NCT04342130

YALE UNIVERSITY
HUMAN INVESTIGATION COMMITTEE

Application to Involve Human Subjects in Biomedical Research
100 FR1 (2015-2)

SECTION I: ADMINISTRATIVE INFORMATION

Title of Research Project: Brain effects of opiate agonist and antagonist			
Principal Investigator: Paul Geha, MD		**Yale Academic Appointment: Assistant Professor**	
Department: Psychiatry			
Campus Address: 290 Congress Ave.			
Campus Phone: 203-903-4334	**Fax:** 203-624-4950	**Pager:**	**E-mail:** paul.geha@yale.edu
Protocol Correspondent Name & Address (*if different than PI*):			
Campus Phone:	**Fax:**	**E-mail:**	
Yale Cancer Center CTO Protocol Correspondent Name & Address (*if applicable*):			
Campus Phone:	**Fax:**	**E-mail:**	
Business Manager:			
Campus Phone :	**Fax :**	**E-mail**	

Faculty Advisor:(required if PI is a student, resident, fellow or other trainee) ☒ **NA**		**Yale Academic Appointment:**	
Campus Address:			
Campus Phone:	**Fax:**	**Pager:**	**E-mail:**

Investigator Interests:

Does the principal investigator, or do any research personnel who are responsible for the design, conduct or reporting of this project or any of their family members (spouse or dependent child) have an incentive or interest, financial or otherwise, that may affect the protection of the human subjects involved in this project, the scientific objectivity of the research or its integrity? Note: The Principal Investigator (Project Director), upon consideration of the individual's role and degree of independence in carrying out the work, will determine who is responsible for the design, conduct, or reporting of the research.

APPROVED BY THE YALE UNIVERSITY IRB 1/5/2018 VALID THROUGH 8/8/2018

See Disclosures and Management of Personal Interests in Human Research
http://www.yale.edu/hrpp/policies/index.html#COI
☐ Yes ☐☐No

Do you or does anyone on the research team who is determined by you to be responsible for the design, conduct or reporting of this research have any patent (sole right to make, use or sell an invention) or copyright (exclusive rights to an original work) interests related to this research protocol?
☐ Yes ☐☐ No

If yes to either question above, list names of the investigator or responsible person:

The Yale University Principal Investigator, all Yale University co-investigators, and all Yale University individuals who are responsible for the design, conduct or reporting of research must have a current disclosure form on file with the University's Conflict of Interest Office. Yale New Haven Hospital personnel who are listed as co-investigators on a protocol with a Yale University Principal Investigator must also have a current financial disclosure form on file with the University's Conflict of Interest Office. If this has not been done, the individual(s) should follow this link to the COI Office Website to complete the form: http://www.yale.edu/coi/

NOTE: The requirement for maintaining a current disclosure form on file with the University's Conflict of Interest Office extends primarily to Yale University and Yale-New Haven Hospital personnel. **Whether or not they are required to maintain a disclosure form with the University's Conflict of Interest Office, all investigators and individuals deemed otherwise responsible by the PI who are listed on the protocol are required to disclose to the PI any interests that are specific to this protocol.**

SECTION II: GENERAL INFORMATION

1. **Performing Organizations:** Identify the hospital, in-patient or outpatient facility, school or other agency that will serve as the location of the research. Choose all that apply:

a. Internal Location[s] of the Study:

☒ Magnetic Resonance Research Center (MR-TAC)
☐ Yale Cancer Center/Clinical Trials Office (CTO)
☐ Yale Cancer Center/Smilow
☐ Yale-New Haven Hospital
☐ Cancer Data Repository/Tumor Registry
☐ Specify Other Yale Location:
☐ Yale University PET Center
☐ YCCI/Church Street Research Unit (CSRU)
☐ YCCI/Hospital Research Unit (HRU)
☐ YCCI/Keck Laboratories
☐ Yale-New Haven Hospital—Saint Raphael Campus

b. External Location[s]:

☐ APT Foundation, Inc.
☐ Connecticut Mental Health Center
☐ Haskins Laboratories
☒ John B. Pierce Laboratory, Inc.

☐ Clinical Neuroscience Research Unit (CNRU) ☐ Veterans Affairs Hospital, West Haven
☐ Other Locations, Specify: ☐ International Research Site
(Specify location(s)):

c. Additional Required Documents *(check all that apply)*: ☐ N/A

☐ *YCCI-Scientific and Safety Committee (YCCI-SSC)	Approval Date:
☐ *Pediatric Protocol Review Committee (PPRC)	Approval Date:
☐ *YCC Protocol Review Committee (YRC-PRC)	Approval Date:
☐ *Dept. of Veterans Affairs, West Haven VA HSS	Approval Date:
☐ *Radioactive Drug Research Committee (RDRC)	Approval Date:
☐ YNHH-Radiation Safety Committee (YNHH-RSC)	Approval Date:
☐ Yale University RSC (YU-RSC)	Approval Date:
☐ Magnetic Resonance Research Center PRC (MRRC-PRC)	Approval Date:
☐ *Nursing Research Committee	Approval Date:
☐ YSM/YNHH Cancer Data Repository (CaDR)	Approval Date:

☐ Dept. of Lab Medicine request for services or specimens form
☐ Imaging on YNHH Diagnostic Radiology equipment request form (YDRCTO request) found at http://radiology.yale.edu/research/ClinTrials.aspx)

Approval from these committees is required before final HIC approval is granted. See instructions for documents required for initial submission and approval of the protocol. Allow sufficient time for these requests. Check with the oversight body for their time requirements.

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities. 3 Years

3. **Research Type/Phase: (Check all that apply)**
   a. **Study Type**
   ☒ Single Center Study
   ☐ Multi-Center Study
   Does the Yale PI serve as the PI of the multi-site study? Yes ☐ No ☐
   ☐ Coordinating Center/Data Management
   ☐ Other:

   b. **Study Phase** ☐ **N/A**
   ☒ Pilot ☐ Phase I ☐ Phase II ☐ Phase III ☐ Phase IV
   ☐ Other (*Specify)*

4. **Area of Research: (Check all that apply)** Note that these are overlapping definitions and more than one category may apply to your research protocol. Definitions for the following can be found in the instructions section 4c:

☒ Clinical Research: Patient-Oriented	☐ Clinical Research: Outcomes and Health Services
☐ Clinical Research: Epidemiologic and Behavioral	
☐ Translational Research #1 ("Bench-to-Bedside")	☐ Interdisciplinary Research

☐ Translational Research #2 ("Bedside-to-Community") ☐ Community-Based Research

5. Is this study a clinical trial? Yes ☒ No ☐

NOTE the current ICMJE (International Committee of Medical Journal Editors) definition of a clinical trial: "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes." Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example, drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and process-of-care changes). Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events"

If yes, where is it registered?

Clinical Trials.gov registry ☒

Other (*Specify*)

*Registration of clinical trials **at their initiation** is required by the FDA, NIH and by the ICMJE.*

If this study is registered on clinicaltrials.gov, there is new language in the consent form and compound authorization that should be used.

For more information on registering clinical trials, including whether your trial must be registered, see the YCCI webpage, http://ycci.yale.edu/researchers/ors/registerstudy.aspx or contact YCCI at 203.785.3482)

6. Does the Clinical Trials Agreement (CTA) require compliance with ICH GCP (E6)?
Yes ☐ No☒

7. Will this study have a billable service? *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.*

Yes ☐ No☒

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

8. Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? **No** ___ *If Yes, please answer questions a through c and note instructions below. If No, proceed to Section III.*

a. Does your YNHH privilege delineation currently include the **specific procedure** that you will perform? **Yes**
b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? **No**

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

If you answered "no" to question 8a, or "yes" to question 8b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

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 signing 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****.*

SECTION III: FUNDING, RESEARCH TEAM AND TRAINING

1. **Funding Source:** Indicate all of the funding source(s) for this study. Check all boxes that apply. Provide information regarding the external funding source. This information should include identification of the agency/sponsor, the funding mechanism (grant or contract), and whether the award is pending or has been awarded. Provide the M/C# and Agency name (if grant-funded). If the funding source associated with a protocol is "pending" at the time of the protocol submission to the HIC (as is the case for most NIH submissions), the PI should note "Pending" in the appropriate section of the protocol application, provide the M/C# and Agency name (if grant-funded) and further note that University (departmental) funds support the research (until such time that an award is made).

PI	Title of Grant	Name of Funding Source	Funding	Funding Mechanism
Paul Geha, MD	Neural Mechanisms of Obesity in Chronic Low Back Pain	NIDA	☒ Federal ☐ State ☐ Non Profit ☐ Industry ☐ Other For Profit ☐ Other	☐ Grant-M# ☐ Contract# ☐ Contract Pending ☒ Investigator/Department Initiated ☐ Sponsor Initiated ☐ Other, Specify:

			☐ Federal ☐ State ☐ Non Profit ☐ Industry ☐ Other For Profit ☐ Other	☐ Grant-M# ☐ Contract# ☐ Contract Pending ☐ Investigator/Department Initiated ☐ Sponsor Initiated ☐ Other, Specify:
			☐ Federal ☐ State ☐ Non Profit ☐ Industry ☐ Other For Profit ☐ Other	☐ Grant-M# ☐ Contract# ☐ Contract Pending ☐ Investigator/Department Initiated ☐ Sponsor Initiated ☐ Other, Specify:

IRB Review fees are charged for projects funded by Industry or Other For-Profit Sponsors. Provide the Name and Address of the Sponsor Representative to whom the invoice should be sent. ***Note: the PI's home department will be billed if this information is not provided.***

Send IRB Review Fee Invoice To:

Name:
Company:
Address:

2. **Research Team:** List all members of the research team. Indicate under the affiliation column whether the investigators or study personnel are part of the Yale faculty or staff, or part of the faculty or staff from a collaborating institution, or are not formally affiliated with any institution. **ALL members of the research team MUST complete Human Subject Protection Training (HSPT) and Health Insurance Portability and Accountability Act (HIPAA) Training before they may be listed on the protocol. See NOTE below.**

NOTE: The HIC will remove from the protocol any personnel who have not completed required training.

	Name	**Affiliation: Yale/Other Institution (Identify)**	**NetID**
Principal Investigator	Paul Geha	Yale	PYG5
Role: Co-PI	Dana Small	Yale	DS537
Role: RA	Gelsina Stanley	John B. Pierce	Gs558
Role:RA	Elizabeth Garcia	John B. Pierce	Eg559
Role : Student	William Oles	Yale	wco5

A personnel protocol amendment will need to be submitted when training is completed.

SECTION IV: PRINCIPAL INVESTIGATOR/FACULTY ADVISOR/ DEPARTMENT CHAIR AGREEMENT

As the **principal investigator** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- I assume full responsibility for the protection of human subjects and the proper conduct of the research.
- Subject safety will be of paramount concern, and every effort will be made to protect subjects' rights and welfare.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- All members of the research team will be kept apprised of research goals.
- I will obtain approval for this research study and any subsequent revisions prior to my initiating the study or any change and I will obtain continuing approval of this study prior to the expiration date of any approval period.
- I will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
- I am in compliance with the requirements set by the University and qualify to serve as the principal investigator of this project or have acquired the appropriate approval from the Dean's Office or Office of the Provost, or the Human Subject Protection Administrator at Yale-New Haven Hospital, or have a faculty advisor.
- I will identify a qualified successor should I cease my role as principal investigator and facilitate a smooth transfer of investigator responsibilities.

PI Name (PRINT) and Signature _____ Date _____

As the **faculty advisor** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- This project has scientific value and merit and that the student or trainee investigator has the necessary resources to complete the project and achieve the aims.
- I will train the student investigator in matters of appropriate research compliance, protection of human subjects and proper conduct of research.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- The student investigator will obtain approval for this research study and any subsequent revisions prior to initiating the study or revision and will obtain continuing approval prior to the expiration of any approval period.
- The student investigator will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
- I am in compliance with the requirements set forth by the University and qualify to serve as the faculty advisor of this project.
- I assume all of the roles and responsibilities of a Principal Investigator even though the student may be called a PI.

Advisor Name (PRINT) and Signature _____ Date _____

Department Chair's Assurance Statement

Do you know of any real or apparent institutional conflict of interest (e.g., Yale ownership of a sponsoring company, patents, licensure) associated with this research project?

☐ Yes (provide a description of that interest in a separate letter addressed to the HIC.)
☒ No

As Chair, do you have any real or apparent protocol-specific conflict of interest between yourself and the sponsor of the research project, or its competitor or any interest in any intervention and/or method tested in the project that might compromise this research project?

☐ Yes (provide a description of that interest in a separate letter addressed to the HIC)
☐ No

I assure the HIC that the principal investigator and all members of the research team are qualified by education, training, licensure and/or experience to assume participation in the conduct of this research trial. I also assure that the principal investigator has departmental support and sufficient resources to conduct this trial appropriately.

_____ _____
Chair Name (PRINT) and Signature Date

_____
Department

YNHH Human Subjects Protection Administrator Assurance Statement

Required when the study is conducted solely at YNHH by YNHH health care providers.

As Human Subject Protection Administrator (HSPA) for YNHH, I certify that:

- I have read a copy of the protocol and approve it being conducted at YNHH.
- I agree to notify the IRB if I am aware of any real or apparent institutional conflict of interest.
- The principal investigator of this study is qualified to serve as P.I. and has the support of the hospital for this research project.

_____ _____
YNHH HSPA Name (PRINT) and Signature Date

SECTION V: RESEARCH PLAN

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

   To determine the effect of *one dose* of morphine, naltrexone and placebo on brain activity in healthy participants and patients suffering from pain.

   To determine whether the effect of *one dose* of morphine, /naltrexone and placebo on brain activity in healthy participants and patients suffering from pain is different depending on Single Nucleotide Polymorphism (SNP) at the gene loci coding for opiate and dopamine related neurotransmission.

   To relate brain response to morphine to performance on reward related decision-making tasks.

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

Opiate medications such as morphine are potent analgesics and frequently used in the treatment of chronic non-cancer pain despite the absence of benefits in randomized clinical trials on pain relief when compared to placebo beyond 3-4 months of treatment [1]. Treatment with opiates put patients at risk of weight gain [2,3], falls [4], overdose, abuse and long-term dependence [5].

Opiate intake has been particularly associated with a shift in the diet towards increased sugar and highly palatable food intake and long-term weight gain [6,7]. In addition, opiate antagonist such as naltrexone is used to prevent binge eating behavior in humans, which is a major contributor to obesity [8]. Extensive animal research is consistent with a major role of μ-opiate agonist in feeding in the absence of hunger (i.e. hedonic feeding) (comprehensive reviews in [9,10]). Binding of μ-opiate agonist in the ventral striatum and amygdala causes hyperphagia in non-hungry animals and shifts their preference towards highly palatable fat [11,12].

Chronic low back pain (CBP) is associated with obesity [13-17]; however, the contribution of opiate prescriptions to increased body weight is still unknown. Our preliminary data show that CBP patients treated with opiate based medications have a decreased brain response to milkshake when compared to CBP patients not on opiate in the whole insular cortex and primary somatosensory motor areas (**Figure 1).** This suggests that CBP patients on opiates might have a decreased orosensory experience during food ingestion since insula contains the primary taste cortex [18] and integrates taste perception with internal state such as hunger or pain [19]. This decreased perception of food might in turn lead to long-term weight gain.

Given the lack of studies comparing brain response of CBP patients treated with opiate medications during food ingestion to CBP patients without opiate treatment we cannot tell whether the functional changes we observe in **Figure 1** are due to an acute effect of opiate medications or due to a long-term adaptations to these drugs. It is therefore possible that acute

administration of opiate may at first lead to increased response to milkshake that would later adapt and decrease upon chronic administration.

Binding of morphine in the brain of healthy participants occurs in areas rich in opioid receptors including ventral striatum, amygdala, and medial prefrontal cortex [20-22]. These areas have been shown to mediate reward related decision making including food [23-25] money, and goods [26,27]. In addition, there is evidence that morphine binding in these areas strongly modulates deicision making about food [28] and money[29]. Hence, it stands to reason that inter-individual response differenes to one dose of morphine could relate to inter-individuals differences on reward related decision-making.

Therefore, as a first step, we would like to understand the effect of acute administration of a μ-opiate agonist (i.e. morphine), a μ-opiate antagonist (i.e. naltrexone) on brain activity at rest and in response to food in comparison to the administration of a placebo in a double blind design. Also we would like to study the acute effects of opioid (morphine) administration in an open label arm. We are adding this arm to generate preliminary results to study the effect of Morphine using a simpler and less time consuming protocol where participation would be easier for subjects. We will relate performance on gambling, motivational and risk taking tasks to brain response to morphine.

In addition, we would like to factor in individual genetic differences in dopamine and opiate neurotransmission since these are well known to affect brain response to opiates [20,30].

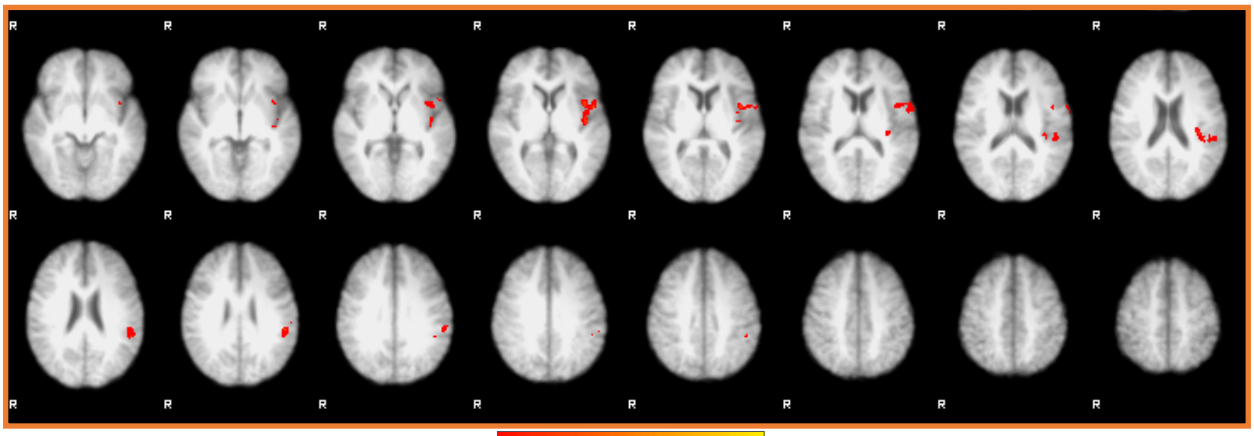


Figure 1. Results of a T-test comparison of brain response to milkshake (corrected for tasteless) between 6 CBP patients taking opiates and 7 CBP patients not taking any analgesic medications. *The two groups did not differ on their ratings of pain intensity*. Results shown at $Z > 2.3$ and $p < 0.05$ corrected for multiple comparisons and using random effects model. We observed decreased brain response with opiate treatment in the right insula, primary somatomotor/sensory areas and frontal operculum.

3. **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.

Procedure:

A. Description of the of the procedures for the double blind placebo controlled arm

Day 1) Phone screening
During an initial telephone conversation, we will provide a brief description of the study, do an initial screening of the subject to ensure that they meet inclusion criteria and do not possess any of the exclusion criteria, and schedule the subject's intake session.

Day 2) Intake session
Subject comes to The John B Pierce Laboratory where written informed consent will be obtained. The subject will be asked to refrain from alcohol use the day before any session. The subject then completes a subset of the following intake measures to determine eligibility:

A. Toxicology/pregnancy screening

We will perform the following screens:

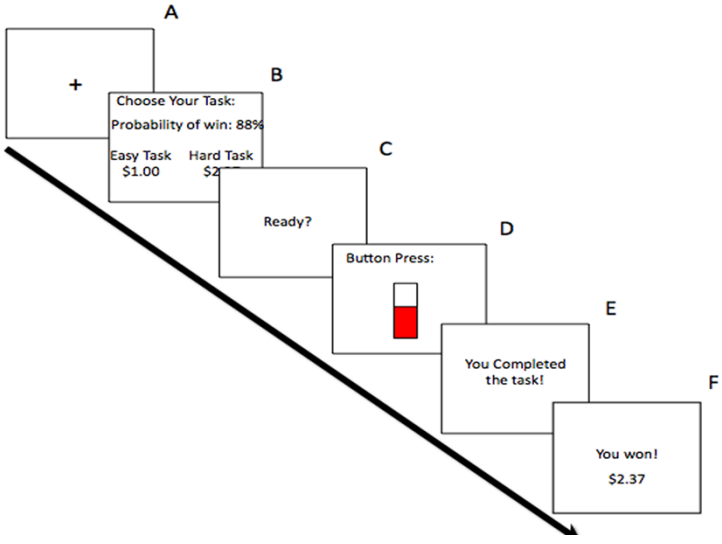
i. Breath alcohol levels will be assessed with the Alcohawk Elite Breathalyzer.
ii. Urine toxicology screens will be conducted using the Integrated E-Z Split Key Cup II (Innovacon Inc., San Diego, CA) for opiates, cocaine, THC, PCP and barbiturate.
iii. We do not wish to study females who may be pregnant. Therefore, all females of childbearing potential will be given a urine pregnancy test.

If a subject tests positive on any of these screens they will be informed of the result and excluded from further participation in the study. The results from these tests will not be recorded for subjects who are excluded for positive results.

Genotyping:
We will collect a saliva sample to genotype for SNPs related to dopaminergic and opiate signaling in the brain. The gene loci tested and their SNPs are attached.

Iowa Gambling Game:

Iowa Gambling Task[31]: Designed to evaluate the ability to postpone immediate reward for a longer-term successful outcome, tests emotional decision-making ability. Subjects play a card game under conditions of limited knowledge about reward and penalty. The participant is presented with 4 decks of card. Two decks are advantageous (A and B); A and B do not give big gains but do not lead to losses after 100 draws. Two decks are disadvantageous (C and D). C and D give big gains but end up leading to big losses after 100 draws. Patients with inability to delay immediate gratification to improve long-term outcomes perform badly on this task. The gains and losses will be in fake Monopoly money.



F

Effort Expenditure for Rewards (EEfRT)

The EEfRT [32]task is a multi-trial game in which participants are given an opportunity on each trial to choose between two different task difficulty levels in order to obtain monetary rewards (see Figure) For all trials, participants made repeated manual button presses within a short period of time. Each button press raised the level of a virtual "bar" viewed onscreen by the participant. Participants are eligible to win the money allotted for each trial if they raised the bar to the "top" within the prescribed time period. Each trial presented the subject with a choice between two levels of task difficulty, a 'hard task' and an 'easy task'. Successful completion of hard-task trials required the subject to make 100 button presses, using the non-dominant little finger within 21 seconds, while successful completion of easy-task trials required the subject to make 30 button presses, using the dominant index finger within 7 seconds.

For easy-task trials, subjects are eligible to win the same amount, $1.00, on each trial if they successfully completed the task. For hard-task choices, subjects are eligible to win higher amounts that varied per trial within a range of $1.24 – $4.30 ("reward magnitude"). Subjects are not guaranteed to win the reward if they complete the task; some trials are "win" trials, in which the subject receive the stated reward amount, while others are "no win" trials, in which the subject receive no money for that trial. To help subjects determine which trials are more likely to be winning trials, subjects are provided with accurate probability cues at the beginning of each trial. Trials had three levels of probability: "high" 88% probability of being a win trial, "medium" 50% and "low" 12%. Probability levels always applied to both the hard task and easy task, and there are equal proportions of each probability level across the experiment. Each level of probability appeared once in conjunction with each level of reward value for the hard task. All subjects received trials presented in the same randomized order.

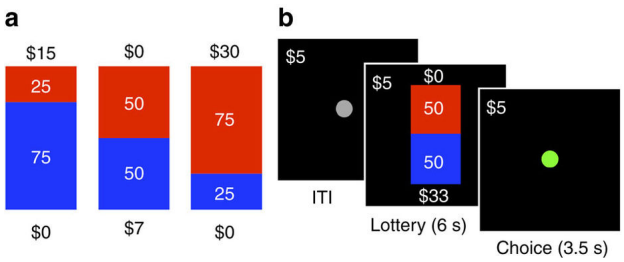
All trials begin with a 1-second fixation cross, following a 5-second choice period in which subjects are presented with information regarding the probability of receiving reward and the reward magnitude of the hard task. Subjects are told that if they did not make a choice within 5 seconds, they would be randomly assigned to either the easy or the hard task for that trial. After making a choice, subjects are then shown a 1-second "Ready" screen and then completed the task. Following task completion, subjects are shown a 2 second feedback screen informing them that the task was successfully or unsuccessfully completed. If subjects successfully completed the task, then a second feedback screen appeared for 2 seconds in which subjects are told whether they had won money for that trial (reward feedback). In total, easy-task trials took approximately 15 seconds, whereas hard-task trials took approximately 30 seconds.

Subjects are told that they would receive a base-rate of compensation for their participation. In addition, they are told that two of their win trials would be randomly selected at the end of the experiment as "incentive trials," for which they would receive the actual amount won on those trials. Subjects are informed that they had twenty minutes to play as many trials as they could. Since hard-task trials take approximately twice as much time to complete as easy-task trials, the number of trials that the subject was able to play depended in part on the choices that he or she made. This meant that making more hard-task trials toward the beginning of the experiment could reduce the total number of trials, which could in turn mean that the subject would not get a chance to play high-value, high-probability trials that might have appeared towards the end of

the playing time. This trade-off will be explained clearly to the subject. Importantly, subjects are not provided with any information regarding the distribution of trial types. The goal of this trade-off is to ensure that neither a strategy of always choosing the easy or the hard option could lead to an 'optimal' performance on the task. Moreover, the complexity of variables (with varying monetary reward levels, probability, and loss of time for future trials), does not lend itself to a formal calculation of an optimal response selection, and subjects are required to make decisions within a brief amount of time. This was done to help ensure that subject decisions reflected individual differences in the willingness to expend effort for a given level of expected reward value. At the end of the experiment the subjects will receive the accumulated earnings in real money.

The EEfRT was programmed in Matlab (Matlab for Windows, Rel. 2007b. Mathworks Inc., Natick, MA) using the Psychtoolbox version 2.0.

Decision making under uncertainty and risk



a) Example trial representing a 25, 50, 75% chance of gaining $15, $7, $30, respectively. (**b**) Example trial sequence.

Participants will receive detailed explanations of the task[26] and of the bonus payment (i.e. accumulated earnings) procedure and are required to pass task comprehension questions before completing practice trials. In the experiment itself, participants will be first given $100 endowment to start playing. They will make 60 binary choices between a certain gain of $5 and a bet of a monetary value (20 amounts: $5–$20 in gains or losses) and probability of payout or loss (3 levels: 0.25, 0.5, 0.75) are systematically manipulated. Each trial will be represented by an image of a bag containing 100 colored poker chips, some red and some blue (See Figure); these images corresponded to physical bags that are present in the experimental room. The size of the colored areas and the numbers written inside indicate the number of chips of each color in the bag. Above and below each color, a number indicate how much a chip of that color would be worth if it are drawn from the bag. Trial order will be randomized independently for each participant. At the end of the experiment the subjects will receive the accumulated earnings in real money if they win money in addition to the $100. If they lose money they will still receive a $100 for participation.

Equipment training:

fMRI training

Subjects will be asked to lie in our fMRI simulator and will be outfitted with the taste delivery device and earphones that will play simulated fMRI scanner noises. The simulator consists of a padded table on which the subject lies supine. A removable wooden replica of the fMRI headcoil is placed over the subjects' head. The gustatory manifold is anchored to the simulated headcoil. New tubing and syringes are used for each subject and the

mouthpiece and nasal mask are cleaned and sterilized between uses by boiling in a 10% bleach solution for 15 min. In the simulator and in the actual fMRI scanner subjects will receive liquids through an fMRI compatible custom designed gustometer built by Dr. Small (in collaboration with colleagues in the Pierce shop). In brief, the gustometer consists of a computer running Matlab, controlling a series of programmable syringe pumps with 60ml syringes and beverage tubing attached and leading to a mouthpiece (gustatory manifold) held in place by anchoring to the fMRI headcoil. This set up has been used successfully by Dr. Small's lab for the past 9 years[33-35]. All subjects will undergo a 10-minute mock fMRI run in which they receive the following stimuli: sucrose, tasteless, and milkshake. The purpose of this mock run is to familiarize subjects with the procedures of the fMRI experiment and to teach subjects how to comfortably swallow while lying on a bed made to look like the MR scanner. Most people have no difficulty learning to swallow small quantities of liquid while lying down. Subjects who have difficulty with supine swallowing, who are uncomfortable in the simulated MRI environment, or unable to swallow without excessive movement will not be asked to continue participating in the studies. This procedure takes 30 minutes.

Meeting with the Physician and discussion of drug side effects:
Each participant will meet with Dr. Paul Geha to go over the possible side effects of 30 mg of Morphine, 50 mg of Naltrexone and placebo given at one dose. Dr. Geha will go over the most common side effects and will emphasize the risk of altered mental status (e.g. sleepiness, drowsiness) after one dose of morphine. Dr. Geha is Yale trained psychiatrist and will collect psychiatric history on possible previous misuse of alcohol, illegal drugs and prescription drugs. Any subject with such previous history will be excluded from the study. In addition, each participant will be given a patient information sheet about each of the medications used in the study.

To avoid fatigue subjects will take a 5-minute breaks every 15-20 minutes. This session takes about 2 hours. If the subject meets all eligibility criteria we will schedule them for a Pre-supplementation session at The John B Pierce Laboratory.

Measurment of body fat composition:
We will measure body fat composition of our participants; body fat and body mass index can be confounding in our analysis given that brain response to food is different between obese and healthy weight participants[36]. The BodPod body composition tracking system is an air displacement plethysmograph which uses whole-body densitometry to determine body composition (fat and fat-free mass).The BodPod is an egg-shaped pod that consists out of two chambers. The front, or Test chamber, is where the subject sits and is comprised of a seat that forms a common wall separating it from the rear, or reference chamber. During the brief data collection period of the volume measurement, the chamber door is secured by a series of electromagnets and a gasket. A diaphragm is mounted on the common wall, which oscillates during testing. This causes small changes in volume inside the chamber, of which the pressure response to these small volume changes is measured. This is done by measuring the interior volume of the empty BodPod chamber, then measuring it again when the subject is seated inside. By subtraction, the subject's body volume is obtained. Once the subject's mass and volume are determined, body density is calculated and the relative proportions of fat and fat-free mass are determined. Thus this procedure is entirely non-invasive. A complete test requires about 5

minutes for which the subject will be asked to change into spandex undergarments, that are provided by the Small lab. The interior of the BodPod accommodates a wide variety of human shapes and sizes, including subjects up to 7 feet tall and 550 pounds. The egg-shaped design of the BodPod maximizes interior space, and can be used routinely for testing a wide variety of subjects, including special populations such as obese subjects. The BodPod's precision, accuracy, and reliability have been validated through independent research studies with various subject populations. The Bioelectric Impedance Analysis device (BIA) uses the flow of various low alternating electrical currents and measures impedance. It produces estimates of total body water, extracellular water, fat-free mass and lean soft tissue for each limb and torso. It consists of a weighing platform that also contains foot electrodes (that the subject steps onto) and a bar with finger electrodes (that the subject holds onto with their hands). A complete measurement takes under 1 minute and does not require a subject to change into separate garments. This system is routinely used in hospitals, medical practices and inpatient care facilities in accordance with regulations. The BIA's precision, accuracy and reliability have been validated through independent research studies.

Below is a list of questionnaires subjects will fill out and a description of the food reinforcement test:

Binge Eating Scale (BES): The BES is a 16-item questionnaire that will assess behavioral manifestations and feelings surrounding a binge episode .

Dutch Eating Behavior Questionnaire (DEBQ): The DEBQ (33 items) will be used to assess emotional eating, externalizing, and dietary restraint.

Three Factor Eating Questionnaire (TFEQ): This 58-item questionnaire will be used to obtain a score on the subscales of "cognitive control of eating", "disinhibition", and "susceptibility to hunger"[37].

International Phsyical Activity Questionnaire (IPAQ): the IPAQ is a 27-item questionnaire that will be used to obtain an estimate of physical activity [38].

Pittsburgh Sleep Quality Index (PSQI): the PSQI is a 19-item questionnaire with a global score and subscales that include sleep quality, latency, duration, sleep efficiency, disturbances, hypnotic use, and daytime dysfunction [39].

Dieting and Weight History Questionnaire: This questionnaire will be used to assess history of weight and weight loss attempts.

Power of Food Scale (PFS): The PFS is an 18-item questionnaire that will asses the psychological influences of food environment [40].

Night Eating Questionnaire: This 16-item questionnaire will be used to characterize night time eating behaviors [41].

Phenotype Questionnaire: 11-item questionnaire that assesses individual eating habits and attitudes towards food.

The Behavioral Inhibition System/Behavioral Activation System (BIS/BAS; will assess behavioral activation and behavioral inhibition which have been proposed as biological systems underlying behavior and affect. The Behavioral Inhibition assesses sensitivity to punishment (BIS scale) and three subscales tap different components of behavioral activation (Reward Responsiveness, Drive and Fun Seeking). This measure has been shown to have good convergent, discriminant, and predictive validity in which the instrument measures sensitivity rather than the person's typical experiences. The Behavioral Inhibition Scale will be used to tap the component of impulsivity related to decreased sensitivity to the negative consequences of

behavior and has been shown to predict nervousness in anticipation of an impending punishment [42].

Yale Food Addiction Scale (YFAS) : will assess participants's food addiction[43].
UPPS Impulsive Behavior Scale: will assess participants impulsivity [44,45]
Barratt Impulsivity Scale: will assess participants impulsivity[46]
The Short Form of the McGill Pain Questionnaire (SFMPQ): will assess pain intensity and different sensory and affective dimensions of pain[47].
Neuropathic Pain Scale: will assess pain intensity and different types of sensory properties of pain[48].
The pain DETECT questionnaire: will assess the neuropathic component of low back pain[49].

Beck's Anxiety Inventory and Beck's Depression Inventory: will assess mood and anxiety scores [50,51]

Positive and Negative Affect (PANAS): will assess participants affect[52].
Pain Catastrophizing Scale: will assess pain "catastrophizing"[53].

Pain Disability Index: will assess to what extent patients are disabled from pain[54].

Day 3) fMRI scan session

1. Upon arrival to the Magnetic Resonance Research Center (MRRC) participants **a urine drug test** will be obtained as well as Breath alcohol levels will be assessed with the Alcohawk Elite Breathalyzer. If any of these tests are positive the study will be cancelled. Next, vitals signs (VS)(blood pressure, heart rate, respiratory rate, pulse oximetry, and temperature). If the urine drug test is positive for opiates or methadone the study will be cancelled and the subject disqualified for this study.

2. Participants with BP < 90/60 and/or heart rate < 60 will be excluded and the study will be cancelled. VS will be logged in to a VS sheet and kept with the participant paper record in our study binders. Mental and neurologic status will be assessed for a baseline using the National Institutes of Health (NIH) Stroke Scale Neurological Assessment flow sheet (see attached form).

3. Next 20 ml of blood will be withdrawn. All blood samples will be placed in pre-chilled test tubes, and centrifuged at 4 C and the plasma stored at -70 C until analyzed according to standard procedures in the YCCI Core Laboratory

4. Next, participants will be undergo fMRI scanning:
   fMRI session: Set up is as above for fMRI simulator in fMRI training. Prior to getting the subject into the MR-room all people involved with the study walk through a detector designed to detect metal objects. We will use a Siemens 3T Trio TIM scanner with a 32-channel head-coil. A T1-weighted 3D MPRAGE sequence (4 minutes) will be performed to obtain a high-resolution anatomical image and echoplanar imaging will be used to measure

the BOLD signal as an indication of cerebral activation in response to various tastes (milkshake and tasteless) during two 9.6-minute runs and in response to sucrose and tasteless during two 9.6-minute runs. A run consists of multiple blocks of taste (milkshake or tasteless). One block is a series of 4 – 8 presentations of tastes or tasteless; Each presentation starts with a 0.75 cc delivery of liquid over 2 s followed by 7 s in which to swallow. Each taste block is followed by a rinse (0.75 cc deionized water). Before the start of a new block there is a rest period of 10 seconds. Blocks vary in length between 32 and 80 seconds and the order of blocks is counterbalanced across subjects. This design is modified from prior event-related designs so as to yield a 61% improvement in design efficiency (calculated by FMRIB's software library FSL), which we confirmed to lead to more extensive and more intense BOLD response. The data can be analyzed offline and used for experimental control variables. Next, two 6 minutes resting state runs will be collected. During these runs, participants will be asked to stare at a cross-hair on the screen. Finally, a diffusion tensor imaging (DTI) scan will be obtained over 5 minutes.

5. Participants will be then taken out of the scanner and given ***one oral dose*** of either 30 mg of Morphine, or 50 mg of Naltrexone or placebo. 60 minutes later, VS will be collected again and logged in to the VS sheet and participants will undergo another scanning session while receiving milkshake, sucrose or tasteless solutions as described in 3 and while at rest. DTI and structural imaging will not be repeated. **Blood pressure and heart rate will be continuously monitored during scanning** using the Biopac system. The same procedure will be followed for the same participants in two subsequent visits (**Day 4 and Day 5**). ***The visits will be scheduled within a period spanning 4 weeks but no two-treatment days will be scheduled less than 48 hours apart***. The overall design of the study will follow the illustration in **Figure 1**. However, the order of the interventions (i.e. Morphine, Naltrexone or placebo) will be randomized. The scanning session after medication administration will last between 45-60 minutes. Participants vital signs and mental and neurological state will be monitored for an additional 2 hours post-scanning at an interval of one hour using the NIH Stroke Scale Neurological Assessment flow sheet (two assessments in total); after 2 hours, if participants mental and neurologic state and VS are stable they will be reminded about side-effects of morphine and naltrexone and released. Morphine sulfate half-life is 2-4 hours. By the time our participants leave the MRRC one to two half-lives would have passed and the blood level of morphine would have dropped 2 to 4 times relative to time at ingestion.

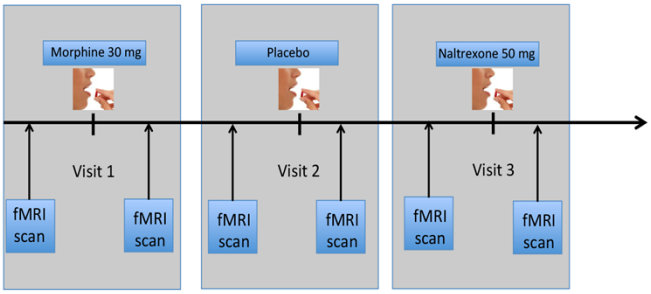


Figure 1. Schematic illustration of study design; the order is just one example for one participants; the interventions will be randomized in a double blind protocol.

B. Description of the open label arm

The same procedures described in A will be used to study 15 CBP patients using an open label design except when participants are taken to the scanner. At that point both the experimenter and the participant will know that morphine 30 mg is being administered. In addition, this arm of the study will have one arm only.

4. Genetic Testing N/A ☐

A. Describe

i. the types of future research to be conducted using the materials, specifying if immortalization of cell lines, whole exome or genome sequencing, genome wide association studies, or animal studies are planned.

No future research is planned with the materials. We will determine the presence or absence of candidate opiate activity-related genes after the subject has provided their saliva.

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

The Oragene-DNA Self-Collection Kit (vial format) will be used to collect DNA samples. This kit is an all-in-one system for the collection, preservation, and purification of DNA from saliva. The subjects will be asked to deliver the saliva in the container of the kit. After the delivery, the container will be capped which results in releasing DNA-preserving fluid that mixes with the saliva. This way, the DNA can be stored for long-term at room temperature. After collection, the DNA samples will be coded by a numeric code. This numeric code corresponds with the numeric code given to that particular subject in the study. The DNA samples will be analyzed in this lab using standard DNA procedures. Different sequence regions will be analyzed from each of the genomic DNA samples. The sequences will first be amplified using polymerase chain reaction (PCR) techniques, based on primer sequences specific for each sequence of interest. The amplified PCR products will then be digested with restriction enzymes as appropriate and analyzed using agarose gel electrophoresis. Images of each processed gel will be taken using a cooled-CCD camera system (ChemiDoc, Bio-Rad) and the presence or absence of a given allele will be determined based on the predicted sizes of the PCR products.

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

No protected health information (PHI) will be kept with the DNA samples. Only authorized staff will have access to the password-protected file that links name and ID number on a secure server. The genetic data will be used in analyses with information participants provided during the previous behavioral and fMRI sessions, which includes demographic information, body mass index, dietary habits, ratings, and brain imaging data (but no PHI data). By linking these data, the genetic

information should provide insight into understanding differential brain response among individuals.

iv. the methods to uphold confidentiality

The collected DNA samples will be stored at The John B. Pierce Laboratory. Only authorized study personnel may remove the samples for analysis. Data will be kept on the password-protected server for a period of seven years to ensure that the researchers have access to results. After seven years, the identifying data will be destroyed.

B. What are the conditions or procedures for sharing of materials and/or distributing for future research projects?
N/A . We do not plan to share of distribute these materials for future research projects.

C. Is widespread sharing of materials planned?
N/A

D. When and under what conditions will materials be stripped of all identifiers?

The materials are stripped of PHI after collection and coded with a subject ID number. After seven years, the identifying data will be destroyed.

E. Can donor-subjects withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials?
   i. How will requests to withdraw materials be handled (e.g., material no longer identified: that is, anonymized) or material destroyed)?

Yes, subjects can withdraw their materials at any time by contacting the PI, a procedure described in the consent form. If a subject wished to withdraw their materials, we will locate the material by the subject ID by accessing the password protected file that links name and ID, and destroy the biological material and any paper or electronic record of their genetic information. The saliva sample will be destroyed and the raw data from these samples will be destroyed by soaking the sample in bleach. This will remove all DNA. We will also remove the subject from any analyses.

F. Describe the provisions for protection of participant privacy

No PHI will be kept with the DNA samples. Only authorized staff will have access to the password-protected file that links name and ID number on a secure server.

G. Describe the methods for the security of storage and sharing of materials

Only authorized staff will have access to the password-protected file that links name and ID number on a secure server. Data will be kept on the password-protected server for a period of seven years to ensure that the researchers have access to results. After seven years, the data will be deleted by zeroing with software as in accordance with policies and procedures as determined by Yale University (procedures 1609 and 1610).

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

The subjects will be healthy human adults, and human adults suffering from pain conditions such as low back pain, knee arthritis, or fibromyalgia with normal gustatory and olfactory function and no medical conditions that would preclude them from being tested in the MR scanner. These subjects will be recruited from the Yale University Community, including undergraduate students, graduate students, and staff, with an age range between 18 and 65 years. Women and minorities will be encouraged to participate in all proposed experiments. We will monitor the subject pool periodically to ensure appropriate representation of all ethnic backgrounds and both sexes.

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

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

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects? ☐ Yes ☒ No (If yes, see Instructions section VII #4 for further requirements)

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

Healthy participants

Patients in pain: suffering from persistent pain more days than not, 3/10 in intensity on a numerical rating scale, for at least 6 weeks or more.

Exclusion criteria: Any DSM diagnosis, diabetes, food allergies, lactose intolerance, participants seeking to quit smoking or to lose weight, participants on any psychotropic medication including opiate based analgesics (e.g. oxycodone, methadone, suboxone), pregnant or nursing women, pacemaker or other implanted electrical devices. Participants with a past history of head trauma or seizures will be excluded. Any past history of illegal drug or alcohol misuse will be an exclusion criterion.

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

Eligibility will be determined by the research coordinator upon initial telephone contact using a screening form (see attached phone screening form). The form asks general information questions (date of birth, handedness, native language, etc.) and queries the participants about their health and any history of conditions known to affect cognitive functioning (e.g. stroke, medications, head trauma), or any conditions that could compromise the safety of conducting an MRI scan (e.g. claustrophobia, metal in the body, pacemaker). A more lengthy MRI safety screening form will be administered when the participant arrives for the scanning session (see attached MRI screening form) at the Magnetic Resonance Research Center in the Congress Avenue building of Yale School of Medicine. We do not wish to study females who are or may be pregnant. Therefore, as part of our MRI safety screening protocol, all females of childbearing potential will be given a urine pregnancy test prior to scanning. Results of the pregnancy test will be given to them only and will remain confidential. If the results indicate a subject is pregnant she will not participate in the fMRI scan, and will be excluded from the study.

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

Risk involved with the questionnaires

It is possible that interviews may cause distress or concern to the participants. One potential risk to participants is that it may be distressing to disclose information about psychiatric difficulties such as previous history of substance misuse. In our estimation, there is a low risk of this possibility and the effects would probably be short lived. We have conducted several hundred of these interviews with no adverse effects. It is possible that subjects may become frustrated with some of the impulsivity or cognitive assessments. We have conducted hundreds of similar cognitive assessments and have had no adverse outcomes.

Risks involved with the mock fMRI scanner

It is also possible that subjects report feeling uncomfortable in the mock scanner, either because they feel claustrophobic or because they do not like swallowing in a supine position. Subjects will be instructed to tell the experimenter if they feel any discomfort with the procedure so that the session can be terminated. We have conducted hundreds of fMRI training sessions. Approximately 1 in 15 subjects report some discomfort with this procedure and the sessions are terminated. We have had no adverse events.

Risks associated with one dose of oral 30 mg Morphine:
Morphine is an opiate agonist and has been used clinically for centuries. There is no clear compelling evidence of long-term toxicity from using one dose of 30 mg oral morphine. However, there are acute medical and neuropsychiatric sequelae that deserve special consideration. Acute administration can lead to dizziness, somonolence, dysphoria, altered mental status, euphoria, edema, diaphoresis, headache, parasthesias, flushing, respiratory depression, hypotension, rash or pruritis, nausea, constipation and vomiting. Very serious but extremely rare side effects include anaphylaxis, apnea, severe bradycardia or hypotension, or shock.

Risks associated with one dose of oral 50 mg Naltrexone:
Naltrexone is an opiate antagonist and has been used clinically for several decades. There are no long-term side effects of one dose of oral naltrexone; in fact, naltrexone is prescribed daily for alcohol misuse disorder to prevent relapse into drinking. Acute administration can be associated with insomnia, dizziness, fatigue, somnolence, headache, anxiety, abdominal pain, nausea, vomiting. Extremely rare side effects include hypersensitivity reaction and hepatotoxicity.

Risks involved with MRI
MRI and MRS are considered to be among the safest ways to examine the human body. They use magnetism and radio waves, not x-rays, to measure chemicals and take pictures of various parts of the body. The United States Food and Drug Administration (FDA) has set guidelines for magnet strength and exposure to radio waves, and we carefully observe those guidelines. For subjects' exposure in this study, no bad effects have been seen. This study has no painful parts. Subjects will be watched closely throughout the study. Some people may feel uncomfortable or anxious during the MRI or MRS. If this happens to a subject, they may ask to stop the study at any time and we will take him/her out of the MR scanner. On rare occasions, some people might feel dizzy, get an upset stomach, have a metallic taste or feel tingling sensations or muscle twitches. These sensations usually go away quickly but subjects should tell the research staff if they have them.

MRI and MRS pose some risks for certain people. If subjects have a pacemaker or some metal objects inside their body, they may not be in this study because the strong magnets in the MR scanner might harm them. Another risk is a metallic object flying through the air toward the magnet and hitting them. To reduce this risk we require that all people involved with the study remove all metal from their clothing and all metal objects from their pockets.

Nothing metal can be brought into the magnet room at any time. Also, once a subject is in the magnet, the door to the room will be closed so that no one from outside accidentally goes near the magnet.

We want subjects to read the questions on the MR Safety Questionnaire and answer them very carefully. Those questions are for their safety. Subjects should take a moment to be sure that they have read the MR safety sheet and be sure to tell us any information they think might is important. Even if they think that it is probably okay, we would rather have them ask us to make sure.

This MR study is for research purposes only and is not in any way a clinical scan to diagnose diseases for subjects. The scans in this study are not designed for diagnosis. The primary investigator, the lab, the MR technologist, and the Magnetic Resonance Research Center are not qualified to interpret the MR scans and cannot give subjects or their doctor a diagnostic evaluation of the images. If we see something on their scan that might be medically significant, we will ask a radiologist or another physician to review the relevant images. If that person recommends that the subject should seek medical advice, then the primary investigator or consulting physician will contact the subject, talk with them about the situation, and recommend that they seek medical advice as a precautionary measure. At that point, the decision to seek advice or treatment is completely up to the subject and their doctor. If the subject's doctor wants to pursue additional MR images, the research scans from this study will not be available, and new scans that are appropriate for medical diagnosis will need to be done. The researchers for this project, the consulting physician, the Magnetic Resonance Research Center, and Yale University are not responsible for any exam or treatment that the subject receives based on these findings.

Risks associated with the physiological recordings of respiration, heart rate, swallowing and galvanic skin response in the MRI environment.:
There are no known risks associated with these recordings. However, should the subjects feel anxious or uncomfortable with the any aspect of the recordings we will simply acquire the fMRI scan without them.

Risks-associated with the BodPod measurement:
There are no known risks associated with the BodPod measurement. However, some people may feel uncomfortable or anxious in the enclosed chamber of the BodPod. After each of the three 50-second measurements the experimenter will open the door. The experimenter can see the subject at all times in the BodPod and will show you the alarm button inside the BodPod that will interrupt the measurement if they feel anxious.

Risks associated with the physiological recordings in the MRI environment:
There are no known risks associated with these recordings. However, should the subjects feel anxious or uncomfortable with the any aspect of the recordings we will simply acquire the fMRI scan without them.

Risks involved with consumption of stimuli:
There are no known risks associated with consumption of any of the odors or liquids that subjects will encounter. All are commercially available products that subjects will have likely encountered before. Subjects with food allergies or sensitivities (for example nuts, lactose, artificial sweeteners) will be excluded.

Risks involved with blood draws:
Potential risks associated with blood sampling include infection from failure to observe proper sterile conditions, and hematoma from careless technique. The latter may be associated with some discomfort, but presents very little danger to the subject's welfare. In any case, a skilled phlebotomist will perform all blood draws.

Risks involved with pregnancy:

MR scans, and a restricted diet could be damaging for a developing fetus. Therefore, pregnant women will be excluded.

Risks for toxicology screenings:
Breath screening and urine collections are performed primarily as safeguards to contamination of data and should add no risks other than those normally associated with these procedures.

Risks for saliva sample collection and genotyping:
There is a slight risk of genetic information being used in inappropriate ways (e.g. to deny health insurance due to genotype).

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

    All researchers and research assistants involved in the study have taken the Human Investigations Training Course either on-line (through the NIH) or in person through the Yale University School of Medicine. All clinical procedures are performed the John B Pierce Laboratory by trained medical and scientific staff. Subjects may become anxious or fatigued during any of the procedures. They will be informed at the outset of the study that, should they experience undue anxiety or discomfort from the procedures, they are free to terminate the study at any time. Trained staff members will be working with the subjects throughout the study and will take appropriate steps to minimize anxiety and fatigue. We will attempt to minimize any discomfort associated with the procedures by informing the subject about what to expect prior to participation. Participants will be told that they are free to not respond or to terminate involvement at any time with no adverse consequences. All lab assessors are extensively trained on how to conduct assessments. Dr. Geha will also closely supervise all assessors.

Minimizing risk involved with administration of one oral dose of Morphine and Naltrexone

We will minimize the acute risk of administration of oral 30 mg Morphine or 50 mg of Naltrexone by carefully monitoring vital signs and mental status using neuro-checks every 60 minutes after the administration. In addition, the study physician Dr. Paul Geha will always be present during the whole duration of the visit when either of these drugs is administered.

Minimizing risk involved with the questionnaires:

Should a subject meet diagnostic criteria for any psychiatric disorder Dr. Geha will refer them for treatment. If a participant appears to be distressed or fatigued during assessments, the assessor will halt the procedure and take a break. The session will only recommence when and if the participant reports feeling capable of continuing

Minimizing risks involved with the mock fMRI scanner

We will attempt to minimize any discomfort associated with the mock fMRI scanner by informing the subject about what to expect prior to participation and explaining to them the equipment, how it works, which parts are replaced for every subject and how we clean any components that are not. Subjects will be instructed to tell the experimenter if they feel any discomfort with the procedure so that the session can be terminated.

Minimizing risks involved with MRI

During the fMRI scans, the participants will be monitored for anxiety or related concerns by research personnel associated with the project. Participants and investigators will be screened for metallic objects prior to entering the scan room. Prior to inclusion in the study, the presence of potential MRI risks, such as pacemakers, surgical clips, or metallic devices will be excluded by medical and surgical history administered during screening. All subjects will wear foam earplugs and sound-reducing headphones to reduce risk of hearing damage due to the loud noise of the scanner. The minor risk of discomfort due to lying still for 60 minutes will be minimized by providing custom pads and pillows designed to make the participants as comfortable as possible. Participants will communicate with the MR technologist and research assistant via an intercom system and may trigger and audible alarm at any time to stop the MRI session if he or she is uncomfortable or anxious. In addition, all imaging center staff, students, post-docs and research assistants will participate in safety training annually. Finally, all subjects are familiarized with MR procedures during the training session in the mock scanner to ensure that subjects that are schedule for the MR scan are comfortable with the procedures.

Minimizing risks related to pregnancy

To minimize risks related to pregnancy, we inform the subject that if they should become pregnant, they should report this to their health care professional, physician and to us immediately. If this happens during the study, the subject will stop his/her participation. We perform pregnancy tests along with toxicology tests during each assessment and intake.

Minimizing risks associated with the BodPod
The experimenter can see the subject at all times in the BodPod and will show them the alarm button inside the BodPod that will interrupt the measurement if they feel anxious.

Minimizing risks for toxicology screenings:
Every subject will use a new separately wrapped mouthpiece that will be attached to the breathalyzer. Bottles containing subject's urine specimens will be not be labeled and will be appropriately discarded in a biohazard container after instant testing. This information is not recorded.

Minimizing risks for saliva sample collection and genotyping:
No protected health information (PHI) will be kept with the DNA samples. Only authorized staff will have access to the password protected file that links name and ID number on a secure server. Identifying data will be destroyed after 7 years. Genetic information will also not be disclosed to participants, physicians in order to maintain confidentiality and limit the possible misuse of genetic information.

11. **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.) For more information, see the Instructions, page 24.
    a. What is the investigator's assessment of the overall risk level for subjects participating in this study?

       The investigator's assessment of the overall risk for subjects participating in this study is moderate.

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

       Not Applicable.

    c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://www.yale.edu/hrpp/forms-templates/biomedical.html for
        i. Minimal risk
        ii. Greater than minimal

    d. For multi-site studies for which the Yale PI serves as the lead investigator:
        i. How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed?
        ii. What provisions are in place for management of interim results?
        iii. What will the multi-site process be for protocol modifications?

Moderate Risk DSMP

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

The principal investigator, Dr. Paul Geha, will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency, which must be conducted at a minimum of every 6 months (including when reapproval of the protocol is sought). During the review process, the principal investigator (monitor) will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. Either the principal investigator, or the IRB have the authority to stop or suspend the study or require modifications.

The risks associated with the current study are deemed greater than minimal for the following reasons: (choose those that apply)

1. We do not view the risks associated with morphine or naltrexone as minimal risk.
2. We do not view the risks associated with the combined use of morphine or naltrexone and fMRI as minimal risks.
3. Given the now established safety and validity of the current _____ in our prior work, we do not view the proposed studies as high risk.
4. Given our experience with the combined co-administration_____, we do not view the proposed studies as high risk.

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

3. Attribution of Adverse Events:
Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design by the principal investigator, Dr. Paul Geha, according to the following categories:

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

4. Plan for Grading Adverse Events:

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

1. Mild adverse event
2. Moderate adverse event

3. Severe

5. Plan for Determining Seriousness of Adverse Events:

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

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

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

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

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

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

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

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

These UPIRSOs/SAEs will be reported to the IRB in accordance with IRB Policy 710, using the appropriate forms found on the website. All related events involving risk but not meeting the

prompt reporting requirements described in IRB Policy 710 should be reported to the IRB in summary form at the time of continuing review. If appropriate, such summary may be a simple brief statement that events have occurred at the expected frequency and level of severity as previously documented**.** In lieu of a summary of external events, a current DSMB report can be submitted for research studies that are subject to oversight by a DSMB (or other monitoring entity that is monitoring the study on behalf of an industry sponsor).

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

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

☐ All Co-Investigators listed on the protocol.

☐ National Institutes of Health

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

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

fMRI Data Analysis: The following measures will be derived from brain data: (1) parameter estimates(**PE**) for milkshake (MS) minus Tls (tasteless) (MS-Tls) will be defined at the single subject level using general linear model (GLM), implemented in FSL toolbox[55];whole brain connectivity of Blood Oxygen Level Dependent (BOLD) signal, using both MS runs or resting state runs, will be calculated between each voxel, or region of interest (ROI), and every other voxel in the brain to obtain (2) functional connectivity ***FC*** of specific ROIs or (3) degree maps (DM). ***FC*** is a measure of the strength of connectivity between an ROI and the rest of the brain; degree ***D*** is calculated as the total number of connections above a specific correlation threshold between a voxel and all the other voxels in the brain; we will study ***D*** over a range of thresholds $0.25 < r < 0.65$ [56]. *DM* identifies brain hubs (with high *D*) and therefore allows between groups comparison in the most densely connected areas [57,58].

The design is a within subject repeated measures design with treatment (Morphine, Naltrexone and Placebo) being the repeated measure and groups (healthy control vs. pain patients) as a factor. We will use repeated measures ANOVA to find differences in brain response (i.e. (***MS-Tls***) or ***D*** or ***FC***) and psychophysical ratings of milkshake. The repeated measures design is a powerful one because it does not suffer from between subject

variability. According to the preliminary data we expect to see decreased response to MS in opiate treated back pain patients and decreased ***D*** and ***FC***.

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

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

A. DRUGS, BIOLOGICS and RADIOTRACERS

1. **Identification of Drug, Biologic or Radiotracer:** What is (are) the **name(s)** of the drug(s) biologic(s) or radiotracer(s) being used? Identify whether FDA approval has been granted and for what indication(s).

- Morphine has U.S. Food and Drug Administration (USFDA) approval for relief of moderate to severe acute and chronic pain for which use of an opioid analgesic is appropriate.
- Naltrexone has USFDA approval for treatment of alcohol dependence and blockade of the effects of exogenously administered opioids.

All protocols, which utilize a drug, biologic, or radiotracer **not** approved by, but regulated by, the FDA, or a radiotracer regulated by the RDRC, must provide the following information:

a. What is the Investigational New Drug (IND) **number** assigned by the FDA?
b. Who holds the IND?
c. All protocols, which utilize a radiotracer not approved by, but regulated by the FDA, must provide the IND number: _____
Alternatively, use of the investigational radiotracer may be under RDRC/RSC oversight: (check if appropriate)_____

For all investigational radiotracers, attach a copy of the RDRC/RSC application (for radioisotopes used in the PET Center, PET Center personnel may complete this step)
Go to http://rsc.med.yale.edu/login.asp?url=myApps.asp. When you have logged in, complete the application and attach a copy to this submission.

Alternatively, an **exemption from IND filing requirements** may be sought for a clinical investigation of a drug product that is lawfully marketed in the United States. If there is no IND and an exemption is being sought, 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:

i. 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. ☒ Yes ☐ No

ii. 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. ☒ Yes ☐ No

iii. 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. ☒ Yes ☐ No

iv. 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). ☒ Yes ☐ No

v. The investigation will be conducted in compliance with the requirements regarding promotion and charging for investigational drugs. ☒ Yes ☐ No

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

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

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

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

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

Exempt Category 3

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

Exempt Category 4

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

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

Oral Morphine is prescribed to millions of patients suffering from pain; it is estimated that the number of prescription filled for opioid medications exceeded 256 millions in 2009 in the

US[59,60]. The starting dose is typically 10 to 30 mg every 4 hours as needed. Patients with prior opioid exposure may require higher initial doses. ***For the purpose of the current proposal we will administer only one dose of 30 mg morphine.*** Therefore, the risks associated with chronic use of morphine are largely minimized by our protocol. Oral Morphine has a wide margin of safety at 2-3 times of the "effective dose". In addition, there is no evidence of long-term toxicity associated with the intake of one dose of Morphine. Several human imaging studies safely administered acute[61-72] or chronic [73] opiate medications, including oral morphine, via the oral or the parenteral route. Morphine side effects are dose and route of administration dependent; the most frequent side effects (> 10%) described are:

- Cardiovascular: Oxygen saturation decreased
- Central nervous system: Drowsiness (9% to >10%), headache (<2% to >10%)
- Gastrointestinal: Constipation (9% to >10%), nausea (7% to >10%), vomiting (2% to >10%)
- Genitourinary: Urinary retention (<2% to 16%; primarily in males; may be prolonged, up to 20 hours, following epidural or intrathecal use)
- Hypersensitivity: Histamine release
- Neuromuscular & skeletal: Weakness

Side effects in 1% to 10%:

- Cardiovascular: Peripheral edema (3% to 10%), chest pain (2% to <3%), atrial fibrillation (<2% to <3%), bradycardia (<2%), edema (<2%), facial flushing (<2%), flushing (<2%), hypertension (<2%), hypotension (<2%), palpitations (<2%), syncope (<2%), tachycardia (<2%), vasodilatation (<2%), circulatory depression, orthostatic hypotension, presyncope, shock
- Central nervous system: Depression (5% to 10%), insomnia (<2% to 10%), paresthesia (<2% to 10%), dizziness (6%), anxiety (<2% to 6%), abnormality in thinking (<2% to <5%), confusion (<2% to <5%), convulsions (<5%), pain (3%), agitation (<2%), amnesia (<2%), apathy (<2%), ataxia (<2%), chills (<2%), decreased cough reflex (<2%), dream abnormalities (<2%), euphoria (<2%), hallucination (<2%), hypoesthesia (<2%), lack of concentration (<2%), lethargy (<2%), malaise (<2%), myoclonus (<2%), seizure (<2%), slurred speech (<2%), vertigo (<2%), voice disorder (<2%), withdrawal syndrome (<2%), abnormal gait, apprehension, coma, delirium, drug dependence, dysphoria, false sense of well-being, feeling abnormal, mood changes, nervousness, restlessness, rigors, sedation
- Dermatologic: Diaphoresis (5% to 10%), skin rash (3% to 10%), decubitus ulcer (<2%), pallor (<2%), pruritus (<2%, may be dose related), urticaria, xeroderma
- Endocrine & metabolic: Gynecomastia (<2% to <3%), amenorrhea (<2%), decreased libido (<2%), hyponatremia (<2%), antidiuretic effect, hypogonadism, hypokalemia, increased release of antidiuretic hormone, increased thirst, weight loss
- Gastrointestinal: Abdominal pain (5% to 10%), diarrhea (5% to 10%), anorexia (3% to 10%), xerostomia (3% to 10%), biliary colic (<2%), delayed gastric emptying (<2%), dyspepsia (<2%), dysphagia (<2%), gastric atony (<2%), gastroesophageal reflux disease (<2%), hiccups (<2%), abdominal distension, dysgeusia, flatulence, gastroenteritis, GI irritation, paralytic ileus, rectal disease

- Genitourinary: Urinary tract infection (5% to 10%), impotence (<2%), prolonged labor (<2%), urinary hesitancy (<2%), urine abnormality (<2%), abnormal ejaculation, bladder spasm, decreased urine output, dysuria, hypogonadism, oliguria
- Hematologic & oncologic: Anemia (2% to <5%), thrombocytopenia (<2% to <5%), leukopenia (2%), hematocrit decreased
- Hepatic: Increased liver function enzymes
- Hypersensitivity: Hypersensitivity reaction
- Infection: Infection
- Local: Local irritation
- Neuromuscular & skeletal: Back pain (<2% to 10%), asthenia (2%), tremor (2%), arthralgia (<2%), bone pain (<2%), foot-drop (<2%), decreased bone mineral density, muscle rigidity, muscle twitching
- Ophthalmic: Amblyopia (<2%), blurred vision (<2%), conjunctivitis (<2%), diplopia (<2%), miosis (<2%), nystagmus (<2%), eye pain, visual disturbance
- Respiratory: Dyspnea (3% to 10%), flu-like symptoms (<2% to 10%), hypoventilation (<5%), asthma (<2%), atelectasis (<2%), hypoxia (<2%), pulmonary edema (noncardiogenic, <2%), respiratory depression (<2%), respiratory insufficiency (<2%), rhinitis (<2%), hypercapnia
- Miscellaneous: Accidental injury (2% to 10%), fever (2% to 10%)

Side effects at < 1%

- <1% (Limited to important or life-threatening): Anaphylaxis, apnea, biliary tract spasm, bronchospasm, decreased cough reflex, dehydration, disorientation, disruption of body temperature regulation, genitourinary tract spasm, hemorrhagic urticaria, hyperalgesia, hypertonia, increased intracranial pressure, intestinal obstruction, laryngospasm, menstrual irregularities, myoclonus, paradoxical central nervous system stimulation, sepsis, toxic psychoses

Oral Morphine is contraindicated in somebody who has bowel obstruction.

Oral Naltrexone: Oral Naltrexone is prescribed for alcohol and opiate dependence; it is estimated that 221 million prescriptions of Naltrexone were dispensed in 2007 [74]. The starting dose is 50 mg daily. Naltrexone has a wide margin of safety. Naltrexone has a low incidence of common adverse events[75]. Naltrexone's FDA-approved label includes a black-box warning regarding hepatotoxicity, although these reversible effects tend to be associated with much higher doses than those used in routine clinical practice (e.g., 300 mg/day or more) and tend to occur only after a patient is on these high doses for extended periods. ***For the purpose of our current protocol we will use one 50 mg dose one time only.*** In addition, there is no evidence of long-term toxicity associated with the intake of one dose of Naltrexone. Naltrexone side effects occurring at > 10% rate are reported for combined oral and injectable form; however, as mentioned above oral Naltrexone has a low risk of side effects.

>10%:

- Cardiovascular: Syncope (13%)
- Central nervous system: Headache (3% to 25%), insomnia (3% to 14%), dizziness (4% to 13%), anxiety (2% to 12%), decreased energy (>10%), nervousness (4% to >10%)
- Gastrointestinal: Nausea (10% to 33%), vomiting (3% to 14%), appetite decreased (14%), diarrhea (13%), abdominal pain (11%), abdominal cramping
- Hepatic: ALT increased (13%)
- Neuromuscular & skeletal: CPK increased (11% to 39%), arthralgia (12%), myalgia (>10%)
- Respiratory: Pharyngitis (7% to 11%)

1% to 10%:

- Cardiovascular: Hypertension (5%)
- Central nervous system: Suicidal ideation (≤10%), depression (8%), somnolence (2% to 4%), fatigue (4%), chills, energy increased, feeling down, irritability
- Dermatologic: Skin rash (6% to 10%)
- Endocrine & metabolic: Increased thirst, polydipsia
- Gastrointestinal: Dry mouth (5%), toothache (4%), constipation
- Genitourinary: Delayed ejaculation (<10%), impotency (<10%)
- Hepatic: AST increased (2% to 10%), GGT increased (7%)
- Neuromuscular & skeletal: Muscle cramps (8%), back pain (6%)
- Miscellaneous: Influenza (5%)

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

   b) Is the drug provided free of charge to subjects? ☒ Yes ☐ No
   If yes, by whom?

4. **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.

   Check applicable Investigational Drug Service utilized:

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

   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.

5. **Use of Placebo:** ☐ **Not applicable to this research project**

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

   1. Describe the safety and efficacy of other available therapies. If there are no other available therapies, state this.

      There are no other therapies

b. State the maximum total length of time a participant may receive placebo while on the study.
One dose one time only

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

The potential harm is an allergic reaction to one dose of placebo which is extremely unlikely

c. Describe the procedures that are in place to safeguard participants receiving placebo.
The protocol is a safeguard to receiving placebo since we are giving one dose only and not withholding any other treatment

6. **Use of Controlled Substances:**
Will this research project involve the use of controlled substances in human subjects?
☒ Yes ☐ No *See HIC Application Instructions to view controlled substance listings*.

If yes, is the use of the controlled substance considered:
☐ Therapeutic: The use of the controlled substance, within the context of the research, has the potential to benefit the research participant.
☒ Non-Therapeutic: *Note, the use of a controlled substance in a non-therapeutic research study involving human subjects may require that the investigator obtain a Laboratory Research License. Examples include controlled substances used for basic imaging, observation or biochemical studies or other non-therapeutic purposes. See Instructions for further information.*

The use of controlled substances in this protocol will follow the Yale Office of Environmental Health Policy for controlled substance according to the following point:

- The controlled medication(s) will be ordered from the Yale New Haven Hospital pharmacy and delivered, used and destroyed on the same day;
- No storage of controlled medications will occur overnight in any research location;
- Only staff members listed on the protocol will sign for and take possession of the controlled medication(s);
- If the medication(s) are not going to be administered immediately to the patient, the medication(s) will be stored in a lockable, secured device within John B. Pierce Lab
- If the controlled medication is not fully used after the procedure, two staff members listed on the protocol (not the patient) will destroy the medication(s) and the destruction paperwork will include the following: prescription number, pharmacy name, medication name, strength, quantity destroyed and signature of both parties that destroyed the medication(s)
- The study medications will be ordered through the YNHH IDS and each research subject will have a YNHH Medical Record. We have registered the study with Yale Center for Clinicial Investigation (YCCI).

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

Are subjects provided the opportunity to continue to receive the study drug(s) after the study has ended?
☐ Yes If yes, describe the conditions under which continued access to study drug(s) may apply as well as conditions for termination of such access.

☒ No If no, explain why this is acceptable.

The drug administration is not intended to study treatment effects but the effects on brain activity.

B. DEVICES

1. Are there any investigational devices used or investigational procedures performed at Yale-New Haven Hospital (YNHH) (e.g., in the YNHH Operating Room or YNHH Heart and Vascular Center)? ☐Yes ☒No *If Yes, please be aware of the following requirements*:

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

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

2. What is the name of the device to be studied in this protocol?

Has this device been FDA approved? ☐ Yes ☐ No
If yes, state for what indication.

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

4. **Source:**
   a) Identify the source of the device to be used.

   b) Is the device provided free of charge to subjects? ☐ Yes ☐ No

5. What is the PI's assessment of risk level (significant or non-significant) associated with the use of the device?

☐ **Significant Risk (SR) Device Study:** A study of a device that presents a potential for serious risk to the health, safety, or welfare of a participant and 1) is intended as an implant; 2) is used in supporting or sustaining human life; or otherwise prevents impairment of human health; 3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or 4) otherwise presents a potential for serious risk to the health, safety, or welfare of a participant.

Significant Risk Devices require an Investigational Device Exemption (IDE) issued by the FDA.

What is the **IDE number** assigned by the FDA?

Did the FDA approve this IDE as **Category A** (experimental/investigational) or as **Category B** (non-experimental/investigational)?

Who holds the IDE?

☐ **Non-Significant Risk (NSR) Device Study:** A study of a device that does not meet the definition for a significant risk device and does not present a potential for serious risk to the health, safety, or welfare of participants. Note that if the HIC concurs with this determination, an IDE is not required.

6. **Abbreviated IDE or Exempt IDE:** There are abbreviated requirements for an IDE and there also are exemptions to the requirement for an IDE. *See the criteria in the HIC Application Instructions,* Section VI.B.4 at http://www.yale.edu/hrpp/resources/docs/100FR1aHICProtocol_Application_Instructions5-25-11.pdf *to determine if these pertain to this study.*

☐ **Abbreviated IDE or Exempt IDE** – *If criteria set forth in the HIC Application Instructions are met, copy and paste the completed relevant section from the Instructions into this application.*

7. **Investigational device accountability**:
   a. State how the PI, or named designee, ensures that an investigational device is used only in accordance with the research protocol approved by the HIC, and maintains control of the investigational device as follows:

Maintains appropriate records, including receipt of shipment, inventory at the site, dispensation or use by each participant, and final disposition and/or the return of the investigational device (or other disposal if applicable):

Documents pertinent information assigned to the investigational device (e.g., date, quantity, batch or serial number, expiration date if applicable, and unique code number):

Stores the investigational device according to the manufacturer's recommendations with respect to temperature, humidity, lighting, and other environmental considerations:

Ensures that the device is stored in a secure area with limited access in accordance with applicable regulatory requirements:

Distributes the investigational device to subjects enrolled in the IRB-approved protocol:

SECTION VII: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:

a. targeted for enrollment at Yale for this protocol_75

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

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

☒ Flyers	☒ Internet/Web Postings	☐ Radio
☐ Posters	☐ Mass E-mail Solicitation	☐ Telephone
☐ Letter	☐ Departmental/Center Website	☐ Television
☐ Medical Record Review	☐ Departmental/Center Research Boards	☐ Newspaper
☐ Departmental/Center Newsletters	☐ Web-Based Clinical Trial Registries	
☐ YCCI Recruitment database	☒ Clinicaltrials.gov Registry (do not send materials to HIC)	
☐ Other (describe):		

3. Recruitment Procedures:

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

Any healthy person or a person with a history of pain for more than 6 weeks between the ages of 18-65 years old is a potential subject. Potential subjects will be identified by a call for subjects via flyers, business cards and ads, describing the key eligibility criteria (18-65 years old). Flyers and business cards will be posted around Yale University (see attached research flyers), and advertisements will be posted in local newspapers or on local websites like Craig's List, the Yale University Bulletin, and websites for social networking, like the "Yalies in New Haven" group on Facebook (see same wording as the flyers). Interested subjects will contact the research coordinators at a telephone number indicated on the flyer. During the initial telephone conversation, she will provide a brief description of the study, schedule the subject's first session, and screen the subject to ensure that they meet inclusion criteria and do not possess any of the exclusion criteria. We request that written informed consent and HIPAA authorization be waived for this part of the screening (see below). Written informed consent will be obtained immediately before the first session at The John B Pierce Laboratory.

4. Screening Procedures

a. Will email or telephone correspondence be used to screen potential subjects for eligibility prior to the potential subject coming to the research office? ☒ Yes ☐ No

b. If yes, identify below all health information to be collected as part of screening and check off any of the following HIPAA identifiers to be collected and retained by the research team during this screening process.

HEALTH INFORMATION TO BE COLLECTED:

HIPAA identifiers:
☒ Names
☒ All geographic subdivisions smaller than a State, including: street address, city, county, precinct, zip codes and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly-available data from the Bureau of the Census: (1) the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people, and (2) the initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.
☒ Telephone numbers
☒ Fax numbers
☒ E-mail addresses
☐ Social Security numbers
☐ Medical record numbers
☐ Health plan beneficiary numbers
☐ Account numbers
☒ All elements of dates (except year) for dates related to an individual, including: birth date, admission date, discharge date, date of death, all ages over 89 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 90 or older
☐ Certificate/license numbers
☐ Vehicle identifiers and serial numbers, including license plate numbers
☐ Device identifiers and serial numbers
☐ Web Universal Resource Locators (URLs)
☐ Internet Protocol (IP) address numbers
☐ Biometric identifiers, including finger and voice prints
☐ Full face photographic images and any comparable images
☐ Any other unique identifying numbers, characteristics, or codes

5. 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.

6. 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 purposes only
☐ For inclusion of non-English speaking subject if short form is being used

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

Since we perform our screenings over the phone, it is impractical to obtain a written HIPAA authorization. However, once eligibility is determined and the subject is willing to participate, the first session will be scheduled. At the beginning of this first session we will obtain Compound Consent and HIPAA Research Authorization for further use of the data.

b.

i. 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;

Since we perform our part of our screenings over the phone, it is impractical to obtain a written HIPAA authorization. Prior to obtaining consent, all participants will be screened on the phone by the research coordinator. During this phone conversation, the research coordinator will provide a brief description of the study, including information about the tasks the subject will have to perform, where the study is conducted, how long the entire study participation will take, and the amount of financial compensation. Subjects will then be asked to verbally consent to us asking them various questions to ensure that they meet inclusion criteria and do not possess any of the exclusion criteria. We will use the following language during our phone screening: "We will keep the information we just talked about in our files until you come in to the first session of the study. If you qualify and choose to be part of the study, this information will become part of your study file. If you don't come in or if you don't qualify for the study, we will keep this information until the study is over and then we will destroy it. We are required by law to keep this information confidential and we will not use it for any purpose other than to see if you qualify for this study and for research oversight." If the subject is eligible and willing to participate, the first session will be scheduled. At the beginning of this first session we will obtain Compound Consent and HIPAA Research Authorization.

By signing this protocol application, 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.

7. **Required HIPAA Authorization:** If the research involves the creation, use or disclosure of protected health information (PHI), separate subject authorization is required under the HIPAA Privacy Rule. Indicate which of the following forms are being provided:
   - ☒ Compound Consent and Authorization form
   - ☐ HIPAA Research Authorization Form

8. **Consent Personnel:** List the names of all members of the research team who will be obtaining consent/assent.
   Paul Geha, Dana Small, Gelsina Stanley, Roberta Delvy, Elizabeth Garcia

9. **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.

   Prior to obtaining consent, all participants will be screened on the phone by the research coordinator at The John B Pierce Laboratory. During this conversation, the research coordinator will provide a brief description of the study, including information about tasks the subject will have to perform in the behavioral assessments, where the study is conducted, the medications used, the risks and benefits of paricipation, how long the entire study participation will take, and the amount of financial compensation. Subjects will also be screened to ensure that they meet inclusion criteria and do not possess any of the exclusion criteria. If the subject is eligible and willing to participate, the first session will be scheduled. Informed consent will be obtained immediately at the beginning of the first session. Personnel obtaining consent have a thorough understanding of the methodology of the protocol and a comprehensive knowledge of the procedures of the protocol and are capable of answering the possible questions raised by the potential subject regarding the study. A subject will sit down at a desk in a room. The study personnel will ask the subject to read through the entire compound research authorization and consent form. After the subject had read the entire form the researcher will verbally summarize the procedure, risks and steps taken to minimize risks. The subject is explicitly asked if they have any questions. All questions will be answered, except in the rare case that providing full disclosure may influence the outcome of the study (e.g. we do not want subjects to be aware that the puddings are manipulated in fat content). In these circumstances, the experimenter will explain that this is the case and offer to provide a fuller answer after the experiment. Subjects will receive additional details about the assessments they are to perform and will be informed that they may withdraw from the study at any time with no penalty. Subjects will be asked if they understand what the study entails and if they have had sufficient opportunity to consider whether or not to participate. If a subject affirms she/he will then be asked to sign the compound consent form and research authorization form and given a copy (attached).

10. **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.

    This research does not involve subjects with limited decision-making capacity. We will not recruit vulnerable subjects. For this reason we do not anticipate recruiting subjects without the ability and capacity to consent. However, we will ask subjects if they understand what the study entails and if they have had sufficient information and opportunity to consider whether or not to participate.

11. Documentation of Consent/Assent: Specify the documents that will be used during the consent/assent process. Copies of all documents should be appended to the protocol, in the same format that they will be given to subjects.

Adult compound consent and research authorization forms are attached.

12. 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.

Our research does not involve non-English-speaking subjects.

12(a) 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 found on our website at: http://www.yale.edu/hrpp/forms-templates/biomedical.html. 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 amendment 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.

13. 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 a consent waiver**
- ☒ **Requesting a waiver of signed consent**
- ☐ **Requesting a full waiver of consent**

A. Waiver of **signed** consent: (Verbal consent from subjects will be obtained. **If PHI is collected, information in this section must match Section VII, Question 6**)

☒ **Requesting a waiver of signed consent for Recruitment/Screening only**

If requesting a waiver of signed consent, please address the following:

a. Would the signed consent form be the only record linking the subject and the research?

☐ Yes ☐ No

b. Does a breach of confidentiality constitute the principal risk to subjects?

☐ Yes ☐ No

OR

c. Does the research activity pose greater than minimal risk?

☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** Please note: Recruitment/screening is generally a minimal risk research activity

☐ No

AND

d. Does the research include any activities that would require signed consent in a non-research context? ☐ Yes ☐ No

☐ **Requesting a waiver of signed consent for the Entire Study (**Note that an information sheet may be required.)

If requesting a waiver of signed consent, please address the following:

a. Would the signed consent form be the only record linking the subject and the research?

☐ Yes ☐ No

b. Does a breach of confidentiality constitute the principal risk to subjects?

☐ Yes ☐ No

OR

c. Does the research pose greater than minimal risk? ☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** ☐ No

AND

d. Does the research include any activities that would require signed consent in a non-research context? ☐ Yes ☐ No

B. **Full waiver** of consent: (No consent from subjects will be obtained for the activity.)

☐ **Requesting a waiver of consent for Recruitment/Screening only**

a. Does the research activity pose greater than minimal risk to subjects?

☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** Please note: Recruitment/screening is generally a minimal risk research activity

☐ No

b. Will the waiver adversely affect subjects' rights and welfare? ☐ Yes ☐ No

c. Why would the research be impracticable to conduct without the waiver?

d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?

☐ **Requesting a full waiver of consent for the <u>Entire Study</u> (Note: If PHI is collected, information here must match Section VII, question 6.)**

If requesting a full waiver of consent, please address the following:

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

SECTION VIII: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

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

Information about (self-reported) alcohol consumption, drug use, medical illness, major psychiatric illness, genetic information, brain images and use of medications will be collected.

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

Data will consist of verbal, written, or computerized ratings of sensory stimuli, questionnaires, and computerized responses to the neuropsychological and impulsivity assessments. All data will be kept confidential. Participant information is maintained in computer files that are password protected, and data from individuals (computer files and hard copy versions) are identified only by code. Only the primary investigator and research staff, the Yale HIC, and the National Institute of Health, which sponsors the study, will have access to these files. The data will be archived in the same manner after the research is completed. Seven years after completion of the study the identifying data will be deleted by zeroing with software as in accordance with policies and procedures as determined by Yale University (procedures 1609 and 1610).

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

The database with subject identifiers and means to link subject names and codes with research data is stored in a database in a separate location on a secured server at The John B Pierce Laboratory. Access to the database itself is password protected. Hardcopy PHI

data is in a locked cabinet. All other digital media (CD, DVD, Laptop computers) only contain research data that are identified by code.

d. 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?
Do all portable devices contain encryption software? ☐ Yes ☒ No
If no, see http://hipaa.yale.edu/guidance/policy.html

None of the portable devices contain PHI or HIPAA identifiers, and they are password protected. The identifying data is stored on a password protected database on a secure server in The John B Pierce Laboratory. Thus identifiers are not kept on the same device as the study information.

d. 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.

Identifying data are retained for a period of seven years after publication.

e. Who will have access to the protected health information (such as the research sponsor, the investigator, the research staff, all research monitors, FDA, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), SSC, etc.)? (please distinguish between PHI and de-identified data)

As NIH is funding the study, rules governing NIH access will apply. No other entities besides research staff and the investigator will have access to PHI or de-identified data, with the exception of presentations of data. These are typically reported as group averages. Where individual data are reported, individuals are not identified except by code.

g. If appropriate, has a Certificate of Confidentiality been obtained? **N/A**

h. Are any of the study procedures likely to yield information subject to mandatory reporting requirements? (e.g. HIV testing – reporting of communicable diseases; parent interview - incidents of child abuse, elderly abuse, etc.). Please verify to whom such instances will need to be reported. **N/A**

SECTION IX: 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 to participating subjects. However, the study will help us understand the brain response to food in the presence and absence of opiate agonist/antagonists, which are highly prescribed nowadays for pain, addiction and obesity. This understanding in turn will help us study the effect on body weight and behavior of prescription opiates in patients with pain.

SECTION X: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

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

The healthy participants for this study are not in need of treatment or seeking treatment. For this reason there is no alternative, except to decline participation in the study.
The pain participants might feel short-term relief of pain; If patients are interested in seeking such treatment they will be asked to talk to their doctor about it.

2. **Payments for Participation (Economic Considerations):** Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation. The subject's payments for the open label and the randomized controlled study are the same per session completed.

Remuneration is as follows for the randomized controlled study:

Type session:	payment:	frequency	Total
behavioral assessment	$ 80	x __1____	= $ __80___
fMRI scan with milkshake	$ 100 *	x __3____	= $ __300___
Computer Games	$100	x __1____	= $ __100___
		Subtotal:	= $ 380_____
Completion Bonus	$ 50	x ___1___	= $ _50____
Accumulated Earnings Bonus		x ___1___	= $ Variable___
		Total payment:	**= $ _530_**

And for the open label study:

Type session:	payment:	frequency	Total
behavioral assessment	$ 80	x 1	= $ 80
fMRI scan with milkshake	$ 100 *	x 2	= $ 200
Computer Games	$100	x _____	= $100_____
		Subtotal:	= $ 280
Accumulated Earning Bonus	$		= $ variable___
Completion Bonus	$ 50		= $ 50
		Total payment:	**= $ 430**

* If the subject spends up to 15 minutes in the scanner but do not complete the study, they will instead be paid $50. If the subject spends more than 15 minutes, they will receive the full $100 regardless of study completion.

Subjects will participate in one Intake Session ($80), 3 fMRI scanning sessions (with milkshake, each $100), and a completion bonus of $50, leading to a maximal remuneration of $430. In addition to this, they make variable earnings depending on their performance on one of the computer tasks.

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.

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

If the subject is injured as a result of participation in this study, treatment will be provided. The subject or the subject's insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available.

References

1. Chou R, Turner JA, Devine EB, et al. The Effectiveness and Risks of Long-Term Opioid Therapy for Chronic Pain: A Systematic Review for a National Institutes of Health Pathways to Prevention Workshop. *Annals of Internal Medicine.* 2015;162(4):276-+.
2. Fenn JM, Laurent JS, Sigmon SC. Increases in body mass index following initiation of methadone treatment. *J Subst Abuse Treat.* 2015;51:59-63.
3. Nolan LJ, Scagnelli LM. Preference for sweet foods and higher body mass index in patients being treated in long-term methadone maintenance. *Subst Use Misuse.* 2007;42(10):1555-1566.
4. Rolita L, Spegman A, Tang X, Cronstein BN. Greater number of narcotic analgesic prescriptions for osteoarthritis is associated with falls and fractures in elderly adults. *Journal of the American Geriatrics Society.* 2013;61(3):335-340.
5. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain - United States, 2016. *MMWR Recomm Rep.* 2016;65(1):1-49.
6. Peles E, Schreiber S, Sason A, Adelson M. Risk Factors for Weight Gain During Methadone Maintenance Treatment. *Subst Abus.* 2016:0.
7. Mysels DJ, Sullivan MA. The relationship between opioid and sugar intake: review of evidence and clinical applications. *J Opioid Manag.* 2010;6(6):445-452.
8. Nathan PJ, Bullmore ET. From taste hedonics to motivational drive: central mu-opioid receptors and binge-eating behaviour. *The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum.* 2009;12(7):995-1008.
9. Baldo BA, Pratt WE, Kelley AE. Control of Fat Intake by Striatal Opioids. 2010.
10. Pecina S, Smith KS, Berridge KC. Hedonic hot spots in the brain. *Neuroscientist.* 2006;12(6):500-511.
11. Zhang M, Kelley AE. Opiate agonists microinjected into the nucleus accumbens enhance sucrose drinking in rats. *Psychopharmacology (Berl).* 1997;132(4):350-360.
12. Will MJ, Franzblau EB, Kelley AE. The amygdala is critical for opioid-mediated binge eating of fat. *Neuroreport.* 2004;15(12):1857-1860.
13. Leboeuf-Yde C. Body weight and low back pain. A systematic literature review of 56 journal articles reporting on 65 epidemiologic studies. *Spine (Phila Pa 1976).* 2000;25(2):226-237.
14. McCarthy LH, Bigal ME, Katz M, Derby C, Lipton RB. Chronic pain and obesity in elderly people: results from the Einstein aging study. *JAmGeriatrSoc.* 2009;57(1):115-119.
15. Wilson AC, Samuelson B, Palermo TM. Obesity in children and adolescents with chronic pain: associations with pain and activity limitations. *ClinJPain.* 2010;26(8):705-711.
16. van Oostrom SH, Monique Verschuren WM, de Vet HC, Picavet HS. Ten year course of low back pain in an adult population-based cohort--the Doetinchem cohort study. *EurJPain.* 2011;15(9):993-998.
17. Shiri R, Karppinen J, Leino-Arjas P, Solovieva S, Viikari-Juntura E. The association between obesity and low back pain: a meta-analysis. *AmJEpidemiol.* 2010;171(2):135-154.

18. de Araujo IE, Geha PY, Small DM. Orosensory and homeostatic functions of the insular taste cortex. *Chem Percept.* 2012;5(1):64-79.
19. Saper CB. The central autonomic nervous system: conscious visceral perception and autonomic pattern generation. *AnnuRevNeurosci.* 2002;25:433-469.
20. Zubieta JK, Smith YR, Bueller JA, et al. Regional mu opioid receptor regulation of sensory and affective dimensions of pain. *Science.* 2001;293(5528):311-315.
21. Zubieta JK, Smith YR, Bueller JA, et al. mu-opioid receptor-mediated antinociceptive responses differ in men and women. *J Neurosci.* 2002;22(12):5100-5107.
22. Zubieta JK, Heitzeg MM, Smith YR, et al. COMT val158met genotype affects mu-opioid neurotransmitter responses to a pain stressor. *Science.* 2003;299(5610):1240-1243.
23. Baldo BA, Sadeghian K, Basso AM, Kelley AE. Effects of selective dopamine D1 or D2 receptor blockade within nucleus accumbens subregions on ingestive behavior and associated motor activity. *BehavBrain Res.* 2002;137(1-2):165-177.
24. Mena JD, Sadeghian K, Baldo BA. Induction of hyperphagia and carbohydrate intake by mu-opioid receptor stimulation in circumscribed regions of frontal cortex. *JNeurosci.* 2011;31(9):3249-3260.
25. Smith KS, Tindell AJ, Aldridge JW, Berridge KC. Ventral pallidum roles in reward and motivation. *BehavBrain Res.* 2009;196(2):155-167.
26. Levy I, Snell J, Nelson AJ, Rustichini A, Glimcher PW. Neural representation of subjective value under risk and ambiguity. *J Neurophysiol.* 2010;103(2):1036-1047.
27. Kable JW, Glimcher PW. The neural correlates of subjective value during intertemporal choice. *Nature neuroscience.* 2007;10(12):1625-1633.
28. Zhang M, Gosnell BA, Kelley AE. Intake of high-fat food is selectively enhanced by mu opioid receptor stimulation within the nucleus accumbens. *JPharmacolExpTher.* 1998;285(2):908-914.
29. Majuri J, Joutsa J, Johansson J, et al. Dopamine and Opioid Neurotransmission in Behavioral Addictions: A Comparative PET Study in Pathological Gambling and Binge Eating. *Neuropsychopharmacology.* 2017;42(5):1169-1177.
30. Pecina M, Love T, Stohler CS, Goldman D, Zubieta JK. Effects of the Mu opioid receptor polymorphism (OPRM1 A118G) on pain regulation, placebo effects and associated personality trait measures. *Neuropsychopharmacology.* 2015;40(4):957-965.
31. Bechara A, Tranel D, Damasio H. Characterization of the decision-making deficit of patients with ventromedial prefrontal cortex lesions. *Brain.* 2000;123 (Pt 11):2189-2202.
32. Treadway MT, Buckholtz JW, Schwartzman AN, Lambert WE, Zald DH. Worth the 'EEfRT'? The effort expenditure for rewards task as an objective measure of motivation and anhedonia. *PloS one.* 2009;4(8):e6598.
33. Geha PY, Aschenbrenner K, Felsted J, O'malley SS, Small DM. Altered hypothalamic response to food in smokers. *AmJClinNutr.* 2013;97(1):15-22.
34. Rudenga KJ, Sinha R, Small DM. Acute stress potentiates brain response to milkshake as a function of body weight and chronic stress. *IntJObes(Lond).* 2012.
35. Stice E, Spoor S, Bohon C, Veldhuizen MG, Small DM. Relation of reward from food intake and anticipated food intake to obesity: a functional magnetic resonance imaging study. *J AbnormPsychol.* 2008;117(4):924-935.
36. Dagher A. Functional brain imaging of appetite. *Trends in endocrinology and metabolism: TEM.* 2012;23(5):250-260.

37. Stunkard AJ, Messick S. The three-factor eating questionnaire to measure dietary restraint, disinhibition and hunger. *J PsychosomRes.* 1985;29(1):71-83.
38. Donny EC, Chaudhri N, Caggiula AR, et al. Operant responding for a visual reinforcer in rats is enhanced by noncontingent nicotine: implications for nicotine self-administration and reinforcement. *Psychopharmacology (Berl).* 2003;169(1):68-76.
39. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res.* 1989;28(2):193-213.
40. Lowe MR, Butryn ML, Didie ER, et al. The Power of Food Scale. A new measure of the psychological influence of the food environment. *Appetite.* 2009;53(1):114-118.
41. Marshall HM, Allison KC, O'Reardon JP, Birketvedt G, Stunkard AJ. Night eating syndrome among nonobese persons. *The International journal of eating disorders.* 2004;35(2):217-222.
42. CS C, TL W. Behavioral inhibition, behavioral activation,and affective responses to impending reward and punishment: the BIS/BAS scales. *J Pers Soc Psychol.* 1994;67:319-333.
43. Gearhardt AN, Corbin WR, Brownell KD. Preliminary validation of the Yale Food Addiction Scale. *Appetite.* 2009;52(2):430-436.
44. Whiteside SP, Lynam DR. The Five Factor Model and impulsivity: using a structural model of personality to understand impulsivity. *Pers Indiv Differ.* 2001;30(4):669-689.
45. Whiteside SP, Lynam DR. Understanding the role of impulsivity and externalizing psychopathology in alcohol abuse: application of the UPPS impulsive behavior scale. *Exp Clin Psychopharmacol.* 2003;11(3):210-217.
46. Patton JH, Stanford MS, Barratt ES. Factor structure of the Barratt impulsiveness scale. *J ClinPsychol.* 1995;51(6):768-774.
47. Melzack R. The short-form McGill Pain Questionnaire. *Pain.* 1987;30(2):191-197.
48. Galer BS, Jensen MP. Development and preliminary validation of a pain measure specific to neuropathic pain: the Neuropathic Pain Scale. *Neurology.* 1997;48(2):332-338.
49. Freynhagen R, Baron R, Gockel U, Tolle TR. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. *CurrMedResOpin.* 2006;22(10):1911-1920.
50. Beck A, Steer R. Manual for the Beck Anxiety Inventory. San Antonio: Psychological Corporation; 1993.
51. Beck A, Steer R. Beck Depression Inventory. San Antonio: Psychological Corporation; 1993.
52. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. *JPersSocPsychol.* 1988;54(6):1063-1070.
53. Sullivan M, Bishop S, Pivik J. The Pain Catastrophizing Scale: development and validation. *PsycholAssess.* 1995;7:524-532.
54. Tait RC, Pollard CA, Margolis RB, Duckro PN, Krause SJ. The Pain Disability Index: psychometric and validity data
1. *ArchPhysMedRehabil.* 1987;68(7):438-441.
55. Smith SM, Jenkinson M, Woolrich MW, et al. Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage.* 2004;23 (S1):208-219.

56. Cole MW, Pathak S, Schneider W. Identifying the brain's most globally connected regions. *Neuroimage.* 2010;49(4):3132-3148.
57. Cecchi GA, Rao AR, Centeno MV, Baliki M, Apkarian AV, Chialvo DR. Identifying directed links in large scale functional networks: application to brain fMRI. *BMCCell Biol.* 2007;8 Suppl 1:S5.
58. Tomasi D, Volkow ND. Functional connectivity density mapping. *Proceedings of the National Academy of Sciences of the United States of America.* 2010;107(21):9885-9890.
59. Manchikanti L, Abdi S, Atluri S, et al. American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: Part 2--guidance. *Pain Physician.* 2012;15(3 Suppl):S67-116.
60. Manchikanti L, Abdi S, Atluri S, et al. American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: Part I--evidence assessment. *Pain Physician.* 2012;15(3 Suppl):S1-65.
61. Hansen TM, Olesen AE, Graversen C, Drewes AM, Frokjaer JB. The Effect of Oral Morphine on Pain-Related Brain Activation - An Experimental Functional Magnetic Resonance Imaging Study. *Basic Clin Pharmacol Toxicol.* 2015;117(5):316-322.
62. Atlas LY, Whittington RA, Lindquist MA, Wielgosz J, Sonty N, Wager TD. Dissociable influences of opiates and expectations on pain. *The Journal of neuroscience : the official journal of the Society for Neuroscience.* 2012;32(23):8053-8064.
63. Wardle MC, Fitzgerald DA, Angstadt M, Rabinak CA, de Wit H, Phan KL. Effects of oxycodone on brain responses to emotional images. *Psychopharmacology (Berl).* 2014;231(22):4403-4415.
64. Lelic D, Olesen AE, Gregersen H, Dahan A, Kolesnikov Y, Drewes AM. Morphine modifies the cingulate-operculum network underlying painful rectal evoked potentials. *Neuropharmacology.* 2014;77:422-427.
65. Oertel BG, Preibisch C, Wallenhorst T, et al. Differential opioid action on sensory and affective cerebral pain processing. *Clin Pharmacol Ther.* 2008;83(4):577-588.
66. Adler LJ, Gyulai FE, Diehl DJ, Mintun MA, Winter PM, Firestone LL. Regional brain activity changes associated with fentanyl analgesia elucidated by positron emission tomography. *AnesthAnalg.* 1997;84(1):120-126.
67. Wagner KJ, Sprenger T, Kochs EF, Tolle TR, Valet M, Willoch F. Imaging human cerebral pain modulation by dose-dependent opioid analgesia: a positron emission tomography activation study using remifentanil. *Anesthesiology.* 2007;106(3):548-556.
68. Wise RG, Rogers R, Painter D, et al. Combining fMRI with a pharmacokinetic model to determine which brain areas activated by painful stimulation are specifically modulated by remifentanil. *Neuroimage.* 2002;16(4):999-1014.
69. Petrovic P, Kalso E, Petersson KM, Ingvar M. Placebo and opioid analgesia-- imaging a shared neuronal network. *Science.* 2002;295(5560):1737-1740.
70. Gear R, Becerra L, Upadhyay J, et al. Pain facilitation brain regions activated by nalbuphine are revealed by pharmacological fMRI. *PloS one.* 2013;8(1):e50169.
71. Wanigasekera V, Lee MC, Rogers R, et al. Baseline reward circuitry activity and trait reward responsiveness predict expression of opioid analgesia in healthy subjects. *Proceedings of the National Academy of Sciences of the United States of America.* 2012;109(43):17705-17710.

72. Gorka SM, Fitzgerald DA, de Wit H, Angstadt M, Phan KL. Opioid modulation of resting-state anterior cingulate cortex functional connectivity. *J Psychopharmacol.* 2014;28(12):1115-1124.
73. Younger JW, Chu LF, D'Arcy NT, Trott KE, Jastrzab LE, Mackey SC. Prescription opioid analgesics rapidly change the human brain. *Pain.* 2011;152(8):1803-1810.
74. Mark TL, Kassed CA, Vandivort-Warren R, Levit KR, Kranzler HR. Alcohol and opioid dependence medications: prescription trends, overall and by physician specialty. *Drug Alcohol Depend.* 2009;99(1-3):345-349.
75. Administration SAaMHS. *Incorporating Alcohol Pharmacotherapies Into Medical Practice.* US Department of Health and Human Services; 2009.