COVER PAGE

"Imaging Glutamate Release from Alcohol"

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HRP-503B – BIOMEDICAL RESEARCH PROTOCOL
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Protocol Title: Imaging Glutamate Release from Alcohol Consumption

Principal Investigator: Ansel T. Hillmer Ph.D

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SECTION I: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.

Dysregulated glutamate signaling is a hallmark of chronic alcohol abuse[1]. Acute alcohol at clinically relevant doses stimulates glutamate release[2], while chronic alcohol leads to enhanced glutamatergic activity. When chronic alcohol is removed, as in withdrawal, a 'hyperglutamatergic state' results, characterized by excessive excitatory signaling and heightened extracellular glutamate levels[3,4]. These alterations to glutamate signaling may be particularly relevant for alcohol craving and relapse propensity[5]. While these dynamics are well characterized in rodent models, limited techniques have stalled translation of these findings to human research. Characterization of dynamic glutamate release in people would dramatically advance our understanding of aberrant glutamate function in alcohol use disorder. **This underscores the need for innovative approaches that measure alcohol-induced glutamate release in humans.**

Positron emission tomography (PET) imaging with radiotracers specific to the metabotropic glutamate receptor 5 (mGlu5), [^{18}F]FPEB and [^{11}C]ABP688[6], provide an established technique to measure glutamate release. Ketamine, which elicits glutamate release, robustly reduces radiotracer distribution volumes (V_T) in human brain[7,8]. **We propose to leverage this imaging technique to measure alcohol-induced glutamate release in people.** However, these radiotracers exhibit subtle differences in the mechanism by which glutamate reduces mGluR5 availability[9]. Therefore, in **Aims 1 and 2** we will evaluate both radiotracers and compare their effects to determine the optimal experimental approach. Each Aim will recruit 10 moderate drinkers who do NOT meet DSM-5 criterion for alcohol use disorder. We will strive to recruit the same subjects to participate in both Aims 1 and 2 for a direct comparison between approaches. For each aim, two mGlu5 PET measurements with arterial blood sampling will be acquired[10]. Scanning will begin immediately following alcohol administration that will achieve 60 mg/dL for at no more than one hour, timed to capture the window of peak glutamate levels[2]. This alcohol dose is similar to doses eliciting glutamate release in rodents[11-13] and dopamine release in people[14]. Subjective alcohol effects will be evaluated with the Biphasic Alcohol Effects Scale at baseline and every 30 min after alcohol for 90 min. The study will administer alcohol as an oral alcohol challenge first, however if sufficient

glutamate release is not achieved orally, then they study will switch to IV alcohol as the challenge in subsequent testing. The collected data will be used to accomplish the following specific aims:

In **Aim 1 we will determine the sensitivity of the PET radioligand [^{18}F]FPEB to the glutamate response from a fixed-dose alcohol session.** [^{18}F]FPEB V_T, an index of the number of mGlu5 available for radioligand binding, will be estimated throughout the brain. We hypothesize that alcohol will significantly reduce [^{18}F]FPEB V_T in the prefrontal cortex and striatum compared to baseline, consistent with glutamate release. The prefrontal cortex and striatum are brain regions with reported alcohol-induced glutamate release in preclinical models[2,12,13,15].

In **Aim 2 we will determine the sensitivity of the PET radioligand [^{11}C]ABP688 to the glutamate response from a fixed-dose alcohol session.** [^{11}C]ABP688 V_T, an index of the number of mGlu5 available for radioligand binding, will be estimated throughout the brain. We hypothesize that alcohol will significantly reduce [^{11}C]ABP688 V_T in the prefrontal cortex and striatum compared to baseline, consistent with glutamate release. The prefrontal cortex and striatum are brain regions with reported alcohol-induced glutamate release in preclinical models[2,12,13,15].

The route of alcohol administration has important effects on brain neurochemistry. While oral alcohol provides a more naturalistic route of administration, the effects of first pass metabolism and gut absorption result in slower acute brain effects, which neuroimaging studies are typically less sensitive to. Therefore, the research plan will first evaluate the glutamate response to acute oral alcohol. However, given the diminished sensitivity of neuroimaging to this route of administration, should no effects of oral alcohol on brain neurochemistry be detected, we then plan to test for sensitivity to i.v. alcohol to leverage the more potent acute effects. This question of route of administration is a critical question in the experimental paradigm optimization, and will be addressed in subaims 1A, 1B, and 2A, 2B, respectively, before continuing to Aim 3.

Based on the results of the first aims, we will identify an optimal experimental paradigm. Using this approach, we next will recruit 30 moderate drinkers and 30 people who meet DSM-5 criteria for alcohol use disorder. Subjects will self-report recent and lifetime drinking patterns. Alcohol-induced glutamate release will be measured with ONE of the experimental approaches identified above to accomplish the following aim:

In **Aim 3 we will compare the alcohol-induced glutamate release in moderate drinkers and individuals with alcohol use disorder.** Chronic alcohol exposure is associated with heightened extracellular glutamate levels. This may contribute to tolerance by diminishing alcohol-induced glutamate release. We hypothesize that more people with AUD will have predict smaller changes in radioligand V_T (ΔV_T) after alcohol compared to moderate drinkers. Such a relationship would provide evidence of dynamic neuroadaptations of glutamatergic signaling relevant to the development and treatment of alcohol use disorder.

As an exploratory aim, we will investigate relationships between subjective effects and the amount of alcohol-induced glutamate release. Diminished subjective effects may also be associated lower amounts of glutamate release (ΔV_T), consistent with previously observed preclinical neuroadaptations[16]. Successful completion of these aims will provide valuable data that will illuminate the role of glutamate in alcohol use disorder and subsequent withdrawal. The findings will inform and evaluate treatment approaches targeting the glutamate system for alcohol use disorder.

2. Probable Duration of Project: State the expected duration of the project, including all follow-up and data analysis activities.
   10 Years

3. Background: Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

Glutamate Function and Neural Reorganization During Alcohol Withdrawal

Alcohol dependence affects over 10% of the population, accruing great cost to individuals and society. Chronic alcohol exposure distorts brain structure and function, inducing gray matter atrophy[18-20], altering function of neurotransmitter systems[21,22,23], and modifying neural organization[24,25] as evaluated by functional magnetic resonance imaging (fMRI) connectivity measures. During extended withdrawal, the alcohol dependent brain again undergoes dynamic changes[26,27], which have vital implications for treatment outcome[28,29]. Since up to 80% of treated abstinence cases result in later problematic drinking[30], we must improve our understanding of how changing brain architecture during withdrawal influences relapse-associated behaviors. These advancements can inform the development of therapies targeting the underlying neural basis of relapse identified by neuroimaging biomarkers rather than treating behavioral or cognitive symptoms themselves.

Glutamate, the major excitatory neurotransmitter, heavily influences cerebral neuroplasticity[31] and has complex interactions with alcohol dependence[1]. Interventions targeting the glutamate system may impede relapse while hastening neural reorganization[5,32]. Acute alcohol directly acts at *N*-methyl-D-aspartate receptors (NMDAR), limiting cortical excitability and indirectly disinhibiting glutamate release[33]. Chronic alcohol exposure upregulates NMDAR subunits[34,35]. Subsequent withdrawal induces a "hyperglutamatergic" state[36,37], characterized by excessive excitatory signaling and extracellular glutamate levels[3,4]. These aggregate changes to glutamate signaling increase relapse propensity[5]. However, no methods currently exist that directly measure glutamate release in people. This research project will dramatically advance our ability to develop and evaluate therapies for alcohol use disorder.

PET Imaging of mGluR5 Receptors

Glutamate neurotransmission is regulated by ionotropic and the G-protein coupled metabotropic glutamate receptors (mGluR), which are divided into 3 groups: group I (mGluR1 and 5), group II (mGluR2 and 3) and group III (mGluR4, 6, 7, 8). To date, the most successful PET radioligands used to image the glutamate system target the metabotropic glutamate 5 (mGlu5) receptor. MGluR5 receptors are located postsynaptically and on glia, and have highest density in the hippocampus, intermediate in the caudate/putamen, cerebral cortex, deep cerebellar nuclei, and thalamus, and lowest in the cerebellum[38,39].

The two PET radioligands most prominently used to image mGlu5 in humans are [^{18}F]FPEB and [^{11}C]ABP688. Both radioligands bind with high specificity and affinity to a negative allosteric site on mGlu5. Both radioligands are synthesized in the Radiochemistry Lab at the Yale PET Center. Production of [^{18}F]FPEB and [^{11}C]ABP688 for use in research protocols involving human subjects are both separately approved by the Yale University Radioactive Drug Research Committee (YU RDRC).Recent work conducted by our colleague, Dr. Irina Esterlis, and others have demonstrated that both ligands are sensitive to ketamine[7,8], which is thought to trigger glutamate release. These findings motivate a similar approach to measure glutamate release triggered by alcohol exposure.

4. Research Plan: Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths. Describe the setting in which the research will take place.

4.1 Overall Research Design:

This research plan proposes experiments that are critical to advance our understanding of glutamatergic signaling in alcohol use disorders. We will recruit moderate drinkers and Alcohol Use Disorder subjects between the ages of 21 to 55 years to participate in the recruitment, evaluation, and imaging. Moderate drinkers are defined as people who report consuming alcohol on at least one occasion in the past three months that would result in an estimated blood alcohol level greater than 80 mg/dl but not meet DSM-5 criteria for AUD. This is operationally defined as more than 3 standard drinks in a single occasion for women and 4 standard drinks in a single occasion for men. All participating subjects will be seen for an initial intake, including a full physical exam and medical coding. Thereafter, they will have an anatomical MRI scan, followed by a series of [^{11}C]ABP688 and/or [^{18}F]FPEB PET scans with alcohol challenge as described in the below aims:

Aim 1 will evaluate the sensitivity of the mGlu5 radioligand [^{18}F]FPEB to alcohol release in the same subjects (moderate drinkers, *n*=10). Subjects will participate in up to two [^{18}F]FPEB scans with alcohol challenge that measure mGlu5 availability under the following conditions: baseline and 60 mg/dL alcohol administration. This will be conducted with the following sub-aims:

Aim 1a will administer the alcohol (targeting 60 mg/dL) as an oral challenge. This will be done in at least the first 5 subjects. At this point, the percent change in mGlu5 receptor availability (i.e., [^{18}F]FPEB V_T) will be evaluated. If this remains within test-retest estimates of this radiotracer (9-12%){Park, 2015 #219} in subjects achieving the targeted alcohol dose, then we may proceed to Aim 1b:

Aim 1b will administer the alcohol (targeting 60 mg/dL) as an i.v. challenge.

Aim 2 will evaluate the sensitivity of the mGlu5 radioligand [^{11}C]ABP688 to alcohol release in the same subjects (moderate drinkers, *n*=10). Subjects will participate in up to two[^{11}C]ABP688 scans with alcohol challenge that measure mGlu5 availability under the following conditions: baseline and 60 mg/dL alcohol administration. This will be conducted with the following sub-aims:

Aim 2a will administer the alcohol (targeting 60 mg/dL) as an oral challenge. This will be done in at least the first 5 subjects. At this point, the percent change in mGlu5 receptor availability (i.e., [^{11}C]ABP688 V_T) will be evaluated. If this remain within test-retest estimates of this radiotracer (<12%)[10] in subjects achieving the targeted alcohol dose, then we may proceed to Aim 2b:

Aim 2b will administer the alcohol (targeting 60 mg/dL) as an i.v. challenge.

We will strive to recruit the same subjects from Aim 1 for Aim 2, in order to directly compare the two experimental approaches in the same people.

The results of these two aims will inform the selection of an optimal experimental design.

Aim 3 will compare the alcohol-induced glutamate release in moderate drinkers (*n*=30, including subjects from the chosen tracer from Aim 1 or 2) and individuals with alcohol use disorder (*n*=30,). Subjects will participate in up to two mGlu5 scans under the following conditions: baseline and 60 mg/dl alcohol administration.

Breakdown of Aims 1-3

- Aim 1: 10 moderate drinkers
- Aim 2: 10 moderate drinkers

- Aim 3: 30 moderate drinkers (minus drinkers from chosen tracer in Aim 1 or 2), and 30 AUD

4.2 Subject Selection:

Moderate drinker participating patients will self-report drinking consistent with at least one binge alcohol event in the past three months but not meet DSM-5 criteria for AUD to ensure that accustomed drinking levels are not exceeded in the laboratory. AUD subjects will meet DSM-5 criteria for current Alcohol Use Disorder. Subjects will be recruited mainly from New Haven County, although enrollment is not limited to this region. All research subjects will be recruited under guidelines of the Yale University Institutional Review Board (Human Investigation Committee). Subjects will be recruited from the community at large via IRB-approved advertising (television, newspaper, postings in community locations, Craigslist, Facebook).

Screening Evaluation

All screening procedures will be performed by a trained research assistant or study coordinator. Initial screening will be performed over the telephone. Potentially eligible subjects will undergo an initial in-person screening evaluation within 2 months of PET scanning, this will be located either at 2 Church St South Suite 511 or Suite 314, the Yale PET Center, CMHC, or HRU. Current non treatment seeking inpatient subjects at the CNRU will be able to participate if participation in their current study is not a conflict with this study, and vice versa. The purpose of this evaluation is to ensure that subjects meet study criteria. Breath alcohol (BAC) levels will be monitored for subjects before the intake session. After informed consent is obtained, the structured clinical interview for DSM-5 Axis I Disorders (SCID-5) will be used to exclude primary psychiatric and substance use disorders other than alcohol use disorder. A C-SSRS will be performed if suicidality is revealed in the SCID or other questionnaires. A medical history, vital signs, physical examination, and EKG will be performed. The Timeline-Follow Back interview for Alcohol (TLFB) will be used to characterize quantity and frequency of alcohol drinking up to 90 days prior to enrollment. The Lifetime Drinking History, a retrospective interview procedure, will be used to characterize lifetime patterns and quantities of alcohol. Subjects will also indicate the maximum amount of drinks consumed in a single 24-hour period over the last three months. Several laboratory tests will be performed at this visit, which include a complete blood count (CBC), chemistry profile, thyroid function studies, HIV, serum ß-HCG (women only), urinalysis, liver function tests, and urine toxicology screen. All female subjects will undergo a pregnancy test at the time of screening. Additionally, urine pregnancy tests will be done on the day of each PET scan before radiotracer injection. Urine drug screens will be done at intake, MRI, and on PET days.

4.3 Assessments:

All participants will be screened initially using a telephone screen that will include questions to evaluate medical history, personal and familial psychiatric and smoking history. A wide range of measures, such as psychiatric and substance abuse history, medical assessments and affective symptoms will be measured during the intake evaluation.

4.3.a. General Intake Assessments

1. Structured Clinical Interview for DSM-5 Axis I Disorders The psychotic screening and depression sections of the Structured Clinical Interview for DSM-5 Axis I Disorders (SCID-5) will be used to determine whether subjects meet exclusion criteria for diagnosis of primary psychiatric and substance use disorders other than alcohol use disorder.
2. Illicit Drug/Pregnancy Screen A urine sample may be collected to determine current illicit drug use (for all potential subjects). In addition, serum samples will be collected at the intake visit and urine samples will be collected on each PET scan day to confirm that the subject is not pregnant.

3. Demographic Questionnaire This questionnaire will obtain: (1) basic demographic information including age, gender, marital status, employment status, occupation, (2) alcohol/drug history, (3) family history of alcohol/drug use, depression, anxiety, and smoking history.
4. Medical History This questionnaire will obtain a basic medical history (personal and family) including past or current conditions such as neurological, endocrine, cardiovascular, renal, liver, and thyroid pathology. Current body weight and current medications will also be assessed.
5. Medical Assessments will include a physical exam by a state licensed physician, an EKG, and laboratory tests which may include a complete blood count, blood urea nitrogen, creatinine, fasting blood sugar, electrolytes, liver function tests, thyroid function tests (including T_3, T_4, T_3RU, estimated free T4), thyroid stimulating hormone levels, urine toxicology, and urinalysis**.** Female subjects will have serum pregnancy tests.
6. Multidimensional Scale of Perceived Social Support (MSPSS) is a brief research tool designed to measure perceptions of support from 3 sources: Family, Friends, and a Significant Other.
7. Barratt Simplified Measure of Social Status (BSMSS) is a measure of socio-economic status.

4.3.b. Mood and Sleep Measures

We may obtain these measures at intake, up to two times on PET scan days, and the morning following the alcohol session.

1. Center for Epidemiological Studies Depression Scale (CES-D) The CES-D[39] is a 20-item self-report instrument, which has been extensively used in both clinical and nonclinical populations to measure the frequency and severity of depressive symptoms over the past week. The CES-D, which has been used to document the severity of depressive symptoms in adults and has been shown to be a sensitive measure of negative affect in smokers, will be used in the proposed studies to measure levels of mild depressive symptoms.
2. Anxiety: The State-Trait Anxiety Inventory[40] is a 40-item, self-report measure, comprised of two subscales. The State-Anxiety scale is 20 items and assesses transitory states characterized by feelings of tension, apprehension, and heightened autonomic reactivity. The Trait-Anxiety scale is 20 items and assesses stable individual differences in anxiety proneness.
3. Impulsivity: Barratt Impulsiveness Scale (BIS; [40]) is a 30 item self-report instrument designed to assess the personality/behavioral construct of impulsiveness.
4. Beck Depression Inventory: This widely used 21 item self-report instrument will be used to assess depressive symptomatology in addition to the SCID (43).
5. Sleep Quality: The Pittsburgh Sleep Quality Index (PSQI) is a 19 item self-rated questionnaire that assesses sleep quality and disturbances over the previous month.
6. Post-Traumatic Stress Disorder Checklist (PCL) is a 20-item self-report measure that assesses the DSM symptoms of PTSD. We will use the PCL-5, a 20-item self-report measure that assesses the 20 DSM-5 symptoms of PTSD.
7. Life Events Checklist LEC-5 assesses several possible traumatic events that a subject may have experienced.
8. The CAPS-5 is a 30-item structured interview that can be used to: Make current (past month) diagnosis of PTSD , make lifetime diagnosis of PTSD, and assess PTSD symptoms over the past week.
9. Columbia Suicide Severity Rating Scale (CSSRS) is a clinician administered questionnaire to assess suicidality. In the event of an unexpected outcome, subjects will be referred to the Emergency Department for risk assessment.

4.3.c. Alcohol and other Drug Measures

We may obtain these measures at intake and also on PET scan days.

1. Timeline Followback for alcohol, tobacco, and illicit drugs. Questionnaire to measure the amount of alcohol, tobacco, and other drugs that have been used in the past 30 days.
2. Lifetime Drinking History is a structured interview designed to provide quantitative indices of alcohol consumption patterns from the onset of regular drinking.
3. Short Inventory of Problems provides a psychometric inventory of adverse consequences from substance use[41].
4. Drinking Motives Questionnaire characterizes individual motivations for consuming alcohol[42].
5. Fagerstrom Test for Nicotine Dependence (FTND). This will be used to measure the severity of nicotine dependence. It is a 6-item scale with an internal consistency of .61 and its total score is closely related to biochemical measures of intensity of smoking.
6. Smoking History. This questionnaire will assess basic smoking status and history such as number of years smoked, number and length of quit attempts, reasons for quitting, and second hand smoke exposure.
7. Nicotine Withdrawal Checklist. This measures the severity of eight withdrawal symptoms on 5-point Likert scales.

4.3.d. Cognitive Measures

We may obtain these measures at intake, up to two times on PET scan days, and the morning following the alcohol session.

1. Cogstate Battery (30 minutes) **–** This computerized test battery will assess memory and cognition. The tasks may include:
a. International Shopping List Task – a computerized task to assess verbal learning and memory.
b. Groton Maze Learning Task – a computerized task to assess executive function and spatial problem solving.
c. Detection Task – a computerized task to assess psychomotor function and speed of processing.
d. Identification Task – a computerized task to assess visual attention and vigilance.
e. One Card Learning Task – a computerized task to assess visual learning and memory.
f. One Back Task and Two Back Task – computerized tasks to assess attention and working memory.

2. Probabilistic Reward Task (PRT) – The PRT has been successfully used to assess reward responsiveness (51-53). In each trial, subjects choose which of two difficult-to-differentiate stimuli was presented. Stimuli consist of simple cartoon faces (diameter: 25 mm; eyes: 7 mm) presented in the center of the monitor. At the beginning of the trial, the face has no mouth. After a given delay, either a straight mouth of 11.5 mm ("short mouth") or 13 mm ("long mouth") is presented for 100 ms. Subjects are instructed to press an appropriate button to decide whether a long or small mouth had been presented. Unbeknownst to subjects, correct identification of one stimulus ("rich stimulus") is rewarded three times more frequently (*"Correct! You won 20 cents"*) than the other ("lean") stimulus. In healthy controls, this reinforcement schedule leads to a response bias (i.e., a preference for the more frequently rewarded stimulus). The degree of response bias toward the more frequently reinforced alternative will be used for operationalizing sensitivity to reward.

3. Probabilistic Reversal Learning Task (PRLT) – The PRLT has been shown to effectively detect "belief updating" behavior through the use of the Hierarchical Gaussian Filter model. This task uses a 3-option probabilistic reversal-learning paradigm which requires participants to choose between options with unknown, unequal probabilities of reward. Three decks of cards are displayed on a computer monitor for 160 trials. Participants select a deck on each trial by pressing a predesignated key on a keyboard. We advise participants that each deck contains either winning or losing cards (e.g. +100, -50 points, etc.), but in different amounts. We also state that the best deck may change. Participants are instructed to find the best deck and

earn as many points as possible. Probabilities switch between decks when the highest probability deck is selected in 9 out of 10 consecutive trials (performance-dependent reversal). It is predicted that AUD participants may interpret probabilistic errors (e.g., the occasional instance when a good option does not yield reward), as reversal errors (the world has changed) and thus switch their choices prematurely.

4.4 Procedures

Screening, Evaluation and Clinical Ratings

Screening, evaluation and clinical ratings (as described above) are obtained during the screening process.

Magnetic Resonance Imaging (up to 1 hour)

Magnetic resonance imaging (MRI) scans (3T) will be collected in each subject to co-register PET and MRI for image analysis as well as collect resting state data. MRI is without contrast. Within approximately two weeks of the PET studies, an MRI will be acquired at the Yale University MRI Center. Subjects will be taken through a ferromagnetic metal detector before entering the scan room.

3T Scan sequence:

Series 1: 3 plane localize
Series 2: Sag 3d tfl; 256fov; 1mm thick slices; 176 slices total; TE 2.77; TR 2530; TI 1100; FA 7; 256X256 1 average.
Series 3 – Resting state: Ep2d bold; 210fov; 2.5mm thick slices; TE 30; TR 3400; FA 85; 84x84 (Run twice).

MR images provide a matching anatomical atlas for creating individualized region-of-interest templates for each subject. We will also examine functional connectivity at rest.
If an MR image is already on file at the PET Center, and has been collected within a reasonable time period, a new MRI may not need to be collected.
A member of the research staff will accompany the subject and stay for the duration of the MRI.

PET Scans

PET experiments will be conducted at the Yale University PET Center. Subjects may have up to three [^{11}C]ABP688 PET scans, and/or up to three [^{18}F]FPEB PET scans for a maximum total of six scans (including possible rescheduled scans, 1 per tracer). Subjects will also be asked to refrain from drinking caffeinated beverages on imaging days, and from drinking alcoholic beverages 48 hours prior to imaging days.

Upon arrival at the PET center, subjects will complete questionnaires on urges, withdrawal symptoms, and mood. Plasma will be drawn before scans to measure drug levels in the blood. Urine drug tests will be performed before all PET scans. To ensure overnight abstinence for individuals with alcohol use disorder, subjects will be invited to stay inpatient at the CNRU the night before their PET scans unless there are scheduling conflicts with the subject. Confirmation of alcohol abstinence over the previous 48 hours will be made via self-report and BAC measures, and session will be rescheduled if positive.
For all women, a urine pregnancy test will be performed at the beginning of the imaging day, prior to radiotracer injection, at the Yale University PET Center.

For all aims, up to three total [^{18}F]FPEB PET scans may be acquired per subject. Imaging data will be acquired using bolus or bolus plus constant infusion of ≤20 mCi [^{18}F]FPEB. After baseline mGlu5 availability is measured, subjects will participate in i.v. alcohol infusion (targeting 60 mg/dL). This dose was selected to achieve mild to moderate levels of intoxication, consistent with the aims of the proposal. [^{18}F]FPEB PET scanning will begin as soon as possible (i.e., not more than 30 min after the subject completes the alcohol challenge) to capture the peak glutamate response[2]. This timing is consistent with previous reports studying dopamine release in response to alcohol challenge[14]. Blood samples will be collected throughout all [^{18}F]FPEB PET scans and during the alcohol administration.

For aims 1 and 2. up to three total [^{11}C]ABP688 PET scans may be acquired per subject. Imaging data will be acquired using bolus or bolus plus constant infusion of ≤20 mCi [^{11}C]ABP688. After baseline mGlu5 availability is measured, subjects will participate in i.v. alcohol administration (targeting 60 mg/dL). [^{11}C]ABP688 PET scanning will begin as soon as possible (i.e., not more than 30 min after the subject completes the alcohol challenge) to capture the peak glutamate response[2]. This timing is consistent with previous reports studying dopamine release in response to alcohol challenge[14]. Blood samples will be collected throughout all [^{11}C]ABP688 PET scans and during the alcohol administration.

PET Data Acquisition and Analysis

Subject preparation consists of intravenous (IV) catheterizations for IV administration of the radiotracer and blood sampling. Risks of radial artery cannulation are minimized by having the procedure performed by an experienced health care provider. The health care provider would be either a physician or an advanced practice registered nurse (APRN) with experience in critical care and placement of arterial catheters, as is the practice at Yale-New Haven Hospital. For an APRN to place the arterial line at the Yale PET Center, they must meet the following criteria:

1.) Be currently credentialed at Yale-New Haven Hospital or similar institute and
2.) Perform 3 arterial line procedures supervised by a currently privileged PET Center physician

The 3 supervised arterial line placements will be documented and signed off by both the APRN and supervising physician. The completed document must be on file at the Yale PET Center prior to an APRN performing any arterial line catherizations independently.

The site will be anesthetized with lidocaine prior to arterial line insertion. The arterial line may remain in place for the whole day of scanning, after which it will be removed by trained nursing staff at the Yale PET Center. PET data are acquired while subjects rest with an HRRT PET scanner (207 slices, resolution better than 3 mm FWHM). A transmission scan will be obtained for each emission scan. Motion correction may be performed dynamically with measurements from the Vicra (NDI Systems, Waterloo, Ontario) used by a dedicated list-mode reconstruction algorithm. Acquisition of list-mode emission data will begin shortly before IV administration of up to 20 mCi of high-specific activity [^{11}C]ABP688 or up to 5 mCi of high-specific activity [^{18}F]FPEB and will continue for up to 120 minutes post-injection for [^{11}C]ABP688 or up to 180 minutes post-injection for [^{18}F]FPEB. Dynamic images of radioactivity concentration will be reconstructed with corrections for measured attenuation, normalization, random events, scatter, and deadtime. Subjects will be asked to void after the scan is completed to reduce radiation exposure to the bladder. Venous blood samples to measure plasma blood alcohol concentration (BAL) and peripheral cytokine levels will also be acquired. After the completion of the days final PET scan, the IVs will be removed. Monitoring of vitals will continue for at least 30 minutes before subject returns to the CNRU or HRU.

List mode data will be reconstructed with MOLAR[43], with corrections for attenuation, normalization, and motion to create high resolution images. Early PET image data will be registered to the subjects T1-weighted

MR image. The T1-weighted MR image will be non-linearly registered to MNI space for region of interest (ROI) identification. ROIs will be selected using the Anatomical Automatic Labeling template for SPM8. To minimize possible partial volume effects, only gray-matter voxels will be included in ROI definition based on MRI segmentations performed with the Computational Anatomy Toolbox[44]. Since glutamate release has been observed throughout the brain, ROI analyses will focus on the primary brain regions of frontal, parietal, temporal, and occipital cortices; striatum, amygdala, hippocampus, thalamus, and cerebellum. The primary outcome measure will be [^{11}C]ABP688 or [^{18}F]FPEB V_T estimated with the 2-tissue compartment model as previously validated[45,46], which yields a test-retest variability of <12%[10].

Laboratory Alcohol Session

Laboratory sessions will occur at the Yale PET Center. Subject body weight will be acquired during intake as part of the medical history and used for alcohol dose calculations. Subjects will be asked not to diet between intake and study days. Alcohol dose will be recalculated if the subject's weight varies by more than 5 pounds for women and 10 pounds for men. Confirmation of alcohol abstinence will be made via self-report and breathalyzer on study day. Subjects will be given a light standardized breakfast on arrival to the laboratory and the morning prior to discharge.

Prior to alcohol administration, subjects will have a standardized light lunch to increase tolerability of the alcohol dose while minimizing the potential for variations in food intake that could affect alcohol metabolism.

Oral alcohol challenge: Alcohol will be administered in the form of 80 proof vodka and a mixer based on the subject's choice of water or a decarbonated noncaffeinated noncaloric soda. The dose will be prepared by the research team and take into account the participant's total body water (based on gender, age, height, and weight), duration of drinking, and ratio of alcohol to mixer, based on Watson et al's update of the Widmark equation. The total volume will be divided into three equal drinks, with each consumed over a 10-minute period to control the rate of consumption. This pacing aims to reduce risk of nausea. After the session subjects may drink water ad lib until scanning. Subjects will be asked to void prior to the second PET scan. Afterwards, subjects will be given dinner based on food preferences. Water, crackers, and other snacks will be available ad lib for the rest of the evening.

I.V. Alcohol Challenge: An antecubital IV line will be placed in one arm, contralateral to the arm used for radioligand administration. Alcohol will be formulated as 6% (volume/volume) alcohol concentration in saline. The dose will be prepared by the research team. The rate of ethanol infusion, not the composition of the infusate, is the only parameter that depends on a subject's height and weight, which will be measured on the test day. Based on the height and weight, an infusion profile will be calculated to map out, step by step, what the pump rates need to be to keep a subject at the designated target blood alcohol level of 60 mg/dL. After the session subjects may drink water ad lib until scanning. Afterwards, subjects will be given dinner based on food preferences. Water, crackers, and other snacks will be available ad lib for the rest of the evening.

Assessments following alcohol administration:

BrAC will be measured at 15 min intervals beginning at alcohol administration and continuing until the end of scanning procedures. Vital signs will be measured concurrently. Should the measured BAC reach or exceed the targeted 60dose, then subjects will end further alcohol drinking. Other assessments that may be collected during these times include inflammation markers, self-reports of alcohol effects and mood.

1. Blood Alcohol Concentrations: Blood samples will be collected in gray stoppered (oxalate, fluoride) tubes and analyzed with gas chromatography analyses in the Yale-New Haven Hospital Clinical Laboratories. After microfuging, serum will be transferred into microtubes and stored at -20^{o}C until assay.
2. Breath Alcohol Concentrations will be determined with an Alcohol-Sensor III (Intoximeter Inc., St. Louis, MO).
3. Inflammation Markers: Serum levels of cytokines, such as TNF-α, IL-1β, IL-4, IL-6, and IL-8, and cortisol will be measured at baseline and when blood is drawn to measure BAL. We may also collect monocytes to assess immune function *in vitro*.
4. Visual Analog Scale (VAS) self-ratings for drug effects. Subjects will answer questions to assess behavioral changes induced by substance use.
5. Subjective Effects of Alcohol Scale is a self-report measure that assesses subjective experience of alcohol effects following alcohol administration[47].
6. Biphasic Alcohol Effects Scale is a self-report questionnaire that assesses subjective experiences of alcohol stimulation and sedation[48].
7. Self-Rating the Effects of Alcohol (SRE) is a retrospective self-report questionnaire measuring the response to alcohol[49].
8. Columbia Suicide Severity Rating Scale (CSSRS) is a clinician administered questionnaire to assess suicidality. In the event of an unexpected outcome, subjects will be referred to the Emergency Department for risk assessment.

The total amount of blood drawn during the study will not exceed 32 tablespoons total.

Discharge

All participants from Aims 1, 2 and 3 will remain under observation by research staff for several hours to allow behavioral effects of alcohol to wear off. Moderate drinkers will remain under observation until BAC reading is under 20 mg/dL, at which point they are free to leave. Cab transportation will be made available. Arrangements to stay at the HRU will also be available for subjects who so choose. Individuals with alcohol use disorder will stay overnight at the CNRU and be discharged the morning following the alcohol session after confirming that vital signs are within normal limits.

A research staff member will contact subjects the following business day for a check on their health status. All subjects will be provided the telephone number of a research psychiatrist or physician on call for any problems that arise in the immediate time period after discharge from the unit. They will also be given a discharge form that has specific instructions for calling one of the physicians if they have any questions or concerns following the study.

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

We plan to use the samples to conduct pharmacogenomics studies related to the targeted neurochemical systems. The samples may also be stored for future research to examine genes related to alcohol drinking. For this we may look through genetic markers throughout the participant's genomes to identify one or more markers near, or within genes, influencing risk of alcohol drinking. We

will decode all or part of the sequence of their DNA. We may also study genes that influence other behaviors and characteristics that may be related to alcohol drinking, such as smoking or impulsivity. We may also study other substances in the blood to help us learn more about genetic variation, gene effects, characteristics, and different population groups. The DNA will also be used to study differences in genes and sequences between individuals. Results from these genetic studies will be shared with public databases (per our data sharing agreement with NIH) but no personal identifying information will be shared.

ii. the plan for the collection of material or the conditions under which material will be received

The genetics samples will be collected at the time of physical exam from those who have consented to providing these samples. The samples will be stored in a -70 freezer prior to being de-identified and transported to the CTNA (Center for the Translational Neuroscience of Alcoholism) data repository under the supervision of Dr. Joel Gelernter's lab.

iii. the types of information about the donor/individual contributors that will be entered into a database

The PI will retain identifiable information about each sample that is collected. The samples identified by code and stripped of any identifiers prior to being transported to Dr. Gelernter's lab.

iv. What are the methods to uphold confidentiality

The identifiers will be stored in a locked file cabinet at the PI's Office.

b. What are the conditions or procedures for sharing of materials and/or distributing for future research projects? Genetic testing will only be conducted for research purposes and the results will be available to investigators on this study. Eventually, DNA extracted may be available to any qualified researcher; so will some of the genetic information from the DNA.

c. Is widespread sharing of materials planned? Yes

d. When and under what conditions will materials be stripped of all identifiers? The PI will retain identifiable information about each sample that is collected. The samples identified by code and stripped of any identifiers prior to being transported to Dr. Gelernter's lab. All samples are made anonymous prior to distribution. Some of the investigators may have commercial interests.

e. Can donor-subjects withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials? Donors will be told during the consenting process that they can choose to withdraw their materials at any time.

i. How will requests to withdraw materials be handled (e.g., material no longer identified: that is, anonymized) or material destroyed)? Donors will be told to contact the PI directly to request withdrawal of participation

f. Describe the provisions for protection of participant privacy. The PI will retain identifiable information about each sample that is collected. The samples identified by code and stripped of any identifiers prior to being transported to Dr. Gelernter's lab.

g. Describe the methods for the security of storage and sharing of materials. The identifiers will be stored in a locked file cabinet at the PI's office.

6. **Subject Population:** Provide a detailed description of the types of human subjects who will be recruited into this study.
Up to 70 subjects (40 moderate drinkers and 30 Alcohol Use Disorder) will participate in the study. According to census figures, minority groups comprise approximately 50% of the population of New Haven (36.1% African-American, 13.2% Hispanic, 0.3% Native American, 2.4% Asian, and 4.1% other). Subjects will self-report a binge alcohol even in the previous 3 months to ensure that subject's customary drinking levels are not exceeded in the laboratory.

All subjects will be 21-55 years of age and physically healthy. All research subjects will be recruited under guidelines of the Yale University Institutional Review Board (Human Investigation Committee). Subjects will be recruited from the community at large via IRB-approved advertising (television, newspaper, postings in community locations, Craigslist, Facebook). All participants will be screened initially on the telephone by a research assistant who will schedule the initial intake assessment. The screening and scanning sessions will involve psychological tests in the form of rating scales and questionnaires. These are all noninvasive questionnaires, e.g., to assess mood and craving, and should add no risk.

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?

General Inclusion Criteria:

1. Men and women, aged 21-55 years
2. Willing and able to give voluntary written informed consent
3. Able to read and write English and communicate effectively with the investigators, and comply with all study requirements, restrictions, and directions of the clinic staff
4. AUD Subjects will meet DSM-5 criteria for current Alcohol Use Disorder

5. Moderate Drinkers will report consuming alcohol on at least one occasion in the past three months that would result in an estimated blood alcohol level greater than 80 mg/dl but not meet DSM-5 criteria for AUD. This is operationally defined as more than 3 standard drinks in a single occasion for women and 4 standard drinks in a single occasion for men. This is to ensure that subjects have prior drinking exposure consistent with levels proposed in this study. Prospective subjects will be asked to recall the heaviest two days of drinking in the previous three months. Using this information, approximate BAC will be calculated for those prior episodes.
6. Medically healthy upon physical examination and laboratory testing.

General Exclusion Criteria:

1. Individuals whom the investigators deem may not be able to comply with alcohol abstinence for 48 hours prior to study day.
2. Current significant medical condition such as neurological, cardiovascular, endocrine, renal, liver, or thyroid pathology.
3. History of or current neurological or significant psychiatric disorder such as schizophrenia or bipolar disorder (DSM-5 Axis 1).
4. Individuals likely to exhibit clinically significant alcohol withdrawal during the study. Specifically, we will exclude subjects who a) have a history of perceptual distortions, seizures, delirium, or hallucinations upon withdrawal, or b) have a score of > 12 on the Clinical Institute Withdrawal Assessment scale at intake appointments.
   Other substance use disorder with the exception of nicotine dependence in smokers as assessed with the SCID or positive urine screen for drugs of abuse.
5. Participants with any significant current medical conditions that would contraindicate the consumption of alcohol, such as history of neurological trauma or diseases, seizures, delirium or hallucinations, hepatic, or other unstable medical conditions.
6. Current suicidal or homicidal intent or behavior, or history of suicidal or homicidal behavior, as revealed by SCID-5 evaluation, a C-SSRS will be performed if suicidality is revealed in the SCID or other questionnaires. In the event of an unexpected outcome, subjects will be referred to the Emergency Department for risk assessment. For individuals with significant suicidal ideation (i.e., intent with a plan as detailed below*) the covering clinician (licensed clinical psychologist or psychiatrist) will be contacted immediately and a plan will be developed in collaboration with the subject, treating physician (if any), and may include inpatient hospitalization at the CNRU or referral or accompaniment to the ER.
7. No barbiturates or other known microsomal enzyme induces or inhibitors in the past month.
8. History of significant head trauma.
9. Women who are pregnant or nursing or fail to use one of the following methods of birth control unless she or partner is surgically sterile or she is postmenopausal (hormone contraceptives [oral, implant, injection, patch, or ring], contraceptive sponge, double barrier [diaphragm or condom plus spermicide], or IUD).
10. Regular or current significant use of any prescription, herbal or illegal psychotropic medications (e.g., antidepressants, antipsychotics, anxiolytics, ecstasy) in the past 6 mo, with no current illegal drug use confirmed by urine toxicology (except for cocaine and marijuana when relevant).

11. Have MRI-incompatible implants and other contraindications for MRI, such as a pacemaker, artificial joints, non-removable body piercings, claustrophobia, etc.
12. Subjects with history of prior radiation exposure for research purposes within the past year such that participation in this study would place them over FDA limits for annual radiation exposure. This guideline is an effective dose of 5 rem received per year.
13. Subjects with current, past or anticipated exposure to radiation in the work place within one year of proposed research PET scans.
14. Subjects with history of IV drug use which would prevent venous access for PET tracer injection.
15. Blood donation within eight weeks of the start of the study
16. History of blooding disorder or currently taking anticoagulants (such as Coumadin, Heparin, Pradaxa, Xarelto).
17. Subjects whose Liver Function Tests are 4x the normal range will be excluded from the study.

***** To quantify significant suicidal ideation, we will evaluate the following items during the intake session and positive responses to the following will be used to identify individuals who should be elevated to a clinician.
-HAMD29 item #18 (3=suicidal ideas or gesture, i.e., has definite plan or cuts self, or begins to carry out suicide but stops for some reason; 4=suicide attempt during past week)
-MADRS item # 10: 5 or 6
-BDI item #9: 2 or 3
OR
-C-SSRS If they answer yes to question 2 (suicidal thoughts), we continue to ask questions 3-6 (3-without specific plan or intent to act, 4-active suicidal thoughts and some intent, 5-intent with plan, 6-suicidal behavior (collecting pills, obtaining a gun, etc.) We would elevate for a 'yes' to questions 4-6.

9. How will **eligibility** be determined, and by whom? Write here
Eligibility to participate in screening session will be determined by the research staff under the guidance of Dr. Ansel Hillmer. Study participation will be determined after the screening session by the study physician and Dr. Hillmer. There are two additional licensed clinical psychologists (Dr. Irina Esterlis and Dr. Maggie Davis) and psychiatrists who are study physicians (Dr. David Matuskey and Dr. Gustavo Angarita) in the group who are also available for clinical issues.

10. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

    Risks Associated with Alcohol Challenge
    Numerous medical conditions, such as liver disease, cardiac abnormality, pancreatitis, diabetes, neurological problems, and gastrointestinal disorders, could potentially be worsened by acute alcohol administration. Therefore, subjects with medical problems identified by physical exam and laboratory findings will be excluded from the study.

    Another area of potential risk to subjects under the influence of alcohol is their safety during intoxication. All subjects will be under the supervision of the experimenters to prevent possible accidents such as falls. Subjects will not leave the laboratory during alcohol infusion procedures. By having the option to stay in the

CNRU or HRU overnight available, the possibility that the subject might leave the session and continue to drink alcohol, which would place them at risk for accidents, is prevented.

Risks Associated with Oral Alcohol

Alcohol may induce nausea in high doses; however, significant nausea is not expected at the targeted dose for this study because subjects will have consumed a light lunch and they will have had recent (in the last three months) experience with the targeted alcohol dose. Other side effects resulting from oral alcohol may include blurred vision, nausea, vomiting, flushing, headache, and lightheadedness. Subjects will be permitted to decline further drinking if they so choose.

Risks Associated with Infusion of Alcohol

Infused ethanol has pharmacologic effects. Side effects resulting from ethanol consumption may include blurred vision, nausea, vomiting, flushing, headache, and lightheadedness. These side effects should reach their peak within 1.5 hours following the alcohol administration and decline thereafter. Significant nausea is not expected at the targeted dose for this study because subjects will have consumed a light lunch and they will have had recent (in the last three months) experience with the targeted alcohol dose. Subjects will be permitted to decline further infusion if they so choose.

Risks Associated with Use of an Arterial Catheter.

On the PET scanning days a radial arterial catheter may be inserted. Some individuals may feel light-headed during placement of the arterial catheter. This procedure may be associated with mild-to-moderate pain, hematoma, inflammation, bleeding, or bruising at the punctures cite. If any of these, or any other symptoms occur, and they do not diminish within 24 to 72 hours after removal of the arterial line, subjects will be advised to call the on-call doctor listed on the PET discharge instructions. In rare instances blocking or tearing of the artery, arterial leakage, poor healing, or infection at the catheter insertion site may occur.

Risks of radial artery cannulation are minimized by having the procedure performed by an experienced health care provider. The health care provider would be a physician or an Advanced Practice Provider (APP): either a physician assistant (PA), or an advanced practice registered nurse (APRN) with experience in placement of arterial catheters. For an APP to place the arterial line at the Yale PET Center, they must meet the following criteria:

1.) Be currently credentialed at Yale-New Haven Hospital or similar institute and

2.) Perform 3 arterial line procedures supervised by a currently privileged PET Center physician.

The 3 supervised arterial line placements will be documented and signed off by both the APP and supervising physician. The completed document must be on file at the Yale PET Center prior to an APP performing any arterial line catheterizations independently.

Risks Associated with Blood Drawing and IV Line Insertion

At the screening visit, a routine venipuncture will be performed for screening laboratory studies. On the PET scan day(s), up to two venous catheters will be inserted for administration of the radiotracer and for blood draws.

Drawing blood and inserting an intravenous line (IV) into an arm vein are safe and standard medical procedures. Sometimes a bruise will occur at the puncture site and rarely a blood clot or infection will occur in the vein. Certain individuals may feel light-headed during venipuncture.

The volume of blood collected during this study will be up to 32 tablespoons. Blood samples will be drawn for routine labs and drug screening; measurement of radiopharmaceutical parent and metabolites, for analysis of plasma drug levels, serum estrogen, progesterone, and follicle stimulating hormone levels. This is not expected to have any serious negative effects on a study participant.

Risks Associated with Radiation

The Yale University Radioactive Drug Research Committee (YU RDRC) will review the use of radiation in this research study, and no subjects will be scanned until approval is obtained. This research study involves exposure to radiation from [^{11}C]ABP688 and/or [^{18}F]FPEB . This radiation exposure is not necessary for medical care and is for research purposes only.

The maximum amount of radiation an individual subject may receive in this study would be if they participated in both Aim 1 and Aim 2 of this study. This participation would involve two injections of ≤ 20 mCi of [^{11}C]ABP688 (0.2360 rem each), two injections of ≤ 5 mCi of [^{18}F]FPEB (0.312 rem each), plus a small amount of radiation from the transmission scans of the brain.

Although each organ will receive a different dose, the maximum amount of radiation exposure subjects could receive from this study is equal to an effective dose of 1.102 rem for a total of up to 40 mCi of [^{11}C]ABP688 and 10 mCi [^{18}F]FPEB from four total injections and 4 transmission scans (.0014rem each). This calculated value is used to relate the dose received by each organ to a single value. Subjects may get an additional injection of either radiotracer if needed due to scan failure after injection, this would bring the total possible rem to 1.652 Rem from 3 injections of each tracer and 6 transmission scans.

Subjects may participate in more than one aim, not to exceed 1.652 Rem total and not to exceed 3 injections of either tracer total.

The amount of radiation subjects will receive in this study is below the dose guidelines established by the FDA and monitored by the Yale University Radioactive Research Committee for research subjects. This guideline sets an effective dose limit of 5 rem per year.

Adverse effects of the radiopharmaceuticals in this study have not been reported. However, the possibility exists for a rare reaction to any of the substances or procedures to which a subject is exposed.

Risks Associated with MRI

MR carries a risk for subjects who are claustrophobic or have pacemakers, metal pieces, aneurysm clips, large colored tattoos, or any other contraindications for MR.

Magnetic resonance imaging (MRI) is a technique that uses magnetism and radio waves, not x- rays, to take pictures and measure chemicals of various 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.

Subjects will be watched closely throughout the MR study. Some people may feel uncomfortable or anxious. If this happens, the subject may ask to stop the study at any time and we will take them out of the MRI scanner. 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 any of these symptoms.

There are some risks with an MRI study for certain people. If subjects have a pacemaker or some metal objects inside their body, they may not be in this study because the strong magnets in the MRI 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.
We want subjects read and answer very carefully the questions on the MRI Safety Questionnaire related to your personal safety. We will be sure that subjects have read the MRI Safety Questionnaire and tell us any information they think might be important.

This MRI 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 primary investigator, the lab, the MRI technologist, and the Magnetic Resonance Research Center 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 will be asked to review the relevant images. Based on his or her recommendation (if any), the primary investigator 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 your physician. The investigators, the consulting physician, the Magnetic Resonance Research Center, 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 MRI exam and for that reason, they will not be made available for diagnostic purposes.

Risks Associated with Drug Use and Suicidal/Homicidal Behavior
Participants will be asked about current or past use of illicit "street" drugs and urine drug screens will be performed at the initial intake appointment to rule out substance abuse that is not relevant to the study. Participants currently using drugs or who have a history of using drugs may not be eligible to participate. Suicidal thoughts and behaviors will also be assessed as this is a prevalent comorbidity in subjects with mood and substance disorders. Any reports of homicidal or significant suicidal tendencies will be immediately directed to treatment for this condition; and appropriate authorities will be notified.

Risks Associated with Unanticipated Events
The subject's health and safety will always be the primary concern of the doctors and staff performing the study. In the event of an unanticipated event, all necessary medical action will be taken. Medication might be administered as needed, per the Yale PET Center standard operating procedure for medical emergencies, in order to treat any unanticipated events/complications.

Risks Associated with Allergic Reactions
All drugs have a potential risk of an allergic reaction, which if not treated promptly, could become life threatening.

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

Risks Associated with Administration of Alcohol:

Risks will be minimized by adhering to the recommended guidelines established by the National Advisory Council on Alcohol Abuse and Alcoholism – Recommended Council Guidelines on Ethyl Alcohol Administration in Human Experimentation – Revised May 2005. People for whom alcohol consumption is contraindicated will be excluded based on the screening process including interviews, physical exams, and laboratory findings.

To reduce the risk of nausea or gross impairment from acute alcohol consumption, we will enroll participants with recent (within the last three months) drinking experience consistent with the blood alcohol concentration targeted for this study. We will provide a light lunch prior to the alcohol session.

Personnel trained in the conduct of alcohol challenges will conduct the sessions. All participants will be under supervision to prevent possible accidents. Following the alcohol sessions, all subjects will remain the CNRU or HRU overnight to prevent the possibility that they might continue drinking after the session, thereby placing themselves at further risk of accidents.

Participants will be strongly encouraged to remain in the research setting until their breath alcohol level is below 0.02. If a participant should insist on leaving the research setting prematurely, they will first demonstrate capacity to make an informed decision. This will be done by assessing subject's ability to understand the risks of an early discharge, understanding the alternatives and benefits of following the set guidelines, assessing comparative and consequential reasoning, and understanding how their final decision was reached. Should a participant insist on withdrawing before BAC of 0.02, the CSSRS will also be administered to confirm the absence of symptoms. Should capacity to make this informed decision be demonstrated, we will provide transportation to their home. The consent form addresses this contingency under voluntary participation.

Risks Associated with Use of an Arterial Catheter:

Risks of radial artery cannulation are minimized by having the procedure performed by an experienced health care provider. The health care provider would be either a physician or an advanced practice registered nurse (APRN) with experience in critical care and placement of arterial catheters, as is the practice at Yale-New Haven Hospital. For an APRN to place the arterial line at the Yale PET Center, they must meet the following criteria:

1.) Be currently credentialed at Yale-New Haven Hospital or similar institute and
2.) Perform 3 arterial line procedures supervised by a currently privileged PET Center physician

The 3 supervised arterial line placements will be documented and signed off by both the APRN and supervising physician. The completed document must be on file at the Yale PET Center prior to an APRN performing any arterial line catherizations independently.

Pain is minimized with the use of local anesthesia. Infection is avoided by adequate cleansing of the skin before intravascular line insertion. After arterial catheter removal, bleeding is prevented by direct pressure applied to the site for a minimum of 15 minutes followed by a pressure dressing (coban) that should be kept clean and dry until evening. Subjects will have their hand and finger blood supply examined after arterial cannulation throughout the study, and again following catheter removal. Also, subjects will be asked to abstain from using aspirin and other NSAIDS for 7-10 days prior to arterial line insertion and 7-10 days following arterial line removal. Subjects will be provided a 24-hour emergency physician contact number to call if they encounter pain, discoloration, numbness, tingling, coolness, hematoma, inflammation, or any other unusual symptoms in the wrist or hand, or fever, chills or drainage from the vascular puncture sites, following the procedure. In addition, if an emergency arises at the time of cannulation or scanning, 911 will be called, and the subject will be sent to the Emergency Department for evaluation and treatment. A nurse

will provide discharge instructions outlining general instructions in addition to post-arterial catheter precautions, problems to watch for, and procedures to follow should such problems occur.

Risks Associated with Blood Drawing & IV Line Insertion:

The risks of bruising, clotting, and infection will be minimized by having venipuncture performed by trained and experienced personnel using aseptic technique. To avoid injury due to fainting, the catheter will be inserted when the subjects are in a recumbent position. The blood draws during PET scanning sessions will be obtained from the already inserted catheter, to minimize discomfort. Subjects who have donated blood within 8 weeks of the present study will be excluded. Participants will be told that they should not give blood for at least 8 weeks.

Risks Associated with Radiation:

The dose of radiation will be submitted for approval to the Yale University Radioactive Drug Research Committee (YU RDRC). All scans will be done in the presence of medical supervision and trained staff in an institution specifically designed to support imaging studies. In the event of serious medical complications, the PET scan facilities have immediate access to or consultation with specialized medical units at the Yale-New Haven Hospital. Preparation of radiopharmaceuticals and performance of PET scans will be by radiochemists, physicians, and technologists of the Department of Diagnostic Radiology, Yale University School of Medicine. These professionals are qualified by training and experience in the safe use and handling of radiopharmaceuticals. Subjects will be asked about their previous radiation exposure and those who have had research exposure within the past year will be excluded if their cumulative annual exposure (including the present study) exceeds FDA limits. The information on the previous radiation exposure of study subjects will be notified to the study doctor.

No PET studies will be performed on pregnant or potentially pregnant women, as confirmed by pregnancy testing during evaluation and on each scan day before initiation of any scan procedures. If subjects are breastfeeding they will not be able to participate in this research study.

Risks Associated with MRI Scanning

To minimize risks, each subject will fill out the Yale Magnetic Resonance Research Center MRI Safety Questionnaire before the study. Only subjects who fulfill the criteria by this questionnaire will be eligible for the study. In addition, subjects will remove all metal (watch, hair pins, jewelry) and walk through the metal detector in the MRRC before entering the MRI room. If the subject has any metallic prostheses/implants 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 Drug Use and Suicidal/Homicidal Behavior

Effective screening will exclude all subjects who would be at greater risk for complications because of medical or psychiatric illnesses. Any subject with a prior suicide attempt or with active suicidal ideation at baseline as determined by psychiatric evaluation and C-SSRS, will be excluded from this study.

The subject's health and safety will always be the primary concern of the doctors and staff performing the study. In the event of an unexpected outcome, all necessary medical action will be taken.

Risks Associated with Unanticipated Events

Medication might be administered as needed, per the Yale PET Center standard operating procedure for medical emergencies, in order to treat complications

The subject's health and safety will always be the primary concern of the doctors and staff performing the study. In the event of an unexpected outcome, all necessary medical action will be taken.

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

1. Personnel responsible for safety review and its frequency:

The principal investigator, in collaboration with Kelly Cosgrove, Ph.D., and Stephanie O'Malley, Ph.D., will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency, which must be conducted at a minimum of every 6 months (including when reapproval of the protocol is sought). During the review process, the principal investigator (monitor) will evaluate whether the study should continue unchanged, require modification/amendment, continue or close to enrollment. The principal investigator, the HIC, the FDA, or the RSC, 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:

We view the risks associated with radiation exposure as greater than minimal.
We do not view the risks associated with alcohol administration as minimal.

Although we have assessed the proposed study as one of greater than minimal 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 Ansel T. Hillmer, PhD. 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 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:
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
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
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. In lieu of a summary of external events, a current DSMB report can be submitted for research studies that are subject to oversight by a DSMB (or other monitoring entity that is monitoring the study on behalf of an industry sponsor).

7. Plan for reporting adverse events:

For the current study, the following individuals, funding, and/or regulatory agencies will be notified (choose those that apply):

☒ All Co-Investigators listed on the protocol.
☒ National Institutes of Health
☒ Yale University Radioactive Drug Research Committee (if applicable)
☒ Yale University Radiation Safety Committee (if applicable)

The principal investigator, Ansel Hillmer, PhD, in collaboration with David Matuskey, MD 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.

d. For multi-site studies for which the Yale PI serves as the lead investigator: N/A

i. How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed?
ii. What provisions are in place for management of interim results?
iii. What will the multi-site process be for protocol modifications?

d. For multi-site studies for which the Yale PI serves as the lead investigator:

iv. How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed? *Write here*
v. What provisions are in place for management of interim results? *Write here*
vi. What will the multi-site process be for protocol modifications? *Write here*

13. **Statistical Considerations:** Describe the statistical analyses that support the study design.
Frequency distributions and descriptive statistics for all variables will be computed before conducting analyses. Should Shapiro-Wilk normality tests indicate non-normality for any continuous variable, we will compute necessary data transformations (e.g., logarithmic) before conducting analyses.

AIMs 1 and 2: To determine which radiotracer is most sensitive to alcohol's effects on glutamate, regional V_T values (estimated for each radiotracer) will be analyzed with a linear mixed model featuring scan state (baseline and post-alcohol) as within-subject fixed factors, and region as a within-subjects factor. We hypothesize that the model will identify a significant main effect of scan state. Planned post-hoc contrasts will examine regional differences in V_T by scan state.
Effect sizes of alcohol relative to baseline will also be estimated. These values will guide selection of the experimental protocol for Aim 3.

AIM 3: The primary outcome measure will be the alcohol-induced change in mGlu5 availability, estimated as $\Delta V_T=(V_{T(Alcohol)}-V_{T(Baseline)})/V_{T(Baseline)}$. The value of ΔV_T will then be used as the primary outcome measurement for subsequent analyses.

To test the hypotheses that glutamate responses to alcohol are lower in heavy drinkers compared to moderate drinkers, a linear mixed model featuring group (heavy alcohol use vs. moderate use) as a between-subject fixed factor and region as a within subjects factor will be constructed. The main effect of group will be examined to test the null hypothesis of no difference in ΔV_T between study groups. The interaction term between the two factors will also be examined. Post-hoc linear contrasts will examine regional differences in radiotracer ΔV_T between groups.

Exploratory analyses at the voxel level will be conducted for all aims using whole brain data and SPM12.

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: **[^{11}C]ABP688 and [^{18}F]FPEB** (radiotracer for PET studies), IV

2. Is the radiotracer FDA approved? ☐YES ☒NO

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

3. Check one: ☐IND# 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.

[^{11}C]ABP688

The radiotracer [^{11}C]ABP688 has been used in human subjects previously, including at Yale University. Over 170 injections and more than 80 individuals have been given this radiotracer at Yale. No subjects have reported any adverse event with this radiotracer. However, subjects will be monitored carefully during and after the PET scan for any potential side effects.

[^{11}C]ABP688 is administered intravenously at doses up to 20 mCi per single injection which is below the 21 CFR 361.1 estimated permissible single administration dose limit of 82 mCi based on dosimetry calculations.

[^{18}F]FPEB

The radiotracer [^{18}F]FPEB has previously been used in human subjects, including Yale University. Over 200 individuals and over 352 injections have been imaged at Yale University. No subjects have reported any adverse event with this radiotracer. However, subjects will be monitored carefully during and after the PET scan for any potential side effects.

[^{18}F]FPEB is administered intravenously at doses up to 5 mCi per single administration which is below the 21 CFR 361.1 estimated permissible single administration dose limit of 7 mCi based on dosimetry calculations with 3.5 h voiding period.

4. **Source:** Identify the source of the radiotracer to be used.
[^{11}C]ABP688 and [^{18}F]FPEB will be synthesized at the Yale University PET Center radiochemistry Laboratory under the supervision of Dr. Henry Huang and Dr. Nabeel Nabulsi.

5. **Storage, Preparation and Use:** Describe the method of storage, preparation, stability information, method of sterilization and method of testing sterility and pyrogenicity.

[^{11}C]ABP688 and [^{18}F]FPEB will be prepared at the Yale PET Center in accordance with procedures and quality specifications described in local Drug Master File (DMF) approved by the Yale University Radioactive Drug Research Committee (YURDRC) and the Yale University Radiation Safety Committee (YURSC).

Due to the short half-life, PET drugs are produced *ex tempore* and formulated immediately before administration, and therefore there are no issues with storage or stability. PET drug products are stored at room temperature and are stable for at least 60 minutes after preparation.

The preparation of sterile and pyrogen free PET drug products is validated prior to human use. Sterility is achieved by passing the PET drug products through a 0.22 micron membrane filter during the last step of the formulation process. Due to the short half-life, a sample of the PET drug product is tested for sterility *ex post facto* for further confirmation. However and prior to release for administration, a bubble point test is performed on the membrane filter used for terminal sterilization in order to validate and verify its integrity during the filtration process. Also prior to release of the final PET drug product for administration, the level of endotoxin in each batch is determined quantitatively using the FDA approved Charles River Laboratory's Portable Testing System (Endosafe®-PTS).

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	☒

4. 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).	☒
5. 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

2. Source: Identify the source of the drug or biologic to be used.

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.

The YNHH IDS will store the vials of alcohol and prepare the solution for IV administration. Oral alcohol mix will be prepared by the team on scan day according to the modified Widmark calculation. For the Oral alcohol challenge only unopened containers of vodka and chosen mixer will be used in the solution.

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.

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

c) Address the greatest potential harm that may come to a participant as a result of receiving placebo.
d) Describe the procedures that are in place to safeguard participants receiving placebo.

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: 150 subjects will be screened to have 70 subjects participate.
   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: Clinical Referral

* 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:
All subjects will be 21-55 years of age and physically healthy. All research subjects will be recruited under guidelines of the Yale University Institutional Review Board (Human Investigation Committee). Subjects will be recruited from the community at large via IRB-approved advertising.

a. Describe how potential subjects are contacted.

The subjects will be asked to call us if they are interested in participating in the research study. Interested individuals contacting the clinic by phone in response to advertisements are told that the information they give over the phone is written down and discussed by the research team. They are advised that if they do not enroll in research with the clinic the information is destroyed, and that if they do, it becomes part of their research chart. If an individual appears to meet enrollment criteria and is interested in participating, a face-to-face interview is conducted by one of the project investigators. A release of information is obtained for review of any available historical and clinical data. A written authorization form is also obtained from each subject, permitting the research team to use, create, or disclose the subject's PHI for research purposes. The nature of the project, procedures, relative risks and benefits, and alternatives to participation in the project are discussed with the individual. Following this discussion, the individual is given a copy of the consent form to review, and any questions are answered. The PI of the protocol will seek written consent from all participants.

b. Who is recruiting potential subjects?

c. Who is recruiting potential subjects? Members of the research team, as identified in the consenting staff section.

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: *Write here*

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: *Write here*

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.
The consent process is a 2-step process, whereby the subject initiates contact via telephone and will undergo a phone screen with a member of the research team. Thereafter, potentially eligible candidates will be scheduled for a face-to-face interview. All subjects who will be asked to volunteer are informed that no immediate personal medical benefits will be derived from participation. The study procedures will be described as a research tool with potential to enhance our knowledge about treating cognitive dysfunction. Subjects are also informed of all potential risks of participation. Informed consent is documented using specific forms for each study, reviewed and approved by the Yale University Human Investigation Committee (HIC).

   Informed consent will be obtained by physicians involved in this study or their designated representatives (see list of consenting personnel above). Subjects are required to read the informed consent form, and the entire form is then reviewed with them by study personnel. In addition, the study physician will ask if the subject has any additional questions and further describe any risks and discomforts. Subjects will be informed that they can decline to participate in the study without penalty, and given the opportunity to withdraw from the study prior to analysis of their data. Following the resolution of any questions, the subjects will be asked to sign the consent form, if he/she agrees to participate.

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.

   We will not recruit subjects with limited decision-making capacity. All of the subjects who sign the consent to participate in the protocol will have completed and met medical (urine and blood tests, EKG, and physical) and psychological (SCID and clinical interview) criteria. As part of the consent process, prospective subjects are asked open-ended questions about the research in order to determine whether the subject recalls and understand the process of the study. If an individual shows poor comprehension of the consent form and study, we will not enroll them. A study doctor supervises the screening and enrollment process.

8. 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 Speakers will not be enrolled in 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.

9. 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? Required private identifiable information about individuals, such as their medical history, current medications, psychiatric problems, and family history, will be collected by research staff and be used for research purposes and charting after consent is obtained. Required private identifiable information about individuals, such as their medical history, current medications, psychiatric problems, and family history, will be collected by research staff and be used for research purposes and charting after consent is obtained.

   Subjects will also provide information about their smoking history, their family smoking and psychiatric history, drinking and drug use history, mood, cardiovascular health, and other demographic variables. Biological specimens to be taken from subjects include urine samples to rule out or confirm drugs of abuse prior to imaging, and blood samples (during imaging) to measure plasma concentration of tracer and other times as well as to measure blood drug levels.

   Subjects who stay at the Connecticut Mental Health Center (CMHC) will have a medical record. If subjects already have a medical record at CMHC, some information about their participation in the study will be included here. If they do not have a medical record at CMHC, one will be made for their visit. The information that will be entered into this medical record will include: name, date of birth, date of admission to the CNRU, date of discharge from the CNRU, phone number, address, medical history, individual and family history of psychiatric problems, and substance abuse history. Subjects will also sign a separate Notice of Privacy Practices specific to CMHC.

2. How will the research data be collected, recorded and stored? T on University encrypted computers. Results are published as group data without the use of characteristics that would identify individual subjects. We quote information only by number in conference discussions, scientific reports, or publications, in order to maintain anonymity.

   Identifiable brain research data are stored on a secure database located on the internal PET Center Network. The PET network is protected by a Cisco PIX firewall operated by ITS. All research data are backed up nightly to

a Dell PV-136T library wit 4 IBM Ultrium-TD2 tape drives using the backup software Legato Networker 7.3 from EMC. Human subjects enrolled in the study are assigned a subject-specific random identifier. Subject identifiers and the means to link the subject names and codes with the research data are stored in separate locations within the database. The software of the database limits the ability to connect the random identifier to the actual subject identification information to research team members only. Access to the database is password protected and each research team member is required to have a unique ID and password to gain access to the database. Authorized users employ their netid and authentication is performed using Yale's central authentication server. Users always access research data through the random identifier only.

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?

   Identifiable paper information is kept in locked file drawers and password protected computer files on University encrypted computers. Results are published as group data without the use of characteristics that would identify individual subjects. We quote information only by number in conference discussions, scientific reports, or publications, in order to maintain anonymity.

   Identifiable brain research data are stored on a secure database located on the internal PET Center Network. The PET network is protected by a Cisco PIX firewall operated by ITS. All research data are backed up nightly to a Dell PV-136T library wit 4 IBM Ultrium-TD2 tape drives using the backup software Legato Networker 7.3 from EMC. Human subjects enrolled in the study are assigned a subject-specific random identifier. Subject identifiers and the means to link the subject names and codes with the research data are stored in separate locations within the database. The software of the database limits the ability to connect the random identifier to the actual subject identification information to research team members only. Access to the database is password protected and each research team member is required to have a unique ID and password to gain access to the database. Authorized users employ their netid and authentication is performed using Yale's central authentication server. Users always access research data through the random identifier only

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. The data will be stored in locked filing cabinets and on the password-protected secure database on the internal Yale University PET Center Network for at least 10 years, accessed only by study personnel.

6. If appropriate, has a Certificate of Confidentiality been obtained? This protocol is funded by NIH. As such, according to the NIH policy issued in October 2017, the information collected from subjects is automatically protected by a Certificate of Confidentiality (CoC).

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.)

These studies are not of direct benefit to subjects. This study will help advance knowledge regarding the brain's neuroimmune response to drinking alcohol.

In the long term, the knowledge mentioned above can guide scientists in their efforts to develop new treatments for drug addiction. There is no direct benefit to these subjects. They will be able to withdraw from the study at any time.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. Alternatives: What other alternatives are available to the study subjects outside of the research?
   The alternative to participation in this research protocol is to not participate. Subjects will be informed that they are free to choose not to participate and, if they do agree to become a subject, they will be free to withdraw from the study at any time during its course. They will also be informed that if they choose not to participate or if they withdraw, it will not adversely affect their relationship with their doctors or the hospital (per the consent form).

2. 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.
   The subjects will be compensated for their time commitment and inconveniences necessary for completing the study. Subjects will have no financial responsibilities for any portion of the study.

   Compensation will be the following:

   - $50 for completing the in-person screening process
   - $400 for each PET scan (i.e., up to $1200 if participating in all three scans)
   - $50 per arterial line placement (up to $150 if scans occur on separate days)
   - $50 for the MRI scan.
   - Up to $60 for Probabilistic Reward Task
   - $100 bonus upon completion of all study procedures

   Subjects participating will receive a total of up to $1610.

Subjects will be paid either by check, and are advised to allow 4-6 weeks for receipt of payment, or they will be given a credit card or cash. In addition, subjects will be provided with a light lunch, valued at no more than $10. They will also be reimbursed for parking on their PET scan days, or they may be compensated for reasonable transportation costs, including taxi fees to and from scans.

Cancellations: If a PET scan should be cancelled by the PET Center for a reason outside of the subject's control (i.e. radiotracer synthesis failure) the subject will be paid $50 minimum, or a higher amount not to exceed the payment for a full scan day. The amount of the payment for cancellation will be based on the subject's length of participation on that scan day prior to the cancellation, and will be up to the discretion of the PI.

3. 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.
   Subjects will not be financially responsible for tests, examinations, and medical care provided to them during their participation in this study.

4. 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? *Write here*

   b. Where and from whom may treatment be obtained? *Write here*
   c. Are there any limits to the treatment being provided? *Write here*
   d. Who will pay for this treatment? *Write here*
   e. How will the medical treatment be accessed by subjects? *Write here*

Medical treatment will be offered to the subjects for any physical injuries that they receive as a result of participating in this research. However, the subject or his/her insurance company is responsible for the cost. Federal regulations require that subjects be told that if they are physically injured, no additional financial compensation is available.

Treatment may be provided by Yale-New Haven Hospital or any health care provider chosen by the study subjects. The study team will provide assistance to the study subjects in accessing medical treatment through referrals, or the study subjects may choose to access treatment on their own.

References

1. Olive MF, Cleva RM, Kalivas PW, Malcolm RJ. Glutamatergic medications for the treatment of drug and behavioral addictions. Pharmacology Biochemistry and Behavior. 2012;100(4):801-810.
2. Moghaddam B, Bolinao ML. Biphasic effect of ethanol on extracellular accumulation of glutamate in the hippocampus and the nucleus accumbens. Neuroscience Letters. 1994;178(1):99-102.
3. Tsai GE, Ragan P, Chang R, Chen S, Linnoila VM, Coyle JT. Increased glutamatergic neurotransmission and oxidative stress after alcohol withdrawal. The American journal of psychiatry. 1998;155(6):726-732.
4. Umhau JC, Momenan R, Schwandt ML, et al. Effect of acamprosate on magnetic resonance spectroscopy measures of central glutamate in detoxified alcohol-dependent individuals: a randomized controlled experimental medicine study. Arch Gen Psychiatry. 2010;67(10):1069-1077.
5. Kalivas P, Volkow N. New medications for drug addiction hiding in glutamatergic neuroplasticity. Molecular psychiatry. 2011;16(10):974-986.

6. Burger C, Deschwanden A, Ametamey S, et al. Evaluation of a bolus/infusion protocol for 11C-ABP688, a PET tracer for mGluR5. Nuclear medicine and biology. 2010;37(7):845-851.

7. DeLorenzo C, DellaGioia N, Bloch M, et al. In Vivo Ketamine-Induced Changes in [11C]ABP688 Binding to Metabotropic Glutamate Receptor Subtype 5. Biological Psychiatry. 2015;77(3):266-275.

8. Esterlis I, DellaGioia N, Pietrzak RH, et al. Ketamine-induced reduction in mGluR5 availability is associated with an antidepressant response: an [11C]ABP688 and PET imaging study in depression. Molecular Psychiatry. 2017;23:824.

9. Esterlis I, Holmes SE, Sharma P, Krystal JH, DeLorenzo C. Metabotropic Glutamatergic Receptor 5 and Stress Disorders: Knowledge Gained From Receptor Imaging Studies. Biological Psychiatry. 2018;84(2):95-105.

10. DeLorenzo C, Gallezot J-D, Gardus J, et al. In vivo variation in same-day estimates of metabotropic glutamate receptor subtype 5 binding using [11C] ABP688 and [18F] FPEB. Journal of Cerebral Blood Flow & Metabolism. 2017;37(8):2716-2727.

11. Roberto M, Schweitzer P, Madamba SG, Stouffer DG, Parsons LH, Siggins GR. Acute and Chronic Ethanol Alter Glutamatergic Transmission in Rat Central Amygdala: an In Vitro and In Vivo Analysis. The Journal of Neuroscience. 2004;24(7):1594-1603.

12. Selim M, Bradberry CW. Effect of ethanol on extracellular 5-HT and glutamate in the nucleus accumbens and prefrontal cortex: Comparison between the Lewis and Fischer 344 rat strains. Brain Research. 1996;716(1):157-164.

13. Szumlinski KK, Diab ME, Friedman R, Henze LM, Lominac KD, Bowers MS. Accumbens neurochemical adaptations produced by binge-like alcohol consumption. Psychopharmacology. 2007;190(4):415-431.

14. Urban NBL, Kegeles LS, Slifstein M, et al. Sex Differences in Striatal Dopamine Release in Young Adults After Oral Alcohol Challenge: A Positron Emission Tomography Imaging Study With [11C]Raclopride. Biological Psychiatry. 2010;68(8):689-696.

15. Smith A, Watson CJ, Frantz KJ, Eppler B, Kennedy RT, Peris J. Differential Increase in Taurine Levels by Low-Dose Ethanol in the Dorsal and Ventral Striatum Revealed by Microdialysis With On-Line Capillary Electrophoresis. Alcoholism: Clinical and Experimental Research. 2004;28(7):1028-1038.

16. Krystal JH, Petrakis IL, Mason G, Trevisan L, D'Souza DC. N-methyl-D-aspartate glutamate receptors and alcoholism: reward, dependence, treatment, and vulnerability. Pharmacology & therapeutics. 2003;99(1):79-94.

17. Holmes SE, Girgenti MJ, Davis MT, et al. Altered metabotropic glutamate receptor 5 markers in PTSD: In vivo and postmortem evidence. Proceedings of the National Academy of Sciences of the United States of America. 2017;114(31):8390-8395.

18. Cardenas VA, Studholme C, Gazdzinski S, Durazzo TC, Meyerhoff DJ. Deformation-based morphometry of brain changes in alcohol dependence and abstinence. Neuroimage. 2007;34(3):879-887.

19. Mechtcheriakov S, Brenneis C, Egger K, Koppelstaetter F, Schocke M, Marksteiner J. A widespread distinct pattern of cerebral atrophy in patients with alcohol addiction revealed by voxel-based morphometry. Journal of Neurology, Neurosurgery & Psychiatry. 2007;78(6):610-614.

20. Pfefferbaum A, Sullivan EV, Rosenbloom MJ, Mathalon DH, Lim KO. A controlled study of cortical gray matter and ventricular changes in alcoholic men over a 5-year interval. Archives of general psychiatry. 1998;55(10):905-912.

21. Cosgrove KP, McKay R, Esterlis I, et al. Tobacco smoking interferes with GABAA receptor neuroadaptations during prolonged alcohol withdrawal. Proc Natl Acad Sci U S A. 2014;111(50):18031-18036.

22. Martinez D, Gil R, Slifstein M, et al. Alcohol dependence is associated with blunted dopamine transmission in the ventral striatum. Biological psychiatry. 2005;58(10):779-786.

23. Narendran R, Mason NS, Paris J, Himes ML, Douaihy AB, Frankle WG. Decreased prefrontal cortical dopamine transmission in alcoholism. The American journal of psychiatry. 2014;171(8):881-888.

24. Chanraud S, Pitel A-L, Pfefferbaum A, Sullivan EV. Disruption of functional connectivity of the default-mode network in alcoholism. Cerebral Cortex. 2011:bhq297.

25. Weiland BJ, Sabbineni A, Calhoun VD, et al. Reduced left executive control network functional connectivity is associated with alcohol use disorders. Alcoholism, clinical and experimental research. 2014;38(9):2445-2453.

26. Rando K, Hong K-I, Bhagwagar Z, et al. Association of frontal and posterior cortical gray matter volume with time to alcohol relapse: a prospective study. 2014.

27. Durazzo TC, Mon A, Gazdzinski S, Yeh PH, Meyerhoff DJ. Serial longitudinal magnetic resonance imaging data indicate non-linear regional gray matter volume recovery in abstinent alcohol-dependent individuals. Addict Biol. 2014.

28. Camchong J, Stenger VA, Fein G. Resting-State Synchrony in Short-Term Versus Long-Term Abstinent Alcoholics. Alcoholism: Clinical and Experimental Research. 2013;37(5):794-803.

29. Sullivan EV, Rosenbloom MJ, Lim KO, Pfefferbaum A. Longitudinal changes in cognition, gait, and balance in abstinent and relapsed alcoholic men: relationships to changes in brain structure. Neuropsychology. 2000;14(2):178.

30. Barrick C, Connors GJ. Relapse prevention and maintaining abstinence in older adults with alcohol-use disorders. Drugs & aging. 2002;19(8):583-594.

31. Larsen RS, Smith IT, Miriyala J, et al. Synapse-specific control of experience-dependent plasticity by presynaptic NMDA receptors. Neuron. 2014;83(4):879-893.

32. Holmes A, Spanagel R, Krystal JH. Glutamatergic targets for new alcohol medications. Psychopharmacology. 2013;229(3):539-554.

33. Bardoni R, Torsney C, Tong C-K, Prandini M, MacDermott AB. Presynaptic NMDA Receptors Modulate Glutamate Release from Primary Sensory Neurons in Rat Spinal Cord Dorsal Horn. The Journal of Neuroscience. 2004;24(11):2774-2781.

34. Nagy J, Kolok S, Dezso P, Boros A, Szombathelyi Z. Differential alterations in the expression of NMDA receptor subunits following chronic ethanol treatment in primary cultures of rat cortical and hippocampal neurones. Neurochemistry international. 2003;42(1):35-43.

35. Nelson TE, Ur CL, Gruol DL. Chronic intermittent ethanol exposure enhances NMDA-receptor-mediated synaptic responses and NMDA receptor expression in hippocampal CA1 region. Brain research. 2005;1048(1-2):69-79.

36. Gass JT, Olive MF. Glutamatergic substrates of drug addiction and alcoholism. Biochemical Pharmacology. 2008;75(1):218-265.

37. Tsai G, Coyle JT. The role of glutamatergic neurotransmission in the pathophysiology of alcoholism. Annual review of medicine. 1998;49:173-184.

38. Daggett LP SA, Akong M, et al. Molecular and functional characterization of recombinant human metabotropic glutamate receptor subtype 5. Neuropharmacology. Aug 1995;34(8):871-886.

39. Ohnuma T AS, Arai H, McKenna PJ, Emson PC. Expression of the human excitatory amino acid transporter 2 and metabotropic glutamate receptors 3 and 5 in the prefontal cortex from normal individuals and patients with schizophrenia. Brain Res Mol Brain Res. May 1998;56(1-2):207-217.

40. Patton JH, Stanford MS, Barratt ES. Factor structure of the Barratt impulsiveness scale. J Clin Psychol. 1995;51(6):768-774.

41. Kiluk BD, Dreifuss JA, Weiss RD, Morgenstern J, Carroll KM. The Short Inventory of Problems - revised (SIP-R): psychometric properties within a large, diverse sample of substance use disorder treatment seekers. Psychology of addictive behaviors : journal of the Society of Psychologists in Addictive Behaviors. 2013;27(1):307-314.

42. Piepponen TP, Kiianmaa K, Ahtee L. Effects of ethanol on the accumbal output of dopamine, GABA and glutamate in alcohol-tolerant and alcohol-nontolerant rats. Pharmacology Biochemistry and Behavior. 2002;74(1):21-30.

43. Carson RE, Barker WC, Liow J-S, Johnson CA. Design of a motion-compensation OSEM list-mode algorithm for resolution-recovery reconstruction for the HRRT. presented at: Nuclear Science Symposium Conference Record, 2003 IEEE2003.
44. Ziegler G, Ridgway GR, Dahnke R, Gaser C, Initiative AsDN. Individualized Gaussian process-based prediction and detection of local and global gray matter abnormalities in elderly subjects. NeuroImage. 2014;97:333-348.
45. Treyer V, Streffer J, Wyss MT, et al. Evaluation of the Metabotropic Glutamate Receptor Subtype 5 Using PET and 11C-ABP688: Assessment of Methods. Journal of Nuclear Medicine. 2007;48(7):1207-1215.
46. Sullivan JM, Lim K, Labaree D, et al. Kinetic analysis of the metabotropic glutamate subtype 5 tracer [(18)F]FPEB in bolus and bolus-plus-constant-infusion studies in humans. Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism. 2013;33(4):532-541.
47. Morean ME, Corbin WR, Treat TA. The Subjective Effects of Alcohol Scale: Development and psychometric evaluation of a novel assessment tool for measuring subjective response to alcohol. Psychological assessment. 2013;25(3):780.
48. Martin CS, Earleywine M, Musty RE, Perrine M, Swift RM. Development and validation of the biphasic alcohol effects scale. Alcoholism: Clinical and Experimental Research. 1993;17(1):140-146.
49. Schuckit MA, Smith TL, Tipp JE. The Self-Rating of the Effects of alcohol (SRE) form as a retrospective measure of the risk for alcoholism. Addiction (Abingdon, England). 1997;92(8):979-988.

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.