NEUROBIOLOGICAL RESPONSES IN ALCOHOLISM AND EARLY TRAUMA

NCT04128228

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HRP-503B – BIOMEDICAL RESEARCH PROTOCOL

Protocol Title: Neurobiological responses in stress and alcoholism

Principal Investigator: Dongju Seo, PhD

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SECTION I: RESEARCH PLAN

1. **Statement of Purpose:**

Early trauma (ET) is a significant obstacle to alcohol recovery. Among treatment-seeking alcohol use disorder (AUD) patients, 55% reported a history of early trauma [1]. AUD patients with ET suffer from more severe clinical symptoms and worse treatment outcomes including frequent and early relapse compared to those with AUD alone [2]. Yet, there is no established model explaining neural mechanisms of AUD, early trauma and high relapse risk. Two systems are implicated in the neurobiology of alcoholism and early trauma: stress-related neural circuits and the hypothalamic–pituitary–adrenal (HPA) axis response. However, studies concurrently examining these two systems are rare, and specific neurobiological mechanisms underlying co-occurring AUD and ET remain unclear. The current research proposes to investigate neurobiological mechanisms of comorbid AUD and ET and their prospective prediction of alcohol relapse using a multimodal neuroimaging technique that combines functional magnetic resonance imaging (fMRI) and HPA axis measures. Our novel, validated approach that allowed simultaneous monitoring of brain and hormone responses found dynamic neurobiological responses to stress during a sustained emotion provocation (SEP) task [3]. New preliminary results in AUD patients with ET showed altered response in the ventromedial prefrontal cortex (VmPFC) and ventral striatum during the SEP task. Specifically, poor dynamic VmPFC recovery over time predicted blunted cortisol response during stress and early relapse in AUD patients, suggesting the crucial role of dynamic VmPFC response in HPA axis disruption and relapse risk. These preliminary data led us to hypothesize that disrupted neural response in the VmPFC during the SEP task may be a novel marker to identify AUD patients with early trauma, and that impaired VmPFC dynamic response is a predictor of HPA axis disruption and high relapse risk in AUD patients. Accordingly, we propose a 5-year study with four demographically-matched groups (total N=160; N=40 each; equal gender) categorized by AUD and early trauma status, including AUD patients with and without early trauma (AUD/ET, AUD/NT), and moderate social drinkers with and without early trauma (MD/ET, MD/NT). The proposed study will utilize our novel SEP task involving exposure to stress, alcohol, and neutral cues in separate blocks, which fMRI and stress hormone monitoring via concurrent blood collection, combined with a prospective clinical outcome design. After the multimodal scan, AUD patients will be engaged in 8-week alcohol treatment and then prospectively followed for 90 days. To accurately capture relapse rate, we will utilize face-to-face follow-up interviews at 14, 30, 90 days as used in our previous work, in conjunction with daily monitoring of stress and alcohol use through a smartphone app.

The following aims and hypotheses will be addressed in this proposal.
Specific Aim 1: To identify impairments in neural systems underlying comorbid AUD/ET by examining fMRI response during a dynamic SEP task
Hypothesis: Ventromedial prefrontal cortex (VmPFC) (stress-baseline). The AUD/ET group will display a lack of dynamic VmPFC response in the Late-Stress period.
Hypothesis 1b: Ventral Striatum (VS) (alcohol cue-baseline). The AUD/ET group will show decreased VS activity during alcohol cue exposure, while AUD/NT group show increased VS response to alcohol cue.
Specific Aim 2: To evaluate neural correlates of HPA axis response using a validated fMRI and HPA approach
Hypothesis 2. Lower dynamic VmPFC response to stress will be associated with blunted cortisol response to stress (stress-baseline) across groups.
Specific Aim 3: To examine whether impaired neural responses during the SEP task predict future relapse after treatment during the 90-day follow-up
Hypothesis 3. Lower dynamic VmPFC response to stress will predict early relapse.

2. Probable Duration of Project:

Duration of the project: 5 years (recruiting 160 participants)

A total of 160 subjects (ages 21-50) will be recruited including four demographically-matched groups (N=40 each; equal sex ratio) of 80 treatment-seeking AUD patients with and without early trauma (AUD/ET, AUD/NT) and 80 moderately drinking controls with and without early trauma (MD/ET, MD/NT). An experiment is proposed using a 2 (AUD, MD) X 2 (ET, NT) x 3 (Condition: Stress, Alcohol, and Neutral) mixed factorial design with the first two factors (Groups) as between-subjects factors and Condition as a within-subjects factor. Equal genders will be included in each group, and the effects of gender will be assessed. All AUD patients will be scheduled for a multimodal fMRI scan during acute abstinence within 3-5 days of last drink. Then patients will receive an 8-week outpatient treatment and scheduled for a second scan in the 8th week of the treatment. Moderate drinking controls will participate in a single MRI session after baseline assessments.

Duration of study participation:

AUD patients: 22 weeks (baseline/MRI session (2 weeks), outpatient treatment (8 weeks) + follow-up (12 weeks))
Control subjects: 6 weeks (baseline/MRI session (2 weeks), follow-up (4 weeks))

3. Background:

AUD patients with ET suffer from more severe clinical symptoms and worse treatment outcomes including frequent relapse compared to those with AUD alone [2]. We have shown that early trauma is a critical predictor of addiction relapse including AUD [4]. Especially, AUD patients with ET are known to be more vulnerable to stress-induced alcohol relapse [5,6]. Although multiple studies have consistently found a strong association between early trauma and increased risk of relapse among AUD patients, there is no previous neurobiological research examining the link between AUD, ET, and high relapse risk. Two stress-related systems have been implicated in the neurobiology of AUD and ET: stress-related prefrontal-limbic-striatal circuits and the hypothalamic–pituitary–adrenal (HPA) axis system. The HPA axis plays a crucial role in associating childhood trauma with alcohol drinking behaviors [7]. Stress responses involve HPA axis arousal [6], whereby glucocorticoids trigger increased dopamine efflux in the prefrontal cortex (PFC), resulting in prefrontal regulatory dysfunction under stress [8]. Early stressors result in long-term alterations in cortisol response and dopamine reward pathways in the brain, enhancing the reinforcing effects of alcohol [7,9]. The HPA axis function is modulated by the ventromedial prefrontal cortex (VmPFC), which plays a key role in controlling emotion, reward, and decision-making [10,11]. VmPFC dysfunction has been reliably associated with greater emotional distress in individuals experiencing high levels of stress and trauma [12], those with PTSD [13], and with high alcohol craving and early relapse in AUD patients [14,15]. These results point to the potential role of the VmPFC linking stress, alcohol consumption, and HPA axis dysfunction in patients with comorbid AUD/ET. However, no study has simultaneously examined these two systems.

To address these gaps, this application proposes novel research aims to investigate neurobiological mechanisms of AUD and ET using multimodal neuroimaging combining fMRI and HPA axis measures in a prospective clinical outcome design. Specifically, the proposed study will examine 1) neurobiological systems specific to comorbid AUD and ET by recruiting four, demographically-matched groups (AUD with and without ET; Moderate drinkers with and without ET). 2) We will utilize a novel technique that allows simultaneous monitoring of brain and stress hormone responses via concurrent blood collection during a fMRI task involving sustained stress and alcohol cues. 3) After the multimodal imaging, all AUD patients will complete an 8-week outpatient treatment and be followed for 90 days to understand the link between the brain-HPA axis system and alcohol relapse.

4. Research Plan:

This study examines neurobiological systems specific to comorbid AUD and ET by recruiting four, demographically matched groups. General study procedures consist of 1) Intake Assessments, 2) Multimodal MRI sessions, 3) Outpatient Treatment and smartphone protocol for AUD patients, and 4) Follow-Up(s) including daily monitoring.

In response to the current COVID-19 epidemic, the following study processes will be carried out. To limit exposure to COVID-19 and ensure the safety of study participants and team members, we will minimize the number of in-person study visits and replace them with virtual options, such as video communications (zoom, Skype for business, or Microsoft team etc. depending on participants' convenience), REDCap, or phone.

Potential subjects will complete an initial screening over the telephone/in person to determine eligibility based on inclusion/exclusion criteria at Yale Stress Center. Following screening, eligible subjects will meet with the PI and research staff for four to five intake sessions (2-3 hours each) to obtain informed consent and assessments including socio-demographic measures; physical health and medical and psychiatric diagnoses; and stress and psychological measures. Participants will also have the options for providing a consent electronically, completing assessments or surveys remotely via a REDCap, a secure HIPAA compliant web application, having video communication sessions with research staff for clinical interviews via secure online tools approved by Yale ITS. All subjects will undergo breathalyzer and urine toxicology screens at in-person appointments to confirm self-report of alcohol and drug information, and women will be given a pregnancy test. An MRI session (2 hours) will be scheduled and conducted for those eligible and willing to participate in the neuroimaging session. A participant will arrive at MRRC at 1:30 pm for scan preparations. . At 2:30 pm, a neuroimaging assessment involving structural MRI and combined functional magnetic resonance imaging (fMRI) and HPA axis data collection will be conducted. A nurse will draw blood during each scan for HPA axis data collection. Brain responses will be examined during the viewing of stress, alcohol cue and neutral visual stimuli at Yale Magnetic Resonance Research Center (MRRC). A member of research staff will accompany the subject to the MRRC and remain there for the entire scan along with MR technicians during the scan.

<u>AUD patients with and without early trauma (AUD/ET, AUD/NT)</u>

AUD patients will complete MRI sessions before and after 8-week outpatient treatment. After the MRI session, AUD subjects will receive an outpatient treatment integrating cognitive-behavioral methods focused on emotion regulation with breathing-based stress management. This program partly adapts the Cognitive Behavioral Relapse Prevention supported by NIAAA manual [16] and resonance breathing techniques. During an 8-week outpatient treatment, participants will also receive two smartphone surveys including a 56-day daily monitoring survey and a 56-day daily intervention exercise. A 56-daily monitoring survey will assess daily stress and alcohol consumption in a real-life setting, and a 56-day intervention exercise will provide breathing exercise instruction with a couple questions asking their experience practicing breathing techniques. After the second MRI session, AUD patients will be engaged in a prospective follow-up, combining conventional interviews with daily monitoring via smartphone app. Subject will also have the option for a 90-day follow-up interview remotely via phone or zoom meeting. Face-to-face or remote follow-up via phone or zoom meeting interviews will be conducted at days 14, 30, and 90 days as described

previously [15,19,20]. In addition, to accurately capture relapse rate, AUD patients will be tracked once daily to monitor their stress, emotion, and alcohol use through a smartphone app technique for 90 days. Then, participants will be scheduled to visit the Stress Center for a 90-day follow-up interview or to have a remote session and will be debriefed. .

Moderate drinkers with and without early trauma (MD/ET, MD/NT)
After the MRI session, all participants will be tracked for 30 days to monitor their stress, emotion, and alcohol use through the same smartphone app technique.

Assessments

All participants will be assessed across the following domains, using psychometrically established measures.

The Structured Clinical Interview for DSM-V (SCID-I) will be used to ascertain DSM-5 Axis 1 psychiatric and substance abuse diagnoses [21] and specifically to determine presence/absence of DSM-5 AUD.

Assessment for Alcohol use and addiction:

Family history of alcoholism (FH) will be assessed using the Family Tree Questionnaire [22]; [23] which provides a method to obtain drinking status and alcohol-related problems for all maternal and paternal first and second degree relatives above the age of 18.

The Time-Line Follow-Back Interview will also be used to assess alcohol, other drugs and nicotine use in the previous ninety days, during the study and during follow-up. This is a reliable experimenter-administered assessment [24], which uses a calendar prompt to facilitate recall of drug use during a targeted period, and well-validated in alcohol and drug abuse treatment studies [25].

Smoking History Questionnaire (Brown et al., 2002): A smoking screening questionnaire consisting of items about current and past smoking habits, will be used to obtain smoking history.

The Alcohol Use Disorders Identification Test (AUDIT) [26] is a 10-item screening tool developed by the World Health Organization (WHO) to assess alcohol consumption, drinking behaviors, and alcohol-related problems.

The Quantity-Frequency Variability Index (CAHALAN) [27] measures alcohol consumption patterns over a specific time period.

The Alcohol Urge Questionnaire (AUQ); [28] is a reliable and valid 8-item self-report craving scale that can be used for repeated assessments. It has been found to be significantly associated with drinking measures and dependence severity.

The Cannabis Use Disorder Identification Test-Revised (CUDIT) will be used to quantify the severity of cannabis use over the past six-months [29]. This questionnaire will be administered at intake and weeks 4, 8, and 12.

The Marijuana Motives Questionnaire (MMQ) (Simons et al., 1998) is a self-report questionnaire that will be administered at baseline to assess reasons for using marijuana, including to cope with stress. This questionnaire will be administered at intake.

The Marijuana Craving Questionnaire – Short Form (MjCQ-SF) (Heishman et al., 2009) will be administered weekly to assess craving for marijuana along four dimensions: compulsivity, emotionality, expectancy, and purposefulness.

Alcohol withdrawal will be measured using the Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA Ar) (Sullivan et al., 1989). CIWA-Ar is a 13-item interviewer guided measure to evaluate current alcohol withdrawal (AW) signs and symptoms. The assessment includes objective measures (e.g., pulse), participants' responses to questions, such as orientation to time and space ("What day is this? Where are you? Who am I?"), and observations by the interviewer (evidence of tremor or paroxysmal sweats). Item responses range from 0 (indicating no evidence of the symptom) to 4 (indicating highest severity of symptoms). Possible total scores range from 0 to 67. A symptom is considered positive if a participant had a score of 1 or more for that item.

Verification of alcohol/drug use: Alcohol abstinence will be assessed by self-report, breathalyzer and urine toxicology screens that will be conducted in each appointment during treatment, and on the day of fMRI session.

Assessment for Emotional/Behavioral Problems associated with Addiction:
The following assessments will be administered to assess stress, impulsivity, depression, trauma, and mood symptoms.

The Perceived Stress Scale (PSS); [30] is a 14 item self-report assessing the degree to which situations are appraised as threatening or demanding.

The Spielberger State/Trait Anxiety Questionnaire [31] is a reliable and valid measure of both state and trait anxiety.

The Beck Depression Inventory [32] is regarded as a well-established, sensitive self-report measure of depression

The Center for Epidemiologic Studies Depression Scale (CES-D) (Lewinsohn et al., 1997) a screening test for depression and depressive disorder.

The Emotion Regulation Scale (ERS, [33] a 36-item questionnaire to provide a comprehensive measure of the difficulties in emotion regulation.

The Self-Control Scale -Brief (SCS-Brief) (Tangney, 2004) is a 13-item measure of self-control that measures processes that directly involve self-control such as breaking a habit or working toward long-term goals, rather than distal behavioral outcomes of self-control. The SCS-Brief will be administered at intake appointments.

The Barratt Impulsiveness Scale (BIS-11) (Patton et al., 1995) is a questionnaire designed to assess the personality/behavioral construct of impulsiveness.

The Shipley Institute of Living Scale (SHIPLEY) [34] has been widely used to assess cognitive functioning and impairment.

The NIH Tool Box Battery will be administered during the intake appointments and includes cognitive tests of executive function.

The Mindfulness Attention Awareness Scale (Brown & Ryan, 2003) is a 15-item scale designed to assess a receptive state of mindfulness and attention.

Childhood Trauma Questionnaires (CTQ) [35]: This is a 28-item test that measures 5 types of maltreatment-emotional, physical, sexual abuse, and emotional and physical neglect.

The Chronic Stress Checklist (CSC) adapted from the Cumulative Adversity Interview [36]. This measures chronic stress and adversity.

The Perseverative Thinking Questionnaire (Ehring et al., 2011) is a 15-item scale designed to measure the broad idea of repetitive negative thought. Intrusive thoughts are one of symptoms of trauma.

Zimbardo Time Perspective Inventory (Zimbardo & Boyd, 1999) is the 56-item Zimbardo Time Perspective Inventory (ZPTI) measures individual differences in time-orientation which has been associated with emotional problems.

The Multidimensional Personality Questionnaire (155 items; Patrick et al., 2002)) provides for a comprehensive analysis of personality including Positive Emotionality, Negative Emotionality, and Constraint embody affect and temperament constructs.

The Dutch Eating Behavior Questionnaire (DEBQ) (van Strien, 1986) measures eating styles that may contribute to or attenuate the development of obesity, through three scales that measure emotional, external and restrained eating. The DEBQ is administered to examine stress driven eating behaviors

The Lifestyle and Behavior Survey, adapted from the Cornell Medical Index [37,38]) and the NHANES is administered at intake.

The COPE Inventory (Carver et al., 1989) was developed to assess individuals' use of different coping strategies. The COPE is composed of fifteen subscales. This scale will be administered at intake.

The Social Media Questionnaire (SMQ) is a brief questionnaire given at intake to assess social media use.

Additional surveys to assess the COVID-19 related stress

The COVID Stress Scales (CSS) (Taylor et al., 2020) is a 36-item designed to measure COVID-19 stress and anxiety symptoms including COVID danger and contamination fears, COVID fears about economic consequences, COVID xenophobia, COVID compulsive checking and reassurance seeking and COVID traumatic stress symptoms.

The Psychosocial Impact of COVID-19 (PIC) (Chung, 2020) is a 2-item assessing the level of difficulties and distress in people's lives over the past two weeks.

The Psychological Stress Associated with the COVID-19 Crisis questionnaire (PSACC) (Adamson, 2020) is a 37-item designed to measure the level of stress during the COVID-19 pandemic and characterize it according to location, gender, income, and other factor.

The UCLA Loneliness Scale (Version3) (Russell, 1996) is a 20-item measure that assesses how often a person feels disconnected from others.

The Interpersonal Support Evaluation List (ISEL) (Cohen et al., 1985) is designed to measure perceptions of social support among individuals in the general population.

The COVID-19 Community Response Survey-Social Distancing Impacts (JHU-SDI) (Johns Hopkins University, 2020) is designed to measure the impact of COVID-19 on people's lives due to a precautionary measure of social distancing.

The COVID-19 Community Response Survey-Substance Use (JHU-SU) (Johns Hopkins University, 2020) is a 15-item designed to assess the use of substance after and during the COVID-19 pandemic.

Multimodal fMRI Session

The multimodal fMRI is adopted from the previously described protocol [3]. A participant will be exposed to each picture only once. During the first and second scans for AUD patients, different sets of pictures with equivalent levels of emotional intensity will be used. All fMRI scans will start at 2:30 pm, when HPA axis diurnal rhythms are at high levels and to control diurnal variations in cortisol response. The schedule of the experiment is illustrated below.

SEP fMRI task [3]. Participants will view a series of visual stimuli presented using E-prime software (Psychological Software Tools, Sharpsburg, USA). The picture stimulus set consists of 198 alcohol, stress, and neutral pictures, with stress, neutral pictures selected from the *International* Affective *Picture* System [41] and alcohol visual cues developed and currently used at the Yale Stress Center (fig. 10). Each condition will include the presentation of 66 pictures in six consecutive blocks to allow sufficient time to elicit hormonal responses, as described previously [3].

MRI Acquisition: MRI images will be obtained using a 3-T Siemens Prisma MRI system equipped with a standard quadrature head coil, using T2*-sensitive gradient-recalled single shot echo planar pulse sequence. Anatomical and functional images, and high-resolution 3D Magnetization Prepared Rapid Gradient Echo sequence will be obtained sequentially. Specifically, functional, blood oxygen level dependent (BOLD) signals will be acquired with a 64 channel head coil with multi-band accelerated, echo planar imaging sequence. Seventy five axial slices parallel to the AC-PC line covering the whole brain will be acquired with TR = 1000 msec, TE = 30 msec, bandwidth = 1894 Hz/pixel, flip angle = 55 degrees, field of view = 220 x 220 mm, slice thickness = 2 mm and no gap. Heart rate and heart rate variability (HRV) data will be obtained using a pulse oximeter. Eye-tracking data will be collected using an MRI-compatible SR Research EyeLink 1000 Plus (SR Research Ltd, ON, Canada), which allows the online monitoring of gaze movements during picture viewing.

Concurrent blood collection: The concurrent blood collection for stress hormones (cortisol, ACTH) will follow the procedure described previously [3]. A nurse will draw blood during each scan. During the SEP task, there will be a total of 9 blood collections with three blood draws per condition (baseline, provocation, recovery) to assess plasma levels of cortisol and adrenocorticotropic hormone (ACTH), a primary stimulator of cortisol release. Blood will be collected in a heparinized tube that will be immediately stored on ice and centrifuged at 4˚C. Aliquots of plasma will be stored in polypropylene tubes at -80˚C and sent to the Yale Center for Clinical Investigation for assay processing. In addition to these 9 samples, there will be blood draws before and after the fMRI scan.

Outpatient Treatment: All AUD patients (with and without ET) will receive 8-week outpatient treatment at YSC using the relapse prevention therapy partly adapted from NIAAA cognitive behavioral therapy manual [16] and breathing-based stress reduction method to ensure alcohol abstinence for the study period. Please see *4.2. intervention* (*clinical trial* section) for the detailed description of 8-week outpatient treatment. Patients will have an option of receiving outpatient treatment remotely via secure video communications (e.g., Yale approved zoom).

Prospective relapse assessments: We will use an integrative follow-up method combining face-to-face (or remote) interviews with an intensive longitudinal method (daily monitoring) via smartphone app. First, as described in our previous studies [4,15,19,20], prospective assessment of relapse will be conducted with face-to-face (or remote) interviews after discharge from the treatment on day 14, 30 and 90.

Real-world smartphone app: In addition, after completing the MRI session, all subjects will then complete a smartphone app phase using the MetricWire app (developed by MetricWire Inc.), through which they will report their momentary and daily experiences. *Daily smartphone surveys vis MetricWire app:* The MetricWire app has previously been used in clinical research and is HIPAA compliant. All participants will complete a daily

questionnaire during the follow-up period that will be prompted in the evening. Before the smartphone app phase, subjects will initially complete an hour training session where a research assistant will assist in installing an app on their smartphone devices which they will use to report their daily experiences. They will be given instructions on how to operate the smartphone app and a guide that they may take home with them that will outline the information covered in the training session. They will also be given contact information should they have any problems or questions with the smartphone app over the course of the study. It will be explained that all data on the app is encrypted and that the data is sent to a secure server where data is identified by subject id only. Subjects will also be informed that we will be monitoring the upload of data from the smartphone app to the secure server to verify that everything is working correctly.

Data Management and Processing:

Data Management: Research data is collected on paper assessments and using Yale University's REDCap system. REDCap is a secure HIPAA compliant web application for building and managing online surveys and databases, supported and approved by Yale ITS. Research data is exported and stored on a secure shared virtual drive maintained by Yale ITS. All subjective data will be kept in locked cabinets at the Yale Stress Center (YSC), New Haven. Biological data (urine,) are stored in locked freezers (-20 for urine) at the YSC and are identified only by study ID. MRI data are de-identified and stored at the workstations Yale Stress Center, which are highly secure and HIPPA compliant. Access to YSC workstations is password restricted and only available to PI and her staff at Yale Stress Center. All research data is kept in two places--one as a hardcopy in a locked file with records identified only by the participants study number and the second in computerized databases protected by two-level password systems that are managed by Yale ITS. Upon completion of the study, all hardcopies will be destroyed. The only documents linking participants' names to their study numbers will be the consent forms. These will be stored in a separate locked file cabinet and may only be accessed by PI and relevant study staff.

Safety planning in response to the COVID-19 epidemic

To limit exposure to COVID-19, one-on-one in-person meetings should be avoided as much as possible. If one-on-one meetings must be held in person, the following guidelines must be carried out.

Before any study visits, research participants will be screened for COVID-19 symptoms by filling out the COVID-19 questionnaires prior to the study visit and at the time of the on-site study visit. Participant will be asked to fill out YSC safety questionnaire for YSC visits and MRRC safety questionnaire for a MRRC visit. If study participants say "yes" to any of the COVID-19 related questions, their appointment will be moved to a later date and they will be directed to the YNHH COVID-19 Support Call Center (203-688-1700 option 1). The study site will be disinfected before and after each study visit based on CDC guideline. The measurements of temperature and oxygen saturation levels of research staff will be taken for both research personnel and study participants with a non-contact forehead thermometer and a pulse oximeter. If temperature is greater than 99.5 degrees Fahrenheit in subject, the research subjects and study staff will be asked to leave and seek medical attention. If oxygen saturation is below 95% in subject or research staff, participants will not be allowed to participate in research appointment, and research staff will be asked to leave and seek medical attention. During in-person visits, both participants and research staff should maintain the required distancing (6 feet) and wear a mask. Anybody entering the study site should properly wash their hands with alcohol-based hand sanitizer (containing at least 60% alcohol) or soap and water in protecting against the spread of germs and viruses. In case participants do not have proper masks to wear, a mask and glove will be provided on-site study visits.

5. Genetic Testing N/A ☒

A. Describe

i. the types of future research to be conducted using the materials, specifying if immortalization of cell lines, whole exome or genome sequencing, genome wide association studies, or animal studies are planned *Write here*
ii. the plan for the collection of material or the conditions under which material will be received *Write here*
iii. the types of information about the donor/individual contributors that will be entered into a database *Write here*
iv. the methods to uphold confidentiality *Write here*

B. What are the conditions or procedures for sharing of materials and/or distributing for future research projects? *Write here*
C. Is widespread sharing of materials planned? *Write here*
D. When and under what conditions will materials be stripped of all identifiers? *Write here*
E. Can donor-subjects withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials? *Write here*
    i. How will requests to withdraw materials be handled (e.g., material no longer identified: that is, anonymized) or material destroyed)? *Write here*
F. Describe the provisions for protection of participant privacy *Write here*
G. Describe the methods for the security of storage and sharing of materials *Write here*

6. Subject Population: Provide a detailed description of the types of human subjects who will be recruited into this study.

A total of 160 participants (ages 21-50) including four demographically-matched groups (N=40 each; equal sex ratio) of 80 treatment-seeking AUD patients with and without early trauma (ET) (AUD/ET, AUD/NT) and 80 moderately drinking controls with and without early trauma (MD/ET, MD/NT).

7. Subject classification: Check off all classifications of subjects that will be specifically recruited for enrollment in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

☐Children	☒ Healthy	☐Fetal material, placenta, or dead fetus
☐Non-English Speaking	☐ Prisoners	☐Economically disadvantaged persons
☐Decisionally Impaired	☐ Employees	☐Pregnant women and/or fetuses
☐Yale Students	☐ Females of childbearing potential	

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects?
Yes ☐ No ☒

8. Inclusion/Exclusion Criteria: What are the criteria used to determine subject inclusion or exclusion?
Inclusion Criteria:
(1) men and women, aged 21-55 years (equal sex ratio)
(2) presence of AUD and early trauma (ET) to match one of the following four groups: AUD with ET, AUD with NT (no trauma), MD (moderate drinkers) with ET, MD with NT
<AUD> meets DSM-V criteria for either moderate or severe Alcohol Use Disorder (AUD).

Regular alcohol use over the past year of, at least 8 standard drinks/week for women and at least 15 standard drinks/week for men (binge drinking allowed).
<MD> never meets DSM-V criteria for AUD
Regular alcohol use over past year not to exceed 7 standard drinks/wk for women and 14 standard drinks/wk for men, with no occasions of binge drinking
<ET> scores above "moderate to severe" range (based on CTQ cut score).
<NT> No history of ET ("non-to-low" range (based on CTQ total score)
(3) good health as verified by physical health exam and lab tests
(4) abstinence of drug use and alcohol in the 72 hours prior to MRI scan
(6) body mass index (BMI) up to 35 (to limit morbid obesity related medical conditions and weight limitations of the MRI scanner)
(7) provide negative breathalyzer and urine toxicology screens at all appointments
(8) able to read/write English, provide informed written/verbal consent, and complete study evaluations

Exclusion Criteria:

(1) current or past substance use disorder other than alcohol; also excluding caffeine and nicotine
(2) current psychiatric disorders; current use of psychiatric medications, including anxiolytics, antidepressants, naltrexone or Antabuse
(3) past psychiatric disorders; except for mood and anxiety disorders (including PTSD) that are highly comorbid with early trauma
(4) any significant current medical condition such as neurological, cardiovascular, endocrine, renal, liver, thyroid pathology; subjects on medications for any medical condition
(5) women on oral contraceptives; peri- and post- menopausal, pregnant (as assessed by a pregnancy test during initial medical evaluation) or lactating women.
(6) history of prior loss of consciousness or brain injury
(7) significant visual or hearing impairment
(8) MRI specific exclusion criteria
(i) history of claustrophobia due to confined MRI scanning environment
(ii) left-handed individuals for the fMRI due to variation in laterality of neuroimaging response resulting from difference in handedness
(iii) have implanted metal in their bodies that would be affected by the strong magnetic field during MRI session (examples: cardiac pacemaker, implanted pacing wires, implanted medication pumps, metal fragments in eyes, intracraniam aneurysm clips, cochlear implant, retinal tack, recently implanted metal clips, shunts, rods, or plates; other ferromagnetic implants above the level of the clavicle, implanted electrodes or neural stimulator, claustrophobia, and orthodontic braces or permanent retainer wires)

9. How will **eligibility** be determined, and by whom? Write here
Research staff will determine eligibility. Potential subjects will complete an initial telephone screening, and then be scheduled to meet with research staff to complete an intake appointment at the Yale Stress Center or via a remote video session. Research staff will review the medical history of the participant to ensure all inclusion and exclusion criteria are met, under the supervision of PI.

10. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.
The potential risks to the subjects in the proposed study are listed below.

The potential risks to the subjects in the proposed study are risks associated with (i) physical examination and psychological assessments, (ii) multimodal MRI scanning, (iii) blood collection for stress hormone monitoring, (iv) visual stimuli task, (v) outpatient treatment, (vi) smartphone app survey, and (vii) alcohol withdrawal and abstinence. These risks are described below.

(i) Physical examination and psychological assessments: All subjects will receive a physical examination involving urine test and breath screening and psychological assessments to ensure good physical health status.
Breath screening and urine collections are performed primarily as safeguards to contamination of data and should add no risks other than those normally associated with these procedures. Confidentiality of the drug toxicology results are specifically protected by Federal laws, and all records will be identified by code number only, with the master file kept under lock by the Principal Investigators and Project Coordinator.
Rating scales and questionnaires are all noninvasive and should add no risk. The major disadvantages are the time taken to complete them, and possible breach of confidentiality. Past experience with these measures at YSC indicates that they are acceptable to subjects. Careful efforts aimed at maintaining confidentiality have been effective in previous research, and only patients' code numbers will be recorded on the forms themselves to protect confidentiality.
(ii) Multimodal MRI Scanning: Magnetic resonance (MR) that will be used in this study is a technique that uses magnetism and radio waves, not x-rays, to take brain pictures. The United States Food and Drug Administration (FDA) has set guidelines for magnet strength and exposure to radio waves, and we carefully observe those guidelines. Subjects will be watched closely throughout the MR scan by a professional MR technician and the research staff. Some people may feel uncomfortable, anxious, or claustrophobic. If this happens, the subject may ask to stop the study at any time and we will take them out of the MR scanner immediately. On rare occasions, some people might feel dizzy, get an upset stomach, have a metallic taste or feel tingling sensations or muscle twitches. These sensations usually go away quickly but we will ask subjects to tell the research staff if they have them. There are some risks with an MR study for certain people. If subjects have a pacemaker or some metal objects inside their body, they will not participate in this study because the strong magnets in the MR scanner might harm them. Another risk is the possibility of metal objects being pulled into the magnet and hitting a subject. To reduce this risk, we require that all people involved with the study remove all metal from their clothing and all metal objects from their pockets. We also ask all people involved with the study to walk through a detector designed to detect metal objects. It is important to know that no metal can be brought into the magnet room at any time. Also, once subjects are in the magnet, the door to the room will be closed so that no one from outside accidentally goes near the magnet. Subjects will wear ear plugs and headphones to minimize any potential temporary hearing discomfort the MRI noise may cause. The MRI noise is typically tolerable for most people, and subjects are informed to let research staff know of any discomfort by speaking into the microphone. We will ensure that subjects read and answer very carefully the questions on the MR Safety Questionnaire related to their personal safety and asked them to tell us any information they think might be important.

The proposed MR study is for research purposes only and is not in any way a clinical examination. The scans performed in this study are not designed to find abnormalities. The PI, the lab, the MR technologist, and the MRRC are not qualified to interpret the MR scans and are not responsible for providing a diagnostic evaluation of the images. If a worrisome finding is seen on a subject's scan, a radiologist or another physician will be asked to review the relevant images. Based on his or her recommendation (if any), the PI or consulting physician will contact the subject, inform them of the finding, and recommend that they seek medical advice as a precautionary measure. The decision for additional examination or treatment would lie solely with the subject and their physician. The investigators, the consulting physician, the MRRC, and Yale University are not responsible for any examination or treatment that a subject receives based on these findings. The images collected in this study are not a clinical MR exam and for that reason, they will not be made available for diagnostic purposes. Eye tracker and Pulse Oximeter: The Eyelink 1000 Plus is noninvasive. Potential harms to the subject caused by light emitted from the device are minimal because the device uses infrared wavelengths that safe to the human eye and visually undetectable for humans. The potential risk of physical discomfort for the subject is minimal, as the eye tracker is connected to the head coil and never comes within 60 centimeters of the subject. Potential harms associated with a pulse oximeter is minimal. Although it is very rare, there is a possibility of minor finger irritation from the placement of the pulse oximeter. However, this mostly goes away after the fMRI session.
(iii) MR compatible Blood Sampling for HPA axis function

(a) Intravenous (IV) Catheter: When an IV is started, there is some risk that subjects may develop a bruise or bleeding where the vein is punctured. If this occurs, appropriate treatment will be instituted immediately. On extremely rare occasions, fainting, blood clot or infection may occur.
(b) Drawing of Blood: During each scan, about three ounces of blood will be drawn to measure stress hormone levels that may change during the session. This is relatively little compared to the usual blood draw at a blood donation.
(iv) Visual Stimuli Task: Precautions will be taken to minimize possible adverse psychological responses occasioned by exposure to visual stimuli used in this study. It should be acknowledged that the purpose of presenting picture is to evoke and assess emotional reactions and alcohol craving. Nevertheless, the PI is mindful of the need to ensure that distress is transient and kept at reasonable levels. In the case of the unpleasant and stressful pictures, this is not a concern because, although they are intended to elicit negative emotion, the pictures depict contents that are likely to be encountered by adults on a regular and non-traumatic basis in everyday media (e.g., film, television). We have used similar emotional induction tasks with young adults using these stimuli in the past without adverse consequences (Sinha et al., 2016). Alcohol cue pictures involve reliving cues associated with alcohol use and alcohol consumption. It is possible that craving for alcohol may linger even after the task. Any subject that reports residual craving or emotional discomfort after completion of the visual stimuli task will receive an individual counseling session by a trained psychologist (the PI) who are experienced in therapy. The focus of this session will be coping with emotions and cravings.
v) Outpatient treatment: Participation in the study is completely voluntary. If a participant feels uncomfortable at any time during the study, counseling can be provided as a means to address these concerns. Outpatient subjects are free to choose not to take part in this study and stop disclosing their health information at any time. Refusing to participate will involve no penalty or loss of benefits to which they are otherwise entitled (i.e. health care outside of study, payment for healthcare, and healthcare benefits). Subjects will not be able to enroll in this research study and will not receive study procedures as a study participant if they do not allow use of their information as part of this study. When permission is withdrawn, no new health information identifying the subject will be gathered after that date, but information that has already been gathered may still be used until the end of the research study, as necessary to insure the integrity of the study and/or study oversight.
vi) Smartphone app survey: Subjects will respond to smartphone surveys as they go about their daily lives, which may occur in the presence of others. However, smartphones are widely used in public for many tasks by people in everyday life and the completion of the surveys will be brief and relatively discrete. Responses gathered on the smartphones will be encrypted and sent to a secure server. Confidentiality will be maintained to the degree permitted by the technology used. Data will be connected with subject id only. The MetricWire smartphone app has been designed to be compliant with HIPAA regulations. The app encrypts data on participants' phones and while data is wirelessly transferred. The app randomly generates a 24-digit identification code that contains numbers, letters, and remains consistent for each subject throughout the smartphone assessment phase. This identification code will be linked by the research team with the numerical Subject ID that is assigned to subjects upon their initial laboratory visit.
vii) Alcohol Withdrawal and Abstinence: Abstinence from alcohol poses a risk of alcohol withdrawal symptoms. As the study requires alcohol abstinence, we will assess alcohol withdrawal symptoms throughout the study period. The risks associated with stopping drinking may include: anxiety, shakiness, confusion, rapid heart rate, fever and in rare cases, life-threatening seizures. In addition, if participants are unable to make an effort to stay abstinent from alcohol during the study, they may be withdrawn from the study.

11. Minimizing Risks: Describe the manner in which the above-mentioned risks will be minimized.
    See above

The PI and all members of the research team have or will have taken the Human Investigations Training Course either on-line (through the NIH) or in person through the Yale University School of Medicine. All clinical research

procedures will be performed by trained research and clinical staff, at the YSC and MRRC. In the event of an injury, medical therapy will be offered to the volunteer with the cost incurred by the subject's medical insurance carrier.
Risks Associated with MRI data collection: Subjects will be screened for the presence of any metallic prostheses or ferromagnetic metal prior to MR imaging. If the subject has any metallic prostheses, they will be excluded from the study. If a subject becomes anxious during the scan, they can request that the MRI scan be stopped.
Risks Associated with Multimodal Neuroimaging:
Blood samples: When an IV is started, there is some risk that subjects may develop a bruise where the vein is punctured. If this occurs, appropriate treatment will be instituted immediately. On extremely rare occasions, a blood clot or infection may occur. Both the Clinical Neuroscience Research Unit (CNRU) and the Yale Center for Clinical Investigation (YCCI) are fully staffed with medical residents, specialist nursing and non-medical mental health professionals. The amount of blood drawn for the tests is equal to about one fourth the blood obtained during a regular blood donation. Thus, the total amount of blood taken would be less than the amount of blood given during a blood donation. People who are in good health are not usually affected by this kind of blood loss. However, to be safe, subjects will be warned against donating blood for at least six weeks after completing this study. Eye tracker: A potential psychological harm of the eye tracker device is that the subject may feel surveilled and become uneasy. However, subjects will be notified of the technology and its purpose during the consent process before it is used in the MRI.
Risks Associated with Questionnaires, brief Smartphone Survey and Visual stimuli: If the subject reports discomfort completing the questionnaires or the visual stimuli task, they are free to drop out at any time without penalty. Any subject that reports emotional discomfort during or after the completion of questionnaires or the visual stimuli task will receive an individual counseling session by a trained psychologist (the PI) who are experienced in therapy. The screening of subjects using the inclusion and exclusion criteria, and the comprehensive physical and psychiatric evaluation will minimize the risk of including subjects who are otherwise inappropriate. As the study involves the collection of sensitive data associated with alcohol and drug use, a *federal Certificate of Confidentiality* will be obtained from NIH to further protect the information provided by subjects for research purposes.
Risks Associated with any Psychological Discomforts during Study Procedures: The PI is a trained psychologist who has extensive clinical and counseling experience with patients with AUD and trauma. The proposed project will be conducted at the Yale Stress Center (YSC), and the YSC research and clinical team has extensive expertise in working with clinical populations. The research and counseling facilities of the Yale Stress Center includes clinical and research professionals trained in psychology, cognitive behavioral therapy, contingency management and counseling for client and patients. The PI, as well as research and clinical processionals with expertise in trauma and emotional difficulties will be on-site during the conduct of all study procedures. The PI will be present at (or on call for) all intake and experimental sessions and will be available to consult on issues of what constitutes imminent risk and to guide procedures for referrals as needed.
Risks Associated with Alcohol Withdrawal and Abstinence: Alcohol withdrawal symptoms will be monitored by research staff throughout the study period. Subjects showing moderate to severe clinical signs of alcohol withdrawal, will be either referred to alcohol detoxification treatment or admitted to the CNRU for a brief stay. The CNRU is a clinical inpatient psychiatric facility fully equipped to manage alcohol detoxification, and detoxification will usually last between 1 to 4 days. The detoxification treatment protocol is not part of this research study and a subject's decision to take part in the research study will have no effect on their clinical treatment at the CNRU. CNRU is a state-run facility and provides free treatment for patients for CNRU principal investigators. One of co-investigators of this project, is a CNRU principal investigator, therefore, CNRU treatment will be provided with no cost.
Confidentiality: All data will be kept confidential except in cases of imminent danger to the participants. Such limits to confidentiality will be clearly explained to participants verbally and in the written consent forms. Confidentiality regarding collected materials will be maintained via a numbered reference system maintained by the investigators. Subjects' names will appear only on a consent form and a "key" form kept by the PI in locked filing

cabinets. Only the PI and relevant research staff will have access to any forms specifying both participant name and subject number. All number coded subjective and biological data will be kept in locked offices with access only to investigators and research staff. Furthermore, good clinical and research practice procedures and HIPAA regulations will be followed.

12. **Data and Safety Monitoring Plan:** Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.)
    a. What is the investigator's assessment of the overall risk level for subjects participating in this study? Greater than minimal risk
    b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? N/A
    c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://your.yale.edu/policies-procedures/forms/420-fr-01-data-and-safety-monitoring-plans-templates for
        i. Minimal risk
        ii. Greater than minimal
    d. For multi-site studies for which the Yale PI serves as the lead investigator:
        i. How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed? *Write here*
        ii. What provisions are in place for management of interim results? *Write here*
        iii. What will the multi-site process be for protocol modifications? *Write here*

Greater than minimal Risk DSMP

1. Personnel Responsible for the safety review and its frequency:

The principal investigator is responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews regularly at a minimum of every 6 months (including when reapproval of the protocol is sought). During the review process the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. The principal investigator and the Institutional Review Board (IRB) have the authority to stop or suspend the study or require modifications.

2. The risks associated with the current study are deemed moderate for the following reasons:

1. We do not view the risks associated with the potential alcohol withdrawal symptoms that patients with alcohol use disorder may experience during outpatient behavioral treatment as minimal risk.
2. Given the now established safety and validity of the current intervention in our prior work, we do not view the proposed studies as high risk.

Although we have assessed the proposed study as one of moderate risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

3. Attribution of Adverse Events:

Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design by the principal investigator according to the following categories:

a.) Definite: Adverse event is clearly related to investigational procedures(s)/agent(s).
b.) Probable: Adverse event is likely related to investigational procedures(s)/agent(s).
c.) Possible: Adverse event may be related to investigational procedures(s)/agent(s).
d.) Unlikely: Adverse event is likely not to be related to the investigational procedures(s)/agent(s).
e.) Unrelated: Adverse event is clearly not related to investigational procedures(s)/agent(s).

4. Plan for grading adverse events:

The following scale will be used in grading the severity of adverse events noted during the study:

1. Mild adverse event
2. Moderate adverse event
3. Severe

5. Plan for Determining Seriousness of the Adverse Events:

Serious Adverse Events:

In addition to grading the adverse event, the PI will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it results in any of the following outcomes:

1. Death;
2. A life-threatening experience in-patient hospitalization or prolongation of existing hospitalization;
3. A persistent or significant disability or incapacity;
4. A congenital anomaly or birth defect; OR
5. Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the IRB is necessary.

6. Plan for reporting UPIRSOs (including Adverse Events) to the IRB:

The principal investigator will report the following types of events to the IRB:

Any incident, experience or outcome that meets ALL 3 of the following criteria:

1. Is unexpected (in terms of nature, specificity, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB-approved protocol and informed consent document and (b) the characteristics of the subject population being studied; AND
2. Is 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
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) may be medical or non-medical in nature, and include – but are not limited to – serious, unexpected, and related adverse events and unanticipated adverse device effects. Please note that adverse events are reportable to the IRB as UPIRSOs only if they meet all 3 criteria listed above.

These UPIRSOs/SAEs will be reported to the IRB in accordance with IRB Policy 710, using the appropriate forms found on the website. All related events involving risk but not meeting the prompt reporting requirements described in IRB Policy 710 should be reported to the IRB in summary form at the time of continuing review. If appropriate, such summary may be a simple brief statement that events have occurred at the expected frequency and level of severity as previously documented.

7. Plan for reporting adverse events to co-investigators on the study, as appropriate the protocol's research monitor(s),e.g., industrial sponsor, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), Protocol Review Committee (PRC), DSMBs, study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies.

For the current study, the following individuals, funding, and/or regulatory agencies will be notified:

x All Co-Investigators listed on the protocol.

☐ Yale Cancer Center Data and Safety Monitoring Committee (DSMC)

x National Institutes of Health (National Institute on Alcohol Abuse and Alcoholism)

☐ Food and Drug Administration (Physician-Sponsored IND #_____)

☐ Medical Research Foundation (Grant_____)
☐ Study Sponsor
☐ Other Data Safety Monitoring Board (DSMB) or Committee (DSMC)

The principal investigator will conduct a review of all adverse events upon completion of every study subject. The principal investigator will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

13. **Statistical Considerations:** Describe the statistical analyses that support the study design.

Procedures for data management will follow the YSC and Yale MRRC procedure, and we will use Research Electronic Data Capture (REDCap), a HIPPA compliant, secure web application. The data analytic plan described below focuses on testing the specific hypotheses in the Aims section.

Behavioral Data Analysis: fMRI task ratings (stress, craving) will be analyzed using linear mixed models, with two groups (AUD, ET) as between-subjects factors and Condition (Alcohol, Stress, Neutral) as within-subjects factors.

Analysis of Stress Hormone: For plasma samples, assay processing will be conducted using standard radioimmunoassay procedures used in our prior work [3,20] at the Core Laboratory of the Yale Center for Clinical Investigation. We will also assess maximal or peak response and area under the curve for each measure, which are commonly used in the literature (e.g., [20]).

Analysis of HRV and Eye Tracking: HR and HRV data will be processed and analyzed using MATLAB and Kubios HRV software. For HRV, the root mean square of successive differences (RMSSD) will be calculated from beat-to-beat intervals. Eye tracking data will be analyzed using R and MATLAB. Position changes of the eye in the *X*–*Y* plane will be recorded, and fixation location, duration and count will be calculated during picture viewing.

fMRI data processing/analysis: fMRI pre-processing and task-related effects will follow the previously described procedure using the SEP task [3]. fMRI data will be preprocessed with slice time correction and motion correction. General Linear Model (GLM) will be used for individual level analysis on each voxel in the entire brain volume with a regressor (time during picture viewing) for each run per condition using BioImageSuite. Temporal filtering will be conducted by including drift correction in the GLM. Each run will be spatially smoothed using a 6 mm Gaussian kernel and individually normalized to generate beta-maps. To account for individual anatomical differences, three sequential registrations will be performed using BioImageSuite, as previously described [3,12]. For voxel-based analyses, whole-brain Family-wise error (FWE) rate correction will be applied using AFNI's 3dClustSim program (corrected version 16.0.09; [42]). Imaging results will use a cluster-forming threshold of p=0.001 at a cluster-level threshold of p<0.05 FWE correction.

Aim 1. neural systems underlying comorbid AUD/ET: To examine specific and comorbid effects of AUD and ET, the AFNI 3dLME (2 x 2 x 3) for linear mixed-effects anlaysis will be conducted on beta weights of dynamic response, especially the VmPFC, to evaluate main effects of AUD Group (AUD, MD), ET group (ET, NT), and Condition (alcohol, stress, neutral) and their interactions (http://afni.nimh.nih.gov/afni/). As a follow-up, simple effect analyses (voxel-wise two-sample *t* tests) will be conducted to clarify the sources of effects from 3dLME. In addition, for the comorbid effects of AUD and ET, conjunction analyses will be performed to identify brain regions commonly involved in levels within each group effect (AUD group, ET group).

Aim 2: neural correlates of HPA axis function: For basal cortisol levels, a 2 X 2 factorial design will be applied with AUD (AUD, MD) and ET (ET, NT) as the between-subjects factors. For changes in stress hormone (cortisol, ACTH) during the SEP task, all data analyses will use change from baseline (provocation minus baseline) values. Then, a 2 X 2 X 3 mixed-factorial design will be used with AUD (AUD, MD) and ET (ET, NT) as the between-subjects factors and Condition (Alcohol, Stress, Neutral) as the within-subjects factors. In addition, to examine the associations between task-related brain activity and stress hormone response, whole-brain correlation analyses will be conducted using BioimageSuite.

Aim 3: neural correlates of relapse: As reported in our previous papers [15,19,20], the primary outcome of relapse and treatment will be time to relapse (event based) and secondary outcome will be percent days of alcohol use during the follow-up period. These measures will also be assessed for their sensitivity and specificity of relapse risk prediction and treatment outcome over and above clinical and demographic measures associated with relapse and treatment outcome. For event-based relapse outcome measures (time to relapse, time to heavy drinking relapse), Cox proportional hazards regression (PHREG) models will be implemented for the primary predictor variable of dynamic VmPFC response controlling for any significant clinical, alcohol history or demographic measures that predict relapse [15,20].

SECTION II: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, check off N/A and delete the rest of the section.

A. RADIOTRACERS ☒N/A

1. Name of the radiotracer: *Write here*
8. Is the radiotracer FDA approved? ☐YES ☐NO

If NO, an FDA issued IND is required for the investigational use unless RDRC assumes oversight.

9. Check one: ☐IND# *Write here* or ☐RDRC oversight (RDRC approval will be required prior to use
4. **Background Information:** Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this radiotracer is being administered to humans, include relevant data on animal models.
Write here
4. **Source:** Identify the source of the radiotracer to be used. *Write here*
5. **Storage, Preparation and Use:** Describe the method of storage, preparation, stability information, method of sterilization and method of testing sterility and pyrogenicity.
Write here

B. DRUGS/BIOLOGICS ☒N/A

1. If an **exemption from IND filing requirements is** sought for a clinical investigation of a drug product that is lawfully marketed in the United States, review the following categories and complete the category that applies (*and delete the inapplicable categories)*:

Exempt Category 1: The clinical investigation of a drug product that is lawfully marketed in the United States can be exempt from IND regulations if all of the following are yes:	
1. The intention of the investigation is NOT to report to the FDA as a well-controlled study in support of a new indication for use or to be used to support any other significant change in the labeling for the drug.	☐
2. The drug that is undergoing investigation is lawfully marketed as a prescription drug product, and the intention of the investigation is NOT to support a significant change in the advertising for the product.	☐
3. The investigation does NOT involve a route of administration or dosage level or use in populations or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product	☐
10. The investigation will be conducted in compliance with the requirements for institutional (HIC) review and with the requirements for informed consent of the FDA regulations (21 CFR Part 50 and 21 CFR Part 56).	☐

11. The investigation will be conducted in compliance with the requirements regarding promotion and charging for investigational drugs.	☐

Exempt Category 2 (all items i, ii, and iii must be checked to grant a category 2 exemption)

☐i. The clinical investigation is for an *in vitro* diagnostic biological product that involves one or more of the following (check all that apply):

- ☐ Blood grouping serum
- ☐ Reagent red blood cells
- ☐ Anti-human globulin

☐ii. The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and

☐iii. The diagnostic test is shipped in compliance with 21 CFR §312.160.

Exempt Category 3

☐ The drug is intended solely for tests in vitro or in laboratory research animals if shipped in accordance with 21 CFR 312.60

Exempt Category 4

☐ A clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND.

2. **Background Information:** Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this drug is being administered to humans, include relevant data on animal models.
Write here

3. **Source:** Identify the source of the drug or biologic to be used. *Write here*
   a) Is the drug provided free of charge to subjects? ☐YES ☐NO
   If yes, by whom? *Write here*

1. **Storage, Preparation and Use:** Describe the method of storage, preparation, stability information, and for parenteral products, method of sterilization and method of testing sterility and pyrogenicity.
   Write here

Check applicable Investigational Drug Service utilized:

- ☐ YNHH IDS
- ☐ CMHC Pharmacy
- ☐ West Haven VA
- ☐ PET Center
- ☐ None
- ☐ Other:

Note: *If the YNHH IDS (or comparable service at CMHC or WHVA) will not be utilized, explain in detail how the PI will oversee these aspects of drug accountability, storage, and preparation*.

2. Use of Placebo: ☒Not applicable to this research project

If use of a placebo is planned, provide a justification which addresses the following:

a) Describe the safety and efficacy of other available therapies. If there are no other available therapies, state this. *Write here*

b) State the maximum total length of time a participant may receive placebo while on the study. *Write here*

c) Address the greatest potential harm that may come to a participant as a result of receiving placebo. *Write here*

d) Describe the procedures that are in place to safeguard participants receiving placebo. *Write here*

3. Continuation of Drug Therapy After Study Closure ☐Not applicable to this project

Are subjects provided the opportunity to continue to receive the study drug(s) after the study has ended?

☐ Yes If yes, describe the conditions under which continued access to study drug(s) may apply as well as conditions for termination of such access. *Write here*

☐ NO If no, explain why this is acceptable. *Write here*

B. DEVICES ☒N/A

1. Are there any investigational devices used or investigational procedures performed at Yale-New Haven Hospital (YNHH) (e.g., in the YNHH Operating Room or YNHH Heart and Vascular Center)? ☐Yes ☐No

If Yes, please be aware of the following requirements:

A YNHH New Product/Trial Request Form must be completed via EPIC: Pull down the Tools tab in the EPIC Banner, Click on Lawson, Click on "Add new" under the New Technology Request Summary and fill out the forms requested including the "Initial Request Form," "Clinical Evidence Summary", and attach any other pertinent documents. Then select "save and submit" to submit your request; AND

Your request must be reviewed and approved in writing by the appropriate YNHH committee before patients/subjects may be scheduled to receive the investigational device or investigational procedure.

2. Background Information: Provide a description of previous human use, known risks, and any other factors that might influence risks. If this is the first time this device is being used in humans, include relevant data on animal models. *Write here*

3. Source:
   a) Identify the source of the device to be used. *Write here*
   b) Is the device provided free of charge to subjects? ☐Yes ☐No

4. Investigational device accountability: State how the PI, or named designee, ensures that an investigational device is used only in accordance with the research protocol approved by the HIC, and maintains control of the investigational device as follows:
   a) Maintains appropriate records, including receipt of shipment, inventory at the site, dispensation or use by each participant, and final disposition and/or the return of the investigational device (or other disposal if applicable): *Write here*
   b) Documents pertinent information assigned to the investigational device (e.g., date, quantity, batch or serial number, expiration date if applicable, and unique code number): *Write here*
   c) Stores the investigational device according to the manufacturer's recommendations with respect to temperature, humidity, lighting, and other environmental considerations: *Write here*

d) Ensures that the device is stored in a secure area with limited access in accordance with applicable regulatory requirements: *Write here*

e) Distributes the investigational device to subjects enrolled in the IRB-approved protocol: *Write here*

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:
   a. Targeted for enrollment at Yale for this protocol: 160
   b. If this is a multi-site study, give the total number of subjects targeted across all sites: n/a
2. Indicate recruitment methods below. Attach copies of any recruitment materials that will be used.

☒ Flyers	☐ Internet/web postings	☐ Radio
☐ Posters	☐ Mass email solicitation	☐ Telephone
☐ Letter	☐ Departmental/Center website	☐ Television
☒ Medical record review*	☐ Departmental/Center research boards	☐ Newspaper
☐ Departmental/Center newsletters	☐ Web-based clinical trial registries	☐ Clinicaltrails.gov
☒ YCCI Recruitment database	☐ Social Media (Twitter/Facebook):	
☐ Other:		

* Requests for medical records should be made through JDAT as described at
http://medicine.yale.edu/ycci/oncore/availableservices/datarequests/datarequests.aspx

3. Recruitment Procedures:

a. Describe how potential subjects will be identified. *Write here*

Recruitment of participants (AUD patients, controls) will be conducted through a dedicated Yale Stress Center (YSC) Recruitment Center specializing in coordinating centralized recruitment of participants into center studies. This recruitment team that has a well-developed treatment referral network comprising a variety of treatment, social service and addiction referral sources in the Greater New Haven area. The YSC Recruitment Team provides coordinated centralized recruitment of participants into YSC affiliated studies Referrals from the Yale Substance Abuse Treatment facilities will also be a source of patients for study participation. This approach has allowed us to recruit subjects from a variety of race and socioeconomic backgrounds.

b. Describe how potential subjects are contacted.

Potential subjects will contact us via our toll-free phone number and be screened by research staff as detailed in HIC protocol 911006003: Telephone Screening and Repository for Stress and Lifestyle Behaviors

c. Who is recruiting potential subjects? Research staff at the Yale Stress Center (HIC 911006003)

4. Assessment of Current Health Provider Relationship for HIPAA Consideration:

Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

☐Yes, all subjects

☐Yes, some of the subjects

☒No

If yes, describe the nature of this relationship. *Write here*

5. Request for waiver of HIPAA authorization: (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)

Choose one:

☐ For entire study

☒ For recruitment/screening purposes only

☐ For inclusion of non-English speaking subject if short form is being used and there is no translated HIPAA research authorization form available on the University's HIPAA website at hipaa.yale.edu.

i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data: Screening is completed over the phone

ii. If requesting a waiver of **signed** authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data:
The recruitment will begin with a screening questionnaire over the phone, for which subjects will be asked to give a verbal consent, but a signature cannot be obtained. Once potential subjects have completed the phone screening and appear to be eligible, they will be invited for an intake appointment, during which a signed authorization and consent will be obtained.

The investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

6. Process of Consent/Assent: Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.
Following the initial telephone screening conducted as part of the Yale Stress Center telephone screening protocol (HIC protocol 0911006003), eligible participants will meet with a research assistant to obtain informed consent. Participants will also have an option of completing a brief phone screening form (an abbreviated version) to accommodate their time and availabilities. The consent process can be done either in person or remotely via a REDCap eConsent if needed. The following procedure will be implemented for the eConsent procedure.

   First, the potential participants will receive a secure REDCap link to view the consent form and have a remote session with research staff. After reviewing the consent form, they will go over the study procedure and all aspects of the consent form with staff and have enough time for study Q & A and the risk involved before making decisions. If they agree to participate, they will be asked to sign their name using a mouse on an eConsent form. Then, they will select "Next Page" at the bottom and a read only copy of the consent will be generated that they can review, download, and/or print. Also, at the bottom of the page they will view "I certify that all the information in the document above is correct, and I understand that signing this form electronically is the equivalent of signing a physical document." Once this is selected, they will be able to submit the consent from. The completed PDFs will be downloaded and stored in a study folder that can only be accessed with a unique password in a 3-lock Yale ITS managed storage. The e-consent also records the IP address of the participant and displays this information in the file repository in order to help regulate potential duplicate forms from a single IP address.

7. Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent: Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.

   After the participant has read over the consent form, research staff will further explain the study, including the risks involved. Research staff will ask the potential subject how well they understood the consent, and answer questions they may have.

Non-English Speaking Subjects: Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.

Non-English speaking individuals will not be recruited for this study.

As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment? YES ☐ NO ☒

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are available on the HRPP website (yale.edu/hrpp) and translated HIPAA Research Authorization Forms are available on the HIPAA website (hipaa.yale.edu). If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via modification prior to enrolling the subject. ***Please review the guidance and presentation on use of the short form available on the HRPP website.***

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

8. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☐Not Requesting any consent waivers

☒Requesting a waiver of signed consent:

☒ Recruitment/Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☐ Entire Study (Note that an information sheet may be required.)

For a waiver of signed consent, address the following:

- Would the signed consent form be the only record linking the subject and the research? YES ☐ NO ☒
- Does a breach of confidentiality constitute the principal risk to subjects? YES ☐ NO ☒

OR

- Does the research pose greater than minimal risk? YES ☐ NO☒
- Does the research include any activities that would require signed consent in a non-research context? YES ☐ NO ☒

☐ Requesting a waiver of consent:

☐ Recruitment/Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☐ Entire Study

For a full waiver of consent, please address all of the following:

- Does the research pose greater than minimal risk to subjects?
  ☐ Yes *If you answered yes, stop. A waiver cannot be granted.*
  ☐ No
- Will the waiver adversely affect subjects' rights and welfare? YES ☐ NO☐
- Why would the research be impracticable to conduct without the waiver? *Write here*
- Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date? *Write here*

SECTION IV: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

1. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research?

Results of the physical examination, psychological assessments, self-reports, blood samples for hormonal function, MRI data and smartphone app data will be collected and used for research. The proposed study will be conducted by specialized and trained research staff using standardized biophysiological and psychosocial assessments. All data will be kept confidential except in cases of imminent danger to the participants. Such limits to confidentiality will be clearly explained to participants verbally and in the written consent forms. Confidentiality regarding collected materials will be maintained via a numbered reference system maintained by the investigators. Subjects' names will appear only on a consent form and a "key" form kept by the PI in locked filing cabinets. Only the PI and relevant research staff will have access to any forms specifying both participant name and subject number. All number coded subjective and biological data will be kept in locked offices with access only to investigators and research staff. Furthermore, good clinical and research practice procedures and HIPAA regulations will be followed.

A Certificate of Confidentiality has been obtained from the NIH

2. How will the research data be collected, recorded and stored?

   Research data will be collected on paper assessments and using Yale University's REDCap system. All research data is stored in two places--one as a hardcopy in a locked file, with records identified only by the participant's study number, and the second in computerized databases protected by two-level password systems on Yale encrypted desktop computers.

3. How will the digital data be stored? ☐CD ☐DVD ☐Flash Drive ☐Portable Hard Drive ☒Secured Server ☐Laptop Computer ☒Desktop Computer ☐Other

4. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?

   Upon enrollment, all study subjects will be assigned a unique study number. The study number—and no personal identifiers—will be used as labels for study records, samples and any other related research documentation. All electronic and digital files will be stored on the secure Yale network, and the PC accessing the network will be password protected and encrypted. All paper files, such as consent forms, will be stored in a locked file cabinet in a locked office and access is limited to members of the study research team.

All portable devices must contain encryption software, per University Policy 5100. If there is a technical reason a device cannot be encrypted please submit an exception request to the Information Security, Policy and Compliance Office by clicking on url http://its.yale.edu/egrc or email it.compliance@yale.edu

5. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.

   Upon completion of study and data analysis, a professional information protection, storage, and disposal company will be retained to dispose of research files and informed consent documentation.

6. If appropriate, has a Certificate of Confidentiality been obtained? A Certificate of Confidentiality will be obtained from the NIH

SECTION V: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

This study does not have direct benefits to the subjects. However, their participation may provide information of the functioning of the different parts of the brain and help understand biobehavioral responses of individuals with early trauma and alcoholism. In addition, MRI data may give insight into brain activity of people when they see different types of objects and stimuli (stress, alcohol cue) and respond differently to these objects. It may also help in understanding what happens in the brain while experiencing various emotions. This information may be useful in the treatment of people who have early trauma and addictive behaviors (e.g., alcoholism) in the future. While there aren't direct benefits to the research subjects, standard outpatient treatment procedure would be helpful for participants with alcoholism. Given these valuable benefits to society at large and the minimal risks of the study procedures, we believe that the study risks are reasonable in relation to the potential benefits.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?
   Subjects need not participate in this study to receive outpatient treatment for alcoholism or substance use counseling.
   Payments for Participation (Economic Considerations): Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.

Moderate Drinkers With and Without Early Trauma (MD/ET, MD/NT):
Moderate drinkers (MD/ET, MD/NT) with/without early trauma will receive $20 per 2- hour intake (up to $100 (5 intakes) for baseline assessments and $150 for a multimodal imaging session (fMRI ($100) & Blood draws ($50)). In addition, subjects will receive up to $90 for the completion of 30-day follow-up ($3 per day) involving daily smartphone monitoring surveys. They will receive an additional weekly bonus for completing 100% ($10) or at least 86% (6 out of 7 days ($8)) of weekly surveys. Also, they will be compensated extra bonus at the end of 30 days for completing at least 93% (($50) 28 out of 30 days), or 87% (($30) 26 out of 30 days) of all the 30-day smartphone app survey respectively. Thus, a total up to $430 remuneration will be provided for the time taken to complete all study procedures.
AUD Subjects With and Without Early Trauma (AUD/ET, AUD/NT):
AUD subjects (AUD/ET, AUD/NT) with/without early trauma will be paid for taking part in this study which is split into three phases: (1) assessments, (2) an 8-week treatment period, and (3) a 90-day follow

(1) For the assessments, the participants will be compensated up to $460 for completing all pre- and post- intake assessments and two fMRI sessions. First, they will receive $20 for completion of each 2-hour intake appointment for baseline assessments and screening (usually up to 5-6 intakes, ($120)). They will receive $150 for each of the multimodal imaging sessions (fMRI scan ($100) and blood draws ($50)), thus, they will receive $300 total for completing the two imaging sessions: one before and one after the 8-week outpatient treatment. In addition, for post-treatment assessments, they will receive up to $40 for 1-2 intakes ($20 for each 2-hour intake).

(2) For the 8-week outpatient treatment, the participants will be compensated up to $936 for completing all treatment sessions and daily smartphone app surveys.

First, they will be compensated up to $520 for participating in the 8-week outpatient treatment and providing negative urine samples. They will receive $20 for completion of each treatment session, which will be held twice a week for 8 weeks (16 sessions total). An additional $10 bonus will be rewarded for the completion of every 2 weeks of treatment during the 8-week treatment period. Also, they will receive an additional $10 for each session that they provide a negative urine sample to verify their abstinence during the treatment.

For completion of all daily smartphone app surveys during the 8-week treatment period (56 days), they will be compensated up to $416. First, they will be compensated $3 for each daily evening survey submitted, which means they will receive $168 for the completion of all 56 days. In addition, they will be compensated $3 for completion of each daily intervention exercise during the 8-week treatment period (56 days: total $168). They will receive an additional weekly bonus of $10 for completing 100% (submitted a total number of two surveys (56-day surveys & daily intervention exercise) per week: 14/14 surveys), $9 for completing at least 92.5% (submitted a total number of two surveys (56-day surveys & daily intervention exercise) per week: 13/14 surveys) or $8 for completing at least 86% (submitted a total number of two surveys (56-day surveys & daily intervention exercise) per week: 12/14 surveys) of the surveys in each week; both the daily evening survey and daily intervention exercise must be completed for a day to count towards the weekly bonus.

(3) For the 90-day follow-up period, they will be compensated up to $640 for completing all daily smartphone app surveys and three follow-up appointments. For completion of the daily smartphone app surveys, they will be compensated up to $400, which includes $3 for each daily evening survey submitted ($270 for the completion of 90 days) and an additional weekly bonus up to $130, which includes $10 for completing 100% (7 days) or $8 for completing at least 86% (6 out of 7 days) of the surveys in each week. For completion of the three follow-up appointments (scheduled at 14, 30, and 90 days after discharge; 3-4 hours each), they will receive up to $240. This includes $50 as well as an additional $30 returning bonus for completion of each follow-up appointment.

To summarize, a total of $2,036 remuneration will be provided for the time taken to complete all study procedures if they complete all intake appointments, both fMRI scans, the 8-week outpatient treatment, the 3 follow-up appointments, and 100% of all daily smartphone surveys during the 8-week treatment and the 90-day follow-up periods. Payment will be prorated for participants who do not complete all components of the study.
In addition, parking vouchers will be provided for those participants who drive and park their car at the Yale Stress Center for their study-related appointment(s). And transportation expenses will be provided as needed at PI's discretion up to $100 (round trip) in certain circumstances (e.g., low-income or homeless conditions).

2. Costs for Participation (Economic Considerations): Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.
   All parts of the research process will be provided at no cost to the subjects.
3. In Case of Injury: This section is required for any research involving more than minimal risk, and for minimal risk research that presents the potential for physical harm (e.g., research involving blood draws).

a. Will medical treatment be available if research-related injury occurs?
Medical therapy will be offered for any physical injuries sustained as a consequence of participation in this research.
b. Where and from whom may treatment be obtained? Any licensed facility / practitioner
c. Are there any limits to the treatment being provided? *No*
d. Who will pay for this treatment? The subject and their insurance carrier will be responsible for the cost of treatment. Financial compensation for injury is not available.
e. How will the medical treatment be accessed by subjects? Subjects will be given the option of treatment and appropriate referrals.

IMPORTANT REMINDERS

Will this study have a billable service? Yes ☐ No☒

A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects.

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities?
Yes ☐ No ☒
If Yes, please answer questions a through c and note instructions below.
a. Does your YNHH privilege delineation currently include the specific procedure that you will perform? Yes ☐ No ☐
b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? Yes ☐ No ☐
c. Will a novel approach using existing equipment be applied? Yes ☐ No ☐

If you answered "no" to question 4a, or "yes" to question 4b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

IMPORTANT REMINDER ABOUT RESEARCH AT YNHH

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. By submitting this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH.

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COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH STUDY

YALE UNIVERSITY SCHOOL OF MEDICINE

Study Title: Neurobiological responses in stress and alcoholism
Principal Investigator (the person who is responsible for this research):
Dongju Seo, PhD, 2 Church Street South, Suite 209
Phone Number: 475-441-3457

Research Study Summary:

- We are asking you to join a research study.
- The purpose of this research study is to examine the effects of stress on alcohol use and recovery from alcohol use disorder.
- Study procedures will include: intake assessment, MRI session, 8-week outpatient treatment and follow-up.
- Approximately 26 appointments are required.
- These appointments will take approximately 45 - 48 hours total.
- There are some risks from participating in this study. These include risks involved in the fMRI sessions, blood draws during the fMRI sessions, and information you provide on questionnaires and smartphone app surveys.
- The study may have no benefits to you. However, this may be useful in developing treatment for those with alcohol use disorders.
- There are other choices available to you outside of this research including enrolling in a similar outpatient treatment program outside of the study.
- Taking part in this study is your choice. You can choose to take part, or you can choose not to take part in this study. You can also change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.
- If you are interested in learning more about the study, please continue reading, or have someone read to you, the rest of this document. Take as much time as you need before you make your decision. Ask the study staff questions about anything you do not understand. Once you understand the study, we will ask you if you wish to participate; if so, you will have to sign this form.

Why is this study being offered to me?
We are asking you to take part in a research study because it is our understanding that you are seeking treatment for your alcohol use. We are looking for 160 participants to be part of this research study.

Who is paying for the study?
National Institute on Alcohol Abuse and Alcoholism; Yale Psychiatry Research Initiative

What is the study about?
The purpose of this study is to examine the effects of stress on alcohol use and recovery from alcohol use disorder.

What are you asking me to do and how long will it take?
If you agree to take part in this study, this is what will happen. You will participate in intake assessments, two fMRI sessions, 8-week outpatient treatment, daily smartphone follow-up surveys, and three follow-up appointments. Each time that you visit the clinic, we will obtain a

urine sample for drugs, and take a sample of your breath by asking you to blow into a breathalyzer to see if you have recently consumed alcohol.

Intake procedures

You will be asked to complete 5-6 intake appointments. Intake appointments take approximately 2 hours to complete. During these appointments we will ask questions about your alcohol use, demographics and health history. You will also complete a physical examination to ensure that all inclusion and exclusion criteria for the study are met. If you are female, we will also give you a pregnancy test.

In addition, to limit exposure to COVID-19 and ensure the safety of our study participants and team members, we will minimize the number of in-person study visits. For some of the intake appointments you will have the option of remote appointments through secure video call. For example, you will meet with research staff via video communications technology (e.g., Zoom or Microsoft Teams) to complete intake assessments.

As this study requires you to stay abstinent from alcohol, during the intake appointments and throughout the study, we will assess for alcohol withdrawal symptoms. The risks associated with stopping drinking may include: anxiety, shakiness, confusion, rapid heart rate, fever, and in rare cases, life-threatening seizures. These risks and the treatment required for these possible risks will be thoroughly reviewed with you during the intake process by the clinical research staff. If you show clinical signs of alcohol withdrawal, you will be evaluated by the study doctor who will refer you for treatment for alcohol withdrawal. Depending on the severity of your alcohol withdrawal symptoms, you may be referred to either a free detoxification program in Connecticut, or to the Clinical Neuroscience Research Unit (CNRU) for detoxification. The detoxification treatment and referral are not part of this research study and your decision to take part in the research study will not be affected by your clinical treatment for alcohol withdrawal. If you are unable to make an effort to stay abstinent from alcohol, you may be withdrawn from the study.

MRI sessions

You will be asked to complete two Magnetic Resonance Imaging (MRI) scans. Each of the scan sessions will take approximately 2 hours. Both scans will take place at 2:30 pm. A member of the research staff will accompany you to the Yale MRRC (Magnetic Resonance Research Center) and remain there for the entire scan. During the MRI sessions you will be viewing different pictures on a screen while we take pictures of your brain. There will be a noninvasive camera mounted into the head coil of the MRI scanner to detect your eye movements and attention during the picture task. We will also ask you to make some ratings on a screen and participate in the MRI task. In addition, we will measure your heart rate and blood pressure, and take blood samples. A nurse will insert an IV needle into a vein in one of your arms so that we can draw blood at regular intervals. The blood samples will be analyzed for naturally occurring chemicals that your body produces regularly. We will also place three small electrocardiogram (ECG) sensors on the surface of the skin in your chest area for the purpose of measuring cardiovascular response.

The first scan will be within 3-5 days of your last drink, and the second scan will be between 4 – 8 weeks of your time in treatment.

We will ask you to remain abstinent from alcohol and drugs for 72 hours before both scans, which should also help you abstain from alcohol. We also ask that you refrain from eating food or drinking caffeine for 2 hours before both scans. Water is allowed at any time.

8-week outpatient treatment

You will receive 8 weeks of outpatient treatment at the Yale Stress Center at 2 Church Street South. You will attend appointments twice a week for individual alcohol counseling with a psychologist or qualified counselor to regulate stress, craving, and alcohol relapse. You will have the option of completing some of the outpatient treatment appointments remotely via secure video communications (e.g., Yale-approved Zoom). During these appointments, you will be asked about your alcohol use and other psychological and physical problems that you may have now or may have had in the past. We will also ask you to complete several paper-and-pencil tests or online tests about your alcohol use and other behaviors. You will also take some cognitive tests. Each time that you visit the clinic, we will obtain a urine sample to test for drugs and take a sample of your breath by asking you to blow into a breathalyzer to see if you have recently consumed alcohol. You will receive $10 for each visit that you provide negative urine and breathalyzer samples. During the 8-week outpatient treatment, you will be also asked to submit two daily monitoring surveys including an 8-week daily survey and daily intervention exercise (breathing technique) using a smartphone app. After your first MRI scan session, there will be an hour-long training session where we will assist in installing the app on your smartphone device and instruct you in its use. This session can also be done remotely via video communications if needed. In the event that you are unable to achieve abstinence, and/or your drinking gets worse, you will be referred to a higher level of care at another facility. Your progress will be reviewed with you at each appointment.

Following the second MRI scan session and the completion of the 8-week treatment, you will be discharged from outpatient treatment. You will be encouraged to attend Alcoholics Anonymous or another aftercare program of your choice.

Follow-up

After you have completed the 8-week outpatient treatment phase of the study, there will be a daily follow-up using the same smartphone app that is used for the daily monitoring surveys during the 8-week treatment. You will be asked to use this app to complete daily surveys for 90 days after discharge. The smartphone app will prompt you every evening at 5pm to complete that day's daily survey. All daily surveys will be open from 5pm to 2am of the next day. The daily surveys will ask interactive questions related to mood, stress, alcohol use, and other health-related behaviors and will take around 10-15 minutes to complete depending on individual speed.

In addition, you will be scheduled for three face-to-face follow-up appointments at 14, 30, and 90 days after discharge. During these appointments, you will fill out some questionnaires and give a urine sample and a breath sample. Each follow-up appointment will take about two hours.

We ask that you provide the names and telephone numbers of three individuals who are likely to know your whereabouts in order to help us locate you for the follow-up appointments. These individuals will be contacted only if we cannot locate you directly first; we will ask them only about where we may contact you (we will not ask about drug use or other problems). We will not give them any information about your participation in this study.

What are the risks and discomforts of participating?

i) Magnetic Resonance Imaging (MRI):

Magnetic resonance imaging (MRI) is a technique that uses magnetism and radio waves, not x-rays, to take pictures and measure chemicals of different parts of the body. The United States Food and Drug Administration (FDA) has set guidelines for magnet strength and exposure to radio waves, and we carefully observe those guidelines.

You will be watched closely throughout the study. Some people may feel uncomfortable or anxious. If this happens to you, you may ask to stop the study at any time and we will take you out of the MR scanner. On rare occasions, some people might feel dizzy, get an upset stomach, have a metallic taste in their mouth, or feel tingling sensations or muscle twitches. These sensations usually go away quickly but please tell the research staff if you have them.

There are some risks associated with an MRI study for certain people. If you have a pacemaker or some metal objects inside your body, you cannot participate in this study because the strong magnets in the MR scanner might harm you. Another risk is the possibility of metal objects being pulled into the magnet and hitting you. To lower this risk, all people involved with the study must remove all metal from their clothing and all metal objects from their pockets. We also ask all people involved with the study to walk through a metal detector. It is important to know that no metal can be brought into the magnet room at any time. Also, once you are in the magnet, the door to the room will be closed so that no one from outside accidentally goes near the magnet.

MRI noise may cause temporary hearing discomfort. You will wear ear plugs and headphones to minimize this discomfort. This is typically tolerable for most people. If you are uncomfortable, please tell research staff by speaking into the microphone.

We will provide an MRI Safety
Questionnaire with questions related to your personal safety. We ask that you read and answer all the questions on the MRI Safety Questionnaire very carefully. Please inform us of any information that you think might be important.

This MRI study is for research purposes only and is not in any way a complete health care imaging examination. The scans performed in this study are not designed to find abnormalities. The principal investigator, the lab, the MR technologist, and the Yale Magnetic Resonance Research Center (MRRC) are not qualified to interpret the MR scans and are not responsible for providing a healthcare evaluation of the images. If a worrisome finding is seen on your scan, a radiologist or another physician will be asked to review the relevant images. Based on his or her recommendation (if any), the principal investigator or consulting physician will contact you, inform you of the finding, and recommend that you seek medical advice as a precautionary measure. The decision for additional examination or treatment would lie only with you and your physician. The investigators, the consulting physician, the Magnetic Resonance Research Center, and Yale University are not responsible for any examination or treatment that you receive based on these findings. The images collected in this study are not a health care MR exam and for that reason, they will not be made available for health care purposes.

ii) Visual Stimuli Task:
Some of the pictures that will be shown during the visual stimuli task (especially the stress-inducing pictures) are graphic and may be disturbing to you. The purpose of presenting these pictures is to evoke and assess emotional reactions. Generally, these images are not a concern because they depict contents that are likely to be encountered by adults in everyday media (e.g., film, television). For any participant that reports emotional discomfort after completion of the visual stimuli task, an individual counseling session will be available.

iii) ECG:
Although it is rare, there is a possibility of minor skin irritation from the placement of the ECG (electrocardiogram) sensors. However, this mostly goes away after the fMRI session.

iv) Drawing of Blood:
The insertion of the intravenous (IV) line for the scan is done by an experienced nurse. There is a slight chance that multiple needle-sticks will be needed to make sure the IV is placed correctly. You might feel a small amount of pain when the IV is placed but it does not last very long. A bruise or a minor infection might develop where the IV is placed. A bruise will go away by itself and it might help if you wrap a warm towel around your arm. Infections can also be treated if necessary. About four and a half ounces of blood will be taken during each MRI session, an amount that is less than the standard amount drawn at a blood donation, and the loss of which your body can easily tolerate. While your body can tolerate this level of blood draw, you should not donate blood for a period of 8 weeks after you finish the study. You also will not be admitted to the study if you have donated blood within a period of 5 weeks prior to admission to the study.

v) Alcohol Withdrawal and Abstinence: Abstinence from alcohol poses a risk of alcohol withdrawal symptoms. As the study requires alcohol abstinence, we will assess alcohol withdrawal symptoms throughout the study period. If you show moderate to severe clinical signs of alcohol withdrawal, we will refer you to alcohol detoxification treatment. These risks and the treatment required for these possible risks will be thoroughly reviewed with you during the intake process by the clinical research staff. The risks associated with stopping drinking may include: anxiety, shakiness, confusion, rapid heart rate, fever, and in rare cases, life-threatening seizures. The detoxification treatment protocol is not part of this research study and your decision to take part in the research study will have no effect on your clinical treatment.

If you are unable to make an effort to stay abstinent from alcohol, you may be withdrawn from the study.

vi) Use of the Smartphone App to Complete Surveys:
You will be provided with a smartphone app on which you will report on your experiences, feelings and behaviors. You may feel self-conscious while completing questionnaires about yourself on the phone. Your responses will be linked to a numbered ID so that they can be paired in our analyses, but do not ask for information that would identify who the responses belong to. These responses will be wirelessly transferred to a secure server that is password protected.

Subject Obligation
We ask that you do not use any drugs or medicines, including street drugs or alcohol, during the study. If you do use any drugs or other medicines during this time, you will need to tell us. The only way you might be dismissed from the study is if you repeatedly do not show up and/or do not tell us the truth about your alcohol and drug use. We will be checking your breath and urine for use of alcohol and drugs. For female participants, you will not be allowed to take part in the study if you are pregnant.

Safety guidelines in response to the COVID-19 pandemic

To limit exposure to COVID-19, in-person meetings will be avoided as much as possible. If one-on-one meetings must be held in person, the following guidelines will be followed.

Before any study visits, you will be screened for COVID-19 symptoms by filling out the COVID-19 questionnaires prior to the study visit and at the time of the on-site study visit.

You will be asked to fill out a Yale Stress Center (YSC) safety questionnaire for all YSC visits and an MRRC safety questionnaire for all MRRC visits. If you say "yes" to any of the COVID-19 related symptom questions, your appointment will be moved to a later date and you will be encouraged to contact the YNHH COVID-19 Support Call Center (203-688-1700, option 1).

For your safety, the study site will be disinfected before and after each study visit according to CDC guidelines. Upon entrance to the study site, all participants and research personnel will have body temperature measured with a non-contact forehead thermometer and oxygen saturation levels measured with a pulse oximeter. If body temperature is greater than 99.5 degrees Fahrenheit or oxygen saturation is below 95%, you will be asked to leave and seek medical attention, and the study appointment will be rescheduled to a later date.

During in-person visits, both you and research staff will be asked to maintain the required social distancing (at least 6 feet) and wear a face mask. You are also required to properly disinfect your hands with alcohol-based hand sanitizer (containing at least 60% alcohol) or clean them with soap and water to help protect against the spread of germs and viruses. In the event that you do not have a suitable face mask to wear, a new surgical mask will be provided for you at each on-site study visit.

How will I know about new risks or important information about the study?
We will tell you if we learn any new information that could change your mind about taking part in this study.

How can the study possibly benefit me?
This study is not designed to be of direct benefit to you. However, it may provide us with information on the functioning of the different parts of the brain when people see and respond to different types of objects and experience emotions. This information may be useful in the treatment of people who have addictive behaviors in the future.

How can the study possibly benefit other people?
The benefits to science and other people may include a better understanding of alcohol use disorder that may lead to new treatments and general advancement of scientific knowledge.

Are there any costs to participation?
You will not have to pay for taking part in this study. The only costs include transportation and the time spent coming to the study visits.

Will I be paid for participation?
You will be paid for taking part in this study which is split into three phases: (1) assessments, (2) an 8-week treatment period, and (3) a 90-day follow-up period.

(1) For the assessments, you will be compensated up to **$460** for completing all pre- and post-intake assessments and two fMRI sessions.
First, you will receive $20 for completion of each 2-hour intake appointment for baseline assessments and screening (usually up to 5-6 intakes). You will receive $150 for each of the multimodal imaging sessions (fMRI scan ($100) and blood draws ($50)), thus, you will receive $300 total for completing the two imaging sessions: one before and one after the 8-week outpatient treatment. In addition, for post-treatment assessments, you will receive up to $40 for 1-2 intakes ($20 for each 2-hour intake).

(2) For the 8-week outpatient treatment, you will be compensated up to **$936** for completing all

treatment sessions and daily smartphone app surveys.
First, you will be compensated up to $520 for participating in the 8-week outpatient treatment and providing negative urine samples. You will receive $20 for completion of each treatment session, which will be held twice a week for 8 weeks (16 sessions total). An additional $10 bonus will be rewarded for the completion of every 2 weeks of treatment during the 8-week treatment period. Also, you will receive an additional $10 for each session that you provide a negative urine sample to verify your abstinence during the treatment.

For completion of all daily smartphone app surveys during the 8-week treatment period (56 days), you will be compensated up to $416. First, you will be compensated $3 for each daily evening survey submitted, which means you will receive $168 for the completion of all 56 days. In addition, you will be compensated $3 for completion of each daily intervention exercise during the 8-week treatment period (56 days: total $168). You will receive an additional weekly bonus of $10 for completing 100% (submitted a total number of two surveys (daily evening surveys + daily intervention exercise) per week: 14/14 surveys), $9 for completing at least 92.5% (submitted a total number of two surveys (daily evening surveys + daily intervention exercise) per week: 13/14 surveys) or $8 for completing at least 86% (submitted a total number of two surveys (daily evening surveys + daily intervention exercise) per week: 12/14 surveys) of the surveys in each week; both the daily evening survey and daily intervention exercise must be completed for a day to count towards the weekly bonus.

(3) For the 90-day follow-up period, you will be compensated up to **$640** for completing all daily smartphone app surveys and three follow-up appointments. For completion of the daily smartphone app surveys, you will be compensated up to $400, which includes $3 for each daily evening survey submitted ($270 for the completion of 90 days) and an additional weekly bonus up to $130, which includes $10 for completing 100% (7 days) or $8 for completing at least 86% (6 out of 7 days) of the surveys in each week. For completion of the three follow-up appointments (scheduled at 14, 30, and 90 days after discharge; 3-4 hours each), you will receive up to $240. This includes $50 as well as an additional $30 returning bonus for completion of each follow-up appointment.

To summarize, a total of **$2,036** remuneration will be provided for the time taken to complete all study procedures if you complete all intake appointments, both fMRI scans, the 8-week outpatient treatment, the 3 follow-up appointments, and 100% of all daily smartphone surveys during the 8-week treatment and the 90-day follow-up periods. Payment will be prorated for participants who do not complete all components of the study.

You are responsible for paying state, federal, or other taxes for the payments you receive for being in this study. Taxes are not withheld from your payments.

For your participation in this study you will receive payment(s) via a Bank of America pre-paid debit card. Please note that your name, address, and telephone number will be shared with Bank of America for ePayments. After your first payment milestone you will receive a card in the mail which you will need to activate over the phone, and any subsequent milestone payments will automatically be added to this card.
In addition, parking vouchers will be provided for those participants who drive and park their car at the Yale Stress Center for their study-related appointment(s). In certain circumstances, and at the discretion of the PI, some participants may be eligible for payment of transportation costs, after discussion with the study team.

What are my choices if I decide not to take part in this study?

Instead of participating in this study, you have some other choices.
You could:

- Get treatment without being in a study. You may be able to enroll in a similar outpatient treatment program outside of this study.
- Take part in another study.
- Receive comfort care only, without any treatment for your disease.

How will you keep my data safe and private?

We will keep information we collect about you confidential. We will share it with others if you agree to it or when we have to do it because U.S. or State law requires it. For example, we will tell somebody if you we learn that you are hurting a child or an older person.

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as permitted by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. All information collected on you will be kept in a locked cabinet or password protected on a computer. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained.

We understand that information about you obtained in connection with your health is personal, and we are committed to protecting the privacy of that information. If you decide to be in this study, the researcher will get information that identifies you and your personal health information. This may include information that might directly identify you, such as your name and date of birth. This information will be de-identified at the earliest reasonable time after we receive it, meaning we will replace your identifying information with a code that does not directly identify you. The principal investigator will keep a link that identifies you to your coded information, and this link will be kept secure and available only to selected members of the research team. Any information that can identify you will remain confidential. The research team will only give this coded information to others to carry out this research study. The link to your personal information will be kept for five years, after which time the link will be destroyed and the data will become anonymous. The data will be kept in this anonymous form indefinitely until it is destroyed.

When we publish the results of the research or talk about it in conferences, we will not use your name. If we want to use your name, we would ask you for your permission.

We will also share information about you with other researchers for future research, but we will not use your name or other identifiers. We will not ask you for any additional permission.

All health care providers subject to HIPAA (Health Insurance Portability and Accountability Act) are required to protect the privacy of your information. The research staff at the Yale School of Medicine are required to comply with HIPAA and to ensure the confidentiality of your information. Some of the individuals or agencies listed above may not be subject to HIPAA and therefore may not be required to provide the same type of confidentiality protection. They could use or disclose your information in ways not mentioned in this form. However, to better protect your health information, agreements are in place with these individuals and/or companies that require that they keep your information confidential.

What Information Will You Collect About Me in this Study?

The information we are asking to use and share is called “Protected Health Information.” It is protected by a federal law called the Privacy Rule of the Health Insurance Portability and

Accountability Act (HIPAA). In general, we cannot use or share your health information for research without your permission. If you want, we can give you more information about the Privacy Rule. Also, if you have any questions about the Privacy Rule and your rights, you can speak to Yale Privacy Officer at 203-432-5919.

The specific information about you and your health that we will collect, use, and share includes:

- Research study records
- Medical and laboratory records of only those services provided in connection with this study
- Records about phone calls made as part of this research
- Records about your study visits
- Information obtained during this research regarding
    - MRI and laboratory test results
    - Questionnaires
    - The diagnosis and treatment of a mental health condition
    - Use of illegal drugs or the study of illegal behavior

How will you use and share my information?

We will use your information to conduct the study described in this consent form.
We may share your information with:

- The U.S. Department of Health and Human Services (DHHS) agencies
- Representatives from Yale University, the Yale Human Research Protection Program and the Institutional Review Board (the committee that reviews, approves, and monitors research on human participants), who are responsible for ensuring research compliance. These individuals are required to keep all information confidential.
- National Institute on Alcohol Abuse and Alcoholism (NIAAA)
- Investigators: Principal investigator, co-investigators, and other investigators
- Laboratories and other individuals and organizations that analyze your health information in connection with this study according to the study plan
- Study Coordinator and Members of the Research Team
- Those individuals at Yale who are responsible for the financial oversight of research including billing and payments
- Data and Safety Monitoring Boards and others authorized to monitor the conduct of the Study

We will do our best to make sure your information stays private. But, if we share information with people who do not have to follow the Privacy Rule, your information will no longer be protected by the Privacy Rule. Let us know if you have questions about this. However, to better protect your health information, agreements are in place with these individuals and/or agencies that require that they keep your information confidential.

If you decide to take part in this research study, you will be required to give us information about your substance use. We have obtained a Certificate of Confidentiality (CoC) issued by the National Institutes of Health. The researchers can use this Certificate to legally refuse to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The protection offered by the CoC does not stop us from voluntarily reporting information about suspected or known sexual, physical, or other abuse of a child or older person, or a participant'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. Because this research is sponsored by the Department of Health and Human Services through NIAAA, staff from that and other DHHS agencies may review records that identify you only for audit or program evaluation. They cannot report anything that would harm you or other research subjects.

Even when a CoC is in place, you and your family members must still continue to actively protect your own privacy. If you voluntarily give your written consent for anyone to receive information about your participation in the research, then we may not use the CoC to withhold this information.

Why must I sign this document?

By signing this form, you will allow researchers to use and disclose your information described above for this research study. This is to ensure that the information related to this research is available to all parties who may need it for research purposes. You always have the right to review and copy your health information in your medical record.

What if I change my mind?

The authorization to use and disclose your health information collected during your participation in this study will never expire. However, you may withdraw or take away your permission at any time. You may withdraw your permission by telling the study staff or by writing to Dr. Dongju Seo at the Yale Stress Center, 2 Church Street South, Suite 209, New Haven, CT 06511.

If you withdraw your permission, you will not be able to stay in this study but the care you get from your doctor outside this study will not change. No new health information identifying you will be gathered after the date you withdraw. Information that has already been collected may still be used and given to others until the end of the research study to insure the integrity of the study and/or study oversight.

Who will pay for treatment if I am injured or become ill due to participation in the study?

If you are injured while on study, seek treatment and contact the study doctor as soon as you are able.

The Yale School of Medicine does not provide funds for the treatment of research-related injury. If you are injured as a result of your participation in this study, treatment will be provided. You or your insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available.

You do not give up any of your legal rights by signing this form.

What if I want to refuse or end participation before the study is over?

Taking part in this study is your choice. You can choose to take part, or you can choose not to take part in this study. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

We would still treat you with standard therapy or, at your request, refer you to a clinic or doctor who can offer this treatment. Not participating or withdrawing later will not harm your relationship with your own doctors or with this institution.

To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part.

The researchers may withdraw you from participating in the research if necessary. These conditions include repeated no-shows for appointments or if you are found ineligible for the study.

What will happen with my data if I stop participating?
When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to insure the integrity of the study and/or study oversight. You will have the ability to withdraw your data from the research once it is collected.

Who should I contact if I have questions?
Please feel free to ask about anything you don't understand.

If you have questions later or if you have a research-related problem, you can call the Principal Investigator at 475-441-3457.

If you have questions about your rights as a research participant, or you have complaints about this research, you call the Yale Institutional Review Boards at (203) 785-4688 or email hrpp@yale.edu.

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Authorization and Permission

Your signature below indicates that you have read this consent document and that you agree to be in this study.

We will give you a copy of this form.

Participant Printed Name	Participant Signature	Date

Person Obtaining Consent Printed Name	Person Obtaining Consent Signature	Date

HIC#: 2000024809

COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH STUDY

YALE UNIVERSITY SCHOOL OF MEDICINE

Study Title: Neurobiological responses in stress and alcoholism
Principal Investigator (the person who is responsible for this research):
Dongju Seo, PhD, 2 Church Street South, Suite 209
Phone Number: 475-441-3457

Research Study Summary:

- We are asking you to join a research study.
- The purpose of this research study is to examine the effects of stress on alcohol use and recovery from alcohol use disorder.
- Study procedures will include: intake assessment, MRI session, and follow-up.
- Approximately 4-5 appointments are required.
- These appointments will take approximately 10 - 12 hours total.
- There are some risks from participating in this study. These include risks involved in fMRI session, blood draws during the fMRI session, and information you provide on questionnaires and smartphone app survey.
- The study may have no benefits to you. However, it may be useful in developing treatment for those with alcohol use disorders.
- There are other choices available to you outside of this research, including enrolling in a similar research program outside of the study.
- Taking part in this study is your choice. You can choose to take part, or you can choose not to take part in this study. You can also change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.
- If you are interested in learning more about the study, please continue reading, or have someone read to you, the rest of this document. Take as much time as you need before you make your decision. Ask the study staff questions about anything you do not understand. Once you understand the study, we will ask you if you wish to participate; if so, you will have to sign this form.

Why is this study being offered to me?
We are asking you to take part in a research study because it is our understanding that you are a healthy individual and your data would be utilized for comparison with the data of alcohol disordered participants. We are looking for 160 participants to be part of this research study.

Who is paying for the study?
National Institute on Alcohol Abuse and Alcoholism; Yale Psychiatry Research Initiative

What is the study about?
The purpose of this study is to examine the effects of stress on alcohol use and recovery from alcohol use disorder.

What are you asking me to do and how long will it take?
If you agree to take part in this study, this is what will happen. You will participate in intake assessments, an fMRI session, and 30-day smartphone survey follow-up. Each time that you visit the clinic, we will obtain a urine sample for drugs, and take a sample of your breath by asking you to blow into a breathalyzer to see if you have recently consumed alcohol.

Intake procedures

If you agree to take part in this study, you will be asked to complete 4-5 intake appointments. Intake appointments take approximately 2 hours to complete. During these appointments we will ask questions about your alcohol use, demographics and health history. You will also complete a physical examination to ensure that all inclusion and exclusion criteria for the study are met. If you are female, we will also give you a pregnancy test.

In addition, to limit exposure to COVID-19 and ensure the safety of our study participants and team members, we will minimize the number of in-person study visits. For some of the intake appointments you will have the option of remote appointments through secure video call. For example, you will meet with research staff via video communications technology (e.g., Zoom or Microsoft Teams) to complete intake assessments.

MRI session

You will be asked to complete one Magnetic Resonance Imaging (MRI) scan. The scan session will take approximately 2 hours. The scan will take place at 2:30pm. A member of the research staff will accompany you to the Yale MRRC (Magnetic Resonance Research Center) and remain there for the entire scan. During the MRI session you will be viewing different pictures on a screen while we take pictures of your brain. There will be a noninvasive camera mounted into the head coil of the MRI scanner to detect your eye movements and attention during the picture task. We will also ask you to make some ratings on a screen and participate in the MRI task. In addition, we will measure your heart rate and blood pressure, and take blood samples. A nurse will insert an IV needle into a vein in one of your arms so that we can draw blood at regular intervals (a total of 4.5 ounces). The blood samples will be analyzed for naturally occurring chemicals that your body produces regularly. We will also place three small electrocardiogram (ECG) sensors on the surface of the skin in your chest area for the purpose of measuring cardiovascular response.

We will ask you to remain abstinent from alcohol and drugs for 72 hours before the scanWe also ask that you refrain from eating food or drinking caffeine in the 2 hours before the scan. Water is allowed at any time.

Follow-up

For the follow-up phase, you will submit daily surveys on a smartphone app for 30 days after the scan. On the day of the MRI scan, you will complete an hour-long training session where we will assist in installing the app on your smartphone device and instruct you on its use. This session can also be done remotely via video communications if needed. Then, you will be asked to use this app over the following 30 days. The smartphone app will prompt you every evening at 5pm to complete that day's daily survey. All daily surveys will be open from 5pm to 2am of the next day. The daily surveys will ask interactive questions related to mood, stress, alcohol use, and other health-related behaviors and will take around 10-15 minutes to complete depending on individual speed.

What are the risks and discomforts of participating?

i) Magnetic Resonance Imaging (MRI):

Magnetic resonance imaging (MRI) is a technique that uses magnetism and radio waves, not x-rays, to take pictures and measure chemicals of different parts of the body. The United States Food and Drug Administration (FDA) has set guidelines for magnet strength and exposure to radio waves, and we carefully observe those guidelines.

You will be watched closely throughout the study. Some people may feel uncomfortable or anxious. If this happens to you, you may ask to stop the study at any time and we will take you out of the MRI scanner. On rare occasions, some people might feel dizzy, get an upset stomach, have a metallic taste in their mouth, or feel tingling sensations or muscle twitches. These sensations usually go away quickly but please tell the research staff if you have them.

There are some risks associated with an MRI study for certain people. If you have a pacemaker or some metal objects inside your body, youcannot participate in this study because the strong magnets in the MRI scanner might harm you. Another risk is the possibility of metal objects being pulled into the magnet and hitting you. To lower this risk, all people involved with the study must remove all metal from their clothing and all metal objects from their pockets. We also ask all people involved with the study to walk through a metal detector. It is important to know that no metal can be brought into the magnet room at any time. Also, once you are in the magnet, the door to the room will be closed so that no one from outside accidentally goes near the magnet.

MRI noise may cause temporary hearing discomfort. You will wear ear plugs and headphones to minimize this discomfort. This is typically tolerable for most people. If you are uncomfortable, please tell research staff by speaking into the microphone.

We will provide an MRI Safety Questionnaire with questions related to your personal safety.We ask that you read and answer all the questions on the MRI Safety Questionnaire very carefully. Please inform us of any information that you think might be important.

This MRI study is for research purposes only and is not in any way a complete health care imaging examination. The scans performed in this study are not designed to find abnormalities. The principal investigator, the lab, the MR technologist, and the Yale Magnetic Resonance Research Center (MRRC) are not qualified to interpret the MR scans and are not responsible for providing a health care evaluation of the images. If a worrisome finding is seen on your scan, a radiologist or another physician will be asked to review the relevant images. Based on his or her recommendation (if any), the principal investigator or consulting physician will contact you, inform you of the finding, and recommend that you seek medical advice as a precautionary measure. The decision for additional examination or treatment would lie only with you and your physician. The investigators, the consulting physician, the Magnetic Resonance Research Center, and Yale University are not responsible for any examination or treatment that you receive based on these findings. The images collected in this study are not a health care MR exam and for that reason, they will not be made available for health care purposes.

ii) Visual Stimuli Task:
Some of the pictures that will be shown during the visual stimuli task (especially the stress-inducing pictures) are graphic and may be disturbing to you. The purpose of presenting these pictures is to evoke and assess emotional reactions. Generally, these images are not a concern because they depict contents that are likely to be encountered by adults in everyday media (e.g., film, television). For any participant that reports emotional discomfort after completion of the visual stimuli task, an individual counseling session will be available.

iii) ECG:
Although it is rare, there is a possibility of minor skin irritation from the placement of the ECG (electrocardiogram) sensors. However, this mostly goes away after the fMRI session.

iv) Drawing of Blood:
The insertion of the intravenous (IV) line for the scan is done by an experienced nurse. There is a slight chance that multiple needle-sticks will be needed to make sure the IV is placed correctly. You might feel a small amount of pain when the IV is placed but it does not last very long. A bruise or a minor infection might develop where the IV is placed. A bruise will go away by itself and it might help if you wrap a warm towel around your arm. Infections can also be treated if necessary. About four and a half ounces of blood will be taken during each MRI session, an amount that is less than the standard amount drawn at a blood donation, and the loss of which your body can easily tolerate. While your body can tolerate this level of blood draw, you should not donate blood for a period of 8 weeks after you finish the study. You also will not be admitted to the study if you have donated blood within a period of 5 weeks prior to admission to the study.

v) Use of the Smartphone App to Complete Surveys:
You will use a smartphone app to complete daily surveys where you will report your experiences, feelings, and behaviors. You may feel self-conscious while completing questionnaires about yourself on the phone. Your responses will be linked to a numbered ID so that they can be paired in our analyses,and you will not be asked for information that would identify the responses to you. These responses will be wirelessly transferred to a secure server that is password-protected.

Subject Obligation
We ask that you do not use any drugs or medicines, including street drugs or alcohol, during the study. If you do use any drugs or other medicines during this time, you will need to tell us. The only way you might be dismissed from the study is if you repeatedly do not show up and/or do not tell us the truth about your alcohol and drug use. We will be checking your breath and urine for use of alcohol and drugs. For female participants, you will not be allowed to take part in the study if you are pregnant.

Safety guidelines in response to the COVID-19 pandemic

To limit exposure to COVID-19, in-person meetings will be avoided as much as possible. If one-on-one meetings must be held in person, the following guidelines will be followed.

Before any study visits, you will be screened for COVID-19 symptoms by filling out the COVID-19 questionnaires prior to the study visit and at the time of the on-site study visit.

You will be asked to fill out a Yale Stress Center (YSC) safety questionnaire for all YSC visits and an MRRC safety questionnaire for the MRRC visit. If you say “yes” to any of the COVID-19 related symptom questions, your appointment will be moved to a later date and you will be encouraged to contact the YNHH COVID-19 Support Call Center (203-688-1700, option 1).

For your safety, the study site will be disinfected before and after each study visit according to CDC guidelines. Upon entrance to the study site, all participants and research personnel will have body temperature measured with a non-contact forehead thermometer and oxygen saturation levels measured with a pulse oximeter . If body temperature is greater than 99.5 degrees Fahrenheit or oxygen saturation is below 95%, you will be asked to leave and seek medical attention, and the study appointment will be rescheduled to a later date.

During in-person visits, both you and research staff will be asked to maintain the required social distancing (at least 6 feet) and wear a face mask. You are also required to properly disinfect your hands with alcohol-based hand sanitizer (containing at least 60% alcohol) or clean them with soap and water to help protect against the spread of germs and viruses. In the event that you do not have a suitable face mask to wear, a new surgical mask will be provided for you at each on-site study visit.

How will I know about new risks or important information about the study?
We will tell you if we learn any new information that could change your mind about taking part in this study.

How can the study possibly benefit me?
This study is not designed to be of direct benefit to you. However, it may provide us with information on the functioning of the different parts of the brain andwhen people see and respond to different types of objects and experience emotions. This information may be useful in the treatment of people who have addictive behaviors in the future.

How can the study possibly benefit other people?
The benefits to science and other people may include a better understanding of alcohol use disorder that may lead to new treatments and general advancement of scientific knowledge.

Are there any costs to participation?
You will not have to pay for taking part in this study. The only costs include transportation and the time spent coming to the study visits.

Will I be paid for participation?
You will be paid for taking part in this study.

You will receive $20 for completion of each 2-hour intake appointment for baseline assessments and screening (usually up to 4-5 intakes), and $150 for a multimodal imaging session (fMRI scan ($100) & blood draws ($50)). In addition, you will receive up to $90 for the completion of a 30-day follow-up ($3 per day) involving a daily smartphone monitoring survey. You will receive an additional bonus of $10 for completing 100% (7 days) or $8 for completing at least 86% (6 out of 7 days) of weekly surveys. Also, you will be compensated an extra one-time bonus of $50 or $30 for completing at least 93% (28 out of 30 days), or 87% (26 out of 30 days) of all 30 daily smartphone app surveys respectively. Thus, a total of $430 remuneration will be provided for the time taken to complete all study procedures.

You are responsible for paying state, federal, or other taxes for the payments you receive for being in this study. Taxes are not withheld from your payments.

For your participation in this study you will receive payment(s) via a Bank of America pre-paid debit card. Please note that your name, address, and telephone number will be shared with Bank of America for ePayments. After your first payment milestone you will receive a card in the mail which you will need to activate over the phone, and any subsequent milestone payments will automatically be added to this card.

In addition, parking vouchers will be provided for those participants who drive and park their car at the Yale Stress Center for their study-related appointment(s). In certain circumstances, and at the discretion of the PI, some participants may be eligible for payment of transportation costs, after discussion with the study team.

What are my choices if I decide not to take part in this study?
Instead of participating in this study, you have some other choices.
You could:

- Take part in another study in a similar format.

How will you keep my data safe and private?
We will keep information we collect about you confidential. We will share it with others if you agree to it or when we have to do it because U.S. or State law requires it. For example, we will tell somebody if you we learn that you are hurting a child or an older person.

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as permitted by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. All information collected on you will be kept in a locked cabinet or password protected on a computer. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained.

We understand that information about you obtained in connection with your health is personal, and we are committed to protecting the privacy of that information. If you decide to be in this study, the researcher will get information that identifies you and your personal health information. This may include information that might directly identify you, such as your name and date of birth. This information will be de-identified at the earliest reasonable time after we receive it, meaning we will replace your identifying information with a code that does not directly identify you. The principal investigator will keep a link that identifies you to your coded information,

and this link will be kept secure and available only to selected members of the research team. Any information that can identify you will remain confidential. The research team will only give this coded information to others to carry out this research study. The link to your personal information will be kept for five years, after which time the link will be destroyed and the data will become anonymous. The data will be kept in this anonymous form indefinitely until it is destroyed.

When we publish the results of the research or talk about it in conferences, we will not use your name. If we want to use your name, we would ask you for your permission.

We will also share information about you with other researchers for future research, but we will not use your name or other identifiers. We will not ask you for any additional permission.

All health care providers subject to HIPAA (Health Insurance Portability and Accountability Act) are required to protect the privacy of your information. The research staff at the Yale School of Medicine are required to comply with HIPAA and to ensure the confidentiality of your information. Some of the individuals or agencies listed above may not be subject to HIPAA and therefore may not be required to provide the same type of confidentiality protection. They could use or disclose your information in ways not mentioned in this form. However, to better protect your health information, agreements are in place with these individuals and/or companies that require that they keep your information confidential.

What Information Will You Collect About Me in this Study?

The information we are asking to use and share is called "Protected Health Information." It is protected by a federal law called the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA). In general, we cannot use or share your health information for research without your permission. If you want, we can give you more information about the Privacy Rule. Also, if you have any questions about the Privacy Rule and your rights, you can speak to Yale Privacy Officer at 203-432-5919.

The specific information about you and your health that we will collect, use, and share includes:

- Research study records
- Medical and laboratory records of only those services provided in connection with this study
- Records about phone calls made as part of this research
- Records about your study visits
- Information obtained during this research regarding
    - MRI and laboratory test results
    - Questionnaires
    - The diagnosis and treatment of a mental health condition
    - Use of illegal drugs or the study of illegal behavior

How will you use and share my information?

We will use your information to conduct the study described in this consent form.
We may share your information with:

- The U.S. Department of Health and Human Services (DHHS) agencies
- Representatives from Yale University, the Yale Human Research Protection Program and the Institutional Review Board (the committee that reviews, approves, and monitors research on human participants), who are responsible for ensuring research compliance. These individuals are required to keep all information confidential.
- National Institute on Alcohol Abuse and Alcoholism (NIAAA)
- Investigators: Principal investigator, co-investigators, and other investigators
- Laboratories and other individuals and organizations that analyze your health information in connection with this study according to the study plan

- Study Coordinator and Members of the Research Team
- Those individuals at Yale who are responsible for the financial oversight of research including billing and payments
- Data and Safety Monitoring Boards and others authorized to monitor the conduct of the Study

We will do our best to make sure your information stays private. But, if we share information with people who do not have to follow the Privacy Rule, your information will no longer be protected by the Privacy Rule. Let us know if you have questions about this. However, to better protect your health information, agreements are in place with these individuals and/or agencies that require that they keep your information confidential.

If you decide to take part in this research study, you will be required to give us information about your substance use. We have obtained a Certificate of Confidentiality (CoC) issued by the National Institutes of Health. The researchers can use this Certificate to legally refuse to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The protection offered by the CoC does not stop us from voluntarily reporting information about suspected or known sexual, physical, or other abuse of a child or older person, or a participant'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 authoritiesBecause this research is sponsored by the Department of Health and Human Services through NIAAA, staff from that and other DHHS agencies may review records that identify you only for audit or program evaluation. They cannot report anything that would harm you or other research subjects.

Even when a CoC is in place, you and your family members must still continue to actively protect your own privacy. If you voluntarily give your written consent for anyone to receive information about your participation in the research, then we may not use the CoC to withhold this information.

Why must I sign this document?

By signing this form, you will allow researchers to use and disclose your information described above for this research study. This is to ensure that the information related to this research is available to all parties who may need it for research purposes. You always have the right to review and copy your health information in your medical record.

What if I change my mind?

The authorization to use and disclose your health information collected during your participation in this study will never expire. However, you may withdraw or take away your permission at any time. You may withdraw your permission by telling the study staff or by writing to Dr. Dongju Seo at the Yale Stress Center, 2 Church Street South, Suite 209, New Haven, CT 06511.

If you withdraw your permission, you will not be able to stay in this study but the care you get from your doctor outside this study will not change. No new health information identifying you will be gathered after the date you withdraw. Information that has already been collected may still be used and given to others until the end of the research study to insure the integrity of the study and/or study oversight.

Who will pay for treatment if I am injured or become ill due to participation in the study?

If you are injured while on study, seek treatment and contact the study doctor as soon as you are able.

The Yale School of Medicine does not provide funds for the treatment of research-related injury. If you are injured as a result of your participation in this study, treatment will be provided. You or your insurance carrier

will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available.

You do not give up any of your legal rights by signing this form.

What if I want to refuse or end participation before the study is over?
Taking part in this study is your choice. You can choose to take part, or you can choose not to take part in this study. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

We would still treat you with standard therapy or, at your request, refer you to a clinic or doctor who can offer this treatment. Not participating or withdrawing later will not harm your relationship with your own doctors or with this institution.

To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part.

The researchers may withdraw you from participating in the research if necessary. These conditions include repeated no-shows for appointments or if you are found ineligible for the study.

What will happen with my data if I stop participating?
When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to insure the integrity of the study and/or study oversight. You will have the ability to withdraw your data from the research once it is collected.

Who should I contact if I have questions?
Please feel free to ask about anything you don't understand.

If you have questions later or if you have a research-related problem, you can call the Principal Investigator at 475-441-3457.

If you have questions about your rights as a research participant, or you have complaints about this research, you call the Yale Institutional Review Boards at (203) 785-4688 or email hrpp@yale.edu.

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov,* as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Authorization and Permission

Your signature below indicates that you have read this consent document and that you agree to be in this study.

We will give you a copy of this form.

Participant Printed Name	Participant Signature	Date

Person Obtaining Consent Printed Name	Person Obtaining Consent Signature	Date