HRP-503B – BIOMEDICAL RESEARCH PROTOCOL
(2016-1)

Protocol Title: Investigation of cocaine addiction using mGluR5 PET and fMRI

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SECTION I: RESEARCH PLAN

1. Statement of Purpose:

Cocaine use disorder (CUD) remains a significant public health concern that is resistant to current treatments. Challenges to treating CUD include an imbalance in neurobiological systems that 're-wire' the brain such that appetitive and habitual processes influence maladaptive decision-making and behavior. This research project aims to provide insight into this reorganized circuitry in CUD by investigating neurofunctional systems related to glutamatergic plasticity and functional brain networks during initial (2-5 days) abstinence. To target this potentially critical period of recovery, currently-using and non-treatment-seeking individuals with CUD will complete [^{18}F]FPEB positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) within days of admission to an inpatient research facility. Healthy comparison (HC) subjects from the community or that have participated in [^{18}F]FPEB PET as part of other Yale approved protocols (HIC#1101007933, HIC#1111009365, HIC#2000027842/2000020186) will be recruited to participate in the fMRI portion of this study.

Aim 1: To determine the availability of mGluR5 using [^{18}F]FPEB PET during initial abstinence in individuals with CUD. We hypothesize individuals with CUD, relative to HC, will exhibit concurrently and regionally specific increases (e.g., in the striatum) and decreases (e.g., in the prefrontal cortex) in mGluR5 availability.

Aim 2: To determine patterns of resting-state, response-inhibition, an automaticity related connectivity within and between large-scale functional networks using fMRI during initial abstinence in individuals with CUD. We hypothesize network-based analyses of fMRI will reveal lower frontoparietal and greater limbic network modulation in CUD as compared to HC.

Aim 3: To explore the relationships between mGluR5 availability and functional network activity during initial abstinence in individuals with CUD. We will perform multi-modal analysis of PET and fMRI data to examine links between molecular and functional systems in CUD using emerging 'fusion' approaches. While exploratory in nature, we expect to find links between alterations in mGluR5 systems and functional reorganization in CUD (e.g., greater dorsostriatal mGluR5 may be linked to blunted frontoparietal inhibition).

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Aim 4: To explore the relationships between mGluR5 availability, functional network activity (and their linkages) with cocaine self-administration (collected in some subjects during a prior version of this protocol), disease severity and chronicity, and psychometric assessments of impulsivity and compulsivity. While exploratory in nature, we expect more substantial neurofunctional alterations during initial abstinence will be associated with greater cocaine self-administration, disease severity, impulsivity and compulsivity in individuals with CUD.

Aim 5 (pilot): To assess the degree to which mGluR5 availability and functional network activity may change during early abstinence in CUD. A pilot sample of CUD participants (up to 10) will be invited to repeat [^{18}F]FPEB PET and fMRI procedures within three weeks of initial scans (typically 5-14 days). A pilot sample of HC individuals (up to 10) will also be recruited to complete longitudinal MRI scanning procedures (i.e., two MRI scans up to 30 days apart) for test-retest comparison purposes. We hypothesize that individuals with CUD will exhibit widespread decreases in mGluR5 availability from levels measured during initial abstinence, and that decreases in mGluR5 will be related to blunted activity of cognitive flexibility-related networks and stable or increased activity within automaticity-related networks.

2. Probable Duration of Project:

5 years.

3. Background:

Illicit-substance-use disorders affect over 8% of individuals in the US (1), leading to negative health outcomes and a substantial impact on society (2). Despite decades of research, cocaine use disorder (CUD) remains one of the most treatment-resistant addictions; there is currently no FDA-approved medication with an indication for the treatment of CUD (3), and behavioral interventions for CUD remain suboptimal with high rates of relapse (4).

CUD-related reorganization of brain circuitry. CUD is associated with a complex set of neurobiological alterations that impact a range of cognitive functions including attentional, emotional, inhibitory and consummatory processes (5, 6). Current models of CUD, and addictions more broadly, implicate a dysfunction in the balance of cognitive systems such that appetitive and habitual processes drive maladaptive decision-making and behavior (7, 8). This imbalance in brain systems develops through neuroplastic adaptations similar to the neural mechanisms underlying learning and memory (9, 10). Furthermore, the maintenance and persistence of chronic drug-use behavior in CUD is supported by 'metaplastic' alterations, or changes in the plasticity of neuroplasticity (11, 12). That is, molecular changes occurring with chronic cocaine exposure enhance learning and memory processes associated with drug use while impairing the potential for learning and memory associated with non-drug-related stimuli (13, 14).

mGluR5 and neuroplasticity in CUD. The metabotropic glutamate 5 receptor (mGluR5) is primarily a postsynaptic receptor located in perisynaptic and extrasynaptic regions (15), and is associated with modulating plasticity through multiple signaling pathways (16). mGluR5 has been linked to key neuroplastic processes in chronic CUD, and during early abstinence (10-14, 17-22). mGluR5-related mechanisms are also critical to 'metaplasticity', or the functioning of neuroadaptive mechanisms in CUD (23). Blocking mGluR5 activity (through deletion or antagonism) interferes with neuroadaptive processes linked to CUD including learning of self-administration behavior (21, 22), cue-induced reinstatement (24, 25), and extinction of cocaine-seeking behavior (20, 26) in animal models. Thus, mGluR5 availability, as an indicator of neuroplastic activity, may lend insight into the functional reorganization in CUD.

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mGluR5 research in CUD. To date, three human studies have examined mGluR5 in CUD. During early abstinence (i.e., 10-14 day from last use), mGluR5 availability was globally reduced in CUD (27). A subsequent study examining a wider range of abstinence in CUD (2-14 days) also observed reductions in mGluR5 availability; and importantly, lower mGluR5 availability was associated with longer abstinence, with an approximate 60-80% reduction in receptor availability after two weeks (28). This finding suggests that the lowered mGluR5 availability in CUD may be the net result of molecular changes that occur through early abstinence (10, 13, 27, 29); however, this has not been directly examined within individuals. These reports are in conflict with an initial study reporting no cocaine-related changes in mGluR5 (30). However, limitations caution against firm conclusions of this study: (i) only half of the cocaine-using sample met criteria for CUD, perhaps indicating an absence of CUD-related functional reorganization; and (ii) nearly half of cocaine-users tested positive for cocaine-metabolites, suggesting data were from a mixture of current users and early-abstinent individuals.

Functional circuitry in CUD. A substantial body of research demonstrates regional alterations in brain activity in individuals with CUD across a range of cognitive tasks, implicating a reorganization in functional circuitry (6, 8). CUD-related impairments are frequently reported in striatal and prefrontal regions that are consistent with models of altered reward-sensitivity, impulsivity, and compulsivity (5, 6, 31). However, these regions are anatomically connected to diverse sets of brain regions (32), and less is known how regional impairments integrate into, and influence functionally distinct brain circuits. Independent component analysis (ICA) is a computational technique that evaluates higher-order data structures, and when applied to fMRI data, identifies networks of brain regions showing coherent patterns of brain activity, forming 'functional brain networks' (33). Several distinct functional brain networks (e.g., fronto-parietal, cingulo-insular, and default-mode) are reliably identified in resting-state and task-based fMRI (34, 35), and exhibit particular functional roles (36). Several functional networks have been implicated in successful and erroneous response inhibition processing (37-39), an executive function central to models of addictive behavior (8, 40). Individuals with CUD exhibit regional alterations in brain activity during response inhibition processing (41, 42); however, activity of functional networks in CUD during response inhibition and automatic/habitual behavior remains largely unexplored. Examining the activity of functional networks at rest, during automatic responding, and response inhibition will lend insight into the nature of brain reorganization in CUD (e.g., altered functional roles, regional integration, or inter-network dynamics).

Multi-modal imaging in CUD. Resting-state connectivity and inhibitory processing have been linked to glutamatergic processes (43-46). Sophisticated analytical techniques that investigate shared higher-order data structures within and across imaging modalities (such as using parallel-ICA to combine PET and fMRI data), will allow greater understanding of the relationships between these neurofunctional systems than simple correlational procedures (47). Links between mGluR5 and functional network activity during resting-state, automatic responding, and response inhibition will provide unique insight into the reorganization of neurocircuitry in CUD.

Summary. CUD is one of the most treatment-resistant addictions, and greater understanding of the functional reorganization and neurobiological risk factors of relapse may improve long-term outcomes. We propose to study mGluR5 (a glutamate receptor linked to neuroplasticity) during initial (2-5 days) abstinence in individuals with CUD to examine brain regions and networks of altered neuroplastic capacity. In addition, investigation of resting-state and task-based functional connectivity using fMRI will help clarify the reorganization of brain circuitry that occurs in CUD. Finally, integration of the two modalities using novel analytic methods will lend unique insight into the relationships between these neurofunctional systems.

4. Research Plan:

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a. General design and overview

Twenty experienced, currently-using, non-treatment-seeking and medically healthy individuals with cocaine-use disorder (CUD) will participate in a multi-modal imaging investigation of neurofunctional systems during initial (2-5 days) abstinence. Subjects determined to meet eligibility criteria through phone and in-person screening will be scheduled for admission to the Clinical Neuroscience Research Unit (CNRU), Connecticut Mental Health Center (CMHC) for the duration of their study participation (up to 10 days). Following admission (approximately 2-5 days), subjects will undergo a single [^{18}F]FPEB PET scan at the Yale PET Center and complete an fMRI scanning session at the Yale Magnetic Resonance Research Center (MRRC). Primary outcome measures will include mGluR5 distribution/availability and activity of functional brain networks. Secondary outcomes will include cocaine administration measures (e.g., amount consumed, inter-response intervals, etc.), cocaine-induced subjective effects (e.g., self-ratings of euphoria, 'high', etc.) for subjects having completed the prior study protocol, and psychometric assessments of impulsivity and compulsivity.

Data from age- and gender-matched healthy comparison (HC) subjects that have participated in [^{18}F]FPEB PET as part of other Yale approved protocols (HIC#1101007933, HIC#1111009365, HIC#2000027842/2000020186) will be recruited to participate in the fMRI portion of this study. These protocols currently obtain written consent from subjects to allow sharing of their information to other Yale research groups for recruitment purposes, along with use of their PET data for research purposes among collaborating groups. Thus, HC participants will not need to undergo an additional [^{18}F]FPEB PET scanning, but may be asked to complete additional screening (e.g., structured interviews), and will be asked to complete appropriate assessments and an fMRI session. Additional community-recruited HC individuals may be enrolled (i.e., those that have not completed [^{18}F]FPEB PET scanning) to participate in longitudinal MRI procedures consistent with Aim 5. These participants will undergo appropriate screening procedures to determine eligibility, may complete self-assessments and complete MRI scanning up to 30 days apart.

b. Subject screening, admission, and assessment

CUD subjects:

Recruitment of CUD subjects will include experienced, currently-using, non-treatment-seeking, medically-healthy, adult volunteers meeting criteria for cocaine-use disorder. CUD subjects that have agreed to participate in similar research at the Cocaine Research Clinic as part of another Yale approved protocol (e.g., HIC#2000029552) may be invited to participate. When possible, these individuals will be recruited to participate in the PET and fMRI portions of this study concurrently with their participation in the other protocols. Simultaneous participation in multiple studies will be permitted at the discretion of the Investigators only if it would lessen subject burden (i.e., minimizing inpatient residencies and repeated assessments) without impacting the integrity of either study. Additional CUD subjects may be recruited through community advertising (e.g., flyers), screened, consented, evaluated, admitted to the CNRU.

Telephone screening. Study staff will initially screen subjects by telephone. During initial telephone screening, study staff will offer a brief explanation of the study, its purpose, duration, risks, and compensation. If the subject is willing to proceed, the study staff will ask a set of questions that will allow for an early exclusion of subjects who do not qualify (e.g., individuals with a major psychiatric disorder, individuals with exclusionary medical conditions or medications, individuals meeting criteria for other drugs/alcohol use disorders, individuals not using smoked/IV cocaine, etc.; see inclusion/exclusion criteria below for specifics). If subjects do not meet criteria and are excluded, or if they are not interested in

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participating, telephone screening information will be discarded in accordance with Yale established procedures.

In-person screening. After telephone screening, potentially eligible subjects will be invited to an in-person screening visit on the Clinical Neuroscience Research Unit (CNRU). The screening visit will last approximately 2 hours. Subjects will first undergo a process of informed consent, during which they will first read the consent form and meet with a study physician and/or trained research staff member. Subjects will receive an explanation of the study's purpose, procedures, benefits, risks, compensation, and alternatives. They will have time to ask any questions and, if interested in participating, will be asked to sign a current, HIC-approved consent form.

Remote screening option. Potential subjects who pass the phone screen portion will have the option to do the consenting screening portion remotely. They will be sent two copies of the consent form and a release of information to review at their leisure through a method that is most convenient for them (i.e., email, fax, or mail). This way subjects have time to review the consent prior to signing and they have their own copy to follow along and ask questions during the consenting phone call. If they agree to participate, subjects can keep one copy of the consent and sign, date, and return the other copy along with a signed released of information back to our research office either by fax, email, or mail in a prepaid envelope. When the consent is also signed by a member of the research team, it will be filed in the subject's research record. Using tele-health platforms (i.e., Zoom) the researcher and subject will thoroughly review and sign the consent form, complete a structured clinical interview (SCID) by a member of the research team, and a medical history and psychiatric interview by a study physician. This will take up to two hours to complete in total. If deemed eligible by initial Zoom call and interviews, potential subjects will be asked to complete the rest of the study procedures as detailed in the protocol.

Consenting individuals will then undergo additional screening evaluation, including a clinical psychiatric interview (including questions regarding patterns/routes of cocaine use) and the collection of other clinical phenotypic information (e.g., body mass index, frequency and amount of cocaine use, comorbid nicotine and alcohol use, etc.) that may be completed in-person or remotely, and an in-person physical examination, including a blood draw for CBC and basic metabolic panel, a pregnancy test if needed, an electrocardiogram, and a urine sample for urinalysis and toxicology tests. Results of these tests are confidential. A qualified physician will inform the subjects of any clinically significant results. Subjects will be asked to complete a release of information form allowing study staff to contact the subject's primary care physician to corroborate aspects of the patient's medical history. If the participant does not have a primary care physician, the release will be completed with another alternative source of collateral information (i.e., parent, relative, or significant other).

Once subjects finish the screening visit, lab results are reviewed, collateral information is verified, and screening interviews are reviewed, the subject's eligibility is confirmed. Up to one month may elapse between the screening and the study visits, although in most instances we anticipate that such visits will be a week apart.

Admission to the CNRU. Once eligibility is confirmed, subjects will be contacted and scheduled for inpatient admission to the CNRU. Subjects will reside on the CNRU for the duration of their study (typically 5-8 days, possibly up to 10 days) to ensure abstinence from non-laboratory cocaine, participate in experimental procedures, and facilitate monitoring. The CNRU is an elective 13-bed, locked inpatient clinical research unit where visitors are restricted, access to drugs prevented (except for nicotine which is restricted to scheduled daily smoking breaks), and drug abstinence confirmed by regular (3x per week) urine toxicology testing. As inpatients, subjects will be required to participate in non-treatment related aspects of a structured program of inpatient activities that may include individual (daily with psychiatry resident) and group modalities (e.g., life skills, occupational therapy, etc.).

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Subject assessments and ratings. Subjects will participate in a variety of structured clinical, psychometric, and behavioral assessments as part of their screening and/or research participation:

i. *Structured Clinical Interview for DSM-V (SCID).* The SCID is a semi-structured, clinician-administered interview for making major DSM-V psychiatric diagnoses and will be used during screening to confirm inclusion criteria such as cocaine use disorder and to identify psychiatric exclusion criteria (48).

ii. *Semi-Structured Assessment of Drug Dependence and Alcoholism (SSADDA)*. Subjects will be assessed with substance-use (e.g., cocaine and alcohol) and psychiatric (e.g., ADHD) sections of the SSADDA during screening as well (49). CUD subjects recruited through similar ongoing studies (e.g., HIC#2000029552) may have completed this interview as part of the other research program. CUD subjects recruited through the community will complete this interview as part of their participation in this protocol.

iii. *The Substance Use Calendar*. The Substance Use Calendar uses the Time-Line Follow-Back Method to assess day-to-day use of cocaine and other drugs during the last 90 days and will be administered during screening and updated at admission (50). CUD subjects recruited through similar ongoing studies (e.g., HIC#2000029552) may have completed this assessment as part of the other research program. CUD subjects recruited through the community will complete this assessment as part of their participation in this protocol.

iv. *Visual Analog Scale (VAS) Ratings of Cocaine-Related Subjective Effects*. During cocaine administration procedures, subject will complete 14 self-rated subjective effects measures according to a graduated scale (0 = not at all; 10 = most ever). VAS ratings are designed to assess several dimensions of stimulant-induced subjective effects, including positive (“high”, “rush”, “good”), negative (“bad”, “anxious”, “paranoid”), psychomotor (“stimulated”, “restless”, “talkative”, “tongue-tied”), appetitive/craving (“want drug”) and drug-valuing effects (“drug liking”, “drug potency”, “drug quality”). Ratings are recorded using a touch-screen laptop computer and will be administered every 5 minutes throughout cocaine sessions (51).

v. *Hedonic Response Questionnaire (HRQ);* (admission and after each cocaine session): The HRQ is a 13-item questionnaire used to assess pleasure derived from a range of activities (e.g., watching sports, exercising, reading, etc.) from “not at all” to “very much so.” The HRQ will administered at admission and following self-administration sessions, to explore general hedonic responses (52).

vi. *Cocaine Selective Severity Assessment (CSSA).* The CSSA will also be administered daily to assess symptoms of acute withdrawal following self-administration until symptoms are no longer reported or study procedures are completed (53). For CUD subject not completing self-administration procedures, the CCSA may be administered daily following admission until no symptoms of withdrawal are reported.

vii. *Assessments of impulsivity and compulsivity.* Subjects will complete a series of standard self-report questionnaires of impulsivity and compulsivity at admission: Barratt Impulsivity Scale (54); Padua Inventory (55); Sensitivity to Reward/Punishment Questionnaire (56), and the UPPS Impulsivity Scale (57). It is expected that these assessments will take approximately one hour to complete in total.

viii. *Additional questionnaires and cognitive testing.* Prior to scanning procedures, subjects will complete additional, standard assessments of depression and anxiety (e.g., Hamilton Rating Scale for Depression (HAM-D) and Hamilton Rating Scale or Anxiety (HAM-A)), as well as a brief series of computerized neurocognitive tests (CogState) in line with on-going research (HIC#1101007933, HIC#1111009365, HIC#2000027842/2000020186) examining relationships between these cognitive and psychological

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factors and mGluR5 availability. It is expected that these additional assessments will take approximately one hour to complete in total.

CUD subjects recruited through similar Yale-approved studies being conducted by the Cocaine Research Clinic (e.g., HIC#2000029552) will have completed assessment items i.-v. as part of the other research program, and will complete assessment items vi.-vii. as part of their participation in this protocol. CUD subjects recruited through the community will complete all assessment items as part of their participation in this protocol, with the exception of items iv. and v. that are not applicable for future CUD subjects (as they will not complete the self-administration procedure). However, existing data collected using these items may be included in future analyses.

HC subjects.

HC subjects that have completed [^{18}F]FPEB PET scanning as part of other Yale approved protocols (HIC#1101007933, HIC#1111009365, HIC#2000027842/2000020186) and have provided written consent to permit sharing of their data from these studies with other Yale approved research programs, and have consented to receive information regarding other research opportunities at Yale, will be contacted to participate in the fMRI portion of this study. Consenting volunteers will have completed the SCID interview (item i. above) as part of the PET research study. Only HC subjects reporting a history of substance use on the SCID will be asked to complete the SSADDA interview (item ii. above). Eligible HC subjects will be asked to complete assessments of impulsivity and compulsivity (item vii. above). Additional HC individuals who have not completed [^{18}F]FPEB PET scanning may be recruited from the community to participate in longitudinal MRI scanning consistent with the goals of Aim 5. These individuals will undergo appropriate screening procedures (that may include remote screening and consenting), self-assessments, and MRI scanning procedures up to 30 days apart.

c. PET imaging of mGluR5 with [^{18}F]FPEB (CUD and HC subjects)

PET scanning sessions will take place at the Yale University PET Center. Subjects will participate in one [^{18}F]FPEB scan. However, in situations where a PET scan is not successful following [^{18}F]FPEB injection (e.g., problems with the PET camera), CUD subjects may be rescheduled to complete an additional PET scan, if possible within the 2-5 day window following inpatient adminission. HC subjects will complete [^{18}F]FPEB PET as part of other Yale approved protocols (HIC#1101007933, HIC#1111009365, HIC#2000027842/2000020186).

The PET scan will be acquired as the subject lies supine on the scanner bed. Venous catheters will be used for intravenous administration of the radiotracer and possibly for additional venous blood sampling. A radial artery catheter may be inserted by an experienced physician before the PET scan to draw arterial blood samples for metabolite analysis and for determination of the fraction of plasma radioactivity unbound to protein. Prior to arterial line placement, the skin will be numbed with a local anesthetic so participants will feel less pain when the catheter is inserted. The goal of the arterial line is to be able to measure absolute physiological functions by mathematically relating the signal (from the PET scanner) to the tracer availability (from the blood). This approach is the gold standard for obtaining quantitative PET data. In some cases, for well-established tracers, methods have been developed and validated that provide comparable results to the gold standard. In those cases, the arterial samples may not be necessary. However, validation of such an approach must be performed in each subject group and for each unique experimental design. In this study, if an arterial line cannot be placed, a second intravenous line may be placed for venous blood sampling.

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PET scans will be performed with the Siemens HRRT. An attenuation correction scan is obtained immediately before or after each emission scan. The PET scan will be acquired using bolus or bolus plus constant infusion administration of up to 5 mCi of [^{18}F]FPEB, followed by up to 120 minutes of dynamic PET data acquisition.

Subjects may be asked to fast (except for water) from midnight until the completion of the test. Vital signs (blood pressure, pulse and respiration) are collected prior to and during the PET scan. Any adverse events will be evaluated and recorded continuously through the PET imaging day. Subjects will be asked to void immediately after each scan is completed to reduce radiation exposure to the bladder.

All scans will be done in the presence of medical supervision and trained staff in an institution specifically designed to support imaging studies in different patient populations.

d. fMRI of resting-state, automatic behavior and response-inhibition (CUD and HC subjects)

Functional and structural MRI data will be acquired using a Siemens Trio TIM 3.0T system at the Yale Magnetic Resonance Research Center. High-resolution structural data will be acquired to facilitate analysis of PET data and may be used in additional analysis of tissue volume and brain structure. Resting-state and task-based functional data will be acquired using multiband echo-planar imaging (EPI) gradient-echo sequences. Diffusion-weighted MRI data will also be acquired using multiband imaging sequences to investigate anatomical connectivity and to inform connectivity-based analyses of functional data. Total scan time will not exceed 1.5 hours.

Resting-state fMRI. Participants will complete up to three 6-min resting-state scans. During this time, they will be presented with a fixation cross to enhance reliability of resting-state network activity (58).

The Habitual and Automatic Behavior and Inhibition Task (HABIT). The HABIT is a modification of the standard Go/NoGo task of response inhibition (39, 59). The modifications include adjustments to the frequency of stimulus presentation, incentivizing performance at times during the task, and switching target stimulus at times during the task in order to examine the neural correlates of automatic responding, and inhibition of automatic, and non-automatic behavior (60-63).

During HABIT performance, participants are instructed to press a button in response to all Go stimuli (e.g., 'X') and withhold responses to NoGo stimuli (e.g., 'K'). Stimuli are presented onscreen for 250-500ms with random inter-trial intervals in order to optimize the analysis of both Go and NoGo events. Task instructions emphasize speed and accuracy equally. At times during the HABIT, participants will be incentivized for their performance (e.g., $0.10 for correct Go responses, and/or $0.25c for successful NoGo inhibition, and/or $-0.10 for failed NoGo inhibition). Task instructions emphasize speed and accuracy equally. Participants will complete up to six runs of up to 6 minutes each, and may earn up to $20 for their performance. Actual achieved earnings during the task are expected to be between $10-20, and no participant will receive less than $5 for task completion, independent of performance (i.e., for subjects earning less than $5 on the task, they will receive the $5 minimum additional compensation).

All scans will be conducted by an MRI technologist, and a member of the research team will accompany the study subject and will stay for the MRI session.

As the PI of this protocol has multiple other HIC approved studies involving neuroimaging, the data from this study may be shared across those protocols. Subjects from this protocol may be recruited for the other protocols run under the PI so their data can be analyzed across studies.

e. Participation timeline

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Eligible CUD subjects recruited through the community will complete the study procedures according to the described timeline, including interviews (day 0 and possibly day 1), self-assessments (possibly day 0 and day 1), and PET and MRI scanning (between day 3 and day 10; depending on scanner availability) (with day 0 indicating a non-consecutive screening appointment to occur at some time prior to CNRU admission on day 1). For CUD participants, CNRU admission will be scheduled at least 1 day (and no more than 5 days) prior to PET/MRI scanning. While community-recruited participants are expected to remain on the unit 5-8 days total, rare occurrences in scheduling may require more flexibility and inpatient stays up to 14 days.

CUD subjects recruited through similar ongoing cocaine studies (e.g., HIC#2000029552) will complete study procedures according to the same timeline. Research-recruited CUD subjects may be discharged from the CNRU according to the procedures and timeline of the referring protocol if additional procedures are to be completed for that study after PET/MRI scanning.

HC subjects recruited through the ongoing [^{18}F]FPEB PET studies (HIC#1101007933, HIC#1111009365, HIC#2000027842/2000020186) will complete interviews and PET scanning as part of participation in those studies. Any additional interviews (e.g. SSADDA) and all self-assessments will be administered following successful PET scanning. HC subjects will complete MRI procedures within a week of PET scanning, or as near the date of PET scanning as equipment availability allows.

f. Pilot addendum: Second PET and fMRI in early abstinence

A pilot sample of CUD participants (up to 10) will be invited to repeat [^{18}F]FPEB PET and fMRI procedures within one month of initial scans (typically 10-20 days). Following completion of primary study procedures described above, CUD participants agreeing to complete the optional scanning procedures will remain on the CNRU until the second PET and fMRI procedures can be successfully completed. Participants may also be asked to repeat additional questionnaires and cognitive testing around the time of scanning procedures. While participants are expected to remain on the unit an additional 10-20 days total, rare occurrences in scheduling may require more flexibility and inpatient stays extended up to approximately one month. Given the current scheduling practices at the Yale PET Center and MRRC, participants will likely be provided information regarding the likely dates of additional scans and thus the approximate duration of the extended stay required to complete the pilot study during the consenting processes. HC subjects (up to 10) will be recruited to participate in the fMRI portion of Aim 5. These community-recruited HC individuals will complete screening procedures (that may include remote interviews and consenting), self-assessments and participate in two MRI scanning session up to 30 days apart as scheduling allows.

5. Genetic Testing: ☒ N/A

6. Subject Population:

CUD subjects. CUD subjects will be 20 experienced, currently-using, non-treatment-seeking, medically-healthy, adult volunteers meeting criteria for cocaine-use disorder (see inclusion/exclusion criteria below; Section I, item 8).

HC subjects. HC subjects will be 20 medically-healthy, adult volunteers that have participated in an [^{18}F]FPEB scan as part of another Yale approved protocol (HIC#1101007933, HIC#1111009365, HIC#2000027842/2000020186), or that are recruited from the community (Aim 5). Subjects will be contacted to participate in the fMRI portion of this study, and may be asked to completed additional assessments and screening procedures (see inclusion/exclusion criteria below; Section I, item 8).

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7. Subject Classification:

☐ 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

Since cocaine dependence often involves serious financial difficulties, it is also possible that some of our subjects may be economically disadvantaged persons. We will carefully screen all participants to make sure that the potential for improvement in their cocaine addiction is the primary motivation for participation. We may enroll females of childbearing potential. All females will be carefully assessed to ensure the absence of pregnancy both before and during study participation.

8. Inclusion/Exclusion Criteria:

Inclusion criteria:

HC and CUD subjects:

- Age 21 - 60 years
- Provide voluntary, written, informed consent
- Physically healthy by medical history, physical, neurological, ECG, and laboratory examinations
- *For females*: non-lactating, no longer of child-bearing potential or agreeing to practice effective contraception during the study (e.g., established use of oral, injected or implanted hormonal methods of contraception; placement of an intrauterine device [IUD] or intrauterine system [IUS]; barrier methods: condom or occlusive cap [diaphragm or cervical/vault caps] with spermicidal foam/gel/film/cream/suppository; male partner sterilization; true abstinence when this is in line with the preferred and usual lifestyle of the subject), and a negative serum pregnancy (β-HCG) test

CUD subjects:

- DSM-5 criteria for moderate or severe cocaine-use disorder
- Positive urine toxicology screen for cocaine

CUD subjects (Pilot addendum):

- Successful completion of primary study procedures
- Provide voluntary, written, informed consent to participate in additional procedures

Exclusion criteria:

HC and CUD subjects:

- Any condition that, in the opinion of investigators, would prevent compliance with the study protocol
- A history of significant medical or neurological illness (e.g., coronary artery disease, significant anemia, seizures)

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- Current use of psychotropic and/or potentially psychoactive medications
- Physical or laboratory (β-HCG) evidence of pregnancy
- Meet any additional PET/MR imaging-related exclusion criteria, including:
  - Presence of MRI incompatible implants and other contraindications for MRI (e.g., pacemaker, artificial joints, non-removable body piercings, etc.)
  - Participation in other research studies involving ionizing radiation within one year of the PET scans that would cause the subject to exceed the yearly dose limits for healthy volunteers
  - History of a bleeding disorder or are currently taking anticoagulants (such as Coumadin, Heparin, Pradaxa, Xarelto).
  - Claustrophobia
  - Severe motor problems that prevent the subject from lying still for PET/MR imaging
  - Complaints of chronic pain (e.g., as the result of rheumatoid arthritis)
  - Current, past or anticipated exposure to radiation in the work place

CUD subjects:

- Other moderate or severe drug use disorder (except for tobacco-use disorder)
- < 1 year of cocaine use disorder
- A DSM-5 major psychiatric diagnosis (schizophrenia, bipolar disorder, etc.) unrelated to cocaine

HC subjects:

- Any DSM-5 major psychiatric diagnosis (schizophrenia, bipolar disorder, etc.), except tobacco-use disorder
- Positive drug screen

9. *How will **eligibility** be determined, and by whom*?

CUD subjects. Potential community-recruited CUD subjects will be initially phone screened by research staff. As part of this screen, subjects will be asked to provide information on medical and psychiatric history, substance use/abuse history, patterns/routes of cocaine use, and whether they are seeking treatment for their cocaine use or not. Potential subjects who pass this phone screening will be scheduled for an in-person screening, which will be done by the study physician, research nurse and/or research coordinator. As part of this screening, subjects will undergo a process of informed consent, including reading the consent form and reviewing it with a study physician and/or trained research staff member. Subjects will receive an explanation of purpose, procedures, benefits, risks, compensation, and alternatives to the study. They will have time to ask any questions and, if interested in participating, will be asked to sign an approved consent form. After providing informed consent for the study, subjects will undergo a physical exam and an informal interview to assess medical, psychiatric, and substance abuse problems, medications, allergies, patterns/routes of cocaine use, and whether they are actively seeking treatment for their cocaine use. They will also undergo a clinician-administered structured interview (i.e., SCID), blood drawing for basic hematologic, chemistry and liver panels, a urine test to detect cocaine and its metabolites, a serum (β-HCG) pregnancy test (if needed) and an electrocardiogram. Information collected during in person screening visits will be discussed by the study physicians, study nurse, research coordinator, and Principal Investigator (who meet on a weekly basis) in order to determine eligibility. CUD subjects recruited through ongoing Cocaine Research Clinic studies (e.g., HIC#2000029552) will have completed this screening process as part of that study, and be invited by study staff to participate in this study.

HC subjects. Subjects that have participated in [^{18}F]FPEB PET as part of other Yale approved protocols (HIC#1101007933, HIC#1111009365, HIC#2000027842/2000020186) will be contacted by research staff to

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participate in the fMRI portion of this study. Additional HC subjects will be recruited through the community. Subjects will undergo a process of informed consent in person or remotely, including reading the consent form and reviewing it with a research staff member. Subjects will receive an explanation of purpose, procedures, benefits, risks, compensation, and alternatives to the study. They will have time to ask any questions and, if interested in participating, will be asked to sign an approved consent form. Subjects from other [^{18}F]FPEB PET studies may be asked to undergo a structured interview (i.e., SCID) to confirm eligibility if this or a comparable assessment was not completed by the referring study.

10. Risks:

a. Risks associated with interviews, questionnaires and neurocognitive testing

The medical and psychiatric interviews, self-report questionnaires, and computerized neurocognitive tests may be stressful, uncomfortable, or tiring for subjects. Unanticipated psychiatric and medical information may be uncovered during evaluation.

b. Risks associated with phlebotomy/intravenous lines

Drawing blood and inserting an intravenous line (IV) are safe and standard medical procedures. Venous sampling may be associated with mild-to-moderate pain or bruising at the puncture site. Bruising and thrombosis can occur during phlebotomy and the placement of the intravenous line. In rare instances poor healing, or infection at the catheter insertion site may occur. Certain individuals may feel light-headed during venipuncture; to avoid injury due to fainting, procedures will be performed when the subjects are seated/recumbent. Blood samples will be drawn for routine labs (up to 60mL) and blood will be taken during each PET scan (up to 120mL).

c. Risks associated with use of an arterial catheter

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

d. Risks associated with MRI

Functional MRI scanning using a 3.0T scanner is non-invasive and has not been associated with any medical risks. However, MRI scanning carries a risk for subjects who are claustrophobic or have pacemakers, metal pieces, aneurysm clips, or any other contraindications for MR. As individuals with contraindications for MR will be excluded, the primary anticipated complication is the experience of claustrophobia during scanning. On rare occasions, some people might feel dizzy, get an upset stomach, have a metallic taste or feel tingling sensations or muscle twitches. Another risk is the possibility of metal objects being pulled into the magnet and striking the subject or heating up during scanning. While the scans performed in this study are not designed for diagnostic purposes, potential abnormalities may be detected by the MR technologist during acquisition, or members of the research team during image analysis.

e. Risks associated with radiation

This research study involves exposure to radiation from [^{18}F]FPEB PET scanning. This radiation exposure is not necessary for medical care and is for research purposes only. The targeted amount of radiation an

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individual subject will receive from participating in Aim 1 of this study is from one injection of ≤ 5mCi (0.57 rem) of [^{18}F]FPEB, plus attenuation correction (i.e., transmission) scans of the brain. Participants that return to complete a second PET scan as part of Aim 5 will receive a second injection of ≤ 5mCi (0.57 rem) of [^{18}F]FPEB, for a total of 1.14 rem.

However, in situations where the PET scan is not successful following injection (e.g., problems with the PET camera) subjects may receive an additional [^{18}F]FPEB injection, if deemed appropriate, for a total of 2 [^{18}F]FPEB injections for those completing Aim 1, and up to 3 [^{18}F]FPEB injections for those subjects also participating in Aim 5.

Although each organ will receive a different dose, the maximum amount of radiation exposure subjects will receive from one scan in this study is equal to an effective dose equivalent of 0.57 rem, for a total of up to 5 mCi of [^{18}F] FPEB in 1 injection, and 1.14 rem from two injections, or two 5 mCi doses (10 mCi total) of [^{18}F] FPEB. This calculated value is used to relate the dose received by each organ to a single value.

In the unexpected case where participants may be asked to undergo an additional PET scan (i.e., if the first or second is not successful), the maximum amount of radiation received from participating in Aim 1 would be 1.14 rem from up to 2 scans (10 mCi of [^{18}F]FPEB total). The maximum amount of radiation for those returning to complete Aim 5 would be 1.71 rem, from up to 3 scans (15 mCi of [^{18}F]FPEB total).

The amount of radiation that subjects will receive in this study is below the dose limit guidelines established by the FDA and monitored by the Yale University Radioactive Drug Research Committee for research subjects.

f. Risks associated with privacy/loss of confidentiality

Since some of the data collected (e.g., history of substance use behavior) is private in nature and may have legal implications, risks related to loss of confidentiality also exist.

g. 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.

i. X-ray to rule out metal

The risk of undergoing an X-ray are minimal as the radiation exposure is low and is no different than an X-ray done as part of routine dentistry or medical screenings.

11. Minimizing Risks:

a. Minimizing risks from interviews, questionnaires, and neurocognitive testing

Subjects will be offered short breaks during and in between interviews, questionnaires, and computerized neurocognitive testing. The staff responsible for the data collection has received training in empathetic/non-judgmental techniques for interviewing, and subjects may discontinue at any time.

b. Minimizing risks from phlebotomy/intravenous lines

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 intravenous catheters will be inserted when the subjects are recumbent. Subjects completing study procedures will have no more than 240mL of blood drawn across study participation (including screening, admission and PET scan), which is less than a standard blood donation (450 mL or roughly a pint). To minimize the risks of blood draws

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and the discomfort associated with it, there will only be one blood draw on the screening visit and blood draws during PET scanning sessions will be obtained from an inserted catheter. Subjects with history of significant anemia will be excluded, and subjects will be asked to abstain from using aspirin, NSAIDS or anticoagulants unless medically necessary (at which point they will be re-assessed for eligibility). Bleeding is minimized by local pressure applied for 5 minutes after the procedure. Infection is avoided by adequate cleansing of the skin prior to venipuncture and by the exclusion of immunocompromised subjects.

c. Minimizing risks from 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 by using local anesthesia. Infection is avoided by adequate cleansing of the skin prior to intravascular line insertion. After arterial catheter removal, bleeding is minimized 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 or 10 hours post PET scan. 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 unless medically necessary. 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.

d. Minimizing risks of MRI

All MRI scanning will be conducted in the presence of experienced research and technical staff. All subjects will be able to terminate the MRI scan at any time for any reason including claustrophobia or discomfort. All subjects will be screened using the Yale MRI Safety Sheet for any metallic objects that they may be holding or have implanted in their bodies and all potential subjects with metallic implants will be excluded. This questionnaire will be repeated prior to imaging to ensure that they are not bringing any metallic materials into close proximity of the magnet, where they might be pulled toward the magnet or heated by the magnet. For additional safety, subjects will be taken through a ferromagnetic metal detector immediately before going to the scan room, and once subjects are in the scanner, the door to the room will be closed. In addition to the MRI operator, a member of the research team will accompany the study subject and will stay for the MRI. All participants may terminate imaging at any time for any reason.

In cases of a possible incidental medical finding, a radiologist will be asked to review the relevant images. Based on his or her recommendation (if any), the principle investigator or consulting physician will contact the subject, inform them of the finding, and recommend that they seek medical advice as a precautionary measure.

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e. Minimizing risks from radiation

The Yale-New Haven Hospital Radiation Safety Committee (Y-NHH RSC) and the Yale University Radiation Safety Committee (YU RSC), will review the use of radiation in this research study, and no subjects will be scanned until approval is obtained. All scans will be done in the presence of medical supervision and nursing staff in an institution specifically designed to support imaging studies. In the event of serious medical complications, the Yale University PET Center facilities have immediate access to, or consultation with, specialized medical units at the Yale-New Haven Hospital. Preparation of radiopharmaceuticals and execution of PET scans will be performed by radiochemists, physicians, and technologists of the Department of Radiology and Biomedical Imaging, Yale University School of Medicine. These professionals are qualified by training and experience in the safe use and handling of radionuclides. 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.

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

f. Minimizing risks related to privacy/loss of confidentiality

Security of subject information is of paramount importance to us. Research personnel will not contact any person or agency without appropriate written release of information. All information collected will be kept in password-protected, HIPAA-compliant computers, secured using the best available methods. Research records will be kept as confidential as possible. Only a code number will identify subject research records. The code number will not be based on any information that could be used to identify subjects (e.g., social security number, initials, birth date, etc.). The master list linking names to code numbers will be kept separately from the research data. This master list, as well as all the other research information, will be kept in locked files at all times. Subjects' identity will not be revealed in any reports or publications resulting from this study. Only authorized persons will have access to the information gathered in this study. As part of the study procedures, some information about subject's participation will become part of their CMHC medical record. If a subject does not already have a medical record at CMHC, one will be made for their visit. Moreover, if a subject has been a patient at CMHC at any time, his or her previous medical records of other visits or admissions will become available to the researchers and to the staff of the CMHC, as part of the screening, or when the information collected for this research is added into their medical record. Information will be stored as per HIPAA guidelines. All staff has been trained in accordance with HIPAA regulations. Information will not be dispensed to anyone outside of this research project, Yale HIC, CMHC, or YNHH HRU without prior written authorization from the subject. If we see or are told that a child is being abused or neglected or that there is a risk of harm to subject or others, we will disclose this information to the proper authorities.

g. Minimizing risks from unanticipated events

Medication might be administered as needed, per the CNRU and Yale PET Center standard operating procedure for medical emergencies, in order to treat any unanticipated events/complications.

12. Data and Safety Monitoring Plan:

a. *What is the investigator's assessment of the overall risk level for subjects participating in this study?*

The overall risk level associated with participating in this protocol is *greater than minimal*.

b. *If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study?*

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Not Applicable.

c. *Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here .*

1. Personnel responsible for the safety review and its frequency

The principal investigator 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 and monitors will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. The principal investigator, IRB/HIC, Y-NHH RSC, and MRRC have the authority to stop or suspend the study or require modifications.

2. The risks associated with the current study are deemed greater than minimal for the following reasons

We do not view the risks associated *with the radiotracer imaging procedure* as minimal risks.

Given the now established safety and validity of the current methods in our prior work, we do not view the proposed studies as high risk.

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 Patrick Worhunsky Ph.D. and Drs. Potenza, Chen or Angarita 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

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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/HIC is necessary.

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

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

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

1. Is unexpected (in terms of nature, specificity, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB-approved protocol and informed consent document and (b) the characteristics of the subject population being studied; AND
2. Is related or possibly related to participation in the research (*possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); AND
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.

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

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

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7. Plan for reporting adverse events to co-investigators on the study as appropriate, the protocol's research monitor(s)

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

- All Co-Investigators listed on the protocol.
- Yale Human Investigations Committee (HIC)
- Yale-New Haven Hospital Radiation Safety Committee (Y-NHH RSC)
- National Institutes of Health

The principal investigator Patrick Worhunsky Ph.D. and Drs. Potenza, Chen or Angarita 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*:

Not Applicable

13. Statistical Considerations:

Standard neuroimaging analysis. Analysis of PET and fMRI data will be performed using standard general linear modeling approaches using regions-of-interest (ROIs) and whole-brain analyses of variance (ANOVAs) in SPM12. ROIs will be defined using the Neuromorphometrics atlas (neuromorphometrics.com) and include basal ganglia structures, subdivisions of the cingulate and other prefrontal and parietal regions that exhibit high [^{18}F]FPEB uptake (64) and are implicated in response inhibition (65). Standard analyses will be performed as the primary investigation of mGluR5 availability in CUD relative to HC, and will support findings from network-based analyses of fMRI and multi-modal fusion techniques.

Network-based analysis. Independent component analyses (ICA) of PET and fMRI data will be performed using the Group ICA of fMRI Toolbox (GIFT; icatb.sourceforge.net). This software package was designed by Dr. Calhoun (co-investigator) and colleagues for functional network analysis of fMRI data, and includes a source-based morphometry (SBM) toolkit for analysis of structural/static biomedical images (66). The principles of ICA for fMRI and PET are largely consistent and have been previously performed in parallel (67, 68)

Multi-modal data fusion. Joint-ICA (jICA), parallel-ICA (pICA) and linked-ICA (lICA) are implementations of the ICA principles to fully integrate, or 'fuse', multiple datasets into a single coherent analysis (69-71). jICA identifies a single set of independent sources (e.g., the same functional brain networks) present in datasets collected in the same individuals under multiple conditions. Thus, jICA is suited to examine activity of functional networks active during *both* resting-state and HABIT performance, and examine changes in network dynamics (i.e., 'connectivity'-like patterns of network-to-network interactions) between conditions, providing advanced insight into the organization of functional systems. By comparison, pICA combines multi-modal data collected in the same individuals, identifying a shared higher-order data structure present in datasets, but that originate from *separate* sources in respective modalities (e.g., receptor-availability networks and functional brain networks. Similar to pICA, lICA combines multiple outcomes from within modality groups (e.g.fMRI group: resting-state and HABIT activity, PET group: V_T and k_1 parameters) toward a more fully integrated fusion analysis.

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Relationships with self-administration and impulsivity. Standard analysis of variance (ANOVA) and linear regression models will be used to examine potential associations between the neuroimaging measures with subjective effects and behavior during cocaine self-administration (e.g., 'high', infusion intervals, doses) collected under and earlier versions of this protocol, and scores on self-report assessments of impulsivity and compulsivity. Additional analysis will explore relationships between neuroimaging measures and self-administration behavior with additional psychological and cognitive factors (e.g., depression, anxiety, neurocognitive performance), which may indicate use of these measures as covariates for primary analyses.

Power considerations. The proposed project will include 20 CUD and 20 HC participants. Prior research of mGluR5 differences in CUD (27), and our work of functional-network differences in addiction-vulnerable populations using the Go/NoGo task (39) indicate this sample will be sufficiently powered (d's>.95) for analysis at a threshold of α=.05 (PET: non-centrality parameter (δ)= 3.60, critical t_{38}=1.81, power (1-β)=0.96; fMRI: δ= 3.06, critical t_{38}=1.54, power (1-β)=0.93). The modified HABIT task is expected to be similarly powered to the Go/NoGo.

Pilot addendum. Standard within-subjects repeated-measures analysis will be conducted to investigate changes in mGluR5 availability and functional network parameters between time points. Mixed effects models will be performed to examine differences in functional brain activity (i.e., fMRI data) and task-performance in CUD relative to HC. While this has not been directly explored previously, prior research examining differences between-subjects suggests a robust change in mGluR5 during the first few weeks of cocaine abstinence [28]. For the current purposes, if hypothesized changes are observed, results will serve as pilot data to estimate effect sizes toward obtaining additional funding.

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

A. RADIOTRACERS ☐ N/A

1. *Name of the radiotracer*: [^{18}F]FPEB

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#59,121 or ☐ RDRC oversight (RDRC approval will be required prior to use)

   This study was previously approved by the YU RDRC (initial approval date: 10/11/17; Aim 5 amendment approval date: 3/1/19). In April 2019 the FDA requested complete [^{18}F]FPEB Chemistry Manufacturing and Controls documentation be submitted for review to support use of [^{18}F]FPEB PET in this study under IND# 59,121. The FDA has reviewed and accepted all documentation (email communication uploaded in IRES IRB) which was subsequently submitted as an amendment to the IND (cover letter uploaded in IRES IRB).. Going forward, FPEB administration is now covered under IND# 59,121.

B. DRUGS/BIOLOGICS ☐ N/A

Cocaine (cocaine hydrochloride), intravenous (IND #59,121; held by: Gustavo A. Angarita , co-investigator)

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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 applicable category that applies.*

   No exemption from IND filing requirements is being requested.

2. Background Information:

   [^{18}F]FPEB:

   The radiotracer [^{18}F]FPEB has previously been used in human subjects; 5 individuals at the Institute for Neurodegenerative Disorders (IND) in New Haven CT, and over 150 individuals and over 200 injections 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.

   The radiation dose estimates are based on the biodistribution data for [^{18}F]FPEB in 6 healthy adults (3 men and 3 women) and calculated using OLINDA/EXM software (72). Based on these numbers, the critical organ is the gallbladder wall (0.191 mGy/MBq, i.e., 0.708 rad/mCi). Another radiation dose study (73) also reported the gallbladder wall (0.193 mGy/MBq, 0.714 rad/mCi) as the critical organ based on the biodistribution data in 9 healthy adults (5 men and 4 women).

   However, (73) reported the urinary bladder wall as the critical organ (0.258 mGy/MBq, 0.955 rad/mCi) when no voiding takes place prior to a 3.5 h period. Thus, the maximum allowable injection doses for [^{18}F]FPEB to remain below the 21 CFR 361.1 dose limits for research subjects are 5.2 mCi per single injection (calculations based upon the urinary bladder wall for a 3.5 h voiding), and 7 mCi per single injection (calculations based upon the gallbladder wall as the critical organs); 3 rads per single study for whole body, active blood forming organs, lens of the eyes and gonads; 5 rads for other organs per single study limit. Additional risks and procedures toward their minimization are detailed above (see Section I, items 10-11).

   .

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

   [^{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.

   a. *Is the drug provided free of charge to subjects?* ☒YES ☐ NO

      If yes, by whom? Supporting research grant(s) (e.g., NIDA) will cover costs of the radiotracer).

4. Storage, Preparation and Use:

   [^{18}F]FPEB:

   Due to the short half-life, PET drugs are prepared *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 8 hours after preparation.

   [^{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) submitted to the FDA (IND# 59121) which was previously approved by the Yale University Radioactive Drug Research Committee (YU RDRC).

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The preparation of sterile PET drug products is validated prior to human use. Sterility is achieved by passing the PET drug product through a 0.22 micron membrane filter during the last step of the formulation process. 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. Due to the short half-life, a sample of the PET drug product is tested for sterility *ex post facto* for further confirmation.

Investigational Drug Service utilized:

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

5. Use of Placebo: ☒ N/A

6. Continuation of Drug Therapy After Study Closure: ☒ N/A

C. DEVICES: ☒ N/A

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: *Give the number of subjects*: 40 completers (20 CUD and 20 HC)

a. *Targeted for enrollment at Yale for this protocol*:

Approximately 40 potential CUD subjects will be enrolled (i.e., sign consent forms) to achieve a target of 20 CUD completers. Up to 25 potential HC subjects will be enrolled (i.e., sign consent forms) to achieve a target of 20 HC completers.

Up to 10 CUD and 10 HC subjects may be invited to complete the pilot addendum procedures. Preliminary analyses will be conducted on an ongoing basis to determine if evidence supports continued data collection or if sufficient data has been collected to support a grant application to continue investigation in a larger sample.

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

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☐ 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	☐ Clinicaltrials.gov
☒ YCCI Recruitment database	☒ Social Media (Twitter/Facebook):	
☐ Other:		

* *Requests for medical records should be made through JDAT as described here.*

3. Recruitment Procedures:

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

Community-recruited CUD and HC subjects will be recruited through the methods listed above (see written material attached to protocol) as well as through word of mouth referrals from other research groups/clinicians at CMHC and/or prior study participants. HIC approved study announcements providing individuals with study contact information may be posted to internet-based community resources (e.g., craigslist.org), on social media (e.g., Facebook), the YCCI recruitment database, and flyers will be posted in the local community. Research-recruited CUD subjects (e.g., from HIC#2000029552) may be invited by study staff or provided contact details in order to inquire about potential participation in this study. Research-recruited HC subjects will have provided consent to be contacted regarding additional research opportunities and will be contacted by study staff to provide information regarding potential participation in this study.

b. Describe how potential subjects are contacted.

Potential community-recruited CUD and HC subjects will be encouraged to contact our study recruitment line for inclusion in our study. Potential research-recruited CUD subjects may be invited to participate by shared research staff or will be given direct phone contact information for study staff. Potential HC subjects will have consented to being contacted by the study staff regarding potential participation.

c. Who is recruiting potential subjects?

A member of our research staff will describe the study to participants who call the recruitment phone line (community-recruited CUD and HC subjects), contact them directly (research-recruited CUD subjects), or are contacted by research staff (research-recruited CUD and HC subjects), answer any questions the potential subjects have and then complete any appropriate phone screening questionnaire to determine the subject's eligibility for an in-person screening visit.

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

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5. Request for waiver of HIPAA authorization:

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*:

ii. *If requesting a waiver of **signed** authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data*:

The initial screening/recruitment information will be collected over the phone and is required prior to the subject being considered for an in-person screening and evaluation appointment. As this screening is done over the phone rather than in person, obtaining signed authorization would be impractical.

6. Process of Consent/Assent:

All subjects will be consented through a multi-step consent process. Subjects are first described the study in detail over the phone during the phone screen. They are then invited to come to the in-person screening appointment or provided the option to complete additional screening and consenting procedures remotely. A trained research staff member will conduct the informed consent process in a private, quiet setting. The research team member and the participant will discuss the basic components described in the consent form. These include: participation is voluntary and participants may withdraw at any time, procedures, visit schedule, risks and benefits, potential compensation, alternatives to study participation, and confidentiality. Potential participants will be provided an opportunity to ask questions and time to consider his/her decision to participate. Anyone who cannot demonstrate appropriate understanding of the study will not be eligible to participate. Those who demonstrate understanding of the study and voluntarily agree to participate will be asked to sign the informed consent form and proceed with the screening assessments. As part of the informed consent procedures, participants will be asked to provide or decline consent to be contacted for future studies. A copy of the signed study consent form will be given to the participant.

7. Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent:

Study staff are trained to assess the subject's understanding of pertinent information given to them and whether or not subjects can appreciate the implications of their decision. Study staff will ask the subject to reiterate the study procedures back to them and will ensure that the subject has had substantial time to ask questions about any/all study procedures. Study staff will also assess the subject's understanding of the study with a 5-item written quiz. Subjects who answer all the questions in the correct way will be able to sign the consent form.

8. Non-English Speaking Subjects:

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There are no plans to recruit or enroll non-English speaking subjects. There are no provisions in the current protocol to accommodate non-English speaking participants (to translate study documents, assessment battery, informed consent form, or other study material into other languages).

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

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.

☐ 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

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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?*

CUD subjects who decide to participate in the study will have a medical record at the Connecticut Mental Health Center (CMHC) and at Yale New Haven Hospital (YNHH). If subjects already have a medical record at CMHC or YNHH, some information about their participation in the study will be included here. If they do not have a medical record at CMHC or YNHH, 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 experiments at the YNHH HRU, date of discharge from the CNRU, X-ray results if required for MRI eligibility, phone number, address, medical history, individual and family history of psychiatric problems, and substance abuse history. One of the instruments used to assess substance abuse history will include questions pertinent to legal problems.

All subjects will be asked to provide their name, date of birth, address, and phone number which will not be used in analyses or presentation of the results. The exact dates of CNRU admission and discharge (CUD subjects only) and exact dates of experiments and procedures will not be used in presentations; however, these dates may be de-identified data (i.e., using coded, subject-specific random identifiers) and used to calculate the time between procedures for use in analyses. All data from medical/psychiatric interviews, urine drug screen results, blood-draws, self-assessments, PET and MRI scans will be collected in the form of de-identified data (i.e., using coded, subject-specific random identifiers) and will be used in analyses and presentations.

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

Research data will be collected over the phone, by paper-pencil and/or electronic self-questionnaires, computerized testing, by interviews, by use of the self-administration paradigm, physical examination, and laboratory work. This information will be recorded/transferred in each subject's Case Report Form and on password protected University computer servers that are kept in locked offices. However, coded data lacking personal identifiers (name, social security #, address, phone, medical record number, etc.) will be kept on other research desktop and/or laptop computers. Imaging data is collected during the PET/fMRI scans by trained technologists and is stored on password-protected and encrypted computers with identifying information carefully in compliance with HIPAA regulations.

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?*

All staff members that come into contact with the data are fully trained to the current HIPAA regulations and are informed as to the proper use of all data. The only ones who have access to this information are the medical personnel and the research staff at the CNRU or at the YNHH HRU. CUD subjects participating in

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research at the CHMC and YHNN HRU will have medical records created for them, if they do not already have such records. The researchers and staff at the CMHC and YHNN/HRU will have access to records of any prior admissions, including the details of those admissions, and some information regarding their participation in this study will be included in those records (e.g., dates of admission/discharge, dates of procedures). All information obtained in this study will be stored in locked cabinets or password protected and encrypted computers and hard drives.

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. Direct identifiers belonging to subjects who withdraw from the study will be stripped from 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.

PET, MRI and assessment data are identified by subject code number rather than name. Users always access research data through the random identifier only. Screening information will remain identified by name. Procedures to protect this PHI have been described above (see Section I, item 11, Section IV, items 2 and 4). After termination of this 5-year study all identifying information will be discarded, but other research data is kept indefinitely. Paper and electronic data will be destroyed by research assistants and study personnel at Yale University following current procedures from the HIC regarding the de-identification, storage, and destruction of records. Private identifiable information will not appear in any publication or be released to anyone without the individual's written consent.

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*.

In accordance with institutional standards and guidelines, after termination of this study and completion of all analysis and publications, all data and screening information will be anonymized and kept in a secure fashion for the purpose of further analyses indefinitely unless prevailing University or Federal guidelines at the time require a change.

6. *If appropriate, has a Certificate of Confidentiality been obtained*?

We have obtained a Certificate of Confidentiality.

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.)*

Subjects will receive a thorough medical and psychiatric evaluation at no cost to themselves, as well as benefit from the knowledge that their participation in such studies may help individuals with cocaine use disorders in the future. It is possible that CUD subjects will experience less cocaine use during the experimental phase of the study. However, it is made clear to subjects that this potential reduction in drug use is not a desired

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outcome for this study. Otherwise, there are no direct benefits to individuals participating in this research. Expanding the current understanding on physiological and biological effects of cocaine use could benefit society in as much as better methods of treatment could be designed.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. Alternatives: *What other alternatives are available to the study subjects outside of the research?*

   As this is not a treatment study, the only alternative is to not participate.

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*.

   Subjects will be compensated for their time commitment and inconveniences for completing the study at standard rates offered by researchers in the Yale community:

Procedure	Group [1]	Amount
Screening interviews/exams (i.e., to determine eligibility)	B, C	$25
Baseline self-reports and cognitive tests	C	$20
Baseline self-reports, cognitive tests, and any repeat exams	B	$25
Additional self-reports, cognitive testing, and exams (pilot addendum)	B	$25
PET scanning		
Arrival and setup (including IV and/or arterial line placement)	B	$50
Injection of radiotracer and/or scan completion [2]	B	$350
MRI scanning		
Arrival and setup	B, C	$15
Scan completion (part or whole) [2]	B, C	$65
Task-performance earnings	B, C	up to $20
Inpatient stay		
Duration of primary study procedures (up to 10 days)	B	$100
Extended duration for pilot addendum (up to 30 days)	B	$200
Travel reimbursement [3]	B, C	

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[1] References corresponding Consent version: B) community-recruited CUD subjects; C) HC subjects.

[2] In cases of technical failures or early termination (either voluntarily or at the discretion of study staff) once procedures have been initiated, subjects will receive full compensation for that procedure

[3] Subjects may be required to provide proof of travel costs to receive reimbursement for travel expenses.

Thus, the total amount of subjects could receive for participating in all relevant study procedures (not including possible travel reimbursements) are:

- *Consent B.* Community- and research- recruited CUD subjects: $650 + $725; up to $1375
- *Consent C.* HC subjects: $245

* NOTE: Consent Forms A and D were related to prior protocol versions and will no longer be used.

Payments will typically be made via a pre-paid debit card in loadable increments after completing individual study procedures using ePayments via Oncore. The debit cards will be provided by the Bank of America and participants will be informed that their name, address, and telephone number will be shared with the bank to order their debit card. Cards may be mailed to subjects or provided in person. Reimbursements may also be made in the form of small cash payments (i.e., for the outpatient appointments) or checks.

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 have no financial responsibilities for any portion of the 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?

   In the event that a participant develops any mental or physical problems as a direct result of being in this study, our staff will be available to help evaluate the problem

   b. Where and from whom may treatment be obtained?

   As noted above (see Section I, item 11) trained medical and research staff will be present or available to provide assistance during study procedures. Medical treatment, or assistance in obtaining medical care through information and referral, will be offered to the subjects for any physical injuries that they receive as a result of participating in this research.

   c. Are there any limits to the treatment being provided?

   For most of the study related sessions there will be trained research staff on hand who have been trained in recognizing medical emergencies and how to activate an emergency response. However, in case of injury, only evaluation and referral to trained medical staff will be provided.

   d. Who will pay for this treatment?

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The participant or his/her insurance carrier will be expected to pay the costs of this treatment. The study will not cover treatment expenses. No additional financial compensation for injury or lost wages is available; however the subject does not waive any of their legal rights.

e. How will the medical treatment be accessed by subjects?

The study will only refer subjects for appropriate treatment. It is the subject's responsibility to access treatment themselves. A follow-up will be completed to ensure the subject sought treatment and if not, why.

IMPORTANT REMINDERS

1. Will this study have a billable service?

   ☐ YES ☒ NO

2. Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities?

   ☐ YES ☒ NO

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REFERENCES

1. Center for Behavioral Health Statistics and Quality (2015): Behavioral health trends in the United States: Results from the 2014 National Survey on Drug Use and Health (HHS Publication No. SMA 15-4927, NSDUH Series H-50).
2. Volkow ND, Baler RD, Goldstein RZ (2011): Addiction: pulling at the neural threads of social behaviors. *Neuron*. 69:599-602.
3. Shorter D, Domingo CB, Kosten TR (2015): Emerging drugs for the treatment of cocaine use disorder: a review of neurobiological targets and pharmacotherapy. *Expert Opinion on Emerging Drugs*. 20:15-29.
4. Carroll K, Onken L (2005): Behavioral therapies for drug abuse. *Am J Psychiatry*. 162:1452-1460.
5. Kalivas PW, Volkow ND (2005): The neural basis of addiction: a pathology of motivation and choice. *Am J Psychiatry*. 162:1403-1413.
6. Volkow ND, Fowler JS, Wang GJ (2003): The addicted human brain: insights from imaging studies. *The Journal of Clinical Investigation*. 111:1444-1451.
7. Everitt BJ, Robbins TW (2015): Neural systems underlying compulsive drug-seeking habits and endophenotypes in addiction. *Annual Review of Psychology*. 67.
8. Volkow ND, Wang GJ, Tomasi D, Baler RD (2013): Unbalanced neuronal circuits in addiction. *Curr Opin Neurobiol*. 23:639-648.
9. Hyman SE, Malenka RC, Nestler EJ (2006): Neural mechanisms of addiction: the role of reward-related learning and memory. *Annual Review of Neuroscience*. 29:565-598.
10. Lüscher C, Malenka RC (2011): Drug-evoked synaptic plasticity in addiction: from molecular changes to circuit remodeling. *Neuron*. 69:650-663.
11. Lee BR, Dong Y (2011): Cocaine-induced metaplasticity in the nucleus accumbens: silent synapse and beyond. *Neuropharmacology*. 61:1060-1069.
12. Hulme SR, Jones OD, Abraham WC (2013): Emerging roles of metaplasticity in behaviour and disease. *Trends in Neurosciences*. 36:353-362.
13. van Huijstee A, Mansvelder H (2013): Glutamatergic synaptic plasticity in the mesocorticolimbic system in addiction. *Front Cell Neurosci*. 8:466-466.
14. Kauer JA, Malenka RC (2007): Synaptic plasticity and addiction. *Nature Reviews Neuroscience*. 8:844-858.
15. Mitrano DA, Smith Y (2007): Comparative analysis of the subcellular and subsynaptic localization of mGluR1a and mGluR5 metabotropic glutamate receptors in the shell and core of the nucleus accumbens in rat and monkey. *Journal of Comparative Neurology*. 500:788-806.
16. Lüscher C, Huber KM (2010): Group 1 mGluR-dependent synaptic long-term depression: mechanisms and implications for circuitry and disease. *Neuron*. 65:445-459.
17. Kalivas PW (2009): The glutamate homeostasis hypothesis of addiction. *Nature Reviews Neuroscience*. 10:561-572.
18. Scofield MD, Kalivas PW (2014): Astrocytic dysfunction and addiction: consequences of impaired glutamate homeostasis. *The Neuroscientist*.1073858413520347.
19. Wolf ME (2010): The Bermuda Triangle of cocaine-induced neuroadaptations. *Trends in Neurosciences*. 33:391-398.
20. Bird MK, Lohmann P, West B, Brown RM, Kirchhoff J, Raymond CR, et al. (2014): The mGlu5 receptor regulates extinction of cocaine-driven behaviours. *Drug Alcohol Depend*. 137:83-89.

APPROVED BY THE YALE UNIVERSITY IRB 3/29/2022

21. Chiamulera C, Epping-Jordan MP, Zocchi A, Marcon C, Cottiny C, Tacconi S, et al. (2001): Reinforcing and locomotor stimulant effects of cocaine are absent in mGluR5 null mutant mice. *Nat Neurosci*. 4:873-874.
22. Kenny PJ, Boutrel B, Gasparini F, Koob GF, Markou A (2005): Metabotropic glutamate 5 receptor blockade may attenuate cocaine self-administration by decreasing brain reward function in rats. *Psychopharmacology*. 179:247-254.
23. Marton TM, Shuler MGH, Worley PF (2015): Homer 1a and mGluR5 phosphorylation in reward-sensitive metaplasticity: A hypothesis of neuronal selection and bidirectional synaptic plasticity. *Brain Res*. 1628:17-28.
24. Bäckström P, Hyytiä P (2006): Ionotropic and metabotropic glutamate receptor antagonism attenuates cue-induced cocaine seeking. *Neuropsychopharmacology*. 31:778-786.
25. Kumaresan V, Yuan M, Yee J, Famous KR, Anderson SM, Schmidt HD, et al. (2009): Metabotropic glutamate receptor 5 (mGluR5) antagonists attenuate cocaine priming-and cue-induced reinstatement of cocaine seeking. *Behavioural Brain Research*. 202:238-244.
26. Cleva RM, Hicks MP, Gass JT, Wischerath KC, Plasters ET, Widholm JJ, et al. (2011): mGluR5 positive allosteric modulation enhances extinction learning following cocaine self-administration. *Behavioral Neuroscience*. 125:10.
27. Martinez D, Slifstein M, Nabulsi N, Grassetti A, Urban NB, Perez A, et al. (2014): Imaging glutamate homeostasis in cocaine addiction with the metabotropic glutamate receptor 5 positron emission tomography radiotracer [11 C] ABP688 and magnetic resonance spectroscopy. *Biol Psychiatry*. 75:165-171.
28. Milella M, Marengo L, Larcher K, Fotros A, Dagher A, Rosa-Neto P, et al. (2014): Limbic system mGluR5 availability in cocaine dependent subjects: A high-resolution PET [11 C] ABP688 study. *NeuroImage*. 98:195-202.
29. Pomierny-Chamiolo L, Miszkiel J, Frankowska M, Pomierny B, Niedzielska E, Smaga I, et al. (2015): Withdrawal from cocaine self-administration and yoked cocaine delivery dysregulates glutamatergic mGlu5 and NMDA receptors in the rat brain. *Neurotoxicity Research*. 27:246-258.
30. Hulka L, Treyer V, Scheidegger M, Preller K, Vonmoos M, Baumgartner M, et al. (2014): Smoking but not cocaine use is associated with lower cerebral metabotropic glutamate receptor 5 density in humans. *Mol Psychiatry*. 19:625-632.
31. Comings DE, Blum K (2000): Reward deficiency syndrome: genetic aspects of behavioral disorders. *Progress in Brain Research*. 126:325-341.
32. Groenewegen HJ, Wright CI, Uylings HB (1997): The anatomical relationships of the prefrontal cortex with limbic structures and the basal ganglia. *Journal of Psychopharmacology*. 11:99-106.
33. Calhoun V, Adali T, Pearlson G, Pekar J (2001): A method for making group inferences from functional MRI data using independent component analysis. *Hum Brain Mapp*. 14:140-151.
34. Smith SM, Fox PT, Miller KL, Glahn DC, Fox PM, Mackay CE, et al. (2009): Correspondence of the brain's functional architecture during activation and rest. *Proceedings of the National Academy of Sciences of the United States of America*. 106:13040-13045.
35. Allen EA, Erhardt EB, Damaraju E, Gruner W, Segall JM, Silva RF, et al. (2011): A baseline for the multivariate comparison of resting-state networks. *Front Syst Neurosci*. 5.
36. Laird AR, Fox PM, Eickhoff SB, Turner JA, Ray KL, McKay DR, et al. (2011): Behavioral interpretations of intrinsic connectivity networks. *J Cogn Neurosci*. 23:4022-4037.
37. Stevens MC, Kiehl KA, Pearlson GD, Calhoun VD (2007): Functional neural networks underlying response inhibition in adolescents and adults. *Behavioural Brain Research*. 181:12-22.

APPROVED BY THE YALE UNIVERSITY IRB 3/29/2022

38. Stevens MC, Kiehl KA, Pearlson GD, Calhoun VD (2009): Brain network dynamics during error commission. *Hum Brain Mapp*. 30:24-37.
39. Worhunsky PD, Dager AD, Meda SA, Khadka S, Stevens MC, Austad CS, et al. (2015): A preliminary prospective study of an escalation in 'maximum daily drinks', fronto-parietal circuitry and impulsivity-related domains in young adult drinkers. *Neuropsychopharmacology*.
40. Everitt BJ, Robbins TW (2016): Drug addiction: updating actions to habits to compulsions ten years on. *Annual Review of Psychology*. 67:23-50.
41. Castelluccio BC, Meda SA, Muska CE, Stevens MC, Pearlson GD (2014): Error processing in current and former cocaine users. *Brain Imaging Behav*. 8:87-96.
42. Kaufman JN, Ross TJ, Stein EA, Garavan H (2003): Cingulate hypoactivity in cocaine users during a GO-NOGO task as revealed by event-related functional magnetic resonance imaging. *J Neurosci*. 23:7839-7843.
43. Cohen-Gilbert JE, Sneider JT, Crowley DJ, Rosso IM, Jensen JE, Silveri MM (2015): Impact of family history of alcoholism on glutamine/glutamate ratio in anterior cingulate cortex in substance-naïve adolescents. *Developmental Cognitive Neuroscience*.
44. Fallgatter A, Ehlis AC, Herrmann M, Hohoff C, Reif A, Freitag C, et al. (2010): DTNBP1 (dysbindin) gene variants modulate prefrontal brain function in schizophrenic patients–support for the glutamate hypothesis of schizophrenias. *Genes, Brain and Behavior*. 9:489-497.
45. Watson TD, Petrakis IL, Edgecombe J, Perrino A, Krystal JH, Mathalon DH (2009): Modulation of the cortical processing of novel and target stimuli by drugs affecting glutamate and GABA neurotransmission. *International Journal of Neuropsychopharmacology*. 12:357-370.
46. Enzi B, Duncan NW, Kaufmann J, Tempelmann C, Wiebking C, Northoff G (2012): Glutamate modulates resting state activity in the perigenual anterior cingulate cortex–a combined fMRI–MRS study. *Neuroscience*. 227:102-109.
47. Calhoun VD, Sui J (2016): Multimodal fusion of brain imaging data: A key to finding the missing link(s) in complex mental illness. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*.
48. First M, Williams J, Karg R, Spitzer R (2015): Structured clinical interview for DSM-5—Research version (SCID-5 for DSM-5, research version; SCID-5-RV). *Arlington: American Psychiatric Association*.
49. Pierucci-Lagha A, Gelernter J, Feinn R, Cubells JF, Pearson D, Pollastri A, et al. (2005): Diagnostic reliability of the Semi-structured Assessment for Drug Dependence and Alcoholism (SSADDA). *Drug Alcohol Depend*. 80:303-312.
50. Miller WR, Del Boca FK (1994): Measurement of drinking behavior using the Form 90 family of instruments. *Journal of Studies on Alcohol, Supplement*.112-118.
51. Kalayasiri R, Sughondhabirom A, Gueorguieva R, Coric V, Lynch WJ, Lappalainen J, et al. (2007): Dopamine β-hydroxylase gene (DβH)-1021C→ T influences self-reported paranoia during cocaine self-administration. *Biol Psychiatry*. 61:1310-1313.
52. O'Brien CP, Gastfriend DR, Forman RF, Schweizer E, Pettinati HM (2011): Long-Term Opioid Blockade and Hedonic Response: Preliminary Data from Two Open-Label Extension Studies with Extended-Release Naltrexone. *The American journal on addictions*. 20:106-112.
53. Kampman KM, Volpicelli JR, McGinnis DE, Alterman AI, Weinrieb RM, D'Angelo L, et al. (1998): Reliability and validity of the cocaine selective severity assessment. *Addict Behav*. 23:449-461.
54. Patton JH, Stanford MS, Barratt ES (1995): Factor structure of the Barratt impulsiveness scale. *Journal of Clinical Psychology*. 51:768-774.

APPROVED BY THE YALE UNIVERSITY IRB 3/29/2022

55. Sanavio E (1988): Obsessions and compulsions: the Padua Inventory. *Behaviour Research and Therapy*. 26:169-177.
56. Torrubia R, Avila C, Moltó J, Caseras X (2001): The Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ) as a measure of Gray's anxiety and impulsivity dimensions. *Pers Individ Dif*. 31:837-862.
57. Whiteside SP, Lynam DR, Miller JD, Reynolds SK (2005): Validation of the UPPS impulsive behaviour scale: a four-factor model of impulsivity. *European Journal of Personality*. 19:559-574.
58. Patriat R, Molloy EK, Meier TB, Kirk GR, Nair VA, Meyerand ME, et al. (2013): The effect of resting condition on resting-state fMRI reliability and consistency: a comparison between resting with eyes open, closed, and fixated. *NeuroImage*. 78:463-473.
59. Kiehl KA, Smith AM, Hare RD, Liddle PF (2000): An event-related potential investigation of response inhibition in schizophrenia and psychopathy. *Biol Psychiatry*. 48:210-221.
60. Anderson BA, Folk CL, Garrison R, Rogers L (2016): Mechanisms of habitual approach: Failure to suppress irrelevant responses evoked by previously reward-associated stimuli. *J Exp Psychol Gen*. 145:796.
61. Cole MW, Braver TS, Meiran N (2017): The task novelty paradox: Flexible control of inflexible neural pathways during rapid instructed task learning. *Neurosci Biobehav Rev*.
62. Criaud M, Longcamp M, Anton J-L, Nazarian B, Roth M, Sescousse G, et al. (2017): Testing the physiological plausibility of conflicting psychological models of response inhibition: A forward inference fMRI study. *Behavioural Brain Research*. 333:192-202.
63. Eryilmaz H, Rodriguez-Thompson A, Tanner AS, Giegold M, Huntington FC, Roffman JL (2017): Neural determinants of human goal-directed vs. habitual action control and their relation to trait motivation. *Sci Rep*. 7.
64. Park E, Sullivan JM, Planeta B, Gallezot J-D, Lim K, Lin S-F, et al. (2015): Test–retest reproducibility of the metabotropic glutamate receptor 5 ligand [18F] FPEB with bolus plus constant infusion in humans. *European Journal of Nuclear Medicine and Molecular Imaging*. 42:1530-1541.
65. Wright L, Lipszyc J, Dupuis A, Thayapararajah SW, Schachar R (2014): Response inhibition and psychopathology: A meta-analysis of go/no-go task performance. *Journal of Abnormal Psychology*. 123:429.
66. Xu L, Groth KM, Pearlson G, Schretlen DJ, Calhoun VD (2009): Source-based morphometry: The use of independent component analysis to identify gray matter differences with application to schizophrenia. *Hum Brain Mapp*. 30:711-724.
67. Di X, Biswal, Alzheimer's Disease Neuroimaging Initiative BB (2012): Metabolic brain covariant networks as revealed by FDG-PET with reference to resting-state fMRI networks. *Brain connectivity*. 2:275-283.
68. Shaffer JL, Petrella JR, Sheldon FC, Choudhury KR, Calhoun VD, Coleman RE, et al. (2013): Predicting cognitive decline in subjects at risk for Alzheimer disease by using combined cerebrospinal fluid, MR imaging, and PET biomarkers. *Radiology*. 266:583-591.
69. Calhoun VD, Liu J, Adali T (2009): A review of group ICA for fMRI data and ICA for joint inference of imaging, genetic, and ERP data. *NeuroImage*. 45:S163-172.
70. Groves AR, Beckmann CF, Smith SM, Woolrich MW (2011): Linked independent component analysis for multimodal data fusion. *Neuroimage*. 54:2198-2217.
71. Liu J, Chen J, Calhoun VD (2015): Parallel group ICA for multimodal biomedical data analyses. *IEEE International Symposium on Biomedical Imaging: Bioinformatics and Biomedicine*: IEEE, pp 1084-1091.

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72. Wong DF, Waterhouse R, Kuwabara H, Kim J, Brašić JR, Chamroonrat W, et al. (2013): 18F-FPEB, a PET radiopharmaceutical for quantifying metabotropic glutamate 5 receptors: a first-in-human study of radiochemical safety, biokinetics, and radiation dosimetry. *J Nucl Med*. 54:388-396.
73. Kessler RM, Seibyl J, Cowan RL, Zald D, Young JS, Ansari MS, et al. (2014): Radiation dosimetry of 18F-FPEB in humans. *J Nucl Med*. 55:1119-1121.

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