CURE Addiction Center of Excellence: Brain Mechanisms of Relapse and Recovery (fMRI CURE)
NCT01587196
06/16/2014

Protocol Details

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SZUCS, REGINA P PS-Psychiatry Yes 06/13/2011
Patient Oriented Research Full Board Review Curriculum – USOM

Name: Department/School/Division: HS Training Completed: Training Expiration Date: Name of course completed:
FRANKLIN, TERESA PS-Addictions Yes 01/14/2014
CITI Protection of Human Subjects Research Training - ORA
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O'BRIEN, CHARLES P PS-Addictions No 09/05/2010
CME Credit for POR Expedited Review - SOM
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SUH, JESSE J PS-Addictions Yes 08/17/2012 CITI Protection of Human Subjects Research Training - ORA
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CME Credit for POR Expedited Review – SOM

Disclosure of Financial Interests*
Does any person who is responsible for the design, conduct, or reporting of this research protocol have a **FINANCIAL INTEREST**? No

Certification
I have reviewed the *Financial Disclosure and Presumptively Prohibited Conflicts for Faculty Participating in Clinical Trials* and the *Financial Disclosure Policy for Research and Sponsored Projects* with all persons who are responsible for the design, conduct, or reporting of this research; and all required Disclosures have been attached to this application.
Yes

The following documents are currently attached to this item:
There are no documents attached for this item.

Biomedical Research

Investigator Initiated Trial
Is this an investigator-initiated trial? No

Drugs or Devices*
Does this research study involve Drugs or Devices? Yes: Drugs, products or devices are used in accordance with FDA approval.

IND Exemption

For studies that fall under an IND exemption, please provide the number below

For studies including IND or IDE's, please provide the number(s) below

IDE Review*
NOTE: For research involving investigational devices, you are required to review the guidance on Managing Research Device Inventory. Consult the Penn Manual for Clinical Research: https:// somapps.med.upenn.edu/pennmanual/secure/ pm/storage-drugsdevices Please check the box Yes if you have reviewed the guidance.
No

Research Device Management*
Please indicate how research device(s) will be managed. Not Applicable (no investigational devices)

If an IDS number has been obtained, enter the number below

Drug, Herbal Product or Other Chemical Element Management *
Please indicate how drugs, herbal products or other chemical entities will be managed. IDS will be used to receive, store or dispense the drug, herbal product or other chemical entity

Radiation Exposure*
Are research subjects receiving any radiation exposure (e.g. X-rays, CT, Fluoroscopy, DEXA, pQCT, FDG, Tc-99m, etc.) that they would not receive if they were not enrolled in this protocol? No

Gene Transfer*
Does this research involve gene transfer (including all vectors) to human subjects? No

Human Source Material*
Does this research include collection or use of human source material (i.e., human blood, blood products, tissues or body fluids)? Yes

CACTIS and CT Studies*
Does the research involve Center for Advanced Computed Tomography Imaging Services (CACTIS) and CT studies that research subjects would not receive if they were not part of this protocol? No

CAMRIS and MRI Studies*
Does the research involve Center for Advanced Magnetic Resonance Imaging and Spectroscopy (CAMRIS) and MRI studies that research subjects would not receive if they were not part of this protocol? Yes

Investigational Agent or Device within the Operating Room*
Does the research project involve the use of an investigational agent or device within the Operating Room?
No

Cancer Related research not being conducted by an NCI cooperative group*
Is this a non-NCI cooperative group protocol involving cancer-related studies in any of the following categories? No

Processing of Materials*
Will the research involve processing (such as over encapsulating, or compounding)? No

In-House Manufacturing of Materials*
Will the research involve processing (such as over encapsulating, or compounding)? No

Medical Information Disclosure*
Does the research proposal involve the use and disclosure of research subject's medical information for research purposes? Yes

If the answer is YES, indicate which items is provided with this submission:
Modified research informed consent document that incorporates HIPAA requirements

CTRC Resources*
Does the research involve CTRC resources? No

Pathology and Laboratory Medicine Resources*
Will samples be collected by hospital phlebotomy and/or processed or analyzed by any of the clinical laboratories of the University of Pennsylvania Health System? No

Research Involves Apheresis, Cell Collection, and/or Blood Product Collection*
Does this research involve blood product collection and/or the use of apheresis for treatment or for collection of cells or other blood components? No

Research involving blood transfusion or drug infusions*
Will your research involve blood transfusion or infusion of study drug in 3 Ravdin Apheresis Unit for research purposes? No

Use of UPHS services*
Does your study require the use of University of Pennsylvania Health System (UPHS) services, tests or procedures* whether considered routine care or strictly for research purposes? Yes

Primary Focus*
Clinical Trial (prospectively assigning subjects to health-related interventions to evaluate outcomes)

Protocol Interventions
x **Sociobehavioral (i.e. cognitive or behavioral therapy)**
x **Drug**
Device - therapeutic
Device - diagnostic (assessing a device for sensitivity or specificity in disease diagnosis)
Surgical
x **Diagnostic test/procedure (research-related diagnostic test or procedure)**
Obtaining human tissue for basic research or biospecimen bank
x **Survey instrument**
None of the above

The following documents are currently attached to this item:
There are no documents attached for this item.

Sponsors
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Funding Sponsors
Name: **PENNSYLVANIA DEPARTMENT OF HEALTH**
Type: **UPENN Commonwealth of Pennsylvania**

Regulatory Sponsor
IND Sponsor
None

Industry Sponsor
None

Project Funding*
Is this project funded by or associated with a grant or contract? Yes

Selected Proposals
Proposal No 10030069
Title A CURE Addiction Center of Excellence: Brain Mechanisms of Relapse and Recovery

Sponsor Funding
Is this study funded by an industry sponsor? No

Status of contract

The following documents are currently attached to this item:
Grant Application (allcurecenterofex2-15-112trk.pdf)

Multi-Site Research

Other Sites
No other sites

Management of Information for Multi-Center Research
The following documents are currently attached to this item:
There are no documents attached for this item.

Protocol

Abstract
The overall goal is to determine whether differential activation in a priori regions of interest to select reward and inhibition probes can predict drug use during and following active treatment in patients addicted to cocaine, marijuana and prescription opiates. The active treatment is a behavioral intervention (Coping with Craving) for cocaine patients, baclofen for marijuana patients and naltrexone for prescription opiate patients. The treatment is directed toward improving the inhibition of cue- induced drug craving. Subjects must be physically healthy, treatment seeking men and women (ages 18-60), be able to read at eighth grade (or above) level, and voluntarily seeking treatment. Females must be non-pregnant, non-lactating and either be of non-childbearing potential or of child-bearing potential, but practicing a medically acceptable method of birth control. The main study interventions are functional magnetic resonance imaging and specific probes for reward and inhibition to determine whether the brain response to these probes can predict the primary clinical outcome of drug use/relapse, and secondary public health outcomes (e.g., unprotected sexual behavior leading to increased HIV risk) in an underserved population receiving state-of-the-art treatments for cocaine, marijuana and prescription opiate dependence.

Objectives

Overall objectives

Objective 1: To determine whether differential activation in a priori brain regions of interest (ROI) to selected reward and inhibition probes can predict drug use during active treatment.

Hypothesis 1a: Greater activation of a priori limbic ROI (e.g., interconnected amygdala/ventral striatal cluster during brief drug cues; bilateral ventral striatum during reward risk) prior to (FMRI 1) and during (FMRI 2) active treatment will predict greater drug use during the active treatment phase.

Hypothesis 1b. Lower activation of a priori prefrontal inhibitory ROI (e.g., lateral orbitofrontal cortex; supragenual anterior cingulate) during affect-congruent Go-NoGo; inhibition of cue-triggered craving) prior to (FMRI 1) and during (FMRI 2) active treatment will predict greater drug use during the active treatment phase.
Objective 2: To determine whether differential activation in a priori brain ROI to selected reward and inhibition probes can predict relapse following active treatment.

Hypothesis 2a: Greater activation of a priori limbic reward ROI (e.g., interconnected amygdala /ventral striatal cluster during brief drug cues; bilateral ventral striatum during reward risk during brief drug cues; reward risk) prior to (FMRI 1), and following (FMRI 3) active treatment will predict greater drug use during the 12-week follow-up period.

Hypothesis 2b: Lower activation of a priori prefrontal inhibitory ROI (e.g., lateral orbitofrontal cortex; supragenual anterior cingulate) during affect-congruent Go-NoGo; inhibition of cue-triggered craving) prior to (FMRI 1) and following (FMRI 3) active treatment will predict greater drug use during the 12 week follow- up period.

Pilot Studies Objective*:*

Objective: The objective is to develop new tasks that test constructs that may be relevant to treatment and relapse prevention in addiction in order to compliment and expand the probes and tasks now being used to determine differential activation in a priori regions of interest to selected reward and inhibition probes as part of our primary studies aim.

The primary CURE project aims are to use measures of brain-behavioral vulnerabilities (e.g., in reward processing, risk-taking, inhibitory function) to help **predict drug relapse** in addicted populations.

The primary project features a few probes that we feel have early promise for **predicting relapse**. In addition to the primary probes, the CURE grant proposed Pilot Testing for probes in other domains that may also have future predictive value for relapse — often, these will necessarily be developed and refined in other populations.

Three examples of currently proposed Pilot Probes are the Extinction Task, the Delay of Gratification Task and the Baby Schema task. The rationale for these Pilot Probes a potential relapse predictors is briefly described:

Extinction Task -- Individuals with **larger** (in magnitude) brain responses to drug reward cues may have increased risk of relapse, and this is tested by our primary "brief cue" probe. However, **the persistence of the response over many presentations, even when not followed by drug ("failure to extinguish"),** may also predict **greater risk for relapse**. Thus, we are measuring this persistence as a possible future relapse predictor, using a task that involves extensive repeated exposure to drug (and comparison) cues.
Delay of gratification — Addicted individuals often have difficult delaying immediate gratification (e.g., drug) in the service of future rewards (e.g., recovery). Individuals with "failure to delay gratification" -- difficulty inhibiting their responses to the promise of reward -- may be at **greater risk for relapse**. We are thus developing a probe to quantify this characteristic. Though there are several "reward delay" tasks in the literature, most of these involve decisions about the secondary, abstract rewards of "money" or "points", which often fail to engage the subjects, and do not produce the heightened positive arousal associated with pursuing a drug of

choice. We are thus developing a delay-of-gratification task that uses stimuli (erotic pictures) that are highly engaging, and that we feel provide a closer parallel to our patients' struggles to inhibit their impulses toward drug reward.

Baby Schema — The "cute" facial configuration of babies (large forehead, big eyes, with the other features compressed into the lower third of the face) is a natural reward for most humans. In the course of addiction, individuals' response to natural rewards — including baby faces — may be blunted or undermined by drug-related changes in the reward system. Individuals with loss of sensitivity to natural rewards may be at **greater risk for relapse**, whereas recovery or retention of the response to natural rewards may predict better outcome — as other natural rewards can "compete" with the promise of drug reward. We will thus develop the Baby Schema task as a potential relapse predictor. **(**The task may have additional value in predicting recovery of care taking in addicted populations —as care-taking deficits in addicted populations are a critical public health issue in the Commonwealth of Pennsylvania and the nation).

Primary outcome variable(s)

For Objective 1: The primary drug use outcome for this objective is illicit-positive urines during the 12 weeks of active treatment (2 Urine Drug Screens per week; 20 total) after FMRI 2.

For Objective 2: The primary drug use outcome for this objective is illicit-positive urines during the 12-week follow-up period (weekly urines; 12 total) after FMRI 3.

Secondary outcome variable(s)

Our addicted patients are at high risk for HIV, both through drug-related activity (sharing crack pipes), and through unprotected sexual activity occasionally in the context of drug use. Our brain variables (hyperresponse to the promise of reward; poor inhibition of impulses toward drug and sexual reward) would be expected to predict these secondary outcomes. We will test for HIV at baseline and at 24-week follow-up using a rapid oral swab method.

Background

The field of human addiction neuroscience has advanced rapidly in the past decade, often using brain imaging to identify a number of ways in which the brains of addicted individuals differ in function [1, 2], even in structure - [3, 4] [5] from the non-addicted.. What has not been determined is which (or whether) these many brain differences may explain the most painful feature of addiction: relapse. This knowledge is critical for changing the harsh statistics of relapse (nearly 80% relapse by 6 months after treatment), and for reducing the enormous health, social and economic toll of addiction.

The addiction field has lagged in attempting to connect brain-imaging findings to drug use outcomes. There are a few hundred (by now) brain imaging studies in addiction, and also a few hundred clinical trials of various interventions (behavioral and pharmacologic), but the two efforts have not been joined on a scale that would offer stable, generalizable results to guide new treatments. Less than 5 studies have been conducted for stimulants [6-11], the sample sizes are very small (less than 20) and there have been no studies at all of this type for opioids and marijuana. The separate but parallel research efforts of brain imaging teams and clinical outcome research groups is at one level understandable. Both kinds of research are expensive and require highly skilled multidisciplinary collaborations. Joining them together effectively requires Center-level support. However, failing to join them fostering separate but parallel efforts severely limits the scientific yield and health benefit from both approaches. The clinical significance of the brain findings will remain indeterminate, and the clinical trials will remain uninformed by brain science that could reveal critical new targets and/or assist in rational matching of patients to available treatments.

Other fields (e.g., depression) have begun to link brain findings to clinical outcomes and treatment response, rapidly moving their treatment research into the 21st century. Our long-term goal is to accomplish this for the field of addiction. Our CURE project will provide the first large-scale effort, in the nation, to join brain measures with clinical outcomes in addiction. We will link carefully selected brain measures of reward and inhibition to drug use and relapse in a large cohort of underserved individuals receiving well-characterized treatments for addiction to crack cocaine, marijuana, and prescription opioids. The expected scientific yield is a

brain-based understanding of relapse vulnerability an understanding that may provide a sea change in addiction treatment, and permanently alter the dark relapse statistics for addiction. These benefits would extend beyond our immediate community, to the Commonwealth, and to the nation.

Neuroscience framework. Our hypotheses for the CURE are guided by advances in two areas of neuroscience 1) the brain actions of rewarding drugs of abuse, and 2) our recent knowledge of brain development in adolescence. Drugs of abuse (even those with different pharmacologies, e.g., cocaine, opioids, marijuana), and the signals for them, have a final-common-path action on the powerful mesocorticolimbic dopamine circuitry mediating the natural rewards of food and sex. Though a powerful response to signals for primary rewards (e.g., food, reproductive opportunity) is critical for human survival, if poorly modulated, reward-driven responses can also have negative consequences, resulting in poor decision-making -- for example, over-eating, impulsive sexual behavior, and drug use. Recent advances in developmental neuroscience [12-21] show that the developing adolescent brain may be at special risk for poor decision-making and poor impulse control: though their reward (GO!) circuitry is relatively mature and sensitive (in preparation for the important task of reproduction), the prefrontal brain STOP! circuitry, responsible for modulating the response to rewards, does not fully develop until the 20s [22]. The parallels between the impulsive, reward-driven choices of adolescents and those of our addicted adults are more than a coincidence. Riskier, more vulnerable, less inhibited adolescents are more likely to be exposed to drugs of abuse and because of their biological constraints, they are more likely to descend into addiction. They carry with them, into adulthood, the dual vulnerabilities of their adolescent brain: high sensitivity to reward, and poor inhibition. The relevance of these findings for aims of the current proposal is that we need to select probes for both the subcortical limbic reward (GO!) circuit and for the prefrontal cortical (STOP! circuit, if we are to capture the full range of decision-making vulnerabilities in our addicted adults.

Study Specific Background Cocaine
The Philadelphia metropolitan area remains in the grip of a 25-year long cocaine epidemic. Cocaine remains the top-ranked drug associated with hospital treatment admissions [23] in the region. Cocaine is first-ranked for presence in the urine of arrestees in the Philadelphia Metropolitan area (National Forensic Laboratory Information System, DEA, 2008), second ranked for presence in the urine of probationers and parolees (Philadelphia Adult Probation and Parole Department, 2008), and the second ranked cause of drug-related deaths (following opiates; [24]). Nationally, cocaine ranks first in Emergency Department visits [25], echoing the local statistics.

Finding interventions psychosocial or pharmacologic -- that will provide sustained impact for a majority of cocaine users, evidenced in controlled trials, has proved difficult. Naturalistic studies of cocaine patients self-selected into community treatment report substantial reductions in cocaine use at 1 [26] and 5 years [27] post-admission. However, in the largest controlled trial of non-pharmacologic treatments for cocaine dependence, the NIDA-sponsored National Collaborative Cocaine Treatment study, fully 40% of the cocaine patients in the best outcome group were still using cocaine at12 month-follow-up [28]. Contingency management approaches with vouchers [29] or prizes [30] have shown promise, though their effects are usually limited to the period of the experimental intervention [31]. The search for effective pharmacotherapies, either for cocaine [32, 33] or for the recent upsurge in methamphetamine use here [34] and abroad [35] has been no easier [36]. Despite preclinical and clinical testing of hundreds of candidate agents, none have demonstrated repeated positive results in the large samples required for FDA approval. Clearly, there is a decades long, unmet need for more effective behavioral and pharmacologic treatments, and their combination, in cocaine dependence. A critical step in meeting this need is better knowledge of the brain vulnerabilities that lead to relapse.

Study Specific Back-ground Marijuana (MJ) is the most commonly used illicit drug in the nation and in the Commonwealth. According to the 2008 National Survey on Drug Use and Health (NSDUH), an estimated 102 million Americans aged 12 or older have tried MJ at least once in their lifetime, representing 41% of the U.S. population in that age group [37]. In Pennsylvania alone, that number is greater than 1.1 million. Fifteen percent of our youth (ages 12-17) have tried MJ within the last year and 9% of them will become addicted [37]. That translates to 1 in 75 of our youth who will become dependent contributing to the mounting impact MJ dependence has on Pennsylvania. The cost of MJ dependence is great both to individuals (e.g., psychiatric

illness, cognitive deficits, and disease such as emphysema and prostate cancer) and to society (e.g., lost productivity, driving accidents and related deaths, healthcare and economic costs, law enforcement and incarceration costs) [38]. It is estimated that the Commonwealth spent $190,445,000 just on policing, prosecuting and incarcerating marijuana offenses in 2008 alone [39].

Presently, there are no FDA approved therapies for MJ dependence however a few treatments have been investigated [40-45]. The results of these trials have been underwhelming with fewer than 50% of MJ dependent subjects remaining abstinent at 4 and 6 months following treatment [46, 47]. A greater understanding of the function-al brain substrate that is compromised in the addicted brain may lead to the development of more effective treatments, increasing the quality of life for our residents and decreasing monetary costs to society. We propose the GABA B agonist, baclofen, as an effective agent to aid in characterizing the signature of recovery. Baclofen has specific effects on the regions of the brain we hypothesize to be involved in addiction (amygdala, ventral striatum, cingulate cortex, prefrontal cortex) [48, 49] and has shown promise in treating MJ, alcohol, nicotine, cocaine and methamphetamine dependence [50] [51] [52] This proposal is specifically targeted to study, treat, and aid low income uneducated and minority MJ dependent individuals who are at greater risk of dependence. Baclofen is safe, tolerable, readily available in an inexpensive generic form, and can be offered through the public health system. Thus, the benefits to both individuals and society will be immediately realized.

Study Specific Background Prescription Opioids Prescription opioid abuse and dependence (POD) is illegal use of prescription opioids obtained on the black market for non-medical purposes. POD is a significant and growing public health problem [53, 54] both nationwide [55-57] and in Pennsylvania [23, 58]. Though the incidence of POD in the US is more than four times higher than heroin abuse and dependence [37], less is known about the clinical characteristics of POD than heroin dependence [59]. Relapse to drug use is a hallmark of opioid addiction. The harm of relapse in POD is compounded by the risk of transition to heroin [60]. The main clinical priorities in POD management are predicting vulnerability to relapse and predicting and monitoring patients' response to pharmacological treatment. Presently, both domains rely on history, physical examination and urine toxicology that are time-consuming and susceptible to subjective distortions [61, 62]. Studies indicate that cue-induced drug craving and impaired ability to consciously regulate ones own behavior are markers of vulnerability to relapse in SUD patients [63]. The brain fMRI correlates of these behavioral domains have been identified and found to be potentially clinically useful as markers of relapse vulnerability and response to treatment [64-66], especially when integrated with behavioral (i.e. relapse, cue-induced craving and decision-making), genetic and pharmacokinetic variables. Such an approach has been termed pharmaco-MRI (phMRI) [67-69]. The two main advantages of phMRI are increased power and additional information about mechanisms of action of the study intervention, which are not available with conventional clinical trials. Despite evidence of utility in other SUDs, phMRI has not yet been applied to POD. The primary objective of this proposal is to develop clinically useful neurobiological markers of vulnerability to relapse in POD, using a phMRI approach.

The second clinical domain with an unmet need for objective biological markers is monitoring the treatment response. POD is epidemiologically distinct from heroin dependence by involvement of a younger patient population with a peak age of 18-25 years, lower daily doses of opioids [70] and a generally higher level of functioning. Hence, POD patients may respond differently to treatment compared to heroin dependent patients [71]. Opioid substitution therapies, such as methadone and buprenorphine, are efficacious in reducing heroin and prescription opioid (PO) use, but they are neither free from cognitive and physiological side effects [72-75] nor prevent relapse [76]. Furthermore, federal regulations limit access to agonist maintenance therapy, and daily treatment is required. Both methadone and buprenorphine because of their opioid effects are subject to illicit diversion. Because of these clinical and regulatory characteristics, antagonist treatment may be the treatment of choice in POD. Extended-release depot naltrexone (XRNT) injection is a once a month antagonist treatment that overcomes the adherence problems of the short acting oral naltrexone [77] and is not associated with the side effects and restrictions of the agonists. One preparation of XRNT (Vivitrol) has been FDA approved for the treatment opioid dependence in October 2010. At this time, there are no published reports of conventional or phMRI trials of feasibility of XRNT in POD. Hence the secondary objective of this proposal is to fill this gap by evaluating the fMRI and behavioral response to XRNT in an open-label uncontrolled feasibility trial of XRNT

in 72 POD patients.

Study Design
Phase*
Not applicable

Design
The proposed project will use functional magnetic resonance imaging (fMRI) and specific probes of reward and inhibition as biomarkers predicting drug use during and after treatment in 216 patients addicted to cocaine, marijuana, and prescription opioids. Participants will be scanned before, during, and after 12 weeks of active treatment specific to each of these drugs of abuse. The brain fMRI measures will be correlated with the primary clinical outcome of drug use (by urine drug screen) during the treatment and follow-up phase. An exploratory objective will examine the impact of genetic (e.g., polymorphisms modulating reward and inhibition) and epigenetic factors (e.g., history of prior trauma/ abuse) on the relapse-relevant brain measures. (Genetics are now collected under the Dr. Oslin's Protocol for The Genetics of Addiction Study approved by Penn IRB for the entire Treatment Research Center that has it own separate protocol (#811705) and consent).

The main strengths of the project are:
1) The Treatment Research Center places a value on direct benefit to the patients participating in our research. Substance-specific pharmacological and/or psychosocial interventions are provided by certified and trained professionals. Using trained providers for the behavioral baseline treatment also reduces sources of variance extraneous to the brain predictors, giving us the best chance to determine their predictive ability.
2) Inclusion of three pharmacologically distinct substances of abuse will provide robust and generalizable data on the brain predictors of relapse.
3) Using a single scanner will eliminate problems inherent to large multi-center studies that rely on more than one imaging facility, such as data incompatibility across scanner platforms.

All participants: Following successful screening, all participants will participate in the fMRI 1 and 2 sessions. Next, cocaine participants will receive a behavioral intervention (Coping with Craving), marijuana participants will be randomized (double-blind), to either baclofen or placebo and prescription opiate participants will receive naltrexone. After 2 weeks of treatment patients will participate in fMRI 3. Prior to and following each probe, craving and withdrawal will be assessed. Participants will participate in fMRI 4 at the end of Treatment. Participants will return weekly for 12 weeks during the follow up period.

Study duration
This project will enroll subjects over a 4-year period that includes startup and data analyses with the potential for an additional year using remaining funds. The plan is to enroll 36 subjects the first and last year and 72 subjects in year 2 and 3. Subjects participate for approximately 6 months. This includes an inpatient stay of about 10 to 15 days for cocaine subjects only and 12 weeks of treatment and 12 weeks of follow-up for all subjects. Prior to entering this study prescription opiate subjects may be detoxed outpatient from prescription opiates using detox medication prescribed by Dr. Langleben, if they needed to be detoxed. This project is due to start August 1, 2011.

Resources necessary for human research protection
Describe research staff and justify that the staff are adequate in number and qualifications to conduct the research. Describe how you will ensure that all staff assisting with the research are adequately informed about the protocol and their research related duties. Describe access to a population that would allow recruitment of the targeted number of subjects. If medical or psychological services as a consequence of the research, describe how the subject will be referred to those services. Describe your facilities and justify that the facilities are adequate. Verify that there is sufficient time to conduct and complete the research.

Dr. Childress, the PI, Dr. Ehrman, and Dr. OBrien, have worked effectively together for nearly 3 decades, and represent more than 60 years of continuously funded clinical and basic research efforts in human addiction.

Their shared interest in the biologic substrates of addiction, especially cue-triggered states and their inhibition, has prompted the development and application of several behavioral and neuroimaging probes in addicted adults. They have developed a stable, multi-disciplinary team for skillful application of these tools, geared toward characterization of deficits that may predict drug use/ relapse. A Certificate of Confidentiality is being obtained as a safeguard to further protect subjects because of the sensitive nature of our research. Dr. Childress, along with Drs. OBrien and Ehrman, will supervise and coordinate the general activities of the CORE; Dr. Childress will assume special responsibility for the Analysis teams, including the fMRI signal processing engineers. Dr. Childress will also Co-lead the Cocaine sub-study drawing on her extensive experience with both imaging and clinical interventions in cocaine-addicted individuals. Dr. Childress will be responsible for ensuring the timely progress of the CURE studies, and for the consistent implementation of the protocols. She is ultimately responsible for protocol adherence/ethics/safety monitoring, and for the integrity of the imaging and clinical research data. Dr. Childress will be responsible for regular dissemination of the research findings in peer-reviewed journals, at professional conferences, and in educational media. Dr. Magland is a recent NIBIB K Awardee and Assistant Professor in the Department of Radiology at the University of Pennsylvania. He will be a Co-Investigator with Dr. Childress on this Cocaine proposal, complementing her clinical imaging expertise with his technical expertise in Real-time fMRI methods. Dr. Childress and Dr. Magland have collaborated together in the past 18 months in an NIH/NIDA R21/ R33 to develop novel real-time fMRI feedback techniques as both assessments of cognitive control (moving a screen cursor with focused, alternating sets of thoughts), and as potential training paradigms for enhancing cognitive control in addicted individuals. Dr. OBrien is an internationally recognized expert in addictions; with a career-long research interest in addressing the causes of addiction and of relapse and will be Co-Principal Investigator for the CURE. He has conducted large-scale, NIH-funded, VA-funded, foundation-funded and pharma funded research for nearly 4 decades. Dr. OBrien will offer monthly updates on the medical and clinical functioning of the CORE. Dr. OBrien will also lend his expertise in data interpretation to each of the components as a Co-Investigator. He will actively participate in dissemination of the study results, and has many venues for this due to his worldwide participation in addiction-relevant conferences. Dr. Ehrman a Co-Investigator has worked closely with Dr. Childress and her team to develop and program several of the novel probes at the core of the proposal, including the brief cue task and the affect-congruent Go-NoGo task (with Dr. Goldman). He developed the novel (on- and off-magnet) affective priming task that enables investigators to determine hedonic valence for briefly presented (visible) drug cues providing a critical behavioral anchor to aid interpretation of the brain data. In addition to his expertise in behavioral assessments, Dr. Ehrman also has statistical experience with the clinical out-come measures (e.g., urine drug screens) to be used in the proposed projects, and has recently been the site investigator for two clinical intervention trials at the VA.

Dr. Teri Franklin is a former NIDA KO1 Awardee and current Research Assistant Professor of Neuroscience in the Department of Psychiatry who has worked closely with Dr. Childress imaging projects for the past 10 years. She will be the lead Co-Investigator for Marijuana CURE sub-study. Dr. Franklin has extensive imaging and clinical research expertise, having been the PI on several prior imaging protocols in nicotine dependence, having conducted a clinical outcome trial, and having recently (successfully) combined imaging and genetics measures in her ongoing work. She led the early lab efforts in documenting less gray matter density in the orbitofrontal, anterior cingulate and insular cortices of addicted (cocaine) patients, as compared to controls, a feature that may underlie their difficulty in inhibiting cue-triggered drug motivation. Dr. Franklin has recently published the imaging signature for cue-induced cigarette craving (with the ventral striatum and amygdala activation a prominent feature), and has now published two papers demonstrating that the brain response to conditioned drug cues may be strongly genetically modulated. For the proposed Marijuana sub-study, she will work with Dr. Marina Goldman to image and treat the marijuana cohort; she and Dr. Goldman have already been collaborating for the past two years and are currently co-authors on two marijuana manuscripts. Dr. Franklin will be responsible for the timely data acquisition for the marijuana sub- study, will report progress to the Steering Committee on a monthly basis, and will bear primary responsibility for the integrity of data collection and analyses for the Marijuana sub-study. Because of her expertise in combining imaging and genetics, Dr. Franklin will also interact with Dr. Berrettini in the Core to accomplish exploratory aims related to genetic modulation of the brain response to marijuana cues and will also guide (at no additional cost to the study) exploratory analysis of the gray matter density data obtained from high resolution structural MRs in all three sub-studies.

Dr. Langleben is an Associate Professor of Psychiatry at the Center for Studies of Addiction at the University of Pennsylvania School of Medicine who has also had a part-time role as a VA clinician for more than a decade. For the CURE, he will be the lead Co-Investigator for the Prescription Opioid Dependence sub-study, assuming primary responsibility for the imaging aspects of the study (non- imaging medical aspects will be shared by his Co-Investigator on Prescription Opioid Dependence sub- study, Dr. Kampman). Dr. Langleben has worked closely with Dr. Childress imaging laboratory for a decade, and has already published evidence of limbic activation to opiate-related cues directly relevant to the probes to be used for predicting relapse in the current CURE proposal. He has acquired encouraging preliminary imaging data with opioid dependent patients on depot naltrexone, showing that the limbic signature is indeed blunted. These encouraging data set the stage for the current inquiry about the ability of these blunted brain responses to predict drug use/relapse. Dr. Langleben will be responsible for the timely collection of imaging data for the Prescription Opioid Dependence sub-study, for monitoring the quality of the data, for data reduction, and for guiding the eventual analyses linking the brain responses to clinical outcome.

Dr. Anita Hole will be the Senior Psychologist in the Clinical Unit of Core. She has more than 3 decades of substance abuse treatment and treatment research, and has collaborated closely with Dr. Childress projects for the past 25 years. She will be a direct provider of the psychosocial baseline intervention common to the 3 sub-studies (Coping with Craving, a widely- used program of tools that she and Dr. Childress developed with NIH support in the 90s), and will provide senior clinical oversight for them as well, including supervision of the Masters level Clinician Ms. Marquez. Dr. Hole will have primary responsibility for evaluation/structured clinical interviewing to obtain a research screening psychological diagnoses based on DSM-IV-TR criteria, as assessed by the MINI, and will confer with all lead Investigators for final determination of each patients eligibility. Dr. Hole will also provide pre-imaging session evaluations (to insure the patient is stable on scan day) and the post-imaging cue session "talk-downs" (to insure any residual craving is reduced to baseline before the patient returns to the residential setting). She will conduct the weekly clinical meeting to review patient status across the Projects. She and Ms. Marquez will monitor the day-to-day clinical status of the patients, ensuring smooth integration of research and clinical elements.

Our Research Manager has over 10 years research experience and her assistant over 5 years. Each staff person is completely trained before starting any new project, given copies of the protocol, consent, all research duties are explained and weekly project meetings are held to go over any project needs. The Treatment Research Center has a regular flow of patients as does the VA Medical Center and Penn Presbyterian Center. For cocaine patients at all three locations, several days of residential stabilization prior to study entry is often appealing, as our patients are often homeless, and without private insurance coverage. Approximately 25-30% of our cocaine patients are excluded for concomitant alcohol dependence; another 10% are now excluded on the basis of opiate dependence (heroin purity has dramatically increased in Philadelphia in the past eight years). Another 10 to 15% have medical or psychiatric problems that preclude their participation, or other historical features (metalworkers or welders). Even with these several restrictions, the remaining number of potential candidates for the proposed study would exceed 400 per year. Since two-dozen or fewer participants per year are needed for the propose project, this is a small fraction of the total sample available. Given the continued cocaine epidemic in the Philadelphia region, and our history of successful recruitment for multiple cocaine studies over the past two decades, we expect a steady stream of interested and eligible individuals. Drs. Goldman and Langleben have successfully recruited needed marijuana and opiate patients in the past by posting advertisements on Craigs list or by using study specific advertisements. They were able to recruit more than 2-dozen subjects a year, which is more than adequate for the current CURE protocol.

Dr. Shing C. Lam is a postdoctoral fellow in our lab who is in this 5th postdoctoral year. He has helped our lab with task development, engineering research needs, and MRI protocol uploads and oversight of scan sessions.

Dr. Kimberly Young is a postdoctoral fellow in our lab who is in this first postdoctoral year with much experience in social interactions. She has participated in a Human Subjects workshop at the University of Pennsylvania, has an approved protocol and has previously collected Baby Schema data.

The proposed investigative team is stable, with all the newer members in place and working productively together for several years. The Treatment Research Center has the appropriate and stable intake, front desk and nursing staff in place and available for prescreening patients requesting research and treatment with adequate facilities, space and staff to do so. Doctors and psychologists are available to make appropriate referrals as needed. There is sufficient time and staff to conduct and complete this research.

Characteristics of the Study Population

Target population

216 treatment-seeking cocaine, marijuana users, and prescription opiate users who meet DSM-IV-TR criteria for dependence will be enrolled into this protocol. Patients will not be excluded based on gender, religion, race, or socioeconomic status. The patient population of our previous cocaine studies is usually 90% African American, with female proportions varying from 15-25% depending on other study requirements. The patient population of previous marijuana studies in our lab was 78% male, 53% African American and averaged 13 years of education. This is representative of the urban population in the northeast region of the United States who seek help for marijuana dependence. The patient population of our previous opiate study was 75% male and 45% African American. We expect our current populations to have similar characteristics.
100 additional physically healthy non-treatment seeking male and female substance abuse participants and controls for pilot study tasks and cues.

Subjects at Penn

316

Subjects at Sites Other than Penn

0

Accrual

Participants will be recruited through word of mouth, flyers, list-serves, as well as Internet and local media advertisements. In addition to participants recruited by public advertising, we have several additional sources of eligible participants for the project, including the natural flow of treatment- seeking patients who come to the Center for Studies of Addiction Treatment Research Clinic (TRC) at the University of Pennsylvania, at 3900 Chestnut Street, to the Penn Presbyterian Center, and to the Philadelphia VA Medical Center. These latter sites have longstanding collaborative relationships with our Center, and the VA is a formal collaborator for the project. For cocaine patients at all three locations, several days of residential stabilization prior to study entry is often appealing, as our patients are often homeless, and without private insurance coverage. In order to increase our recruitment effort chances, we plan to advertise/recruit using Google. A Google search for different words like Cocaine, treatment or Philadelphia will connect a person to the Center for Studies of Addictions Department of Psychiatry Penn Behavioral Health web page that lists our current research studies and contact information. We also plan to advertise/recruit from ResearchMatch.org and in newspapers. Approximately 25-30% of our cocaine patients are excluded for concomitant alcohol dependence; another 10% are now excluded on the basis of opiate dependence (heroin purity has dramatically increased in Philadelphia in the past eight years). Another 10 to 15% have medical or psychiatric problems that preclude their participation, or other historical features (metalworkers or welders). Even with these several restrictions, the remaining number of potential candidates for the proposed study would exceed 400 per year. Two-dozen or fewer participants per year are needed for the proposed project, a small fraction of the total sample available. Given the continued cocaine epidemic in the Philadelphia region, and our history of successful recruitment for multiple cocaine studies over the past two decades, we expect a steady stream of interested and eligible individuals. Given the continued cocaine epidemic in the Philadelphia region, and our history of successful recruitment for multiple cocaine studies over the past two decades, we expect a steady stream of interested and eligible individuals. Drs. Goldman and Langleben have successfully recruited needed marijuana and opiate patients in the past by posting advertisements on Craigs list or by using study specific advertisements. They were able to recruit more than 2-dozen subjects a year, which is more than adequate for the current CURE protocol. If recruitment lags, we have both the local connections and additional (shared) Center resources to enhance advertising and outreach. Our ongoing contact

with the Philadelphia recovery community is also a source of referrals, as relapse is an ongoing threat.

For each of Objective 1 and 2, we have four hypotheses, one for each of the four brain regions. As the two objectives address conceptually distinct questions, we set an overall alpha level of 5% within each objective, by using an alpha level of 0.0125=0.05/4 for each hypothesis. We use a combination of the methods of Hsieh et al (1998) for sample size estimation for the effects of continuous covariates in logistic regression models, and the methods of Diggle et al (2004) to allow for the within subject correlations. As described in the Missing Data section, we anticipate loss to attrition of 10% at fMRI 1, 20% at fMRI 2, and about 33% by the end of treatment. Based on prior longitudinal studies in our Center we anticipate a within subjects correlation of between 0.3 and 0.5. For each hypothesis, the effect of interest is the (log) odds ratio for the response corresponding to an increase of 1 unit on one of our measures. To calculate the detectable effect, we need to know the rate of drug use at the mean level of our covariate. As there is no prior data linking our outcome and the explanatory variables, we consider a plausible range of such rates, from 0.2 to 0.5, noting that the power for a value of 0.6 is the same as the power for 0.4, and similarly for higher rates of use at the covariate mean. For hypotheses 1a and 1b, for a two-sided test, we have 80% power to detect odds ratios of between 1.35 and 1.89, depending on the values of the rate of use at the mean of the brain measure (between 0.1 and 0.9) and of the within subjects correlations (between 0.3 and 0.5).
For hypotheses 2a and 2b on the rates of use after treatment, we have similar models, but fewer subjects. We expect to have 144 subjects at the start of the follow-up phase, and expect a 15% loss over the 12 weeks of follow up. With the same assumptions on correlations and rates of use as above, we have 80% power to detect odds ratios of between 1.41 and 2.04, depending on the values of the rate of use at the mean of the brain measure and of the within subjects correlations. In addition to the primary outcomes of drug use, the same ROI-based analyses can be applied to secondary outcomes of STD. And in addition to these ROI-based analyses we will also conduct whole brain regression analyses, with drug use outcome as a continuous regressor vs. the whole brain map. This approach will reveal any (novel) predictors, and the findings are data-driven (not requiring an a priori analysis). Finally, we will also explore other novel imaging analyses, including connectivity approaches (for the tasks) and classifier approaches (relapsers vs. non-relapsers, etc) . These several convergent approaches will give us a high probability of identifying the strongest predictors of drug use and relapse.

Key inclusion criteria
Cocaine Inclusion criteria:
1) Physically healthy male or female cocaine dependent (based on DSM-IV- TR criteria, as assessed by the MINI) subjects ages 18-60.
2) Females must be non-pregnant, non- lactating and either be of non-childbearing potential (i.e. sterilized via hysterectomy or bilateral tubal ligation or at least 1 year post-menopausal) or of child bearing potential, but practicing a medically acceptable method of birth control. Examples of medically acceptable methods for this protocol include barrier (diaphragm or condom) with spermicide, an intrauterine device (IUD), oral contraceptives, a levonorgestrel implant, intrauterine progesterone contraceptive system, medroxyprogesterone acetate contraceptive injection, and abstinence.
3) Subjects must read on eighth grade (or above) level.
4) Voluntarily seeking treatment for cocaine dependence.
5) Subjects provide voluntary informed consent.

Marijuana Inclusion Criteria:
1) Physically and mentally healthy male/female marijuana dependent (based on DSM-IV-TR criteria, as assessed by the MINI) smokers ages 18-60 without other current drug dependence (except for nicotine dependence) or psychiatric diagnosis.
2) Females must be non-pregnant, non-lactating and either be of non-childbearing potential (i.e. sterilized via hysterectomy or bilateral tubal ligation or at least 1 year post-menopausal) or of child bearing potential, but practicing a medically acceptable method of birth control from at least 2 weeks prior to screening until 30 days after the last dose of baclofen. Examples of medically acceptable methods for this protocol include barrier (diaphragm or condom) with spermicide, an intrauterine (IUD), oral contraceptives, a levonorgestrel implant, intrauterine progesterone contraceptive system, medroxyprogesterone acetate contraceptive injection, and

abstinence. (Pregnancy testing will be done on all females of childbearing age)
3) Voluntarily seeking treatment for marijuana dependence.
4) Subjects provide voluntary informed consent.
5) Subjects must read on eighth grade (or above) level.

Prescription Opiate Inclusion Criteria:
1) Subjects provide voluntarily informed consent;
2) Be between the ages of 18 and 60;
3) Have a diagnosis of opioid dependence according to DSM IV-TR criteria (as assessed by the MINI);
4) Be in good general health as determined by complete physical examination and laboratory tests.
5) Subjects must read on eighth grade (or above) level
6) Female subjects must be non-pregnant, non-lactating, and either non-childbearing potential (i.e. sterilized via hysterectomy or bilateral tubal ligation or at least 1 year post-menopausal) or of childbearing potential, but using acceptable birth control (oral contraceptives, barrier (diaphragm or condom) plus spermicide, or levonorgestrel implant); (Pregnancy testing will be done on all females of child bearing age)

Key exclusion criteria -
Cocaine Exclusion Criteria:
1) Participation in clinical trial and receipt of investigational drug(s) during previous 60 days, except as explicitly approved by the Principal Investigator.
2) Clinically significant cardiovascular, hematologic, hepatic, renal, neurological or endocrinological abnormalities.
3) History of serious head trauma or injury causing loss of consciousness that lasted more than 3 minutes or associated with skull fracture or inter-cranial bleeding or abnormal MRI.
4) Presence of magnetically active prosthetics, plates, pins, broken needles, permanent retainer, bullets, etc. in patient's body (unless a radiologist confirms that its presence is unproblematic). An x-ray may be obtained to determine eligibility.
5) Claustrophobia or other medical condition that disables the subject from lying in the MRI for approximately 60 minutes.
6) Current or prior gambling problems (This will be assessed by subjects self-report)
7) Non-removable skin patches

Marijuana Exclusion Criteria:
1) Participation in clinical trial and receipt of investigational drug(s) during previous 60 days, except as explicitly approved by the Principal Investigator.
2) History of head trauma or injury causing loss of consciousness, lasting more than three minutes or associated with skull fracture or inter-cranial bleeding or abnormal MRI.
3) Presence of magnetically active prosthetics, plates, pins, permanent retainer, intrauterine devices, bullets, etc. in smoker's body (unless a radiologist confirms that its presence is non-problematic). An x-ray may be obtained to determine eligibility.
4) Clinically significant cardiovascular, hepatic (liver), renal (kidney), neurological, or endocrinological abnormalities. Patients with uncontrolled diabetes or hypertension will be excluded.
5) History of psychosis, stroke, seizures, or organic brain syndrome.
6) Claustrophobia or other medical condition that precludes subject from lying in the MRI for approximately 60 minutes.
7) Current or prior gambling problems (This will be assessed by subjects self-report)
8) Non-removable skin patches
9) Current treatment for marijuana dependence.
10) No other current drug dependence diagnoses (except nicotine).
11) No uncontrolled diabetes or uncontrolled hypertension

Prescription Opiate Exclusion Criteria:
1) Participation in clinical trial and receipt of investigational drug(s) during previous 60 days, except as

explicitly approved by the Principal Investigator.
2) Current severe alcohol dependence that requires medical supervision for alcohol withdrawal;
3) Presence of magnetically active prosthetics, plates, pins, broken needles, permanent retainer, bullets, etc. in patient's body (unless a radiologist confirms that its presence is unproblematic). An x-ray may be obtained to determine eligibility.
4) Current psychosis, dementia, mental retardation, or history of schizophrenia;
5) History of head trauma or injury causing loss of consciousness, lasting more than three minutes or associated with skull fracture or inter-cranial bleeding or abnormal MRI.
6) Significant clinical abnormalities in hematology, chemistry, or urinalysis; as well as significant clinical cardiovascular, neurological, hepatic, renal, pulmonary, metabolic, endocrine, or gastrointestinal disorders;
7) Current or prior gambling problems (This will be assessed by subjects self-report)
8) Non-removable skin patches
9) Claustrophobia or other medical condition that precludes subject from lying in the MRI for approximately 60 minutes.
10) Current diagnosis of chronic pain disorder.

Vulnerable Populations

Children (refer to SOP 501 for definition of children) Form
Pregnant women (if the study procedures may affect the condition of the pregnant woman or fetus) Form
Fetuses and/or Neonates Form Prisoners Form Other
x **None of the above populations are included in the research study**

The following documents are currently attached to this item:
There are no documents attached for this item.

Populations vulnerable to undue influence or coercion
Subject payments are limited to $100 per week (for this CURE study subjects will be given gift cards as payment) and are contingent upon a clean urine. Also, payments are not made on Friday, holidays or weekends.

Subject recruitment
Patients are recruited through IRB-approved advertising modalities: word of mouth, fliers, list-serves, as well as Internet and local media advertisement. Patients will be recruited from the Center for Studies of Addiction Treatment Research Clinic at the University of Pennsylvania, at 3900 Chestnut Street, and in response to fliers hung, pamphlets and letters sent to Valley Forge Medical Center and Hospital, Kirkbride Center, Keystone Center, Seabrook Hourse, Physicians, Counseling Centers and like places in order to forge a relationship for reciprocal referrals. Radio advertising has been conducted previously with major AM and FM stations based in Philadelphia; future radio advertising campaigns would be similar. Flyers and billboards may be pasted in prominent, high-traffic areas around the city. Printed ads may be placed in city or university-specific circulars and/or periodicals. Internet ads may be placed on university websites or on sites not affiliated with the University. Subjects are often recruited through word-of-mouth. In order to increase our recruitment efforts, we plan to advertise/recruit using Google. A Google search for different words like Cocaine, treatment or Philadelphia will connect a person to the Center for Studies of Addictions Department of Psychiatry Penn Behavioral Health web page that lists our current research studies and contact information. We also plan to advertise/recruit from ResearchMatch.org, Facebook, Penn Video Network Video Bulletin Board (and like venues at various univeristies and colleges, at business and other places that allow us, and in newspapers. An 800 number may be added in order to allow potential participants to call without cost if needed. The name "TreatmentInPhilly.com" was purchased so that we can add this name to currently used and new advertisements because it is a much easier web address to remember then the Center for Studies of Addiction web address (***http://www.med.upenn.edu/csa/brain_clinicaltrials.html***). It is hoped that participants will be able to remember this address that take them directly to our CURE research web page once the connection of these 2 addresses is made by the University of Pennsylvania Center's web page staff.

The following documents are currently attached to this item:

Subject compensation*
Will subjects be financially compensated for their participation? Yes

The following documents are currently attached to this item:
There are no documents attached for this item.

If there is subject compensation, provide the schedule for compensation per study visit or session and total amount for entire participation, either as text or separate document

For the CURE studies, we have proposed a mix of tokens, vouchers and gift cards at both the VA and Penn for reimbursements. Thus all participant reimbursements, except reimbursed travel costs, will be in non-monetary form. We have worked to achieve a local community standard that values our addicted individuals contributed research time at the same rate as other non-addicted research participants within the community, while carefully protecting against misuse of reimbursements (e.g., toward illicit drug use). We will continue these several protections that include: 1) Reimbursements are divided into several smaller installments; 2) initial reimbursement for time spent in computerized tasks/scan participation is contingent on an illicit-free urine on day-of-scan, 3) each subsequent installment for scan participation is contingent on a drug-free urine submissions and 4) scan reimbursements are scheduled to avoid Fridays, weekends, or holidays (times of potentially higher relapse vulnerability). Urines positive for illicit drugs or illegally obtained prescription medications will delay receipt of reimbursement until an urine sample free of these is given by the participant. Our participants accept and understand these several protections. Since marijuana stays in the system for a much longer period of time a marijuana positive urine will not delay payments for any subjects.

Participants receive several sources of compensation, shown by our previous research to greatly enhance compliance with the study requirements (including completion of scans and off-magnet measures) and the overall retention important to the clinical outcome assessment. Completion of screening measures (about 6 hours total) $60 for those eligible to participate in the study (VISA like gift cards) and $20 (CVS gift cards) for those ineligible. Compensation for scans is $50 for scan 1 and $75 for scan 2 plus $25 for the neuropsych battery after scan 2. For both scan three and four fMRI sessions, compensation is $100. If you complete al 4 scans and required paperwork and tasks you will receive $100 bonus; payment is contingent on completion of paper-and-pencil measures and the computerized neuropsych battery, and a negative urine screen on scan day. Travel reimbursement (tokens) to enable attendance at treatment sessions (many of our patients are indigent), $360 across 6 months. Fish-bowl retention procedure, offering increasing draws for kept appointments (about $480, across 6 months if participant attends all visits). Completion of Follow-up measures, 12 and 24 weeks, $50 x 2 = $100. Total potential compensation is about $1400 per patient depending on fishbowl gift vouchers received from study visit draws, which is explained in the next paragraph. Marijuana participants will be paid $10 for bringing their medication card to their visit on Scan Day 3, if they bring their card with them and take the medication in front of a study staff person.

If participants are owed prior compensation because they have not been able to receive their payment due to prior positive urine sample results, a 10-panel urine dipstick will be done from the urine sample collected as part of theirr regular visit so that they can be paid right away if the results are negative.

If participants pay for parking or for other public transportation beside Septa, their travel will be reimbursed using $5 CVS gift cards. At each study visit when they provide us with a dated receipt that lists their travel cost on it, they will be receive $5 CVS gift cards that cover their travel costs. If participants take Septa transportation, they will receive $5.00 in cash to compensate them for their transportation cost to return home and back to the Center for another scheduled visit. Thus, they will receive $2.50 each way. If they are not scheduled to return they will just receive $2.50 to cover the cost of their Septa fare to the Center.

In order to retain participants, they will be eligible to earn vouchers exchangeable for goods and services in the community in exchange for attendance at each of their twice-weekly or once-weekly scheduled appointment visits over 6 months. For each visit that they attend subjects will earn draws from our attendance voucher

fishbowl if they complete all study activities for that visit. The attendance fishbowl has 500 slips in it. Many of the slips have a value of $1, some have a value of $25, one slip is worth $100, and half of the slips just say "Good job." If participants attend all required visits in a week, they will earn a bonus draw for that week, which they will make on the last visit of the week. Once subjects have earned a voucher, it is theirs to keep. Vouchers for the $25 and $100 value slips will be given in the form of a gift card. For the $1 slips, we will give subjects $1 in cash. Gift cards will not be able to be used for purchase of alcohol, tobacco or firearms/ammunition.

Participants can earn 4 additional fishbowl draws during the consent and screening process. They can earn 1 draw for completing the consent process, 1 draw for meeting with the technician and completing the required assessments, 1 draw for meeting with the nurse for your completing the medical screen, and 1 draw for completing the psychological screen. In addition, participants can earn 1 draw for completing their baseline visit.

For CURE Pilot Studies under the Pilot Project Program:
CURE pilot participants will be paid $25.00 in CVS gift cards for completion of all required screening measures. For the MRI screening and fMRI session/s, they will receive $75 per fMRI session. The fMRI compensation will be in the form of American Express, VISA or similar types of gift cards. The total will range from $25-250 in CVS/American Express gift cards, depending on if they complete the screening and the number of fMRI scan sessions in which they participate. Installments ($100 or less) are based on a drug-free urine sample and payment will be deferred until the next clean urine is given. Payments will require urine drug tests negative for illicit drugs or illegally obtained prescription medications, with the exception of marijuana. Payments are not made on weekends (Fri-Sat-Sun) or holidays, and will be deferred if participants are intoxicated or fail a Breathalyzer test.

Suicidal Ideation and Behavior Does this research qualify as a clinical investigation that will utilize a test article (ie- drug or biological) which may carry a potential for central nervous system (CNS) effect(s)?

- Centeral nervous system(CNS) effect: the ability of a test article to enter into and potentially interact with the central nervoous system (brain and spinal cord).
- Clinical Investigation: Any experiment that involves a test article and one or more human subjects that either is subject to requirements for prior submission to the Food and Drug Adminstration (FDA) under section 505(i) or 520(g) of the Federal Food, Drug, and Cosmetic Act, or is not subject to the requirements for prior submission to the FDA under these sections of the act, but, the results of which are intended to be submitted later to, or held for inspection by, the FDA as part of an application for a research or marketing permit.

Yes

Baclofen has been FDA-approved for over 40 years for spasticity. It has never been associated with suicidal or homicidal ideation. Please see the previously attached Physicians Desk Reference (PDF) for baclofen. Additionally, in our 15 years of experience with baclofen at our Center no research subjects experienced suicidal or homicidal ideation adverse events.

Study Procedures

Procedures

All patients who call for treatment will be briefly screened over the phone by a trained intake technician and will be scheduled to come in for an intake appointment. At intake, all patients will be given a psychosocial and physical examination to confirm medical health. These procedures will be performed after signing an informed consent for study screening approved for use by the IRB under the Treatment Research Center overall Center grant protocol. After this brief screening patients who still appear to be eligible for this study will attend a subsequent visit to sign one of the informed consents for this project. All other study procedures will be completed after the study-specific informed consent is reviewed and signed at the first study visit.

Genetics are drawn at this time under Dr. David Oslin's "Genetics of Addiction" Center protocol #811705. The TRC has a Genetics Research Bank located at Dr. Wade Berrettinis University of Pennsylvania genetic lab with

the purpose of collecting and storing genetic samples from individuals participating in research studies at the University of Pennsylvania Treatment Research Center (TRC). Individuals providing blood samples will have screened and/or participated in various research studies focused on an addictive disorder. These samples will be used to study various candidate genes and/or whole genome comparisons to clinical and demographic data collected as part of the other research studies that the individual has participated. The study proposed in this protocol will be one of the studies that may have overlapping recruitment of participants for the Genetics of Addiction study. As such, the data acquired from the Genetics of Addictions study may be used by the Investigators of this study, according to the protocol and consent of the Genetics of Addiction study. Persons participating in the intake process, for research studies at the TRC or our satellite Media site will be eligible to sign a separate consent for the Genetics of Addiction study. Persons reporting for intake have usually undergone a telephone or in-person screening to see if they are eligible for ongoing studies at the TRC. If they sign consent, participants in the Genetics of Addiction study will have two vials of blood drawn to analyze their genotype, as outlined in the Genetics of Addiction protocol. Dr. Oslin, the Principal Investigator of the Genetics of Addiction study, will therefore make the results of the information obtained from the genetics blood drawn in these studies available to the Principal Investigators of this proposed CURE project. Participants will also be asked to complete a locator form. This form provides space for them to list the names, addresses and telephone numbers of 3 additional contact people that can help us locate them if needed. This will be used to contact participants when staff are unable to reach them using the original contact information given us at the time of consent.

If a patient expresses interest in participating in a described study, the intake worker contacts the study research tech, giving the patient's name and citing his/her interest in the study. The research tech then follows up on the referred candidate by speaking with him/her in person, usually within the same day. The research tech describes the ongoing imaging/ outcome studies in more detail and provides the patient with an informed consent describing the specific screening procedures required for the imaging study and the imaging procedures themselves. The PI will also be available to provide additional detail and to answer questions the patient may have regarding the procedures.

If the patient decides to participate in screening and in imaging, s/he signs a written informed consent. S/he is also given a multiple-choice quiz highlighting the requirements of the study; s/he must answer every question correctly before being allowed to proceed into the study. S/he is also reminded that this consent expresses willingness to participate, but that the subsequent screening process will determine final eligibility. If s/he does not qualify for the study, s/he is paid $20 for participation in the initial screening procedures.

Generally marijuana and prescription opiates participants and some cocaine participants will call study staff specific extensions after seeing posted advertisements specific for these CURE studies. These participants will be screened by study staff using a substance specific CURE phone screen and will not go through the Treatment Research Center intake process, but instead will scheduled for medical and psychological screenings by our study staff. This process will include the signing of the separate genetics consent under Dr. Oslin's Genetics of Addictions study.

Female participants will be asked to initial that they agree to follow one of the acceptable forms of birth control listed in the consent form for the component for which they participate.

Screening Procedures: [All Procedures are done for Research Purposes]
1. Urine drug screens (UDS) Urine drug screens for the target drug (using standard cut-offs), will be the primary outcome measure. These will be obtained twice weekly during the 12- week active treatment period, and once weekly during the 12-week follow-up period. They will be processed as part of the VA collaboration. A 10-panel dipstick urine drug screen and a urine pregnancy test (females) will be done prior to each naltrexone injection for prescription opiate participants during the first 3 treatment months and may be done once a month during follow-up as well or if the VA is able to add the 2 additional tests (buprenorphine and oxyContin) to their urine drug screen then the VA option may be used during follow-up. Also, a 10-panel dipstick urine drug screen will be done once for all the studies as part of the screening process. For prescription opiate participants additional 10-panel dipstick urine drug screens may be done for detox, encouragement and safety reasons.

2. Sexually-transmitted infections/HIV testing. Our addicted patients are at high risk for HIV, both through drug-related activity (sharing crack pipes), and through unprotected sexual activity occasionally in the context of drug use. Our brain variables (hyperresponse to the promise of reward; poor inhibition of impulses toward drug and sexual reward) would be expected to predict these secondary outcomes. We will test for HIV at baseline and at 24-week follow- up.

3. Genetics. Blood samples for DNA analysis will be obtained from each participant during initial screening. Dr. Berrettinis lab will provide the genetic analysis. Genomic DNA will be extracted from anticoagulated venous blood samples using a standard salting out method [96]. Genotyping of the DRD4, DAT VNTR and OPRM1 will be performed using standard methods as described previously [97-99]. DRD2 and COMT genotypes will be determined using the Applied Biosystems Inc. (ABI) Assays-on-demand (ABI, Foster City, CA, USA) SNP genotyping assay as per manufacturers protocol. Genotyping quality control steps for all markers will include Hardy-Weinberg equilibrium determination and genotyping of 20% duplicates for each marker. (Collected under Dr. Oslin's IRB approved genetic protocol #811705.)

4. Baseline psychosocial intervention. The Coping with Craving Program [100] is a manually guided behavioral treatment developed by Dr. Childress and Dr. Hole in the 1990s with NIH support. It has been widely distributed by NIH/NIDA, has been translated into several languages, is easily modified for a target drug of abuse, and has shown treatment benefit [101]. It demonstrates sensitivity to baseline differences (good prognosis vs. poor prognosis) in our patients --- a useful feature for the current prediction proposal. In the approach, patients are asked at the outset of a session to recount a craving episode in the presence of a trained clinician, and they are then taught a Tool of the Day in an effort to help them reduce the craving/arousal. The tools include 1) practicing relaxation training to counter arousal; 2) delaying use of cocaine while engaging in behavioral alternatives; 3) recalling explicit negative consequences of cocaine use, and positive consequences of abstaining from cocaine use; 4) using negative and positive imagery related to consequences of cocaine use; 5) using mastery imagery to personify craving and counter cocaine use; and 6) replacing cognitive distortions (thought traps) related to drug use, with logical, rational thinking. Forty-five minute sessions will be scheduled twice weekly during weeks 1-12; the treatment will be provided by skilled practitioners (Masters and Doctoral level) who are already highly familiar with the methods.

5. Incentives for attendance, scanning and completion of follow-up. Based upon prior experience with clinical outcome and imaging studies, we provide clear incentives for attendance, for completion of scanning, and for completion of the several assessments at scheduled follow-ups. These incentives have been critical for preventing data loss and attrition [102, 103]. Recent use of the fishbowl strategy (patients draw vouchers that can be redeemed at a nearby CVS) had a strong impact on retention in our cocaine outpatient trials, improving retention to nearly 90% at 8 weeks.

6. Screening and Research Assessments: [All Procedures are done for Research Purposes]

SCREENING: Addiction Severity Index (ASI) [104]: The ASI is a structured interview yielding composite scores reflecting the patient's functioning in seven areas: drug use, alcohol use, medical, employment, psychiatric, legal, and family- social problems. Composite scores are computed in each area to provide an indication of recent problem severity. This instrument has been shown to have good reliability and its concurrent and predictive validity have been demonstrated.

PTSD Checklist Civilian (PCL-C): The PCL is a standardized self-report rating scale for PTSD comprising 17 items that correspond to the key symptoms of PTSD.

Edinburgh Handedness Inventory [106]: This 10-item questionnaire reliably assesses the dominance and preference of the individuals right or left hand in daily activities.

Mini International Neuropsychiatric Interview (MINI) [107]: The MINI is a 15-30 minute structured diagnostic interview providing DSM-IV Axis I diagnose, and will be used to screen for psychosis, bipolar disorder, current

major depression and suicidal risk, and to assess for Antisocial Personality Disorder. A clinician trained and certified to administer this instrument.

Wechsler Abbreviated Scale of Intelligence (WASI) [108]: As a brief and reliable measure of intelligence for both clinical and research settings, WASI is a valid screening measure of verbal, performance, and general intellectual ability. A trained diagnostician will administer the two-subtest form (vocabulary and matrix reasoning) during screening that yields a Full Scale IQ score, which serves as a good estimate of the individuals cognitive functioning.

Parent-Child Relationship Inventory (PCRI): The PRCI is a 78-item inventory completed by parents, which gives a clear, quantified description of the parent-child relationship and identifies specific areas in which problems may occur.

RESEARCH ASSESSMENTS/ QUESTIONNAIRES: [All Procedures are done for Research Purposes]

Beck Anxiety Inventory (BAI) [109]: The BAI is a 5-minute self-administered 4-point, 21 item questionnaire, which examines common symptoms of anxiety. Though patients with anxiety disorders will be excluded, this instrument can monitor symptoms, which fall below diagnostic levels. BAI will take approximately 5 minutes to complete.

Beck Depression Inventory (BDI) [110]: The BDI is a self-administered 4-point, 21 item questionnaire probing cognitive and somatic symptoms of depression. Though patients with major depression will be excluded, this instrument can monitor depression symptoms, which fall below diagnostic levels. BDI will take approximately 5 minutes to complete.

Craving Scale: a 10 question scale that asks to what degree a person is feeling craving, high-like feelings, good feelings, withdrawal and how the person feels using on a 0 to 9 scale.

Marijuana Craving Scale: Is a 12-item self-report instrument that assesses marijuana craving along four dimensions - compulsivity, emotionality, expectancy, and purposefulness.

Cannabis Withdrawal Assessment Scale [112, 113]: This clinician- administered questionnaire probes for subjective reports on marijuana withdrawal symptoms, such as changes in mood, appetite and sleep (Component 2 only).

Clinical Opiate Withdrawal Scale (COWS) [115]: COWS is a clinician-administered instrument that assesses the degree of opiate withdrawal examining eleven common opiate withdrawal signs or symptoms (Component 3 only.)

Medication Compliance/Pill Count: A form that records pill prescribed and pills taken for marijuana and injections received for prescription opiates (yes/no) and dates.

HAM A/D: The Hamilton Anxiety Rating Scale (HAM-A) is a widely used and well-validated tool for measuring the severity of a patient's anxiety. The Hamilton Depression Rating Scale (HAM-D) has proven useful for many years as a way of determining a patient’s level of depression before, during, and after treatment.

Bradycardia Assessment: Bradycardia is a slower than normal heart rate. Nurses will take this measure at Weeks 0, 3, and 12. A score from 0-7 will be entered.

Daily Diary and Rating Scale: A daily diary will be used to record use of all substances and intensity of craving. This form will be collected on a weekly basis.

Modified Cigarette Evaluation Questionnaire (mCEQ) [117]: The mCEQ assesses the degree to which subjects

experience the reinforcing effects of smoking. It is a validated and reliable measure with multi-item domains on smoking satisfaction, psychological reward and aversion, as well as the single-item assessment on enjoyment of respiratory tract sensations and on craving reduction.

Positive and Negative Affect Scale (PANAS) [119]: This is a brief, computerized self-report rating scale that examines the degree to which the subject is experiencing positive and negative moods in the moment. The scales will be administered immediately before the imaging and the neuropsychological tasks, to control for mood/affective state during task performance.

Risk Assessment Battery (RAB) [120]: RAV is a self-administered questionnaire to assess HIV risk behavior in the previous 6 months, and consists of sexual- and drug- risk subscales.

Menstrual Cycle Questionnaire (MCQ): An instrument developed by our lab for the purpose of collecting data on Menstrual Cycle Phase and PMS/PMDD symptomatology to examine their impact on addiction/smoking behavior. Physical and emotional symptoms of PMS are separated and a history of menstrual cycle characteristics are collected.

Toronto Alexithymia Scale (TAS): The TAS is a 20-item instrument that is one of the most commonly used measures of alexithymia. Alexithymia refers to people who have trouble identifying and describing emotions and who tend to minimize emotional experience and focus attention externally.

Quality of Life and Functioning (MOS- SF) [121]: The MOS-SF-12 is used to measure general physical and mental health function. The SF-12 has good reliability and validity.

Mother -to-Infant Bonding Scale: An 8-item self-report research instrument that uses a 4-point Likert-style scale to assess the feeling of a mother toward her infant. The questionnaire was modified to probe the mother's feelings toward her child during the first few years of the child's life instead of the first few weeks.

Shiffman-Jarvik Smoking WD questionnaire (S-J) [122]: A widely used self-report 25-item questionnaire, SJ has been developed to assess WD symptoms. This will be administered pre-and post cue exposure to determine whether WD has accrued over the time in the scanner.

WASI Working Memory Index (WMI): Requires working memory processes applied to the manipulation of orally presented verbal sequences. Tests the ability to temporarily retain information in memory, by performing some operation or manipulation with it, and produce a result. Involves attention, concentration, mental control, and reasoning. Essential component of other cognitive higher order progresses.

Smoking History Questionnaire (SHQ): This is a laboratory-developed questionnaire that includes the Fagerstrom Test for Nicotine Dependence [123], and assesses smoking topography and severity of nicotine dependence.

Time-Line Follow-Back (TLFB) [124]: The TLFB will be used at baseline and weekly assessment to measure alcohol and drug use. The TLFB will cover the 30 days prior to the study (at baseline) as well as the seven days (at weekly assessment) during the study.

Within Session Rating Scale (WSRS) [125]: This scale is used to assess craving and other subjective responses, and has been adapted to measure cocaine, marijuana and opiate craving. WSRS is administered on three occasions on each scan day: prior to scan, after cue-exposure, and after craving modulation attempts.

Cannabis Withdrawal Scale (CWS): This is a modified version of a 19-item scale used to measure the intensity of marijuana withdrawal symtoms since last use. This will be administered on scan days to marijuana participants only.

LABORATORY ASSESSMENTS: [All Procedures are done for Research Purposes] Genotyping: Blood sample will be collected for genotyping. Genomic DNA will be extracted from blood samples by standard methods.

Urine Toxicology: Baseline and weekly urine drug screen will be collected and submitted for analyses at the PVAMC. The urine drug screen will be used to detect the following drugs: amphetamines, barbiturates, benzodiazepines, cocaine, marijuana, opiates, methadone and PCP. It will also be used to test for cotinine at Scan Day 1, Scan Day 3 and Scan Day 4 (for prescription opiates all cotinine tests will be done either on or prior to each of the injection days). This may also be done for the Baby Schema pilot on scan day.

Saliva Drug Test (SDT; Drager Drug Test 5000) - Saliva samples may be collected to determine recent use of illicit substances, including amphetamine, methamphetamine, cocaine, opiates, cannabis, and benzodiazepines. The test is carried out in four straightforward steps. First, the protective cap is removed from the oral test collector and the test cassette is handed to the donor. The donor then places the collector inside his or her mouth and, by using a sideways motion between the cheek and gum, takes an oral fluid sample. As soon as sufficient fluid has been gathered, the built-in indicator will turn blue and the test cassette can be handed back to the study personnel. The study personnel will then transport the sample to the Analyzer to obtain the results of the test. This will only be done for the marijuana component. This is being done since it is able to determine that substances were used within a recent window (a couple of hours to a few days depending on the substance) and can be used as an outcome measure for marijuana since this test is more sensitive to recent marijuana use and will not be positive for prior use that still shows as positive in an urine sample.

ADDITIONAL MEASUREMENTS (Safety): [All Procedures are done for Research Purposes]

Adverse Events (AE) Assessment: A semi-structured interview is designed to assess and track the onset, course, and severity of adverse events. AE will be collected and recorded at each weekly visit. Type, severity, relatedness to standard treatment, action taken, and outcome will be recorded. Designations of mild, moderate, and severe will be used to assess severity of any adverse effects. All locally relevant Internal Review Board (IRB) regulations and practices concerning adverse event reporting will be followed.

Concomitant Medications: Concomitant medications are recorded during the study period on a weekly basis.

Medical History and Physical Exam: After obtaining informed consent, a complete medical history and physical exam will be conducted by a physician or a nurse during screening.

Treatment Services: All treatments for substance use disorders and other conditions received during past seven days will be obtained by way of self-report during the second weekly meeting.

NEUROPSYCHOLOGICAL ASSESSMENTS (OUT OF SCANNER): [All Procedures are done for Research Purposes]
Affect Congruent Go-NoGo Task [127]: The 5-minute Go-NoGo task is a computerized motor response suppression task that probes the ability to inhibit prepotent motor response. As a simple and engaging task, the task introduces demands related to negative affective processing, by using stimuli with inherent ecological validity; thus, it reduces the confounds of vigilance and memory.

Balloon Analog Risk Task (BART) [128]: This computerized task is designed to provide a context in which risky behavior can be evaluated, and assesses impulsiveness (i.e., risk taking behavior). Performance on BART has been associated with sensation seeking, impulsivity and deficiencies in behavioral constraint.

Behavioral Inhibition System and Behavioral Activation System (BIS/BAS) [129]: This 20-item computer administered, Likert-type format questionnaire yields scores for behavioral inhibition system (anxiety proneness), behavioral activation system (e.g., drive), BAS reward responsiveness, and BAS Fun-seeking.

Cognitive Bias Tasks: This set of tasks includes Attention Bias Task [130, 131], Affective Priming Task [132], and Implicit Association Task, and assesses various cognitive and affective biases toward visual cues, including drug-related, appetitive and aversive cues. For example, attention to drug cues represents one important cognitive component of addictions and this bias toward drug cues may represent a precursor of cue-induced craving.

The Baby Schema Task (off-magnet): Participants will be shown still frames of portraits of children and babies, some of which have been graphically manipulated to change the Baby Schema features to make a face appear more or less cute (Glocker 2009; Glocker 2009). Participants will be asked to rate their motivation to care for the babies pictured ("would not like to take care of " to "would like very much to take care of" on a scale of 1 to 5). It is about 15/20 minutes.

Cue-Rater Task: A task design to enable participants to rate 24 cues and 24 video snips they have seen by answering 3 questions using either a scale of 1 to 7 or by marking a vertical line on a visual analogue scale that is 100 millimeters long. It is about 20/30 minutes.

Difficulties in Emotion Regulation Scale (DERS) [133]: This 36-item questionnaire measures ones experience of difficulties with various dimensions of emotional regulation. Computer-programmed DERS will be used to administer this measure.

Novaco Anger Scale [134]: The Novaco Anger Scale Short Form (25 items) tells you how an individual experiences anger. The entire questionnaire can be completed in 2 minutes.

Zuckerman Kuhlman Personality Questionnaire (ZKPQ) [135]: The ZKPQ is a personality measure that will provide subscale scores on Impulsivity/Sensation Seeking, and Neurotic Anxiety, two traits associated with decision-making.

Imaging Assessments
Functional Magnetic Resonance Imaging (fMRI): Blood-Oxygenation-Level-Dependent (BOLD) fMRI is a well established clinical and research imaging method that reflects regional brain activity [136]. BOLD fMRI uses the inherent differences in magnetic susceptibility between oxygenated and de-oxygenated hemoglobin to create a contrast image of the brain with high spatial and temporal resolution and without any exposure to ionizing radiation. Target stimuli and comparison stimuli are typically presented (alternating, or quasi-random order) several times, and subtraction reveals the relative change in signal at each voxel. BOLD fMRIs excellent temporal resolution, enables it to capture the rapid changes in the brain states that take place during cognitive processes.

Description and justification of imaging probes for reward and for inhibitory control. We will use well-characterized tasks to probe reward (reward cue sensitivity; reward risk) and reward inhibitory control (general, and drug-cue specific). Three of the fMRI probes were developed within our own lab; colleagues at our university have developed an effective fMRI version of the fourth (reward risk) task.

a) Reward cue sensitivity. We will characterize the reward circuitry response to cues for drug reward (matched to the population, i.e., visual cues for cocaine, marijuana or opioids) and to cues for the primary survival-driven reward of sex in the novel Brief Drug Cues task developed within our own lab [132]. In the Unseen phase of this paradigm, 48 random 33 msec targets in each of four categories (left, interspersed with grey-screen nulls) are immediately followed by a 467 msec neutral masking stimulus. Under these conditions, the 33 msec stimuli escape conscious detection; only the 467 msec masks are later recognized at levels above chance. The use of unseen cues reveals the immediate response of the reward circuit, without the influence of slower-to- respond cortical (modulatory) brain regions involved in conscious processing. The unseen reward probe thus avoids potential confounds of regret, shame, ambivalence, embarrassment or other secondary responses that can occur with conscious processing of socially sensitive stimuli such as drug and sexual cues. A second phase of the task involves visible,

1500 msec. versions of the same cues; these cues are processed consciously and will provide a conventional comparison to the other (monetary or points) reward tasks in the literature.

There is no response requirement in either phase of the task, avoiding the possible confounds of individual differences in motor coordination/reaction time. Encouragingly, our preliminary data suggests the response of brain reward circuitry to unseen drug cues can indeed predict relapse status and may thus provide a novel and sensitive biomarker for relapse. Though cues have long been hypothesized to play a potential role in relapse, to our knowledge this is the first cue-related task with potential predictive validity for relapse in addiction.

b) Reward risk. To complement the Brief Drug Cue task, which involves passive exposure to reward cues, we will also assess the reward circuit response during risk-taking: the active pursuit of reward in the context of uncertainty and possible negative consequences. Risk-taking tasks are intended to model some of the real-world choices that our patients face: e.g., whether to take the significant health risk of drug use (or unprotected sex) when in pursuit of immediate pleasure despite potential negative consequences. We will use an fMRI adaptation of LeJuezs Balloon Analog Risk task (BART; 2002; 2003), recently developed by Hengyi Rao at our University (see Rao, et al., 2008 in Preliminary Data), to measure the brain response during active risk in our three cohort. The task is straightforward: each key press further inflates the balloon, and accrues monetary reward but if the balloon bursts (this is random), all the accrued reward is lost for the given trial. The fMRI version of the task contrasts the response of the brain during active risk-taking choice to inflate the balloon, vs. a passive no-choice condition in which the balloon inflation and bursting is simply viewed. The fMRI adapted BART robustly activates the mesolimbic reward circuitry, including the striatum, in adults. As the original off-magnet BART has predicted real-world risk behaviors, both in LeJuezs cohorts (LeJuez, et al, 2003;) and in our own (MacDougall, et al.), the brain response to the task also has promise as a biomarker of relapse.

c) Reward Inhibitory control - general. Go-NoGo tasks are commonly used to model difficulty with inhibitory control (Carter et al 1998; Braver, et al 2001; Kaufman, et al 2003; Forman et al. 2004). Typical Go-NoGo tasks use abstract letters or symbols to signal Go (Press the button) vs. NoGo (Dont press). These arbitrary signals make significant demands on learning and working memory, which may confound performance in the task, especially with addicted individuals. To reduce the learning confounds, to make the task more engaging and to better simulate deficits in responding to real-world stop signals for inhibiting impulses toward reward, we created an affect-congruent picture version of Go-NoGo. In this task (right), the Go pictures are positive (rewarding), while the NoGo pictures represent natural danger (scorpions, spiders). As with standard tasks, difficulty inhibiting is reflected in errors of commission. The task has been well accepted by our populations, and has produced a reliable limbic brain signature for the Go-NoGo contrast. This brain response may be a good biomarker for predicting drug use, reflecting a general deficit for inhibition of in the moment impulses toward reward.

d) Reward inhibitory control drug-cue specific. Our final fMRI task involves attempted inhibition of cue triggered craving during alternating, semi-random, 20 sec epochs (Neutral video, Just Watch, Drug Video Just Watch, Drug Video - Decrease: Try to decrease your craving by considering the potential negative consequences of using (name of drug). We have studied several variations of this paradigm (including longer video clips), and find that short epochs are better tolerated by our patient population. Most patients have difficulty with this task (it models the real-world struggle to inhibit drug craving); the successful ones demonstrate activation of modulatory regions (e.g., anterior cingulate; ventromedial prefrontal cortex), and simultaneous reduction in limbic activity. These preliminary data guided our selection of the region of interest for the outcome prediction analyses in the proposed CURE project.

Potential Pilot tasks for Scan day 2: Affect Regulation Paradigm: The affect regulation paradigm is a set of tasks using active, voluntary regulation of emotion by cognitive reappraisal, as employed by Ochsner et al. (25, 35) and Phan et al. (24). Our paradigm, which has been shortened to 5 minutes from previous

versions 12- minute task duration, has been modified in order to accommodate the participant's difficulties with attention and impulsivity (72, 73) in patients with PTSD and SUD. On the basis of normative ratings, 48 pictures (24 aversive; 24 neutral) are selected from the International Affective Picture System (74). The pictures have been matched for general content and balanced on valence and arousal. The affect regulation paradigm consists of three task conditions of interest, Passive, Maintain, and Suppress, alternating across blocks in a counterbalanced order across subjects, with Neutral condition initiating all tasks. During Passive task, subjects are instructed to Watch the picture naturally like you would do at a movie theatre. During Maintain condition, they are asked to try to increase feeling whatever the picture made you feel. During Suppression condition, they will be instructed to try your best to not feel that feeling anymore. In each block, the subject will be exposed to two new aversive cues on a computer screen for 20 seconds. Each image, chosen randomly between two images, will be presented for 1500msec on 15 occasions, followed by 500msec interstimulus interval with a fixation cross. Each block will be preceded by 4-second Relax screen. Each run will be preceded by a 10-second baseline block to minimize carryover effects and to allow the blood oxygen-level dependent (BOLD) signals to return to baseline.

The Baby Schema Task: Participants will be shown still frames of portraits of children and babies, some of which have been graphically manipulated to change the Baby Schema features to make a face appear more or less cute (Glocker 2009; Glocker 2009). Participants will be asked to rate their motivation to care for the babies pictured, using the response pad described earlier (FORP) These tasks may be presented concurrently with an MRI session or separately.

Cyberball is an online ball-tossing game in which participants believe they are playing with two or three others. In fact, the "others" are controlled by the programmer. The course and speed of the game, the frequency of inclusion, player information, and iconic representation are all options the researcher can regulate. The game was designed to manipulate independent variables (e.g., ostracism) but can also be used study social rejection. The game is freely available and avatar or WII type look-alikes can be made from subject's description of others they know.

Wait to See Task: This is approximately 3a 0 minutes delay of gratification that asks you to wait to see pictures of women using a computerized task.
BART was described earlier.

Real-time fMRI is a novel neuroimaging probe that uses real-time fMRI to enhance cognitive control over the limbic brain response to drug cues. In the Pilot Project Program (Core), real-time fMRI feedback training will be tested as a novel outcome predictor – and potential future intervention. Recent advances in fMRI technology make it now possible to monitor and analyze brain activity **while it is happening**, rather than later. This **"real-time" fMRI** approach also offers the opportunity to give rapid **feedback** about the pattern of brain activity to the individual being scanned. Giving the individual rapid feedback from brain regions used to control craving, while being scanned, may be helpful in learning to control drug craving. In collaboration with Dr. Magland, we have recently developed real-time fMRI feedback technology at Penn. In an initial demonstration manuscript, we showed that individuals, including cocaine patients, can rapidly learn to use brain feedback for controlling a screen cursor. This technology has promise as both a sensitive **probe of cognitive control**, but also as an intervention for enhancing cognitive control over problematic states such as drug craving. For the CURE projects, we will feature the Real-time fMRI feedback paradigm in the Pilot Project Program, using performance in the cognitive control paradigm as a potential predictor of drug use /relapse. We demonstrated that individuals, including cocaine patients can use real-time fMRI feedback training to learn cognitive control of a screen cursor by alternating their thoughts between two distinct states (e.g., thinking about hitting a tennis ball repeatedly vs. going from room to room in a familiar place). Thus we will test how well individuals maintain control in the face of cocaine cues. Real-time fMRI feedback training from distinctive task related regions (SMA for motor activity; PPA for spatial navigation, B, left) can be used for training rapid control of a screen cursor by thought.

General Procedures for fMRI sessions

Following the recruitment, screening and informed consent procedures detailed in the Human Subjects Section, subjects will be escorted by the imaging tech to the 3T scanner located at the Hospital of the University of Pennsylvania for scanning. An additional safety check (for metal in the body) is obtained prior to scanning.

The CFN is equipped with two Siemens MRI scanners and supported by a team of physicists and research MRI technologists. The scanner to be used in this project is a 3 Tesla Siemens Trio system, FDA-approved for clinical use and fully dedicated to research. The scanner is equipped with a clinically approved Siemens receive-only 8-channel head coil and a body-coil transmitter, systems for cardiac and respiratory rate monitoring, eye tracking, rear-projection of the visual stimuli to the headcoil-mounted mirror in the center of the visual field (Epson PowerLite 7300 video projector, interfaced with the stimuli delivery computer) and subject response collection through a non-ferromagnetic response keypad (FORP; Current Design Inc., Philadelphia, PA) system. Auditory stimuli are delivered through CONFON HP-SI01 electrodynamic MRI-compatible headphones.

The parameters for each type of scan acquired are listed below; the order of these scans in the session is illustrated in the MRI Scanning Session Timeline:

1. Anatomical localizer (30 sec) is used for within-session orienting of the acquisition planes.
2. Resting baseline scan will employ Continuous Arterial Spin Labeled fMRI [137] as one of the secondary Bonus measures of resting brain activity. Ten minutes of resting baseline brain CBF (5 Bold and 5 Perfusion counter balance on day scan days 1 and 2 - 200 acquisitions) will be acquired. Interleaved images with and without labeling will be obtained using a gradient echo echo-planar imaging sequence with a delay of 1000ms inserted between the end of the labeling pulse and image acquisition (FOV = 220 mm, matrix = 64x64, TR/TE = 3000/17ms, flip angle = 90°, 14 sequential slices with thickness = 8 mm with a 2 mm inter-slice gap.
3. Blood Oxygen- Level-Dependent (BOLD) fMRI for each probe of reward or inhibition: T2*-weighted images with single shot gradient echo (GRE) echo planar imaging (EPI) sequence (field of view (FOV)= 192 mm, matrix 64x64, TR=2 sec, TE=30 msec, flip angle=80°, effective voxel resolution 3x3x3mm).
4. A high- resolution structural scan (MPRAGE: TR1620 msec, TE3.87msec, FOV 250mm, matrics 192x256, effective voxel resolution of 1x1x1mm) is used for coregistration of the functional MRI data, and also provides a bonus measure (no additional cost) of gray matter density that can be examined as a predictor of drug use in the Pilot project program (see Bonus Measures, Pilot Project Program).

Duration of the imaging session is about 46 minutes (43 scan minutes, plus approximately 3 or 4 1- minute breaks between the tasks). Immediately following the session, participants will meet with a study clinician to address any residual drug craving. Task details relevant to data reduction are provided in the MRI Scanning Session Timeline.

Procedures that apply to all 3 studies: A complete psychiatric and medical examination with routine laboratory tests will be performed to ensure that participants have no medical illnesses that would keep you from participating in the study. If the participant comes to us from a residential setting such as, Gaudenzia, Inc. and has had the required medical examination and routine laboratory tests within the last 30 days these may suffice and with the participants permission will be requested/released to us for our records. About 4 tablespoons of blood will be drawn for laboratory tests. For Marijuana participants who are HIV+ and participate in the study an additional tablespoon of blood will be collected to check for CD4 counts. Participants who have a CD4 count that is 200 or less will not be eligible to participate. Participants will undergo a series of interviews and be required to fill out research forms that allow the doctors working on the study to get basic information concerning drug use, medical history, and mood state. The initial screening procedures will last approximately 3.5 hours. An x-ray may be needed to determine eligibility. This screening process may be done over 2 days depending on nurse and therapist schedules.

For cocaine participants their present physical status, vital signs and a uring pregnancy test will be reassessed prior to theirr admission to Presbyterian Hospital. A breathalyzer test will also be done.

The results of the initial screening procedures, after participants sign informed consent, will determine whether they can enter the study. Included in this are a medical screening with a physical, a psychological screening, an electrocardiogram, a urine pregnancy test (females), the Edinburgh Handedness Scale and the Addiction Severity Index.

If participants are found to be eligible after the initial screening additional assessments and Neurobehavioral Tasks will be done, which take about 2 hours to complete part at baseline (12 minutes), part at week 12 (43 minutes) and most of the tasks are repeated after scan day 1 (1 hour and 35 minutes).

Next participants will be scheduled for their first and second fMRI scan sessions and first psychosocial treatment appointment or medication appointment. After 3 weeks of psychosocial treatment and/or medication, a third fMRI will take place (2 weeks for prescription opiates). After week twelve treatment will stop, and participants will undergo a fourth fMRI once treatment ends.

Between MRI scan sessions participants will meet with study personnel and a therapist twice a week. At these visits study assessments, interviews and therapy will be done. Any issues will also be discussed, new medication received as required, and a urine sample collected at each visit.

Week 1 through 12 visits: (Twice a week about 1 hour to 1 hour 20 minutes) You will complete a therapy session along with safety and other questionnaires.

Week 13 through 23 visits: (Once a week about 1 hour to 1 hour 20 minutes) You will complete safety and other questionnaires.

Week 12 (about 2 hours) and 24 (about 50 minutes): (Additional tasks and questionnaires) You will also repeat 3 sections of Neurobehavioral Tasks (Week 12 only). You will complete 2 additional questionnaires.

Imaging Day: All participants meet with a therapist before they are scanned to do a “talk up” and at this time if the therapist identifies that the participant is under the influence of any substances then the participant will be told they cannot be scanned. If necessary participants will be asked to meet with a nurse who may recommend that it is best for them to remain at the Addiction Treatment Research Center until it is felt that they are safe to leave or they are referred for help if required. Participants will be escorted to the MRI Center in the Founders Building at the Hospital of the University of Pennsylvania (HUP). During the session participants will be in a separate room attached to the room where the MRI technician and study staff person is located at the University of Pennsylvania Hospital. Participants will be lying flat on a hard surface that slides into the MRI for the scan session. Blankets are available for comfort. There is a harness for participants head in order to cut down on movement and a headset is provided to cut down on the noise of the scanner. Participants will be able to communicate with the technician and study staff throughout the scan session.

Scan Day 1: (about 2.5 to 4.5 hours) Urine sample collected WAIS Working Memory Index (WMI) Clinician Talk Up Urine Pregnancy Test (females) Scan day questionnaires Subjects will lie supine in the magnet for 60 minutes and view a variety of drug-related and non-drug-related (sexy, scary, neutral, etc.) cues via a projection panel (or goggles) placed at the foot of the scanner The technician will ask the subject to rate their craving at predetermined intervals during the scan Computerized On-Magnet Tasks Meet with physician if needed Imaging results will be reviewed by a neuroradiologist for anomalies, as per standard policy for research studies within the HUP MRI facility. Neurobehavioral off-magnet tasks (Scan day 1 only) Baby Schema off-magnet task (Scan day 2 only - not done for the marijuana study) Off-magnet BART (Scan day 3) Cue-rater off-magnet task (Scan day 1 and 3 only) Final Recovery and Talk Down (addresses residual arousal) with a therapist. COWS and blood pressure (pre and post scan prescription opiates only). Blood pressure will be assessed for cocaine and marijuana as well on scan days. Instead of doing the full Menstrual Cycle Questionnaire (MCQ) on scan days only 1 question from it will be asked of females by the nurses, which is “what is the first day of your last menstrual cycle/period?” The full MCQ will now only be done at screening.

Scan Day 2: (Same as Scan Day 1 activities without WMI and check for anomalies) Scan Day 3: (Same as Scan Day 1 activities without check for anomalies and as noted above) Scan Day 4: (Same as Scan Day 1 activities without check for anomalies)

Inpatient discharge will occur the day after the final scan for cocaine participants only who stay inpatient for the first week.

Marijuana Baclofen Medication Schedule: Medication will be dispensed according to the schedule below. Medication will be packaged in blister packs containing 1 weeks worth of medication, distributed and managed by IDS (Investigational Drug Service) at the University of Pennsylvania. Our prior experience administering baclofen in cigarette smokers provide the rationale for the dose. In our Baclofen for Smoking Reduction Study 20 mg q.i.d. reduced the number of cigarettes smoked per day without differences between baclofen and placebo subjects in adverse events, including sedation. We attribute this to our slow induction schedule wherein subjects are titrated up to full dose over 12 days.

On Scan Days 3 marijuana participants will be asked to bring their medication card with them and to take their medication dose in the presence of Study Staff.

Prescription Opiate Naltrexone Dosing Schedule: (Prescription Opioid Subjects only)

All doses of depot naltrexone will be 380 mg and will be administered by a project physician (Dr. Langleben) or a study nurse during scheduled research visits. The naltrexone medication will be stored in compliance with Good Clinical Practice requirements.

Week 1: Subjects who successfully pass the naloxone challenge test will be started immediately on depot naltrexone. The initial dose of depot naltrexone will be injected into the gluteal (buttock) muscle. Subsequent injections of naltrexone will occur monthly, approximately 30 days apart, for months 2 and 3 for subjects for prescription opiate dependent subjects. Alternate gluteal muscles will be used for each month's injection. Up to 6 additional blood draws may be done in order to check 6-beta naltrexol plasma and liver function levels during the month following each of the naltrexone injections. When possible these blood draws will be combined.

Weeks 2 to 12: All subjects will be scheduled for research visits twice each week.

Recently, technology has been developed that enables naltrexone to be prepared in a depot form. Depot form can provide effective blood levels for 30 days or more following a single intramuscular injection. This preparation is now FDA-approved for general use, and has already been used in clinical trials with alcohol-dependent and opioid dependent patients. Depot naltrexone was tested in a trial of alcoholics and in a separate trial of opioid dependent subjects by the Treatment Research Center and Center for the Studies of Addiction at the University of Pennsylvania. The retention rate at three months was greater than 80% and the complication rate for this particular preparation (i.e., pain at the injection site) is relatively low. (Donald Wesson, personal communication, 2001).

Prescription Opiate Detoxification: Research study participants will have to become "clean" (detoxify) from prescription opiates prior to receiving the medication for this study. Participants may detoxify on their own, or get help with detoxification from Dr. Langleben or the TRC doctors or nurses associated with this study by visiting the Treatment Research Center. At the TRC, Dr. Langleben or another qualified physician or nurse appointed by Dr. Langleben, will provide standard supportive medical care to help participants achieve abstinence from prescription opiates, as outlined below. In addition, routine general medical care may be provided at the discretion of the study physicians, unless in the judgment of the research physician the participant should and can see their own private physician

CURE Detox Protocol prior to Depot Naltrexone Injection

This protocol is intended only for individuals who express interest in participating in the CURE Addiction Center of Excellence: Brain Mechanisms of Relapse and Recovery Prescription Opiate study but report

current use of or urine test positive for opioids.

Outpatient clonidine-naltrexone detoxification

Participants who require detoxification from opioids to receive the study medication will be offered pharmacological that would follow the detoxification guidelines that have been shown to be safe and effective (Vining et al. Brit J Addiction 83, 567-575; Ockert et al. J Addict Med 5, 110-114) in this population and are in keeping with current standards of care (Tetrault & O'Connor. Management of Opioid Intoxication and Withdrawal. Principles of Addiction Medicine, 4th Edition. NY: Lippincott, 2009) along with psychological support. Dosing will follow the guidelines listed in the Handbook of Psychiatric Drug Therapy, 5th ed. (Rosenbaum JF, et al. Lippincott, 2005). Patients may be given alternative dosages within the FDA approved indication if medically necessary. As part of the signed consent procedure, individuals will sign an agreement not to drive while on this detoxification protocol. Individuals will be seen and urine toxicology done at each visit. Dosing will be based on rating on the subjective and objective severity of the withdrawal symptoms, such as anxiety, elevated blood pressure and heart rate, dilated pupils, sweating, diarrhea and muscle cramps. Individuals will be given enough medication to last them until their next scheduled visit and no more than 5 days worth. The individual will be given instructions how to contact the study clinician for any detoxification-related issues after-hours. Standard medications used will include divided doses of Clonidine, 0.1 to 1.2 mg a day, Hydroxyzine 25 to 400 mg a day, Dicyclomine 10 to 80 mg a day, Ibuprofen 400 to 2,400 mg a day, Trazodone 25 to 150 mg a day. In addition to the standard opiate detoxification protocol, oral naltrexone 50 to 100 mg a day and benzodiazepines may be prescribed to help alleviate physiological or subjective symptoms of withdrawal. The following benzodiazepines medications may be used: Lorazepam (Ativan) 0.5, 1.0, or 2.0 mg tablets every 12 hours, PRN anxiety, Oxazepam (Serax) 10, 15, or 30mg tablets every 8 hours, PRN anxiety, Clonazepam (Klonopin) 0.5, 1.0, or 2.0 mg tablets every 12 hours, PRN anxiety. Each and all of these medications are commonly used and will be prescribed by a licensed and board certified physician, guided by clinical medical need, and will not involve any experimental use. The risks and benefits of each medication will be discussed with participants before it is administered in accordance with Good Clinical Practices principles.

As part of this detoxification participants may receive oral naltrexone (50 mg per daily dose) to aid in opioid detoxification up to 1 week prior to their first depot-naltrexone injection, up to two weeks during the study as needed and up 1 week following their final scan (when their depot-naltrexone levels have declined to near zero to reduce the risk of relapse).

A Vivitrol Medical Information Card for emergency treatment will be given to all prescription opiate participants when they are given their first depot-naltrexone injection.

Since Aldermes will be providing Vivitrol (depot naltrexone) medication for the prescription opiate part of this protocol, they asked that we add the following statement to this protocol:. "If SAEs for the Vivitrol are assessed as unrelated to Vivitrol, they may be summarized on the required Quarterly Study Report that is submitted to Alkermes. If an SAE in the Vivitrol treated cohort is deemed to be a SUSAR (i.e. Serious, unexpected and is assessed as at least possibly related to Vivitrol), it should be reported to the FDA within required reporting timelines, as well as copied to Alkermes Drug Safety at the time of FDA submission. Such expedited reports may be submitted by fax to: (617) 494-5202 or by email to drsafety@alkermes.com"

CURE Pilot Project Program (separate consent): Approximately 100 separate pilot subjects will participate as part of the pilot project program using the separate pilot consent.

Pilot assessments: Social Assessments and Tasks:

Care-taking Motivation Task (CMT) (Glocker 2009): This is a computerized task used to assess the degree to which infant faces elicit care-taking motivation. The task presents high, low and unmanipulated baby schema infant faces in random order. Participants are asked to rate the extent of their motivation to

take care of the infant in the picture on a 5-point scale. Our previous studies in healthy women have demonstrated that high baby schema infants elicit stronger motivation for care taking than low baby schema infants. Prior to completion of the CMT, participants will be asked to complete a similar practice task that displays baby animal, rather than human, faces. (approx. 10-20 min)

Cuteness Perception Task (CPT) **(Glocker 2009)**: This is a computerized task used to assess the degree to which infant faces are perceived as cute. The task presents high, low and unmanipulated baby schema infant faces in random order. Participants are asked to rate the cuteness of an infant in the picture on a 5-point scale. Our previous studies in healthy women have demonstrated that high baby schema infants are perceived as cuter than low baby schema infants. Prior to completion of the CPT, participants will be asked to complete a similar practice task that displays baby animal, rather than human, faces. (approx. 10-20 min)

The Mother-to-Infant Bonding Scale (MIBS) **(Taylor, Atkins et al. 2005)**: This 8-item self-report research instrument uses a 4-point Likert-style scale to assess the feelings of a mother toward her infant. The questionnaire will be modified to probe a parents' (mothers' or fathers') feelings toward their child during the first few years of the child's life. A higher overall score will indicate a weaker parent-to-child bond. Should a participant report a high score on a negative item of the MIBS (i.e., "aggressive", etc.), they will be referred to a licensed clinician for evaluation. (2 min)

The Parental Bonding Instrument (PBI): This is a brief 25-item self-report questionnaire which asks subjects to rate the level of care and overprotection provided to them by their mother and father during their first 16 years. Ratings are generated on a 4-point Likert-style scale and allow researchers to assess the parenting styles that the subject experienced growing up (Parker, Tupling et al. 1979). This information is of import as parental care and overprotection are thought to influence child development and neural (e.g., response of reward circuitry to stressors) and behavioral outcomes (e.g., psychiatric disorders, substance use) later in life. (5 min)

Questionnaire on Experience with Children (QEC): This is a survey instrument assessing whether the subject has children, younger siblings, or any other experience with children, as well as marital status and plans to have children in the future. (2 min)

Psychological Assessments: ***The Mini International Neuropsychiatric Interview (MINI*)**: This is a brief structured diagnostic interview with excellent validity and reliability (inter-rater and test-retest). It will be used to assess for current DSM-IV Axis I diagnoses, and Antisocial Personality Disorder, particularly substance use disorder diagnoses. It will also be used to screen for severe psychiatric disorders (e.g., psychosis, mania, acute suicidal ideation) that would exclude the individual from further participation in the study. A doctoral level clinician trained and certified in the administration of this measure will administer this interview. (15-20 min)

Beck Depression Inventory (BDI): A self-administered 4-point, 21 item questionnaire probing cognitive and somatic symptoms of depression. (5 min).

Edinburgh Handedness Inventory (EHI) **(Oldfield 1971)**: This is a common 10-item subjective measure of hand laterality, which provides a laterality quotient. (1 min)

Drug Taking Questionnaire: Assesses substances used over the past 30 days related variables, such as treatment received, years of use, amount spent on use, route of administration, etc..

The Fagerstrom Test for Nicotine Dependence (FTND): This is a self-administered 11-item questionnaire that measures subjects' levels of nicotine dependence as either very low addiction, low addiction, medium addiction, high addiction, or very high addiction. (5 min)

Behavioral Inhibition System and Behavioral Activation System (BIS/BAS) [129]: This 20-item computer administered, Likert-type format questionnaire yields scores for behavioral inhibition system (anxiety

proneness), behavioral activation system (e.g., drive), BAS reward responsiveness, and BAS Fun-seeking.

Physiological Assessments: ***Last Menstrual Period (LMP) Questionnaire:*** Information concerning menstrual cycle phase and use of oral contraceptives (OC) and will be recorded, as these factors might contribute to the perception of infant cues (Alley 1983; Sprengelmeyer, Perrett et al. 2009). (2 min)

Urine Drug Screen (UDS): All participants will be required to provide urine samples to confirm the absence or presence and/or levels of relevant drugs and toxins, may include cotinine, a nicotine metabolite.

Saliva Drug Test (SDT; Drager Drug Test 5000) - Saliva samples may be collected to determine recent use of illicit substances, including amphetamine, methamphetamine, cocaine, opiates, cannabis, and benzodiazepines. The test is carried out in four straightforward steps. First, the protective cap is removed from the oral test collector and the test cassette is handed to the donor. The donor then places the collector inside his or her mouth and, by using a sideways motion between the cheek and gum, takes an oral fluid sample. As soon as sufficient fluid has been gathered, the built-in indicator will turn blue and the test cassette can be handed back to the study personnel. The study personnel will then transport the sample to the Analyzer to obtain the results of the test.

Urine Pregnancy Test (bHCG): A urine pregnancy test will be administered to women prior to the MRI session.

Neuropsychological Activation Tasks:
*"**Baby Schema" Task*** **(Glocker 2009):** This task involves viewing still frames of portraits of babies. Participants will be asked to rate the cuteness of the babies and/or the degree to which they are motivated to care for the babies pictured. (approx. 10 min)

Baby Schema Activities	Time Required (min)	Compensation ($)
Consent	20	0
Baseline Screening and Assessments **1. Demographics** **2. BDI -** *Beck Depression Inventory* **3. QEC-** *Questionnaire on Experience with Children* **4. LMP-** *Last Menstrual Period Questionnaire* **5. MIBS-** *The Mother-to-Infant Bonding Scale* **6. PBI-** *The Parental Bonding Instrument* **7. MINI-** *Mini International Neuropsychiatric Interview* **8. Drug Questions** **9. FTND-** *Fagerstrom Test for Nicotine Dependence* **10. CMT-** *Care-taking Motivation Task and practice task.* **11. CPT-** *Cuteness Perception Task and practice task.* **12. BIS/BAS** - ***Behavioral Inhibition System and Behavioral Activation System*** 13**. UDS and/or SDT –** *Urine Drug Screen/Saliva Drug Test*	60-90	25 CVS gift card

14. **bHCG –** *Urine Pregnancy Test (females)*		
MRI Screening (if consented to do} 1. **EHI-** *Edinburgh Handedness Inventory* 2. **Medical History and Physical**	60	
MRI Session 1. **UDS and/or SDT** 2. **bHCG-** *Urine Pregnancy Test (females)* 3. **Scan**	90	75 gift card– if UDS and bHCG is negative and they complete scan

Dr. Kimberly Young or a trained technician will consent participants, assessments that do not require a therapist as well as administer the Baby Schema task off and on-magnet.

Wait to See Task: Participants will first rate the attractiveness of a series of females whose pictures of their head are randomly displayed on the computer screen in a private room. Then, according to their ratings, a portion of the shown pictures will be selected for the Wait to See Task. During each trial of the Wait to See Task, the selected head picture will be shown to the participates again and they will be told that they are going to see the same female with some or all of their clothes off depending on how long they can wait by press a preset button – the longer they can wait, the more naked of the female they can see. The task will be repeated in another MRI session for those who agree to do an fMRI session. This is approximately a 30 minutes delay of gratification task that asks you try to wait to see pictures of women using a computerized task. After consenting and 2 to 5 days prior to the task participants will be asked to rate pictures of women online. No identifiable information will be collected online.

For the "Wait to See" off-magnet task after consent demographics are collected, pictures of women are rated online, and then 2 to 5 days later participants do the approximately 30 minute delay of gratification task that asks them to wait to see pictures of women. Dr. Lam will administer do handle the picture rating and administer the task. Currently, this pilot will include only heterosexual males.

"Wait to See" / Extinction Activities – fMRI only	Time Required (min)	Compensation ($)
Consent	20	0
Baseline Screening and Assessments **1. Demographics** **2. Addiction Severity Index (ASI)** **3. PTSD Checklist (PCL)** **4. Edinburgh Handedness Inventory** **5. Mini International Neuropsychiatric Interview** **6. Wechsler Abbreviated Scale of Intelligence** **7. Medical History/Physical Exam** **8. Blood Chemistries** **9. Medical Urinalysis** **10. Electrocardiogram** **(Control participants will not do a physical or psychological screening)** **(*6 through 10 will only be done for participants who are not controls doing an MRI)**	60-90	25 CVS gift card
MRI Session Questionnaires (if consented to do) 1. **Novaco Anger Scale** 2. **Shiffman-Jarvik (smokers only)** 3. **Positive and Negative Affect Scale (PANAS**	15	

4. Within Session Rating Scale (WSRS) **5. Smoking History Questionnaire**		
MRI Session **1. UDS-** *Urine Drug Screen* **2. Scan**	90	75 gift card– if UDS and bHCG is negative and they complete scan

Dr. Shing C. Lam or a trained technician will consent participants, assessments that do not require a therapist as well as administer the Wait to See task off and on-magnet.

Extinction:

Patients who abuse substances show a remarkable persistence of desire and arousal to cues, months or even years after the last dose of drug. These "extinction-resistant" responses may be due to patients' documented (structural and functional) ***deficits in the prefrontal cortex (PFC)* –** a region necessary for modulating the downstream limbic ("GO!") regions – and for the new learning that underlies ***extinction***. Adding to this anatomical challenge, patients undergoing laboratory-based extinction remain keenly ***aware*** that "real-world" cues are still an excellent predictor of drug availability. This discrimination is not difficult (despite a PFC deficit!), and undermines generalization of laboratory extinction to "real-world" cues. We have recently developed ***a novel "unseen" cue paradigm*** that may ***minimize*** both ***"the PFC problem"*** and ***" the awareness problem"*** undermining conventional extinction efforts. This paradigm recently provided the first evidence that cues (33 msec, backward-masked) can trigger the subcortical limbic reward circuitry (amygdala, striatum/pallidum, insula, OFC) even when presented entirely ***outside awareness***–i.e., ***"unseen"*** (*PLoS ONE*, *2008)***.** Further, repeated, unreinforced presentations of the "unseen" cues did not activate the dorsal PFC, suggesting the PFC may not be as important for+ outside awareness.

Extinction conducted outside awareness, using "unseen" cocaine cues, will be more effective than conventional extinction with visible cues as indexed by reduced limbic activation to the same cues, 1 hour and 1 day later ("savings") and to realistic cocaine videos 48 hours later ("generalization").

See Wait to See/Extinction table above, which is the same. A trained technician will consent participants, assessments that do not require a therapist as well as administer the Wait to See task off and on-magnet.

All pilot participants meet with study staff before they are scanned and at this time if it is identified that the participant is under the influence of any substances then the participant will be told they cannot be scanned. If necessary participants will be asked to meet with a therapist and/or nurse who may recommend that it is best for them to remain at the Addiction Treatment Research Center until it is felt that they are safe to leave or they are referred for help if required.

The following documents are currently attached to this item:

Procedures (cureoverviewofstudyassessment_11-30-11.xls)
Procedures (scansandtreatmentphase10-27-11.docx) **(**Page 26 of 35)

Procedures (cureoverviewofstudyassessment_10.27.11.xls)
Procedures (curefigures.pdf) Procedures (fishbowlfor24weeks4)
Procedures (cureoverviewofstudyassessment_05.25.11.xls)

Analysis Plan

Objective 1: To determine whether differential activation in a priori brain regions of interest (ROI) to selected reward and inhibition probes can predict drug use during active treatment.

For hypothesis 1a, the two brain predictors will be the extracted signal change in the interconnected left amygdala-striatal cluster during the Brief Drug Cues task, and the extracted signal change in the bilateral ventral

striatum in the Balloon Analog Risk Task. For Hypothesis 1b, the predictors will be based on the left amygdala for the Go-NoGO contrast in the Affect-congruent Go-NoGo task, and the dorsal anterior cingulate in the Craving Inhibition task. These measures will be obtained from the fMRI 1 and fMRI 2 scans.

The four brain responses will be analyzed in a similar way. In each case, the responses will be the repeated urine screens obtained during the last ten weeks of treatment. These urine results will be binary, indicating either cocaine use, opiate use, or marijuana use, since the previous test. For each of hypotheses 1a and 1b, we will use mixed effects logistic regression (McCulloch et al, 2008) to relate variation in these responses to a measure of brain activation occurring during one of four tasks. We anticipate that using a random intercept will be sufficient to take account of within-subject correlations across the time points, although more complex covariance structures will be examined. As we are interested in assessing the separate effects of each brain region on the responses, our main analyses will consider the brain regions separately, so Hypotheses 1a and 1b will be addressed by four separate models, with the treatment urines as responses, and one brain predictor as an explanatory variable. These models will be estimated for the fMRI 1 and fMRI 3 scans.

The primary hypotheses will be addressed by the point estimates and tests of significance associated with the regression coefficients for the brain predictors in these analyses. In further analyses, we will examine the joint effects of the brain predictors for the different regions in the same model, and will use model selection based on information criteria (BIC) to determine the simplest model that provides a good fit to the data.

Objective 2: To determine whether differential activation in a priori brain ROI to selected reward and inhibition probes can predict relapse following active treatment.

Hypothesis 2a: Greater activation of a priori limbic reward ROI (e.g., interconnected amygdala /ventral striatal cluster during brief drug cues; bilateral ventral striatum during reward risk during brief drug cues; reward risk) prior to (FMRI 1), and following (FMRI 3) active treatment will predict greater drug use during the 12-week follow-up period.

Hypothesis 2b: Lower activation of a priori prefrontal inhibitory ROI (e.g., lateral orbitofrontal cortex; supragenual anterior cingulate) during affect-congruent Go-NoGo; inhibition of cue-triggered craving) prior to (FMRI 1) and following (FMRI 3) active treatment will predict greater drug use during the 12 week follow-up period.

The statistical models and analyses for Objective 2 will be very similar to those described above for Objective 1. For these hypotheses, the response will be the urine drug screens obtained in each week of the post-treatment phase. The same brain measures used for Objective 1 will be used, with the distinction that they will be obtained during fMRI 3, following treatment. The same type of mixed effects logistic regression models described above for Objective 1 will be used here also.

ASL (Arterial Spin Label) fMRI analysis (for video tasks) and resting perfusion baseline SPM 2 software, which employs the modified General Linear Model, will be used for data analysis. After reconstruction, the data will be sinc interpolated (by shifting the phase of the Fourier components) in time to correct for the differential timing of fMRI slice acquisition in space. The data will then be motion-corrected using a six parameter-rigid-body least squares realignment routine. Odd and even images of each time series will be separately realigned to the first and second images (respectively) of the first scan. This controls for the different image intensities of the label and control images. Conversion to CBF (for perfusion studies) will be calculated on a voxel-wise basis, allowing us to use perfusion in a selected region (e.g. ventromedial prefrontal cortex, VMPFC) as a predictor for drug use or other task behaviors. Image data are then convolved in space, with a 3-D nonisotropic Gaussian kernel, as well as in time, using an empirical estimate of the hemodynamic response function (HRF). Images are kept in native space for analysis of individual's S activation. For group analysis the images are automatically transformed into standard space based on high-resolution 3D T1 data. A linear model for autocorrected observations is applied voxel-wise to each data set, yielding a parametric map (SPM) for each subject or group of subjects. Inclusion of regressors for frequencies above and below that of the task as well as global signal

covariate has previously been shown to improve sensitivity while not decreasing specificity of the mode. An ANCOVA model (provided by SPM), for single or multiple subjects, which permits determination of statistical significance for the image space as a whole by correcting the significance of the map for the multiple comparisons inherent in the pixel by pixel analysis will be used for thresholding.

Group data will be analyzed in accordance with the study objectives.

For DTI analyses we will calculate diffusion trace and anisotropy differences within and between our study groups to determine whether any differences in the values found are consistent with hypotheses about how brain tissue may have been affected. Comparisons will be made by constructing statistical parametric maps (SPMs) of the whole brain and then using these to search for differences. The normalized maps of diffusion measures will be obtained by registering the corresponding structural MRI data to a cohort specific anatomic template and then applying the high dimensional transformations to the diffusion tensor data using the preservation of principal directions method. A conventional SPM analysis will be conducted on the diffusion measures by applying the general linear model and Gaussian random field theory, as implemented in the SPM software (Wellcome Department of Cognitive Neurology, Institute of Neurology, London). Specifically, an SPM group comparison (compare populations; two-sample t test) will be performed with appropriate covariates. Two one-sided comparisons (patients controls and patients controls) will be run, and the results thresholded at P 0.001 (uncorrected), then tested for false-positive results with permutation tests. An extent threshold of 25 contiguous voxels will be specified to exclude small clusters. As an ancillary test, we will calculate p- values corrected for multiple comparisons using SPM even though these may be overly strict for the proposed analysis.

b. BOLD (Blood Oxygen Level Dependent) fMRI analysis (for other tasks). A Siemens 3T scanner is used for acquiring T2*-weighted Blood Oxygen-Level-Dependent (BOLD) images with single shot gradient echo (GRE) echo planar imaging (EPI) sequence (field of view (FOV) =192 mm, matrix 64x64, TR=2 sec, TE=30 msec, flip angle=80°. After slice-timing correction of the images, SPM2 22was used for image realignment, smoothing with a 3-D 9mm isotropic Gaussian kernel, and normalization into the Montreal Neurological Institute averaged template based on structural MRIs from 152 brains. The General Linear Model with a canonical HRF as the basis function was used for three pre-planned contrasts (cocaine vs. neutral, sex. vs. neutral, aversive vs. neutral) at the individual and group level. For the correlational analysis, affective bias scores from the off-magnet affective priming task were used as covariates in a simple regression (e.g., cocaine vs. neutral contrast). Contrasts and correlations were displayed within MRICro, using the MNI single-subject t1 structural MRI brain template (the Colin brain template, closest to the average of the MNI 152 template; Colins brain was scanned multiple times by MNI to result in a crisp visual display).

The following documents are currently attached to this item:
There are no documents attached for this item.

Data confidentiality

x **Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study.**
x **Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords.**
x **Prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information.**
x **Wherever feasible, identifiers will be removed from study-related information.**
x **A Certificate of Confidentiality will be obtained, because the research could place the subject at risk of criminal or civil liability or cause damage to the subject's financial standing, employability, or liability.**
A waiver of documentation of consent is being requested, because the only link between the subject and the study would be the consent document and the primary risk is a breach of confidentiality. (This is not an option for FDA-regulated research.)
Precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys.

Audio and/or video recordings will be transcribed and then destroyed to eliminate audible identification of subjects

Subject Confidentiality
Every attempt will be made by the investigators to maintain all information collected in this study strictly confidential, unless a subject says he intends to harm himself or another or that he has abused a child or an elderly person. However, authorized representatives of the Sponsor(s) (if any), the University of Pennsylvania, as well as the Food and Drug Administration (FDA), will have access to and may copy, both medical records and records from participation in this study. This access is necessary to insure the accuracy of the findings and subject safety and welfare. If any publication or presentations result from this research, subjects will not be identified by name. The data are kept in secure, locked filing cabinets in locked rooms and access to these areas is possible only through the investigator or research technician. Also, databases are password protected and are on computers that are password protected as well.

4. Subject Privacy/Protected Health Information The following personal health information will be collected, used for research and may be disclosed or released during subjects involvement with this research study:
- Name
- Address
- Telephone number
- Date of Birth
- Social Security Number
- Mother's and Father's name
- Medical Record Number
- Billing Code, date and time
- Family medical history
- Allergies
- Current and past medications or therapies
- Information from a physical examination that generally also includes blood pressure reading, heart rate, breathing rate and temperature
- List all other tests and procedures that will be performed in the study: A complete psychiatric and medical exam with routine labs, a series of interviews and associated forms, questionnaires, MRI scans, urine samples, talk downs with a licensed therapist, therapy for 12 weeks, employment, medical, substance abuse, family/ social, legal, and psychiatric histories, and Neurobehavioral tasks.

As stated above every attempt will be made by the investigators to maintain all information collected in this study strictly confidential, unless a subject says he intends to harm oneself or another or that he has abused a child or an elderly person. However, authorized representatives of the Sponsor(s) (if any), the University of Pennsylvania, as well as the Food and Drug Administration (FDA), will have access to and may copy, both medical records and records from participation in this study. This access is necessary to insure the accuracy of the findings and subject safety and welfare. If any publication or presentations result from this research, subjects will not be identified by name. The data are kept in secure, locked areas and access to these areas is possible only through the investigator or research technician. All of the study staff that will have access to collected data are listed on section 1 of the application. If a new technician is hired for this study then they will be trained and have access to the data. In addition, the following individuals and University of Pennsylvania organizations may use or disclose subjects' personal health information for this research project:
- The Principal Investigator and the Investigators study team (other University staff associated with the study) - The University of Pennsylvania Institutional Review Boards (the committees charged with overseeing research on human subjects) and University of Pennsylvania Office of Regulatory Affairs
- The University of Pennsylvania Office of Human Research (the office which monitors research studies)
- Authorized members of the University of Pennsylvania and the University of Pennsylvania Health System and School of Medicine workforce who may need to access subjects' information in the performance of their duties (for example: to provide treatment, to ensure integrity of the research, accounting or billing matters, etc.). Those outside the university that may use or disclose subjects' personal health information for this research project:

- Government agency and/or their representative: Pennsylvania Department of Health and the FDA When all study data is analyzed, written and disseminated all identifiers will be destroyed. Only de-identified data will be published.

Subject Privacy
Privacy refers to the person's desire to control access of others to themselves. Privacy concerns people, whereas confidentiality concerns data. Describe the strategies to protect privacy giving consideration to the following: The degree to which privacy can be expected in the proposed research and the safeguards that will be put into place to respect those boundaries. The methods used to identify and contact potential participants. The settings in which an individual will be interacting with an investigator. The privacy guidelines developed by relevant professions, professional associations and scholarly disciplines (e.g., psychiatry, genetic counseling, oral history, anthropology, psychology).

Privacy is of the utmost importance in our lab. Participants are interviewed behind closed doors, screens, testing, physicals, and all other measures are done in a private space behind a closed door. All personnel receive HIPAA and CITI Human Subjects Good Clinical Practice training with emphasis on participant privacy.

Participants are recruited through IRB-approved advertising modalities: word of mouth, fliers, list-serves, as well as Internet and local media advertisements. Patients will also be recruited from the Center for Studies of Addiction Treatment Research Clinic (TRC) at the University of Pennsylvania, at 3900 Chestnut Street, and in response to fliers hung, pamphlets and letters sent to Valley Forge Medical Center and Hospital, Kirkbride Center, Keystone Center, Seabrook Hourse, Physicians, Counseling Centers and like places in order to forge a relationship for reciprocal referrals. In addition to participants recruited by public advertising, we have several additional sources of eligible participants for the project, including the natural flow of treatment-seeking cocaine patients who come to the Center for Studies of Addiction Treatment Research Clinic (TRC) at the University of Pennsylvania, at 3900 Chestnut Street, to the Penn Presbyterian Center, and to the Philadelphia VA Medical Center. These latter sites have longstanding collaborative relationships with our Center, and the VA is a formal collaborator for the CURE project. In order to increase our recruitment effort chances, we plan to advertise/recruit using Google. A Google search for different words like Cocaine, treatment or Philadelphia will connect a person to the Center for Studies of Addictions Department of Psychiatry Penn Behavioral Health web page that lists our current research studies and contact information. We also plan to advertise/recruit from ResearchMatch.org, Facebook, Penn Video Network Video Bulletin Board (and like venues at universities and colleges), at business and other places that allow us, and in newspapers. The name "TreatmentInPhilly.com" was purchased so that we can add this name to currently used and new advertisements because it is a much easier web address to remember then the Center for Studies of Addiction web address (http://www.med.upenn.edu/csa/brain_clinicaltrials.html). It is hoped that participants will be able to remember this address that take them directly to our CURE research web page once the connection of these 2 addresses is made by the University of Pennsylvania Center's web page staff.

Individuals will be interacting with investigators in a private closed-door setting (in a lockable office space) and possibly at the MRI scanning session that is located in a close door space with a separate MRI area.

Data Disclosure
Will the data be disclosed to anyone who is not listed under Personnel? No

Data Protection*
x **Name** x **Street address, city, county, precinct, zip code, and equivalent geocodes**
x **All elements of dates (except year) for dates directly related to an individual and all ages over 89**
x **Telephone and fax number**
x **Electronic mail addresses**
x **Social security numbers**
x **Medical record numbers**
Health plan ID numbers

Account numbers
Certificate/license numbers
Vehicle identifiers and serial numbers, including license plate numbers
Device identifiers/serial numbers
Web addresses (URLs)
Internet IP addresses
Biometric identifiers, incl. finger and voiceprints
Full face photographic images and any comparable images
Any other unique identifying number, characteristic, or code
None

Tissue Specimens Obtained as Part of Research*
Are Tissue Specimens being obtained for research? No

Tissue Specimens - Collected during regular care*
Will tissue specimens be collected during regulator clinical care (for treatment or diagnosis)? No

Tissue Specimens - otherwise discarded*
Would specimens otherwise be discarded? No

Tissue Specimens - publicly available*
Will tissue specimens be publicly available? No

Tissue Specimens - Collected as part of research protocol*
Will tissue specimens be collected as part of the research protocol? No

x **Name** x **Street address, city, county, precinct, zip code, and equivalent geocodes** x **All elements of dates (except year) for dates directly related to an individual and all ages over 89** x **Telephone and fax number** x **Electronic mail addresses** x **Social security numbers** x **Medical record numbers**
Health plan ID numbers Account numbers Certificate/license numbers Vehicle identifiers and serial numbers, including license plate numbers Device identifiers/serial numbers
Web addresses (URLs) Internet IP addresses Biometric identifiers, incl. finger and voice prints Full face photographic images and any comparable images Any other unique identifying number, characteristic, or code None **(**Page 30 of 35)

Tissue Specimens - Banking of blood, tissue etc. for future use*
Does research involve banking of blood, tissue, etc. for future use? No

Genetic testing
If genetic testing is involved, describe the nature of the tests, including if the testing is predicative or exploratory in nature. If predictive, please describe plan for disclosing results to subjects and provision of genetic counseling. Describe how subject confidentiality will be protected Note: If no genetic testing is to be obtained, write: "Not applicable."

Blood samples for DNA analysis will be obtained from each participant during initial TRC Center screening under Dr. David Oslin's "Genetics of Addiction" protocol #811705. Dr. Berrettinis lab will provide the genetic analysis. Genomic DNA will be extracted from anticoagulated venous blood samples using a standard salting out method [96]. Genotyping of the DRD4, DAT VNTR and OPRM1 will be performed using standard methods as described previously [97-99]. DRD2 and COMT genotypes will be determined using the Applied Biosystems Inc. (ABI) Assays-on-demand (ABI, Foster City, CA, USA) SNP genotyping assay as per manufacturers protocol. Genotyping quality control steps for all markers will include Hardy-Weinberg equilibrium determination and genotyping of 20% duplicates for each marker.

Consent

1. Consent Process

Overview

If a patient expresses interest in participating in the study, the intake technician contacts the study research tech, giving the patient's name and citing his/her interest in the study. The research tech then follows up on the referred candidate by speaking with him/her in person, usually within the same day in a private room with a door. The research tech describes the imaging study and all risks, procedures and assessments in detail and provides the patient with a copy of the informed consent describing the specific screening procedures required for the study and the imaging procedures themselves. The PI will also be available to provide additional detail and to answer any questions the patient may have regarding the procedures. Patients will be given sufficient time to consult with others prior to signing the study consent and be given as much time as they need.

Generally marijuana and prescription opiates participants and some cocaine participants will call study staff specific extensions after seeing posted advertisements specific for these CURE studies. These participants will be screened by study staff using a substance specific CURE phone screen and will not go through the Treatment Research Center intake process, but instead will scheduled for medical and psychological screenings by our study staff. This process will include the signing of the separate genetics consent under Dr. Oslin's Genetics of Addictions study.

If the patient decides to participate, s/he signs a written informed consent in the presence of the PI or a trained designee. S/he is also given a multiple-choice quiz highlighting the requirements of the study; s/he must answer every question correctly before being allowed to proceed into the study. S/he is also reminded that this consent to do research is voluntary and that s/he can withdraw consent at any time with no consequences.

All study participants will be competent to give informed consent and will understand English the language used by those obtaining consent.

Children and Adolescents

N/A

Adult Subjects Not Competent to Give Consent

All adult subjects will be competent to give informed consent

2. Waiver of Consent

Waiver or Alteration of Informed Consent*

No Waiver Requested

Minimal Risk*

Impact on Subject Rights and Welfare*

Waiver Essential to Research*

Additional Information to Subjects **(**Page 31 of 35)

Written Statement of Research*

No

If no written statement will be provided, please provide justification

The following documents are currently attached to this item:

There are no documents attached for this item.

Risk / Benefit

Potential Study Risks
Risks that cut across Cocaine, Marijuana and Prescriptions Opiate studies:

Magnetic Fields (MRI): There are no known adverse health effects as a result of exposure to the magnetic fields. The primary risk of MRI is the possibility of undisclosed metal in the patient's body (pins, pacemakers, metal fragments in the eye) that could become dislodged by the magnet. Some patients (10-15%) may experience unexpected claustrophobia when entering the magnet bore, or may notice the change in magnetic field upon entering or leaving the bore. The 3.0 Tesla Siemens magnet to be used in the proposed study is an FDA-approved device for standard clinical use. Its specifications (including the specific pulse sequences used for each protocol) meet all the stringent safety requirements of the regulatory bodies within and outside the University. Confidentiality: There is a potential risk for a loss of confidentiality in any research participation. Because our patients carry a substance abuse diagnosis, this is a risk we take especially seriously.

Craving: Viewing drug-related cues can sometimes trigger drug-related craving and arousal in patients with a drug-use history. This craving may cause some arousal, but it does not pose a medical risk.

Blood draw: The risk of drawing blood is very small, but includes minor pain, skin bruising, bleeding from where the needle goes in, or anxiety about needles. These risks are the same as for a standard blood test.

Magnetic Fields (MRI): Patients are carefully screened by our staff and again by the MRI Center staff for any metal that could pose a danger, and the importance of this screening is repeatedly emphasized. Patients are warned of possible claustrophobia in the consent form, and the session is immediately terminated if they express any discomfort. Patients who know they are claustrophobic are excluded from the study. Patients are assisted in exiting from the MRI gantry, to prevent a possible stumble/fall. To prevent accidental entry of metallic objects into the imaging room/magnetic field during an MR imaging session, there are large warning signs and loose-link plastic chain across entrance to the area of higher field strength. A certified MR technologist is present at all times, and guards against visitors or others who could unknowingly pose a metal risk. Although there are no known adverse effects for exposure to the magnetic field of the MRI studies (people have been exposed to much higher fields for longer times without harm), we will record exposure time and the exposure characteristics. These will be kept on file with a copy of the MRI Screening form at the MRI Imaging Facility of the Radiology Department of the University of Pennsylvania, Philadelphia, Pennsylvania.

Confidentiality: Following completion of an imaging session, the raw data will immediately be transferred to electronic storage by the nuclear medicine/MR technician for later processing. This storage is in a locked room with access limited to the investigators and data processors. Subjective and physiological data are likewise kept in a locked area accessible only to the investigators/data processors. No published or presented materials will identify patients by names, initials, or any other means that could be used to identify the participant. If you screen positive for HIV the lab is required to report this to health agencies such as the Department of Health.

As part of consent procedures, patients will be advised of precautions taken to preserve confidentiality. Further, all participants in the data collection procedures have been instructed to not divulge any information concerning patients to any person or agency without the written and explicit consent of the patients. These procedures have been effective in completely protecting patient information in past studies. All study staff receive Good Clinic Practice and Human Subjects Protection training as well as HIPAA privacy training before working with any patients.

All medical records and research information will be kept confidential. Additionally, a Certificate of Confidentiality will be obtained from the Department of Health and Human Services to help insure patient's privacy. This certificate helps researchers protect the privacy of patients in biomedical, behavioral, and clinical or other research projects against compulsory legal demands (e. g. court orders and subpoenas) that seek the names or other identifying characteristics of research subjects. Medical records, and research data may only be accessed by staff engaged in the research project or clinical care of the patients, or by representatives of the National Institute on Drug Abuse, the Food and Drug Administration, or other government agencies as required

and permitted by law.

No one other than study staff will have access to the genetic sample blood, and it will not be stored after the study, without patient's specific permission. The genetic testing laboratory will not have access to patients name, and all information will be stored in restricted areas and locked cabinets. A unique genetic number only on the computerized database will identify patients. As part of consent procedures, patients will be advised of the precautions taken to preserve confidentiality.

DNA samples will be stored in the laboratory of the study geneticist, Wade Berrettini, M.D., Ph.D. at the University of Pennsylvania. Access to stored samples will be limited to approval by Dr. Anna Rose Childress (215-222-3200) or her designee. Future studies involving stored DNA samples must receive University of Pennsylvania approval and will be limited to studies related to addictions. DNA samples will not become part of the clinical record and will not be made available for commercial use.

Craving It is our practice for a trained clinician, often the PI, to be available in case the patient is still experiencing any continued arousal or discomfort, either from the cues or for any other reason, at the end of the scan. If the patient is still aroused, the clinician has a number of psychological strategies (deep relaxation; imagery, distraction, consequences tool, etc.) that can quickly help the patient inhibit craving, feeling more comfortable and back in control of her/his feelings. Taking these precautions not only increases the patients' comfort but their safety: it reduces the likelihood that they would abruptly discharge themselves from the residential setting before completing treatment. It is a testament to the effectiveness of this precaution that, after testing more than a hundred patients, most as inpatients, no patient has ever left in connection with a drug-related cue exposure session. We have demonstrated that even outpatient cue sessions, when handled with our precautions, do not lead to an increase in drug use in the week subsequent to the scan (compared to baseline).

Blood draw: The doctors and nurses at the Center for the Studies of Addictions Treatment Research Clinic are very experienced at drawing blood without any problems.

Protections are in place to minimize even the small risks that exist. Patients have twice-weekly appointments during the study and once weekly visits during follow-up where study staff will check to see if there are any problems.

Since Aldermes will be providing Vivitrol (depot naltrexone) medication for the prescription opiate part of this protocol, they asked that we add the following statement to this protocol:. "If SAEs for the Vivitrol are assessed as unrelated to Vivitrol, they may be summarized on the required Quarterly Study Report that is submitted to Alkermes. If an SAE in the Vivitrol treated cohort is deemed to be a SUSAR (i.e. Serious, unexpected and is assessed as at least possibly related to Vivitrol), it should be reported to the FDA within required reporting timelines, as well as copied to Alkermes Drug Safety at the time of FDA submission. Such expedited reports may be submitted by fax to: (617) 494-5202 or by email to drsafety@alkermes.com"

Pilot Studies Risks for just tasks:

Confidentiality: There is a potential risk for a loss of confidentiality in any research participation. Because our patients carry a substance abuse diagnosis, this is a risk we take especially seriously.

Time, Embarrassment and Anxiety: Participants will have to take the time to come to the clinic. Some of the questions about personal and sexual habits, lifestyle, and drug and alcohol use may embarrass them.

Pilot Studies Risks for those who agree to do fMRI:

Magnetic Fields (MRI): There are no known adverse health effects as a result of exposure to the magnetic fields. The primary risk of MRI is the possibility of undisclosed metal in the patient's body (pins, pacemakers, metal fragments in the eye) that could become dislodged by the magnet. Some patients (10-15%) may experience

unexpected claustrophobia when entering the magnet bore, or may notice the change in magnetic field upon entering or leaving the bore. The 3.0 Tesla Siemens magnet to be used in the proposed study is an FDA-approved device for standard clinical use. Its specifications (including the specific pulse sequences used for each protocol) meet all the stringent safety requirements of the regulatory bodies within and outside the University.

Confidentiality: There is a potential risk for a loss of confidentiality in any research participation. Because our patients carry a substance abuse diagnosis, this is a risk we take especially seriously.

Time, Embarrassment and Anxiety: Participants will have to take the time to come to the clinic. Some of the questions about personal and sexual habits, lifestyle, and drug and alcohol use may embarrass them. Waiting for an HIV screen results or lab results that confirm a positive screen may make participants feel anxious if they decided to be tested.

Craving: Viewing drug-related cues can sometimes trigger drug-related craving and arousal in patients with a drug-use history. This craving may cause some arousal, but it does not pose a medical risk.

Blood draw: The risk of drawing blood is very small, but includes minor pain, skin bruising, bleeding from where the needle goes in, or anxiety about needles. These risks are the same as for a standard blood test.

Magnetic Fields (MRI): Patients are carefully screened by our staff and again by the MRI Center staff for any metal that could pose a danger, and the importance of this screening is repeatedly emphasized. Patients are warned of possible claustrophobia in the consent form, and the session is immediately terminated if they express any discomfort. Patients who know they are claustrophobic are excluded from the study. Patients are assisted in exiting from the MRI gantry, to prevent a possible stumble/fall. To prevent accidental entry of metallic objects into the imaging room/magnetic field during an MR imaging session, there are large warning signs and loose- link plastic chain across entrance to the area of higher field strength. A certified MR technologist is present at all times, and guards against visitors or others who could unknowingly pose a metal risk. Although there are no known adverse effects for exposure to the magnetic field of the MRI studies (people have been exposed to much higher fields for longer times without harm), we will record exposure time and the exposure characteristics. These will be kept on file with a copy of the MRI Screening form at the MRI Imaging Facility of the Radiology Department of the University of Pennsylvania, Philadelphia, Pennsylvania.

Confidentiality: Following completion of an imaging session, the raw data will immediately be transferred to electronic storage by the nuclear medicine/MR technician for later processing. This storage is in a locked room with access limited to the investigators and data processors. Subjective and physiological data are likewise kept in a locked area accessible only to the investigators/data processors. No published or presented materials will identify patients by names, initials, or any other means that could be used to identify the participant. If you screen positive for HIV the lab is required to report this to health agencies such as the Department of Health. As part of consent procedures, patients will be advised of precautions taken to preserve confidentiality. Further, all participants in the data collection procedures have been instructed to not divulge any information concerning patients to any person or agency without the written and explicit consent of the patients. These procedures have been effective in completely protecting patient information in past studies. All study staff receive Good Clinic Practice and Human Subjects Protection training as well as HIPAA privacy training before working with any patients. All medical records and research information will be kept confidential. Additionally, a Certificate of Confidentiality will be obtained from the Department of Health and Human Services to help insure patient's privacy. This certificate helps researchers protect the privacy of patients in biomedical, behavioral, and clinical or other research projects against compulsory legal demands (e. g. court orders and subpoenas) that seek the names or other identifying characteristics of research subjects. Medical records, and research data may only be accessed by staff engaged in the research project or clinical care of the patients, or by representatives of the National Institute on Drug Abuse, the Food and Drug Administration, or other government agencies as required and permitted by law. No one other than study staff will have access to the genetic sample blood, and it will not be stored after the study, without patient's specific permission. The genetic testing laboratory will not have access to patients name, and all information will be stored in restricted areas and locked cabinets. A unique genetic number only on the computerized database will identify

patients. As part of consent procedures, patients will be advised of the precautions taken to preserve confidentiality. DNA samples will be stored in the laboratory of the study geneticist, Wade Berrettini, M.D., Ph.D. at the University of Pennsylvania. Access to stored samples will be limited to approval by Dr. Anna Rose Childress (215-222-3200) or her designee. Future studies involving stored DNA samples must receive University of Pennsylvania approval and will be limited to studies related to addictions. DNA samples will not become part of the clinical record and will not be made available for commercial use. Craving It is our practice for a trained clinician, often the PI, to be available in case the patient is still experiencing any continued arousal or discomfort, either from the cues or for any other reason, at the end of the scan. If the patient is still aroused, the clinician has a number of psychological strategies (deep relaxation; imagery, distraction, consequences tool, etc.) that can quickly help the patient inhibit craving, feeling more comfortable and back in control of her/his feelings. Taking these precautions not only increases the patients' comfort but their safety: it reduces the likelihood that they would abruptly discharge themselves from the residential setting before completing treatment. It is a testament to the effectiveness of this precaution that, after testing more than a hundred patients, most as inpatients, no patient has ever left in connection with a drug-related cue exposure session. We have demonstrated that even outpatient cue sessions, when handled with our precautions, do not lead to an increase in drug use in the week subsequent to the scan (compared to baseline).

Blood draw: The doctors and nurses at the Center for the Studies of Addictions Treatment Research Clinic are very experienced at drawing blood without any problems. Protections are in place to minimize even the small risks that exist. Patients have twice-weekly appointments during the study and once weekly visits during follow-up where study staff will check to see if there are any problems.

Electronic Medical Record (EMR)
Electronic Medical Record (EMR) information was added to all consents since all research fMRI scans are now entered into the EPIC system, which produces an EMR.

Potential Study Benefits
There is no direct benefit to participants. Yet, potential benefits may include an increased awareness of their response to drug-related cues and the processes underlying their dependence, the feeling of contributing to medical research, and the potential benefit from substance abuse treatment. All (Page 33 of 35) participants who participate in this research protocol will receive 12 weeks of free treatment (professional drug counseling and/or behavioral strategies for Coping with Craving, urine monitoring, linkage with social services, etc). Participants do place a value on this benefit. Though publicly funded outpatient treatment is available in the community for those without insurance coverage, the level of care and caretakers at our Center generally make it an appealing alternative. Prescription Opioid subjects will have the chance to receive depot naltrexone treatment that may help them abate their use of opiates and concomitantly reduce their use of alcohol.

Alternatives to Participation (optional)
Subjects may choose not to participate in this study. Completion of this project will not influence any other treatments that subjects are eligible for either at the VA Medical Center or the Treatment Research Center. Subjects may withdraw at any time without prejudicing their care. Other treatments in the community include self-help groups and private treatment. Subjects may discuss alternatives with their personal physician.

Data and Safety Monitoring
Principal Investigator Data Safety Monitoring Board A study monitor who is knowledgeable in the protocol, regulations, and university approved procedures for conducting and monitoring clinical investigations will be assigned to monitor the study. The monitor will be selected from one of the Study Coordinators working at the University of Pennsylvania Center for the Studies of Addictions. This individual will have direct access to investigators and physicians qualified to diagnose and treat addictions and who are experienced in medication studies. The study monitor is independent of the study and cannot be fired for any reports that are issued concerning the study. This is a low risk, single- site study involving the use of medications already approved and marketed for the treatment of other illnesses (cigarette smoking) and opiate use. This study design is straightforward and familiar to the research staff at the Treatment Research Center (TRC). Therefore, one monitor should be sufficient to complete the monitoring process.

The following documents are currently attached to this item:
There are no documents attached for this item.

Risk / Benefit Assessment
Potential benefits to society include greater knowledge regarding the neurobiology underlying cocaine, marijuana and prescription opioid dependence, relapse and the recovery path. A better understanding of the mechanisms underlying relapse and addiction will help to identify more effective treatments. The benefits to the field are considerable, as there are still no FDA approved medications or other interventions for cocaine, marijuana or prescription opiate dependence. General knowledge from this study will identify brain regions that have inhibitory deficits or are powerfully activated by drug reward cues; this will greatly aid in development of ever-more-effective behavioral and pharmacologic interventions to treat these brain vulnerabilities, targeting the high rate of relapse in cocaine dependence. This study will also enable a systematic assessment of the brain at baseline, characterizing vulnerabilities that are still without effective treatment. The anticipated contributions to drug addiction research, and thus to future addiction treatment, can thus be substantial. The risk is low in relationship to the benefit for society.

The risks of developing new tasks that test constructs that may be relevant to treatment and relapse prevention in addiction in order to compliment and expand the probes and tasks now being used to determine differential activation in a priori regions of interest to selected reward and inhibition probes as part of our primary studies aim is minimal. These participants will view new tasks off magnet and if they agree on-magnet during an fMRI as well. The subject's participation in the pilot studies will involve approximately 2 to 4 visits at the most. There will be a consent visit that includes assessments and the off-magnet task/rating, a second visit for the Wait to See

task participants, and then an fMRI visit for all who agree to do fMRI. For the Extinction participants 2 additional fMRI scans will be scheduled for participants willing to participate in this pilot piece. Overall the risks are the same or less for those participating in the pilot studies as they can decide not to do the FMRI part of the study and there is no medications involved.