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

Protocol Title: Influence of medication on functional connectivity

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SECTION I: RESEARCH PLAN

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

This study will assess the effects of acute low-dose opioid administration on functional neuroimaging measures in healthy individuals (N=40, 20 male, 20 female). The objective of this research is to develop an understanding of factors that may influence individual variability on resting state functional connectivity in response to low-dose opioid administration with the longer term aim of understanding addictions vulnerability. Specifically, the proposed pilot research will explore the effects of single dose of oxycodone (15mg) on resting state functional connectivity and other common neuroimaging measures (e.g., diffusion MRI, structural MRI). Previous work has found 10-20mg doses well-tolerated, but has found increased ratings of nausea following 20mg doses (Gorka, Fitzgerald et al. 2014, Wardle, Fitzgerald et al. 2014). Preliminary data (Gorka, Fitzgerald et al. 2014) suggest that 10mg and 20mg doses have similar effects on FC. However, a 10mg dose of oxycodone may not be clinically sufficient for CYP3A4 fast metabolizers (Samer, Daali et al. 2010, Brennan 2012). To balance concerns related to excluding potential participants based on this relatively common genetic variation (thus potentially limiting the applicability of study findings) with those of a higher dose of oxycodone (e.g., 20mg), we will use a 15mg dose and test for genotype effects on neural responses post-hoc. Other laboratory studies in healthy controls have found doses between 15mg and 20mg to be well tolerated (Zacny and Lichtor 2008, Samer, Daali et al. 2010, Cooper, Sullivan et al. 2012).

Given the high prevalence of prescription opioid exposure in youth (McCabe, West et al. 2012), it is not feasible to study exclusively opioid-naïve individuals. Prior neuroimaging work using oxycodone has not excluded for lifetime exposure, but has excluded for abuse or dependence (Gorka, Fitzgerald et al. 2014). To minimize the possible influence of individual differences in prior exposure, we will exclude for prior 6 month use, as well for significant prior medical (>5 days of consecutive medical use) or nonmedical use (>5 prior uses of oxycodone).

Peak plasma concentrations of orally administered immediate release 10mg OXY occur approximately 1 hour following ingestion and has a half life of 3-4 hours(Ordonez Gallego, Gonzalez Baron et al. 2007, Gronlund, Saari et al. 2010, Saari, Gronlund et al. 2010). We are therefore confident that a 6-month washout period will be more than sufficient to ensure clearance.

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All participants will be seen for an initial intake by a research assistant either in person or virtually via Zoom and who will begin the review process of eligibility, obtain medical history, provider information and relevant releases. Physical examination findings and laboratory tests will inform eligibility decisions. Potential participants will undergo medical screening to determine eligibility to receive a single dose of oxycodone 15mg. Medical screening for contraindication to low-dose opioid administration (e.g., medication allergies, kidney or liver problems, personal or familial history of opioid- or alcohol-use disorders) will be conducted by a licensed physician. Lab tests will be ordered at the discretion of the physician to determine eligibility for study participation. Final determination of eligibility will be determined by the study physician and investigators. Monitoring will occur during and after all procedures with participants remaining in our lab for one hour post scan (3.5-4 hours after opioid administration). In addition, a follow up phone call will be made one day and again one month after scan with additional medical care, if indicated, being facilitated.

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

   The proposed research is a pilot project and will be complete in May 2023 (including data analysis).

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.

   Resting state functional connectivity, as assessed using functional magnetic resonance imaging (fMRI), is a widely used method of studying in vivo spontaneous neural activity across a range of populations, including (though not limited to) individuals with psychiatric disorders and healthy controls. Prescription of low-dose opioids for symptomatic pain relief is common and most individuals prescribed low-dose, short-term opioids do not develop problems with opioid use. However, non-medical opioid use remains a major public health problem (Substance Abuse and Mental Health Services Administration Center for Behavioral Health Statistics and Quality 2014, Volkow, Frieden et al. 2014, Palamar, Shearston et al. 2016). Very little is known about the effects of acute low-dose opioid administration within the brain, particularly within the context of large-scale intrinsic brain networks. To address this gap, this pilot study will explore the effects of acute low-dose opioid administration on resting state functional connectivity, using a placebo-controlled, double-blind within-subjects design in healthy individuals.

   Approach: This study will assess the effects of acute low-dose opioid administration using a within-subjects design. Eligible participants will be asked to participate in 2 separate 90 minute fMRI sessions (Scan 1 and Scan 2), one of which will involve taking oxycodone (15mg) and one of which will involve taking a placebo pill. Neuroimaging parameters will be the same for all scans. Approximately one hour prior to scanning, participants will be given either a single dose of oxycodone 15mg or placebo. Participants will be randomized using urn randomization, as in our ongoing studies to receive either oxycodone or placebo during scan 1, and will be 'crossed-over' to the other condition (oxycodone or placebo, whichever was not administered at scan 1) for scan 2. Participants will only participate in sessions for which they are determined eligible and for which they have provided written informed consent (total N=40). The order of scans (oxy/placebo) will be counter-balanced across participants to control for order effects. Participants will either be randomized to participant in Scan A first, or will be randomized to participate in Scan B first.

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Participants and study personnel (research assistant and PI) will be blind to which medication participants receive.

Hypothesis:

Specific decreases in functional connectivity following acute low-dose opioid administration (Oxy Scan < Placebo B) within cortico-limbic tracts (e.g., insular-striatal; ventrolateral PFC-amygdala tracts).

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.

Research strategy:

Participants and recruitment: Forty healthy adults will be recruited for participation in this pilot study.

Measures: All participants will also be given the Shipley Institute of Living Scale to assess general intellectual function (Shipley 1967), in addition to other non-fMRI measures including measures of depression and affective symptoms (Beck Depression Inventory-II) (Beck, Steer et al. 1996), Difficulties in Emotion Regulation Scale (Gratz and Roemer 2004)) and self-reported impulsivity (Barratt Impulsiveness Scale(Patton 1995).

Image acquisition: fMRI data will be acquired using 3.0T scanner and multiband echo-planar imaging (EPI) gradient-echo sequences. Resting state fMRI, diffusion MRI and high-resolution structural data will also be acquired. Total scan time will not exceed 1.5 hours.

Testing for fast metabolizers: Differences in metabolizing of opioid medications can arise from variations in genes encoding for the liver enzymes CPY3A4 and CPY3A5 and this can lead to significant variation in subjective responses (Gudin 2012). To allow for statistical analysis exploring the effects of this variable, we will collect Buccal samples to be tested for CPY450 3A4/3A5 genotype. The procedure for collecting Buccal swabs is to have the study physician (Dr. Camenga) obtain attestation and patient consent, followed by sample collection, at the time of medical screening. The sample will be used to test for CPY450 3A4/3A5 genotype. The samples will be coded with a number directly related to that participant. At no time will the participant's identity be linked to that number. The "key" will be kept in a locked file in the Research Coordinator's office.

Analyses:

We will use ICD and CBF-adjusted ICD to address Specific Aims 1 & 2. As shown in Figure 5 (below), the basic steps of ICD include, 5A, voxelwise correlation of timecourses (i.e., the timecourse of a given voxel is correlated with that of every other voxel in the brain; and, 5B, voxelwise summary of correlations with a network-theory metric (α). The network theory metric is

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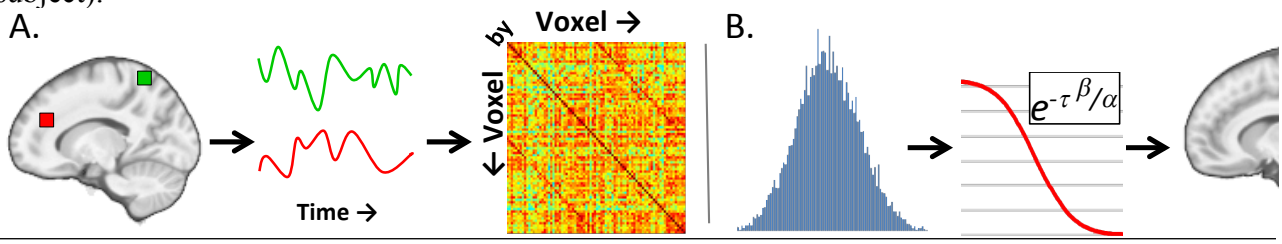
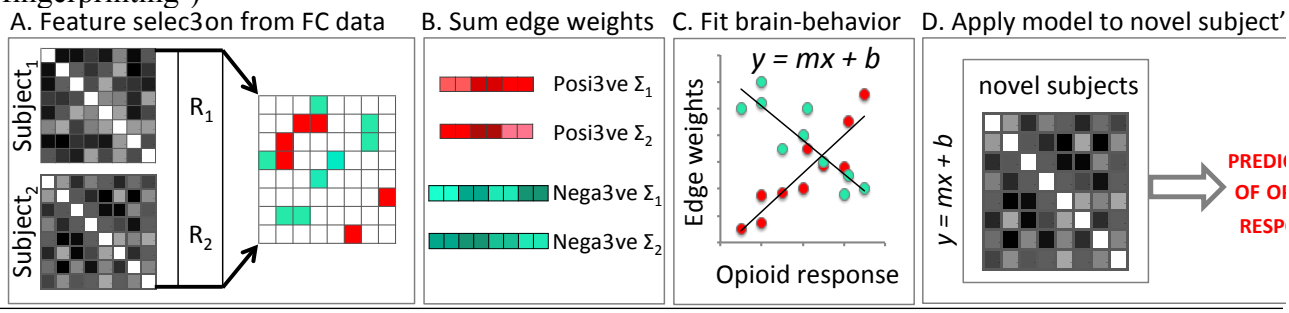
Figure 5 – Schematic diagram of intrinsic connectivity distribution (ICD) analysis steps (single-subject).



calculated by converting the distribution of correlations for a given voxel (histogram in 5B) into a survival function fitted with a stretched exponential with variance α. Since α corresponds to the spread of the distribution of connections, high α values indicate high connectivity. Individual α values are computed for all grey-matter containing voxels in the brain to create parametric images of the α parameter, to be used for groupwise analyses. To account for physiological confounds associated with pharmacological FC, we will also conduct CBF-adjusted ICD. Formally, instead of constructing a histogram of correlations as in ICD, a weighted histogram of correlations is used for CBF-adjusted ICD. The weighting factor for the count of each correlation between two voxels is the inverse of the product of the two voxels' CBF. After creating the weighted histogram, the same procedures for ICD are followed as described above. For the proposed research, two parametric images per participant will be created (1 OXY, 1 placebo) and entered into group-level analyses. Whole-brain, ANOVAs including medication (OXY/placebo) and order (OXY/placebo at Scan 1) as between-subjects factors and voxelwise FC (α) as a within-subjects factor will be used to identify OXY-associated changes. Subjective ratings of drug effects will be entered into regression analyses with FC indices from OXY (vs. placebo) scans to identify network-level individual difference factors related to subjective responses. Consistent with current recommendations, group-level analyses will be conducted using a cluster-forming threshold of $p<.001$ and a family-wise error (FWE) correction of $p<.05$. Clusters exhibiting significant main effects of medication will be entered into seed-based analyses to facilitate characterization of FC changes.

FC data from placebo scans will be entered into CPM analyses to identify networks predictive of subjective responses to active drug (OXY). Peak DEQ responses collected during active drug sessions and resting state and MID task data from placebo scans will be entered into CPM analyses. CPM analyses will be conducted using leave-one-out cross-validation and permutation testing, as in our prior work.

Figure 6 – Schematic diagram of connectome-based predictive modeling (CPM; 'neural fingerprinting')



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During CPM, **6A**, edges (correlations between nodes in FC matrix) and behavioral data from a training dataset are correlated using regression analyses to identify positive and negative predictive networks (networks not shown). Single-subject summary statistics, **6B**, are created as the sum of the edge weights in each network and, **6C**, used to create predictive models assuming linear relationships with behavioral data. Resultant polynomial coefficients are applied to novel subject's FC matrices (**6D,** test data) to generate behavioral predictions. Performance is evaluated using mean squared error (MSE) or correlation between predicted and actual values. Lower MSE and higher correlation indicate more predictive models.

Procedures for Recruitment, Informed Consent and Initial Screening

Recruitment will be conducted using flyers distributed on the Yale campus and in New Haven, as well as by word of mouth. Initial meetings will take place either in person or via Zoom in a private setting with a trained member of the research team. At this meeting, potential participants will be provided with an overview of the study protocols including a complete description of the study procedures, and will provide written, informed consent. 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; (iii) study purpose and procedures; (iv) schedule of study visits; (v) neuroimaging procedures; (vi) risks and benefits of participation; (vii) potential compensation; (viii) alternatives to study participation; and (ix) confidentiality. All potential participants will be allowed to ask questions and given sufficient time to consider the decision to participate. All potential participants will be given a copy of the consent form.

Following informed consent, potential participants will be screened for eligibility by specially trained members of the research team either in person or via Zoom. This will involve structured clinical interview and baseline self-report rating forms, including the following.

List of assessments:

Structured Clinical Interview for DSM (SCID-5)– The SCID-5 is a reliable semi-structured instrument that is standard in the field for diagnosing selected current and lifetime Axis I disorders. It will be used to diagnose comorbid disorders. The SCID-II, which assesses personality disorders, will also be used as the presence of personality disorders may bear on treatment retention and outcome.

Magnetic Resonance Research Center (MRRC) Safety Form – The MRRC Safety Questionnaire will be used to confirm eligibility for MRI scanning, consistent with the guidelines of Yale's MRRC center.

Positive and Negative Affect Scales (PANAS) – Trait and state positive and negative affect will be evaluated using these well-validated, brief self-report scales (Watson et al., 1998).

Shipley Institute of Living Scale (SILS) - General intellectual functioning will be evaluated using the SILS (Shipley 1967), a widely-used and brief screening tool that assesses general level of intellectual functioning.

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The **Beck Depression Inventory (BDI)** (Beck 1978) and **Beck Anxiety Inventory (BAI)** (Beck 1988) are well-validated self-report measures of depression (BDI) and anxiety (BAI) symptoms.

The **Difficulties in Emotion Regulation Scale (DERS)** (Gratz and Roemer 2004) is a well-validated 36-item self-report measure assessing six domains related to emotion regulation. Difficulties in emotion regulation using this scale have been previously reported among newly abstinent cocaine users (Fox, Axelrod et al. 2007).

The **Affective Reactivity Index (ARI)** (Stringaris, Goodman et al. 2012) is a well-validated self-report measure of irritability.

Barratt Impulsiveness Scale (BIS-11) (Patton, Stanford et al. 1995) - This is a 30-item, valid and reliable self-report scale designed to assess the personality/behavioral construct of impulsiveness.

Drug Effects Questionnaire (DEQ) (Kirk and de Wit 2000) – Subjective effects of acute opioids will be assessed using the DEQ, a set of four visual analogue scales assessing subjective effects (e.g., 'Do you feel any drug effects?').

UPPS Impulsive Behavior Scale (Whiteside, et al. 2001) – Self report of impulse behaviors.

Screener and Opioid Assessment for Patients with Pain (Butler et al. 2008/Akbik et al. 2006)—Screening for opioid risk related to pain.

State Trait Anxiety Inventory (STAI) (Spielberger 1991)—This is an 40 item self- report of two types of anxiety, anxiety about an event (state) or anxiety on a personal level (trait)

Monetary Choice Questionnaire (Kirby et al. 1999)—delay discounting measure used for testing impulsivity.

I. Safety and eligibility screening and baseline assessments

1. Pre-enrollment screening (by phone, Zoom or in person) - RA

- Medical history
- Substance use history
- Psychiatric history

2. Eligibility assessment (in person or via Zoom) - Initial assessments and screening (1-3 hours) – RA

- Informed consent (including informed consent quiz)
- Assessment of Inclusion/Exclusion criteria
- Demographics
- Follow-up contact form
- Drug screen

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- SCID
- MRRC Safety Form
- BDI/BAI
- DERS
- BIS 11
- UPPS
- SOAPP-R
- STAI
- Delay Discounting
- Schedule medical screening and start date for fMRI

Procedures for Conducting SCIDs and BDI Remotely

Prior to beginning interview:

- Only schedule remote when Dr. Sarah Lichenstein is available to be 'on call'
- When scheduling SCID with a participant, discuss where she will be and ensure she will have adequate privacy for the interview.
- Before beginning the SCID, obtain the participant's phone number and current location (including specific address) so that you have an alternative way to get in touch with the participant just in case.

If the participant expresses active suicidal intent during a remote/online visit:

- Try to keep the participants on the phone, ***TRY NOT TO HANG UP***
- Confirm with the participant that you have the right address where she is currently located.
- Tell the participant everything you are doing, as you do it; inform her that you are going to call a supervisor for some assistance. Avoid using the word 'police', which can be very distressing to some participants.
- Text Sarah Lichenstein (clinical psychologist) without hanging up on the participant.
- You can use the ***language below*** to assess whether this is a case of active suicide intent and whether the participant has access to means to execute their plan– however, you are not required to make a judgment call. The clinician you contact (i.e., Sarah Lichenstein) will do that.
- Provide the participant with resources, including the National Suicide Hotline (1-800-273-8255), SAMHSA's National Helpline (1-800-662-HELP (4357), United Way of Connecticut (211), and local Emergency Rooms (911).
- **After speaking with Sarah Lichenstein, and based on her judgment of whether this is considered a case of active suicidal ideation warranting immediate clinical follow-up –**
  Have Sarah Lichenstein call the participant while RA is still on the line. If warranted, then
  - Call mobile crisis and inform dispatch that a research participant expressed suicidal intent, and relay her contact information (name, phone number, current address). This can be done on a three-way call if RA is alone, otherwise RA can have someone else call mobile crisis while RA remains on the line with the participant.

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- It is not the RAs responsibility to ensure that the participant arrives at the hospital, nor to follow-up clinically. Their responsibility is a duty to warn of the suicidal or homicidal intent, and to document the event in the participant's notes/records.

3. Medical screening (in person) – approximately 1 hour

Potential participants will undergo medical screening (Dr. Deepa Camenga (FC1166683(DEA)) to determine eligibility to receive a single dose of oxycodone (15mg). Medical screening for contraindication to low-dose opioid administration (e.g., medication allergies, kidney or liver problems, personal or familial history of opioid- or alcohol-use disorders) will be conducted by a licensed physician. Per standard clinical practice in the state of CT, Dr. Camenga will check the Connecticut Prescription Monitoring program to confirm participant- reported history of previous opioid or prescription drug prescriptions received, and to confirm that the participant does NOT have a significant lifetime use of prescription opioids (>7 days of consecutive medical use). Lab tests will be ordered at the discretion of the physician to determine eligibility for study participation, as in our as in our other ongoing studies (HIC#: 1510016617). Subjects participating in one of our other protocols involving a medical screening may have the results from that screening used to determine eligibility on this protocol if within the last 3 months. Once determined eligible for the study, the study physician will access their Yale medical chart once for the purpose of attaining their medical record number for the prescription of oxycodone.

Neuroimaging

Participants will be asked to abstain from drugs or alcohol for 24 hours prior to scanning. MRI data will be collected using a 3.0T scanner and will be stored using a numbered reference system known only to the Project Coordinator. All data collection and management procedures are fully compliant with HIPAA. Study participants will participate in two MRI scanning sessions (some subjects may have more than two sessions should one of the initial scans prove to be incomplete or if the data was found to be unusable, i.e., too much movement during the scan). Neuroimaging will take place at Yale University's Magnetic Resonance Research Center (MRRC). All MRI data will be acquired using a 3.0T scanner and multiband acquisition parameters. MRI scanning using a 3.0T scanner is non-invasive and has not been associated with any medical risks. A member of the research team will accompany the subjects and will stay for the MRI.

During each scanning session, we will acquire resting state functional data and, in some cases, task-based fMRI data using a reward task (details below). Resting data will be acquired using up to 5 separate acquisitions, each of approximately 6 minute duration. Between each session, participants will be asked to rate how they are feeling on a Likert-type scale. Diffusion-weighted data, T1-weighted and T2-weighted images will also be obtained. In addition, a high-resolution structural MPRAGE scan will be obtained to aid in co-registering each subject to the template space and to assess gray matter volume. To allow for assessment of cerebral perfusion, arterial spin labeling (ASL) data will also be collected. Scan time will not exceed 90 minutes.

Functional MRI data will be acquired during performance of a monetary incentive delay task. During performance of the Monetary Incentive Delay Task, at the start of each trial, participants are

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presented with an initial cue, indicating an amount of money to be won or lost (e.g., 'WIN $1'), followed by a fixation cross (A1 phase). Participants are then presented with a target stimulus for a variable duration (individually calibrated). In order to win (or avoid losing) money on each trial, participants respond with a single button press while the target is on the screen. Following the target stimulus, a fixation cross is again presented (A2). Finally, participants are given feedback on the outcome of the trial (outcome phase). The task includes 55 trials (22 win trials, 22 loss trials, 11 neutral trials).

Medication administration

Approximately one hour prior to scans, participants will receive either a single oral dose of oxycodone (15mg) or placebo in pill form. Medication will be prescribed by a licensed physician, Dr. Marc Potenza (DEA license BP5110541) or Dr. Deepa Camenga (DEA license FC1166683) and will be stored and dispensed by the Yale New Haven Hospital (YNHH) pharmacy. Medication will be collected from the YNHH by a trained member of the research team and collection and administration to the participant will be documented using paper and/or electronic logs, as in our ongoing studies (HIC#: 1510016617). All subjects will be screened by a licensed physician for medication allergies and other contraindications (e.g., familial history of opioid-use disorder; details above). As per MRRC protocols a licensed physician will be on call during the scan. Although the risk is minimal, a dose of naloxone will be on hand to counteract any effects from the opioid should the need arise, as determined by the study physician.

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.

Assessment of subjective effects

Subjective drug effects (e.g., 'drug liking') will be assessed at multiple time points on each scanning day. Subjective effects will be assessed using measures recommended by the PhenX Toolkit (Morean, de Wit et al. 2013). This will include the Drug Effects Questionnaire (DEQ)(Kirk and de Wit 2000), as in prior work in opioids(Comer, Collins et al. 1999, Comer, Metz et al. 2013, Gorka, Fitzgerald et al. 2014). The DEQ includes visual analogue scales for 'FEEL', 'WANT', 'LIKE' 'DISLIKE', 'HIGH' and 'MORE'. Physiological (pulse, blood pressure) and subjective DEQ ratings will be acquired at baseline. Subsequent ratings will be acquired at 30, 60, 90, 120, 180 and 240minute timepoints. Ratings will be acquired electronically using a sliding visual analogue scale (VAS). Physiological measures will be acquired at baseline, 60, 120, 180 and 240min time points. In addition, the Addiction Research Center Inventory (ARCI) Morphine-Benzedrine Scale (McNair, Lorr et al. 1981) and VAS ratings of nausea, euphoria and light-headedness will be acquired at baseline and before and after neuroimaging.

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.

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This study will include up to 40 healthy men and women between the ages of 18 and 30. We will recruit through the general community using established recruitment procedures such as posting flyers, word-of-mouth, craigslist ads, Facebook and advertisements in local papers.

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

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

We plan to recruit healthy young adults from the general community. It is therefore possible that this will include Yale students.

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

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

Inclusion criteria:

a) males or females, ages 18-30

b) for women of a child-bearing age, acceptable birth control methods or a negative pregnancy test prior to MRI scanning

c) ability to provide written, informed consent

d) eligibility and willingness to participate in fMRI scanning and to receive oxycodone

e) normal to overweight, as indicated by a body mass index (BMI) between 18.5 to 29.9

Exclusion criteria:

a) current DSM-5 Axis I disorder

b) any psychotropic medication or medication known to interfere with metabolism of opioids

c) medical contraindication to participate in study activities (acute low-dose opioid admin) as determined by study physician

d) known family history (first-degree relative) of opioid-use disorder or alcohol-use disorder

e) not eligible for MRI scanning

f) positive drug screen

g) recent (past 6 months) medical or non-medical opioid-use

h) current or previous chronic pain disorder

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i) significant lifetime use of prescription opioids (>7 days of consecutive medical use or nonmedical use on more than 5 occasions)

j) alcohol naïve participants who may have never experienced the effects of an altering substance

k) pregnant or nursing mothers

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

Eligibility will be determined based on the above eligibility criteria as assessed by specially trained medical and research staff.

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

Risks to subject privacy: There is a chance that personal information may inadvertently not be kept confidential. Some answers participants give during the research visits (like whether they use illegal drugs) may put them at risk if other people find out.

Acute low-dose opioid administration: Risks associated with oxycodone use include gastrointestinal upset, constipation, nausea, vomiting, somnolence, dizziness, lightheadedness, itching, headache, blurred vision and xerostomia. As subjects will receive only a single 15 mg oxycodone, risks are minimal. All subjects will be screened by a licensed physician for medication allergies and other contraindications (e.g., familial history of opioid-use disorder; details above).

MRI scanning: Functional MRI scanning using a 3.0T scanner is non-invasive and has not been associated with any medical risks. Thus, the primary anticipated complication is the experience of claustrophobia during scanning. All subjects will be able to terminate the MRI scan at any time for any reason including claustrophobia. 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.

Completing the baseline assessments has minimal potential for harm and at any time during the course of this study, subjects may ask us to stop.

Non-specific risks: Subjects will participate in a psychiatric evaluation, thus they will be exposed to undefined risks associated with these procedures.

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

Protection of Subject Privacy and Confidentiality: All of the research and clinical staff members involved in both studies receive annual Good Clinical Practice, Human Subjects Protection and HIPAA training, and all data collection and management procedures are also fully compliant with HIPAA guidelines. In addition:

1. Study forms are specifically designed to avoid collecting identifiable information, thus no personal health information is collected on case report forms (CRFs). We generally collect only protocol session dates.
2. Research data are collected on CRFs, and sent to data managers in our research offices on a closed secure network. All computers used by research staff are password protected and encrypted. No identifying information is on CRFs.
3. Limits to confidentiality include only disclosure of acute suicidality, homicidality, or abuse of a minor, as is standard in clinical practice.
4. Data are stored at our secure data management center and data sets do not include identifying information. At the conclusion of the study, all locator data are destroyed. Source data are generally destroyed 3 years after completion of the study at a secure location (e.g., Jefferson Archives) and destroyed by Jefferson Archives or Shred-It. We will follow current guidelines (federal and University) at the conclusion of the study.

Protection During Neuroimaging: There are no associated medical risks of MRI scanning at 3.0T. All MRI scanning will be conducted in the presence of experienced research and technical staff. As indicated above, all participants will be thoroughly screened for any contraindication to MRI scanning (e.g., metal implants, claustrophobia) using the Yale MRI Safety Sheet and potential participants not meeting safety requirements will be excluded. In addition, subjects will walk through a ferromagnetic detector to minimize the risk of projectile injury. In addition to the MRI operator, a member of the research team will accompany the study subject and will stay for the MRI. Women of child-bearing age will be given a pregnancy test prior to scanning to rule out pregnancy.

All participants may terminate imaging at any time for any reason. In rare cases, participants may report minor dizziness or nausea. Should this or any other unanticipated event occur, appropriate treatment will be immediately initiated for symptomatic relief.

Risks associated with use of 15 mg oxycodone: As subjects will be given a small dose the risks are minimal. All subjects will be screened by a licensed physician for medication allergies and other contraindications (e.g., familial history of opioid-use disorder; details above).This is an additional safeguard as per MRRC protocols a licensed physician will be on call during the scan. Subjects will be required to have transportation home from the study and if they cannot get a ride from someone else (friend, family, bus) we will arrange for a taxi to pick up and drop off the subjects on testing days.

To further minimize risks, we will exclude participants with family histories of alcohol or opioid addiction (exclusion criteria, above) or with any past or current substance-use disorder. In addition, all potential participants will be given a copy of the SAMHSA Opioid Overdose Prevention toolkit to read through so they are aware of the signs and symptoms of opioid overdose/dependence8. We will also have a list of addiction recovery centers and helplines available in the area that we will provide to every participant. Every effort will be made to ensure subjects understand the issues surrounding opioid abuse and what to look for in the first few hours of taking the 15 mg oxycodone as well as signs and symptoms that they may be developing an addiction to opioid medications. We will ensure participants understand the risk and are aware they can reach out to us or to the list of recovery centers/helplines should they (or someone they know) develop a problem.

All participants will be given a wallet card with contact details for the study physician. In addition to close monitoring during study visits involving oxycodone, participants will be contacted

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via phone following each study visit (OXY and placebo) and at one-month follow-up by a trained member of the research staff to check for any possible any adverse effects and will be referred to the study physician if necessary. The study physician, Dr. Camenga has significant expertise in adolescent and young adult substance use and addiction and emergency medicine. She is also a licensed buprenorphine provider (FC1166683(DEA)/XC1166693(X-waiver)) and runs an outpatient treatment program for adolescents and young adults with opioid use disorders in New Haven. She is therefore extremely well qualified to deal with possible oxycodone-associated risks, in the unlikely event that they arise. If at any time during the study participants are found to be at risk for hurting themselves they may be hospitalized as a safety measure.

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

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

DATA AND SAFETY MONITORING PLAN (DSMP)
Personnel responsible for the safety review and its frequency:

This project will be monitored by a Data and Safety Monitoring Board (DSMB), because the study involves administration of oxycodone. Specifically, this study will assess the effects of acute low-dose opioid administration on functional neuroimaging measures in healthy individuals (N=40, 20 male, 20 female). The objective of this research is to develop an understanding of factors that may influence individual variability on resting state functional connectivity in response to low-dose opioid administration with the longer term aim of understanding addictions vulnerability. Specifically, the proposed pilot research will explore the effects of single dose of oxycodone (15mg) on resting state functional connectivity and other common neuroimaging measures (e.g., diffusion MRI, structural MRI). Previous work has found 10-20mg doses well-tolerated, but has found increased ratings of nausea following 20mg doses (Gorka, Fitzgerald et al. 2014, Wardle, Fitzgerald et al. 2014). Preliminary data (Gorka, Fitzgerald et al. 2014) suggest that 10mg and 20mg doses have similar effects on FC. However, a 10mg dose of oxycodone may not be clinically sufficient for CYP3A4 fast metabolizers (Samer, Daali et al. 2010, Brennan 2012). To balance concerns related to excluding potential participants based on this relatively common genetic variation (thus potentially limiting the applicability of study findings) with those of a higher dose of oxycodone (e.g., 20mg), we will use a 15mg dose. Other laboratory studies in healthy controls have found doses between 15mg and 20mg to be well tolerated (Zacny and Lichtor 2008, Samer, Daali et al. 2010, Cooper, Sullivan et al. 2012).

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Given the high prevalence of prescription opioid exposure in youth (McCabe, West et al. 2012), it is not feasible to study exclusively opioid-naïve individuals. Prior neuroimaging work using oxycodone has not excluded for lifetime exposure, but has excluded for abuse or dependence (Gorka, Fitzgerald et al. 2014). To minimize the possible influence of individual differences in prior exposure, we will exclude for prior 6 month use, as well for significant prior medical (>5 days of consecutive medical use) or nonmedical use (>5 prior uses of oxycodone).

Peak plasma concentrations of orally administered immediate release 10mg OXY occur approximately 1 hour following ingestion and has a half life of 3-4 hours (Ordonez Gallego, Gonzalez Baron et al. 2007, Gronlund, Saari et al. 2010, Saari, Gronlund et al. 2010). We are therefore confident that a 6-month washout period will be more than sufficient to ensure clearance.

All participants will be seen for an initial intake by a research assistant either in person or virtually via Zoom and who will begin the review process of eligibility, obtain medical history, provider information and relevant releases. Physical examination findings and laboratory tests will inform eligibility decisions. Potential participants will undergo medical screening to determine eligibility to receive a single dose of oxycodone 15mg. Medical screening for contraindication to low-dose opioid administration (e.g., medication allergies, kidney or liver problems, personal or familial history of opioid- or alcohol-use disorders) will be conducted by a licensed physician. Lab tests will be ordered at the discretion of the physician to determine eligibility for study participation. Final determination of eligibility will be determined by the study physician and investigators. Monitoring will occur during and after all procedures with participants remaining in our lab for one hour post scan (3.5-4 hours after opioid administration). In addition, a follow up phone call will be made one day and again one month after scan with additional medical care, if indicated, being facilitated.

The Principal Investigator (PI) will be responsible for monitoring the data, assuring protocol compliance, and ensuring safety reviews are conducted every 6 months (including when reapproval of the protocol is sought). During the review process, the PI (monitor) will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. Either the PI, the IRB, or the DSMB will have the authority to stop or suspend the study or require modifications.

The DSMB is composed of persons not otherwise affiliated with the trial who are experienced in various aspects of the conduct of trials. We propose four who are not directly involved in this trial but who serve are members of the Departments of Psychiatry and Child Study—Declan Barry, PhD, Stephanie O'Malley, PhD, Godfrey Pearlson, MA, MBBS and Linda Mayes, MD—as the membership of the DSMB. These four individuals have appropriate expertise in drug challenge studies, clinical trials, research in young adults and/or opioid use disorder. None of these three are directly involved with this proposed trial and consequently should not pose a conflict of interest. The members of the DSMB and all study Investigators will complete Conflict of Interest forms created by Yale's IRB in accordance with NIH guidelines.

For the DSMB to fulfill its mission of assuring the safety of human subjects and the scientific integrity of the studies conducted, the Board will have access to accumulating study outcome data in a manner that will protect its confidentiality and preserve its statistical integrity. The Board will examine accumulating data to assure that the risks and benefits of participation remain acceptable and that the results of the trial will be considered scientifically reliable. The conditions under which the Board will

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examine this data are described below. This monitoring will be consistent with NIH policy regarding the protection of human subjects in research, and FDA guidance on statistical practices for clinical trials (ICH E9) and good clinical practices (ICH E6). In general, the data to be reviewed will include the following.

1. Recruitment, retention, and follow-up rates for the study for comparison to target rates
2. Rates of data completeness and availability of primary outcome data
3. Occurrence of adverse events (AEs) and serious adverse events (SAEs; see below for definition)
4. Report of study progress since the last report
5. Rates of recruitment of women and minorities with respect to targeted rates

This will allow board members to ensure that the risks and benefits of participation remain acceptable and that the results of the research will be considered scientifically reliable, in accordance with NIH policies on the protection of human subjects in research. Following each report, each DSMB member will complete a form making one of two recommendations:

1. Continuation of recruitment as planned
2. Immediate scheduling of a formal DSMB meeting

In the event of option #2 (recommendation of an immediate meeting), this will be scheduled within one week, minutes will be kept, the report will be reviewed with the PI (Dr. Yip), the study physician (Dr. Camenga) and both of the PI's primary K01 mentor (Dr. Potenza), and the committee will vote on whether the study should:

1. Continue recruitment without any changes
2. Continue recruitment following protocol amendment
3. Stop recruitment pending further investigation

In the event of option #3 (cessation of recruitment), the Yale School of Medicine Human Investigation Committee will be informed.

Adverse event data and other data intended for the monitoring of safety will be presented to the DSMB. Within the scope of the proposed study, an adverse effect is defined as any reaction, side effect, or untoward event that occurs during the course of the study, whether or not the event is considered medication-related or clinically significant. A side effects scale will be used that enquires regarding physical or health problems since the last visit, including changes in physical appearance and changes in functioning due to physical condition. This will be followed by an assessment of whether the patient experienced specific problems such as nausea/vomiting, diarrhea, abdominal pain, change in appetite, headaches, dizziness, fatigue, nervousness/anxiety. If the patient answers 'yes' to any of the above questions, date of onset and duration, and pattern of symptom will be documented, and a severity rating will be elicited.

Attribution of Adverse Events:

We will use the Yale University School of Medicine – Human Investigation Committee (HIC) recommended
guidelines for assessing the attribution of adverse events. The PI will conduct a review of all adverse events
and determine the attribution of the adverse event by using the following categories:

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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).

Plan for Grading Adverse Events:

We will use the following scale in grading the severity of adverse events noted during the study:

0: No adverse event or within normal limits
1: Mild adverse event- discomfort noticed, but no disruption of normal daily activity
2: Moderate adverse event- discomfort sufficient to reduce or affect normal daily activity
3: Severe adverse event resulting in hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect
4: Life-threatening or disabling adverse event
5: Fatal adverse event

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;
3. In-patient hospitalization or prolongation of existing hospitalization;
4. A persistent or significant disability or incapacity;
5. A congenital anomaly or birth defect; OR
6. 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. The PI will consider the grade of the event as well as its "seriousness" when determining whether reporting to the IRB is necessary.

The PI (Sarah Yip, Ph.D.) will assume full responsibility for reporting serious adverse events and will consult with the study nurse and/or physician in making attribution of risk and relatedness. Subjects will be terminated from participation if the investigator feels that subjects' health or well-being may be threatened by continuation in the study.

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

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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 possibly, probably or definitely 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.

UPIRSOs meeting these criteria will be reported to the Yale IRB in accordance with the timeline(s) detailed within IRB Policy 710, specifically:

- Events that may require a temporary or permanent interruption of study activities by the Principal Investigator (PI) or sponsor to avoid potential harm to subjects will be reported to the IRB **immediately** (if possible), followed by a written report to the IRB using the UPIRSO Reporting Form (710 FR 4) **no more than 5 calendar days** after the Yale PI becomes aware of the event.
- Internal Events meeting the criteria above will be reported to the IRB using the UPIRSO Reporting Form (710 FR 4) **within 5 calendar days** of the PI becoming aware of the event.

All related events involving risk but not meeting the *prompt* reporting requirements described above will be reported to the IRB in summary form at the time of continuing review. If appropriate, such a summary may be a simple brief statement that events have occurred at the expected frequency and level of severity as previously documented**.** A current DSMB report may be submitted in lieu of a summary of external events.

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

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

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X All Co-Investigators listed on the protocol.

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

X National Institutes of Health

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

☐ Medical Research Foundation (Grant_____)

☐ Study Sponsor

X Other Data Safety Monitoring Board (DSMB) or Committee (DSMC)

UPIRSOs will be reported to the IRB in accordance with IRB Policy 710 (detailed above in **Section 6. Plan for reporting UPIRSOs (including Adverse Events) to the IRB**). In addition, serious anticipated adverse events (SAE) that occur with a greater frequency than expected, and unanticipated adverse events that are possibly, probably, or definitely related to study procedures will be reported in writing to the Data Safety Monitoring Board (DSMB) constituted for this study according to the timeline outlined above in **Section 6**, and will be reported to NIDA according to NIDA's reporting guidelines (e.g., within 48 hours of the event becoming known). The study team, in consultation with the DSMB, will evaluate the adverse event and determine whether the adverse event affects the Risk/Benefit ratio of the study and whether modifications to the protocol or consent form are required. In addition, they will conduct a review of all adverse events at least semi-annually, and they will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required. The sequence of events that will determine if this clinical trial is to be terminated are: a) evaluation of individual stopping rules; b) evaluations of several individuals as aggregate data; c) determination of the likelihood that the adverse events are study-related; d) if the severity of study-related adverse experience(s) is judged extreme, then the study will be terminated; and e) emergence of unexpected serious adverse experience(s).

Following each DSMB meeting written minutes will be prepared and distributed to the PI summarizing any recommendations including any recommendations for interim analyses. These written reports will ensure timely communication with the study PI with preparation of any protocol amendments necessary. After each DSMB meeting, this written report will describe all recommendations including additional safety steps. The FDA adverse drug experience reporting timelines will be utilized as timelines to disseminate feedback from the DSMB to the PI and co-investigators. That is, three days for acute circumstances and ten days for nonacute circumstances. We will report substantial protocol amendments or changes in the informed consent to NIDA as well as any temporary or permanent suspension of patient accrual.

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

Based on findings reported by Gorka and colleagues[3], we anticipate that a sample size of 30 individuals will be sufficiently powered (>.90) to detect changes in FC following OXY versus placebo (noncentrality parameter (δ)=7.26, critical t-value=2.05, df=29, power (1-β)=0.99). We are

therefore confident that our recruitment aim of N=40 will be sufficiently powered, even after accounting for possible subject drop-out and/or data exclusion due to excessive motion (approximately 20% in prior studies).

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

Generic name: oxycodone

Chemical name: 14-hydroxydihydrocodeinone

FDA approved? Yes, by prescription only

Indications: This is a medicine used to relieve moderate to severe pain

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

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

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

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Peak plasma concentrations of orally administered immediate release 10mg OXY occur approximately 1 hour following ingestion (Gronlund et al., 2010; Saari et al., 2010), as do peak ratings of subjective 'high'(Wardle et al., 2014). Oxycodone (or generic equivalent) will be administered orally in a private medical room at Yale University's Magnetic Resonance Research Center (MRRC) 1 hour prior to scanning by a trained member of the research team. The study physician will be available via pager (and in close proximity to the MRRC) during medication administration and scanning, consistent with Yale safety policies. All participants will be closely monitored for any possible adverse side effects. As subjects will receive only a single oral dose of 15 mg oxycodone, risks are minimal. The most common risks associated with oxycodone include constipation (in 25-30% of individuals), nausea (25%), drowsiness (25%), dizziness (15%), vomiting (10-15%) and pruritis (10-15%) (Ordonez Gallego, Gonzalez Baron, & Espinosa Arranz, 2007). Should these side effects occur, participants will be offered symptomatic relief by the study physician (Dr. Camenga) as appropriate based on her clinical judgement. Participants will be monitored closely until side effects have subsided. The study physician, Dr. Camenga has significant expertise in adolescent and young adult substance use and addiction and emergency medicine. She is also a licensed buprenorphine provider (FC1166683(DEA)/XC1166693(X-waiver)) and runs an outpatient treatment program for adolescents and young adults with opioid use disorders in New Haven. She is therefore extremely well qualified to deal with possible oxycodone-associated side effects, in the unlikely event that they arise.

Although the risks are minimal, a dose of naloxone will be on hand to counteract any effects from the opioid should the need arise (as determined based on the discretion of the study physician). Previous experimental work using up to 20mg of OXY found both 10mg and 20mg doses to be well-tolerated, but found increased ratings of nausea following 20mg doses (Gorka, Fitzgerald, de Wit, Angstadt, & Phan, 2014; Wardle et al., 2014). As preliminary data (Gorka et al., 2014) suggest that 10mg and 20mg doses have similar effects on FC, we chose to use 15mg to further minimize possible risk to participants. The starting initial dose for oxycodone in healthy adults is between 5 and 15mg, thus 15mg should be well tolerated

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

The YNHH pharmacy will be ordering the medications from their established vendors.

a) Is the drug provided free of charge to subjects? ☒YES ☐NO
If yes, by whom?

The study investigator will be responsible for purchasing the drug in order to provide it free of charge to participants.

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

The YNHH pharmacy will be in charge of the necessary storage, stability, testing, etc. The research pharmacist and his staff will prepare the prescribed drugs. Once prepared, the study staff will pick it up, bring it to the appropriate study location and hand it over directly to the subject. The study staff will also collect from the subject any unused drugs and return it to the pharmacy. Drug delivery and

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distribution will be tracked via a drug accountability form and other pharmacy or sponsor-required paperwork.

Check applicable Investigational Drug Service utilized:

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

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

2. Use of Placebo: Yes - applicable to this research project

This protocol is being conducted to determine if oxycodone influences neural functional responses in healthy young adults. To control for possible 'placebo effects' – i.e., neural responses related to the expectation of receiving an active drug - we have added a placebo condition. Note that this randomized, counter-balanced, within-subject, cross-over design is considered the 'gold standard' for pharmacotherapy research. As this is not a treatment trial, administration of placebo will not involve any additional risks in comparison to administration of oxycodone. All participants will be closely monitored for any possible adverse side effects by the study physician researchers. Placebo medications will be prepared by IDS, YNHH or APT pharmacy staff, as in our other ongoing protocols (HIC# 1510016617). Placebo and active drug (15mg OXY) will be encapsulated in identical capsules and administration will be documented by research and pharmacy staff, as in our other studies.

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

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: **40 (may screen up to 100 individuals)**
   b. If this is a multi-site study, give the total number of subjects targeted across all sites: **N/A**

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

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

3. Recruitment Procedures:

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

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Healthy individuals will be recruited by community advertisement (all announcements have been approved by the HIC) through print or internet media. In addition, subjects may learn about our study and be given contact info through research staff of other IRB-approved studies. We will provide research staff of other research groups with a letter explaining our study procedures, need for subjects, and eligibility criteria. They will be asked to tell their subjects about the possibility of participating in our study and how to contact us for more info. Through this process of collaboration, our 'collaborators' will not be screening our subjects, they will only be telling them about an additional research opportunity that may or may not be available to the subject. Study personnel listed on this protocol may also inform subjects with whom they have contact about other research opportunities regarding other studies for which they are also listed as study personnel. In this case, they may provide contact information to the subject. 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

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:

   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:

   Subjects are, in most cases, screened by phone, Zoom 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.

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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.

A trained research staff member at the performance site will obtain written informed consent prior to any study related procedures either in person or via Zoom. For those consents conducted via Zoom a photo will be taken of the consent form including signature page for verification per Yale's guidelines.. The informed consent process will be conducted 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: Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.

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.

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. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☐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.)

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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 ☒

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?

   Medical/psychiatric history, urine drug screen results, psychological assessments, MRI data, email addresses, phone numbers, all geographic subdivisions smaller than a State, including: street address, city, county, precinct, zip codes, all elements of dates related to an individual, including: birth date, admission date, discharge date, date of death, and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 18 or older.

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

   Assessment, screening, and interview data will be recorded on paper, and in Qualtrics on password-protected computers, and on Yale ITS shared server with limited access to approved research staff. Data from scans and assessments will be labeled with a corresponding subject identification number and stored as described above. A 'master file' will record the identity of the subject numbers and be kept in a secure fashion either in a locked cabinet or an encrypted password-protected file stored on a password-protected computer. Access to data and PHI will be strictly limited to approved study personnel and others allowed through disclosure policies.

   De-identified MRI data will be stored on a secure server and may be archived and/or backed-up to a portable hard drive/flash drive, CD or DVD.

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?

   MRI data and assessment data will be identified by subject number rather than name. Screening information will remain identified by name. Procedures to protect this PHI have been described above. After termination of this study and completion of all analysis and publications,, we will follow current procedures from the HIC when de-identifying and storing/destroying records. Private identifiable

information will not appear in any publication or be released to anyone without the individual's written consent.

Human subjects enrolled in the study are assigned a subject-specific random identifier. Subject identifiers and the means to link the subject names and codes with the research data are stored in separate locations within the database. The software of the database limits the ability to connect the random identifier to the actual subject identification information to research team members only. Access to the database is password protected and each research team member is required to have a unique ID and password to gain access to the database. Authorized users employ their netid and authentication is performed using Yale's central authentication server. Users always access research data through the random identifier only. Direct identifiers belonging to subjects who withdraw from the study, will be stripped from the key.

Data is protected by storage in locked file cabinets, password protected computers, and shared limited access server. Please refer to section IV question 2 above for more details.

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 de-identified 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?
   Coverage defined by the COC regulation is automatic and in compliance with the requirements of the law and is a term and condition of award for grant recipients who are collecting identifiable, sensitive information as part of their NIH funded research.

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.)

There are no direct benefits from participation in this research protocol. However, knowledge gained may help us to better understand how individual difference factors that contribute to variation in neuroimaging studies, which may be used to design more effective research protocols for use in psychiatric populations.

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.

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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.

   Potential participants will be paid $25 to participate in a baseline screening session and $10 for a medical screening session. Eligible participants will be paid $145 for participation in each fMRI session, with a bonus of $75 for completing both sessions. The total possible compensation for participants is therefore $400.

   In addition, subjects may be paid a referral payment up to $25 for each eligible participant they refer to this 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 to the subject for participation.

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?

      When appropriate, the subject may be referred to a suitable treatment program.

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

      The study staff will not provide treatment. In case of injury, only evaluation and referral will be provided. A follow-up will be completed to ensure the subject sought treatment and if not, why.

   d. Who will pay for this treatment?

      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.

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IMPORTANT REMINDERS

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

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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