University of Pennsylvania

Annual Progress Report: 2010 Nonformula Grant

Reporting Period

July 1, 2011 – June 30, 2012

Nonformula Grant Overview

The University of Pennsylvania received $4,999,999 in new nonformula funds for the grant award period June 1, 2011 through May 31, 2015.

Research Project: Project Title and Purpose

CURE Addiction Center of Excellence: Brain Mechanisms of Relapse and Recovery -- The overall goal of the proposed project is to develop an understanding of the biological mechanisms of relapse that may be common across drugs of abuse – knowledge that is lacking, but critical for changing the harsh relapse statistics for addiction (up to 80% of treated individuals have relapsed by 6 months following treatment). The expected scientific yield is a brain-based understanding of relapse vulnerability that will enable targeted, novel (medication and behavioral) interventions to improve the health of addicted Pennsylvanians, save billions in addiction-related costs, and offer new hope for recovery to all those afflicted with these painful disorders.

Anticipated Duration of Project


Project Overview

Understanding the biological mechanisms of relapse shared by drugs of abuse is the over-arching goal of our CURE project. The expected scientific yield is a brain-based understanding of relapse vulnerability that can permanently alter the harsh relapse statistics for addiction enabling sustained recovery for millions.

Our over-arching hypothesis is that addicted individuals differ from the non-addicted in two ways that could fuel relapse: 1) their limbic reward circuitry (e.g., interconnected amygdala, ventral striatum/pallidum, medial orbitofrontal cortex, insula) “over-responds” to signals for drug, while their 2) prefrontal inhibitory circuitry (e.g., lateral orbitofrontal cortex, supragenual anterior cingulate) often “under-responds” when challenged to inhibit reward impulses (“bad brain brakes”). However, the relationship of these brain differences, or “biomarkers”, to actual drug use during treatment, and to relapse following treatment, needs to be determined. An adequate study requires both the scale (more than one population/treatment, to permit generalizability) and the multi-disciplinary expertise (in brain imaging, in behavioral probes, and
in addiction treatment research) enabled by a Center-level effort. Our project will be the first scaled effort to link brain measures and drug use.

Toward this goal, the CURE Addiction Treatment Center of Excellence will use functional magnetic resonance imaging (fMRI) and specific probes of reward and inhibition as biomarkers predicting drug use during (Aim 1) and after (Aim 2) treatment in 216 patients addicted to cocaine (Component 1), marijuana (Component 2), and prescription opioids (Component 3). Participants will be scanned before, during, and after a 12-week active treatment specific to each of these drugs of abuse. The brain fMRI measures will be correlated with the primary clinical marker of drug use (urine drug screen, UDS) during the treatment and follow-up phase. Exploratory Aim 3 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. Aim 4 will offer mentored research internships to Lincoln University undergraduates selected for their interest in health science and addiction research.

The project reflects an integrated collaborative effort between the University of Pennsylvania School of Medicine, the Philadelphia Department of Veteran’s Affairs Medical Center, Lincoln University, and community addiction treatment organizations, with guidance from (internal and external) Scientific Advisors and from Community Advisors in organizations supporting the recovery of addicted individuals (e.g., The Philadelphia Alliance, PROACT, PeerStar, and the Kirkbride Center).

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Expected Research Outcomes and Benefits

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, even in structure - 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, 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 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.

Summary of Research Completed

This year constitutes the start-up phase of our project, including: submission and approval of IRB protocols, development of new cues for use as probes in the MRI tasks, refinement of tasks and instruments, initiation of study enrollment, and preliminary examination of fMRI data (to check for artifacts, acceptable signal-to-noise ratios, and evidence of brain responses in a priori regions of interest).

Project Milestones
Our Project Milestones for the FY 2011 reporting period were to enroll 36 individuals into the CURE project (across Components 1-3); to begin imaging analyses; to submit two abstracts to professional conferences, and to mentor two interns in summer 2011 (Aim 4). As outlined below, we have met or exceeded each of these Project Milestones:
**Enrollment:** We have enrolled 39 individuals in the project, modestly exceeding the goal of 36 enrollees in the start-up year. These individuals are well-distributed across the three Components, and the recruitment success reflects an effective multi-modal effort: advertisements in newspapers, on the radio, on the web, and personal contacts with community treatment facilities, including those represented by our Community Advisors.

**Preliminary imaging analyses:** Our imaging data are usually quality-checked and pre-processed within 24-48 hours after acquisition, allowing detection of artifacts (due to subject movement or equipment problems), and preliminary assessment of whether a selected brain probe is producing sufficient signal (proportionate to the noise inherent in the scanning situation). We have thus far acquired 49 scanning sessions (across 39 enrollees), with data loss (due to movement artifact or equipment malfunction) remaining low, in the expected 10% range.

Very encouragingly, preliminary “proof of probe” analyses from our baseline data already demonstrate that one of our important novel reward probes (the ultra-brief, “unseen” drug cues) is indeed capable of activating limbic reward circuitry in patients with marijuana-dependence or prescription opioid dependence. Though we had previously established this “unseen” capability for cocaine cues (Childress et al PLoS One, 2008; [http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0001506](http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0001506)), we needed to demonstrate efficacy of the paradigm and our newly created cues for the new CURE cohorts. As relapse predictors, “unseen” cues have some special advantages over visible drug cues. Because the cues ( ultra-brief 33 msec pictures) remain outside awareness, the brain response to “unseen” drug cues is not contaminated by social desirability, embarrassment, guilt, shame, or other effects that depend on conscious processing; the responses instead reflect “pure” reward processing at the subcortical level. As shown in our original CURE proposal, the brain response to “unseen” cocaine cues predicts relapse. Details for our “unseen” cue paradigms are offered below, in Research Accomplishments, and illustrations of these findings are shown in Figures 2 and 3.

**Abstracts submitted to professional conferences:** We have exceeded the FY 2011 milestone of two CURE-relevant abstracts submitted to professional conferences. Our team has submitted 4 CURE-relevant abstracts. All four abstracts have been accepted; two were presented at the College on Problems of Drug Dependence in June 2012, and two will be presented at the Society for Neuroscience in October 2012. Two of these abstracts (Lam, et al.) feature development of analytic techniques (wavelet transform analysis; multivariate discriminant analysis) that will be applied to our CURE imaging datasets with the goal of characterizing successful outcome (low relapse v. high relapse) phenotypes. Two abstracts (Young, et al.) highlight one of our CURE Pilot tasks, a reward probe known as the “baby schema” task. Though addicted individuals have a strong brain response to drug cues, the response to natural rewards such as infant faces (“baby schema”) may be impaired – and may be associated with relapse/poor clinical outcome. Drs. Lam and Young are new Post-doctoral Fellows who are contributing to the project; the use of imaging probes to predict relapse synergizes with their career goal of translational research in addiction. Engaging these promising Post-doctoral Fellows in the CURE project also fulfills our project goal of developing the next generation of addiction researchers for the Commonwealth, and for our nation.


**Minority Intern Training:** We met our Minority Intern Training (Aim 4) milestone for Year 1, selecting two Lincoln undergraduates for a research experience in our laboratories in summer 2011. Our Training Directors (Dr. James Cornish and Sabrina Poole) worked with Dr. Patricia Joseph, our collaborator at Lincoln, in the early spring of 2011, with the goal of selecting two candidates with an interest in health sciences research, including addiction. Two excellent candidates, Sabrina Smalls and Kori DeVaughn, were selected on the basis of their academic achievement, teacher recommendations, and personal essays describing their motivation for the internship. Our two candidates arrived in June, and enthusiastically interacted with mentors in the lab and within the umbrella Minority Training Program at our Center. The interns’ research projects utilized a large dataset characterizing HIV sexual risk behaviors in young urban women (collaborative with Dr. Anne Teitelman in the School of Nursing, also an Internal Advisor to the CURE). In the course of the mentored internship, both trainees learned to probe the dataset (e.g., querying whether drug use would be associated with increase in unprotected sexual behavior), to express their findings in graphical form, and to create a scientific presentation (offered to peers and mentors).

**Brief summary of research accomplishments for FY 2011 (start-up year):**

1. **Strengthening win-win-win connections with community treatment facilities.** Opioid-dependent patients entering CURE Component 3 must be opioid-free in order to receive the naltrexone depot intervention (otherwise the naltrexone injection would precipitate withdrawal). Achieving an opioid-free state through outpatient detox consumes a great deal of physician time and energy, so one critical accomplishment has been establishing close connections with several community inpatient facilities. These connections offer the community providers the option of a referral for depot naltrexone -- and they offer drug-free opiate patients a valuable recovery resource (though FDA-approved, depot naltrexone is expensive and not yet widely available), while simultaneously enhancing scientific progress for the project. Our CURE connection with the community has been a true “win-win-win”.
2. Developing drug-related cues for our new CURE populations. Matching of visual cues to the individual’s “conditioning” history (reminders of the drug, and the way it is used) is a critical factor in creating an effective cue paradigm. Though we had a variety of cocaine cues on hand, we needed to carefully create visual cues for our new CURE cohorts of MJ smokers and prescription opioid users. This presented significant challenges, as both these cohorts use their preferred drug in a variety of ways (e.g., opiate pills can be swallowed, but can also be crushed for snorting, smoking or injecting; marijuana can be smoked from joints, ‘blunts’, bongs; please see Figure 1). We successfully developed the multiple sets of cues required by our paradigm, and they are proving effective probes for the brain reward circuitry.

3. Demonstrating preliminary brain efficacy (“proof of probe”) for our new drug cues. To determine whether our newly-developed cues were effective probes for the limbic reward circuitry, we presented these stimuli for passive viewing in a fast event-related BOLD (Blood Oxygen-Level-Dependent) fMRI paradigm. 24 unique stimuli in each of 4 cue categories (drug, neutral, aversive, and sexual) were presented in randomized order, and repeated. The “target” stimuli were 33 msec in duration; each target was immediately followed by a neutral picture of 467–466 msec. Under these conditions, the 33 msec targets remain outside awareness: “unseen”. Image acquisition parameters: 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° were acquired on a Siemens 3T scanner. Image preprocessing and statistical analysis. After slice-timing correction of the images, statistical mapping software (SPM8) was used for image realignment, smoothing with a 3-D 9mm isotropic Gaussian kernel, and normalization into the Montreal Neurological Institute 152 averaged template. The General Linear Model with a canonical HRF as the basis function was used for pre-planned contrasts (e.g., drug vs. neutral cues). Parametric maps thresholded for examining our a priori reward regions (e.g., amygdala, ventral striatum, insula, medial orbitofrontal cortex) showed that both the marijuana (see Figure 2) and prescription opioid (see Figure 3) cues are likely to be effective probes for activating limbic reward circuitry in our CURE projects. This preliminary finding is very encouraging for our project to use the brain response to drug reward cues as a predictor for relapse/drug use outcome. Preliminary analyses of our other (reward and inhibition) probes are ongoing.

4. Developing additional novel relapse probes through our CURE Pilot program. As a final note, our CURE Pilot program has met with a strong positive response. Both junior investigators and post-doctoral Fellows are piloting measures and tasks (e.g., affect regulation; “loss of cognitive control” in real-time fMRI) that may have promise as future relapse-predictors in addiction – the over-arching goal of our project. These measures are considered “exploratory” or “pilot”, as they complement the primary measures in Aims 1 and 2, and promise to enhance the scientific yield of our primary Aims 1 and 2, but they are generally in earlier stages of testing and development. Importantly, these measures and tasks enable young investigators to gather data that can be used to leverage relapse-relevant external funding that will sustain the scientific efforts beyond 2015 – an important goal of the CURE.
Figure 1. As described in the text, one of the clear challenges for developing cue probes in both the opioid and marijuana studies is the wide variety of paraphernalia used for taking the drug of choice. To be effective, each cue set should represent the several drug-administration modalities. Examples of cues for these wide-ranging modalities are shown to the right. From left to right: Glass pipe and lighter, Caucasian male smoking a bong, a blunt (cigar emptied of its contents and filled with MJ) held by African American male, MJ and rolling papers, preparing a blunt, half-smoked lit joint, close-up of MJ buds, lighting a bong, Caucasian female smoking a blunt.
Figure 2. The amygdala, a region that rapidly processes environmental stimuli and assigns hedonic value, was strongly activated by 33 msec MJ cues, even when presented entirely outside awareness (n=5; p<0.05). Limbic (e.g., amygdala, insula, medial orbitofrontal cortex) activation by “unseen” MJ cues may represent relapse vulnerability, thus a treatment target -- and a relapse predictor. CURE Component 2 will also assess the impact of the GABA B agonist, baclofen (v. placebo) on the brain response to drug reward cues.
Figure 3. “Unseen” 33 msec prescription opioid cues (vs. neutral cues) also had a widespread impact on the brain, supporting the promise of these cues as an effective reward probe for CURE Component 3. Encouragingly, the brain response to the unseen cues showed a good inter-subject range – this will allow us to test the utility of this sensitive brain probe as a relapse predictor. The individual brain response shown below was one of the strongest observed, and involved a number of reward-relevant regions (bilateral amygdala, striatum, insula, etc.), as well as some frontal cortical regions (medial prefrontal cortex; dorsal anterior cingulate) that are commonly activated in response to conscious drug cues. This latter finding suggests an overlap, and a possible continuity, between the brain responses to drug cues “inside” and “outside” awareness.