Behavioral Effects of Drugs Inpatient 44 Neurobehavioral Mechanisms of Opioid Choice (BED(In)(44))

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PROTOCOL

1. BACKGROUND

The US is experiencing an opioid crisis stemming from the over-prescription of opioid analgesics that led to diversion and misuse, and for some, a progression to illicit opioid abuse. In under 20 years, the yearly number of dispensed opioids nearly tripled to 248 million. Of the patients receiving opioids, an estimated 21-29% misuse them, 8-12% develop opioid use disorder (OUD) and 4-6% transition to illicit opioid use. Of US respondents at least 12 years and older, 12.5 million reported past year opioid misuse and 2.4 million people met OUD criteria. A recent surveillance reported 33,091 opioid overdose deaths in 2015 (mean = 91/day), a near tripling since 2002. In addition to the incalculable social and personal consequences of OUD, the economic burden is staggering, at an estimated $127 billion each year. Thus, there is a substantial public health cost of opioid use, highlighting the need for innovative research to inform treatment and prevention strategies.

Intervention design is informed by an understanding of the mechanisms contributing to the initiation and perpetuation of drug use. At its core, substance use disorders are characterized by the decision to seek and use drugs at the expense of other activities. Lab-based studies have therefore used choice procedures and decision-making tasks to model this central feature of the disorder to study substance use disorder (SUD) mechanisms. Studies using these procedures have typically scheduled competing reinforcers so that the probabilities are certain. However, such deterministic outcomes are not representative of real-world scenarios in which the consequences from drug-related decisions are often unpredictable. Importantly, prior research has shown that decision-making in a dynamic, uncertain context significantly alters the value of choice options and requires continuous updating of option values, which engages learning processes and related corticostriatal networks that might be functioning abnormally in OUD.

Decision-making in dynamic environments has been successfully modeled using probabilistic reinforcement-learning choice (PRLC) tasks. In a simple version of this type of task, two options signaled by distinct cues are available and choosing either could result in the delivery of the same commodity, but the reinforcement probabilities of the options differ, and change during the task. Under such conditions, humans and lab animals optimize their choices according to learned reinforcement probabilities and track changing probabilities over time. The integration of these types of tasks with reinforcement-learning (RL) modeling has been used to capture moment-to-moment changes in the mechanisms of dynamic choice, and the application of neuroscience techniques has begun to identify the underlying neurobiology. This research has emphasized the importance of dopamine neurons in the striatum encoding a continuously updating reward prediction error, derived from expected-vs-experienced reinforcers, which guides future choices. Ongoing efforts across diverse disciplines are extending this work by characterizing corticostriatal networks (e.g., dorsal prefrontal, dorsal anterior cingulate, orbital frontal, ventromedial prefrontal cortices) and other inter-connected brain regions (e.g., insula, amygdala, thalamus), as well as other neurotransmitter systems (e.g., serotonin, glutamate, GABA) that control dynamic choice.

This approach has uncovered abnormalities in decision-making and associated neural activity in multiple psychiatric/neurological disorders (e.g., Parkinson's Disease, Major Depressive Disorder, Obsessive Compulsive Disorder), but has yet to be systematically applied to the experimental study of the disordered use of substances such as opioids. The limited studies that applied computational modeling to data from probabilistic reinforcement tasks to examine decision-making in OUD identified differences between OUD patients and controls. One study showed that subjects maintained on buprenorphine or methadone had lower values on a perseveration parameter on a stimulus categorization task and another study found that abstinent (mean = 3 years) OUD patients had lower values on a loss aversion parameter from the Iowa Gambling Task. Those studies identified impairment in learning mechanisms in OUD patients, but did not assess choices for competing commodities specifically, which is more relevant to OUD. Further, those studies enrolled "stable" OUD patients (i.e., agonist maintained or long-term abstinent) who might have more normalized decision-making capacity. Lastly, and perhaps most importantly, that research did not determine decision-making during spontaneous opioid withdrawal, despite the ability of withdrawal to suppress striatal DA function, negatively impact cognition (including decision-making), and drive drug choice in animals and humans.

2. OBJECTIVES

The objective of this protocol is to use probabilistic choice tasks, reinforcement learning modeling and fMRI to determine the neurobehavioral mechanisms of decision-making during hydromorphone treatment versus opioid withdrawal in individuals with opioid use disorder and physical opioid dependence.

3. STUDY DESIGN

A placebo-controlled, randomized, within-subjects design will be used to assess choice (money-vs-money, cued money-vs-money and drug-vs-money) during fMRI in individuals with opioid use disorder and physical opioid dependence, as a function of alternative reinforcer value and withdrawal status.

4. STUDY POPULATION

Up to 288 men and women of various race/ethnicities will be enrolled for participation in this study in order to collect data from 18 completing subjects.

Inclusion criteria:

-Individuals must meet criteria for moderate/severe opioid use disorder, report past month opioid misuse, and be physically dependent on short-acting opioids (e.g., heroin, hydromorphone, fentanyl), as evidenced by either urine sample positive for recent opioid use during each visit or if opioid negative, displaying frank withdrawal during screening.

-History of intravenous opioid use.

-Baseline O_2 saturation of 95% or greater.

-Between the ages of 18-50 years.

-Female subjects must be using an effective form of birth control (e.g., birth control pills, surgical sterilization, IUD, cervical cap with a spermicide, or abstinence). Urine pregnancy tests will be conducted prior to sessions to ensure that female subjects do not participate if pregnant.

-Able to speak and read English.

-Otherwise healthy.

Exclusion Criteria:

-History of, or current, clinically significant physical disease (e.g., respiratory disease [asthma, COPD, sleep apnea], impaired cardiovascular functioning, seizure disorder or CNS tumors) or current or past history of psychiatric disorder that would limit compliance in the studies, other than substance use disorder.

-Meet diagnostic criteria for psychoactive substance use disorder for substances other than opioids (OUD subjects only) or nicotine/caffeine that would require detoxification (i.e., alcohol, benzodiazepines or barbiturates). Negative urine/breath samples for these substances, and the absence of withdrawal, will be required during screening.

-ECG or laboratory values outside of normal ranges that are deemed clinically significant by a study physician.

-Contraindications for MRI scanning (e.g., pacemaker, metal implants, claustrophobia, or any other implanted medical device).

-Vision or hearing problems that would preclude completion of experimental tasks.

-Poor venous access.

-Regular use of other medications, with the exception of hormone-based contraceptives for female subjects, daily multivitamins, short-term antibiotic prescriptions or Hepatitis C medications.

-At risk for respiratory complications and have predictors of difficult bag mask ventilation (e.g., short thyromental distance), in case emergency respiratory intervention is needed.

-Seeking treatment for SUD or currently taking buprenorphine or methadone as the primary opioid of use.

Screening procedures for all subjects will include a medical-history questionnaire, drug-use questionnaire, brief psychiatric assessment and physical examination. These procedures will be conducted under the screening protocol for the Psychopharmacology of Addiction Laboratory (PAL; IRB#44379). During screening, potential subjects will be asked to provide a urine specimen that will be screened for the presence of recent use of abused drugs. Urine samples from females will also be tested for pregnancy; women testing positive for pregnancy will be notified and discontinued from the screening process for this protocol.

5. SUBJECT RECRUITMENT METHODS AND PRIVACY

Subjects are recruited primarily through formal advertisement (i.e., regular newspaper advertisements), local flyers posted in public areas (e.g., bars, marketplaces), online classifieds and social media (e.g., Craigslist, Facebook) and by word-of-mouth. The Terms of Use for all online advertising sites will be followed. These advertisements are approved under our screening protocols. Subjects will make initial contact by phone with one of our recruiters who have completed the research training and regulatory compliance web-based teaching models. If the subject self-discloses information that would make him/her potentially eligible for the study, they will be invited to come in for a screening appointment. Screening is completed by one of our research assistants at the PAL. Study investigators may interact with subjects in this setting and appropriate cautions are in place to ensure privacy during the intake process.

6. INFORMED CONSENT PROCESS

All potential subjects that are identified using the subject recruitment methods noted above will provide informed consent prior to participating in the protocol. Subjects that meet the eligibility criteria noted above will come to the PAL and will undergo a field sobriety test and provide an expired air sample that will be tested for the presence of alcohol. If the subject passes the field sobriety test (walk and turn, one-leg balance [timed], finger-to-nose and backwards-counting tasks) and the expired air sample is negative, he or she will then be given a copy of the approved informed consent document to read and sign. After reading the consent document, the PI or one of the Co-Is on this protocol approved to obtain consent will review the protocol and address any questions the subject may have in order to assess the subject's understanding. After this, the subject will receive a copy of the informed consent document and sign a form indicating that they have received a copy of the form they read and signed.

7. RESEARCH PROCEDURES

Subjects will participate at the UK PAL, NSL, CCTS Clinical Research Unit (CRU) and Magnetic Resonance Imaging and Spectroscopy Center (MRISC).

Prior to inpatient admission, subjects will complete 2 screening/behavioral qualification sessions, which will also include scanner acclimation in one of the sessions. During the screening/behavioral qualification sessions, subjects will complete a battery of cognitive tasks (see below) and complete a training variant of the PRLC task. Subjects who are unable to meet a predefined criterion will be discharged from the protocol. For these outpatient sessions, check-in and check-out procedures will be the standard for studies we have conducted under previously approved protocols. Upon arrival, subjects will relinquish their keys, watch and mobile phones, which will be stored securely until the end of the session. Next, a field sobriety test will be conducted, and urine and expired breath samples collected. Subjects could be observed by a same-sex staff member when providing urine samples, but they will be told beforehand. Subjects must agree to abstain from illicit drugs and alcohol for the 12 hours prior to each experimental session. Breath samples positive for alcohol or signs of intoxication will preclude the subject from participation in that experimental session, and an additional day will be added to the schedule. Repeated violations will result in dismissal from study participation. Female subjects testing positive for pregnancy will be notified and discontinued from participation. Subjects must also agree to abstain from tobacco/nicotine products, solid food and caffeine for 4 hours before each experimental session, and will be provided with a standard, fat- and caffeine-free snack upon arrival. Subjects who smoke cigarettes will be allowed to smoke a single cigarette. Subjects will not be allowed to smoke again until the experimental session has ended. At the end of the session, subjects will be paid for their participation, their personal belongings will be returned to them and they will be released.

The inpatient protocol will typically require a minimum of 17 days and will consist of an initial 7-day acclimation phase (to permit clearance of abused drugs and stabilization on the maintenance medication prior to experimental sessions), followed by 1 behavioral data collection session (outside the MRI scanner), 1 remifentanil-vs-placebo medical safety session (0.6 mcg/kg/infusion; outside the MRI scanner; same day as the behavioral data collection session), 1 PRLC money-vs-money ($0.25) session (in the MRI scanner), 1 PRLC money-vs-money ($0.25) session (in the MRI scanner) during withdrawal (placebo substitution of hydromorphone), 1 PRLC drug cued money-vs-money ($0.25) session (in the MRI scanner), a PRLC $0.25-vs-remifentanil (0.6 mcg/kg) session (in the MRI scanner) during active hydromorphone maintenance (120 mg/day), a PRLC $4.00-vs-remifentanil (0.6 mcg/kg) session (in the MRI scanner) during active hydromorphone maintenance (120 mg/day) and a PRLC $0.25-vs-remifentanil (0.6 mcg/kg) session (in the MRI scanner) during withdrawal. Following scanning on experimental session days, the delay discounting and purchase tasks will be administered.

Subjects will be maintained on oral hydromorphone maintenance throughout their inpatient enrollment. The starting hydromorphone dose will be 20 mg, administered six times/day at 0800, 1200, 1600, 2000, 0000 and 0400 h. This dosing schedule is based on our currently approved protocol (#80485) using this approach. We acknowledge that subjects will be wakened to receive their maintenance doses throughout the night but feel this is necessary to properly prevent opioid withdrawal. To further minimize the emergence of withdrawal, the first dose will be administered immediately following admission to the inpatient unit and assessment by the study physician; a minimum of 4 hours will separate all subsequent doses that day. The timing of dose administrations on the day of admit will depend on the time of admit and could vary from the typical schedule.

To enhance subject comfort, the hydromorphone dose will be increased daily by 4 mg on an individual subject basis, as needed, to manage withdrawal, throughout the 7-day acclimation period. Withdrawal will be monitored by nursing staff by administering the 11-item Clinical Opiate Withdrawal Scale (COWS), which also includes a locally developed question that asks subjects about the overall severity of withdrawal on a scale of 1-100. The COWS will be taken three times daily (0800, 1400 and 1800), and the COWS score at 1400 will be used to determine if a higher hydromorphone dose is indicated. If the COWS is 5 or greater, the Investigational Drug Service (IDS) will be notified so that the higher dose will be available for administration at 1600. The study physicians will be contacted for their approval prior to any dose adjustments above 24 mg. If an increased dose must be held because the dosing parameters (see below) were exceeded, the physician will be contacted to determine if the dose should be reduced to the prior level. Held doses will be returned to the pyxis machine for storage until IDS can retrieve and dispose of them.

On session days in which remifentanil will be administered, the maintenance dose immediately preceding the session will contain placebo instead of active hydromorphone, which will not elicit withdrawal, but will enhance subject safety. Hydromorphone will not be administered if O_2 saturation is < 95%, respiration rate (manual) is < 10 breaths per minute, if the subject appears sedated/intoxicated, or if they are nodding or keeping eyes closed.

The table accompanying the protocol summarizes the study schedule. Please note three important points relating to the table: 1) The sequence of hydromorphone maintenance and withdrawn conditions is illustrative; the order will be random; the order of the alternative money values will also be random. 2) Participation could require additional sessions to avoid experimental testing on weekends and depending on the day of the week that a subject is admitted to the unit.

During inpatient participation, volunteers will not be allowed to leave the CRU, nor will visitors be allowed. Volunteers will be maintained on a caffeine-free diet. All volunteers will provide urine and expired air samples daily during study participation. Subjects could be observed by a same-sex staff member when providing urine samples, but they will be told beforehand. The presence of non-nicotine, non-cannabinoid or non-stimulant drugs of abuse or alcohol not administered experimentally in the research protocol and not detected at the time of admission will result in immediate dismissal from the research study. Evidence of alcohol consumption during inpatient participation will also result in immediate dismissal. Maintenance doses will be administered by nursing staff; to avoid misuse/diversion of hydromorphone, the nurse will place the dose directly in the subject's mouth, the subject will be required to consume a full cup of water with the capsule, the nurse will complete a mouth

check with a tongue depressor (checking cheeks and gumline) and then the subject will be required to sit at the nursing station for 5 min. The COWS will be taken three times daily: prior to the 0800 and 1800 dose administrations and at 1400. Meals must be consumed at least one hour prior to sessions in which remifentanil is administered.

The initial remifentanil-vs-placebo session will be conducted to demonstrate that this dose of remifentanil functions as a reinforcer in each subject and will also serve as a medical safety session. If >10% of the chosen infusions must be held (e.g., >4 out of the maximum 40 infusions), the dose will be reduced to 0.3 mcg/kg/infusion for the subsequent remifentanil vs. money choice sessions. This session will not occur in the MRI scanner; all subsequent experimental sessions in which remifentanil is administered will be conducted in the scanner at the MRISC. MRI scanning will be scheduled between 0900-1200 based on scanner availability and will take approximately 1 hour. Opioid withdrawal will be required for one of the four experimental sessions, which will be accomplished via double-blind substitution of placebo for the hydromorphone doses scheduled for 0000, 0400 and 0800 h on the session day and 2000 h on the preceding day. Withdrawal will be verified using self-reported and observer-rated withdrawal scales (see below). In preparation for remifentanil sessions, subjects will be prepared with an intravenous midline catheter in the non-dominant arm by the UK Healthcare Vascular Access Team. In addition, a second, standard peripheral IV will be placed by the VAT or 5N/CCTS nurse staff for the medical safety session, which requires two venous access points, and removed after that session. A peripheral IV catheter might also be necessary if issues are encountered with the midline catheter. IV access will be placed and maintained according to UKHC policies.

Infusions of 0.6 mcg/kg/infusion (5-s duration) remifentanil will be available for self-administration as an alternative to placebo (medical safety session) or money (experimental sessions). This dose is based on our dose-ranging study that tested 0.1, 0.3 and 1.0 mcg/kg/infusion in this population (#47844; see section on risks for more detail; Lile et al., 2024). Doses will be delivered by an FDA-cleared infusion pump. Heart rate, end tidal carbon dioxide ($EtCO_2$) and O_2 saturation will be determined prior to, and on a continuous basis during, remifentanil sessions. Blood pressure will also be collected prior to initiating dosing, and at regular intervals during dosing. Due to the time required for the blood pressure reading to occur (i.e. cuff inflation and deflation) and the recommended 1-min interval between assessments, measuring BP before each infusion is incompatible with the infusion delivery schedule. Because of these limits on measuring BP in relation to dosing, BP will be assessed at 5-min intervals, consistent with our initial remifentanil dose-ranging study. If, following any BP assessment, systolic blood pressure ≥ 165 mm Hg or diastolic blood pressure ≥ 100 mm Hg, dosing will be paused. If dose stopping criteria are met, the task will be paused, and vital signs will be monitored by ACLS-certified nursing staff every minute until dosing criteria are met. If dosing criteria are not met within 10 minutes, a physician and the study PI will be contacted for further instructions. Any remaining remifentanil in the syringe will be returned to the pyxis for storage until IDS can retrieve and dispose of it.

An IV dose will not be administered, and a study physician will be contacted if any of the following criteria are met and are verified (i.e., remain out of range) once over a 5-minute observation period.

1. Systolic Blood Pressure <85 ***OR*** >150
2. Diastolic Blood Pressure <45 ***OR*** >100
3. Heart Rate <50 ***OR*** >110
4. ***OR*** a 30% change in baseline for HR or BP
5. O_2 saturation <95%
6. $EtCO_2$ > 60mmHg ***OR*** a 20 mmHg increase over baseline ***OR*** a 30% increase over baseline
7. Participant appears sedated (e.g., is no longer responding on the task)

Drugs will be administered under double-blind conditions and medical supervision. IV remifentanil will be prepared by reconstituting commercial remifentanil powder in 0.9% sodium chloride and administered via a programmable pump. Oral hydromorphone capsules will contain commercially available tablets and cornstarch (active), or only cornstarch (placebo). Detailed information about the management of risks associated with hydromorphone and remifentanil administration are provided below.

Volunteers will be free to engage in recreational activities (e.g., watch television, read, listen to music, arts and crafts, play video or board games) during non-session times. Research volunteers will be required to be in bed with the lights out by 2300 hours.

To minimize the emergence of withdrawal after discharge and help protect against accidental overdose, subjects will receive Suboxone (buprenorphine/naloxone) prior to discharge. All subjects will receive 8/2 mg of buprenorphine/naloxone on the final experimental session day (i.e., the day before discharge), administered as two 4/1 mg doses, separated by 1 h. Suboxone will not be administered until withdrawal signs/symptoms are present (COWS > 9), per dosing guidelines. On the day of discharge, subjects with OUD will be offered a treatment referral. Those interested in transitioning to treatment will receive 16/4 mg Suboxone; those not interested in treatment will receive 8/2 mg. These procedures have been used in our other ongoing protocol that enrolls this population. Subjects will also be given a Narcan® overdose rescue kit (i.e., 4 mg intranasal naloxone). After completing the research protocol, all subjects will be debriefed and paid for their participation.

Study Outcomes (*Medical Safety Session)*

An initial remifentanil-vs-placebo session (outside the MRI scanner) will be conducted to demonstrate that this dose of remifentanil functions as a reinforcer in each subject and will also serve as a medical safety session. For this task (conducted at the CRU), the two choice options will be placebo and 0.6 mcg/kg/infusion remifentanil, labeled Drug A and Drug B. For each trial of this task, the drug and placebo options will be available for self-administration on a fixed-ratio 1 (FR1) schedule of reinforcement, with an inter-trial-interval of 1 min. Prior to the start of the session, subjects will receive a non-contingent sampling dose of Drug A and Drug B to provide experience with the dose effects prior to choice trials. The total number of remifentanil infusions is limited to 40. Subjects will complete the task using a laptop.

Study Outcomes (Experimental Sessions)

Probabilistic Reinforcement-Learning Choice Tasks. In the non-drug (i.e., money-vs-money) version of the task, subjects complete a series of trials (e.g., 300-650). In each trial, subjects choose one of two options, signaled by neutral cues (e.g., blue and green boxes). When reinforcement is scheduled for the chosen option, subjects are notified that they have earned money ($0.25) or are informed that they did not earn money. Four probability ratios for the two options are used (e.g., 6:1, 3:1, 1:3, and 1:6) for the behavioral data collection session, yielding approximately 50-100 possible reinforcers per option across the task. An abbreviated version of the task with fewer trials (e.g., 300) and only two probabilities (e.g., 6:1 and 1:6) will be used in the scanner to minimize subject fatigue and movement. Trials are divided into un-signaled blocks, in which the identity of the higher reward probability option is reversed. Once a reinforcer is scheduled for an option, it remains available until that option is chosen, so that the longer an option remains un-chosen, the greater the probability that a reinforcer will be delivered by choosing it. Subjects will complete the task using a laptop (non-MRI sessions) or a desktop computer connected to an MRI-compatible keypad and visual display (MRI sessions). For MRI sessions, choice trials will be interspersed with control trials, in which subjects will be instructed to select a randomly scheduled option and will be provided feedback that is visually similar to choice trials. Control trials will permit neural activity related to decision-making to be isolated from activity associated with performing the task (e.g., visual, motor).

In the opioid and neutral cued version of the money-vs-money PRLC task, the two choice options will also be $0.25, but the options will be signaled by various opioid-related images and neutral images. To enhance the salience of the opioid cues, subjects will be asked to select 40 images from a database of validated drug images (Ekhtiari et al., 2020) that best represents their preferred route of opioid use and associated paraphernalia, which will be used in the task. Subjects will complete the task inside the MRI scanner using an MRI-compatible keypad and visual display, and control trials will be included.

In the drug-vs-money version of the PRLC task (conducted at the MRISC), the remifentanil dose will again be 0.6 mcg/kg. Due to the probabilistic nature of the task, the maximum number of drug infusions will vary. Our recent study using a similar task revealed that subjects received an average of 30.4 reinforcers (stdev=6.5) across the approximately 40-45 minute drug-vs-money task. The maximum number of infusions will be 50. The abbreviated version of the task with fewer trials (e.g., 200) and only two probabilities (e.g., 6:1 and 1:6) will be

used. Subjects will complete the task inside the MRI scanner using an MRI-compatible keypad and visual display, and control trials will be included.

Neuroimaging Data. Magnetic Resonance Imaging (MRI) data are collected on a high-resolution 3T Siemens MAGNETOM Prisma scanner. We implement several state-of-the-art methods for ensuring quality in data acquisition, opportunity for data sharing, and transparency in data processing. This includes acquiring the data with Human Connectome Project (HCP) scanning parameters, organizing the data in Brain Imaging Data Structure (BIDS) configuration, and preprocessing the data with fMRIPrep: A robust and uniform preprocessing pipeline for MRI data. This approach is currently considered best practice for compliance with national standards.

Data collection involves of a high-resolution 64-channel head coil. Data include a T1-weighted (T1w) anatomical scan (1mm^3 voxels) and sets of functional echo-planar imaging (EPI) scans. Two sets of EPI scans will be acquired in opposing orientations and used to quantify magnetic field inhomogeneities for field distortion correction via B0-nonuniformity map (fieldmap) estimation and application with topup (FSL 6.0.5.1:57b01774). EPI functional scans will also be acquired during the performance of runs of the experimental task with the following parameters: 64 slices; multi-slice factor of 8; repetition time (TR) of 607ms; echo time (TE) of .032ms; flip angle of 50 degrees; voxel size of 2.5 mm^3.

Anatomical data are corrected for intensity non-uniformity (INU) with N4BiasFieldCorrection, distributed with ANTs 2.3.3, and used as the T1w-reference throughout the workflow. The T1w-reference is skull-stripped with a Nipype implementation of the antsBrainExtraction.sh workflow (from ANTs), using OASIS30ANTs as target template. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) is performed on the brain-extracted T1w using fast (FSL 6.0.5.1:57b01774, RRID:SCR_002823). Volume-based spatial normalization to MNI standard space is performed through nonlinear registration with antsRegistration (ANTs 2.3.3), using brain-extracted versions of both T1w reference and the T1w template. The ICBM 152 Nonlinear Asymmetrical template version 2009c is used for spatial normalization.

For functional data from each experimental run, a reference volume and its skull-stripped version are generated. Head-motion parameters with respect to the blood-oxygen-level-dependent (BOLD) reference (transformation matrices, and six corresponding rotation and translation parameters) are estimated before spatiotemporal filtering using mcflirt (FSL 6.0.5.1:57b01774). The estimated fieldmap is then aligned with rigid-registration to the target EPI reference run. The field coefficients are mapped on to the reference EPI using the transform. BOLD runs are slice-time corrected to 0.5 of slice acquisition range using 3dTshift from AFNI (RRID:SCR_005927). The BOLD reference is then co-registered to the T1w reference using mri_coreg (FreeSurfer) followed by flirt (FSL 6.0.5.1:57b01774) with the boundary-based registration cost-function. Co-registration is configured with six degrees of freedom. The BOLD time-series are resampled into standard space, generating an unsmoothed preprocessed BOLD run in MNI space. First, a reference volume and its skull-stripped version are generated. All resamplings can be performed with a single interpolation step by composing all the pertinent transformations (i.e., head-motion transform matrices, susceptibility distortion correction when available, and co-registrations to anatomical and output spaces). Gridded (volumetric) resamplings are performed using antsApplyTransforms (ANTs), configured with Lanczos interpolation to minimize the smoothing effects of other kernels. Data to be included in mass-univariate analyses are then smoothed, typically using a 6mm full-width, half-maximum (FWHM) Gaussian kernel (SPM).

Confounding time-series are calculated based on the preprocessed BOLD signal and placed within a confounds file for later denoising or nuisance variable isolation. These include framewise displacement (FD), DVARS, and three region-wise global signals. FD is computed using two formulations: absolute sum of relative motions and relative root mean square displacement between affines. DVARS is the spatial root mean square of the data after temporal differencing. FD and DVARS are calculated for each functional run, both using their implementations in Nipype. The head-motion estimates calculated in the correction step are also placed within the confounds file. The time series derived from six head motion estimates (three [x,y,z] rotations in radians) and global signals (three [x,y,z] movements in mm) are expanded with the inclusion of temporal derivatives and quadratic terms for each (resulting in up to 24 movement-related confounds per data volume). Volumes that exceed a threshold of 0.9mm FD or 5.0 standardized DVARS are annotated as motion outliers.

Physiological measures. During the medical safety session, in which remifentanil is administered outside the scanner, heart rate, O_2 saturation, breathing rate and end tidal CO_2 will be measured with the Medtronic Capnostream 35, pupil diameter will be measured with the NeurOptics PLR-200 and blood pressure will be measured with the Dinamap Pro400V2 prior to and during remifentanil administration. During the experimental sessions at the MRISC, in which remifentanil is administered in the MRI scanner, the Invivio Precess 3160 MRI-compatible physiological monitoring unit will be used to measure heart rate, blood pressure and O_2 saturation, prior to and during remifentanil administration. In addition, pupil diameter will be measured with the NeurOptics PLR-200 before and after the session.

Opioid withdrawal signs/symptoms will be assessed using self-reported and observer-rated withdrawal scales, the 11-item Clinical Opiate Withdrawal Scale [COWS], a locally developed question that asks subjects about the overall severity of withdrawal on a scale of 1-100 and a 16-item Subjective Opioid Withdrawal Scale (SubjOWS). These scales will be assessed prior to and after sessions involving remifentanil administration. The COWS scales will also be used to monitor withdrawal signs and symptoms throughout inpatient admission. These scales are administered outside of the scanner, except for the single-item overall withdrawal severity rating, which will be obtained during scanning. See attached.

Street value questionnaire. Subjects will be asked to provide a monetary estimate of the street value of the dose they just received. This questionnaire is administered outside of the scanner.

Discounting Measures. A 5-trial adjusting discounting task will be used to rapidly assess discounting rates for money and opioids (Koffarnus & Bickel 2014). In this task, subjects making a series of 5 choices between two options (e.g., an immediately available, smaller reinforcer and a larger reinforcer at various delays in the delay discounting of gains task). Four settings will be used including probability discounting of gains and losses and delay discounting of gains and losses. In all cases the values of the gains (or losses) will be: $1000 delayed (or uncertain) vs. $500 now (or certain). Subjects will be told that all choices are hypothetical. The primary outcome of this task is the delay discounting rate (k) or probability discounting rate (h). Previous research has demonstrated that this measure provides rapid and accurate discounting rates across a range of commodities (Cox & Dallery 2016; Koffarnus & Bickel 2014). This task is administered outside of the scanner.

Drug Purchase Tasks. Purchase tasks will be used to assess economic demand for opioids. In these task subjects are asked to indicate a) the hypothetical number of individual infusions received that day they would purchase at monetary increments and b) the hypothetical likelihood of purchasing the total amount of infusions received that day at monetary increments. All choices are hypothetical and will not be purchased or administered. Data from these purchase task will be analyzed using economic demand equations previously applied to purchase task data (e.g., Amlung & MacKillop 2015; Murphy & MacKillop 2006). Primary outcomes of this task include elasticity of demand (α) and intensity of demand (Q_0). These values are derived using nonlinear regression with the exponential demand equation (Hursh & Silberberg 2008): $Log_{10}Q = log_{10}(Q_0) + k(e^{-\alpha*Q0*C}-1)$, where Q = consumption at a price; Q_0 = derived intensity of demand (consumption at zero price); k = a constant that denotes the range of consumption values in log_{10} units; C = the price of the commodity; and α = derived essential value (a measure of elasticity of demand). Greater values of Q_0 indicate greater consumption at unconstrained price (i.e., a theoretical price of zero). Greater values of α indicate a higher elasticity of demand or change in consumption with change in unit price. These tasks are administered outside of the scanner.

Additional Study Outcomes

n-back task. This task is a continuous performance task used to measure working memory capacity which is important for the cognitive control of decision-making and is important for reinforcement learning task performance (Collins and Frank, 2012). In this task, subjects are presented with a sequence of stimuli, and are asked to indicate when the current stimulus matches one from *n* steps earlier in the sequence.

Wechsler Abbreviated Scale of Intelligence (2nd ed.; WASI-II). This assessment provides a brief, reliable measure of cognitive ability. Scores on this Wechsler intelligence scales have previously been associated with performance on reinforcement learning tasks (Hawes et al., 2014; Van den Bos et al., 2012).

8. RESOURCES

This study will take place at the PAL, NSL, CRU and MRISC, which contain all the necessary space, medical oversight, neuroimaging, physiologic and computer equipment for the study. Dr. Lile will provide scientific oversight for the study and has extensive background in human laboratory research, including human subjects protection. A research team with all of the necessary expertise to conduct this research and provide medical oversight has been assembled. Overall, the study team and resources described above are well equipped to protect participants and successfully implement, carry out and complete this protocol.

9. POTENTIAL RISKS

The behavioral, subjective and physiological assessment procedures employed in these studies are benign. Adverse events identified as possible risks in this study include:

1. Subject's protected health information (PHI) may be viewed by others not directly involved in the conduct of the proposed research. PHI is considered individually identifiable health information transmitted or maintained in any form (electronic means, on paper, or through oral communication) that relates to the past, present or future physical or mental health or conditions of an individual that may be used or disclosed. The following PHI will be collected as part of this project: names (individual, employer, relatives, etc.), address, telephone number, Social Security number, dates (birth, admission, discharge), medical record numbers, driver's license numbers, mental and physical health history, drug use history, results from mental and physical health screening, results from personality questionnaires and data from experimental measures. This risk will be minimized since all appropriate precautions will be taken to protect subjects' PHI, according to the guidelines established by the HIPAA.
2. Embarrassment in disclosing sensitive personal information.
3. Discomfort due to study procedures.
4. Dissatisfaction with the study procedures.
5. Side effects associated with the neuroimaging. Subjects will participate in MRI scanning. In studies involving MRI, movement or heating of metallic implants is a risk, and subjects might also experience mild discomfort or anxiety in the scanner. The 3.0 Tesla (3T) scanner used at the Magnetic Resonance Imaging and Spectroscopy Center (MRISC) is FDA approved. However, there may be additional risks associated with scanning at 3.0 T compared to the conventional clinical scanners, which are typically 1.5 or 2.0 T. There is risk associated with exposure to the static magnetic field. Although there is no conclusive evidence for irreversible or hazardous effects to acute, short-term exposure to a 1.5 T magnetic field side effects reported at 4.0 T have included nausea, vertigo, and metallic taste. There is no evidence, however, that these effects are irreversible or harmful. There is also risk of exposure to the gradient magnetic field. MRI operates by rapidly changing small magnetic fields, called gradients, within the larger static field. This process can induce small electrical currents in any conductor. Thus, MRI could theoretically induce mild peripheral nerve stimulation. This risk is not substantially different at higher magnetic fields, however, because gradients are distinct from the larger static magnetic field. There is no evidence that gradients at 3.0 T are different than those at 1.5 or 2.0 T. Lastly, there is risk associated with radio frequency (RF) electromagnetic field pulses used for functional MRI (fMRI). Higher static field strengths require higher RF frequency pulses in order to excite protons in the brain. The FDA has defined the limits of RF energy that can be safely given to humans, and the MRISC adheres to these FDA recommendations by limiting the maximum RF power level.

6. Opioid drug administration and withdrawal. The short-acting opioids hydromorphone and remifentanil will be administered to the subjects with OUD in this study. The relative safety, as well as the contraindications and possible side effects of these compounds are well known and documented. These drugs could produce side effects typical of mu opioid agonists, including nausea, vomiting, headache, dry mouth, itchiness, drowsiness, sweating, dizziness, stimulation, somnolence, lightheadedness, restlessness, a feeling of well-being, talkativeness, urinary retention, constipation, hypotension, bradycardia and non-clinically significant respiratory depression. It is likely that subjects will experience one or more of these side effects. More serious side effects may include allergic reaction and clinically significant respiratory depression. In addition, remifentanil can cause skeletal muscle rigidity, including chest wall rigidity; the likelihood of this occurring is related to the dose and speed of administration. It is unlikely that subjects will experience these more serious side effects. The doses

were selected minimize the risk of clinically relevant respiratory depression and muscle rigidity and are consistent with doses that have been administered to opioid-dependent individuals in prior studies without serious adverse events.

During the initial hydromorphone maintenance stabilization phase, and during double-blind substitution of placebo for hydromorphone maintenance, some participants may experience mild opioid withdrawal. These symptoms include nausea, vomiting, teary eyes, runny nose, loose stool, stomach cramps, shakiness, anxiety/irritability, increased heart rate, sweating/chills, restlessness, and body aces/discomfort.

7. Needle insertion. This study will require placement of an indwelling venous midline catheter to be placed prior to the start of experimental sessions involving IV solution delivery, and a standard peripheral IV stick for the duration of the medical safety session, to permit intravenous saline and remifentanil administration. In addition, a peripheral IV catheter might also be necessary for drug solution delivery if issues are encountered with the midline catheter. These procedures are accompanied by the risk of bruising, blood clotting, soreness, infection, bleeding, pain, swelling and irritation from the insertion of a needle. There is also a risk that the indwelling catheter could come out of the vein or penetrate the vein; if this occurs, any fluid infused into the catheter could deposit in the arm tissue, resulting in soreness, pain, swelling and irritation. Lastly, there is a risk of syncope.

10. SAFETY PRECAUTIONS

The standard safety precautions used for studies at the PAL, NSL, MRISC and CRU will be used for the present experiment. Protocol management forms will include prompts for research staff members to record any protocol anomalies, data collection problems, concerns with study subjects, or any unusual events that could impact the safety of the subjects or the integrity of the protocol. In addition, the PI, as well as the study physician or his appointed representative, are available at all times by telephone to respond to any questions or concerns that occur during the study. Furthermore, the PI meets with the project staff on a regular basis in the laboratory or by telephone contact to review the study activities.

Study Stopping Criteria

1. If any subject has an unexpected, serious, life threatening adverse event that is related to the study procedures, the study will be stopped.
2. If, after 6 subjects have been enrolled and have completed at least one remifentanil dosing session (33% of the proposed sample), and for all subsequent subjects, dosing was stopped in greater than 33% of the remifentanil dosing sessions, the study will be stopped.

1. Violation of confidentiality.

All subject PHI is confidential and will be protected according to the guidelines established by the HIPAA. An "Authorization to use and disclose PHI for research purposes" approved by the UK IRB will be obtained. This allows the investigators on this project to use or share health information with the United States Department of Health and Human Services (DHHS) representatives, the UK IRB, the UK Office of Research Integrity (ORI), UK medical center representatives, other research collaborators or when required by law. In addition, a Certificate of Confidentiality will be issued. All data will be kept locked either on password-protected computers or in secure filing cabinets all behind locked doors and accessible only to key personnel involved in the research. Electronic and paper copies of data will be stored at the UK PAL, NSL, CRU, MRISC and/or Department of Behavioral Science.

2. Embarrassment in disclosing sensitive personal information.

The risk is minimized through the use of confidentiality safeguards described above and below. Subjects can refuse to answer any questions regarding sensitive personal information, although this might impact their ability to continue in the study.

3. Discomfort due to study procedures.

Subjects are informed that they have the right to withdraw from study protocols at any time. A research staff member will always be available to answer questions, and the study subjects have telephone contact information to reach both the PI and the study physician. If individuals become overly distressed or distraught, participation

in the study is discontinued immediately, and private consultation with the study physician and/or PI is offered immediately.

4. Dissatisfaction with the study procedures.

As noted, during the course of participation in the research, a subject could experience dissatisfaction or discomfort with the experimental procedures. A research staff member will be immediately available to address these issues, and the study subjects have telephone contact information to reach both the PI and the study physician. In addition, if individuals become overly distressed or distraught, participation in the study is discontinued immediately, Suboxone induction will be offered and private consultation with the study physician and/or PI will be offered.

5. MRI.

The neuroimaging protocol is considered a minimal risk procedure, and our Co-Investigator Michael Wesley, Ph.D., has over 15 years of experience in this field. In studies involving MRI, movement or heating of metallic implants is a potential risk. Some individuals may experience mild discomfort or anxiety in the scanner, and all subjects will be informed of this possibility prior to the study. Throughout scanning procedures subjects will be able to communicate with the investigators via intercom, and any subject reporting discomfort will be removed from the MRI scanner immediately.

The 3.0 Tesla (T) scanner used at the MRISC is FDA approved. However, there may be additional risks associated with scanning at 3.0 T compared to the conventional clinical scanners at 1.5 or 2.0 T. There is risk associated with exposure to the static magnetic field. Although there is no conclusive evidence for irreversible or hazardous effects to acute, short-term exposure to a 1.5 T magnetic field, side effects reported at 4.0 T have included nausea, vertigo, and metallic taste. There is no evidence, however, that these effects are irreversible or harmful. There is also risk of exposure to the gradient magnetic field. MRI operates by rapidly changing small magnetic fields, called gradients, within the larger static field. This process can induce small electrical currents in any conductor. Thus, MRI could theoretically induce mild peripheral nerve stimulation. This risk is not substantially different at higher magnetic fields, however, because gradients are distinct from the larger static magnetic field. There is no evidence that gradients at 3.0 T are different than those at 1.5 or 2.0 T. Lastly, there is risk associated with radio frequency (RF) electromagnetic field pulses used for functional MRI (fMRI). Higher static field strengths require higher RF frequency pulses in order to excite protons in the brain. The FDA has defined the limits of RF energy that can be safely given to humans, and the MRISC adheres to these FDA recommendations by limiting the maximum RF power level. If subjects experience unusual sensations and/or peripheral nerve stimulation resulting in nerve tingling or twitching, they will be withdrawn.

In addition to the measures to ensure the safety and comfort of subjects noted above, every effort will be made to provide information and support to subjects to minimize discomfort during brain scanning sessions. Specifically, the following will be carefully explained *prior* to participation, and will be included in the consent form:

> "While in the MRI scanner you may become too hot or too cold, in which case you may ask for an adjustment of room temperature or a blanket. Some people may become nervous or feel claustrophobic while in the scanner. If this happens, you may ask to be withdrawn and will be withdrawn from the scanner immediately. A small number of people experience a sense of dizziness or vertigo while in the scanner due to the magnetic field. Although rare, nerve tingling or twitching might occur. If any of these occurs and disturbs you, you may ask to be withdrawn and you will be withdrawn immediately. You will be instructed to remove all jewelry and other metal-containing objects. Because the magnetic field will affect any metallic object, you should not participate if you have any type of metallic implant in your body, including pacemakers, aneurysm clips, shrapnel, metal fragments, orthopedic pins, screws, or plates, IUDs, piercings or any other implanted medical device that you cannot remove."

Dr. Wesley or the MR technologist in the MRISC will assess each subject to ensure that they meet all criteria to have an MRI scan. In the event of uncertainty of a subject's suitability, Dr. Wesley will consult with the MR technologist (or vice-versa). MR images will be visually evaluated by Dr. Wesley or the MR technologist

to detect possible findings that would require urgent notification of the subject or their primary care physician. In the event that possible findings are detected, Dr. Wesley will contact Dr. Hays, who will coordinate verification of the findings with a neurologist, and if needed, referrals to the subject.

6. Opioid administration and withdrawal. The primary risks to subjects are those related to the administration of hydromorphone and remifentanil. The hydromorphone maintenance procedure is being used in ongoing studies at Johns Hopkins University and the overall exposure to hydromorphone will likely be less than subjects' ongoing drug use outside of the study. The doses of remifentanil have been previously administered and are appropriate for those who have an extensive history of non-medical opioid use with current physical dependence. Moreover, we have used oxycodone maintenance and double-blind placebo substitution to study opioid withdrawal in past protocols. In addition, our Co-Investigator Kevin Hatton, M.D. has extensive experience administering intravenous remifentanil as part of his clinical duties at UK and in our ongoing project (#47844). Subjects in this group will be thoroughly informed of the various drug side-effects which they might experience. Participation is voluntary, so individuals can withdraw at any time if they find the drug effects undesirable. The drug doses to be administered in the present experiments were chosen to minimize, if not eliminate, the chance of these side effects occurring. Drs. Hatton, Hays and Anderson will screen all potential research subjects for medical contraindications, and Dr. Gurley, or his representative, will review the ECG, prior to study participation. Drs. Hatton, Hays and Anderson will monitor research subjects every day of their inpatient admission. Urine samples will be monitored throughout each study to ensure that female subjects are not pregnant and that all subjects are adhering to the drug use restrictions. A crash cart, including naloxone syringes and oxygen, is always on site, and the hospital code team is available in the case of emergency. We anticipate that careful subject selection, dose selection and subject monitoring will greatly reduce, if not eliminate, the occurrence of serious side effects. To monitor for adverse events/side effects, the Udvalg for Kliniske UndersØgelser (UKU) Side Effects Rating Scale will be completed daily with subjects by CRU nursing staff. Staff observations and spontaneous subject report will also be used to monitor for adverse events.

Potential subjects must be physically dependent on opioids to be enrolled. To minimize the emergence of withdrawal signs and symptoms once admitted to the CRU, subjects will be maintained on oral hydromorphone. PRN medications will be made available, including oral alumina/magnesia/simethicone (30 ml PO every 4 hrs PRN for dyspepsia or nausea), oral bismuth subsalicylate (30 ml PO every 4 hrs PRN for diarrhea; no more than 6 doses/24 hrs), oral Colace (100 mg PO twice daily PRN for constipation), oral acetaminophen (650 mg PO q 8 hours PRN for pain), and oral ibuprofen (800 mg PO q 8 hrs PRN for pain). In addition, during initial stabilization, available PRNs will include clonidine (0.1 mg PO every 6 hrs up to 3 times a day for increased blood pressure, pulse, anxiety, chills or piloerection), ondansetron (4-8 mg PO up to 3 times per day for nausea/vomiting; maximum daily dose of 24 mg), hydroxyzine (25-50 mg PO every 6 hrs for anxiety and insomnia), trazodone (100 mg before bed, may repeat 1x after 1 h for insomnia) and cyclobenzaprine (10 mg up to 3x a day for muscle aches). On session days, PRNs will only be available after session completion, to avoid interference with the emergence of experimentally induced mild opioid withdrawal. Hydromorphone maintenance will be offered for approximately 10 days. Subjects who are unable to achieve adequate stabilization during this time will be discharged from the protocol. Subjects unable to tolerate experimentally induced withdrawal will also be discharged from the protocol. All discharged (early or following study completion) participants will be asked to remain in the hospital for induction onto Suboxone and will also be offered a take-home Narcan® kit (i.e., 4 mg intranasal naloxone) and treatment referrals. Note that subjects have the option of refusing Suboxone induction and will be asked to sign a form acknowledging the risks associated with this refusal.

The remifentanil product information indicates that chest wall rigidity (inability to ventilate) is possible after single doses of > 1 mcg/kg administered over 30-60 s. In a prior study (Hay et al., 2008), doses of up to 3.5 mcg/kg/inf (administered over a period of 1 min for 20 minutes at each dose) were tested in methadone-maintained opioid-dependent subjects; statistically significant (though clinically safe) effects on respiration rate and analgesia were detected starting at the 1.0 and 2.0 mcg/kg/inf/min doses, respectively, and persisted with higher doses, but no muscle rigidity was observed. Note that the total amount of remifentanil received by a 70 kg subject was 19.6 mg across a 2.5 h timeframe in the Hay et al., 2008 study, whereas the proposed dose (0.6

mcg/kg/infusion) and dosing schedule in this protocol would deliver an estimated 1.7 mg of remifentanil across ~40 min. Morever, the present study and the prior study will enroll/enrolled opioid-maintained, dependent individuals. Overall, the amount of remifentanil delivered appears unlikely to be result in chest wall rigidity, and our initial results (#47844) support this assertion. The product information also states that chest wall rigidity is possible with infusion rates > 0.1 mcg/kg/min. Each infusion in this protocol will be delivered over a 5-s duration, which is consistent with naturalistic intravenous opioid use (Zernig et al., 2003), but exceeds the recommended 30-60 s infusion duration typically used in clinical practice. The dose to be tested in this protocol, 0.6 mcg/kg/infusion, exceeds the > 0.1 mcg/kg/min threshold at which chest wall rigidity is possible, as described in the product information. However, we believe this is safe given the potency differences in opioid-dependent individuals demonstrated in the Hay et al., 2008 study, and our initial experience administering up to 1.0 mcg/kg/infusion using procedures like those described here. Four subjects who participated in our ongoing protocol received infusions of 1.0 mcg/kg/infusion remifentanil, with infusions administered over a 5-s duration at 1-min intervals. These remifentanil infusions were generally well tolerated, though this dosing block was stopped in one subject due to sedation, and some infusions were held in the other three subjects, typically because respiration rate or oxygen saturation fell below dosing parameters. Importantly, however, no interventions (i.e., oxygen supplementation, naloxone administration) other than verbal prompts have been necessary to keep subjects awake and breathing normally during remifentanil administration. The 1.0 mcg/kg/infusion remifentanil dose significantly decreased oxygen saturation (i.e., mean pre-dose = 98.5%, during 1.0 mcg/kg/infusion = 94.1 mmHg), but respiration rate and $EtCO_2$ did not change in an orderly manner. This dose of remifentanil non-significantly reduced heart rate (i.e., mean pre-dose = 79.2 bpm, during 1.0 mcg/kg/infusion = 72.8 bpm), systolic blood pressure (i.e., mean pre-dose = 120.1 mmHg, during 1.0 mcg/kg/infusion = 111.1 mmHg) and diastolic blood pressure (i.e., mean pre-dose = 74.3 mmHg, during 1.0 mcg/kg/infusion = 67.1 mmHg). These changes were not considered clinically significant for an acute drug effect. Pupil diameter also decreased (i.e., mean pre-dose = 4.7 mm, during 1.0 mcg/kg/infusion = 2.9 mm). The 0.3 mcg/kg/infusion dose produced significant effects on these outcomes as well, though of lower magnitude; in particular, the subjective response to the 0.3 mcg/kg/infusion dose was minimal (e.g., mean score of 17 out of 100 on a visual analog scale rating of Drug Effect), suggesting that a larger dose is needed for a study assessing drug reinforcement. Given the responses observed in our ongoing study, we are selecting a remifentanil dose (0.6 mcg/kg/infusion) for this study that is in between (in ¼ log units) the 0.3 and 1.0 mcg/kg/infusion doses. We anticipate that repeated administration of the 0.6 mcg/kg/infusion dose will be well tolerated and that dose holding will be infrequent. However, as noted above, if >10% of the chosen infusions must be held (e.g., >4 out of the maximum 40 infusions), the dose will be reduced to 0.3 mcg/kg/infusion for the subsequent remifentanil vs. money choice sessions. These dosing procedures have been considered in the context of the risk of chest wall rigidity and other potential side effects of IV remifentanil administration, as well as our initial findings, by Dr. Hatton, who also conferred with his colleagues.

Subjects will receive intravenous remifentanil during maintenance on oral hydromorphone, and the combination of these two opioid agonists could further increase the risk for adverse events. However, extensive human laboratory research has demonstrated the safety and tolerability of administering a short-acting opioid agonist during maintenance on another opioid agonist. In fact, in an effort to avoid withdrawal in opioid-dependent subjects participating in inpatient research, maintaining subjects on an opioid agonist is a typical procedure. Worth noting is that the hydromorphone maintenance dose scheduled immediately before experimental sessions will be substituted with placebo, which will not result in the emergence of withdrawal, but will enhance subject safety.

Prior to each experimental session in which remifentanil is administered, Dr. Hatton or his designee will be notified that the session is beginning by pager/text. During experimental sessions, an ACLS-certified Registered Nurse will administer intravenous remifentanil under the indirect supervision of an ACLS-certified physician or anesthesiologist. Heart rate, blood pressure and oxygen saturation will be monitored throughout sessions. A trained research assistant will also be present in the room with subjects during experimental sessions, so that subjects are never left unattended during a test session. Experimental drug infusions will be withheld if oxygen saturation is 95% or below or if a subject is experiencing significant sedation. Subjects who exhibit

hypersensitivity (i.e., experience a serious adverse event) following drug administration will not receive further doses, will be followed until symptom resolution, and will be excluded from further research participation.

During experimental sessions in which drugs are administered, we will employ our standard criteria for nursing staff and research personnel for monitoring individuals. Subjects will be monitored during IV infusions and for a minimum of 2 h after. If respiration parameters are out of range and accompanied by sedation, subjects are simply prompted verbally to breathe. In our experience, physical and verbal prompts are typically sufficient to restore normal respiration. Subjects will be monitored with a "watchful waiting" approach. If clinical evaluation determines that sedation is significantly worsening (moderate sedation or <8 breaths/min), Dr. Hatton will be contacted and will intervene if necessary. If O_2 saturation is <95% after reminding to breathe (verified for 60 s), supplemental oxygen (positive pressure ventilation with 100% O_2 and bag mask) can be given for 2-3 minutes or per physician orders: 2 LPM via nasal cannula if oxygen saturation is 90-94%, 4 LPM via nasal cannula if oxygen saturation is 86-89% **or** 4 LPM via non-rebreathing mask if oxygen saturation is <86%. If O_2 is not effective, as indicated by absence of chest rise during breathing or continued oxygen desaturation, 0.4 mg IV naloxone will be administered. Should opioid-induced sedation persist, repeat naloxone administration or oral naltrexone will be administered for prolonged opioid receptor blockade. In our extensive experience administering opioids to human subjects, even at high doses, there have been very few incidents requiring intervention with naloxone/naltrexone.

Although it is possible that subjects could experience an allergic reaction to hydromorphone and/or remifentanil, this is unlikely because they are required to have a history of opioid use. However, if a subject experiences an allergic reaction, diphenhydramine will be available for oral or parenteral administration.

7. Needle insertion. Risks of bruising, blood clotting, soreness, infection, bleeding, pain and irritation are minimal since standard sterile procedures will be used. The likelihood of syncope is uncertain and will vary across subjects; however, all medical staff is prepared to manage the occurrence of syncope.

11. BENEFIT vs. RISK

The degree of risk to which individual study subjects are exposed as a consequence of their research participation is low. In contrast, the potential and probable benefits to be derived by society, in general and by patients with opioid use disorder appear to be considerable. The major benefits of these studies are scientific and clinical ones related to the knowledge gained concerning the neurobehavioral and neurobiological underpinnings of maladaptive choice in opioid use disorder. Individual study subjects are expected to benefit personally from the medical and psychiatric evaluations and from referrals for medical and psychiatric treatment that are provided whenever appropriate. Overall, the risk/benefit ratio appears favorable and the conduct of this research seems well justified.

12. AVAILABLE ALTERNATIVES TO PARTICIPATION

If subjects do not want to be in the study, there are no other choices except not to take part in the study.

13. RESEARCH MATERIALS, RECORDS AND PRIVACY

Information about subjects' drug histories and physical/mental health will be collected for the purpose of selecting subjects for approved research protocols. Similarly, urine samples will be collected and tested for the presence of a full range of drugs of abuse. Females will also be given a pregnancy test. These screening materials will be collected under our screening protocol. During the experiment proper, urine drug and pregnancy tests will be conducted prior to the conduct of each session. Expired breath samples will be used to test for the presence of alcohol prior to the conduct of each session. Other data obtained from the subjects will include questionnaires to assess recent activities, drug use and physical/mental status, in addition to computerized brain imaging, performance and physiological measures, described above, collected during experimental session, along with non-intrusive staff observations and ratings. Collection of these materials should not impact subject privacy because the environment in which these materials will be obtained is not associated specifically with drug abuse research and all personal health information will be kept confidential.

14. CONFIDENTIALITY

Identifying information will be stored in a separate, locked area from all coded data and codes linking the two will be kept under lock and key or on password-protected computers at the PAL, NSL, MRISC and/or Department of Behavioral Science. Subjects will also be informed that there is a possibility that the data collected may be shared with other investigators in the future. If that is the case the data will not contain identifying information unless further consent is obtained or unless approved by the UK Institutional Review Board. Study materials, including data, will be stored for 6 years after study closure and then destroyed per ORI policy.

15. PAYMENT

Subjects will receive $30 each for the 2 outpatient screening/behavioral qualification sessions, and they will also receive a completion bonus of $30 for completing each session. Subjects will also receive $60/inpatient day (plus $60/inpatient day completion bonus), for a total payment of $2160 (if 17 inpatient days are completed). In addition, subjects can earn additional money on the PRLC task. Subjects will receive payments in no more than $500 increments at 1-week intervals beginning on the day of discharge, or the day after (for early discharges), until they receive all money earned in the study.

16. COSTS TO SUBJECTS

Costs for all study procedures and materials will be paid by the study investigators. The subjects will be responsible for the costs associated with traveling to and from the research facility.

17. DATA MONITORING

The purpose of this project is to use dynamic probabilistic reinforcement-learning choice (PRLC) tasks, combined with RL modeling and neuroimaging techniques, to reveal the neurobehavioral processes underlying drug choice in opioid use disorder (OUD) that can be targeted for the development of novel prevention and treatment strategies.

All subjects must provide informed consent to participate. This sample will be recruited from the community and will participate as outpatients at the UK PAL, NSL and MRISC and inpatients at the UK CRU and MRISC.

Dr. Joshua Lile will be the Principal Investigator responsible for monitoring the safety and efficacy of this trial, executing the DSMP, and complying with the reporting requirements. The PI will provide a summary of the DSM report to NIDA on an annual basis as part of the progress report. The DSM report will include the subject sociodemographic characteristics, expected versus actual recruitment rates, retention rates, any quality assurance or regulatory issues that occurred during the past year, summary of serious adverse events (SAEs), and any substantial actions or changes with respect to the protocol. The DSM report to NIDA will also include, if applicable, the results of any data analysis conducted. There are no conflicts of interest.

Data Monitoring Plan

Data will be collected using a computerized data collection and management system. This system automates the collection of the PRLC task, neuroimaging, physiological and subjective effects data, which ensures the accuracy and completeness of data collection. The data are stored in unique files on the hard-drive of the computers and are electronically backed-up at the end of each session. In all instances, the data files do not contain the name of the subject, but instead, each subject is identified by a unique four-digit number. The computer file linking subject names and numbers will be encrypted and only key personnel will have access. Data files for experimental tasks and physiological measures from each subject and experimental session will be managed and combined by automated macros, and subsequently analyzed using SPSS software. Neuroimaging data will be analyzed using customized Matlab scripts and an array of neuroimaging software packages, including but not limited to SPM and FSL primary platforms and their associated neuroimaging toolboxes.

This study will compare task performance under opioid-maintained and -withdrawn conditions. The primary outcome measure is the PRLC task, which will yield (1) "molar" choice performance (i.e., number of monetary reinforcers delivered), analyzed with a linear mixed-model, (2) "molecular" trial-by-trial performance, including parameters and model fits analyzed using reinforcement-learning modeling, and (3) regional and network neuroimaging data, modeled using traditional mass-univariate approaches (e.g., general linear models and statistical parametric mapping) and newer multivariate approaches (e.g., multivariate pattern analysis).

The quality of manipulated data and data analyses will be monitored by random inspection by the PIs and/or Co-Investigators. Preprocessing and analysis of subject-specific behavior and brain profiles will begin as individual data are collected. Interim analysis of the data will be conducted when 50% of the sample is accrued. If statistically significant differences are revealed for all outcome measures, the study will be ended.

Safety Monitoring Plan

Potential subjects will provide information regarding their drug use history and will undergo an extensive physical and psychiatric health screening to determine their eligibility and safety of their participation. All study subjects will be judged by the medical staff to be psychiatrically and physically healthy, and without contraindications for participation. Potential subjects must meet DSM V criteria for moderate/severe OUD, be physically dependent on opioids and report prior history of intravenous opioid use.

Methods for monitoring adverse events (AEs) will include observations by the medical and research staff, spontaneous report by the subjects, regular measurement of respiratory and cardiovascular indices and use of the UKU Side Effects Rating Scale. Subjects will not receive study drug if they have any signs or symptoms that may contraindicate its administration (e.g., development of serious side effects).

All AEs occurring during the course of the study will be collected, documented, and reported to the PI following each occurrence. The occurrence of AEs will be assessed daily for the duration of participation, as needed and follow-up visits will be scheduled as appropriate. The study investigators will follow all AEs to the point of a satisfactory resolution. Subjects may be withdrawn from the study if the investigators determine it is the best decision in order to protect the safety of the subject. All AEs will be assessed to determine if they meet criteria for a serious adverse event (SAE).

Serious adverse events, as defined by the FDA, will be systematically evaluated daily for the duration of participation, as needed and follow-up visits will be scheduled as appropriate. Any SAE, whether or not related to the study drug, will be reported to the IRB, NIDA, and the FDA. In the event that a subject either withdraws from the study or the investigator decides to discontinue a subject due to an SAE, the subject will have appropriate follow-up medical monitoring. Monitoring will continue until the problem requiring hospitalization has resolved or stabilized with no further change expected, is clearly unrelated to the study drugs, or results in death.

Data and Safety Monitoring Board

NIH requires the establishment of a Data and Safety Monitoring Board (DSMB) for 1) multi-site clinical trials involving interventions that entail risk to the participants, and 2) for most Phase III clinical trials. This project meets neither of these definitions.

18. SUBJECT COMPLAINTS

Subjects may at any time ask study personnel questions about the study procedures or make complaints. All staff will be aware to notify Dr. Lile or another investigator-level study personnel (e.g., Drs. Wesley, Hays or Anderson) about any subject concern or complaint as it arises. Subjects will be allowed the opportunity to discuss any concerns or questions with an investigator promptly, in person and in confidence. It should be noted, however, that subjects will be told that some concerns and complaints will not be kept private such as an adverse event, protocol deviation or threat to the safety of participants or integrity of the research study. In these cases, all information will be made available to the PI in order to determine any further course of action. All subjects will be provided the contact information for the study coordinators as well as the University of Kentucky ORI in the consent form.

19. RESEARCH INVOLVING NON-ENGLISH SPEAKING SUBJECTS OR SUBJECTS FROM A FOREIGN CULTURE Not Applicable.

20. HIV/AIDS RESEARCH POLICY Not applicable.

21. PI SPONSORED FDA-REGULATED RESEARCH Dr. Lile currently holds an IND for remifentanil (#146,522), which will be amended by Dr. Lile to include this protocol.

22. **FUTURE USE AND SHARING OF RESEARCH DATA**

De-identified data may be used for future research or shared with other researchers without additional informed consent. Data will be de-identified (codes destroyed) once all manuscripts describing anticipated primary and secondary analyses have been published. The information will be stored at the University of Kentucky PAL, NSL and/or Center for Clinical and Translational Research (CCTS) indefinitely. There is a risk that someone could get access to the samples in spite of the security measures and safeguards. There may also be risks that at this time are unknown. Information will be de-identified and stored on password- and firewall-protected data servers. Information from our study could be shared with other researchers. An investigator at UK who receives de-identified information will sign an agreement promising not to try to use any of the sample to identify the subject. If a researcher from another institution is to receive de-identified information, that request will be reviewed by the IRB. Information will not be shared with researchers in other countries. Subjects may withdraw their permission to allow their information to be used for future research by sending a written withdraw request to the PI.