IRB# 2000025618

HRP-503B – BIOMEDICAL RESEARCH PROTOCOL
(2017-1)

Protocol Title: Neurofeedback in individuals with substance use disorders

Principal Investigator: Kathleen Garrison
Co-investigators: Sarah Yip, Dustin Scheinost (MPI)

Version Date: 10-03-22

(*If applicable***) Clinicaltrials.gov Registration #:** NCT04188288

INSTRUCTIONS

This template is intended to help investigators prepare a protocol that includes all of the necessary information needed by the IRB to determine whether a study meets approval criteria.
Read the following instructions before proceeding:

1. Use this protocol template for a PI initiated study that includes direct interactions with research subjects. Additional templates for other types of research protocols are available in the system Library.

2. If a section or question does not apply to your research study, type "Not Applicable" underneath.

3. Once completed, upload your protocol in the "Basic Information" screen in IRES IRB system.

APPROVED BY THE YALE UNIVERSITY IRB 10/11/2022

SECTION I: RESEARCH PLAN

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

Methadone is a widely used and mostly effective medication for opioid-use disorder (OUD), yet low-level opioid use remains common in some methadone-treated individuals. Further, very little is known about the functional neurobiology of individuals treated with methadone, particularly at the level of neural network connectivity[1]. Improved neurobiological understanding of treatment-refractory populations (i.e. individuals continuing to use opioids during methadone treatment) is an essential step toward **(i)** identifying individual characteristics that contribute to opioid relapse and **(ii)** ultimately developing effective adjunct interventions to improve outcomes. This application leverages recent advances in neurofeedback to assess functional connectivity dynamics among methadone-treated individuals with continued opioid use.

Real-time functional magnetic resonance imaging (rt-fMRI) is a powerful tool for measuring both patterns of neural activity and individual abilities to modify said activity. Rt-fMRI may be used to elucidate brain mechanisms related to cognitive processes including those implicated in addictions such as OUD[2-4]. In addition, rt-fMRI neurofeedback is emerging as a non-invasive, non-pharmacological therapeutic tool that enables an individual to learn to modulate their neural activity in order to effect behavioral change. However, previous efforts to reduce clinical symptoms via rt-fMRI neurofeedback—i.e. to link brain training with clinical outcomes, including in addiction—have had only limited success[5].

With one exception[6], all prior rt-fMRI studies in addiction used feedback derived solely from one or two brain regions. However, machine learning and meta-analytic data indicate that many behaviors, including substance-use, rely on the orchestrated activity of a distributed array of regions[7-12]. The best feedback signal therefore is not likely to be the magnitude of activity in a single brain region, but rather the degree to which activity is coordinated across large-scale brain networks. Consistent with this, our recently developed approach—connectome-based neurofeedback—provides a translational framework for assessing dynamic control of complex neural networks, but has not yet been applied to study addictions. This recently developed approach is extremely novel as it **(i)** provides a translational pathway to directly target previously validated brain-behavior models based on functional connectivity, and **(ii)** vastly increases the scale of prior addiction rt-fMRI work from feedback based on one or two brain regions to feedback based on hundreds of individual connections between hundreds of brain regions.

We will utilize connectome-based neurofeedback to assess patterns of functional connectivity within a previously identified "opioid abstinence network". This network was identified using a whole-brain machine learning approach and predicted subsequent opioid relapse among methadone-maintained individuals. This network was robust, relatively unchanged in follow-up analyses controlling for other clinical variables (e.g., methadone dose, years of opioid use), predicted opioid relapse from different fMRI tasks as well as resting state, and predicted opioid use at multiple time points (two scanning sessions conducted 3 months apart). Design: Individuals on methadone (N=24) will receive active (n=24) connectome-based neurofeedback at 3 weekly scanning sessions (training scans 1-3). Training scans will include both feedback and transfer (i.e. no feedback) runs. Baseline (one week prior to training scan 1) and follow-up (one week following training scan 3) scans will be conducted to test the effects of feedback training on intrinsic connectivity during resting state and fMRI tasks, as in our pilot data. Clinical features of OUD (opioid use, craving, negative affect) will be assessed weekly and at one month follow-up.

Aim 1. To determine if connectome-based neurofeedback is associated with reduced opioid use. *Aim 1a.* We predict that individuals who receive active feedback will report lower

levels of opioid use from baseline to follow-up scans. *Aim 1b.* We predict that this reduction will persist over time as assessed at 1-month follow-up.

Aim 2. To determine if connectome-based neurofeedback is associated with changes in intrinsic connectivity. *Aim 2a.* Based on evidence that neurofeedback induces changes in intrinsic connectivity[13], we predict that subjects receiving active feedback will show increased opioid abstinence network connectivity during resting state at follow-up versus baseline scans. *Aim 2b.* We predict that this effect will generalize to increased connectivity during fMRI reward and cognitive tasks at these timepoints.

Aim 3. To determine if connectome-based neurofeedback is associated with greater improvements in clinical features of opioid use disorder than sham feedback. *Aim 3a*. We predict that subjects who receive active feedback will show reduced craving and negative affect at follow-up versus baseline scans. *Aim 3b.* We predict that increased opioid abstinence network connectivity during transfer (no feedback) runs will be correlated with reduced craving and negative affect.

*This proposal is significant by **testing for the first time the effects of neurofeedback on large-scale network dynamics among individuals with opioid use disorder.** This is a critical step toward understanding the neurobiology of opioid relapse and will pave the way for further treatment-oriented research.*

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

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

Need to understand brain functions in methadone treated individuals: Opioid use disorder (OUD) is a significant public health problem with opioid-associated overdoses and deaths rising significantly in recent years[14-16]. Methadone is a widely used and generally effective treatment for OUD, yet relapse rates remain high and treatment retention durations are suboptimal (e.g., <6 months in 30-50% of settings)[17-19]. As risk of overdose is highest following unsuccessful treatment (i.e., during a relapse)[20], improved mechanistic understanding of factors contributing to relapse in methadone patients is urgently needed to inform development of adjunct interventions to improve outcomes. We will leverage recent advances in connectome-based neurofeedback to probe large-scale patterns of brain functional connectivity previously linked to relapse among methadone-treated individuals with OUD. This is critical to improve our understanding of mechanisms contributing to relapse and an essential first step toward development of improved, evidence-based relapse prevention strategies.

Importance of systems-level assessment: Recovery from addiction involves complex interactions across biological and clinical domains[21]. Investigation of the functional organization of the brain through connectivity analysis ('connectomics') has provided novel insights into brain-behavior relationships in healthy controls[22-29] but have only recently been introduced to addictions research[10]. Connectome-based approaches enable characterization of complex neural networks at the whole-brain level in a data-driven manner[30, 31]. Such systems-level analyses are particularly well-suited for assessment of multifaceted clinical phenomena (*e.g.*, relapse to opioids) which likely act across spatially distinct—yet functionally coherent—brain regions, and are statistically more robust than traditional approaches[30, 32].

Clinical relevance of predictive models: A challenge facing neuroimaging of addictions is the

effective translation of research into real-world clinical settings[33]. Despite significant advances, brain-behavior studies too often rely on prospective associations, and the term 'predict' is sometimes inaccurately used to describe correlation. True predictive models require cross-validation[31, 34, 35] and such models are necessary to translate fMRI findings into tools with clinical utility. Connectome-based predictive modeling (CPM) is a machine learning method of identifying and cross-validating brain networks that subserve specific behaviors (e.g., opioid-use), that has been successfully used to predict a range of complex behaviors; e.g., attention, IQ and cocaine abstinence[10, 11, 30]. Our recent CPM work identified a network that predicted opioid relapse among methadone-maintained individuals with OUD. This "opioid abstinence network" was robust and predicted subsequent opioid use across different brain states (i.e., during task and resting state) and at two time points (Yip et al., In Prep).

Connectome-based neurofeedback can be used to target clinically-relevant brain networks: Both connectome-based models of behavior and real-time fMRI (rt-fMRI) feedback are novel techniques at the cutting-edge of neuroimaging methodology. Functional connectivity patterns are unique to each individual and contain information about each individual's behavior, such that generalizable models can be constructed to predict behavior in novel subjects—for example, as implemented using CPM. Rt-fMRI is a non-invasive, non-pharmacological tool that enables an individual to learn to modulate their brain activity. It thus enables concurrent assessment of brain activation patterns related to specific functions, and of individual abilities to regulate such functions. However, prior rt-fMRI research in addictions and other disorders have not focused on functional connectivity, but have primarily provided feedback based on activation patterns in a single brain region. In contrast, connectome-based neurofeedback is based on network-level patterns of functional connectivity. Predictive brain networks can then be targeted in an individual using rt-fMRI neurofeedback to modify brain dynamics. *To improve understanding of mechanisms of opioid relapse, this project will use connectome-based neurofeedback to target the previously identified opioid abstinence network.*

Rt-fMRI in addiction: Rt-fMRI is a powerful method for individualized assessment of patterns of brain functions and of individual abilities to regulate such functions, yet most studies fail to demonstrate clinical benefits[36]. Most rt-fMRI studies in addiction have focused on drug cue-reactivity and craving, typically providing feedback as mean activation in a brain region of interest (ROI). Most of this work has focused on smoking. Studies have shown that smokers are able to reduce cue-reactivity in targeted brain regions and reduce subjective craving[37, 38], yet only one study has used a control group[37] and none have measured effects on smoking. More recent work suggests that including functional connectivity in the feedback signal leads to greater reduction of nicotine craving compared with ROI feedback alone[6]. Preliminary evidence exist that individuals with alcohol use disorder can learn to modulate brain activity during alcohol cue exposure[39, 40] including transfer to a no feedback run[40]. Yet, no prior study has applied rt-fMRI feedback to assess neural network function among individuals with OUD. More advanced rt-fMRI methods may lead to more clinically meaningful outcomes. In particular, providing feedback from functional connectivity rather than ROI activation may be more clinically relevant[41]. Machine learning and meta-analytic data indicate that many behaviors including substance use rely on the orchestrated activity of a distributed array of brain regions[7-12]. Therefore, the best feedback signal is not likely to be the magnitude of activity in a single brain region, but the degree to which activity is coordinated across large-scale brain networks. Accordingly, feedback from functional connectivity has become the focus of studies examining connections (edges) between pairs of nodes or networks[42-44] and recent data indicate utility of this approach in addictions[6]. Moreover, most predictive brain models of behavior utilize connectivity derived from hundreds of regions and thousands of edges, rather than a single edge[10, 11, 30, 31, 45]. To realize its promise, rt-fMRI in addiction must provide feedback based

on complex large-scale brain networks—e.g., empirically defined networks derived from whole-brain machine learning methods such as the opioid abstinence network.

Table 1: **Study overview**	Baseline	Training 1-3	Follow-up	1 mo.
Resting state fMRI	X	X	X	
Rt-fMRI Training runs		X		
Rt-fMRI Transfer runs	X	X	X	
Task fMRI (MIDT, Stroop)	X		X	
Behavioral (craving, affect)	X	X	X	X

Connectome-based predictive modeling (CPM): We have developed and applied CPM to predict complex behavioral phenotypes in healthy and clinical populations[11, 12, 30, 45-47] including methadone populations[10]. CPM is a data-driven method for generating predictive models of brain-behavior relationships from functional connectivity matrices using cross-validation[11, 30, 31, 45], developed by members of the investigative team (MPI Scheinost). This approach has been validated in several studies[e.g.,[11, 30, 45]]. CPM is composed of the following steps: (1) edge selection, in which linear regression is used to relate each edge (correlations between node pairs in the matrix) in the connectome to a behavioral variable of interest (e.g., opioid use) in the training dataset; (2) edge summarization, in which weights of edges identified in Step 1 are summed to create a single summary value for each subject; (3) model building, in which summary scores (the independent variable) are linearly related to the behavioral variable (the dependent variable); (4) model application, in which resultant coefficients from Step 3 are applied to novel connectomes in the testing dataset to generate behavioral predictions; and (5) model evaluation, in which the predictive ability of the CPM is evaluated using either mean squared error or the correlation between predicted and observed behavioral values. Testing models on independent samples ensures that models do not over-fit a specific dataset; rather they generalize and will likely replicate in future work[e.g.,[11, 30, 45]]. We previously used CPM to predict cocaine abstinence during a 12-week treatment using task data from individuals scanned prior to treatment for cocaine-use[10]. CPM successfully predicted abstinence during treatment (% negative urines) (p=0.002). To determine the generalizability of our findings, we tested the ability of the identified networks to predict cocaine-negative urine toxicology outcomes in a separate, heterogeneous sample of cocaine-dependent individuals (n=45). Network strength in this independent sample also predicted abstinence during treatment (p=0.016)[10]. More recently, we have used CPM to identify a neural network predictive of opioid use among individuals receiving methadone for OUD (Yip et al., In Prep). As with the cocaine network, this network was robust and was not significantly altered in follow-up analyses controlling for other baseline clinical variables including past-month opioid-use or methadone dose. Further consistent with prior CPM work[10, 11, 30, 45], the opioid network was complex and composed of multiple adjacent and nonadjacent nodes with varying degrees of connectivity (i.e., high- versus low-degree nodes). *These data demonstrate the ability of CPM to identify complex neural networks subserving specific addiction outcomes that replicate in independent samples.*

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

Study design: Participants will receive active (*n*=24) connectome-based feedback at three separate scanning sessions (training scans 1-3). . Training scans will include both neurofeedback and transfer (i.e., no feedback) runs conducted at weekly intervals (**Table 1**).

U-Tox	X	X	X	X
TLFB for substance use	X	X	X	X

Additionally, to test the effects of feedback training on intrinsic connectivity, baseline (one week prior to training scan 1) and follow-up (one week following training scan 3) scans will be conducted and will include resting state and reward and cognitive task fMRI runs, to compare networks across brain states as in our prior work[49].

Screening visit: To determine eligibility subjects will first take part in a screening visit involving surveys about their health, smoking, substance use behaviors and attitudes, and the ways in which they view themselves. They will also complete a urine drug test. The screening session will take about 1 and ½ hours. If they are eligible, we will also schedule their MRI appointments during this visit.

Debriefing: At the end of the one month study visit, participants will be fully debriefed by study personnel, who will explain more thoroughly the purpose of the study and answer any questions they may have.

Opioid use: Opioid and other substance use will be monitored weekly at each MRI session from baseline to follow-up using urinalysis and the Timeline Followback (TLFB) [50] method, as in our prior work[10, 48]. Behavioral measures of clinical variables (e.g., pain, other substance use, craving and negative affect) will also be collected.

Imaging Protocol: Scanning will be conducted 2-3 hours following daily methadone on a 3T Siemens Prisma scanner with a 32-channel head coil. A member of the research staff will accompany each subject to the MRRC and stay with them for the duration of the study.
Baseline and follow-up scans: Will include resting state (10 min), cognitive task (Stroop[51, 52]; 10 min), reward task (monetary incentive delay[48, 53, 54]; 10 min), and a transfer task (5 min; see below); collected using a T2* sensitive gradient-recalled single shot echo planar pulse sequence. A high-resolution T1-weighted 3D anatomical scan will be acquired at the baseline scan using a magnetization prepared rapid gradient echo sequence.
Training scans: Subjects will perform five 5-minute runs of active neurofeedback and a 5-minute transfer run before and after the feedback runs. Table 1 summarizes data collection. fMRI data will not be multiband due to the need to reconstruct and process data in real-time.
Other measures: Participants will be given self-report measures of general intellectual function (Shipley Institute of Living Scale[55]), impulsivity (UPPS impulsive behavior scale[56]), negative affect (Quick Inventory of Depressive Symptomatology[57]), craving (Opioid Craving Scale[58]) and withdrawal (Clinical Opiate Withdrawal Scale[59]). As previously noted, these measures may be collected in-person but in an effort to reduce the amount of time participants are physically present at the MRRC we will perform this data collection remotely whenever possible.

Imaging parameters: MRI data will be collected with a 3T Siemens Primsa system and 32-channel head coil. Functional runs will be acquired using an EPI sequence with the following parameters: TR = 2000 ms, TE = 25 ms, flip angle = 90°, acquisition matrix = 64 × 64, in-plane resolution = 3.5 mm2, 34 axial-oblique slices parallel to the AC-PC line, slice thickness = 4. Parameters of the anatomical MPRAGE sequence were as follows: TR = 1900 ms, TE = 2.52, flip angle = 9°, acquisition matrix = 256 × 256, in-plane resolution = 1.0 mm2, slice thickness = 1.0 mm, 176 sagittal slices. A 2D T1-weighted image coplanar to the functional images was collected for registration.

Connectome-based neurofeedback uses a similar approach to CPM (described above) but summarizes connectivity for a previously defined predictive network, here calculated in real time and used to construct a feedback signal (**Fig 1**).

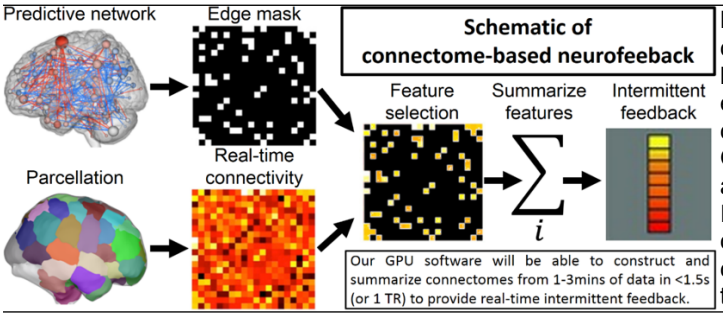

Fig. 1: Connectome-based neurofeedback: A parcellation used to calculate a connectivity matrix and one or more networks that predict behavior are the inputs. The predictive network(s) defines which edges are used to provide feedback. A connectivity matrix is calculated over a discrete block of data (~1-3 minutes) in real time. Once calculated, the predictive edges are selected from the matrix and summarized into a single network summary score per network. Intermittent feedback is then provided to the subject based on a combination of these network summary scores. The total time from collecting the last volume in the data block to displaying feedback to the subject will be under 1.5 sec (or 1 TR of conventional data).

This approach requires two inputs: a parcellation to calculate a connectivity matrix, and networks (i.e., a collection of edges or elements in the connectivity matrix) to summarize connectivity. The parcellation/networks can be as simple as two ROIs and the single connection between them or can be ~300-400 node parcellations with multiple networks composed of hundreds of edges. When using inputs based on CPM, the parcellation will typically contain ~300 nodes and the positive and negative components will include ~500 edges each. Connectivity will be calculated using 30s blocks of fMRI data collected in real-time. Unlike other approaches using sliding window correlations or continuous feedback [42, 43] the blocks of data will be non-overlapping and feedback will be intermittent. This approach reduces noise in the feedback signal, allows adequate time to calculate the feedback score, and reduces cognitive and attentional load and potential distraction of evaluating continuous feedback[60]. After a matrix is computed, edges will be summarized to a single number reflecting the strength of connectivity in the opioid abstinence network.

Processing pipeline: Data will be motion corrected with our validated rt-fMRI motion correction algorithm[61]. Data cleaning will include linear and quadratic drift removal; regression of cerebrospinal fluid, white matter and global signals; calculation and removal of a 24-parameter motion model (6 motion parameters, 6 temporal derivatives and their squares)[62]; motion censoring[63]; and low-pass filtering via temporal smoothing with a Gaussian filter. Connectivity will be calculated using Pearson correlation. As connectivity is very sensitive to head motion[64], we include two types of motion censoring to remove confounding effects of motion on connectivity and the resulting feedback signal. For each frame, we will calculate the frame-to-frame displacement as defined in[64]. Frames with motion >0.15mm and the two frames immediately before and after (to account for temporal smoothing) will be excluded. We will also censor whole blocks of feedback if a large number of frames (*e.g.*, 10%) have been censored. These features minimize the likelihood of subjects receiving feedback mainly reflecting motion artifacts. After calculating connectivity for all predefined nodes, edge strength for all connections in the predefined network will be summarized in the same manner as Step 2 in CPM (**see Connectome-based predictive modeling**, above)[31]. The feedback signal will be the overall strength of the opioid abstinence network. For data harmonization, imaging data collected at baseline and follow-up scans will be processed (off-line) in the same manner as the neurofeedback data.

Neurofeedback and transfer runs: Feedback and transfer runs will consist of 30 sec blocks during which subjects try to increase connectivity in the opioid abstinence network. During feedback runs, subjects in the active feedback group will be given feedback as the difference between positive and negative edges: $\text{feedback} = \sum_{edges} r(positive\ edges) - \sum_{edges} r(negative\ edges)$. Feedback will be presented as a bar graph with hot colors for positive differences and cool colors for negative differences (similar to **Fig 1**). Subjects will be instructed to increase the feedback bar (*i.e.* increase overall network strength), as indicated by a green arrow pointing up for 30 sec, and feedback will be presented intermittently

for 10 seconds. We will use implicit feedback, in which subjects are kept unaware of the purpose of feedback, in order to more confidently attribute changes in behavior to modification of brain network dynamics by minimizing the use of explicit cognitive strategies and instead focusing on targeted neural processing[41]. This also avoids complicated instructions, reducing potential experimenter effects. Implicit feedback has been found to be robust and may be advantageous over explicit feedback[41]. The instructions will be, "Try methods that you have found to help you not use opioids or cope with craving in the past. The main thing is to try different strategies and see what works the best for you." Participants will be debriefed after each scan to ask whether they felt that they could control the feedback, and what strategies they used to try to control the feedback. This approach has been used previously including in our own work. [2-6] Transfer runs will be used to test control of the opioid abstinence network without feedback and will be exactly the same as feedback runs with the exception that a fixation cross will be displayed instead of the feedback bar. Subjects will be shown the same arrow cues and given the same instructions to increase the feedback bar.

Hypothesis testing: Network connectivity strength assessed at each scanning session will be entered into SPSS to test the following Specific Aims:
Aim 1: *To determine if connectome-based neurofeedback is associated with reduced opioid use compared with sham feedback. H1a.* Subjects receiving active versus sham feedback will report lower levels of opioid use from baseline to follow-up scans. *H1b.* This reduction will persist over time, as indicated by reduced opioid use through 1-mo follow-up.
Approach: Opioid use will be monitored by weekly urinalysis and TLFB across the five weeks from baseline to follow-up scans and measured as % negative urines (H1a); or will be measured using TLFB at 1-mo follow-up with abstinence at 1-mo confirmed by urinalysis (H1b). Medication compliance will be tracked via clinic records. Opioid use will be entered into a linear effects model with the between-subject factor of feedback group (active/sham).
Aim 2: *To determine if connectome-based neurofeedback is associated with changes in intrinsic connectivity. H2a.* Subjects receiving active versus sham feedback will show increased opioid abstinence network connectivity between resting state acquired at follow-up versus baseline scans. *H2b.* This effect will generalize to increased connectivity during fMRI reward and cognitive tasks as in our pilot data.
Approach: Opioid abstinence network connectivity strength will be calculated during resting state (H2a), MIDT and Stroop tasks (H2b) as in our pilot data, and will be entered into a linear mixed effects model with the between-subject factor of feedback group (active/sham) and the within-subject factor of time (baseline/follow-up scans).
Aim 3: *To determine if connectome-based neurofeedback is associated with greater improvements in clinical features of OUD than sham feedback. H3a.* Subjects receiving active versus sham feedback will show reduced craving and negative affect at follow-up versus baseline scans. *H3b.* Increased opioid abstinence network connectivity during transfer runs will be correlated with reduced craving and negative affect.
Approach: Craving (Opioid Craving Scale) and negative affect (Quick Inventory of Depressive Symptomatology) will be calculated at follow-up and baseline scans and compared between groups using repeated measures analysis of variance. Change in opioid abstinence network connectivity strength will be calculated during transfer runs at baseline and follow-up scans. We will test for Pearson's correlations between change in connectivity strength and changes in craving and negative affect.

5. Genetic Testing N/A ☒

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

Write here

We plan to enroll twenty-four individuals (12 male, 12 female) receiving methadone for OUD. Eligibility criteria: (i) non-methadone opioid positive urine screen (as assessed during standard treatment at APT) or indicated via Utox or self-reported past-month opioid use at screening); (ii) DSM-5 criteria for OUD, as assessed via structured clinical interview (SCID)[66]; (iii) ≥3 months of methadone treatment; (iv) eligibility for MRI; (v) age 18-50; (vi) baseline scanning with acceptable motion (i.e., <.15mm frame-to-frame displacement), as in prior work. Retention: APT patients attend clinic on a daily basis to receive methadone and this has contributed to high retention rates (e.g., 86% over three months) in our studies[10, 67] in this population.

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

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

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects?

Yes ☐ No ☒

8. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion?

Write here

i. Inclusion criteria
   1. non-methadone opioid positive urine screen (as assessed during standard treatment at APT) or indicated via Utox or self-reported past-month opioid use at screening
   2. DSM-5 criteria for opioid use disorder, as assessed via structured clinical interview (SCID)
   3. ≥3 months of methadone treatment
   4. Age 18 to 50

ii. Exclusion criteria
   1. Meet DSM-5 psychiatric classifications for lifetime schizophrenia or bipolar disorder with psychotic features, or exhibit significant current suicidal or homicidal plans and intent such that hospitalization is required
   2. Failure to pass an MRI screening
   3. Women who are pregnant or nursing
   4. Baseline scanning with excessive motion based on frame-to-frame displacement

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

Participants will be recruited via clinician referrals from the APT Foundation, one of the largest methadone providers in CT, consistent with our prior[10, 48] and ongoing work. In

addition to regular attendance for methadone, APT patients meet regularly with clinicians, as per federal guidelines. As Dr. Barry (Co-I) is Director of Research for the APT, he is ideally suited to facilitate participant referral and longitudinal clinical assessment for this study.

Individuals will be informed about the study by their clinician at their regular APT clinic visits and provided with verbal information and brochures containing project information. Interested individuals will contact the study team and set up a screening visit. At the screening visit, eligibility will be determined by members of the research team.

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

i. Potential risks: This protocol presents minimal risks to subjects. Possible risks include:
   1. Magnetic resonance imaging: MRI is a non-invasive procedure with minimum anticipated discomfort and a safety screening process. Prior studies have not found any adverse effects of MRI. The possible risks and discomforts of MRI are as follows:
      a. Claustrophobia
      b. Acoustic noise
      c. Metal implants are a risk within the magnetic MRI environment
      d. Discomfort lying in the MRI scanner
      e. Very slight warming of the body, tingling or involuntary muscle twitches
      f. Unknown risk to a fetus
   2. Behavioral assessments: These are all non-invasive and should add no risk. The major disadvantage will be the time taken to complete the questionnaires. Our past experience with these and related measures indicates that they are acceptable to subjects including individuals with substance use disorders.
   3. Urine toxicology test and its result: This is non-invasive and should add no risk. Our past experience indicates that urine screens are acceptable to subjects including individuals with substance use disorders.
   4. Limits to confidentiality: All participants will be specifically told that we will not reveal any personal information collected as part of the research procedures, including their reported substance use. However, there is always the possibility that participation in this study may make others, such as friends and family members, aware of their information. They will be told that if they do not feel comfortable with this, then they should not participate. They will additionally be told that if they report any information to us about abuse or homicidal or suicidal behavior, we will be required to report this information to the appropriate authorities. They will also be informed that their de-identified data will be shared with NIH.

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

All procedures will be approved by the Yale IRB. All procedures will follow applicable HIPAA regulations to ensure the protection of participant's information. All investigators and staff have completed training in the ethical conduct of research with human subjects.

i. Overall risks: Risks will be reduced in the following ways:
   1. Obtaining informed consent.
   2. Using well-defined inclusion/exclusion criteria and MRI screening to rule out pre-existing medical conditions.

3. Using study staff who have extensive expertise conducting neuroimaging research and working with individuals with substance use disorders and who are sensitive to the issues that may arise.
4. Protecting right to privacy through coding of data and proper storage of research records.
5. Obtaining an NIH certificate of confidentiality to further protect the research records of these participants.

ii. Magnetic resonance imaging: To minimize risk associated with MRI, participants will be required to pass an MRI safety screening and pass through a metal detector immediately prior to scanning. They will be sensitized to the MRI environment in a mock scanner prior to scanning. All MRI procedures will take place under constant supervision by an experienced researcher and MR technician in an environment specifically designed, equipped and functioning for MR research studies. Though we do not anticipate any problems, if any effects occur during MRI, appropriate treatment will be obtained. Participants will be informed of the possible risks and discomforts of MRI:

1. Claustrophobia: A history of claustrophobia is exclusion criteria for the study. If a participant becomes claustrophobic during their MRI, they will alert the MR technician immediately via the intercom and/or a hand-held emergency button (both options are available at all times) and will be immediately removed from the scanner.
2. Acoustic noise: Participants will be provided earplugs and protective earphone to reduce MR noise to a comfortable level.
3. Metal implants: Metal implants are exclusion criteria for the study. Participants will be required to complete an MRI safety screening form and pass through a metal detector prior to scanning.
4. Discomfort in MRI scanner: An adaptation session in a mock scanner will be offered to participants as an opportunity to experience lying in an MRI scanner. Participants will be positioned for comfort with adequate head support, a bolster under the knees and elbows, and a blanket. They will be asked to use the restroom prior to scanning. They will be closely monitored for discomfort during scanning. Finally, they can terminate the scan at any time using the MRI intercom or emergency button.
5. Unknown risk to a fetus: Pregnancy is exclusion criteria for the study.

iii. Behavioral assessments: Confidentiality will be maintained as described below.

iv. Urine screen: At the screening visit and during the consent process, participants will be told that urine test results will only be shared with the individual.

v. Limits to confidentiality: All limits to confidentiality will be explained to the participant. They will be told that we will protect their confidentiality and that we will not share any personal information. They will be informed that if they report any information to us about abuse or homicidal/suicidal behavior, we will be required to report this information to the appropriate authorities.

vi. Incidental findings on MRI: Following procedures of the Yale Magnetic Resonance Research Center, participants will be informed via the consent form and process that the MRI study is for research purposes only and is in no way a clinical examination; the scan is not designed to find abnormalities and the research team is not qualified to interpret the MRI scan to provide any diagnostic information. If any incidental finding is detected, a staff neuroradiologist will be asked to review the MRI and make a recommendation, including whether or not to seek an additional examination or treatment. Any incidental finding will be evaluated on a case by case basis and remain confidential unless there is concern about imminent danger. This will be clearly stipulated in the consent forms. Participants will be informed that it is solely their decision to seek additional examination

or treatment. They will be informed that the research team, consulting neuroradiologist, Yale MRRC and Yale University are not responsible for any examination or treatment that they receive based on an incidental finding. The MRI is not a clinical scan and therefore the images will not be made available for diagnostic purposes.

12. **Data and Safety Monitoring Plan:** Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.)
    a. What is the investigator's assessment of the overall risk level for subjects participating in this study?
    Minimal risk
    b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? NA
    c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://your.yale.edu/policies-procedures/forms/420-fr-01-data-and-safety-monitoring-plans-templates for
        i. Minimal risk
        ii. Greater than minimal

The principal investigators are responsible for monitoring the data, assuring protocol compliance, and conducting safety reviews every 6 months. During the review process the principal investigators will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment.

The principal investigator, the Institutional Review Board (IRB), the Yale MRRC and NIDA have the authority to stop or suspend the study or require modifications.

This protocol presents minimal risks to the subjects and Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs), including adverse events, are not anticipated. In the unlikely event that such events occur, Reportable Events (which are events that are serious or life-threatening and unanticipated (or anticipated but occurring with a greater frequency than expected) and possibly, probably, or definitely related) or Unanticipated Problems Involving Risks to Subjects or Others that may require a temporary or permanent interruption of study activities will be reported immediately (if possible), followed by a written report within 5 calendar days of the Principal Investigators becoming aware of the event to the IRB (using the appropriate forms from the website) and any appropriate funding and regulatory agencies. The investigators will apprise fellow investigators and study personnel of all UPIRSOs and adverse events that occur during the conduct of this research project through regular study emails or via email as they are reviewed by the principal investigators. The protocol's research monitor(s), study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies will be informed of serious and unanticipated and related adverse events or unanticipated problems involving risks to subjects or others will be reported adverse events within 5 days of the event becoming known to the principal investigator.

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

Our previous neurofeedback work showed that data from 10-20 subjects is adequate for demonstrating significant control of activity in a single brain region[13, 65, 68, 69] and that data from two groups of 10-20 subjects is adequate for detecting group differences in control of activity[13, 68]. Our prior CPM work showed that data from N=10 per group is sufficiently powered

(>.90) to detect differences in connectome-based networks (noncentrality parameter (δ)=5.36, critical t-value=2.10, df=18, power (1-β)=0.99). Finally, we have established retention rates of >85% over 3-months for fMRI studies with methadone patients[10, 70]. Thus, we are confident that a sample size of N=24 (N=12 per group) is sufficiently powered.

The statistical tests will be as follows: Aim 1: Opioid use will be entered into a linear effects model with the between-subject factor of feedback group (active/sham). Aim 2: Opioid abstinence network strength during resting state and task fMRI runs will be compared between time points using linear mixed models with the between-subject factor of group (active/sham) and the within-subject factor of time (baseline/follow-up scan). Aim 3: Craving and negative affect will be compared using linear mixed effects model with the between-subject factor of group (active/sham) and the within-subject factor of time (baseline/follow-up scan). Associations between craving and negative affect and opioid abstinence network connectivity strength during transfer runs will be tested using Pearson's or Spearman's correlations, as appropriate depending on the distribution of the data. Replication: For replication of our pilot data (Figure 2 of research strategy), Pearson's correlations will be tested between opioid abstinence network connectivity strength at baseline and percent opioid-negative urines across the study.

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

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

A. RADIOTRACERS ☒**N/A**

B. DRUGS/BIOLOGICS ☒**N/A**

C. DEVICES ☒**N/A**

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:

a. Targeted for enrollment at Yale for this protocol:
24 completers (individuals participating in all scanning sessions).

b. If this is a multi-site study, give the total number of subjects targeted across all sites: NA

2. Indicate recruitment methods below. Attach copies of any recruitment materials that will be used.

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

We plan to collect full data from twenty-four individuals (12 M, 12 F) receiving methadone for OUD. Thus, in order to account for possible participant attrition, we will likely scan up to 40 individuals (and anticipate screening up to 100). Participants will be recruited via clinician referrals from the APT Foundation, one of the largest methadone providers in CT, consistent with our prior[48, 49] and ongoing work. While rates of other forms of medication-assisted treatment (e.g., buprenorphine, naltrexone) have increased in recent years, methadone remains the most prevalent treatment for OUD in the US[20], therefore, to reduce sample variability, this study will only recruit individuals treated with methadone. For regular attendance for methadone, APT patients meet regularly with clinicians, as per federal guidelines. Dr. Barry (Co-I), Director of Research for APT, is ideally suited to facilitate participant referral and longitudinal clinical assessment for this study.

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

3. Recruitment Procedures:

a. Describe how potential subjects will be identified. *Write here*
b. Describe how potential subjects are contacted. *Write here*
c. Who is recruiting potential subjects? *Write here*

Consistent with previous studies conducted by the PI and co-investigators, participants in methadone treatment for an opioid-use disorder will be recruited from the APT Foundation. Interested participants entering the methadone treatment program at APT will be referred by APT personnel to research staff when possible for eligibility screening. Dr. Barry, a co-investigator for this study, is both the Director of Research and the Director of Pain Services for the APT Foundation, he is ideally suited to facilitate participant referral and longitudinal clinical assessment for this study. Participants may also be referred to the study by word of mouth from other participants. HIC approved recruitment materials will provide information about how to contact research staff to learn more about the study. All recruitment will be conducted by local HIC-approved study personnel who completed HIC training requirements.

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

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

☐Yes, all subjects
☒Yes, some of the subjects
☐No

If yes, describe the nature of this relationship. *Write here*
Some of the participants may have an existing clinical relationship with Dr. Barry (Co-I on this study), a Yale researcher with clinical responsibilities at APT.

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

Choose one:

☐ For entire study
☒ For recruitment/screening purposes only

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

i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data: *Write here*

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

Subjects are, in most cases, screened by phone or are screened off-site. Both situations are not suitable or practical for obtaining signed authorization.

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

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

6. **Process of Consent/Assent:** Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.

Interested individuals will contact the study team and set up a screening visit. The screening visit will be in-person or will be conducted remotely. At the screening visit, eligible participants will be provided a complete description of the study procedures, and then they will be asked to provide informed consent. Due to COVID-19 it may be necessary to obtain informed consent remotely via Yale secure video (e.g., Zoom or Skype for business) or Yale secure online survey software (Qualtrics). A trained member of the research team will perform the informed consent procedure in a private setting. This procedure will include description of the components described in the consent form, including: (i) voluntary nature of participation; (ii) participants may withdraw without consequences to clinic services received; (iii) study purpose and procedures; (v) schedule of study visits; (vi) neuroimaging procedures; (vii) risks and benefits of participation; (viii) potential compensation; (ix) alternatives to study participation; and (x) confidentiality. All potential participants will be allowed to ask questions and given sufficient time to consider the decision to participate. All participants will be given a copy of the consent form. If all study criteria are met and consent is obtained, the individual will be enrolled in the study and schedule their first scanning session. These procedures are in line with policies and procedures of the Yale Institutional Review Board (IRB).

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

Write here

Comprehension will be assessed during the informed consent process through a verbal interaction between the prospective subject and study personnel obtaining informed consent.

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

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

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

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

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

☐**Not Requesting any consent waivers**

☒**Requesting a waiver of signed consent:**

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

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

For a waiver of signed consent, address the following:

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

OR

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

☐ **Requesting a waiver of consent:**

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

☐ **Entire Study**

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

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

SECTION IV: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

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

The following data may be collected at each study visit: 1) health information including substance use history; 2) experimental data from structural and functional MRI; 3) survey data, including an MRI safety screening form and measures of craving, negative affect and other constructs; 4) urine toxicology screening. Additional PHI includes participants' name, address, email address and telephone number, birthdate and age.

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

MRI data will be transferred from the scanner to a password-protected study computer using a secure server on the Yale University network. Survey data will be collected via online surveys using the secure Yale Qualtrics survey software approved for use with EPI and EPHI records. Survey data that are exported from Qualtrics for analysis and urine toxicology data will be coded by subject identification number and stored on a password-protected study computer.

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? *Write here*

   MRI data are coded by scan number and never linked to identifying information and will be transferred from the scanner to a password-protected study computer using a secure server on the Yale University network. Survey data will be collected via online surveys using the secure Yale Qualtrics survey software approved for use with EPI and EPHI records. Survey data that are exported from Qualtrics for analysis and urine toxicology data will be coded by

subject identification number and stored on a password-protected study computer. The key that links the participant to their subject identification and scan numbers and any other paperwork (e.g., MRI safety screening form, informed consent form) will be stored in a locked file on the study computer. Only Yale IRB-approved members of the research team will have access to study data and computers or to personal-identifying information about subjects. All hardcopy paperwork will be stored in a secured office in the Yale Imaging and Psychopharmacology Lab. These procedures have been used previously to protect the privacy of individuals and confidentiality of data for research studies in the proposed environment.

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

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

Data collected in the study will reside in our electronic storage mechanism for 7 years. All data analyses (deidentified and coded as described above) will be performed under approved HIC protocols.

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

This project has NIH funding (1R21DA049583-01) and therefore a CoC was automatically issued in accordance with NIH CoC Policy (NOT-OD-17-109).

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.)
Write here There are no direct benefits for taking part in the study. The potential benefits research to society are considerable. Opioid misuse and addiction is a significant public health crisis, yet current treatment options remain suboptimal. Isolation of the neural mechanisms associated with effective treatment interventions will inform current understanding of the neurobiology of opioid dependence and aid in the development of more effective treatments. This research may also aid in the identification of neurobiological predictors of treatment responses, which could be used in the *a priori* assignment of individual patients to the most appropriate interventions, reducing the overall burden of care for the clinician, patient and society. In sum, the risks to subjects are minimal, therefore the risk-benefit ratio of the study is favorable. The proposed research may aid in the development of more effective treatments for opioid use disorder. Thus, the minimal risks appear reasonable in relation to the importance of the knowledge to be gained.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?
   Write here
   The alternative to participation is not to participate in the study

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.
   Write here
   All participants will receive $25 per screening session, $50 per scanning session, $25 for the follow-up session and a $200 study completion bonus. For the $50 scanning session payment at baseline and follow-up scans, participants will be told that they will receive "up to $50 based on their performance on the MID task." In reality, all participants will receive exactly $50 per scanning session regardless of MID performance. Additionally, to increase engagement, participants will be told that they will receive a bonus payment based on the outcome of a randomly selected feedback or transfer run from each session. Because some participants received sham feedback, in reality all participants will receive a $15 bonus per training scan to increase engagement (total $45). Total compensation will be $545. They will additionally be compensated as needed for travel to appointments (up to $50 per study visit).

   In the event that a participant cannot complete a full scanning session due to unforeseen circumstances (e.g., due to not feeling well during their MRI scan, tardiness, etc.), they may still be paid for that scanning session (at the discretion of the research team) and therefore their total payment may exceed $545 (if they complete all other parts of the study).

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.
   There are no costs for participation in the study. They will additionally be compensated as needed for travel to appointments (up to $50 per study visit).

4. **In Case of Injury:** This section is required for any research involving more than minimal risk, and for minimal risk research that presents the potential for physical harm (e.g., research involving blood draws).
   a. Will medical treatment be available if research-related injury occurs? *Write here*
   b. Where and from whom may treatment be obtained? *Write here*
   c. Are there any limits to the treatment being provided? *Write here*
   d. Who will pay for this treatment? *Write here*
   e. How will the medical treatment be accessed by subjects? *Write here*

This protocol is deemed to be of minimal risk. If subjects develop a mental or physical problem as a result of involvement in this study, they will seek their own treatment independently from the study. The subject's insurance carrier will be expected to pay the costs of such treatment. No financial compensation is available for this treatment.

IRB# 2000025618

IMPORTANT REMINDERS

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

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

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

Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? **Yes ☐ No ☒**

If Yes, please answer questions a through c and note instructions below.

a. Does your YNHH privilege delineation currently include the **specific procedure** that you will perform? **Yes ☐ No ☐**

b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? **Yes ☐ No ☐**

c. Will a novel approach using existing equipment be applied? **Yes ☐ No ☐**

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

IMPORTANT REMINDER ABOUT RESEARCH AT YNHH

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

APPROVED BY THE YALE UNIVERSITY IRB 10/11/2022

References:

1. Moningka, H., et al., *Can neuroimaging help combat the opioid epidemic? A systematic review of clinical and pharmacological challenge fMRI studies with recommendations for future research.* Neuropsychopharmacology, 2018. **44**(2): p. 259-273.
2. Garrison, K.A. and M.N. Potenza, *Neuroimaging and biomarkers in addiction treatment.* Curr Psychiatry Rep, 2014. **16**(12): p. 513.
3. Garrison, K.A., et al., *Real-time fMRI links subjective experience with brain activity during focused attention.* Neuroimage, 2013. **81**: p. 110-118.
4. Stoeckel, L.E., et al., *Optimizing Real Time fMRI Neurofeedback for Therapeutic Discovery and Development.* Neuroimage Clinical, 2014. **5**: p. 245-255.
5. Fovet, T., R. Jardri, and D. Linden, *Current Issues in the Use of fMRI-Based Neurofeedback to Relieve Psychiatric Symptoms.* Curr Pharm Des, 2015. **21**(23): p. 3384-94.
6. Kim, D.Y., et al., *The inclusion of functional connectivity information into fMRI-based neurofeedback improves its efficacy in the reduction of cigarette cravings.* J Cogn Neurosci, 2015. **27**(8): p. 1552-72.
7. Yarkoni, T., et al., *Large-scale automated synthesis of human functional neuroimaging data.* Nat Methods, 2011. **8**(8): p. 665-70.
8. Laird, A.R., J.L. Lancaster, and P.T. Fox, *BrainMap: the social evolution of a human brain mapping database.* Neuroinformatics, 2005. **3**(1): p. 65-78.
9. Konova, A.B., S.J. Moeller, and R.Z. Goldstein, *Common and distinct neural targets of treatment: changing brain function in substance addiction.* Neurosci Biobehav Rev, 2013. **37**(10 Pt 2): p. 2806-17.
10. Yip, S.W., et al., *Connectome-based prediction of cocaine abstinence.* American Journal of Psychiatry, In Press.
11. Rosenberg, M.D., et al., *A neuromarker of sustained attention from whole-brain functional connectivity.* Nat Neurosci, 2016. **19**(1): p. 165-71.
12. Rosenberg, M.D., et al., *Connectome-based Models Predict Separable Components of Attention in Novel Individuals.* J Cogn Neurosci, 2018. **30**(2): p. 160-173.
13. Scheinost, D., et al., *Orbitofrontal cortex neurofeedback produces lasting changes in contamination anxiety and resting-state connectivity.* Transl Psychiatry, 2013. **3**: p. e250.
14. Palamar, J.J., et al., *Nonmedical opioid use and heroin use in a nationally representative sample of us high school seniors.* Drug Alcohol Depend, 2016. **158**: p. 132-8.
15. Substance Abuse and Mental Health Services Administration - Center for Behavioral Health Statistics and Quality, *Combined Substance Use and Mental Health Treatment Episode Data Set (TEDS)*. 2014, SAMSHA: Rockville, MD.
16. Volkow, N.D., et al., *Medication-assisted therapies--tackling the opioid-overdose epidemic.* N Engl J Med, 2014. **370**(22): p. 2063-6.
17. Timko, C., et al., *Retention in medication-assisted treatment for opiate dependence: A systematic review.* J Addict Dis, 2016. **35**(1): p. 22-35.
18. Williams, A., E. Nunes, and M. Olfson. *To battle the opioid overdose epidemic, deploy the "Cascade of Care" model.* Health Affairs Blog 2017 08/13/19];

Available from: https://www.healthaffairs.org/do/10.1377/hblog20170313.059163/full/.
19. Williams, A.R., et al., *Developing an opioid use disorder treatment cascade: A review of quality measures.* J Subst Abuse Treat, 2018. **91**: p. 57-68.
20. Connery, H.S., *Medication-assisted treatment of opioid use disorder: review of the evidence and future directions.* Harv Rev Psychiatry, 2015. **23**(2): p. 63-75.
21. Volkow, N.D. and M. Boyle, *Neuroscience of Addiction: Relevance to Prevention and Treatment.* Am J Psychiatry, 2018: p. appiajp201817101174.
22. Dosenbach, N.U., et al., *Prediction of individual brain maturity using fMRI.* Science, 2010. **329**(5997): p. 1358-61.
23. Di Martino, A., et al., *Unraveling the Miswired Connectome: A Developmental Perspective.* Neuron, 2014. **83**(6): p. 1335-1353.
24. Fair, D.A., et al., *Functional brain networks develop from a "local to distributed" organization.* PLoS Comput Biol, 2009. **5**(5): p. e1000381.
25. Satterthwaite, T.D., et al., *Heterogeneous impact of motion on fundamental patterns of developmental changes in functional connectivity during youth.* Neuroimage, 2013. **83**: p. 45-57.
26. Ingalhalikar, M., et al., *Sex differences in the structural connectome of the human brain.* Proc Natl Acad Sci U S A, 2014. **111**(2): p. 823-8.
27. Grayson, D.S., et al., *Structural and functional rich club organization of the brain in children and adults.* PLoS One, 2014. **9**(2): p. e88297.
28. Bullmore, E. and O. Sporns, *The economy of brain network organization.* Nat Rev Neurosci, 2012. **13**(5): p. 336-49.
29. Collin, G. and M.P. van den Heuvel, *The ontogeny of the human connectome: development and dynamic changes of brain connectivity across the life span.* Neuroscientist, 2013. **19**(6): p. 616-28.
30. Finn, E.S., et al., *Functional connectome fingerprinting: identifying individuals using patterns of brain connectivity.* Nat Neurosci, 2015. **18**(11): p. 1664-1671.
31. Shen, X., et al., *Using connectome-based predictive modeling to predict individual behavior from brain connectivity.* Nat. Protocols, 2017. **12**(3): p. 506-518.
32. Xu, J., et al., *Large-scale functional network overlap is a general property of brain functional organization: Reconciling inconsistent fMRI findings from general-linear-model-based analyses.* Neurosci Biobehav Rev, 2016. **71**: p. 83-100.
33. Yip, S., K. Carroll, and M. Potenza, *An overview of translational approaches to the treatment of addictions*, in *Neuroimaging and Psychosocial Addiction Treatment: An Integrative Guide for Researchers and Clinicians*, S. Feldstein Ewing, K. Witkiewitz, and F. Filbey, Editors. 2015, Palgrave.
34. Vul, E., et al., *Puzzlingly High Correlations in fMRI Studies of Emotion, Personality, and Social Cognition.* Perspect Psychol Sci, 2009. **4**(3): p. 274-90.
35. Garavan, H., et al., *The neurobiology of successful abstinence.* Curr Opin Neurobiol, 2013. **23**(4): p. 668-74.
36. Thibault, R.T., et al., *Neurofeedback with fMRI: A critical systematic review.* Neuroimage, 2018. **172**: p. 786-807.

37. Hartwell, K.J., et al., *Individualized real-time fMRI neurofeedback to attenuate craving in nicotine-dependent smokers.* J Psychiatry Neurosci, 2016. **41**(1): p. 48-55.
38. Li, X., et al., *Volitional reduction of anterior cingulate cortex activity produces decreased cue craving in smoking cessation: a preliminary real-time fMRI study.* Addict Biol, 2013. **18**(4): p. 739-48.
39. Karch, S., et al., *Modulation of Craving Related Brain Responses Using Real-Time fMRI in Patients with Alcohol Use Disorder.* PLoS One, 2015. **10**(7): p. e0133034.
40. Kirsch, M., et al., *Real-time functional magnetic resonance imaging neurofeedback can reduce striatal cue-reactivity to alcohol stimuli.* Addict Biol, 2016. **21**(4): p. 982-92.
41. Watanabe, T., et al., *Advances in fMRI Real-Time Neurofeedback.* Trends Cogn Sci, 2017. **21**(12): p. 997-1010.
42. Yuan, H., et al., *Resting-state functional connectivity modulation and sustained changes after real-time functional magnetic resonance imaging neurofeedback training in depression.* Brain Connect, 2014. **4**(9): p. 690-701.
43. Monti, R.P., et al., *Real-time estimation of dynamic functional connectivity networks.* Hum Brain Mapp, 2017. **38**(1): p. 202-220.
44. Koush, Y., et al., *Connectivity-based neurofeedback: dynamic causal modeling for real-time fMRI.* Neuroimage, 2013. **81**: p. 422-30.
45. Rosenberg, M.D., et al., *Methylphenidate Modulates Functional Network Connectivity to Enhance Attention.* J Neurosci, 2016. **36**(37): p. 9547-57.
46. Hsu, W.T., et al., *Resting-state functional connectivity predicts neuroticism and extraversion in novel individuals.* Soc Cogn Affect Neurosci, 2018. **13**(2): p. 224-232.
47. Greene, A., et al., *Task-induced brain state manipulation improves prediction of individual traits.* Nature Communications, 2018. **9**(1): p. 2807.
48. Yip, S.W., et al., *Anticipatory reward processing among cocaine-dependent individuals with and without concurrent methadone-maintenance treatment: Relationship to treatment response.* Drug Alcohol Depend, 2016. **166**: p. 134-42.
49. Yip, S.W., et al., *Connectome-Based Prediction of Cocaine Abstinence.* Am J Psychiatry, 2019. **176**(2): p. 156-164.
50. Sobell, L. and M. Sobell, *Timeline follow-back: A technique for assessing self-reported alcohol consumption*. Measuring alcohol consumption: Psychosocial and biochemical methods. 1992, Totowa, NJ: Humana Press. 41-72.
51. Zhai, Z.W., et al., *Childhood trauma moderates inhibitory control and anterior cingulate cortex activation during stress.* Neuroimage, 2019. **185**: p. 111-118.
52. Yip, S.W., et al., *Intra-individual changes in Stroop-related activations linked to cigarette abstinence in adolescent tobacco smokers: Preliminary findings.* Drug Alcohol Depend, 2016. **167**: p. 182-9.
53. Garrison, K.A., et al., *Reward-related frontostriatal activity and smoking behavior among adolescents in treatment for smoking cessation.* Drug Alcohol Depend, 2017. **177**: p. 268-276.

54. Yip, S.W., et al., *Hypoactivation of the ventral and dorsal striatum during reward and loss anticipation in antipsychotic and mood stabilizer-naive bipolar disorder.* Neuropsychopharmacology, 2015. **40**(3): p. 658-66.
55. Shipley, W., *Shipley Institute of Living Scale*. 1967, Los Angeles, CA: Western Psychological Services
56. Whiteside, S.P. and D.R. Lynam, *The Five Factor Model and impulsivity: Using a structural model of personality to understand impulsivity.* Personality and Individual Differences, 2001. **30**(4): p. 669-689.
57. Rush, A.J., et al., *The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression.* Biol Psychiatry, 2003. **54**(5): p. 573-83.
58. McHugh, R.K., et al., *Assessing craving and its relationship to subsequent prescription opioid use among treatment-seeking prescription opioid dependent patients.* Drug Alcohol Depend, 2014. **145**: p. 121-6.
59. Wesson, D. and W. Ling, *The Clinical Opiate Withdrawal Scale (COWS).* J Psychoactive Drugs, 2003. **35**(2): p. 243-9.
60. Johnson, K.A., et al., *Intermittent "real-time" fMRI feedback is superior to continuous presentation for a motor imagery task: a pilot study.* J Neuroimaging, 2012. **22**(1): p. 58-66.
61. Scheinost, D., et al., *A Graphics Processing Unit Accelerated Motion Correction Algorithm and Modular System for Real-time fMRI.* Neuroinformatics, 2013. **11**(3): p. 291-300.
62. Satterthwaite, T.D., et al., *Impact of in-scanner head motion on multiple measures of functional connectivity: relevance for studies of neurodevelopment in youth.* Neuroimage, 2012. **60**(1): p. 623-32.
63. Power, J.D., et al., *Methods to detect, characterize, and remove motion artifact in resting state fMRI.* Neuroimage, 2014. **84**: p. 320-341.
64. Yan, C.G., et al., *A comprehensive assessment of regional variation in the impact of head micromovements on functional connectomics.* Neuroimage, 2013. **76**: p. 183-201.
65. Scheinost, D., et al., *Resting state functional connectivity predicts neurofeedback response.* Front Behav Neurosci, 2014. **8**: p. 338.
66. First, M.B., et al., *Structured Clinical Interview for DSM-5 Disorders, Clinician Version*. 2016, Arlington, VA: American Psychiatric Association.
67. Carroll, K.M., et al., *Galantamine and Computerized Cognitive Behavioral Therapy for Cocaine Dependence: A Randomized Clinical Trial.* J Clincal Psychiatry, 2018. **79**(1): p. pii: 17m11669.
68. Garrison, K.A., et al., *Real-time fMRI links subjective experience with brain activity during focused attention.* Neuroimage, 2013. **81**: p. 110-8.
69. Hampson, M., et al., *Biofeedback of Real-Time Functional Magnetic Resonance Imaging Data from the Supplementary Motor Area Reduces Functional Connectivity to Subcortical Regions.* Brain Connectivity, 2011. **1**(1): p. 91-98.
70. Carroll, K.M., et al., *Galantamine and Computerized Cognitive Behavioral Therapy for Cocaine Dependence: A Randomized Clinical Trial.* J Clincal Psychiatry, 2018. **doi: 10.4088/JCP.17m11669.**

APPROVED BY THE YALE UNIVERSITY IRB 10/11/2022