

Abbreviated Title: Socioemotional Processing in Alcohol Use Disorder

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**Title:** Investigating a Response Modulation Hypothesis of Socioemotional Processing associated with Alcohol Use Disorder

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## **STATEMENT OF COMPLIANCE**

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)
- National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

## **A. PROTOCOL SUMMARY**

### **A.1: Synopsis**

**Title:** Investigating a Response Modulation Hypothesis of Socioemotional Processing associated with Alcohol Use Disorder

**Study Description:** In the first stage, participants will undergo functional magnetic resonance imaging while looking at socioemotional stimuli and alcohol cues and will pilot a neurofeedback training protocol. Personality traits and executive function will also be investigated. In the second stage, inpatient participants with alcohol use disorder will be randomly assigned to receive active or sham neurofeedback. Participants will undergo two functional magnetic resonance imaging sessions including looking at socioemotional stimuli and alcohol cues, resting state fMRI, and real time neurofeedback during alcohol craving. Ability to inhibit attention to alcohol cues and craving will be assessed prior to and following the neurofeedback as well. Participants will be contacted approximately 1 month, 3 months, and 6 months post release from inpatient treatment to assess outcomes.

**Objectives:** The purpose of this protocol is to understand the mechanism whereby neural processes of socioemotional cognition associated with alcohol use disorders lead to negative drinking consequences. This study is a two-stage procedure to both provide evidence of a response modulation deficit associated with socioemotional processing in individuals with alcohol use disorder and investigate how moderating that deficit affects socioemotional processing and negative drinking consequences.

**Endpoints:** Brain engagement during exposure to socioemotional stimuli, alcohol cues, and neurofeedback training (fMRI-Scan Portion)

**Study Population:** Community participants both with and without alcohol use disorder and inpatients with alcohol use disorder

**Phase:** Interventional

**Description of Sites/Facilities Enrolling Participants:** NIH Clinical Center, Bethesda, MD

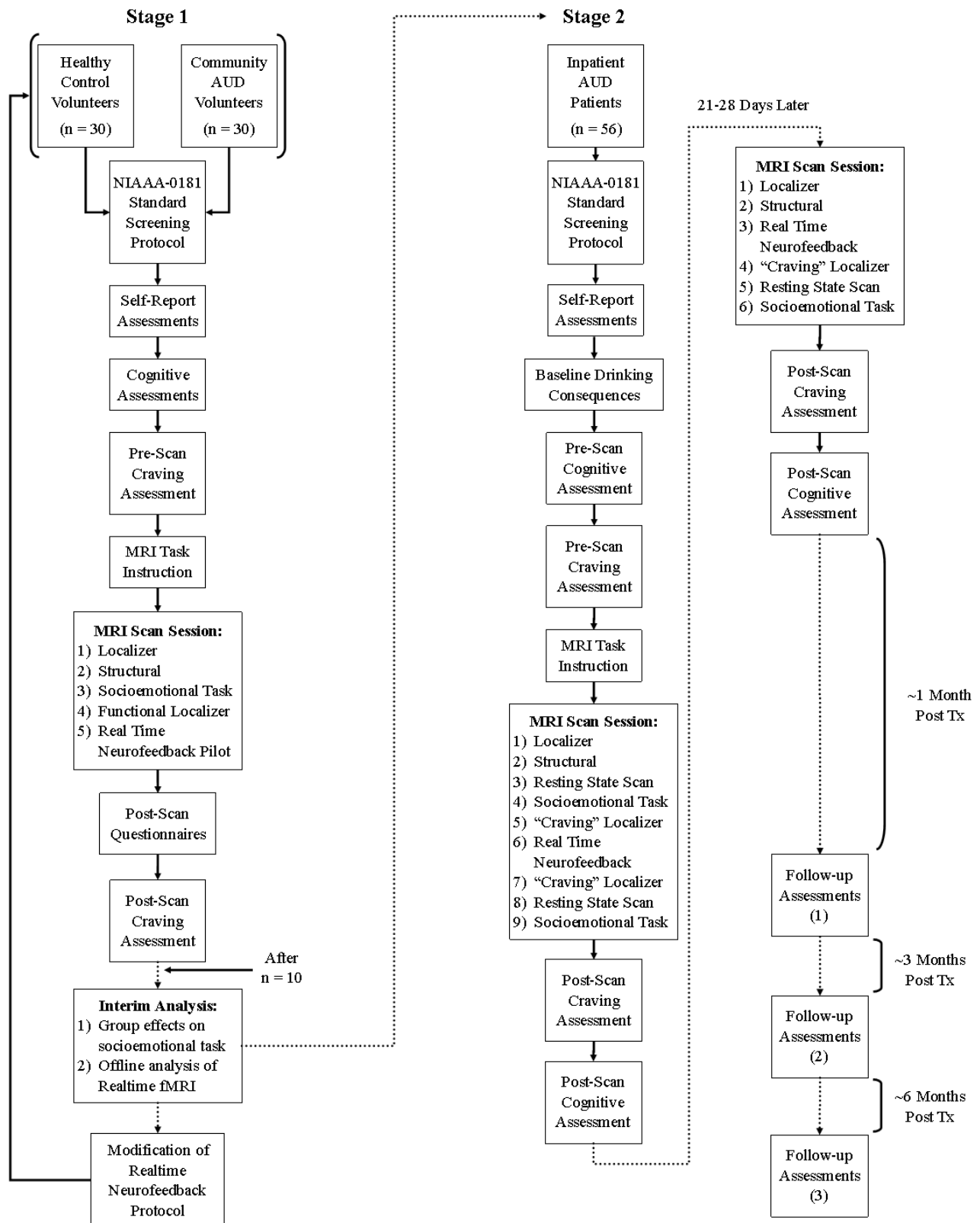
**Description of Study Intervention:** Realtime fMRI Neurofeedback Training

**Study Duration:** 5 years

**Participant Duration:** 1 day – 7 months

## A.2: Schema/ Schedule of Activities

**Figure 2.** Flowchart of Two-Stage Study Procedures



## **B. INTRODUCTION**

### **B.1: Study Rationale**

In the current protocol, we plan a two-stage investigation of the response modulation hypothesis as a mechanism for abnormalities in socioemotional processing and negative drinking consequences in individuals with AUD. In Stage 1, we will conduct a study of implicit socioemotional processing while exposed to alcohol versus neutral cues in community AUD versus healthy community volunteers (HCVs). Then, in Stage 2, we will use real time functional magnetic resonance imaging (rt-fMRI) neurofeedback as an investigational tool to guide treatment seeking inpatients with AUD in reducing the salience of alcohol cues. The results will be consistent with the hypothesized response modulation hypothesis if individuals who receive neurofeedback have a reduction of deficit associated with socioemotional processing, and if the individuals who receive neurofeedback have less negative drinking consequences at follow-up.

A total of 86 individuals with AUD and 30 HCVs will be studied using: **a)** whole brain functional imaging during a socioemotional processing task, **b)** cognitive and behavioral measures of attention, including eye tracking, and **c)** self report measures of executive function, empathy, moral reasoning, and personality. 30 individuals with AUD and 30 HCVs will participate in a 1 session initial study of socioemotional processing with a neurofeedback pilot component. Then, 56 treatment-seeking patients with AUD will complete two sessions of a rt-fMRI protocol with active NF ( $n = 28$ ) or with sham NF ( $n = 28$ ), and will repeat (a) and (b) following neurofeedback. Following departure from inpatient treatment, patients will be contacted at three time points (approximately 1 month, 3 months, and 6 months post-treatment) to collect outcome data including: alcohol use, community functioning, and aggression, victimization, and crime.

### **B.2: Background**

#### *Alcohol Use Disorder and Socioemotional Processing:*

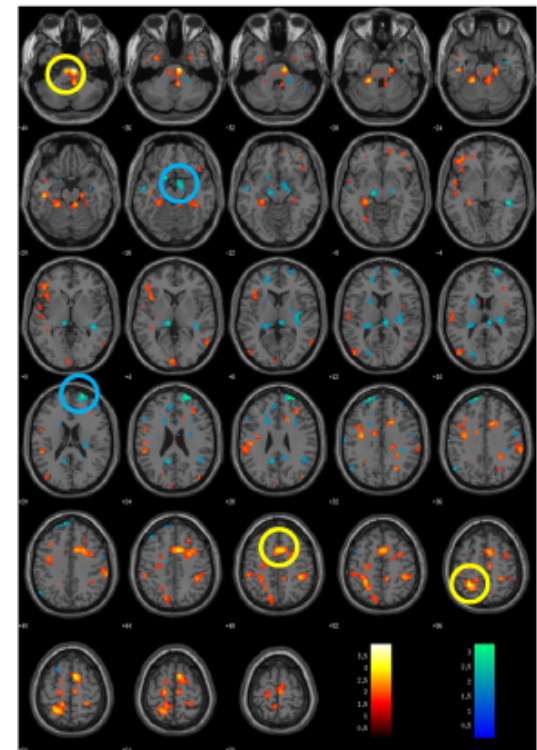
Alcohol use is extremely prevalent in the United States; according to the 2015 National Survey on Drug Use and Health, 56% of adults report drinking in the last month (SAMHSA, 2015). More importantly, problematic drinking affects nearly half of those drinking alcohol, with 27 percent of people reporting binge drinking and 7 percent reporting heavy alcohol use in the last month; in fact, 23 % of alcohol drinkers in the United States are estimated to have alcohol use disorder (AUD). Excessive alcohol use has major impacts on individuals and society; the Centers for Disease Control and Prevention estimates that 88,000 people die per year from alcohol related causes, that 10% of children in the US lives with parents with alcohol problems, and that alcohol misuse costs about \$249 billion every year in the United States (Sacks et al., 2015).

Much of this cost of alcohol misuse is related to negative consequences of using alcohol, including lost workplace productivity, criminal justice costs, and motor vehicle accident costs. There is an established relationship between excessive alcohol use and crime commission (Lee, 2013; Popovici et al., 2012), financial difficulties (Gual et al., 2009), intimate partner aggression (Lewis et al., 2015; Watkins et al., 2015), poor work performance (Gual et al., 2009; Mangione et al., 1999), and homicide (Pridemore, 2004). In fact, according to a Bureau of Justice Statistics study, 37% of violent criminals report being under the influence of alcohol at the time of their offense, and more than 50,000 additional individuals are estimated to be convicted of DUI/DWI and alcohol-related public order offenses per year (Snyder et al., 2012).

Negative drinking outcomes may in part be driven by socioemotional processing deficits related

to alcohol use disorder. Chronic alcohol users are more likely to make utilitarian moral judgments (Khemiri et al., 2012), similar to other patient groups (Baez et al., 2014; Koenigs et al., 2012); this utilitarian moral bias is predicted by deficits in decoding emotional facial expressions (Carmona-Perera et al., 2014). Acute alcohol intoxication in social drinkers also increased utilitarian judgment (Duke and Bègue, 2015). Moral disengagement has also been found to be related to alcohol use and binge drinking in adolescents (Newton et al., 2014), while moral reasoning impairments are associated with driving under the influence of alcohol (Denton and Krebs, 1990; Little and Robinson, 1989), and alcohol dependence (Brevers et al., 2013). Theory of mind processes may also be selectively impaired by alcohol use; one study found emotion recognition deficits in individuals with AUD during theory of mind processes but did not find deficits in intention attribution (Nandrino et al., 2014), while another found that acute alcohol led to reduced emotion recognition and identification of social rule violations (Mitchell et al., 2011). The neurobiological underpinnings of these socioemotional behavior atypicalities are not yet clearly defined, though several studies support the sense that these correspond to differences in neural engagement. Acute alcohol intoxication leads to more effortful emotion regulation, as demonstrated in an EEG study of emotional response inhibition by larger N200 amplitude during response inhibition for emotional stimuli and reduced P300 during response execution for emotional stimuli (Euser and Franken, 2012). fMRI investigation has demonstrated that alcohol consumption reduces anterior insula response during emotional face recognition (Padula et al., 2011), consonant with studies finding acute alcohol administration leading to specific deficits in facial emotion decoding (Attwood & Munafo, 2014; though some studies do

Figure 1. *Neural engagement during moral processing related to years of regular alcohol use*



not find this i.e., Felisberti and Terry; Walter et al., 2011). The anterior insula is an area of the brain strongly implicated in empathy (Singer et al., 2009). Despite these findings, little work has been done on the association between alcohol use disorder and integrated socioemotional processing, although there is significant overlap between brain regions involved in moral cognition, empathy, and theory of mind (Bzdok et al., 2012). Initial, unpublished work by an associate investigator on this protocol found during explicit moral processing, years of regular alcohol use was associated with reduced hypothalamic but increased pre-supplementary motor (SMA) and temporoparietal junction (TPJ) response, suggesting that problem alcohol users may engage the pre-SMA to suppress non-task based activity in hypothalamic and striatal areas while relying on TPJ response to make social rule based judgment (see Figure 1; Fede et al., unpublished). Indeed, this pattern of compensation during explicit moral processing mirrors findings of the neural correlates of explicit moral processing in stimulant users (Fede et al., 2016).

#### *Response Modulation Hypothesis:*

These findings in AUD are consistent with a mechanism for impaired socioemotional decision making put forward in the psychopathy literature, termed the response modulation hypothesis (Gorenstein and Newman, 1980). Rather than a deficit in empathy or socioemotional processing, Newman and colleagues find evidence that psychopaths may fail to modulate attention to peripheral stimuli (neutral or negative) outside of goal directed behavior (Lorenz and Newman, 2002; Newman et al., 1987; Newman et al., 1997). Newman and Lorenz suggest that this can be specific to situations in which the dominant cues are particularly salient to the individual (Newman and Lorenz, 2003), such as alcohol cues are to an individual with AUD. This failure to modulate response (i.e., attend to information on the periphery) results in a lack of awareness that behavior is causing problems, and lack of ability to regulate the problem behavior. Although premorbid deficits in response modulation may lead to failure to develop the innate mores that underlie typical socioemotional function (Blair, 2007), the deficit can be corrected in laboratory settings through effortful or external remodulation of focus towards the stimuli of interest; for example, psychopaths display a deficit in fear potentiated startle under standard conditions, but normal fear potentiated startle response when directed towards threat stimuli (Newman et al., 2010).

Despite the extensive literature supporting the response modulation hypothesis in psychopathy, no investigation has been done into whether this mechanism may also drive socioemotional deficits sometimes associated with alcohol use. We propose that deficits in response modulation in the presence of alcohol cues drive atypical socioemotional processing and resulting negative drinking behaviors. Previous studies have shown that individuals with AUD have an attentional bias towards alcohol stimuli (McAteer et al., 2015; Weafer and Fillmore, 2013), and that the presence of alcohol stimuli reduces inhibitory control (Petit et al., 2012; Weafer and Fillmore,

2015). Moreover, individuals with AUD have reduced neural response to emotional stimuli in the presence of alcohol cues compared to neutral cues (Gilman and Hommer, 2008). These findings are consistent with the response modulation hypothesis, but have not been extended to socioemotional processing or behavior.

Establishment of deficits in response modulation as a mediator of the relationship between AUD and negative drinking outcomes and other socioemotional problems would provide important insights into treatments designed to reduce the impact of AUD. For example, the response modulation hypothesis in psychopathy has led to the development of cognitive training that improves consideration of contextual information and affective processing (Baskin-Sommers et al., 2015) and goal-oriented rather than punishment-oriented incarceration programs that significantly reduce recidivism (Caldwell et al., 2007). In the case of AUD, this response modulation mechanism would indicate therapies like mindfulness-based relapse prevention, which encourages patients to be more aware of internal and external experiences but not to be caught up in or dwell on them, allowing patients to choose more modulated responses (Witkiewitz et al., 2014). Currently, less than 10% of people affected by AUD receive treatment (SAMHSA, 2015). The most effective interventions are brief intervention and motivational enhancement, but only around 70% of studies into these interventions indicate an effect of treatment (Miller and Wilbourne, 2002). Failure to address specific neural mechanisms may contribute to the inconsistent performance of these therapies.

#### *Real Time Functional Magnetic Resonance Imaging Neurofeedback:*

Real time fMRI neurofeedback (rt-fMRI-NF) guided neuromodulation is supported by many proof-of-concept studies. rt-fMRI-NF training enabled participants to upregulate regional brain activity including: the anterior insula (Caria et al., 2010; Ruiz et al., 2013), amygdala (Zotев et al., 2011), SN/VTA (Sulzer et al., 2013), and inferior frontal gyrus (Rota et al., 2009), as well as to downregulate subgenual anterior cingulate (ACC) activity (Hamilton et al., 2011). Some early work supports sustained effects of rt-fMRI-NF. A clinical trial by Young and colleagues found two sessions of rt-fMRI-NF focusing on training patients to upregulate the amygdala significantly reduced depression symptoms one week later in major depression patients (Young et al., 2017). Also, rt-fMRI-NF guided modulation of the rostral ACC was related to reductions in levels of chronic pain (deCharms et al., 2005; Emmert et al., 2014; Guan et al., 2015). In some cases, training and transfer effects of neurofeedback may be sustained up to 14 months post-initial training (Robineau et al., 2017).

The rt-fMRI-NF technique has previously been investigated for feasibility in substance use samples. It has enabled cocaine users to downregulate the SN/VTA (Kirschner et al., 2017), and in smokers, nicotine craving was reduced via downregulation of ventral ACC (Brady et al., 2015; Hanlon et al., 2013). Social heavy alcohol drinkers have been able to downregulate their VS

responses to alcohol cues (Kirsch et al., 2016); in another study, individuals with AUD modulated neural response to alcohol cues in individualized ROIs (ACC, dorsolateral prefrontal cortex (PFC), or insula), and rt-fMRI-NF corresponded to reduced craving (Karch et al., 2015). Initial evidence from conference proceedings indicates that rt-fMRI-NF may also be able to reduce short-term impulsivity in social drinkers (Deshpande et al., 2017). Typically, rt-fMRI neurofeedback designed to limit craving is administered in one to three sessions, although Hanlon and colleagues reported significant feasibility problems with 3 neurofeedback visits (2013).

### **B.3: Risk/Benefit Assessment**

Though risks in the study are likely to be minimal, aspects that may cause any form of discomfort will be explained to subjects with written details provided in the informed consent document. These will include:

#### **Known Potential Risks**

- *Urine Drug Screen:* Results of the drug screen will be part of the participant's medical record. This record could be accessed for employment, insurance, or other purposes.
- *Self-Report Measures:* The participant may experience distress related to discussion of potentially negative life events, such as interpersonal conflict, legal trouble, and addiction.
- *Attention Tasks:* Participants may experience frustration or boredom while completing some of the attention and thinking tests.
- *Bar-Like Environment:* Subjects will complete tasks in a bar-like environment that is designed to make them think about alcohol. Participants may express distress by feeling like they want to drink alcohol.
- *Alcohol Cues:* Participants may experience distress related to craving when shown visual, olfactory, and environmental alcohol stimuli.
- *Pictures of Negative Things:* Some of the pictures viewed in the MRI are disturbing. Subjects may feel upset or uncomfortable when looking at the pictures.
- *Neurofeedback:* Participants who participate in rt-fMRI-NF training may experience frustration when trying to modulate their brain activity.
- *MRI Risk:* There are no known long-term risks of MRI scans. However, people are at risk for injury from the MRI magnet if they have certain metal objects in their bodies. These include implanted electrical devices such as pacemakers, cochlear implants, delivery pumps or brain stimulators. People with implanted metal such as aneurysm clips (metal clips on the wall of a large artery), permanent eyeliner, shrapnel fragments or some dental implants and prostheses (including metal pins and rods, heart valves) are also at risk. Welders and metal workers are also at risk for injury because of possible small metal fragments in the eye.

The risk of MRI to a fetus is not known. Therefore, volunteers who are pregnant or planning to become pregnant during the study cannot participate. For female participants, a urine pregnancy test will be given no more than 24 hours before each MRI session. If a pregnancy test is positive or uncertain, she may not be in the study.

Individuals with back problems may have back pain or discomfort from lying in the scanner. Individuals with fear of confined spaces may become anxious during an MRI.

The noise of the MRI machine can be loud enough to damage one's hearing, especially in people who already have hearing loss. The participant will be fitted with earplugs and/or headphones to muffle the sound. The participant may still experience some temporary problems hearing soft sounds after the session.

If the expanding foam is used to stabilize participant's head in the magnet, it may get warm for a few minutes while it expands. It is possible that the participant could feel discomfort or get a mild burn from the heat. The chemicals in the foam may cause skin or eye irritation if in touch with the participant's face and eyes. However, to protect the participant, the foam is always inside two plastic bags.

- *Claustrophobia*: People with a fear of closed spaces may become scared during an MRI.
- *Surveys and Interviews*: Questions about money, jobs, housing, crime, and conflicts with people may make some people uncomfortable. Interviews, questionnaires, and tasks may cause frustration or boredom.
- *Costs and stress resulting from discovery of previously undiagnosed abnormalities*: It is possible that the study procedures will reveal previously undiagnosed abnormalities (e.g., the potential finding of a tumor from the brain MRI studies). If this happens it may result in stress and time and financial costs to the study participant and their family. The investigators are not assuming responsibility for such potential consequences, but will make every effort to help such families to deal with whatever findings arise.
- *Confidentiality*: Participation in research may mean a loss of privacy. Study records will be kept as confidential as possible under the law. No individual identities will be used in any reports or publications resulting from the study. Study information will be coded with a code number unique to the study. All information will be kept in locked files, with access limited to study personnel. A Certificate of Confidentiality will protect information from legal requests for information disclosure (i.e., subpoenas), although may not provide complete protection.

### **Known Potential Benefits**

Participants may receive no direct benefit from participation in this study. Patients who participate in active rt-fMRI-NF training might experience improvements in suppressing craving. This study may lead to development of new interventions designed to reduce negative drinking outcomes, and may increase the overall understanding of the neural correlates of alcohol use disorder.

### **Assessment of Potential Risks and Benefits**

Risks will be minimized in the following way:

- All study participants will be accompanied at the NMR Center by a study team member. All study team members have completed CPR Training, NMR Center Safety Training, and the NMR Center Emergency Preparedness Training, including standard emergency procedures to be followed in the event of a fire (code red) or if a participant is in respiratory and/or cardiac arrest (code blue). These procedures include removing and evacuating the participant from the scanner, contacting the appropriate emergency response teams as well as the MAI of the study, and being aware of the locations of emergency items such as the emergency drug box, crash cart, AED, and fire extinguisher. Presence of a healthcare professional will not be required in the MR sessions for any participants in this study. In the event that a subject communicates distress while completing tasks, they will be given the option to choose not to answer any questions and can stop at any time. If they are bothered by alcohol craving following exposure to the bar-like environment or other alcohol-related cues, we will have staff on hand to talk with them about getting help. Subjects will be permitted to stop if they experience distress from disturbing images shown in the MRI scanner. If they are still distressed after stopping, we can have clinical staff talk to them or give them information about how to get help to feel better. Everyone having a MRI scan will be given earplugs and/or headphones. If the participant experiences claustrophobia in the MRI machine, they can press an alarm in the scanner and we will remove s/he from the MRI machine immediately. Subjects can communicate with staff at all times and can be removed from the scanner at any time for any reason and be given earplugs or headphones for hearing protection. Subjects may stop participation at any time for any reason. Clinical staff are available to provide consultation if needed.

Participants' confidentiality will be maintained by having data coded to mask participants' identities. Further, files containing participant names and the master list of participants will be kept in a locked file under the supervision of the Principal Investigator. All participants will be provided with a daytime phone number through which Dr. Momenan may be contacted to answer questions.

Discovery of previously unknown abnormalities may result in stress and time and financial costs to the study participant and their family. The investigators are not assuming responsibility for such potential consequences but will make every effort to help such families to deal with whatever findings arise.

All staff will be trained in matters relative to confidentiality and other forms of participant risk. If at any time a participant expresses discomfort over any aspect of the study, staff will be told to discontinue the distressing activity and seek consultation so as to minimize risk. The confidential nature of all data collected in this study will be

thoroughly explained to potential participants, as will data safeguarding procedures (e.g., locked file cabinets, password controlled databases and file servers).

Participants who have any questions regarding their informed consent or any aspects of the study at any time will be directed to the Principal Investigator. Participants who have questions regarding their rights as Human Research Subjects will be referred to the Clinical Center Patient Representative at (301) 496-2626.

Participants who display a clinically significant increase in craving during a study session will be counselled by NIAAA medical staff after completing the session. They will then be advised of care options available to them. For inpatients, we do not plan for them to leave treatment for at least 48 hours after they see the alcohol pictures or until they do not feel a craving for alcohol unless they choose to leave “against medical advice.”

Participants may be monitored for signs of craving-related distress while in the alcohol-cued environment by study staff in another room through a closed-circuit video display (no sound). No data (electronic or otherwise) will be recorded during these observations. Upon observing any visible signs of distress, such as emotional or physical reactions the clinical staff (the MAI or CRNPs) will be notified immediately for assessment and to provide the appropriate care.

- *Availability of Medical or Professional Intervention:* Risks associated with the study procedures described above will be minimized by giving participants freedom to decline to answer distressing questions. Adequate preparation before MRI sessions and scheduling adequate time to set-up and complete the procedure will minimize pressure on subjects. Clinically-relevant incidental findings will be reported to subjects and a referral will be made to appropriate treatment settings, facilitated by the study investigators. If participants experience distress related to participation in the research study, consultation with medical staff or information about community resources can be arranged by the study investigators

As described above, the minimal study risks are further minimized through study procedures, and the study has the potential to provide information about socioemotional processing and negative drinking outcomes.

## C. STUDY OBJECTIVES

- *Primary Objectives:*
  1. Use fMRI to investigate whether response modulation deficits in the presence of alcohol drive AUD-related abnormalities in socioemotional processing.

2. Use rt-fMRI-based neurofeedback to aid self-modulation of alcohol craving.
- *Secondary Objectives:*
    1. Investigate drinking behaviors and consequences associated with active versus sham neurofeedback.
    2. Investigate how measures of resting state fMRI change before and after neurofeedback.
    3. Explore how alcohol use severity is associated with the neural correlates of socioemotional processing in an alcohol cued environment.
    4. Asses the relationship between behavioral and self-report assessments and the functional imaging data.
  - *Tertiary Objective:* To explore predictors of future drinking behaviors by investigating the associations between baseline measures of alcohol use, personality, cognitive function, and socioemotional processing, with future drinking behaviors and negative drinking consequences.

## D. STUDY DESIGN

### Overall Design

- Single Site – NIH Clinical Center, Bethesda, MD
- *Primary Hypotheses:*

Based on the general hypothesis that a deficit in response modulation in the context of alcohol cues leads to reduced socioemotional processing in laboratory and real-world scenarios, and based on published literature, we predict:

- 1) During implicit socioemotional picture viewing, in individuals with AUD but not HCVs, **a)** there will be less neural engagement in socioemotional brain regions (mPFC, PCC, amygdala, parahippocampal gyrus, TPJ, dlPFC, frontal pole) in alcohol-distractor conditions compared to neutral-distractor conditions, **b)** the ratio of eye gaze time on socioemotional compared to distractor stimuli will be lower for alcohol compared to neutral distractors, and **c)** baseline levels of alcohol use severity and attentional deficits will predict greater attenuation of neural activity.
- 2) **a)** Active but not sham NF will relate to a within-patient increase in neural engagement of socioemotional brain regions (as in 1a) during socioemotional processing in the presence of alcohol versus neutral distractor cues and greater whole brain connectivity and synchrony during resting state, **b)** active but not sham NF will relate to within-patient reduction in alcohol-cued craving, and **c)** active but not sham NF will relate to within-patient improvement in attention tasks.
- 3) In long term follow up, **a)** greater deficits in alcohol-cued socioemotional processing in the brain will predict less time to relapse, more drinking days, less community functioning and greater incidence of violence or legal contact, but that **b)** individuals

who participated in the active NF protocol would have better outcomes than those who participated in sham NF (less drinking days, greater time to relapse, less negative drinking consequences and better community functioning), and further **c)** within-patient improvement in neural engagement during socioemotional processing in the presence of alcohol versus neutral distractor cues would explain the relationship between NF and outcomes.

## Study Procedures.

For a complete flowchart of procedures, see Figure 2.

### **Stage 1:**

*Magnetic Resonance Imaging:* All MRI scans will be conducted in a 3 Tesla MRI scanner at the NIH Clinical Center. Individuals in the HCV and AUD group will complete one MRI session: 1) a localizer, 2) a whole brain structural scan, 3) whole brain socioemotional task fMRI scan, 4) a functional locator scan for use during rt-fMRI, and 5/6) two blocks of rt-fMRI-NF. We expect that scan order may vary for technical reasons; the actual order of scans will be recorded. Participants will then complete post-scan questionnaires about the socioemotional task and rt-fMRI-NF procedure.

- *Socioemotional Alcohol Attention Task (SAAT):* The task will consist of presentation of a picture cue stimulus alongside a picture distractor stimulus. It was designed based on the fMRI task of implicit moral processing used in Caldwell et al., 2015. The simultaneous presentation of an alcohol distractor follows principles of biased competition tasks, such as Pessoa et al., 2002. Participants will be instructed to press a button to indicate if the picture stimuli are “indoors” or “outdoors”. Three types of cue stimuli will be used: negative socioemotional (e.g., a child being abused), negative emotional (e.g., child crying), and neutral (e.g., a child writing on a chalkboard). Two types of distractor stimuli will be used: alcohol and non-alcohol neutral. Images will be selected from the International Affective Picture System (IAPS) pool, as well as similar images from other sources. Each type of cue stimulus will be presented with each type of distractor stimulus. Finally, stimuli will be counter-balanced with equal probability across location on screen (left or right) and location (indoor or outdoor). Stimuli will be presented in a randomized order. Each pair of images will be presented for 3 seconds, with an inter-stimulus interval (consisting of presentation of a fixation cross) jittered for 1-3 seconds. 40 of each cue stimuli type will be used for 120 (60 alcohol and 60 non-alcohol distractor cues) will be used, which are uniformly distributed among stimuli types. The total run time of the task will be approximately 10 minutes.

This task is designed to engage socioemotional processing circuits, including medial prefrontal, limbic, and temporoparietal areas. An eye-tracking device will be used to record eye gaze during SAAT in order to measure time spent actively attending to each stimuli. A post-scan questionnaire will ask subjects to rate each distractor

- stimuli on evoked craving and each cue stimuli on arousal, valence, social acceptability, and moral content.
- *Real Time Functional Magnetic Resonance Imaging Neurofeedback (rt-fMRI-NF)*: The rt-fMRI-NF procedure will consist of an alcohol cued rt-fMRI task, such as the one used in Karch et al., 2015. In that study, addiction-related cues were presented to subjects during fMRI and subjects were instructed to decrease their response to the addiction cue (as indicated through real time feedback presented through a graphical thermometer). The purpose of this task at this stage is to develop a real-time fMRI procedure that effectively allows individuals to moderate craving response to alcohol cue stimuli. The following parameters will be used as a starting point for this task. However, the individual sessions will also be examined post-hoc and the task may be modified as appropriate.

We will use a *functional localizer*, consisting of alcohol craving, food craving and non-craving (neutral, e.g. chair, fan) blocks, to identify typical, non-modulated neural brain response to craving signals. Participants will be first shown a block of neutral pictures, a block of food pictures, then a block of alcohol pictures (specific to beverage type of choice e.g., beer, wine, liquor). Food craving pictures will be used during piloting given that HCVs are not expected to have significant craving associated with alcohol use. Fixation crosses will be presented in the center of the display prior to each block. Four 20 second blocks of each type will be presented. Each block will contain 4 images of a specific type. Each image will be displayed for 5 seconds without any inter-stimulus interval.

We will display neurofeedback based on mean signal in five regions of interest (ROIs): VTA/SN, anterior insula, VS, dlPFC and mPFC/vACC. These regions have been used in prior neurofeedback studies, indicating that individuals are capable of modulating activity in these regions in response to neurofeedback (Karch et al., 2015; Kirsch et al., 2016; Sherwood et al., 2016; Young et al., 2017). The *functional localizer* task will be used to establish baseline alcohol cue related activation in each ROI; participants will receive neurofeedback based on percentage signal change from that baseline for each ROI. The *functional localizer* task will also be used to define baseline for the ROI-based neurofeedback training procedure, where participants will be asked to modulate their neural response during craving from that baseline.

BOLD fMRI data during rt-fMRI will be processed in real-time using AFNI to measure and compute the signal changes associated with craving downregulation, which establishes the neurofeedback stimulus display. The stimulus display will consist of craving cue images alongside a brain activity “thermometer”. Hemodynamic response and signal processing will account for additional delay between subject cognition and feedback; BOLD response to a stimulus typically lags for about 3-4 seconds, then proceeds over 4-6 seconds, and feedback computation takes approximately 1 second.

A composite index will be calculated from the ROIs as part of the computation in real time to provide feedback to the participant on a 100 point “thermometer” scale. We expect this composite index to be the average percent signal change from individual baseline. Corresponding to downregulation of craving, we expect the VTA/SN, anterior insula, VS, dlPFC and ACC/mPFC values to be to be negative, as they have been in previous studies of neurofeedback associated downregulation of alcohol craving in individuals with AUD (Karch et al., 2015; Kirsch et al., 2016). Participants will be told that the level indicated on this 100-point “thermometer” represents their response to the alcohol pictures. Baseline will be defined as 80 on this 100-point scale.

$$temperature = 80 - standard \% signal change$$

*standard % signal chang* =

$$\left( \frac{\frac{S_{VTA}(baseline) - S_{VTA}(current)}{S_{VTA}(baseline)} \cdot u_{VTA}(t) + \frac{S_{AI}(baseline) - S_{AI}(current)}{S_{AI}(baseline)} \cdot u_{AI}(t)}{u_{VTA}(t) + u_{AI}(t) + u_{VS}(t) + u_{dlPFC}(t) + u_{ACC}(t)} + \frac{\frac{S_{VS}(baseline) - S_{VS}(current)}{S_{VS}(baseline)} \cdot u_{VS}(t)}{u_{VTA}(t) + u_{AI}(t) + u_{VS}(t) + u_{dlPFC}(t) + u_{ACC}(t)} + \frac{\frac{S_{dlPFC}(baseline) - S_{dlPFC}(current)}{S_{dlPFC}(baseline)} \cdot u_{dlPFC}(t) + \frac{S_{ACC}(baseline) - S_{ACC}(current)}{S_{ACC}(baseline)} \cdot u_{ACC}(t)}{u_{VTA}(t) + u_{AI}(t) + u_{VS}(t) + u_{dlPFC}(t) + u_{ACC}(t)} \right)$$

*Notes:* S = signal where  $S_{ROI}(t)$  is the signal associated with craving in the indicated ROI,  $t$  = timepoint [baseline or current],  $u$  = step function where  $u_{ROI}(t)$  are zero for each subject if the specific ROI does not present any signal changes during the localization and 1 otherwise. ROIs are ventral tegmental area (VTA), anterior insula (AI), ventral striatum (VS), dorsolateral prefrontal cortex (dlPFC) and anterior cingulate (ACC).

Participants will be directed to try to reduce their response to a target level (indicated on the thermometer feedback image), and will be given time prior to the task to think about individualized strategies to reduce craving response. During initial piloting, the only strategy provided to them will be to “try not to crave”. For every trial where the target level is hit for at least 1 second, the participant will earn \$0.50 and receive positive feedback. Each trial will last 15 seconds, with 50 trials per block. Target level will increase in difficulty progressively. After 3 successful trials (sequentially), thresholds will become further from baseline, leading to a more difficult task. If there are 3 unsuccessful trials in a row, the threshold will revert to 50% of the previous successful threshold. If response drops below 15% of baseline for three seconds, a message will be displayed reminding the participant to pay attention to the task and a noise will sound via headphones; participants will lose \$0.50 per round where they were not attending. This is to ensure participants pay attention to the task. Subjects

will start with \$5.00 “in the bank” to allow for these losses. Although a negative monetary value is possible, no money will be owed or taken out of other compensation for participation.

All participants will receive active neurofeedback during this piloting phase. No control procedure is necessary in neurofeedback piloting of Stage 1 because it aims at testing and refining the neurofeedback parameters and procedure. BOLD response associated with cue reactivity will be compared between neurofeedback downregulation and baseline. Baseline data are those time points collected during “functional localizer” described above. It has already been established that neurofeedback compared to control allows individuals to regulate neural activity in the SN/VTA (Sulzer et al., 2013), VS (Kirsch et al., 2016), anterior insula (Caria et al., 2010), and ACC (Karch et al., 2015). Neurofeedback is also already established as feasible in alcohol-using and AUD populations (Karch et al., 2015; Kirsch et al., 2016), as well as in other patient groups such as depression (Young et al., 2017) and stroke (Liew et al., 2016). Feasibility of ROIs selected and patient performance are not being investigated in this pilot, since it is already demonstrated. Moreover, differential effects of neurofeedback and group effects of neurofeedback are not being investigated at this stage of the study.

If following initial piloting, this neurofeedback calculation and display procedure is not sensitive to neuromodulation during alcohol cueing, alternative calculation procedures will be explored. For example, if we find evidence of increase in neural engagement associated with downregulation in some ROIs, we will make the following change: prior to calculating the average percent signal change, the sign of these “positive” down regulation correlates will be reversed. A post-scan questionnaire will ask subjects to rate each stimuli on evoked craving, to rate the overall difficulty of self-modulating responses to alcohol and food cues, and to report strategies used for down regulation.

Based on initial piloting, a neurofeedback calculation procedure using a support vector machine (SVM) machine learning algorithm is more greatly indicated than a ROI based approach. SVM compares new data points across the whole brain to the brain-states identified in the “functional localizer” step and provides individualized feedback based on proximity to “neutral” versus “craving” states. This technique is well established (Fede et al., 2020; LaConte, 2011). However, the ROI based approach showed more improvement in self-reported craving. Therefore, in Stage 2 we have utilized the ROI based approach.

*Cognitive Assessment:* We will administer the following tests: the Continuous Performance Test (CPT; following Conners et al., 2000), the Stroop Color and Word Test (Golden and Freshwater, 1978), and the Behavior Rating Inventory of Executive Function (BRIEF-A; Gioia et al., 2000). We selected these tasks to provide information on generalized attention, divided attention, and general executive function, but to minimally add to the assessments subjects will undergo.

- The Continuous Performance Test (CPT) will be administered in a neutral environment order to assess general attention-related problems in participants. This will help us quantify individual differences in attention that are not specifically related to response modulation in a biased competition context. It can be administered on a computer and typically takes 15 minutes to administer. The CPT will be implemented using PsychoPy (Peirce, 2007).
- The Stroop Color Word Test will be administered in both a neutral and an alcohol cued environment to assess divided attention. It takes approximately 5 minutes to administer. This will help us assess the ability of participants to inhibit attention to peripheral stimuli.
- The Behavior Rating Inventory of Executive Function-Adult Version (BRIEF-A) will be administered in a neutral environment to assess self-reported ability on nine executive functioning subscales (Gioia et al., 2000). It will help us assess the baseline ability of participants to inhibit, self and task monitor, plan, and control emotional response, processes that may be important moderators of socioemotional processing or drinking outcomes. This self-report measure has several advantages over a traditional full neuropsychologic assessment; it is less time-consuming (15-20 minutes) and can be administered electronically.

*Self-Report Assessments:* A modified version of the Alcohol Craving Questionnaire (ACQ; Higley et al., 2011) will be administered pre-and post-scan in an alcohol cued environment. Questionnaires designed to identify individual differences and traits related to socioemotional processing and drinking behaviors will also be administered: The MacArthur Scale of Subjective Social Status (Adler and Stewart, 2007), the Moral Foundations Questionnaire (MFQ; Davies et al., 2014), Interpersonal Reactivity Index (IRI; Davis, 1983), the Self-Report Psychopathy (SRP-II) scale (Paulhus et al., 2009), the Toronto Alexithymia Scale (TAS; Bagby et al., 1994), and the State General Food Craving Questionnaire (GFCQ-S; Nijs et al., 2007). We are aware that honesty on self-report measures are a limitation of their use; however, these are well validated and the ability of participants to fill them out quickly means that the inconvenience for them is much lower and their use is more feasible than 2 hour clinical interviews (such as the Psychopathy Checklist Revised).

- The MacArthur Scale of Subjective Social Status will be used to assess socioeconomic status (SES) in addition to objective demographics. This scale shows a picture of a ladder and asks individuals to graphically indicate where they are on the ladder compared to their community, and then compared to most people in the United States.
- The Moral Foundations Questionnaire (MFQ) assesses individual differences in several domains of moral values including Harm/Care, Fairness/Reciprocity, Ingroup/Loyalty, Authority/Respect, and Purity/Sanctity. This scale asks individuals to indicate how they evaluate whether something is “right” or “wrong”. This will help us identify baseline differences in moral priorities that could moderate socioemotional cognition within or between groups.

- The Interpersonal Reactivity Index (IRI) assesses individual differences in empathy, particularly in four subdomains: perspective taking, fantasy, empathetic concern, and personal distress. This will help us identify baseline differences in empathy and theory of mind that could moderate socioemotional cognition within or between groups.
- The Self-Report Psychopathy (SRP-II) scale assesses individual levels of psychopathic traits in community, non-criminal samples. Psychopathy is a personality disorder made up of affective, interpersonal, antisocial, and lifestyle traits. Psychopathy is associated with moral transgressions, so this measure will help us identify baseline differences in levels of those traits that could moderate socioemotional cognition within or between groups.
- A modified version of the Alcohol Craving Questionnaire (ACQ) as used by Higley and colleagues (2011) will be administered in order to assess baseline and post-scan alcohol craving in an alcohol-challenge environment. This information will be used first to assess whether baseline levels of craving affect socioemotional processing and post-scan whether neurofeedback down regulation of craving transfers post-scan.
- The State General Food Cravings Questionnaires (G-FCQ-S) assesses current food craving in general, particularly the desire to eat, anticipation of positive reinforcement from eating, anticipation of reduction in negative states from eating, preoccupation with eating, and physiological craving. This questionnaire will be administered at baseline and post-scan. This information will be used to assess whether neurofeedback down regulation of craving transfers post-scan, and whether baseline craving impacts cue reactivity. Time and content of last meal will also be recorded at baseline.
- The Toronto Alexithymia Scale (TAS) assesses individual levels of alexithymia, particularly on three subdomains: difficulty describing feelings, difficulty identifying feelings, and externally-oriented thinking. This will help us identify baseline differences in emotional processing that could moderate socioemotional cognition within or between groups.

### ***Stage 2:***

AUD patients will complete two MRI sessions. During session 1, prior to completing their MRI, AUD patients will complete the cognitive, craving, and self-report measures described in Stage 1. After consent but prior to participating in the study, patients will be assigned to active or sham condition. A master list, with access restricted to the PI and Lead AI, will contain the random assignment for subjects. We will collect baseline information for our outcome measures prior to scanning. Following the scan in session 1 and session 2, cognitive and alcohol craving measures will be collected again.

*Magnetic Resonance Imaging:* The first MRI session will occur within one week of admission, after active withdrawal ( $CIWA < 8$ ), and will consist of: 1) a localizer, 2) a whole brain structural scan, 3) a whole brain resting state BOLD fMRI scan, 4) the whole brain SAAT fMRI scan, 5) a functional “craving” locator scan, 6/7) two blocks of rt-fMRI-NF, 8) a post-NF functional “craving” locator scan, 9) a post-NF whole brain resting state BOLD fMRI scan, and

10) post-NF SAAT fMRI scan. The second MRI session will occur within 21-28 days of the first MRI session, and will consist of: 1) a localizer, 2) a whole brain structural scan, 3/4) two blocks of rt-fMRI-NF, 5) a functional “craving” locator scan, 6) a whole brain resting state BOLD and fMRI scan, and 7) whole brain SAAT fMRI scan. We expect that scan order may vary or may need to be repeated for technical reasons; the actual order of scans will be recorded.

- *SAAT task*: Three versions of the task will present the stimuli in different orders to be used prior to and post the NF scans. Participants will be counterbalanced to receive the versions in orders ABC, ACB, BCA, BAC, CAB, or CBA.
- *Functional “craving” locator scan*: This corresponds to the functional localizer scan used in Stage 1, but will also serve as a baseline measurement of the neural correlates of craving and as such, will be repeated after NF scans to assess changes. Three versions of the task will be used and counterbalanced as in the *SAAT* task, described above.
- *rt-fMRI-NF*: Participants will be randomly assigned to receive either rt-fMRI based active or sham neurofeedback. This will be done using a random sorting algorithm to balance conditions. This will be a pseudo-double-blind study in that the patients and individuals working with patients (except the PI and Lead AI) will be blind to NF type. Participants who are assigned to the sham condition will be yoked to an active condition participant\*. The rt-fMRI-NF protocol will be optimized based on piloting from Stage 1; however, the procedure used in Stage 2 will only contain alcohol craving cues, not food craving cues. Moreover, participants in Stage 2 will be given strategies other participants found useful for neuromodulation.
  - *Sham condition*: Sham neurofeedback will differ from active feedback only in that rather than displaying signal from the patient’s own neural signal, signal from his or her yoked active participant will be fed into the receiver and displayed to the sham condition patient. The sham condition patient will also be compensated at the same level as the active condition participant. The procedure will allow us to determine the effect of neurofeedback, regardless of perceived performance or monetary earnings.

#### **Other MRI Scan Information.**

- Various physiological measures such as heart rate, skin conductance, blood flow, and eye position may be recorded during the practice and fMRI scan sessions.
- We are conducting the MRI scans using FDA-approved 3T along with approved head coils, pulse sequences and software in the NMR Research Center. The scanners used for this protocol is a Siemens Magnetom Prisma.
- Participants will complete a resting-state fMRI scan at each session to assess changes in intrinsic network connectivity.
- Participants will get a whole-brain structural MRI scan.
- All study participants will be accompanied at the NMR Center by study team members and/or medically responsible staff. All study team members have completed CPR Training, NMR Center Safety Training, and the NMR Center Emergency Preparedness Training, including standard emergency procedures to be followed in the event of a fire (code red) or if a participant is in respiratory and/or cardiac arrest (code blue). These

procedures include removing and evacuating the participant from the scanner, contacting the appropriate emergency response teams as well as the MAI of the study, and being aware of the locations of emergency items such as the emergency drug box, crash cart, AED, and fire extinguisher.

### **General Procedures.**

- *Urinalysis and Breath Alcohol Testing: Urinalysis and Breath Alcohol Testing:* Participants will be required to provide a urine sample for a qualitative urine drug test at the beginning of all study visits. The Qualitative (DLM) tests for cocaine, methamphetamines, benzodiazepines (except for inpatients) and opiates must be negative for all participants. Tests for THC will be carried out and recorded for data purposes but will not be exclusionary. In addition, they will have to complete and pass a breath alcohol test at the beginning of each study visit in order to participate. To pass, they must not have a positive BrAC value (greater than 0.00 g/dL). Individuals capable of becoming pregnant also must have a negative pregnancy test before they can participate in the study.
- Portions of this study (cognitive assessments) will be conducted in an alcohol-cued “bar-like” environment. This space is a bar-like room at the CRC. This room includes bar-like furniture and décor, liquor bottles (filled with water), as well as a chair and a table. The room is also equipped with a two-way intercom system and a closed-circuit camera (no sound) through which participants may be monitored for signs of craving-related distress by study staff in another room. The use of a bar-like room has never been associated with an increased risk of drinking after the experiment. Alcohol cue-reactivity experiments are performed on a regular basis at NIAAA. However, increased craving and distress may appear during the exposure to the bar-like environment. Should clinically significant symptoms appear, participants will have immediate access to licensed health care professionals.

### **E. STUDY POPULATION**

- *Stage 1:*  
We plan to study up to 30 individuals with moderate to severe AUD and 30 non-alcohol naive healthy control volunteers (HCVs).

Individuals with AUD will be recruited from the surrounding community. Individuals may or may not be treatment seeking, but must meet diagnostic criteria for AUD. Male healthy volunteers must, on average, drink 14 or less standard drinks and female healthy volunteers must, on average, drink 7 or less standard drinks per week in order to be considered for this study based on most recent Timeline Followback (TLFB) within the last 90 days. AUD participants will not undergo any long-term follow-up for the Stage 1 of this study.

- **Stage 2:**

We plan to study up to 56 inpatients with AUD. Over the past two years, there have been just over 90 inpatients per year, with the vast majority being between 30 and 60 years of age, with about a 3:1 male:female ratio, and with about 55% African American, 40% Caucasian, 5 % other races. We plan our inpatient recruitment to be within these general guidelines.

The inpatient individuals with AUD will be recruited from alcohol treatment conducted at the NIAAA inpatient unit within the first week of treatment. All inpatients go through similar treatment regimens, take similar medications, and have similar opportunities to participate in research. The impact of these factors is expected to differ between neurofeedback conditions only at random, and is not expected to impact the research outcome.

- **Randomization:**

The second stage of this study uses randomized group assignment. Patients will be assigned to active or sham condition using a random number generator, with balanced probability across conditions. A master list, with access restricted to the PI and Lead AI, will contain the random assignment for subjects.

## **E.1: INCLUSION AND EXCLUSION CRITERIA**

### **Stage 1:**

#### **A. Inclusion Criteria**

1. 21 to 65 years old
3. Healthy volunteers only: Consuming on average 7 or less standard drinks/week if female; 14 or less standard drinks/week if male (as determined by the most recent measurement within the past 90 days Alcohol Timeline Followback)
4. AUD participants only: Diagnosed with current moderate to severe alcohol use disorder according to most recent SCID 5 diagnosis

#### **B. Exclusion Criteria**

1. Significant history of head trauma or cranial surgery
2. History of neurological disease based on self-report and neuromotor physical exam, conducted by a health care provider, that would interfere with neuroimaging research. Posthoc, clinical MRI scans done according to NIH Clinical Center policy may be reviewed and if there is evidence from that scan of past or current neuroabnormalities that, in the PI or MAI's expert opinion, interfere with research neuroimaging data, the subject may be excluded from data analysis.
3. Physical health concern that would significantly impair or increase the risk of study participation.
4. Healthy volunteers only: Have fulfilled DSM-5 criteria for a current substance or alcohol use disorder
5. Female participants only: Currently pregnant

6. Presence of any ferromagnetic objects in the body that may be adversely affected by or contraindicated for MRI as determined by the NIAAA MRI Safety Screening Questionnaire
7. Any flag on the NIAAA MRI Safety Screening Questionnaire, unless cleared by medically responsible staff (MD/NP)
8. History of non-substance related psychosis
9. Lack of experience with alcohol (defined as less than 3 lifetime drinks reported in history and physical or on Lifetime Drinking History)

***Stage 2\*:***

A. Inclusion Criteria

1. 21 to 65 years old
3. Inpatient currently seeking treatment for alcohol use disorder

B. Exclusion Criteria

1. Significant history of head trauma or cranial surgery,
2. History of neurological disease based on self-report and neuromotor physical exam, conducted by a health care provider, that would interfere with neuroimaging research.
3. Physical health concern that would significantly impair or increase the risk of study participation.
4. Presence of any ferromagnetic objects in the body that may be adversely affected by or contraindicated for MRI as determined by the NIAAA MRI Safety Screening Questionnaire
5. Any flag on the NIAAA MRI Safety Screening Questionnaire, unless cleared by medically responsible staff (MD/NP)
6. History of non-substance related psychosis
7. Female participants only: Currently pregnant

\* Inpatients who have been admitted into the behavioral unit at the Clinical Center for AUD treatment, maybe considered for this study. Upon completion of consenting procedure, any data necessary (but not readily available) to determine eligibility maybe collected under this study. However, to avoid undue discomfort, burden, and inconvenience, this information, if available, can be gathered from routine clinical care or other NIAAA clinical studies and data up to 30 days prior to the consenting date. Participants who do not satisfy any of the above criteria will not participate in the study procedures at the time. They may be re-scheduled for a future date(s) when they fulfill all inclusion/exclusionary criteria.

We will utilize SCID diagnoses (from other studies such as 14-AA-0181) to determine AUD diagnosis and any potential Axis I disorders. However, for inpatients, since the nursing practice is initially focused on patient detoxification and treatment, the SCID diagnoses might not always take place within the first week of the patient admission to the alcohol unit. This could seriously hamper the subject recruitment in the second stage of this study. We will conduct the MR scan of eligible participants (based on the above inclusion/exclusion criterion) according to study timeline regardless of the availability of SCID diagnoses.

Inpatients are admitted based on the clinical opinion of medical staff that the individual has a pattern of alcohol use disorder. We will enroll inpatients with this opinion but the SCID diagnoses will be completed in order to have consistent research data on symptomology and severity, and to use any potential Axis I disorder as a study confound. Additionally, we will collect information on medications being taken by patients currently or within the last month, including dose, schedule, and timeline. This will be used as a covariate in the statistical design to control for variation associated with these medications.

## **E.2: Clinical and Laboratory Methods**

All primary procedures will be conducted for research purposes. Clinical procedures will be collected prior to participation primarily for eligibility determination. Participants will be required to provide a urine sample for a qualitative urine drug test at the beginning of all study visits. Females also must have a negative pregnancy test before they can have a MRI scan.

In coordination with this study, participants may have a clinical MRI scan under any other NIAAA protocol. As part of NIH Clinical Center policy, this MRI may only be done on subjects who have qualified for and will participate in an NIAAA study that requires MRI or fMRI scans and also have not received a clinical MRI scan at the NIH in the past 12 months. A clinical MRI of the brain is a minimal risk procedure that allows the diagnosis of brain damage. This MRI scan may include any standard clinical MR sequence.

## **E.3: Inclusion of Vulnerable Populations**

This study does not involve vulnerable populations. NIH employees will be eligible to participate as subjects; while NIH employees are not technically a vulnerable population under federal regulation, they will be recruited consistent with NIH Manual Chapter 3014-404-Research Involving NIH Staff as Subjects (<https://policymanual.nih.gov/3014-404>)

Employees of the NIAAA will not be enrolled in this study, since their participation and potential knowledge of the research study may influence research outcomes.

### *Justification for exclusion of vulnerable populations*

*Children* : The inpatient alcohol use disorder treatment clinic from which patients will be recruited in stage 2 is an adult sample; stage 1 recruitment is planned to recruit comparable adults from the community. Moreover, since in the United States, it is illegal for children under the age of 21 to drink alcohol, inclusion of children in this study is an ethical concern. The problem of adolescent alcohol drinking is important, but outside the scope of this study. So, children under 21 will not be included in this study.

*Pregnant Women, Human Fetuses, Neonates* : It is not known if it is safe for a developing fetus to be in the MRI environment. Since this study's primary outcome and its primary manipulation require patients to be in an MRI environment, this would present an unnecessary risk for pregnant women. So, pregnant women will not be included in this study.

*Prisoners:* The inpatient alcohol use disorder treatment clinic from which patients will be recruited in stage 2 does not include individuals who are prisoners, since inpatient treatment requires a stay at the clinic; prisoners are not able to leave custody for such a treatment program. Stage 1 recruitment is planned to recruit comparable adults from the community. Moreover, inclusion of prisoners would require supervised transport from a controlled facility to the hospital for a MRI; this would entail procedures for the prisoner that are an unnecessary discomfort. Finally, given that prisoners are in a controlled environment, their drinking habits would not be representative of their drinking behaviors or disorder status in the community. This may be comparable to a treatment seeking population; we are recruiting non-treatment seeking individuals from the community. In fact, prisoners may be receiving substance use counseling while incarcerated. So, prisoners will not be included in this study.

*Adults Who Are or May be Unable to Consent:* Adults who are unable to consent will not be included in this study. If individuals do not have the communication or mental capacity to provide informed consent, they will likely also be unable to complete study procedures (e.g., filling out questionnaires). Since this study does not provide a known direct benefit to the participants, exclusion of this vulnerable population will not differentially prevent them from obtaining a benefit. If the inability to consent is temporary (i.e., acute intoxication), the individual may be eligible to consent on a different occasion.

#### **E.4: Strategies for Recruitment and Retention**

*Rationale for subject selection based on a review of gender/ethnic/race categories at risk for the disease/condition being studied:*

Subjects will be selected equitably based on the population demographics of the greater Washington, D.C. and Baltimore metropolitan regions

Healthy control volunteers (HCV) and individuals with AUD will be recruited from the protocol 14-AA-0181: “NIAAA Natural History Protocol.” Subjects will be recruited from a pool of previous participants or through advertisements placed in electronic and non-electronic local and social media and bulletin boards or announcement areas. Subjects will be recruited through the following methods:

- Advertisements placed in electronic and non-electronic local and social media, bulletin boards, or displays, or given out as flyers or cards. Advertisements may also be used in the form of radio or newspaper ads, or as banners. Advertisements may be posted on NIH’s campus as well as in community locations and businesses.
- The participants enrolled in the protocol 14-AA-0181.
- The subject’s eligibility requirements are completed after consenting and enrolling into this protocol. No study sessions will commence until eligibility is reviewed by

the PI or an AI (designated by the PI to obtain consent) together with the physician or nurse practitioner involved in the evaluation of the participant, and their concurrence of the participant's eligibility is documented on the eligibility checklist form. Further, a third signature by an independent clinician or quality assurance monitor will be obtained following their verification of the participant's eligibility for the study. All signatures will be obtained prior to obtaining consent of the participant.

- See appendixes and attachments for recruitment materials

*Costs:* It is possible that the study procedures will reveal previously undiagnosed abnormalities (e.g., the potential finding of a tumor from the brain MRI studies). If this happens it may result in stress and time and financial costs to the study participant and their family. The investigators are not assuming responsibility for such potential consequences, but will make every effort to help such families to deal with whatever findings arise.

*Compensation:* Participants will be compensated for research-related time dedicated, discomfort, and inconveniences in accord with NIH guidelines. Participants will be compensated for the parts that they complete.

Activity	Time (+ inconvenience units)	Cost
<b><u>Stage 1 Visit</u></b>		
Behavioral Assessments	1.5 hours (1)	40.00
MRI Session	2 hours (3)	80.00
Earnings from rt-fMRI task	----	0.00-60.00
Post-NF Assessments	.5 hour (1)	20.00
<b>Total</b>		<b>\$140.00 – \$200.00</b>
<b><u>Screening Procedures*</u></b>		
Blood work / UDS	0.5 hours (1)	\$20.00
Clinical exam (e.g., H&P)	0.5 hours (1)	\$20.00
Timeline Followback (TLFB)	0.5 hours (1)	\$20.00
Psychopathology assessment (e.g., SCID)	2 hours (1)	\$50.00
<b>Total</b>		<b>\$0.00 - \$110.00</b>
<b><u>Stage 2 Session 1</u></b>		
Baseline Behavioral Assessments	1.5 hours (1)	40.00
MRI Session	2 hours (3)	80.00

Earnings from rt-fMRI task	----	0.00-60.00
Post-NF Assessments	1 hour (1)	30.00
<b>Total</b>		<b>\$150.00 - \$210.00</b>

### **Stage 2 Session 2**

MRI Session	2 hours (3)	80.00
Earnings from rt-fMRI task	----	0.00-60.00
Post-NF Assessments	1 hour (1)	30.00
<b>Total</b>		<b>\$110.00 - \$170.00</b>

### **Follow up 1**

Behavioral Assessments	1 hours (1)	35.00
<b>Total</b>		<b>\$35.00</b>

### **Follow up 2**

Behavioral Assessments	1 hours (1)	50.00
<b>Total</b>		<b>\$50.00</b>

### **Follow up 3**

Behavioral Assessments	1 hours (1)	65.00
<b>Total</b>		<b>\$65.00</b>

**Total Compensation Range:** **\$140-\$530**

\* This procedure is performed only if screening this data is not available from NIAAA natural history or other study or the participant has not had a clinical MRI at the NIH within the last 12 months.

## **F. PARTICIPANT DISCONTINUATION/ WITHDRAWAL**

Participants are free to withdraw from participation in the study at any time upon request. Additionally, subjects may be discontinued or withdrawn from the study at any time if the investigators or the medical staff feel that further participation would pose a risk for the subject or for study staff, if they have reason to believe the integrity of the data collected from the subject is in question, or if the subject is unwilling or unable to complete study procedures.

## **G. STUDY ASSESSMENTS AND PROCEDURES**

### **G.1: Screening:**

As mentioned before, inpatients who have been admitted into the behavioral unit at the Clinical Center for AUD treatment, maybe considered for this study. To avoid undue discomfort, burden, and inconvenience, any information necessary to determine participant's eligibility, if available, can be gathered from routine clinical care or other NIAAA clinical studies such as 14-AA-0181 up to 30 days prior to the consenting date. The eligibility of a potential participant may be determined any time before or after consenting in this study. Therefore, we have requested a pre-eligibility consent waiver for this part of the study prior to consenting for the procedures outlined in this study. This research involves no more than minimal risk to the subjects. The research cannot be carried out unless we are able to brief the participant, verify their age and participation in other NIAAA studies, and gather information regarding their handedness, pregnancy status, and presence of non-removable metal in their body before consenting them in this study. This waiver will not adversely affect the rights and welfare of the subjects. We will not collect and store any information from these individuals once their qualification is found implausible or they express lack of desire to participate in the study.

The subject's eligibility is evaluated prior to first study session in this protocol. The eligibility is reviewed by the PI or an AI (designated by the PI to obtain consent) together with the physician or nurse practitioner involved in the screening and/or evaluation of the participant, and their concurrence of the participant's eligibility is documented on the eligibility checklist form. Further, a third signature by an independent clinician or quality assurance monitor will be obtained following their verification of the participant's eligibility for the study. All signatures will be obtained prior to obtaining consent of the participant.

As part of NIH Clinical Center policy, a clinical MRI scan must be done on subjects who will undergo any research involving MRI within 12 months prior to the study. If at the time of this study such scan is not available, we will conduct the clinical scan within this study session as well. A clinical MRI of the brain is a minimal risk procedure that allows the diagnosis of brain damage. This MRI scan may include any standard clinical MR sequence.

*Withdrawal Assessment:* Under this study, outpatient AUD participants will be assessed for withdrawal symptoms during screening procedures and prior to study session. As part of inpatient treatment, AUD participants are monitored and treated for withdrawal. The Clinical Institute Withdrawal Assessment (CIWA-Ar) for alcohol will be used. The study session will not commence for AUD participants with most recent CIWA score of 8 or greater.

*Urinalysis and Breath Alcohol Testing:* Participants will be required to provide a urine sample for a qualitative urine drug test at the beginning of all study visits. The Qualitative (DLM) tests for cocaine, methamphetamines, and opiates must be negative for all participants. Tests for THC and benzodiazapines will be carried out and recorded for data purposes but will not be exclusionary. This is because benzodiazapines are often prescribed for withdrawal symptoms

(Mayo-Smith, 1997) or anxiety (Kushner et al., 2000), which is comorbid with AUD with cannabis use as a comorbidity as well (Degenhardt et al., 2001). In addition, they will have to complete and pass a breath alcohol test at the beginning of each study visit in order to participate. To pass, they must not have a positive BrAC value (greater than 0.00 g/dL). For MRI sessions only, females also must have a negative pregnancy test before they can participate in the study.

## **G.2: Assessments:**

### **Interviews and Questionnaires.**

- *Outcome Measures (Stage 2 only):* Inpatient AUD subjects will be contacted approximately 1 month, 3 months, and 6 months post-release from inpatient treatment. Treatment release date is part of patient files and will be accessed to determine these time points. Follow-up sessions will be conducted via the phone and/or through self-administered secure online data collection (e.g., through Qualtrics) unless the subject prefers to come to the NIH Clinical Center for in-person follow up. Participants will be asked for follow-up contact information at baseline, including people for whom we have permission to contact to try to reach the patient, and permission to search public records for related information (e.g., incarceration). Participants will be asked about behaviors in the last month including: 1) alcohol and substance use and craving; 2) contacts with the legal system; 3) employment; 4) negative drinking consequences like DUIs, fighting while drunk, and blackouts; 5) intimate partner aggression, and 6) fulfillment of social responsibilities. These measures will also be given at the first in-person session to establish a baseline for each participant. Given the sensitive nature of many of these measures, participants will be reminded about the availability of resources for counseling and the parameters of confidentiality conferred by the Certificate of Confidentiality.
  - *Alcohol Use Outcomes:* The Alcohol Timeline Followback (administered initially as part of the standard NIAAA Office of the Clinical Director screening session) will be conducted to identify patterns of drinking alcohol since release from treatment, including amount, variability, relapse and drinking days (Sobell and Sobell, 1992). Patients will use a calendar to aid them in specific day by day recall of drinking activities. The Alcohol Craving Questionnaire will also be administered at follow-ups.
  - *Community Functioning Outcomes:* The Drinker Inventory of Consequences (DrInC) will be administered to assess drinking-related behaviors and outcomes including: acute and chronic health problems, personal feeling states, fulfillment of social responsibilities, relationship health, and impulsive/risky behaviors (Miller et al., 1995). Participants will also be asked for employment status information, including hours worked.

- *Aggression, victimization, and antisocial behavior outcomes:* The Revised Conflict Tactics Scales (CTS2) will be administered to assess intimate partner aggression, including type, severity, and regularity of behavior (Straus et al., 1996). Participants will also be asked to self-report contacts with the police, convictions, and other alcohol-related criminal behaviors (such as driving under the influence of alcohol, disorderly conduct, and probation violations). Offenses will be categorized into one of 27 common categories, following the procedure in Aharoni et al., 2013 (Aharoni et al., 2013).
- *Other Measures:* Patients will complete the self-report measures of individual differences at their first study visit prior to scanning. Patients will complete the cognitive assessments and ACQ before and after the first neurofeedback scan, and after the second neurofeedback scan.

### *General Procedures*

- Portions of this study will be conducted in an alcohol-cued environment (priming procedures and the second Stroop Test). This space is a bar-like room at the CRC. This room includes bar-like furniture and décor, liquor bottles (filled with water), as well as a chair and a table. The room is also equipped with a two-way intercom system and a closed-circuit camera (no sound) through which participants may be monitored for signs of craving-related distress by study staff in another room. The use of a bar-like room has never been associated with an increased risk of drinking after the experiment. Alcohol cue-reactivity experiments are performed on a regular basis at NIAAA. However, increased craving and distress may appear during the exposure to the bar-like environment. Should clinically significant symptoms appear, participants will have immediate access to licensed health care professionals. Participants will not be exposed to any alcohol.
- Any data collected via online surveys will be hosted on Qualtrics, which offers a platform that can securely collect participant data while protecting sensitive information. The data collected will be linked to the participant by a subject ID code; names, birthdates, and similar PII will not be hosted on Qualtrics. The Qualtrics platform has security and privacy controls that are consistent with NIH data security requirements, and the platform has been approved by the NIAAA ISSO. Qualtrics provides several metrics of the survey implementation, including completion times, which will be tracked as a measure of compliance. Qualtrics will be used within NIAAA ISSO approved parameters.

*MRI-Scan Portion:* Prior to entering the scanner, participants will complete a training protocol designed to eliminate the need for practice in the MR environment. This may consist of verbal and/or written instructions, and/or examples of what they will see on the screen when they are in

the scanner. Participants will be given the opportunity to ask questions until an understanding of the task is established.

All study participants will be accompanied at the NMR Center by the study team members. All study team members have completed CPR Training, NMR Center Safety Training, and the NMR Center Emergency Preparedness Training, including standard emergency procedures to be followed in the event of a fire (code red) or if a participant is in respiratory and/or cardiac arrest (code blue). These procedures include removing and evacuating the participant from the scanner, contacting the appropriate emergency response teams as well as the MAI of the study, and being aware of the locations of emergency items such as the emergency drug box, crash cart, AED, and fire extinguisher. The presence of a healthcare professional will not be required in the MR sessions for any participants in this study.

### **Study Agents/Interventions**

No research drugs or devices will be used in this study. rt-fMRI-NF will be investigated as an intervention for alcohol cue salience/ response modulation atypicalities related to alcohol use disorder

### **G.3: Adverse Event Reporting:**

Adverse events, protocol deviations, unanticipated problems (UP), Unanticipated Adverse Device Effects (UADEs), serious adverse events, sponsor and serious, are defined as described in NIH HRPP SOP 16 (“Reporting Requirements for Unanticipated Problems, Adverse Events and Protocol Deviations.”) or as required by subsequent NIH HRPP SOPs. All adverse events occurring during the study, including those observed by or reported to the research team, will be recorded. Reportable events will be tracked and submitted to the IRB as outlined in Policy 801. Serious unanticipated problems, Unanticipated Adverse Device Effects and serious protocol deviations, will be reported to the IRB and CD as soon as possible but not more than 7 days after the PI first learns of the event. Not-serious adverse events will be reported to the IRB and CD as soon as possible but not more than 7 days after the PI first learns of the event.

### **Serious Adverse Events**

The study investigator will immediately report to the IRB any serious adverse event, whether or not considered study intervention related, including those listed in the protocol and must include an assessment of whether there is a reasonable possibility that the study caused the event.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the Data Coordinating Center (DCC)/study sponsor and should be provided as soon as possible.

Unexpected fatal or life-threatening suspected adverse reactions will be reported to the Clinical Director as soon as possible, but in no case later than 7 calendar days after the PI first learns of the event.

## Reporting of Pregnancy

We will test for pregnancy at each study visit in individuals capable of becoming pregnant. If a subject finds out after participating that they may have been pregnant during study procedures (i.e., drinking alcohol), and the study staff becomes aware of this, the participant will be discontinued and it will be reported to IRB and the Clinical Director.

## G.4: Unanticipated Problems:

### Definition of Unanticipated Problems (UP)

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied; and
- Related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others (which many include research staff, family members or other individuals not directly participating in the research) at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or expected.

### Unanticipated Problem Reporting

The investigator will report unanticipated problems (UPs) to the NIH Institutional Review Board (IRB) as per Policy 801. Not-serious unanticipated problems will be reported to the IRB and CD as soon as possible but not more than 14 days after the PI first learns of the event.

## H. STATISTICAL CONSIDERATIONS

### H.1: Statistical Analysis Plan:

#### *Stage 1:*

1. To address primary objective 1, data analysis of neural response during the SAAT task will be conducted using AFNI (Cox, 1996). Six conditions of interest will be modeled based on stimuli onset time: *socioemotional-alcohol*, *socioemotional-neutral*, *not socioemotional-alcohol*, *not socioemotional-neutral*, *neutral-alcohol*, and *neutral-neutral*. A 3 [cue type] x 2 [distractor type] x 2 [group] mixed-factorial multivariate model will then be run. The primary comparison of interest is the group effect on the contrast of the *socioemotional-alcohol* > *socioemotional-neutral* conditions.
2. To address primary objective 1, eye tracking and attention task data will also be examined using this analysis procedure, conducted in R using the lme4 package (Bates et al., 2014; R Core Team, 2017) and other relevant statistical packages.

3. To pilot the rt-fMRI-NF training procedure, we will evaluate performance of the task based on a) whether neural response during downregulation is less than neural response during functional localization and b) what percentage of trials participants are successfully able to hit down-regulation targets (target percentage: 50%). The protocol will also be optimized based on post-scan questionnaire responses. Benchmark (a) will be evaluated offline post-scan using AFNI and other established neuroimaging analysis tools, modeling neural responses from the functional locator and from the down regulation trails in a within-subject design. Benchmark (b) will be evaluated offline post-scan using R to calculate the average behavioral performance by group. Modifications will be made to the task as required.

### ***Stage 2:***

1. To address primary objective 1, we will analyze neural response during the SAAT task by modeling conditions using the procedure described in Stage 1, Step 1. A 3 [cue type] x 2 [distractor type] x 2 [neurofeedback condition] x 3 [time point] mixed-factorial multivariate model will then be run. The primary comparison of interest is the neurofeedback condition x time point effect on the contrast of the *socioemotional-alcohol* > *socioemotional-neutral* conditions.
2. To address primary objectives 1 and 2, eye tracking, craving, and attention task data will also be examined using this analysis procedure, conducted in R using the lme4 package (Bates et al., 2014; R Core Team, 2017) and other relevant statistical packages.
3. To address primary objectives 1 and 2, and secondary objective 1, we will examine negative drinking consequences and drinking behaviors following release from inpatient treatment as usual with or without rt-fMRI-NF training using a mixed-factorial 2 [NF condition: active/sham] x 4 [time point: baseline, 1/3/6 months post] multivariate model design. The comparison of interest is the neurofeedback condition x time point effect on 1) alcohol use outcomes, 2) community functioning outcomes, and 3) legal contact and problem behavior outcomes. We will also conduct a mediation analysis using the mediation package in R (Tingley et al., 2014). Specifically, we will examine whether the association between neurofeedback and outcomes is mediated by the change in neural engagement corresponding to *socioemotional-alcohol* > *socioemotional-neutral* conditions before and after neurofeedback.

### ***Secondary Objectives:***

1. To address secondary objective 2, we will use a data-driven independent components analysis approach to investigate whole brain network connectivity using the GIFT package to analyze BOLD resting state fMRI scan data (Calhoun, 2004). Our analysis of interest is the neurofeedback condition x time point effect on resting state BOLD dynamics.
2. To address secondary objective 3, we will conduct a modification of Stage 1, analysis 1. Within individuals with mild to severe AUD, continuous measures of alcohol use severity, such as the Lifetime Drinking History, Alcohol Timeline

Followback, and Alcohol Use Disorders Identification Test (maybe collected as part of this or any other NIAAA procedure) will be modeled as quantitative variables of interest within the 3 [cue type] x 2 [distractor type] mixed-factorial multivariate model. The primary comparison of interest is the alcohol use severity effect on the contrast of the *socioemotional-alcohol* > *socioemotional-neutral* conditions. Baseline SAAT task data from Stage 2 may also be included in this analysis.

3. To address secondary objective 4, we will conduct modifications of the Stage 1 and Stage 2, part 1 planned analyses. Data from the IRI, MFQ, and SRP-II will be used as quantitative variables of interest within the 3 [cue type] x 2 [distractor type] mixed-factorial multivariate model, where the comparisons of interest are the empathy, moral foundations, and psychopathy effects on the contrast of the *socioemotional-alcohol* > *socioemotional-neutral* conditions. Similar analyses will be carried out using demographic variables (age, IQ, sex) and attentional task performance.

**General Analysis Procedures:**

1. ALL BOLD fMRI scans will be preprocessed using a standard pipeline in AFNI: despiking, temporal alignment, coregistration, smoothing, and motion correction (Cox, 1996).
2. Where relevant, appropriate whole brain false positive rate control for the neuroimaging analyses will be implemented through 3dClustSim based on the updated procedure using autocorrelation functions (ACF) and as recommended by Cox and colleagues (2016). Cluster-size thresholds will be set based on a per-voxel p-value threshold of  $p = .001$  and whole-mask threshold of  $\alpha = .05$ .
3. Preprocessing of the data will take place as the collection of data for each session is completed.
4. In order to optimize the study and minimize subjecting the patients to undue MR procedures, we will conduct group analysis after every 10 subjects in each group. Upon determining statistically significant outcomes the study may be terminated.

**Power Analysis:*****Stage 1:***

In order to detect differences in socioemotional processing in the presence of alcohol cues between individuals with AUD and healthy controls, we conducted a power analysis based on reported effect sizes from studies of moral processing and substance use and emotional processing in the presence of alcohol cues or under the influence of alcohol (Table 1). Power analysis was conducted using the pwr package in R (Champely, 2009; Champely et al., 2017). The analyses were conducted with an estimated average effect size  $d = 1.235$ ,  $\alpha = .001$ , power = 0.8. An estimated sample of  $n = 25$  per group (total  $N = 50$ ) is required to detect group effects.

*Table 1. Effect Sizes for Stage 1 Power Analysis*

Study	Effect Size (d)	Description
Caldwell et al., 2015	0.58	Implicit moral processing in cocaine users versus non cocaine users
Fede et al., 2016	0.67	Explicit moral processing in stimulant users versus non stimulant users
Padula et al., 2011	1.85	Emotional face decoding in alcohol administration versus placebo
Gilman & Hommer, 2008	1.84	Emotional processing in the presence of alcohol cues
<b>Average</b>	<b>1.235</b>	

Note: Cohen's  $d$  effect size values were estimated based on reported significant  $t$ -values in referenced publications

***Stage 2:***

In order to detect rt-fMRI-NF related effects, we conducted a power analysis based on studies of rt-fMRI neurofeedback. The analyses were conducted with the average effect size estimated at  $d = 2.403$ . With  $\alpha = .001$ , and an estimated power of 0.8, an estimated sample of  $n = 8$  per group (total  $N = 16$ ) is required to detect condition effects of neurofeedback. However, given that we are also interested in sustained transfer effects of neurofeedback, we ran power analysis with an estimated transfer effect size of neurofeedback from Young et al., 2017 of  $d = .80$ ,  $\alpha = .05$ , and an estimated power of 0.8. An estimated sample of  $n = 23$  per group (total  $N = 46$ ) would be required to detect those group effects. For neuroimaging power analysis,  $\alpha$  was estimated at the more conservative .001 to account for multiple correction significance thresholds; this is not required for hypothesis driven behavioral analysis. We selected the larger subject recruitment numbers to be able to address our primary objectives completely.

Following power analysis, we added 20% to our planned recruitment numbers to account for attrition, data collection issues, and variability in effect strength. For both stages, we expect some participants may not complete a session due to unanticipated logistical challenges (e.g., urinalysis results are delayed from the laboratory), uncomfortable or excessive movement in the MRI, or personal reasons. For Stage 2, we expect that some participants will not complete the planned sessions due to leaving treatment early, or schedule problems. We also anticipate that some participants may not be locatable for some or all follow-ups post-treatment release. *The resulting planned recruitment for Stage 1 is N = 60 (per group n = 30) and for Stage 2 is N = 56 (per group n = 28).*

Table 2. Effect Sizes for Stage 2 Power Analysis

Study	Effect Size (d)	Description
Young et al., 2017	0.80	Neurofeedback intervention for depression
Kirsch et al., 2016	1.54	Neurofeedback modulation of alcohol cue reactivity in the striatum
Karch et al., 2015	3.71	Neurofeedback modulation of craving related brain responses
Robineau et al., 2017	3.56	Increase in neuromodulation of visual cortex over two sessions of neurofeedback
<b>Average</b>	<b>2.403</b>	

Note: Cohen's d effect size values were estimated based on reported significant t-values or F values in referenced publications

## I. REGULATORY AND OPERATIONAL CONSIDERATIONS

### I.1: Informed Consent.

Any investigator obtaining informed consent will complete the NIMH Human Subject Protection Unit's "Informed Consent" training, or an equivalent NIH approved informed consent training. The informed consent document describes each of the procedures and their risks and benefits in layman's terms. The consent process will take place in a private setting where adequate opportunity will be afforded to all subjects to ask any questions they may have, and these will be addressed to their satisfaction prior to completing the informed consent process. The consent procedure is not in any way binding. Participants will be informed of the following:

1. They have the choice to participate or not in this study.
2. All subjects will be asked to participate in the following assessments:
  - a) Complete tests of attention/executive function, personality/individual differences, craving, and baseline problem behaviors prior to scanning. Total testing time will be approximately 70 minutes.
  - b) Complete a baseline magnetic resonance imaging protocol, including the SAAT task described previously (approximately 35 minutes)
3. Some subjects may also be asked to participate in some of the following additional assessments:
  - a) Complete post scan questionnaires rating pictures used in the scanning task (approximately 15 minutes).
  - b) rt-fMRI-NF training protocol (sham or active) for made up of two 13 minute blocks (approximately 26 minutes)

- c) Complete tests of attention and craving after scanning. Total testing time will be approximately 25 minutes.
  - d) Complete post NF magnetic resonance imaging protocol, including a different version of the SAAT task (approximately 35 minutes)
  - e) Complete a second MRI scan visit approximately 3 weeks after the first scan, including the SAAT task, the neurofeedback task, craving measures, and attentional tests.
  - f) Study staff may attempt to contact participants by phone, mail, or email approximately 1 month, 3 months, and 6 months after they leave or complete treatment; a phone or in person interview will then be scheduled to collect follow up information and about drinking, problem behaviors, and community functioning. All or some questions may be asked in the form of a secure online survey, rather than verbal interview when appropriate.
- 4. All subjects will be exposed to pictures of alcohol in the scanner and will be asked to complete tasks in a controlled environment where alcohol is present.
  - 5. Some subjects who have received active neurofeedback brain activity training will have their anonymous feedback displayed to another participant as a placebo neurofeedback signal.
  - 6. Some subjects will be randomly assigned to a placebo version of brain activity training, in which case their option to earn extra money through performance would be tied to the performance of another participant; however, subjects will not be informed of whether or not they are in the placebo or active group.

## **I.2: Confidentiality and Privacy.**

Participant confidentiality and privacy is strictly held in trust by the participating investigators and their staff. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval.

There are two types of stored data resulting from this protocol: (1) cognitive and brain imaging data which are stored electronically in secure, password-protected NIAAA computers located in the labs of the Clinical NeuroImaging Research Core in the NIH Clinical Center; (2) paper questionnaires and evaluation forms stored in locked file cabinets in locked rooms assigned to the Clinical NeuroImaging Research Core in the NIH Clinical Center. Access to all the study data will be restricted to authorized personnel

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements. Data from participants will be maintained by having data coded to mask participants' identities. Further, files containing participant names and the master list of participants will be kept in a locked file under the supervision of the Principal Investigator.

Access to all the study data will be restricted to authorized personnel via an Active Directory user account. Each authorized staff member will have a unique logon ID and password. All project staff with access to data will be trained on procedures for protecting the confidentiality and security of sensitive information.

All research activities will be conducted in as private a setting as possible.

The study monitor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

Following study completion, study participant research data, which is for purposes of statistical analysis and scientific reporting, will be submitted to NIAAA Repository Protocol (PI: Melanie Schwandt, Ph.D.), and any future research will be conducted, following appropriate agreements and IRB review, under that protocol. Any data transmitted outside of the NIH will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by collaborating research staff will be secured and password protected.

Study investigators funded by the National Institutes of Health are automatically granted a Certificate of Confidentiality (CoC) issued by the NIH, U.S. Department of Health and Human Services (US:DHHS), per NIH policy NOT-OD-17-109 as of October 1<sup>st</sup>, 2017. A CoC prevents the Investigators from being forced to tell people who are not connected with this study about subjects' participation in this research, even under a subpoena. Disclosure will be necessary, however, upon request by DHHS, for the purpose of audit or evaluation, and is limited only to DHHS employees involved in the review. The protection offered by the CoC does not stop study investigators from voluntarily reporting information about suspected or known sexual, physical, or other abuse of a child or older person, or a subject's threats of violence to self or others. If any member of the research team is given such information, he or she will make a report to the appropriate authorities. Even with this CoC in place, the consent attached to this study explains to participants that they and their family members must still continue to actively protect the participant's privacy. If a participant voluntarily gives their written consent to anyone to receive information about their participation in the research, then we may not use the CoC to withhold this information.

### **I.3: Collection and Storage of Human Specimens or Data**

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

- National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit

final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

- This trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov
- In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers after the completion of the primary endpoint by contacting the PI; some journals may require de-identified data to be uploaded directly alongside publications as possible. Every effort will be made to comply with these regulations where doing so does not threaten to identify an individual research participant.

*Intended Use of the Samples:* No human specimens/samples will be stored as part of this study. There are two types of stored data resulting from this protocol: (1) cognitive and brain imaging data, which are stored electronically in secure, password-protected NIAAA computers located in the labs of the Clinical NeuroImaging Research Core in the NIH Clinical Center; (2) paper questionnaires and evaluation forms stored in locked file cabinets in locked rooms assigned to the Clinical NeuroImaging Research Core in the NIH Clinical Center. The purpose of storing this data is to conduct group statistical analysis following completion of data collection in order to address the study aims. We may also use this stored data to answer additional research questions. The proposed research will include data from participants recruited through the NIAAA natural history protocol, 14-AA-0181 and screening. The final dataset might include self-reported demographic, behavioral, and MR scan data from participants

The proposed research will include data from up to 116 participants and the final dataset will consist of behavioral, clinical, and neuroimaging data, including laboratory results. Data will be stored securely in the NIAAA intramural clinical database that is available to the investigators and collaborators named in the protocol for the research specified in the protocol. Data from other NIAAA protocols may also be shared with this protocol for assessment of eligibility as well as for data analysis. Data may also be shared with other NIAAA protocols to allow for greater power to detect otherwise small effect size analyses.

Current and future collaborators within and outside of the NIH Intramural Research Program may be provided with de-identified data for the purposes of scientifically motivated analysis to answer additional research questions. We will make the data and associated documentation available to additional users only under a specific data-sharing agreement that provides for: (1) a commitment to using the data only for research purposes and not to identify any individual participant, (2) a commitment to securing the data using appropriate computer technology.

Future collaborators within and outside of the NIH Intramural Research Program may be provided with this data under appropriate agreements. The agreements will include a commitment to use the data only for research purposes, to secure the data using

appropriate computer technology, and to destroy the data after analyses are completed, as appropriate. Data will be transferred using secure file transfer protocols.

#### **I.4: Data Handling and Record Keeping.**

All data from the participants will be maintained by having data coded to mask participants' identities. Further, files containing participant names and the master list of participants will be kept in a locked file under the supervision of the Principal Investigator. There are two types of stored data resulting from this protocol: (1) cognitive and brain imaging data which are stored electronically in secure, password-protected NIAAA computers located in the labs of the Clinical NeuroImaging Research Core in the NIH Clinical Center; (2) paper questionnaires and evaluation forms stored in locked file cabinets in locked rooms assigned to the Clinical NeuroImaging Research Core in the NIH Clinical Center.

- 1) *Data Storage:* Data from participants will be maintained by having data coded to mask participants' identities. Further, files containing participant names and the master list of participants will be kept in a locked file under the supervision of the Principal Investigator. Access to all the study data will be restricted to authorized personnel via an Active Directory user account. Each authorized staff member will have a unique logon ID and password. All project staff with access to data will be trained on procedures for protecting the confidentiality and security of sensitive information.
- 2) *Data Tracking:* All attempts to access files containing confidential data will be logged and periodically reviewed to ensure that only authorized staff is accessing the data. Hard copies of data will be signed in and out, under the supervision of the QA monitor. Trackers will also be maintained through Filemaker for data tracking.
- 3) *Data following study completion:* Following completion of the study, the data will be submitted to NIAAA Repository Protocol (PI: Melanie Schwandt, Ph.D.), and any future research will be conducted, following appropriate agreements and IRB review, under that protocol.
- 4) *IRB reporting:* . We will be collecting identifiable information. Even though the final dataset will be stripped of identifiers prior to release for sharing, we believe that there remains the possibility of deductive disclosure of subjects with unusual characteristics, particularly the participants with alcohol use disorder. In the event of breach of data security measures or evidence of loss or destruction of personally identifiable data the PI will inform the IRB.

No human specimens/samples will be stored as part of this study.

#### **I.5: Monitoring and Quality Assurance**

The Principal Investigator and the Medical Advisory Investigator (MAI), along with key research staff will be monitoring data collection and the study on an ongoing basis.

- 1) *Monitoring Mechanism:* This protocol will be monitored by the PI and MAI. Participant flowsheets will be reviewed by Investigators for completeness and compliance with study procedures. Adverse events will be evaluated by the MAI.

Event reporting will be done following the procedure outlined in the previous section.

- 2) *Frequency*: QA monitoring will be done after the first participant has completed the study, and then following every 5 participants who have completed the study, or after six months (whichever occurs first). Investigators will review participant eligibility, accrual, and study progress at weekly staff meetings. Participant flowsheets will be reviewed by section staff at least monthly.
- 3) *Stop or Change Rules for Study*: In case of serious adverse event the study will be suspended until determination about cause of such an event is made. If following interim analyses, described in the statistical analysis section, the study has robust results, the PI may elect to terminate the study early to avoid unnecessary burden to additional patients.
- 4) *Advanced Plans*: Interim analyses will be run every 10 subjects, or as needed, to evaluate need for continuation of patient accrual or issues in study procedure that might need modification in order to avoid unnecessary patient accrual.
- 5) *Information to be Monitored*:
  - a. Overall study progress, including participant eligibility, accrual, and completion as well as data quality and timeliness of processes and procedures.
  - b. Adverse event data and outcomes will be reviewed at the time of annual review reporting for IRB.
  - c. Any external factors or relevant published information that might impact the safe and ethical conduct of the study at the time of annual review reporting for IRB, or whenever such information emerges.
- 6) *Communication*: The monitors will produce reports after each evaluation that will be sent to the PI and research team. The Investigators and research staff have daily interactions and communications regarding the study, as well as at weekly staff meetings. Adverse events, unanticipated problems (UP), protocol deviations, and non-compliance will be reported to the NIAAA Office of the Clinical Director and IRB.

## **Data and Safety Monitoring**

The Principal Investigator and the Medical Advisory Investigator (MAI), along with key research staff will be monitoring data collection and the study on an ongoing basis. Quality assurance (QA), including monitoring of Compliance with Good Clinical Practice standards, will

be performed by PI, MAI or a designated staff after the enrollment of every 5 participants or every six months (whichever occurs first) .

1) *Mechanism:*

- i. The QA monitor will review participant flowsheets and establish their agreement with relevant source documents, as well as review the study Regulatory Binder for completeness to confirm compliance with all regulatory requirements.

2) *Information Being Monitored:*

- a) Eligibility checklist  
Filled out completely
- b) NIAAA or NMR Center MRI safety screening questionnaire  
Filled out- signed by physician if needed
- c) Signed and dated protocol consent
- d) Consent quiz administered and number of needed responses correct
- e) Initial Breath alcohol (Stage 1 only)
- f) Study-specific items checked:
  - i. Flow sheets completely filled out
  - ii. Questionnaires completely filled out
  - iii. MRI scans or tasks documented as done

- 3) *Communication:* The monitors will produce reports after each evaluation that will be sent to the PI and research team.

### **Medical Safety Monitor**

This is a minimal risk study; as such no Medical Safety Monitor is required. The Principal Investigator and Medical Advisory Investigator will be responsible for **noting and reporting any problem or adverse event, specifically focusing on a change to the subject's risk/benefit ratio.**

### **I.6: Protocol Deviations**

It is the responsibility of the investigator to use continuous vigilance to identify and report deviations to the NIH Institutional Review Board as per Policy 801. All deviations must be addressed in study source documents and reported to the NIAAA program. The investigator is responsible for knowing and adhering to the reviewing IRB requirements.

### **NIH Definition of Protocol Deviation**

A protocol deviation is any changed, divergence, or departure from the IRB-approved research protocol.

- Major deviations: Deviations from the IRB approved protocol that have, or may have the potential to, negatively impact the rights, welfare or safety of the subject, or to substantially negatively impact the scientific integrity or validity of the study.
- Minor deviations: Deviations that do not have the potential to negatively impact the rights, safety or welfare of subjects or others, or the scientific integrity or validity of the study.

#### **I.7: Responsibilities of Investigators**

In regard to human subjects' protection, the primary role of the investigators will be to ensure that proper consent procedures are being followed and that all subjects are protected from the risks associated with this study. The subject's eligibility is evaluated prior to consenting and enrolling into this protocol. Consent will not be obtained until eligibility is reviewed by the PI or AI (designated by the PI to obtain consent) together with the physician or nurse practitioner involved in the screening evaluation of the participant, and their concurrence of the participant's eligibility is documented on the eligibility checklist form. Further, a third signature by an independent clinician or quality assurance monitor will be obtained following their verification of the participant's eligibility for the study. This third review and signature will be obtained prior to obtaining consent of the participant.

The investigators will also contribute to study design and ensure that the design continues to meet the goals of the study without altering the subjects' risk/benefit ratio. Investigators and Post-doctoral fellows will also be responsible for data analysis and manuscript preparation. The MAI will be responsible for medical oversight on all subjects. In addition, staff physicians and nurse practitioners will contribute to the medical safety of the subjects. Post-baccalaureate Intramural Research Training Awardees (IRTAs) will be responsible for day-to-day study procedures, such as recruiting, conducting scans, and administering cognitive tests.

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