Frontal-Striatal Reward Circuit Neuromodulation and Alcohol Self-Administration

Principal Investigator:
Susan Conroy, MD
Department of Psychiatry
IU School of Medicine

Co-Investigator:
Michael Francis, MD
Department of Psychiatry
IU School of Medicine

Co-Investigator:
Martin Plawecki, MD, PhD
Department of Psychiatry
IU School of Medicine

NCT04971681

Table of Contents:

1.0 Background and Rationale

Alcohol Use Disorders (AUDs) are among the most common and undertreated psychiatric conditions in developed countries[1], contributing to 4% of the global burden of disease[2]. AUDs occur in over 16.6 million adults in the United States alone[3]. Alcohol consumption has been causally linked to 60 different diseases[4], and is the leading contributor to premature death and disability among ages 15-49[5] via associations with injuries, alcoholic liver disease, heart disease and stroke, cancers, and gastrointestinal disease[2,4]. AUDs also represent an important societal concern, contributing to an estimated economic burden of $223.5 billion in the United States[6]. With fewer than 10% receiving treatment[7] and high rates of relapse in those that do,[8-11] there is a clear need for novel and effective therapeutic interventions.

Prevailing views on addiction suggest that altered function of neural reward circuitry is a key mechanism underlying the development of alcohol dependence[12], as abnormal limbic drive may result in increased impulsivity and salience to alcohol related cues[13,14]. Research has demonstrated that aberrant hyperactivation within fronto-striatal reward (FSR) circuitry is an important biologic correlate of AUD onset, progression, and severity[13]. The medial prefrontal cortex (mPFC) is a central component of the valuation and reward system of the brain[15-22]. mPFC activation has been associated with saliency and attribution as well as enhanced motivation to use alcohol[14,23,24]. Research has consistently demonstrated that alcohol cue exposure evokes increased functional activation within the mPFC[13,25]. Furthermore, this increased activation may predict transition to heavy drinking and is positively correlated with AUD severity[26] as well as craving and relapse[14,25,27-29]. In light of the role that disordered mPFC function plays in AUD, investigators have proposed that this may represent an important target for novel therapeutic interventions. Recent work have demonstrated that transcranial magnetic stimulation (TMS) is a mechanism by which investigators can modulate function of the mPFC and affect AUD relevant phenomenon such as craving[30].

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive neuromodulation technique that received FDA clearance for use in treatment resistant major depressive disorder in 2008 and has become commonly used in clinical practice. rTMS utilizes the application of a repetitively pulsed magnetic field over the scalp to induce an electric field within a discrete area of the cerebral cortex. This electric field results in altered ion flow across the neuronal cellular membrane and ultimately changes in neuronal polarization[31]. rTMS modulates cortical activation depending on the stimulation parameters used[31,32]. Physiological studies have provided evidence that low-frequency (LF) rTMS, or rTMS delivered at a frequency of 1 Hz or less, produces an inhibitory effect on local cortical excitability. Studies have also demonstrated that LF rTMS can decrease functional connectivity between separate but related cortical structures[33-36]. Work by our group and others have shown that rTMS is a viable tool for investigating the neural correlates of psychiatric illness as well as a potential therapeutic option for these same conditions[30,33,37]. Our group has significant experience in rTMS investigations utilizing the treatment paradigm in this protocol, having completed a pilot-study investigating rTMS as a therapeutic in schizophrenia. We are currently conducting

two additional studies of rTMS as a probe of the role that neural circuit aberrations play in cognitive impairment in early-phase psychosis (EPP)[37]. Additionally, Dr. Colleen Hanlon, a consultant on this study, is a nationally recognized expert and pioneer in the use of rTMS in studies of substance use disorder. Dr. Hanlon's work has focused on rTMS as a probe of frontal-striatal reward (FSR) circuit modulation and its effects on craving[13,30]. However, though craving is an important phenomenon in substance use disorders, it is neither necessary nor sufficient in treatment of the conditions.

This pilot study intends to address the **critical unmet need** to develop novel treatments for AUD, such as rTMS, that directly impact *drinking behavior*. Binge drinking and high intensity drinking, or consumption meeting *at least* binge criteria, is a high-risk alcohol self-administration (ASA) pattern associated with the binge-intoxication stage of AUD and the rewarding effects of alcohol. We propose to quantify the impact of mPFC rTMS on ASA using our novel "rate-control" paradigm. The rate control paradigm allows subjects to determine how quickly their breath alcohol concentration (BrAC) will change (increase, decrease, or stay the same) over the next 3-5 minute epoch, at the end of which brief computer-assisted assay of craving for alcohol and subjective response attributed to alcohol's effect on stimulation, sedation, liking and well-being in a manner comparable to the Brief BAES[38,39]. Each assay requires less than 20 seconds to complete and will be administered during the last ~0.5 minutes of alcohol delivery but before selection of the next rate of exposure. The ensemble provides detailed self-administered time course of alcohol exposure and corresponding time-stamped series of quantified perceptions for analysis. This approach has demonstrated sensitivity in associating self-reported high intensity drinking and the time until a binge alcohol exposure of 80 mg/dL (Figure 1).

Our premise is that clinically impactful neuromodulation should change ASA. Coupling rTMS to a laboratory-assessed ASA paradigm could document *causal* changes in drinking behavior attributable to modulation of specific neural circuits. The ***goal of this project*** is to generate preliminary data supporting our ***central hypothesis*** - rTMS targeting to the mPFC, a primary cortical input to the FSR circuit, will decrease the rate of alcohol self-administration.

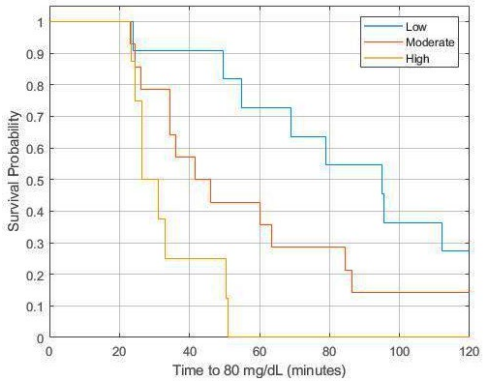

Figure 1: High Intensity Drinking Groups and Time to 80 mg/dL. N=33 subjects completing the rate control ASA paradigm. Groups are defined by multiples of self-reported binge intensity for display. Time to 80 mg/dL is sensitive to drinking intensity (p = 0.0035). Report in preparation.

2.0 Objective(s)

Primary Objective

The **primary objective** of this pilot study is to determine the effect size of the relationship between mPFC LF rTMS and a change in the time required to self-administer at least a binge-level alcohol exposure of 80 mg/dL. We hypothesize that,

compared to sham stimulation, mPFC LF rTMS will slow the time to a breath alcohol concentration (BrAC) of 80 mg/dL.

Secondary Objective
The **secondary objective** is to explore the effects of mPFC rTMS on subjective responses to alcohol, time until a high intensity drinking exposure, and, during a 4-week follow-up period, self-reported alcohol consumption patterns.

3.0 Outcome Measures/Endpoints

Primary Outcome Measures
The primary outcome measure will be the amount of time subjects take to self-administer enough alcohol to raise their BrAC to 80 mg/dL in the rTMS treatment condition compared to the rTMS sham condition during the two alcohol self-administration sessions.

Secondary Outcome Measures
The secondary outcome measures will be the subjective responses to alcohol during the self-administration sessions and the amount of daily alcohol consumption as measured by Time Line Follow Back (TLFB) during the 4-week follow-up period.

4.0 Eligibility Criteria

Inclusion criteria:

1. Overtly healthy men and women aged 21 – 35
2. Able to give informed consent
3. Able to understand/complete questionnaires and procedures in English
4. Willing and able to adhere to the study schedule
5. At least 2 binge drinking events (at least 4 or 5 drinks on a drinking day for women and men respectively over the last 5 weeks, unless determined by study physicians that drinking history meets study objectives
6. Have venous access sufficient to allow blood sampling

Exclusion criteria:

1. Pregnant or breast-feeding
2. Desire to be treated for any substance use disorder or court ordered to not drink alcohol
3. Medical disorders or other conditions, such as lifetime history of a seizure, including history of ECT but excluding febrile seizures and those induced by substance withdrawal, that may influence study outcome or subject safety
4. First degree relative with idiopathic epilepsy or other seizure disorder
5. DSM 5 Disorders (non-AUD) or current/history of neurological disease of cerebral origin, or head injury with > 20 min loss of consciousness, if determined by the study physicians to affect subject safety or data integrity

6. Positive urine drug screen for amphetamines/ methamphetamines, barbiturates, benzodiazepines, cocaine, opiates, or phencyclidine if determined by the study physicians to adversely affect subject safety or data integrity
7. Medications (past 30 days) that could influence subject data/subject safety (e.g. antidepressants, antipsychotics, benzodiazepines, etc.) as determined by study physicians
8. Positive BrAC reading at beginning of any study session
9. Actively suicidal (for example, any suicide attempts within the past 3 months or any current suicidal intent, including a plan) or are at serious suicidal risk, by clinical judgment of the study physicians
10. Any condition for which the study physicians determine it is unsafe or not prudent to enroll a subject

5.0 Study Design

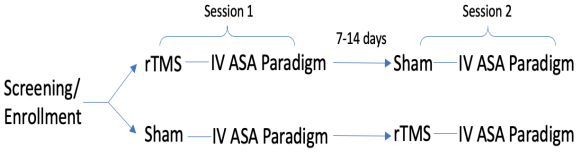

Figure 2: Study Design for rTMS Modulation of ASA

This will be a single site randomized, 2-session, within-subject cross-over design pilot study (Figure 2). 20 enrolled (of 30 consented) subjects reporting varying levels of binge and high intensity drinking, defined as at least 2 episodes of drinking 4 (for women) or 5 (for men) drinks on an occasion over the last 5 weeks, (unless determined by PI that drinking history meets study objectives), will be enrolled. Subjects will be randomized to undergo one session of rTMS or sham immediately followed by our rate control IV ASA paradigm. Subjects will then return 7-14 days later and undergo the same sequence of events with the opposite intervention (i.e. rTMS or sham) from session 1.

Duration of Treatment
Subjects will complete two stimulation (LF and sham) and IV ASA paradigm sessions over two to three weeks, with one session occurring every 7-14 days. Previous work has demonstrated that a single session of rTMS is sufficient to modulate AUD related behavior[30].

Clinical Research Sites
rTMS treatments and alcohol challenge sessions and lab visits will take place at the Indiana Clinical Research Center, in either Goodman Hall at the Neuroscience Center and/or in the Neural Systems Laboratory at Indiana University Hospital.

Dr. Conroy is the Medical Director of the IU Neurostimulation Program and is a psychiatrist in the IU Department of Psychiatry. Dr. Conroy and associated research personnel will conduct TMS procedures, help with subject transportation and monitoring, and assist with gathering demographic data. The program has 1 research psychiatrist and 1 research coordinator.

Dr. Francis is the Research Medical Director of the IU Psychotic Disorders Program (IUPDP). The IUPDP is located in Indianapolis, IN. and is part of the IU Department of Psychiatry. IUPDP research personnel will conduct TMS procedures, help with subject transportation and monitoring, and assist with gathering demographic data. The IUPDP has 2 research psychiatrists, a fully dedicated study manager, a fully dedicated study coordinator, one dedicated subject recruiter, and two raters (1 PhD, 1 Masters level) who have been trained and have extensive experience in conducting the assessments and cognitive tests used as outcome measures.

Dr. Plawecki is the Director of the Neural Systems Lab (NSL) in Indianapolis and is also a psychiatrist with the IU Department of Psychiatry. Dr. Plawecki and the NSL will manage the day-to-day activities of conducting the trial, consenting and screening subjects, the alcohol self-administration portion of the study, and subject monitoring (in conjunction with the CRC). The NSL has 1 research psychiatrist, 1 research scientist, and four technicians with extensive training and experience conducting alcohol challenge experiments.

6.0 Enrollment/Randomization

Subjects will be recruited through the NSL registry, and self-referrals through advertisement and word-of-mouth. Subjects that meet inclusion/exclusion criteria will be enrolled at the discretion of the Principle investigator and randomly assigned to one of the two schedules (rTMS first, or Sham first).

7.0 Study Procedures

Recruitment and Screening

Subjects from the NSL registry will be contacted by phone or email, while other subjects will contact the study phone line or email after learning about the study from print, electronic advertising, or word of mouth. Subjects who meet basic criteria will either 1) be invited for an in-person interview when they will consent to participate in the study, or 2) arrange for a remote interview where they will consent to participate and complete interview measures electronically and converse with study staff via IU Zoom Health or similar secure platform. Subjects will complete some or all of the following measures, at the discretion of the principal investigators:

<u>Self-Report Measures:</u>

- The Alcohol Use Disorders Identification Test (AUDIT)
- The Family History of Alcoholism Module of the SSAGA
- The UPPS-P Impulsive Behaviors Scale measures impulsivity traits
- Self-Rating of Effect of Alcohol assessing retrospective sensitivity to the subjective response to alcohol (SRE).
- Short Inventory of Problems – Revised (SIP-r)
- Medical History (including menstrual phase for women)

- Nicotine History Measure
- Penn Alcohol Craving Scale (PACS)
- Subjective Response Questions
- Five Factor Model Form
- Drinking Refusal Self-Efficacy Questionnaire-Revised (DRSEQ-R)
- Alcohol Expectancy Questionnaire (Full and Brief versions)
- Drinking Motives Questionnaire (Full and Brief versions)
- COVID-19 Questionnaire

Interviews:
- The Semi-structured Assessment for the Genetics of Alcoholism – II, Alcohol

Diary Measures:
- Timeline Follow-back (TLFB) modified to assess for one-month recall of alcohol, tobacco, drug, and cannabis use

Screening tools:
- Clinical Institute Withdrawal Assessment for Alcohol Scale (CIWA)
- GAD-7 and GAD-2 Generalized Anxiety Disorder Assessment, 7 and 2 item scales assessing anxiety symptoms over the last 2 weeks
- PHQ-9 and PHQ-2 Patient Health Questionnaire, 9 and 2 item scales assessing depressive symptoms over the last 2 weeks
- Urine pregnancy and drug screen (UPS, UDS, including EtG urine screen at discretion of study physicians)
- Breath Alcohol Concentration Measurement
- Liver function assessment
- TMS Screening Checklist

Miscellaneous:
- Contact Form and Follow-up questionnaires

Note: Screening tool score above the cutoff or concerning patterns as determined by the study technician may prompt additional testing from the set of measures completed at the interview (For example, PHQ-2 score greater than or equal to the cutoff of 3 will prompt completion of the PHQ-9.).

Subjects that complete part of the interview remotely and appear to meet study criteria will be asked to visit the ICRC for a short visit where they will provide a blood sample, urine, and be paid the interview fee of $25. Blood samples may be stored indefinitely in a secure location for future genetic research. There is not a plan to submit to the NIH genomic database. At this time, there is no planned analysis for these samples and due to our sample size, we do not meet the requirements for inclusion in the NIH genomic database. Subjects who complete part of the interview remotely and do not meet study criteria will be informed of the decision and mailed a check or gift card in the amount of $25.

Based on the information collected at the screening interview, the investigators will decide whether or not to enroll the subject in the study. If the subject is enrolled in the

study, they will be either randomly assigned to one of the two schedules, or assigned to one of the two schedules based on group enrollment balance or subject safety at the discretion of the study physicians, and contacted to schedule their experimental sessions. If the subject agrees to enroll in the study and schedules their study visits, they will be sent an email with pertinent information.

Procedures on the testing day

Orientation to Laboratory: On the days of testing, the subject will arrive at the ICRC between 7:00 and 9:00 am and undergo a brief physical exam by ICRC Nurses, testing of urine for hCG in females and a drug screen for all subjects, and documentation of zero BrAC before a 550 cal breakfast is served. *Study protocol will be reviewed and car keys, if the subject drove themselves, taken for safekeeping or confirmed that the keys are held by the hospital valet service.* Age, sex, blood pressure, heart rate, temperature, height, and weight will be measured.

rTMS Treatment

Immediately before rTMS administration, subjects will be prompted to recall their most recent experience using alcohol through a standardized series of cue-induced questions. During the rTMS/sham sessions, subjects will be instructed to imagine themselves in that scenario. These mental priming techniques have been previously employed by study collaborator Dr. Hanlon[30].

rTMS will be delivered using the Magventure MagPro X100 Magnetic Stimulator (Magventure Inc., Alpharetta, Georgia). Motor threshold (MT) will be determined using single pulse stimulation over the left primary motor cortex, assessed as the lowest intensity producing five visible movements of the right abductor pollicis brevis out of ten stimulations. The Magventure MagPro X100 is equipped with a research-dedicated coil with combined active and sham stimulation capabilities, with both functions sharing the same acoustic properties. The sham condition additionally mimics cutaneous stimulation, facilitating subject blinding. Study conditions (1 Hz, sham) will be assigned a label, such as A or B, by a non-blinded staff member who is not directly involved with the research team. Subjects will be assigned a sequence of blinded study conditions in randomized and counterbalanced fashion.

The rTMS coil is held in place by a movable arm attached to the chair in which the subject sits. The coil is placed, by the PI, over the intended target and rests gently on the subject's head. The movable arm is then locked in place by the PI, who is present during the entire stimulation session to assess for subject comfort.

Low frequency rTMS: Low frequency rTMS, or rTMS at 1 Hz or less, is able to produce an inhibitory effect on local brain activity. This has been observed in healthy subject motor corticospinal output[40]. Previous studies have demonstrated that a single session of 1 Hz rTMS is capable of inhibiting local brain activity and modulating distal but related circuitry[33]. This work is in-line with the use of 1 Hz stimulation proposed in this study.
Low Frequency rTMS Protocol: Subjects will receive one session of low frequency rTMS

targeting the mPFC, delivered over FP1 per the 10-20 international scalp electrode location system (an approach taken by our consultant[41,42]), within the following stimulation parameters: Continuous 20-minute train of 1 Hz rTMS, at 110% of MT, for a total of 1200 pulses. This protocol was shown by Chen et al. (2013) to produce an inhibitory effect on local cortical excitability as well as effects on connectivity of related circuitry[33]. The stimulation design is within safety limits for rTMS[32,40,43]. If needed for tolerability, stimulation intensity (% MT) may be decreased, down to but not beyond the subjects resting MT, during the course of the study section.

rTMS administration monitoring
All subjects will be instructed to wear earplugs during each rTMS session and will be monitored by medically trained research staff throughout the entirety of each rTMS session.

Subjects will complete the rate control IV alcohol self-administration session as soon as feasible after rTMS administration. Upon completion of the alcohol self-administration session, subjects be taken to the ICRC for post-session monitoring until the time for discharge.

Alcohol Administration
Laboratory Testing: Each subject will be tested during each of two outpatient visits spanning Goodman Hall and University Hospital. After testing is complete, subjects will remain at the ICRC until at least 7 pm or their BrAC reaches 35 mg/dL, whichever is later.

Preparation for Testing: Using sterile technique, a 20 gauge (or 22 gauge if necessary) indwelling venous catheter will be placed in an antecubital vein by an ICRC nurse, then flushed with saline and capped with a heparin lock. The subject will be instructed in the use of the Draeger® BrAC meter and familiarized with the subjective response procedures under NSL technician supervision.

Preparation for Infusion: After the subject is prompted for a bathroom break, the venous catheter will be Y-connected to 2 parallel infusion pumps, each capable of delivering up to 999 ml/hr and set to deliver 4 ml/hr to keep the vein open. Subject concerns of any kind will be addressed, and the start of the infusion, marking the beginning of experimental time, Txp = 0, will be announced. Subjects will be unaware of BrAC readings and infusion rates at all times. The subject will be able to talk to the technician at any time without manual effort.

Infusion rate profile computation:
Using individualized PBPK parameters[44], the Computer-assisted Alcohol Infusion Software[45-48] will deliver an approximately 6.0 % (v/v) alcohol solution prepared by the Research Pharmacy. The infusion rate profile is based on individualized physiologically-based pharmacokinetic model parameters to achieve specified incremental alcohol exposure rates independent of the subject's age, height weight and gender. The safety limit will be set to 170 mg/dL, but subject inputs that would exceed 165 mg/dL are

disabled, allowing subjects to self-administer to a high-intensity drinking threshold of 160 mg/dL if they so choose and accommodating potential deviance from our pharmacokinetic modelling or measurement error.

We will use the rate control paradigm during the 90-minute alcohol self-administration session to allow the subject to determine their alcohol exposure trajectory (Figure 3). For the first self-administration epoch and at the end of each subsequent 3-5 min self-administration interval, the subject will specify the next alcohol exposure rate. Alcohol delivery raises the subject's BrAC by the specified rate over 3-5 minutes. During the last ~0.5 minutes of the exposure, the subject may complete the brief computer-assisted assay of craving for alcohol and subjective response and then select the next exposure rate, all while the current exposure rate is maintained.

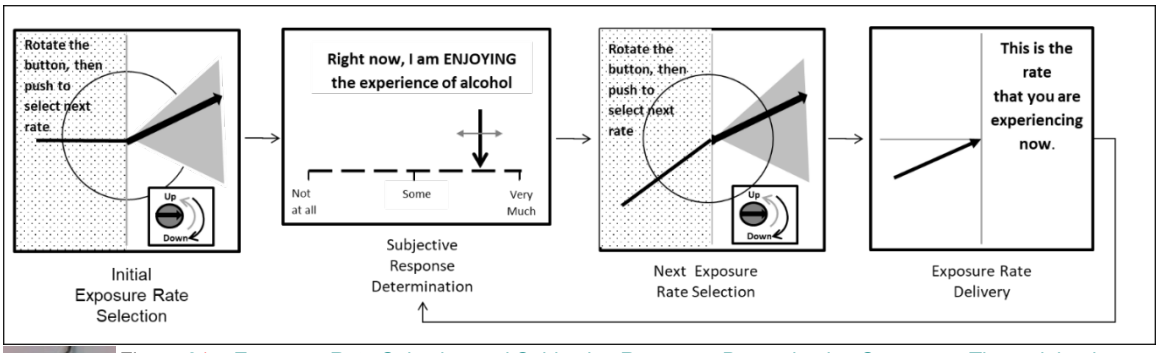

Figure 3~~1~~: : Exposure Rate Selection and Subjective Response Determination Sequence. The task begins with an initial exposure rate selection, with the display indicating no past rate of change (baseline). After 2.5 minutes, a set of subjective responses are collected over approximately 20 sec after which time the next exposure rate selection prompt is displayed, now indicating the prior selection in the left hand (shaded) portion of the display. The choice and subjective response sequence is repeated throughout the experiment. The next exposure rate is then selected by rotation of the CAIS response button (Griffin Technologies Powermate®, inset) to a position within the available range depicted in gray. The arrow position follows button rotation in real time, and rate chosen by single button press. Text instructions are for illustrative purposes.

Subjects approaching the functional exposure limit of 165 mg/dL will have their range of BrAC choices limited in a corresponding way. An alcohol self-administration session may be terminated early at the discretion of the study investigators if the outcome measures have been obtained (for example, the safety limit has been reached and thus binge and high intensity drinking alcohol exposures achieved with corresponding subjective responses). Subject payment will not change and they will not be informed of the reason for early termination to preclude change in behavior at any subsequent sessions.

Except for *ad-libitum* bathroom breaks, participants remain in the testing environment for the duration of the experiment; technician interaction is limited to occasional BrAC samples and dependent-measure data collection.

Upon completion of the infusion and return to the ICRC, participants are served a meal from the ICRC kitchen and remain in a room until at least 7:00 pm, or until BrAC < 35 mg/dL. Subjects may discharge earlier at the discretion of the principal investigator and if transportation has been arranged for them, however subjects are not informed of this

option as it is exercised only in emergencies or urgent situations. If the BrAC is 40 mg/dL or higher at 5:30pm, the participant will be offered a dinner from the ICRC kitchen, *gratis*. Participants will be paid in cash upon discharge from each session, with an escalating payment schedule used to encourage retention. Subjects will be compensated $25 for the screening interview, $125 for the first rTMS/Alcohol session, and $175 for the second rTMS/Alcohol session. Subjects that complete only a portion of any study procedure will be compensated at a rate of $15 per hour at the discretion of the study physicians.

Alcohol consumption follow-up
Subjects will be contacted and compensated $25 four weeks after Session 2 for a timeline follow-back assessment of drinking[49].

8.0 Reportable Events

Serious adverse events resulting in any physical harm associated with testing will be reported to the IRB within 24 hours; minor adverse events (e.g. nausea, infusate infiltration, discomfort associated with infusion) will be reported to the Alcohol Studies DSMB meeting at least annually.

Adverse events (AEs), especially those for which the relationship to study treatment is not “unrelated,” will be followed up until they have returned to baseline status or stabilized at the discretion of the PI. If after the follow-up period, return to baseline or stabilization cannot be established an explanation will be recorded in the source documentation.

9.0 Study Calendar

rTMS Study	Screening		Experimental Visits		Follow-up
Procedure	**Phone**	**Interview**	**Usual 1**	**Usual 2**	**1**
Phone Screen	X				
Informed Consent		X			
Audit		X			
SSAGA		X			
SKID V		X			
UPPS-P		X			
SRE		X			
PHQ-9		X			
SIP-r		X			
Medical History		X			
Nicotine History Measure		X			
Five Factor Model Form		X			
APT		X			
PACS		X			
TLFB		X	X	X	X
CIWA		X			
GAD-7		X			
UDS		X	X	X	
UPS		X	X	X	
BrAC			X	X	
Liver Function		X			
Genotype Sampling		X			
rTMS			X	X	
Alcohol Exposure			X	X	
Subjective Measures			X	X	X
CAGE		X			
General Self-Efficacy Scale		X			
DRSEQ-R		X			
AEQ		X			
DMQ		X			
TMS Screening Checklist		X			

10.0 Data Safety Monitoring

The Data Safety and Monitoring Board (DSMB) that monitors virtually all the alcohol studies at IUSM, chaired by Dr. Laura Tormoehlen, who is independent of the sponsor and investigators, and comprised of other faculty with like status, will review this study at six-month intervals. The following will be monitored as part of the Data Safety Monitoring Plan (DSMP): data quality, subject recruitment, accrual, retention, outcome and adverse event data, assessment of scientific reports or therapeutic development, results of related studies that may impact subject safety, and procedures designed to protect the privacy of subjects.

The IRB is notified of significant findings by way of the DSMB meeting minutes at the time of continuing review. Due to the small sample size and single site design of this protocol, there is not sufficient justification for conducting interim analyses to examine trends. Data on the number of subjects enrolled and the number of adverse events will be reviewed by the DSMB every six months and more frequently if needed. The resultant report will be issued to the Indiana University IRB at least at the time of continuing review or more frequently by request. Any unanticipated events will be immediately directed to the PI who will follow the Indiana University IRB reporting procedures.

11.0 Study Withdrawal/Discontinuation

The participant may withdraw from the study at any time for any reason, and will be paid an amount pro-rated to the duration of their participation on the testing day, including time to recover to a BrAC < 35 mg/dL. The PI may choose to terminate any subject's participation at any time if it is deemed that s/he cannot participate or cooperate in testing procedures safely, with the same pro-rated compensation to the subject.

12.0 Statistical Considerations

Analyses

Sample Size

We plan to consent and screen 30 subjects, enroll 20 subjects and anticipate a 30% drop out rate, yielding 14 completers. This is consistent with our previous clinical trial efforts, including a study of adjunct rTMS for cognitive impairment in first-episode psychosis[37].

Statistical and Power Analyses

We will conduct a Cox proportional hazards survival analysis, which will control for drinking intensity, to determine effect sizes for a subsequent, properly powered formal study of the effect of rTMS on rate control alcohol self-administration. A recent review reported Cohen's d from 0.05 to 4.42 of rTMS on craving and other substance use disorder related outcomes[50]. Our previous alcohol self-administration work showed effect sizes from 0.49 to 1.31 depending on the phenotype. Thus, overall, we hope for an effect size of at least 0.5 across SA1 and SA2.

Finally, with consent, we are collecting blood samples to allow for the combination of data from this project with previously collected human samples; enabling future analysis of polygenetic risk in the combined sample.

13.0 Statistical Data Management

Primary data will be collected via paper source documents, phone interviews, and direct data capture from clinical and symptom measurements. Data will be stored electronically on a department server and paper source documents will be stored in a double locked and access-controlled research records room. The storage location will be backed up automatically on a daily basis. Other data sources include pathology lab data and Scram systems data that will be stored in separate electronic files and merged with the primary data as needed. The following data quality control methods will be used: single entry with random checks of accuracy, range checks, testing of database by study team prior to moving to data analysis, and regular, periodic extraction and cleaning of data.

14.0 Privacy/Confidentiality Issues

Confidentiality will be protected by ensuring all research staff have been properly trained in confidentiality and human subject research procedures, coding all subject information when possible, and by securing subject files in a locked filing cabinet or on secured databases with access available only to the study physicians and research staff. Furthermore, data entered into a computer database will only use subject codes on secured computers that will be password protected with access available only to the study physicians and research staff. Limited screening information (first name, phone number) obtained from potential research subjects who subsequently do not participate in the research study will be held for 6 months and then destroyed.

15.0 Follow-up and Record Retention

Paper copies of medical records and source documentation will be kept for seven years after the study is closed with the IRB. One year after study closure, the documents will

be shipped to the Indiana University Department of Psychiatry long-term storage facility until destruction.

16.0 References

1. Rehm J, Anderson P, Barry J, et al. Prevalence of and potential influencing factors for alcohol dependence in Europe. *European addiction research.* 2015;21(1):6-18.
2. Connor JP, Haber PS, Hall WD. Alcohol use disorders. *Lancet.* 2016;387(10022):988-998.
3. Administration SAaMHS. *Results from the 2013 National Survey on Drug Use and Health: Summary of National Findings, NSDUH Series H-48, HHS Publication No. (SMA) 14-4863. Rockville, MD: Substance Abuse and Mental Health Services Admnistration, 2014.*: NSDUH Ser.
4. Roerecke M, Rehm J. Cause-specific mortality risk in alcohol use disorder treatment patients: a systematic review and meta-analysis. *International journal of epidemiology.* 2014;43(3):906-919.
5. World Health Organization WHOMoSAU. *Global status report on alcohol and health, 2014.* 2014.
6. Bouchery EE, Harwood HJ, Sacks JJ, Simon CJ, Brewer RD. Economic costs of excessive alcohol consumption in the U.S., 2006. *American journal of preventive medicine.* 2011;41(5):516-524.
7. https://www.niaaa.nih.gov/alcohols-effects-health/alcohol-use-disorder#:~:text=However%20severe%20the%20problem%20may%20seem%2C%20most%20people,an%20individual%E2%80%99s%20chances%20of%20success%20in%20overcoming%20AUD. Accessed.
8. Anton RF, O'Malley SS, Ciraulo DA, et al. Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. *JAMA.* 2006;295(17):2003-2017.
9. Czapla M, Simon JJ, Richter B, et al. The impact of cognitive impairment and impulsivity on relapse of alcohol-dependent patients: implications for psychotherapeutic treatment. *Addiction biology.* 2016;21(4):873-884.
10. Hunt WA, Barnett LW, Branch LG. Relapse rates in addiction programs. *J Clin Psychol.* 1971;27(4):455-456.
11. Costello RM, Biever, P., & Baillargeon J.G. Alcoholism treatment programming: Historical trends and modern approaches. *Alcoholism: Clinical and Experimental Research.* 1977;1(4):311-318.
12. Becker A, Kirsch M, Gerchen MF, Kiefer F, Kirsch P. Striatal activation and frontostriatal connectivity during non-drug reward anticipation in alcohol dependence. *Addiction biology.* 2017;22(3):833-843.
13. Hanlon CA, Dowdle LT, Henderson JS. Modulating Neural Circuits with Transcranial Magnetic Stimulation: Implications for Addiction Treatment Development. *Pharmacol Rev.* 2018;70(3):661-683.
14. Zhang R, Volkow ND. Brain default-mode network dysfunction in addiction. *NeuroImage.* 2019;200:313-331.
15. Bartra O, McGuire JT, Kable JW. The valuation system: a coordinate-based meta-analysis of BOLD fMRI experiments examining neural correlates of subjective value. *NeuroImage.* 2013;76:412-427.

16. Hare TA, Camerer CF, Rangel A. Self-control in decision-making involves modulation of the vmPFC valuation system. *Science.* 2009;324(5927):646-648.
17. Hare TA, Malmaud J, Rangel A. Focusing attention on the health aspects of foods changes value signals in vmPFC and improves dietary choice. *J Neurosci.* 2011;31(30):11077-11087.
18. Hare TA, O'Doherty J, Camerer CF, Schultz W, Rangel A. Dissociating the role of the orbitofrontal cortex and the striatum in the computation of goal values and prediction errors. *J Neurosci.* 2008;28(22):5623-5630.
19. Levy DJ, Glimcher PW. Comparing apples and oranges: using reward-specific and reward-general subjective value representation in the brain. *J Neurosci.* 2011;31(41):14693-14707.
20. O'Doherty J, Kringelbach ML, Rolls ET, Hornak J, Andrews C. Abstract reward and punishment representations in the human orbitofrontal cortex. *Nat Neurosci.* 2001;4(1):95-102.
21. Plassmann H, O'Doherty J, Rangel A. Orbitofrontal cortex encodes willingness to pay in everyday economic transactions. *J Neurosci.* 2007;27(37):9984-9988.
22. Plassmann H, O'Doherty JP, Rangel A. Appetitive and aversive goal values are encoded in the medial orbitofrontal cortex at the time of decision making. *J Neurosci.* 2010;30(32):10799-10808.
23. Volkow ND, Fowler JS, Wang GJ. The addicted human brain: insights from imaging studies. *The Journal of clinical investigation.* 2003;111(10):1444-1451.
24. Volkow ND, Hitzemann R, Wang GJ, et al. Long-term frontal brain metabolic changes in cocaine abusers. *Synapse.* 1992;11(3):184-190.
25. Oberlin BG, Shen YI, Kareken DA. Alcohol Use Disorder Interventions Targeting Brain Sites for Both Conditioned Reward and Delayed Gratification. *Neurotherapeutics.* 2020;17(1):70-86.
26. Claus ED, Ewing SW, Filbey FM, Sabbineni A, Hutchison KE. Identifying neurobiological phenotypes associated with alcohol use disorder severity. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology.* 2011;36(10):2086-2096.
27. Courtney AL, Rapuano KM, Sargent JD, Heatherton TF, Kelley WM. Reward System Activation in Response to Alcohol Advertisements Predicts College Drinking. *J Stud Alcohol Drugs.* 2018;79(1):29-38.
28. Grusser SM, Wrase J, Klein S, et al. Cue-induced activation of the striatum and medial prefrontal cortex is associated with subsequent relapse in abstinent alcoholics. *Psychopharmacology (Berl).* 2004;175(3):296-302.
29. Seo D, Lacadie CM, Tuit K, Hong KI, Constable RT, Sinha R. Disrupted ventromedial prefrontal function, alcohol craving, and subsequent relapse risk. *JAMA Psychiatry.* 2013;70(7):727-739.
30. Hanlon CA, Dowdle LT, Correia B, et al. Left frontal pole theta burst stimulation decreases orbitofrontal and insula activity in cocaine users and alcohol users. *Drug Alcohol Depend.* 2017;178:310-317.
31. Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Safety of TMSCG. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol.* 2009;120(12):2008-2039.

32. Chen R, Gerloff C, Classen J, Wassermann EM, Hallett M, Cohen LG. Safety of different inter-train intervals for repetitive transcranial magnetic stimulation and recommendations for safe ranges of stimulation parameters. *Electroencephalogr Clin Neurophysiol.* 1997;105(6):415-421.
33. Chen AC, Oathes DJ, Chang C, et al. Causal interactions between fronto-parietal central executive and default-mode networks in humans. *Proceedings of the National Academy of Sciences of the United States of America.* 2013;110(49):19944-19949.
34. Graziano B, Kaskie, R. E., & Ferrarelli, F. Transcranial Magnetic Stimulation (TMS) as a treatment tool in schizophrenia: A review. . *Journal of Brain and Neurology,.* 2017;1(1):14-24.
35. Driver J, Blankenburg F, Bestmann S, Vanduffel W, Ruff CC. Concurrent brain-stimulation and neuroimaging for studies of cognition. *Trends in cognitive sciences.* 2009;13(7):319-327.
36. Brady RO, Jr., Gonsalvez I, Lee I, et al. Cerebellar-Prefrontal Network Connectivity and Negative Symptoms in Schizophrenia. *The American journal of psychiatry.* 2019:appiajp201818040429.
37. Francis MM, Hummer TA, Vohs JL, et al. Cognitive effects of bilateral high frequency repetitive transcranial magnetic stimulation in early phase psychosis: a pilot study. *Brain imaging and behavior.* 2018.
38. Rueger SY, King AC. Validation of the brief Biphasic Alcohol Effects Scale (B-BAES). *Alcoholism, clinical and experimental research.* 2013;37(3):470-476.
39. Rueger SY, McNamara PJ, King AC. Expanding the utility of the Biphasic Alcohol Effects Scale (BAES) and initial psychometric support for the Brief-BAES (B-BAES). *Alcoholism, clinical and experimental research.* 2009;33(5):916-924.
40. Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology.* 2009;120(12):2008-2039.
41. Hanlon CA, Dowdle LT, Austelle CW, et al. What goes up, can come down: Novel brain stimulation paradigms may attenuate craving and craving-related neural circuitry in substance dependent individuals. *Brain research.* 2015;1628(Pt A):199-209.
42. Kearney-Ramos TE, Dowdle LT, Lench DH, et al. Transdiagnostic Effects of Ventromedial Prefrontal Cortex Transcranial Magnetic Stimulation on Cue Reactivity. *Biol Psychiatry Cogn Neurosci Neuroimaging.* 2018;3(7):599-609.
43. Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. *Electroencephalography and clinical neurophysiology.* 1998;108(1):1-16.
44. Plawecki MH, Decarlo R, Ramchandani VA, O'Connor S. Improved Transformation of Morphometric Measurements for a Priori Parameter Estimation in a Physiologically-Based Pharmacokinetic Model of Ethanol. *Biomed Signal Process Control.* 2007;2(2):97-110.
45. Zimmermann US, Mick I, Vitvitskyi V, Plawecki MH, Mann KF, O'Connor S. Development and pilot validation of computer-assisted self-infusion of ethanol

(CASE): a new method to study alcohol self-administration in humans. *Alcoholism, clinical and experimental research.* 2008;32(7):1321-1328.
46. Zimmermann US, Mick I, Laucht M, et al. Offspring of parents with an alcohol use disorder prefer higher levels of brain alcohol exposure in experiments involving computer-assisted self-infusion of ethanol (CASE). *Psychopharmacology (Berl).* 2009;202(4):689-697.
47. Plawecki MH, Wetherill L, Vitvitskiy V, et al. Voluntary intravenous self-administration of alcohol detects an interaction between GABAergic manipulation and GABRG1 polymorphism genotype: a pilot study. *Alcohol Clin Exp Res.* 2013;37 Suppl 1:E152-160.
48. Plawecki MH, White K, Kosobud AEK, et al. Sex Differences in Motivation to Self-Administer Alcohol After 2 Weeks of Abstinence in Young-Adult Heavy Drinkers. *Alcoholism, clinical and experimental research.* 2018;42(10):1897-1908.
49. Sobell LC, Brown J, Leo GI, Sobell MB. The reliability of the Alcohol Timeline Followback when administered by telephone and by computer. *Drug Alcohol Depend.* 1996;42(1):49-54.
50. Coles AS, Kozak K, George TP. A review of brain stimulation methods to treat substance use disorders. *Am J Addict.* 2018;27(2):71-91.

17.0 Appendix

Attachment 1: Concomitant Medication Table

Medication	Allowed	Notes
Amitriptyline	No	
Amphetamines et., methylphenidate, dextroamphetamine)	No	
Antiemetics (eg., metoclopramide, domperidone, others with dopamine blocking properties)	No	
Antiepileptic mood stabilizers	Yes	Stable dose, no changes or additions
Antihistamines, nonsedating (eg., loratidine, fexofenadine, cetirizine)	Yes	
Antihistamines, sedating (eg., diphenhydramine, hydroxyzine, meclizine, benztropine)	Yes-Episodic Use Only	No use within 24 hours of cognitive assessments
Antipsychotic medications	Yes	Stable dose over four weeks prior to randomization, no changes or additions during duration of trial
Barbiturates	No	
Benzodiazepines	Yes-Episodic Use Only	No use within 24 hours of cognitive assessments
Chlorpromazine	No	
Bupriopion	No	
Clozapine	No	
Decongestants (eg., pseudophedrine)	Yes-episodic use only	No use within 24 hours of cognitive assessments
Doxepine	No	
Dicyclomine	No	
Herbal medications or Over the Counter Medications w/ primary CNS activity	No	
Lithium	Yes	
MAOIs	Yes	
Methadone	No	
Mirtazepine	Yes	Stable dose, no changes or additions

Muscle Relaxants	Yes-Episodic Use Only	No use within 24 hours of cognitive assessments
Nicotine Replacement	Yes	
Nortriptyline	No	
Opiates	No	
Benzodiazepine derivative sleep agents (eg., Zolpidem)	Yes-Episodic Use Only	No use within 24 hours of cognitive assessments
SNRIs	Yes	
SSRIs	Yes	
Tricyclic antidepressants	Yes	
Trazodone	Yes-Episodic Use Only	