University of Pennsylvania

Annual Progress Report: 2010 Nonformula Grant

Reporting Period

July 1, 2013 – June 30, 2014

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

6/1/2011 – 5/31/2015

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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Other Participating Researchers

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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

Our CURE Addiction Center of Excellence remains on pace, and is showing continued progress toward characterizing the brain-behavioral vulnerabilities that may predict relapse in addiction.

Project Milestones
Our Project Milestones for the FY 2013 reporting period were to: 1) Enroll 72 individuals; 2) continue imaging analyses; 3) continue outcome analyses, 4) submit two abstracts to professional conferences; 5) use data from CURE in preparation of at least one proposal for external funding. 6) mentor two interns, summer 2013.
As outlined below, we have made excellent progress on the Year 3 *Project Milestones.*

Milestone 1: Enrollment. Study enrollment continues apace: as of this report, we have now enrolled 173 individuals in the CURE project, out of the 180 projected for the current end-of-Year 3 timepoint (> 96%). *Table 1* (at the end of the narrative report) shows the distribution and demographics for the first 170 CURE enrollees.

Milestones 2) and 3) – continued imaging (brain-behavioral) analyses, and preliminary outcome analyses: Analyses are ongoing across our probes, and we have begun preliminary examinations for candidate relapse predictors, the over-arching aim of the CURE. Below we highlight six new findings from the past year; *additional detail is provided in the Figures and captions following the narrative report:*

- *Outcome prediction* ***(Figure 1):*** In **cocaine-addicted** individuals (Component 1), the brain response to visible drug cues can predict "success" in establishing early abstinence following inpatient discharge.
- *Outcome prediction* ***(Figure 2):*** In **opioid-addicted** individuals (Component 3), the brain response to drug visible cues can predict compliance: which patients will return for additional naltrexone depot injections.
- *Brain mechanism of medication action* ***(Figure 3):*** Baclofen (Component 2) reduces resting perfusion in the motivational regions of **cannabis-addicted** individuals; this action may underlie future clinical benefits.
- *Structural brain differences* ***(Figure 4):*** As many **cannabis-addicted** individuals (Component 2) also smoke tobacco, previous structural MRI studies in cannabis patients may have been confounded; this potential confound can be addressed by using informative comparison groups.
- *Affect Dysregulation as a potential relapse vulnerability* ***(Figure 5):*** As compared to demographically similar healthy controls, **cocaine-addicted** individuals show poor affect regulation (Pilot Task), and reduced functional connectivity between the amygdala and a regulatory region, the dorsal prefrontal cortex (PFC).
- *Poor inhibition as a potential relapse vulnerability* ***(Figure 6):*** As compared to demographically similar healthy controls, **cocaine-addicted** individuals (Component 2) have more errors at the easiest level of our "Spiders-No-Puppies-Go!" task.

Milestone 4: Abstracts submitted to professional conferences. We have far exceeded the FY 2013 milestone of two CURE-relevant abstracts submitted to professional conferences, presenting 12 scientific abstracts. Two peer-reviewed manuscripts have been published, and five are under review.

Abstracts (July 1, 2013 – June 30, 2014)

Childress, A.R., Li, Y., Goldman, M., Suh, J.J., Singer, Z., Ehrman, R., Franklin, T.R., Langleben, D.D., Young, K.A., Wetherill, R., Gawrysiak, M., and O'Brien, C.P. How does the brain "put on the brakes" in addiction? Modeling inhibition of a pre-potent response to affect-positive stimuli. *Society for Neuroscience Annual Meeting, San Diego, CA.* November, 2013.

Wang, Z. Suh, J., Li, Y., Singer, Z., Ehrman, R., Hole, A.V., Frankling, T. , O'Brien, C.P. and Childress, A.R. Limbic resting brain entropy predicts drug dependence and risk-taking behavior in cocaine-addicted brain. *Society for Neuroscience Annual Meeting, San Diego, CA.* November, 2013.

Childress AR, Young K, Franklin TR, Jagganathan K, Li Y, Suh J, Ehrman R, Wang Z, Monge Z, Singer Z, Langleben D, O'Brien CP. Trouble waiting to happen? Heightened striatal resting perfusion in cocaine patients predicts limbic vulnerability to drug cues. *American*

College of Neuropsychopharmacology Annual Meeting, Hollywood, Florida. December 9, 2013.

Franklin TR, Jagannathan K, Wetherill RR, Bender J, Johnson B, Mumma J, Kampman K, O'Brien CP, Childress AR. Modulation of resting brain cerebral blood flow by the GABA B agonist, Baclofen: A longitudinal perfusion fMRI study in marijuana dependent treatment seeking individuals. *American College of Neuropsychopharmacology Annual Meeting, Hollywood, Florida.* December 9, 2013.

Young K, Franklin TR, Yi Y, Jaggannathan K, Wetherill RR, Suh J, Singer Z, Davidson S, Monge Z, O'Brien CP, Childress AR. Baclofen reduces resting blood flow, and correlations with limbic cue reactivity, in the ventral striatum of cocaine-dependent men. *American College of Neuropsychopharmacology Annual Meeting, Hollywood, Florida.* December 9, 2013.

Childress AR, Suh J, Jagannathan K, Young KA, Franklin TR, Ehrman R, Monge Z, Langleben D, Kampman KM, Wetherill RR, Gawrysiak MJ, O'Brien CP. "Destined for success? Brain responses during drug cue exposure foretell clinical outcome in cocaine patients" *College on Problems of Drug Dependence, San Juan, Puerto Rico CPDD.* June 18, 2014.

Langleben D, Dowd E, Jagannathan K, Suh J, Kampman KM, Wang A, O'Brien CP, Childress AR. Prefrontal and striatal fMRI response predicts adherence to injectable extended-release naltrexone in opioid dependence. *College on Problems of Drug Dependence, San Juan Puerto Rico.* June 18, 2014.

Monge ZA, Jagannathan K, Suh J, Ehrman R, Young KA, Franklin TR, Langleben D,O'Brien CP, Childress AR. Can we use cue-related brain responses to predict which cocaine patients will take more risks?" *College on Problems of Drug Dependence, San Juan, Puerto Rico* June 17, 2014.

Suh J, Ehrman R, Goldman M, Singer Z, Franklin TR, Marquez K, O'Brien CP, and Childress AR. Poorer pre-potent response inhibition in cocaine-dependent patients vs. healthy controls during an affect-congruent Go-NoGo task. *College on Problems of Drug Dependence, San Juan Puerto.* June 18, 2014.

Wang Ze, Suh J, Monge ZA, O'Brien CP, Childress AR. A hyper-connected and resilient small-world network in the cocaine-dependent brain. *College on Problems of Drug Dependence, San Juan, Puerto Rico.* June 17, 2014.

Wetherill RR, Jagannathan K, Mumma J, Johnson B, Rao H, Childress AR, and Franklin TR. Effects of
cannabis and cigarette smoking on gray matter volume: A voxel-based morphometry study. *College on Problems of Drug Dependence, San Juan, Puerto Rico.* June 17, 2014.

Milestone 5: Use CURE data in preparation of at least one application for external grant funding. We have greatly exceeded Milestone 5, using CURE data as pilot/preliminary data in 14 grant applications across the past FY. Seven of these 14 have either been funded or are expected to receive funding.

Funded/Funding expected:

1) Suh, JJ. VA VISN4 Competitive Pilot Project Fund: Using Brain-Behavioral Markers to Predict Clinical Outcome in Veterans with Co-occurring Alcohol Use Disorders and Post-Traumatic Stress Disorder Symptoms. (Funded 2013-2015).

2) Childress, A. R. and Lowe, M. (Co-PIs) NIH/NIMH Weight History, Brain Activation to Food Cues and Eating Disorder Psychopathology. Funded April 4, 2014. [Preliminary data from both the reward and Go-NoGo probes were used in the application].
3) Wetherill and Franklin, Co-PIs (Foundation for Alcoholism Research; $17,000) Baclofen for Alcohol Dependence. Funded July 2, 2014. [Experience with drug reward cues and with baclofen cited in Prelim Data].
4) Wang, Z. NIH/NIDA R56 Imaging data re-analysis for cocaine addiction study. R56 is a one-year mechanism that will supported gender-related re-analysis of the functional connectome in existing addiction datasets. Funding expected fall 2014. [CURE provided preliminary data].
5) Kampman, KM. NIH/NIDA U54 Cocaine Cooperative Medication Development Center. Submitted August 2013; April 25, 2014. Dr. Childress is PI for Project 2, Brain-behavioral targets in cocaine medication development. Funding expected late fall 2014. [CURE cocaine data were used in Preliminary Data for this project].
6) Wetherill RR. NIH/NIAAA R21: Brain Mechanisms of Topiramate's Effects on Heavy Drinking. Submitted 10-5-2013. Funding expected fall 2014. [experience in cue-reactivity from CURE used in Preliminary Data for the grant]. .
7) Wetherill, RR. NIH/NIAAA R21AA02303301: Neural and Behavioral Mechanisms of Extended-Release Baclofen in Alcoholism. Submitted 2-5-2014. Funding expected fall 2014. [CURE experience in cue-reactivity, and with baclofen, used in Preliminary Data for the grant].

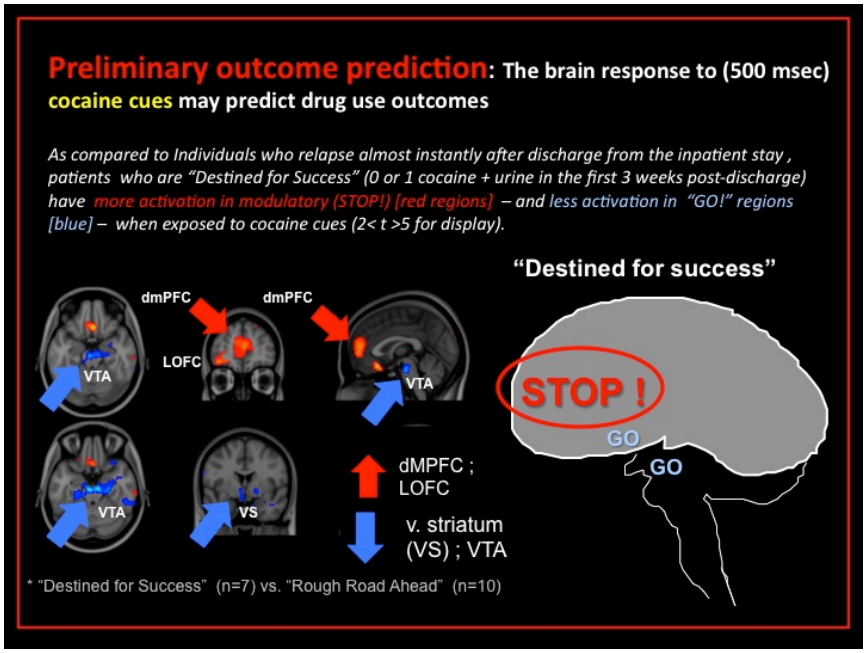
Milestone 6: Minority Intern Training: We met our Minority Intern Training (Aim 4) milestone for Year 3 of the CURE, selecting two Lincoln undergraduates, Ms. Shakeema Jones and Ms. Tierra Hill, to work in our research laboratories in summer 2013. The two interns received guidance from Drs. Joseph and Wadley (from Lincoln), from the program co-directors at Penn: Dr. James Cornish, Sabrina Poole, and Tamara Boney, and especially from Zach Monge, a Research Assistant who provided direct day-to-day mentoring. Shakeema and Tierra gave well-received oral presentations on their work at the end of the internship.

Table 1. Characteristics of enrolled participants at screening

	All n = 170*	Cocaine n = 49	Marijuana n = 59	Opiate n = 63
Race				
Caucasian	60	4	8	48
African American	97	45	43	9
Other	13	0	7	6
Gender				
Male	124	39	41	44
Female	46	10	17	19
Mean (± SEM)				
Age (yrs)	35.6 (0.9)	47.4 (2.0)	31.0 (1.4)	28.3 (1.3)
Education (yrs)	13.1 (1.9)	12.4 (0.3)	13.2 (0.2)	13.7 (0.3)
Years of use	14.3 (0.8)	20.9 (1.6)	16.9 (1.2)	5.0 (1.3)
Days of use past 30	20.6 (0.7)	18.7 (1.3)	26.5 (1.0)	16.7 (1.4)
Prior Treatments	1.9 (0.2)	2.9 (0.4)	0.2 (0.3)	2.5 (0.2)

* **Table 1** (left) describes demographics for the first 170 enrolled participants in the CURE. At this report, we have enrolled 173 participants (96% of the cumulative goal). Demographics reflect the known epidemiology of the disorders: for example, though prescription opiate patients have a short (5 yr.) drug use history, their severe addiction leads to treatment contacts -- they have nearly as many prior treatments as the much older cocaine cohort (20 yr. drug use history).

Figure 1 (right). As compared to individuals who relapse almost immediately after discharge from the inpatient stay, cocaine patients who demonstrate early abstinence (0 or 1 cocaine + urine in the first 3 outpatient weeks, "Destined for Success") show a predicted pattern of **increased** activation in modulatory (STOP!) regions (in red) – and **less** activation in GO! regions (in blue), during exposure to visible cocaine cues (brain t-map images thresholded 2<t<5, for display).



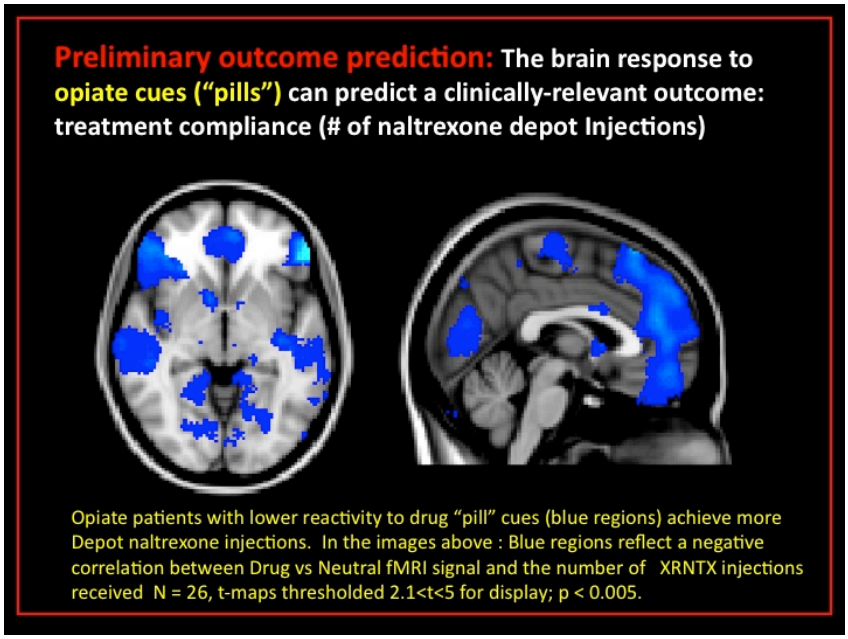
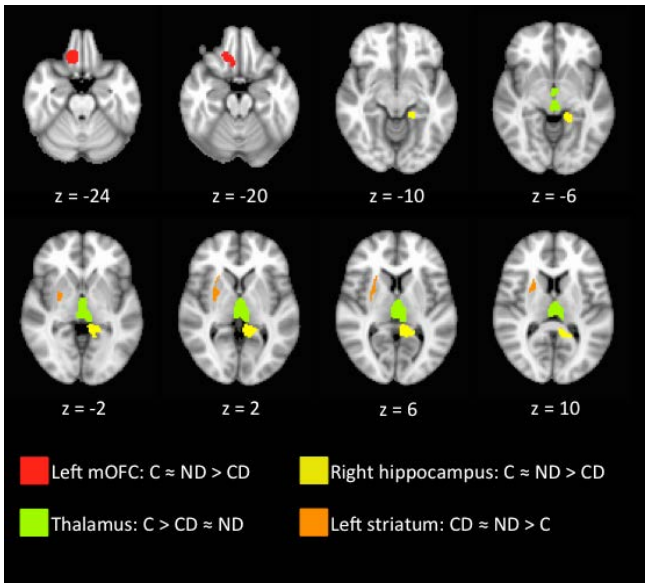


Figure 2 (left). Opioid-addicted individuals (n=26) with **lower reactivity to drug ("pills) cues** in several motivationally-relevant brain regions achieve **more** Depot naltrexone injections – an index of treatment compliance and an important clinical outcome. Images on the left depict an inverse correlation between several brain regions (in blue, e.g., ventral striatum, mOFC, ant. insula) and number of injections. (brain t-map images thresholded 2.1 <t<5, for display).



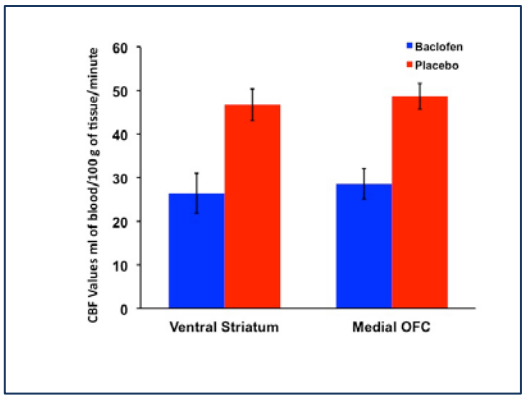


Figure 3 (above). Baclofen (20 mg qid) reduces resting perfusion (CBF) in motivation-relevant regions (VS and MOFC) of cannabis patients, a mechanism of action that may relate to its potential clinical outcome benefits.

Figure 4 (above). Differences in brain gray matter volumes (GMVs) when comparing CD, cannabis – dependent (n=26); ND, nicotine-dependent (n=26); and C, healthy controls (n=26) using voxel-based morphometry (VBM) with SPM 8. Differences between groups are superimposed on one representative brain image. CDs showed reduced gray matter volume (GMV) in the orbitofrontal cortex (mOFC) and greater GMV in the hippocampus (HIPP) compared to Cs and NDs. CDs and NDs showed reduced GMV in the thalamus and greater GMV in the striatum (putamen) compared to Cs. (All clusters significant at $p < 0.001$, FWE cluster-corrected $p < 0.05$). These findings highlight the importance of careful comparison groups for studying substance users who also smoke cigarettes – and they add to a growing literature on the effects of cannabis use for brain regions involved in memory (HIPP), reward valuation (OFC), and salience (striatum).

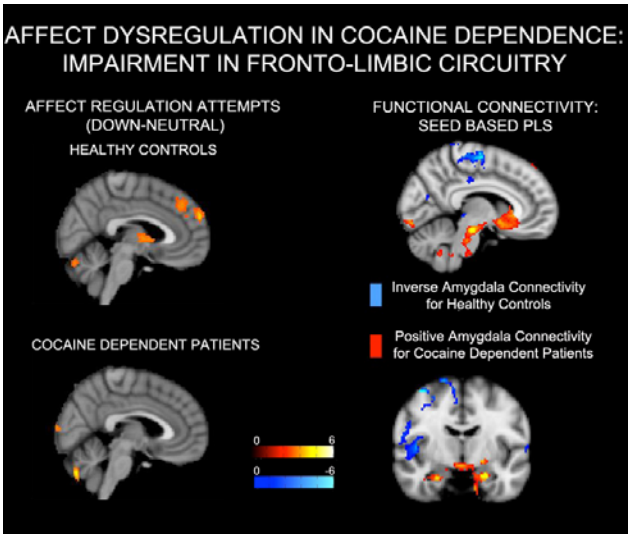


Figure 5 (above). As compared to demographically-similar controls (n=25), cocaine-addicted individuals (n=16) have both reduced ability to inhibit negative affect (not shown), and poor inverse connectivity between a modulatory region (e.g., dorsal PFC) and the downstream amygdala during attempts to regulate arousal to aversive visual stimuli.

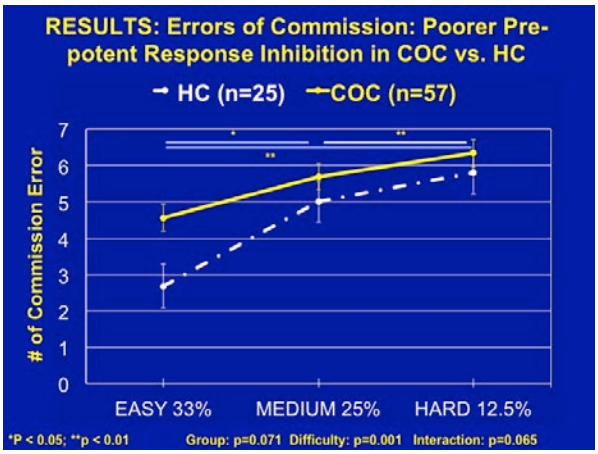


Figure 6 (above). As compared to demographically – similar controls (n=25), a multi-study cohort of cocaine patients (n=57; 32 from CURE) demonstrate failed inhibition (more errors of commission) in the "Easy" condition of the "Spiders-No, Puppies-Go" Affect-Congruent Go-NoGo task. Poor inhibition in this task may be an index of relapse vulnerability, and can be tested as a stand-alone predictor of relapse.