Stimulation* 1 (3): 206–23.

Nitsche, M. A., S. Doemkes, T. Karakose, A. Antal, D. Liebetanz, N. Lang, F. Tergau, and W. Paulus. 2007. "Shaping the Effects of Transcranial Direct Current Stimulation of the Human Motor Cortex." *Journal of Neurophysiology* 97 (4): 3109–17.

Poreisz, Csaba, Klára Boros, Andrea Antal, and Walter Paulus. 2007. "Safety Aspects of Transcranial Direct Current Stimulation Concerning Healthy Subjects and Patients." *Brain Research Bulletin* 72 (4-6): 208–14.

Sweis B.M., Redish AD, Thomas MJ. 2018. "Prolonged abstinence from cocaine or morphine disrupts separable valuations during decision conflict" *Nat Commun*. 9(1):2521.

Zhang R, Tomasi D, Manza P, Shokri-Kojori E, Demiral SB, Feldman DE, Kroll DS, Biesecker CL, McPherson KL, Wang GJ, Wiers CE, Volkow ND. Sleep disturbances are associated with cortical and subcortical atrophy in alcohol use disorder. Transl Psychiatry. 2021 Aug 16;11(1):428. doi: 10.1038/s41398-021-01534-0. PMID: 34400604; PMCID: PMC8368207.