NEURAL DYSFUNCTION DURING DECISION-MAKING AS A

PREDICTOR OF COCAINE RELAPSE

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The University of Texas Southwestern Medical Center, 2012

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Cocaine dependence is a costly disorder characterized by recurrent relapse events. The current investigation used functional magnetic resonance imaging (fMRI) during a decision-making task to predict relapse to drug use in a cocaine-dependent sample. Forty-five treatment-seeking cocaine-dependent subjects, two to four weeks abstinent, and 23 healthy control subjects underwent 3T fMRI. The Response Reversal Task was administered in the scanner to elicit decision-making processes. Individuals were followed for up to six months post-discharge from inpatient substance use treatment to determine time-to-relapse. Seventy-eight percent of the patient sample relapsed an average of 35 days after treatment; ten individuals did not relapse during the follow-up

period. No group differences were found between healthy control and cocaine-addicted groups in activation patterns or behavioral measures of decision-making performance. Mean percent BOLD signal change in the patient group was used to identify regions of interest (ROIs) for discriminant analyses to classify patients by short- and long-term relapse. The fMRI activation patterns in the precuneus, bilateral orbitofrontal cortex, left insula, right dorsolateral prefrontal cortex, paracingulate, left hippocampus, and bilateral amygdala correctly classified 71% of patients by short-term and long-term relapse. This investigation suggests that neuroimaging may be a valid predictor of cocaine relapse, which could allow for better individual tailoring of treatment options for improving long-term abstinence.

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BET	Brain Extraction Tool
BIS-11	Barrett Impulsivity Scale – 11
BOLD	Blood Oxygenation Level Dependent
CCQ	Cocaine Craving Questionnaire
DLPFC	Dorsolateral Prefrontal Cortex
EPI	Echo Planar Imaging
EV	Explanatory Variable
FA	Fractional Anisotropy
FEAT	FMRIB's Expert Analysis Tool
FILM	FMRIB's Improved Linear Model
FLAME	FMRIB's Local Analysis of Mixed Effects
fMRI	Functional Magnetic Resonance Imaging
FOV	Field of View
FSL	FMRIB's Software Library
LossAcq	Loss Acquisition
LossRev	Loss Reversal
MPRAGE	Magnetization Prepared RApid Gradient Echo
OFC	Orbitofrontal Cortex
PersLoss	Perseverative Loss
PersWin	Perseverative Win
rCBF	Resting Cerebral Blood Flow
RespRev	Response Reversal

ROI	Region of Interest
RRT	Response Reversal Task
SCID	Structured Clinical Interview for DSM-IV-TR
TE	Echo Time
TLFB	Timeline Follow-back
TR	Repetition Time
WCST	Wisconsin Card Sorting Test
WinAcq	Win Acquisition
WinRev	Win Reversal
WTAR	Wechsler Test of Adult Reading

SECTION ONE

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Introduction

Cocaine use is an individual and societal crisis due to its involvement in over 400,000 emergency room visits annually and its association with increased risk of cardiovascular, respiratory, neuronal, and psychiatric complications (Allred & Ewer, 1981; Dell'Osso et al., 2011; Guerot, Sanchez, Diehl, & Fagon, 2002; Han, Gfroerer, & Colliver, 2010; Kilbey, Breslau, & Andreski, 1992; Kuzenko et al., 2011; Levine et al., 1987; Majlesi, Shih, Fiesseler, Hung, & Debellonio, 2010; O'Leary & Hancox, 2010; Santucci & Rosario, 2010). Many who use cocaine encounter repetitive legal, social, and financial problems associated with its use, but continue to use despite these negative consequences. Unfortunately, substance use treatment options do not result in prolonged abstinence, with approximately 50 to 65% of stimulant-dependent individuals relapsing within a year of seeking treatment (Sinha, Garcia, Paliwal, Kreek, & Rounsaville, 2006). Relapse is a complex, multi-determined process involving psychosocial components, such as environmental context, presence of drug cues or acute stressors, mood symptoms, cravings, and personal coping resources, as well as biological and neurological components. Neurological factors affecting relapse have received less attention but are a promising venue for future research given advances in imaging techniques that allow for exploration of underlying neural processes associated with cognition related to cocaine use.

The cognitive ability to evaluate potential outcomes of a decision while planning for future action is particularly relevant to substance abusing populations for maintaining abstinence both in community treatment settings and following discharge from substance abuse treatment

(Passetti et al., 2011). Relapse results from the selection of choices associated with the immediate benefits of intoxication (e.g., euphoria, symptom relief), even if those choices are coupled with maladaptive future outcomes (Bechara & Damasio, 2002). Research studies investigating decision-making abilities have found that cocaine-dependent subjects tend to select smaller, immediate monetary rewards over larger, delayed monetary rewards and discount the monetary reward more rapidly over time than healthy controls (Coffey, Gudleski, Saladin, & Brady, 2003; Kirby & Petry, 2004). Cocaine-addicted individuals also tend to persist in making disadvantageous choices favoring high immediate gains despite larger future and overall losses (Bartzokis et al., 2000; Bechara et al., 2001; Bechara & Martin, 2004; Grant, Contoreggi, & London, 2000). These studies suggest that cocaine-dependent individuals display problems evaluating outcomes for effective decision-making, which may create a challenge to abstinence maintenance. Decision-making deficits are likely exacerbated when the principles governing an outcome choice are altered.

Response reversal is a type of decision-making process involving the changing of response contingencies, such as amount of reward, type of outcome (e.g., reward to punishment), or time it takes to receive a reward. Following a contingency change, a person must reevaluate the positive and negative qualities of potential responses, and then decide to either continue or change their current pattern of responding. Anecdotal, preclinical (Krueger et al., 2009), and clinical (Ersche, Roiser, Robbins, & Sahakian, 2008; Fillmore & Rush, 2006; A. Verdejo-Garcia, Bechara, Recknor, & Perez-Garcia, 2006) evidence suggests that chronic cocaine users exhibit an inability to adjust their responses to changes in reward contingencies, leading to perseverative responding. O'Doherty and colleagues (2001) established a reversal learning task that has been

used to assess decision-making abilities in healthy individuals and persons with orbitofrontal cortex (OFC) lesions, but has not been applied to drug abuse populations (Hornak et al., 2003; O'Doherty, Critchley, Deichmann, & Dolan, 2003). Damage to the OFC produces deficits in the ability to perform this task, such that subjects perseverate on the previously rewarded response. It was anticipated that individuals with addiction would perform similarly to individuals with OFC lesions on this reversal learning task (Calu et al., 2007; Schoenbaum, Saddoris, Ramus, Shaham, & Setlow, 2004). The O'Doherty et al. reversal learning paradigm has several advantages: contingency changes do not occur until after mastery of the initial contingency, there are multiple contingency changes in the task, salient rewards and punishments (variable monetary values) are used, and brain activation in response to reward and punishment is assessed. Due to its use of monetary feedback, the O'Doherty reversal learning task may be an ecologically valid and effective means of eliciting decision-making processes in individuals—particularly cocaine users, who invest considerable time and effort pursuing money to obtain cocaine, and demographically similar healthy individuals. For all these reasons, this response reversal task was administered within the scanner environment of the present study to generate decision-making processes for observation.

Chronic cocaine use has been associated with structural and functional brain alterations that could be important to decision-making processes. Notably, cocaine dependence has been linked to reductions in grey matter concentrations in multiple cortical, subcortical, and cerebellar areas relative to controls, including the medial OFC, lateral prefrontal, anterior cingulate cortex (ACC), insula, thalamus, and superior temporal cortex, with the average grey matter reductions ranging from 5% to 11% (Ersche et al., 2011; Fein, Di Sclafani, & Meyerhoff, 2002; Fillmore &

Rush, 2006; Franklin et al., 2002; Sim et al., 2007). Additionally, reductions in cerebral glucose metabolism have been observed following acute cocaine use and prolonged cocaine abstinence (London et al., 1990; Volkow, Hitzemann, Wang, Fowler, Wolf, et al., 1992), and these metabolic reductions have been associated with lower levels of striatal D2 receptor availability (Goldstein & Volkow, 2002; Martinez et al., 2009; Volkow et al., 1993). Further, chronic cocaine abuse has been linked with cerebral hypoperfusion in the frontal, periventricular, and temporal-parietal cortices, including the bilateral OFC and putamen (Adinoff et al., 2001; Browndyke et al., 2004; Strickland et al., 1993). Chronic cocaine abuse is also associated with increased resting cerebral blood flow (CBF) in the frontal white matter relative to healthy controls (T. Ernst, Chang, Oropilla, Gustavson, & Speck, 2000). Neuroimaging studies suggest that these frontal, temporal-parietal, and subcortical regions may be altered by cocaine use, and thus, may contribute to neurocognitive abnormalities, impaired decision-making, and possibly relapse rates in cocaine-addicted individuals.

Further research has provided evidence that underlying neural processes are associated with decision-making deficits in cocaine-addicted populations. Browndyke and colleagues (2004) found significant deficits in complex attention, a function relevant to decision-making processes, in 37 cocaine-addicted individuals with higher abnormal perfusion severity. Additionally, increased regional CBF in the ACC, dorsolateral prefrontal cortex (DLPFC), and middle, medial, and superior frontal gyri was found to be significantly correlated with better decision making performance (Adinoff et al., 2003; Tucker et al., 2004). Utilizing positron emission tomography (PET) during performance of a decision-making measure [i.e., the Gambling Task (Bechara, Damasio, Damasio, & Anderson, 1994)], 13, 25-day abstinent cocaine

abusers displayed greater activation in the right OFC and displayed less activation in the right DLPFC and left medial prefrontal cortex relative to 13 controls (Bolla et al., 2003). Further, Ersche and colleagues (2011) found that greater attentional control difficulties were associated with reduced grey matter volume in the insular cortex and increased volume in the caudate nucleus, and found that greater compulsive drug use was associated with reduced OFC volume in a sample of 60 cocaine-dependent and 60 healthy control subjects. While these studies illustrate the associations between neural activation changes and cognitive abilities—particularly decision-making—in a cocaine-addicted group, there remains a lack of studies exploring the connection between these neural changes during decision-making and measures of relapse (e.g., time to first use) in this population.

Early explorations into the relationship between decision-making deficits, neuroimaging, and relapse have recently begun in substance use populations. For example, Paulus, Tapert, and Schuckit (2005) investigated the predictive probability of neuroimaging in 40 treatment-seeking methamphetamine dependent males three to four weeks after cessation using fMRI during a simple dual-choice prediction task. In that study, relapse data were obtained at a one-year follow-up contact and was defined as the time until first use of methamphetamine after cessation. The authors found that fMRI activation patterns in the right insular, posterior cingulate, and temporal cortex predicted 91% of subjects who did not relapse (n = 22) and about 94% of subjects who did relapse (n = 18). The combination of right middle frontal gyrus, middle temporal gyrus, and posterior cingulate activation was the best predictor of time to relapse. This investigation demonstrated for the first time the possibility of using functional neuroimaging to predict relapse in individuals with methamphetamine addiction. However, the sample utilized

did not meet criteria for cocaine dependence or another substance use disorder; thus, it is unclear how these findings generalize to other substance use disorders apart from methamphetamine dependence. Further, brain activation (fMRI) during drug cue exposure has been associated with vulnerability to treatment dropout and relapse to cocaine use (Kosten et al., 2006). Specifically, greater activation in the posterior cingulate was found in relapsers compared to non-relapsers during the first 30 seconds of cue exposure (e.g., videotape of a man smoking cocaine), suggesting more active engagement in viewing the drug cue stimuli. The authors proposed that the posterior cingulate operates to initiate habitual behavior upon exposure to a drug cue. This study was one of the first to show an association between neural activation during drug cue exposure and relapse to cocaine use. However, this study focused on drug cue exposure, not decision-making, and explored the relationship between neural activation and relapse without attempting to predict future relapse.

Research suggests that individuals addicted to cocaine experience enhanced salience of drug-related cues and display maladaptive decision-making impairing their ability to resist the urge to use. The present study used an fMRI response reversal decision-making task to examine neural activation in cocaine-addicted subjects relative to healthy controls as a means of predicting relapse to cocaine use. While studies have investigated changes in neural functioning and decision-making impairments within cocaine-addicted populations, there have been no known studies examining the ability of these measures to predict cocaine relapse. If the neural regions necessary for making adaptive choices are dysfunctional, then the success of interventions utilizing decision-making skills may be hindered by the ineffectiveness of the brain regions normally supporting these activities. Thus, to appropriately treat cocaine addiction, we

must gain a better understanding of the neural mechanisms contributing to cognitive errors and relapse. It is hoped that this research will lead to the construction of a more precise model for predicting relapse that will allow for the tailoring of treatment options for individual's needs and hopefully improve long-term abstinence.

Method

Participants

Participant data were collected as part of a grant sponsored by the National Institute of Drug Abuse. The institutional review boards of the University of Texas Southwestern Medical Center at Dallas and the Veterans Administration (VA) North Texas Health Care System approved this protocol. Funding for this grant allowed for data collection on sixty-five cocaine-addicted and twenty-five healthy control participants; however, twenty-three participants were excluded from analyses due to their inability to learn the response reversal task (eight patients; one control), movement in scanner (one control), participation in a structured addiction treatment program following inpatient discharge (ten patients), or poor task performance as defined by a 'money won' score greater than or less than three standard deviations from the group mean (one control performed below three standard deviations). Thus, 23 healthy control (15 males; 8 females) and 45 cocaine-addicted (39 males; 6 females) volunteers participated in this study. All volunteers gave written informed consent prior to enrollment and were compensated for their time upon completion of study procedures.

Cocaine-Addicted Group. Cocaine-addicted volunteers were recruited from treatment programs at the VA Medical Center (VAMC) in Dallas, Homeward Bound, Inc., and Nexus Recovery Center (Appendix C). Enrolled patients identified cocaine as their primary present and

lifetime drug of choice and met criteria for cocaine dependence on the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I) (First, 2007). Cocaine lifetime and previous ninety-day amount spent and days used, and other substance use history were obtained from cocaine-dependent participants using the Time Line Follow Back (TLFB) (M. B. Sobell & Sobell, 1978). Patients had to live within 50 miles of their respective treatment facilities to facilitate follow-up visits. Individuals were excluded from enrollment if they actively met criteria for a major medical or neurological disorder, DSM-IV Axis I Affective, Anxiety, or Psychotic Disorder. Individuals reporting a head injury with loss of consciousness (LOC) were excluded if LOC exceeded two hours, was accompanied by persistent symptoms (e.g., nausea, vomiting, dizziness, memory loss, or perseverations), or resulted in subsequent imaging positive for lesions/damage. Due to the complicated nature of substance-induced mood, anxiety, and psychotic disorders, these conditions were not cause for exclusion if symptoms did not persist during cocaine abstinence. Patients taking psychoactive medications known to affect brain function or changes in perception, consciousness, cognition, behavior, or mood (e.g., psychotropics, beta blockers, and certain pain medications) were excluded. Due to the extensive use of nicotine and other substances within cocaine-addicted populations, patients using these other substances were not excluded from this study if they had a primary diagnosis of cocaine-dependence and identified cocaine as their primary drug of choice.

Control Group. Control subjects were recruited using newspaper and internet advertisements and fliers posted on community bulletin boards. Controls were recruited to be similar to the patient group on age, race, and education. Healthy controls with a lifetime history of psychoactive substance use or dependence (except nicotine or caffeine dependence) were

excluded. Additionally, controls with a first degree relative with a substance use disorder were excluded. Medical, psychiatric, and medication criteria were otherwise the same as for the cocaine-addicted subjects.

Exclusion Criteria for all Participants. Individuals were excluded for contraindications with MRI, such as incompatible metal implants and claustrophobia. Women who were pregnant or planning to become pregnant during the course of the study were excluded from participation due to the unclear risk of harm to an embryo or fetus with fMRI. Finally, all participants were required to be native English speakers with an estimated IQ of at least 70 (per the Wechsler Test of Adult Reading [WTAR]) due to the neurocognitive battery used and to ensure comprehension of study instructions and procedures.

Design

All participants completed a full medical history and physical examination, SCID-I, clinical laboratory tests (e.g., complete metabolic panel, HIV testing, and Hepatitis B and C testing), urine drug screen, and a pregnancy test (for women) as part of the study screening process following consent. Screening procedures and assessments of psychiatric (SCID-I) and substance abuse history (TLFB), as well as, assessments of demographic information, traumatic brain injury, intellectual functioning (WTAR), impulsivity (Barrett Impulsivity Scale-11 [BIS-11]), and craving (Cocaine Craving Questionnaire [CCQ]; patients only) were administered during the first and second weeks of inpatient treatment. Detailed descriptions of these measures can be found in Appendix D. Neuroimaging procedures occurred between two and four weeks abstinence. Participants completed a mock fMRI at least one day prior to the actual fMRI study session. The mock fMRI served two purposes: preparation of subjects for the fMRI environment

(e.g., confined space and loud noises) and training of the Response Reversal Task. Functional MRI study sessions were conducted at approximately the same time of day across subjects to reduce the potential effects of diurnal fluctuations in neural activity. Subjects were asked to restrict caffeine and nicotine intake to at least one hour before fMRI to help control for potential acute effects of caffeine and nicotine or withdrawal from these substances.

Response Reversal Task. The RRT was adapted from O'Doherty et al. (2001), and allows for the trial-by-trial measurement of the individual hemodynamic responses related to the acquisition of rewards and punishments and the reversal of contingencies. This reversal requires the suppression of one set of cognitive processes and the implementation of a new set. The RRT consisted of 51 trials of stimuli, administered in three consecutive sessions (total of 153 trials), each lasting approximately nine minutes with a one minute intersession break. In each trial, two unique fractals were displayed on the screen (Figure 1). The two fractals were randomly displayed on the right or the left side of the screen for each trial. The subject was instructed to select one of the two fractals. Following selection of a fractal, the subject was informed that they either won or lost money through a text message visible on the screen above the chosen fractal. A bar graph indicating total money acquired at that point in the task also appeared on the screen below the fractals. Fractal (stimulus) presentation appeared on the screen for a total of three seconds. Win or loss feedback then appeared on the screen for three seconds, followed by a fixation cross for a mean of four seconds (pseudorandom jitter of two, four, or six seconds) prior to the next trial.

In this task, two fractals were presented and designated as either an S+ (resulted in overall monetary gain) or as an S- (resulted in overall monetary loss) (Table1). If the S+ was

chosen, the feedback stimulus revealed a large win (simulated $) or a small loss. If the S- was chosen, the feedback revealed a small win or a large loss. After the S+ was chosen four or five times consecutively, the contingencies changed, meaning the S+ became the S- and vice versa within the next one to two trials (randomly determined). The subject's task was to ascertain which fractal was more profitable ("good shape") and to switch strategies when a reversal occurred.

Event-related analysis allowed the BOLD response to be assessed during the stimulus presentation and fractal selection or during the feedback stimulus. Seven specific event types were identified within this task. Events of interest during stimulus presentation included the hemodynamic response function when the subject appropriately switches the fractal chosen in response to a change in the contingencies (RespRev), or alternatively, persisted in choosing the S- despite a previous large loss (PersLoss) or a small gain (PersWin). Events of interest during feedback included wins or losses during S+ acquisition (WinAcq or LossAcq, respectively) or wins and losses following the reversal of contingencies and the selection of S- (WinRev or LossRev). Trials were coded with one feedback stimulus event type, one presentation stimulus event type, or both. Individuals were instructed that a portion of their compensation depended on their performance on this task to encourage optimal performance. Participants were debriefed regarding this deception following completion of the study.

Follow-up. Following acquisition of baseline measures, cocaine-dependent participants were followed twice weekly, once by phone and once in-person (clinic visit), for up to 24 weeks (168 days) to obtain return to use information. At each follow-up appointment, patients were interviewed about substance use since their previous visit, and a urine drug screen was obtained.

Phone contacts also queried substance use since last visit and provided a reminder for upcoming in-person visits. If sessions were missed, interviews covered the period since the last study visit. Strategies to improve compliance with follow-up included 1) gathering of patient and collateral contact information at initial assessment, 2) updating of contact information at each visit, 3) providing toll-free number to patients to facilitate contact with research coordinator, 4) using phone contact to complete interviews if patient unable to come to office for visit, 5) providing compensation for completed phone calls and in-office visits, 6) providing reminder and follow-up phone calls as needed, 7) sending letters for multiple missed appointments, and 8) scheduling follow-up appointments to coincide with other hospital/center appointments or therapy sessions. Additionally, a contingency management program was implemented to encourage participation in follow-up. As part of this program, patients received a raffle ticket(s) for each session attended, and these tickets increased relative to the number of in-person sessions consistently attended. Raffle tickets allowed for the periodic opportunity to win a modest prize (e.g., portable DVD player or stereo).

Time to first use served as the measure of relapse and described the time in days from treatment discharge until the first cocaine use. Follow-up ceased after the initial use was reported or confirmed via urine drug screen. Cocaine-addicted subjects were not informed in advance that their participation in follow-up would cease after cocaine use to help dissuade concealing of use during follow-up appointments. Subjects who returned to use were provided approximately one additional follow-up appointment prior to withdrawal from follow-ups. Information regarding relapse was obtained via structured interview (developed within this lab for purposes of obtaining detailed information regarding the relapse process), TLFB (calendars

to guide recollection of use), and urine drug screen. Further, the intention-to-treat principle was applied to follow-up data (Gibaldi & Sullivan, 1997), meaning that all individuals scanned and discharged to outpatient status were included in analyses regardless of compliance with follow-up procedures, with the clinical assumption that individuals lost to follow-up return to use. As a result, patients missing two consecutive appointments without phone contact were considered relapsed as of their first missed appointment. Attempts to contact missing individuals either directly (e.g., phone, email, or standard mail) or through collateral contacts (e.g., family members, friends, case workers, or probation officers) continued for at least six months following treatment discharge. Retrospective relapse data were collected if the missing individual could be reached within this six-month period and appeared to be a reliable historian. One individual left inpatient treatment against medical advice following completion of the imaging session, and thus, was treated as having relapsed the day of voluntary discharge from treatment.

Image Acquisition and Processing

Stimuli for the decision-making task was generated using Presentation (Neurobehavioral Systems, Inc., Albany, CA) running on a Dell 3.2 GHz processor laptop with its video output directed to LCD goggles (Resonance Technology Corp, Northridge, CA) that were MRI scanner compatible. This display presented NTSC screen resolution (512x384 pixels with 24-bit color depth) with a nominal visual angle of about 30º. During the scans, subjects responded manually to stimuli utilizing button boxes with a solo button on each box requiring a soft thumb press. The key presses were carried via light signals through fiber optic cables to and from the MRI instrument. The Presentation program automatically recorded both the stimulus presented and

the behavioral response. Subjects received task instructions immediately preceding task initiation while situated in the scanner.

Magnetic resonance images were obtained using a 3T Siemens Trio (60 cm diameter patient bore), equipped with AutoAlign for automated and reproducible slice positioning between subjects and scan sessions and navigator-guided 3D PACE for prospective slice realignment to track head motion. The following sequences were obtained over a period of approximately one hour and fifteen minutes, including scout scans to set slice locations. Parameters were selected to reduce susceptibility signal losses, including thinner slices and reduced echo time (TE) appropriate to a 3T magnet. All areas of brain to be assessed in our hypotheses were covered by the proposed acquisition parameters. Anatomical T1-weighted high resolution images of the whole brain [magnetization prepared rapid acquisition gradient echo, TR = 1240 ms, TE = 2.6 ms, T1 (recovery) = 725 ms, FA = 10º, 0.94 mm in-plane resolution (FOV = 240 x 240, 256 x 256 matrix, 0.9 x 0.9 x 1.2 resolution)] were obtained in 128 sagittal slices to facilitate localization of fMRI activation. During the RRT, 271 mosaic whole brain frames of T2-weighted EPI sequence images were obtained [36, 3.5-mm contiguous sagittal slices from right to left, 3.3 x 3.3 x 3.5 mm resolution (64 x 64 matrix, FOV = 210 mm x 210 mm), TR = 1.7 s, TE = 13 ms]. Each RRT run was approximately 9.06 minutes for a total session time of 30 minutes.

Imaging analyses were conducted using fMRI Expert Analysis Tool (FEAT), part of FMRIB's Software Library (FSL) (S. M. Smith et al., 2004; Woolrich et al., 2009). FSL is a comprehensive library of image analysis and statistical tools for fMRI, MRI, and diffusion tensor imaging (DTI) data. The following pre-statistics processing was applied: slice-timing correction

using Fourier-space time-series phase-shifting, motion correction using MCFLIRT, non-brain removal using BET, spatial smoothing using a Gaussian kernel with full width at half maximum of 5 mm, mean-based intensity normalization of all volumes by the same factor, and highpass temporal filtering (Gaussian-weighted LSF straight line fitting with sigma = 15.0 seconds). Time-series statistical analyses were carried out using FILM with local autocorrelation correction.

Within FEAT, a three level analysis was conducted. The initial analysis paired time points within the response reversal task with co-occurring changes in BOLD response for each trial of the task for each individual. Primary explanatory variables (EVs) included in the general linear model at first- and mid-level analyses were WinAcq and LossRev with four contrasts: WinAcq only, LossRev only, WinAcq-LossRev, and LossRev-WinAcq. WinAcq represents a large reward in response to consistent choice of the correct stimulus, and is the clearest indicator to the participant that they are being rewarded for an appropriate response. LossRev was chosen as it represents a large loss in response to a change in contingencies, and is the most apparent indicator to the participant that the contingency has changed and they should begin choosing the other shape. Choice of these events and contrasts allowed for comparisons that showed the brain areas more activated following a rewarding outcome than a punishing outcome and a punishing outcome than a rewarding outcome (O'Doherty, et al., 2001). Registration to high resolution and/or standard images was conducted within FEAT. Higher-level analysis was carried out using FLAME (FMRIB's Local Analysis of Mixed Effects). For the second level analysis, the same four contrasts were used and the data from the three trials of the RRT were combined to

provide an individual mapping of significant voxels. Subsequently, a third level analysis was conducted to derive group differences in activation for each of the four contrasts.

Planned Statistical Analyses

Non-imaging data was analyzed using the Statistical Packages for the Social Sciences, version 19.0 (SPSS, Inc. Chicago, IL). Nominal data was analyzed via chi square crosstabs analysis (e.g., race and gender). Independent-sample *t*-tests were used to explore group differences in demographic variables, WTAR full scale IQ, total BIS-11 scores, and RRT 'money won' scores. All tests were two-tailed and an effect was deemed significant at $p < 0.05$. Pearson product-moment correlations assessed the relationship between time to relapse, percent BOLD signal change, and demographic, clinical, and behavioral variables. Variables that were significantly different between groups and/or correlated with time to relapse or percent BOLD signal change were considered as covariates in subsequent analyses.

Disruptions in neural activation between groups (cocaine-addicted versus control subjects; short-term versus long-term relapsers) were assessed utilizing an exploratory analysis of significant voxels. Z (Gaussianised T/F) statistic images were thresholded using clusters determined by $Z > 3.29$ and a (corrected) cluster significance threshold of $P = 0.05$. To increase specificity for the creation of regions of interest (ROIs) with maximum activation, voxel-based metrics were employed. Z (Gaussianised T/F) statistic images were thresholded using GRF-theory-based maximum height thresholding with a corrected significance threshold of $P = 0.15$. Functional clusters encompassing more than one anatomical structure were separated along anatomical parameters established by the Harvard-Oxford Cortical Structural Atlas, which is an atlas based on population probability maps of cortical and subcortical structural areas (Desikan et

al., 2006). Subsequently, ROIs were isolated with a "mask" and mean percent BOLD signal change for each individual in all identified regions was assessed using FEAT query.

Linear discriminant function analysis (F_{enter}: $P<.05$) was computed with time-to-relapse (categorical; short-term versus long-term) as the dependent measure and the mean % BOLD signal change in the identified ROIs as the independent measure. Short-term relapse was defined as relapse taking place in less than or equal to one month (30 days) of treatment discharge. One month post-discharge was chosen to define this subgroup due to its use within the DSM-IV-TR as a criterion for remission specifiers (DSM-IV, 2000). Long-term relapse captured those individuals who relapsed after one month post-discharge or who did not relapse within the 6 month follow-up period. Cross-validation using a leave-one-out classification method (predictions generated by resampling with 1 subject removed) was used to determine sensitivity and specificity of the activation patterns to predict relapse.

Results

Clinical and Behavioral Characteristics

Descriptive information regarding demographic and clinical variables for the cocaine-addicted and healthy control groups are displayed in Table 2. The two groups were similar in terms of age, racial distribution, and BIS-11 total impulsivity scores. The cocaine-addicted group was comprised of more smokers (36 of 45 patients versus 1 of 23 controls) and males and had fewer years of education and lower estimated intelligence scores than the control group. All subjects in the patient group reported a history of cocaine dependence with the majority also presenting with a history of at least one other substance use disorder (82% alcohol, 51% cannabis, 18% opiate, 16% other stimulants, 7% sedatives/hypnotics/anxiolytics or

hallucinogens/PCP, and 4% other). Cocaine users' RRT performance did not significantly differ from the control group as measured by total money won.

During the follow-up period, 35 of 45 patients (24 self-reported relapse, two identified by urine drug screen, and nine were missing) relapsed an average of 35 days after initial testing and treatment discharge (SD = 42.63; range, 0-141 days). These individuals relapsed to cocaine use, except one individual who relapsed to methamphetamine. Since methamphetamine is also a stimulant, relapse to this substance was treated similarly to cocaine relapse and the individual was removed from follow-up. Patients lost to follow-up did not significantly differ from individuals with confirmed relapse or with non-relapsers on all clinical and behavioral measures (three group ANOVA), except lifetime money spent on cocaine, which differed significantly between non-relapsing subjects and subjects with missing follow-up data (p = .026), with non-relapsing subjects using less cocaine over their lifetime than subjects with missing relapse data (Table 3). Further, six individuals returned to alcohol use prior to or in the absence of cocaine use, five individuals returned to alcohol use concurrently with their return to cocaine use, and one individual reported marijuana use prior to cocaine relapse. Ten cocaine-addicted individuals did not relapse during the 6-month follow-up period. Due to the size of this group of non-relapsers, these individuals were included within the group of long-term relapsers for subsequent analyses, creating groups of 22 short-term relapsers (mean = 8.32 days, SD = 6.14, range of 0-25 days) and 23 long-term relapsers (mean = 118 days, SD = 53.27, range of 35-168 days, non-relapsers = 168 days).

Demographic and clinical data for the cocaine-addicted group separated by short-term and long-term relapse are displayed in Table 4. Sociodemographic characteristics, baseline

symptom indicators, use characteristics, and behavioral measures of RRT performance did not significantly differ between those in the short-term relapse group and those in the long-term relapse group. The relapse groups significantly differed in years of education, with the short-term relapsing group receiving fewer years of education; however, these groups did not differ in WTAR FSIQ. The patient groups were also not significantly different based on treatment centers attended ($x^2 = 1.11$, $p = 0.57$) or duration of recent inpatient treatment ($t = -0.11$, $p = 0.91$), with six short-term relapsers and four long-term relapsers attending the VA Medical Center, 13 short-term relapsers and 17 long-term relapsers attending Homeward Bound, Inc., and three short-term relapsers and two long-term relapsers attending Nexus Recovery Center. Finally, no significant correlations were noted between demographic, clinical, and behavioral (RRT money won) measures and time-to-relapse.

Functional Neuroimaging Characteristics

Similar to previous studies investigating decision-making during neuroimaging, changes in activation were noted in multiple cortical and subcortical areas (22 total areas). Figure 2 displays areas of significant activation. Frontal medial cortex, subcallosal cortex, posterior cingulate gyrus, and precuneus displayed decreased activation in the patient group during the LossRev-WinAcq (or increase on the WinAcq-LossRev) contrast. Bilateral lateral OFC, bilateral insula, bilateral DLPFC, supplementary motor cortex, paracingulate, anterior cingulate gyrus, and superior frontal gyrus displayed increased activation in the patient group during the LossRev-WinAcq (or decrease on the WinAcq-LossRev) contrast. Further, bilateral middle and superior temporal gyri exhibited decreased activation in the patient group during the LossRev to baseline contrast, and bilateral amygdala and hippocampus showed increased activation in the

patient group during the WinAcq to baseline contrast. The observed activation patterns were robust as they remained significant across various adjustments to the Z-threshold ($Z > 3.29$, $Z > 2.3$) and cluster significance threshold ($P = .05$, $P = .01$) within cluster-level inference analyses and across various adjustments to the corrected significance threshold ($P = .05$, $P = .10$, $P = .15$) within voxel-level inference analyses. Additionally, the ROI clusters were not observed to vary when a leave-one-out procedure was employed within FSL. However, activation did not significantly differ between cocaine-addicted and healthy control groups. Analyses were also repeated examining differences in BOLD activation between short-term and long-term relapsers and between all three groups (controls, short-term relapsers and long-term relapsers); however, no differences in activation were observed between these groups.

Neuroimaging and Relapse Findings

As activation patterns during the decision-making task were not significantly different between control and cocaine-addicted groups, regions of interest used in the creation of a relapse prediction model were defined by areas of significant BOLD activation change within the patient group. However, to reduce cluster size and increase cluster specificity around the maximum activation in a cluster, voxel-level inference ($P = 0.15$) was used to create the final clusters for future analyses. This statistically stringent measure reduced the number of ROIs included in the discriminant analysis, excluding the posterior cingulate, subcallosal cortex, left DLPFC, right middle temporal gyrus, and right superior temporal gyrus. Voxel-level inference also allowed for further discrimination between the orbitofrontal and insula clusters and identified two distinct maxima within the right DLPFC cluster. Mean percent BOLD signal change data was extracted

from each of the remaining 18 ROIs and included in the discriminant function analysis as predictor variables.

Discriminant analysis was conducted to predict whether a cocaine-addicted patient would relapse in the short-term (within 30-days) or long-term (more than 30-days) following inpatient acute substance abuse treatment. No significant mean differences were observed for the predictors on relapse status (using group means and ANOVA results data), and the assumption of equality of covariance matrices was violated (Box's M = 443.37, F = 1.40, p = .001). The discriminant function revealed no significant association between groups and all predictors (Wilk's $\lambda = 0.49$, $\chi^2 = 23.98$, p = .156), accounting for 51% of between-group variability. Further, this analysis yielded a model with a specificity of 82.2%, correctly predicting 17 of 22 individuals with short-term relapse and 20 of 23 with long-term relapse. However, cross-validation analysis accurately classified 64.4%, correctly predicting 14 of 22 who relapsed short-term and 15 of 23 who relapsed long-term. The standardized canonical discriminant function coefficients stemming from this analysis, which provide an index of the importance of each predictor, were utilized to focus the selection of ROIs to the strongest set of predictors for inclusion in a subsequent discriminant analysis (Table 5). This discriminant function analysis with 10 ROI predictors again found no significant differences between ROIs on relapse status (Table 6); however, it no longer violated the assumption of equality of covariance matrices. This discriminant function also revealed a significant association between groups and all predictors (Wilk's $\lambda = 0.559$, $\chi^2 = 22.10$, p = .015), accounting for 44% of between group variability. The cross validated classification showed that overall 71.1% were correctly classified (Table 7). Stepwise discriminant analysis was also conducted with these groups of ROI predictors to create

a more precise prediction model; however, no individual ROI met the critical significance level for independent inclusion in the model.

Exploratory Analyses

Finally, additional discriminant function analyses were conducted with the same ten ROIs to explore the robustness of this neuroimaging prediction model if individuals were removed due to missing follow-up data (nine individuals) or due to a LOC event greater than 30 minutes (four individuals) or if the patient subgroups were divided based on relapsing or not relapsing in the six-month follow-up period. When the discriminant function analysis was repeated excluding those individuals with missing follow-up data, a significant association was revealed between short-term and long-term relapsing groups and all predictors (Wilk's $\lambda = 0.485$, $\chi^2 = 21.01$, $p = .021$), accounting for 52% of between group variability. This analysis also yielded a model with a specificity of 80.6% and the cross validated classification showed that overall 72.2% were correctly classified, correctly predicting 11 of 16 who relapsed short-term and 15 of 20 who relapsed long-term. When the discriminant function analysis was repeated excluding only those individuals with a LOC event greater than 30 minutes, a significant association was revealed between short-term and long-term relapsing groups and all predictors (Wilk's $\lambda = 0.584$, $\chi^2 = 18.29$, $p = .05$), accounting for 42% of between group variability. This analysis yielded a model that correctly classified 82.9% of original grouped cases. The cross validated classification showed that overall 65.9% were correctly classified, correctly predicting 12 of 19 who relapsed short-term and 15 of 22 who relapsed long-term.

When the discriminant function analysis was repeated with patient subgroups based on relapse versus no relapse, no significant association was revealed between groups and all

predictors (Wilk's $\lambda = 0.646$, $\chi^2 = 16.59$, $p = .084$), accounting for 35% of between group variability. This analysis yielded a model that correctly classified 82.2% of original grouped cases; the cross validated classification showed that overall 73.3% were correctly classified, correctly predicting 30 of 35 who relapsed and 3 of 10 who did not relapse. Repeating this discriminant function analysis with relapse and non-relapse groups and excluding the nine individuals with missing follow-up data also did not reveal a significant association between groups and all predictors (Wilk's $\lambda = 0.613$, $\chi^2 = 14.22$, $p = .163$), accounting for 39% of between group variability. This analysis yielded a model that correctly classified 83.3% of original grouped cases. The cross validated classification showed that overall 66.7% were correctly classified, accurately predicting 21 of 26 who relapsed and 3 of 10 who did not relapse.

Caution should be taken when reviewing these additional analyses as group sizes were uneven and sample sizes were significantly reduced relative to the initial analyses. In general, these additional findings excluding specific individual cases from the subject pool do not vary much from the original findings of 80% (original grouped) and 71% (cross-validated) classification probabilities. Dividing the patient subgroups by relapse versus non-relapse might be a worthwhile comparison; however, no significance was found in these discriminant analyses likely due to decreased power with the small sample size of this non-relapsing group.

Discussion

By utilizing changes in BOLD response during decision-making to predict cocaine relapse, this study sought to expand upon previous research detailing decision-making deficits and neural changes in cocaine-addicted subjects relative to healthy controls (J. L. Aron & Paulus, 2007; Beveridge, Gill, Hanlon, & Porrino, 2008). While the decision-making task utilized

appeared to generate changes in activation in brain regions associated with processing decisions, no group differences in activation were noted between cocaine-addicted subjects and healthy controls or between short-term and long-term relapsers, as predicted in the first hypothesis. Consistent with hypothesis two, a statistically significant (i.e., calculated hit ratio was better than that achieved by chance) model was constructed using neuroimaging to predict relapse in individuals with cocaine dependence. Although less significant than previous prediction models (Paulus, et al., 2005), the degree of probability observed across these studies (71% – 90%) supports the idea that neuroimaging may be a valuable tool for assessing relapse.

The ROI activation patterns observed in the cocaine-addicted and healthy control groups and used to form the prediction model are part of a system involved in decision-making. Specifically, increased activation was observed in the OFC, an area of the brain that has been implicated in the regulation of planning, emotional and social functioning, reversal learning, mental flexibility, and reforming stimulus-response associations (Adinoff, et al., 2003; Bechara, et al., 2001; Berlin, Rolls, & Kischka, 2004; Ghahremani, Monterosso, Jentsch, Bilder, & Poldrack, 2010; Hornak, et al., 2003; Volkow & Fowler, 2000). Additionally, orbitofrontal and medial prefrontal cortex serve as a link between situational facts and emotions previously paired with an event (Bechara, Damasio, & Damasio, 2000). These structures are involved in representing outcome and activity in this area predicts the behavioral choice (O'Doherty, et al., 2003). In this way, the OFC integrates rewarding and punishing feedback for affective decision making. Moreover, studies exploring OFC lateralization suggest that medial OFC activity is related to monitoring the reward value of a reinforcer; whereas, the lateral OFC activity is related to the evaluation of punishers (Kringelbach & Rolls, 2004). Consistent with this hypothesis

regarding the localization of OFC function, both groups displayed increased activation in the lateral OFC following receipt of a large loss suggestive of a contingency change. However, this study did not find group differences in OFC activation as anticipated based on observed group differences in OFC regional cerebral blood flow (Adinoff, Braud, Devous, & Harris, 2011), grey matter volume (Ersche, et al., 2011; Franklin, et al., 2002), and activation during performance of the Iowa Gambling Task (Bolla, et al., 2003).

Amygdala activation was present during the WinAcq condition, in which the individual correctly chooses the 'good shape' based on previous feedback and receives a reward that reinforces the current stimulus choice. Previous studies have also found that left amygdala activation is associated with anticipation of working for monetary reward (i.e., reward anticipation) in both healthy controls and individuals with cocaine dependence (Jia et al., 2011). The amygdala has a central role in emotional learning, improving memory, and in decision-making wherein it encodes events in relation to their somatosensory features and motivational or affective significance (Balleine & Killcross, 2006). The impairment in decision-making after amygdala damage is an indirect consequence of the role of the amygdala in attaching affective attributes to stimuli (Bechara, Damasio, Damasio, & Lee, 1999). Thus, selection of a particular shape followed by a large monetary reward likely generates a positive emotional association with the stimulus that guides its continued choice until contingencies change. Additionally, decision-making requires the appropriate use of memories of past experiences, as well as knowledge about situations, actors, options for action, and outcomes to aide selection of the most advantageous response. Thus, it seems plausible that the hippocampus would be activated

during receipt of an expected reward, as the anticipation of a reward relies upon memories of previous experiences receiving a reward when the specific stimulus was selected.

Increased DLPFC activation was observed during the LossRev-WinAcq contrast, suggesting that this region had heightened activation following a large unexpected loss. Similarly, Paulus and colleagues (2003) found that both healthy controls and methamphetamine-dependent individuals demonstrated activation in the DLPFC during a two-choice prediction decision-making task; however, their drug use group showed less task-related activation than the healthy controls. The DLPFC is involved primarily in executive control and working memory (Bechara, Damasio, Tranel, & Anderson, 1998; Cohen et al., 1997). Specifically, the right DLPFC is involved in the preliminary processing that precedes task-switching, in which advance cues communicate which one of multiple possible tasks is to be performed on an upcoming ambiguous stimuli, irrespective of performance-based reward incentives (Ruge, Braver, & Meiran, 2009; Savine & Braver, 2010). Thus, the response reversal process of decision-making likely employs this cognitive control function within the DLPFC to recognize cues signaling a need for a change in responding to future stimuli that may be inhibited when the individual is receiving feedback that a change is not needed (decrease on WinAcq).

An increase in percentage BOLD signal change was also observed in the anterior insula during the LossRev-WinAcq contrast. Insula activation occurs in a variety of conditions, including processing facial expressions of disgust (M. L. Phillips et al., 1998), anticipation of adverse events (Chua, Krams, Toni, Passingham, & Dolan, 1999), differentiating positive versus negative emotion processing (Liotti et al., 2000), response inhibition (Volkow et al., 2010), neuroticism (Deckersbach et al., 2006), decision-making (Feinstein, Stein, & Paulus, 2006), and

response risk assessment. Additionally, the insula, particularly its more anterior regions, has reciprocal connections to several limbic and frontal regions supporting emotional decision-making. Further, caudolateral OFC-anterior insula was activated by punishing feedback preceding a switch in stimulus (but not a failure to switch or by rewarding stimuli), suggesting a possible role for this region in signaling a change in reward contingencies (O'Doherty, et al., 2003). Previously, cocaine users have exhibited less mean BOLD activation in the right insula during successful inhibition and greater hypoactivation in the left insula during failures to inhibit pre-potent responses (GO-NOGO task) relative to healthy controls (Kaufman, Ross, Stein, & Garavan, 2003). Given these results and the previous finding that cocaine dependence was associated with decreased grey matter volume in the insular cortex (Ardila, Rosselli, & Strumwasser, 1991; Ersche, et al., 2011), it was presumed that cocaine-dependent subjects would exhibit differences in activation relative to healthy controls in this study. However, both groups demonstrated left insula activation following an unexpected loss, which is consistent with the insula's role in signaling contingency change, assessing future risk or unpleasantness, and response inhibition.

Functional studies propose that the precuneus is engaged in abstract cognitive processes involving visuo-spatial information (i.e., voluntary attention shifts between targets), episodic memory retrieval and mental imagery, self-processing, environment representation and monitoring, self-focused attention and conscious experience (Cavanna & Trimble, 2006). The precuneus is considered by some to be part of the default mode network (DMN), a neural network active during resting state that suspends processes (deactivates) during goal-directed cognitive processing or behaviors (Gusnard & Raichle, 2001); whereas, others omit the

precuneus from the DMN, opting for inclusion only of its neighbor, the posterior cingulate/retrosplenial cortex (BA 29/30 and 23/31) (Buckner, Andrews-Hanna, & Schacter, 2008). In this study, we observed a deactivation in the precuneus on the LossRev-WinAcq contrast that was accounted for by a large deactivation during the LossRev only condition (unexpected loss). At present, deactivations are not well understood and multiple interpretations have been put forth. Most notable for this study is the possibility that the precuneus is acting as part of the DMN and attenuating its activity while the individual is engaged in processing the feedback.

The anterior paracingulate cortex is active in understanding the intentions of others in social interactions, such as representing the intentions of people "actually" involved in social interaction, mentalizing future social interaction, and reasoning about the contents of another person's mind (Walter et al., 2004; Yoshida, Seymour, Friston, & Dolan, 2010). While this task did not explicitly engage the subjects in a social interaction, it could have engaged the paracingulate cortex due to its involvement in reasoning about another persons' mind. Task instructions clearly stated to participants that there would be a change in reward contingencies in which the 'good shape' would become the 'bad shape' and that this switch would occur randomly. However, multiple subjects reported efforts to "figure out" the task or predict the switch pattern, essentially attempting to reason about the mental mind of the computer. This tendency to mentalize the computer's subsequent action and activate the paracingulate cortex was evident in the increased BOLD response associated with the unexpected large loss.

Response reversal decision-making processes generated activation increases and decreases in multiple ROIs within the limbic and frontal systems and DMN for selection of

appropriate outcomes. We used contrast analyses comparing events that clearly indicated to the subjects that they were being rewarded and should maintain their pattern of responding (WinAcq) or that they received a punishment and should change their pattern of responding (LossRev). The contrast analyses allowed examination of differences between the two most extreme events of the task. When each component of the difference contrasts were examined in relation to baseline, the results suggested that receipt of a large loss or punishment accompanied by a change in contingencies elicited increased activation in brain areas that evaluate punishers and reform stimulus-response associations (OFC), signal changes in reward contingencies and allow for inhibition (insula), and mental reasoning (paracingulate). Further, the ability to assess a stimulus that was rewarded and associate it with previous outcomes for continued selection of that choice stimulated increased activation in brain areas associated with reward anticipation, attaching affective attributes to stimuli, memories, and knowledge of situations and outcome options (i.e., amygdala and hippocampus), while decreased activation was prompted in an area involved in processing cues prior to task switching (DLPFC) when continued choice of an outcome is warranted.

Additionally, decreased activation was observed in areas of the brain associated with the default mode network (i.e., precuneus, posterior cingulate, and frontal medial cortex) when a large loss was received signaling a change in contingencies. This network of brain areas is typically activated during rest and suppresses activation during goal-directed processes, such as decision-making. Finally, response reversal decision-making processes require multiple areas working together versus a single brain region to assess when a particular choice is advantageous or no longer advantageous requiring a re-evaluation of choices. The proposal that there is a

network of regions important for decision-making supports using functional connectivity to explore networks of brain activation during cognitive processes in future research. Functional connectivity MRI is a technique that tracks the intensity of blood fluctuations in regions of interest over time, and calculates temporal correlations between spatially remote neurophysiological events to determine the degree to which those regions of the brain work in relationship with one another (Fingelkurts & Kahkonen, 2005). This technique might allow for more definitive interpretations about how the identified brain regions (insula, OFC, precuneus, amygdala, hippocampus, DLPFC, and paracingulate) work in cooperation with one another to execute response reversal decision-making processes.

The anterior cingulate cortex is neuroanatomically connected to many of the structures described here and is a frontal cortical area frequently implicated in drug addiction and decision-making processes. Following a reversal in contingencies, the ACC displayed activation during an unexpected large loss and a deactivation during an expected large win. The activation change present in this region did not withstand the more stringent criteria used to select ROIs for the final relapse prediction model analyses, nor did activation in this area differ between healthy controls and cocaine-addicted subjects. Similarly, Paulus, Tapert and Schuckit (2005) found that ACC activation did not survive stepwise discriminant function analysis for inclusion in their prediction model for methamphetamine relapse. Instead, Paulus and his colleagues found that right middle frontal gyrus, right middle temporal gyrus, and right posterior cingulate cortex activation best predicted time-to-relapse, and that activation in these areas differed between relapsing and non-relapsing subjects. Kosten and colleagues (2006) used fMRI to explore the association between brain activation during cocaine-cue exposure and relapse to drug use in

cocaine-dependent subjects. They also failed to find activation in the ACC. Instead, they found that poor treatment effectiveness scores (calculated with urine toxicologies) were associated with BOLD activation in the left precentral, superior and right middle temporal, lingual, and posterior cingulate cortices. Further, these authors divided their patient group into eight non-relapsers and nine relapsers, and found that relapsers displayed greater posterior cingulate activation than non-relapsers during cue exposure.

Several differences exist between the present study and the Paulus and Kosten studies that may account for differences found in activation and relapse prediction model. First, patient groups in the current study were categorized as short- and long-term relapsers based on a one month split used by the DSM-IV-TR to establish remission qualifiers. Splitting groups by short- and long-term relapse may not be sufficient for clear differentiation of subsets of addicted individuals. The Paulus and Kosten studies defined their groups between relapsing and non-relapsing subjects, which may be more worthwhile for finding differences. In this study, ten of 45 subjects did not relapse within the six-month follow-up period post-discharge from acute, inpatient treatment. This sample of non-relapsing individuals was too small to incorporate into analyses as a separate group and lacked the power necessary to find significant differences between groups. It is also recommended for discriminant analyses that group sizes of the dependent variable be at least five times the number of independent variables included (Burns & Burns, 2009). Thus, a group size of ten individuals would be insufficient to power this type of analysis. Further, Paulus and colleagues utilized a block-design with two-choice prediction task requiring subjects to predict the location of a future stimulus based on their sequences of previous responses or outcomes. While the Paulus prediction task allows for isolation of a

decision-making process, it does not utilize monetary rewards and punishments to provide feedback regarding choice accuracy, and appears to focus on the acquisition of knowledge and future uncertainty without reversal of contingencies. The adapted O'Doherty paradigm employed in this study incorporated rewards and punishments (variable monetary values) as selection feedback, which may be a more ecologically valid and effective means of eliciting decision-making processes. This study also utilized an event-related fMRI design that allowed for better isolation of decision-making processes accounting for activation differences. Additionally, Kosten and colleagues utilized a drug-cue exposure paradigm. The authors proposed that the cue-induced activation found was rapid and occurring below awareness; thus, cue-induced neural activity might appear prior to the decision-making processes elicited here in which the individual is consciously attending to stimuli and contemplating outcomes of choices. Finally, the Paulus study created a prediction model for methamphetamine relapse. While methamphetamine and cocaine are both classified as stimulant drugs, differences exist in the pharmacokinetics and pharmacodynamics of each substance that account for unique neurotoxic effects (Cho & Melega, 2002; Ersche, et al., 2008).

Despite the lack of group differences in behavioral performance on the decision-making task, it was anticipated that alterations in neural activation would be found given previous findings of group differences in neural activation in the absence of behavioral differences. For example, cocaine-dependent patients exhibited lower activation in the right fronto-parietal network associated with Stroop interference, even though no behavioral differences were observed in Stroop performance (Barros-Loscertales et al., 2011). Since subjects were trained on the response reversal task prior to entering the scanner, it was anticipated that no statistically

significant differences in inter-group performance would be present. As mentioned previously, however, differences in neural activation were expected, but not observed. One possible explanation for the absence of group activation alterations could be the striking similarity across other demographic and clinical measures, particularly self-reported impulsivity. Previous research has shown that cocaine users perceive themselves as highly impulsive and score significantly higher on impulsivity measures than healthy volunteers (Coffey, et al., 2003; Ersche, et al., 2011; Moeller et al., 2005; Patkar et al., 2004; Swann, Dougherty, Pazzaglia, Pham, & Moeller, 2004). Lack of healthy control versus cocaine-addicted group differences in self-reported trait impulsivity diverges from this previous research. The impulsivity scores for the healthy control and cocaine-dependent groups were within normal limits for impulsiveness, albeit at the high end of the normal range (range is between 52 and 71) (Stanford et al., 2009); however, the healthy control group scored higher on the BIS-11 than control groups in previous research and the cocaine-addicted subjects scored lower than some patient groups in previous research (Coffey, et al., 2003; Ersche, et al., 2011; Moeller, et al., 2005). Selection of a healthy control group with high normal impulsivity may account for the lack of significant differences in impulsivity in this sample relative to previous research. Additionally, impulsivity was assessed in the cocaine-addicted group following approximately one week of inpatient treatment, whereas, other studies assessed impulsivity at the time of treatment entry (Patkar, et al., 2004) or during active use (Ersche, et al., 2011), which suggests that cocaine-addicted subjects may present as more impulsive closer to their last use. Healthy control and cocaine dependent groups were demographically fairly similar across these studies. Further, preclinical studies have found that impulsive choice predicts persistent cocaine seeking during extinction and enhanced propensity

to relapse (Broos, Diergaarde, Schoffelmeer, Pattij, & De Vries, 2012). Thus, training subjects on the response reversal task prior to imaging may have removed the element of impulsive choice from their decision-making that tends to differentiate their decision-making abilities from healthy controls.

Differences in activation between groups were also anticipated given reported structural and functional brain changes in cocaine-addicted subjects. Cocaine-addicted subject groups in these studies reporting changes were similar to the present sample in that they were primarily comprised of African-American males in their thirties to early forties with an average of 12 or 13 years of education (Adinoff, et al., 2003; Fein, et al., 2002; Fillmore & Rush, 2006; Franklin, et al., 2002; Tucker, et al., 2004). This suggests that the cocaine-addicted sample in this study was demographically similar to samples in the literature. Additionally, previous research typically attempted to match cocaine-addicted and control groups on demographic characteristics (similarly-matched in present study), such as age and education, with some studies still reporting group differences on these characteristics (Bolla, et al., 2003; Browndyke, et al., 2004; Fillmore & Rush, 2006; Franklin, et al., 2002), demonstrating the difficulty in matching patient and control groups in substance use research. Similar to the present study, past research also excluded co-morbid Axis I disorders other than substance use disorders, neurological disorders, and medical disorders, but allowed inclusion of individuals with other substance use as long as cocaine dependence was met. However, past structural and functional studies tended to differ on length of abstinence at time of assessment, with some studies reporting recent (e.g., within the last 28 days) or current use (Bolla, et al., 2003; Sim, et al., 2007; Volkow, et al., 2010) and others reporting abstinence between two and six weeks (Adinoff, et al., 2003; Browndyke, et al., 2004;

Fein, et al., 2002), which affects the generalizability of the significance findings. Further, few previous studies had criteria for inclusion regarding amount of recent and past cocaine use, meaning amount spent on cocaine and days used was variable between studies. Thus, it does not appear that the inability to find group differences with the current sample was due to demographic characteristics of the cocaine-addicted group. The lack of group differences in comparison to previous studies in cocaine addiction is more likely a result of the differences in amount of cocaine used, neuroimaging techniques employed (e.g., SPECT versus PET versus fMRI), or the tasks utilized in the scanner (e.g., response reversal task versus the Gambling Task).

Limitations and Future Directions

While the outcome predictability based on neuroimaging was significant, consideration should be given to the following protocol changes to help improve results. The current investigation trained subjects on the response reversal task prior to entering the scanner to ensure measurement of decision-making processes, as opposed to learning of a novel task, and to ensure an adequate number of reversals and feedback events (e.g., WinAcq and LossRev). Strict training criteria were employed to prevent those who had not fully learned the task from continuing on with neuroimaging, meaning that those individuals who could not learn the task with three step-down prompts were excluded from further study participation. However, it may be valuable to obtain neuroimaging data on all individuals regardless of ability to pass training, as failing the training exercise may imply something unique about the decision-making abilities of this subset of subjects (i.e., one healthy control and ten cocaine-addicted volunteers). Another component of the decision-making process accessible with the current paradigm is the number of

consecutive responses to the incorrect stimulus following a reversal, or perseverations. In other probabilistic reversal-learning tasks, chronic cocaine users have demonstrated perseverative responding to previously rewarded stimuli regardless of their ability to complete reversal stages successfully (Ersche, et al., 2008). In the current data set, perseverations may appear as either a failure to switch stimuli following a change in contingencies or possibly a return to the previously reinforced stimulus (S-), despite receipt of feedback that the other stimulus is being rewarded.

There are several limitations to the current findings. Sample sizes for the cocaine-addicted and healthy control groups were 45 and 23, respectively, and the cocaine use group was further reduced to 22 subjects in the short-term and 23 subjects in the long-term relapse subgroups. While these are reasonable sample sizes for neuroimaging studies, it is conceivable that increasing sample size and statistical power could alter findings regarding group differences, neural alterations, ROI inclusion, and prediction probabilities. Increasing sample size may also allow for a larger group of non-relapsing individuals for independent group study. Seventy-eight percent of the current study sample relapsed within the six-month follow-up period. These relapse rates appear somewhat higher than relapse rates reported in other relapse and treatment outcome studies (Aharonovich et al., 2006; Dutra et al., 2008; Sinha, et al., 2006). Additionally, these samples were carefully screened, and neither the control nor addicted participants had active Axis I disorders (other than substance use), major medical or neurological disorders, or were on psychotropic medications. While these rigorous inclusion/exclusion criteria provide increased experimental control, they may limit the generalizability of our findings as most substance-dependent individuals present with co-morbid DSM Axis I disorders, medical

complications, and multiple medications. Further, this study is cross-sectional, which does not allow for assumptions regarding the causal relationship between decision-making deficits, BOLD response, and substance use; however, this distinction may not be critical for predicting the probability that one will relapse. Despite best efforts to retain individuals in follow-up, ten subjects disappeared from follow-up and their relapse data was assumed as part of an intent-to-treat analysis. As a result, it is possible that the real time-to-relapse for these individuals was underestimated. Finally, a potential limitation of this study was the use of self-report and once weekly (nonrandom) UDS to identify relapse.

Another potential limitation was the use of the response reversal task to elicit decision-making processes in the subject groups. It is uncertain whether the RRT is useful for examining differences between cocaine-dependent and healthy control subjects. As this was the first study to employ the adapted O'Doherty paradigm to a substance use population, there are no references with which to compare this task with this population. Ersche and colleagues (2008) administered a probabilistic reversal-learning task to chronic cocaine users and healthy controls, and found that cocaine users demonstrated perseverative responding to previously rewarded stimuli regardless of their ability to complete reversal stages successfully. While these authors were able to find differences in behavioral performance, this measure was not applied as part of a neuroimaging paradigm to allow suppositions about its effect on neural activation, and the measure prompted differences in perseverations without differences in the ability to reverse responses. Thus, it may be that group differences are not particularly salient in response reversal per se, or that the method of isolating the reversal event in this study was not the most effective method for eliciting group differences. Future studies could investigate changes in neural

activation during perseverative responding (PersLoss and PersWin), as well as, consider more relevant contrasts of response reversal. It is premature to say that this task is ineffective for studying decision-making errors in this population because the full range of performances were not included in the study (e.g., subjects who could not learn the task to criterion were excluded). Further, cocaine-addicted individuals are often faced with real-world situations in which the rewards of using cocaine (e.g., euphoria, escape) are contrasted with negative financial consequences (e.g., loss of job/income and inability to pay rent – loss of home). While this task does not directly mimic these real world situations, it similarly uses monetary rewards and punishments to motivate changes in decision-making. The prediction model and neural activation results suggest that the activation elicited by the conditions in the task represent a valid approach in assessing decision-making and predicting relapse. Finally, further investigation is needed to help clarify the primary process (reversal, punishment, or both) responsible for generating the increases and decreases in neural activation during the LossRev event. The RRT provides multiple event types and avenues for exploring decision-making processes; however, only LossRev and WinAcq event types were examined in the current analyses.

Future research investigating the ability of neuroimaging to predict cocaine relapse may benefit from several of the considerations described above, such as a larger sample size, inclusion of individuals with comorbid psychiatric disorders, inclusion of individuals without successful training on the task utilized, and measurements of task performance without prior training. In addition, the current study focused on examining the predictive ability of alterations in neural activation during relapse. However, future models of relapse will need to incorporate

cognitive, biological, demographic, social, and psychological factors to assess the added contribution of these factors and to better understand their relationship with brain activation patterns. Neuroimaging procedures are often timely, costly, and inconvenient to perform; thus, future research will need to examine the clinical utility of neuroimaging in comparison to other measures assessing relapse factors to help determine if the benefits of neuroimaging for prediction outweigh the costs.

In summary, decision-making requires temporal delay and attentional control for the consideration of potentially rewarding or punishing outcomes. Determination of the outcome is based on previously acquired memories, affective and social associations, and one's capacity for logical deduction. Response reversal requires the additional element of mental flexibility to shift one's response or focus from a previously rewarded behavior that is no longer advantageous to another option. Thus, decision-making is a complex construct incorporating multiple cognitive processes mediated by activity in the orbitofrontal cortex, insula, dorsolateral prefrontal cortex, amygdala, hippocampus, cingulate cortex, paracingulate, precuneus, superior frontal gyrus, supplementary motor area, and superior and middle temporal cortex. While differences in neural activation were not exhibited between healthy control and cocaine-dependent individuals or between patient subgroups, several of these neural substrates (OFC, insula, DLPFC, amygdala, hippocampus, paracingulate, and precuneus) were determined to be important predictors of cocaine relapse, correctly classifying 71% of individuals into short- and long-term relapsing groups. Better understanding of these increases and decreases in activation and their relationship with relapse may help in the development of individually tailored treatment approaches that improve long-term abstinence. For example, knowing that someone has a 71% chance of

relapsing in the short-term based on a collection of activation and deactivation patterns in various ROIs allows for decisions about treatment options, such as extending length of stay in inpatient treatment, providing more intensive individual treatment, or enrollment in a structured residential program following discharge.

Table 1. Magnitude and ratios of wins to losses in the response reversal task.

	S+	**S-**
Win:Loss Ratio	2:1	1:2
Win Ranges	$75 - $200	$25 - $50
Loss Ranges	$25 - $50	$75 - $200

Note. Choosing the S+ fractal (good shape) results in high gains (wins) or low losses; whereas, choosing the S- fractal (bad shape) results in low gains (wins) or high losses.

Table 2. Clinical characteristics of all subjects.

	Healthy Controls (n = 23)	Cocaine-Dependent (n = 45)	T-Stat	p-Value
Gender, *n* (%)			4.28[b]	.038*
Male	15 (65)	39 (87)		
Female	8 (35)	6 (13)		
Age, mean (SD) (years)	41.8 (7.4)	43.1 (7.4)	-0.67[a]	.507
Race, *n* (%)			3.32[b]	.190
Caucasian	10 (44)	10 (22)		
African-American	12 (52)	32 (71)		
Hispanic	1 (4)	3 (7)		
Other	0	0		
Education, mean (SD) (years)	14 (1.6)	12.6 (2)	3.05 [a]	.003*
WTAR FSIQ, mean (SD)	98.6 (9.4)	92.3 (8.9)	2.69 [a]	.009*
BIS total, mean (SD)	69.9 (5.2)	69 (6.5)	0.57 [a]	.570
RRT, mean (SD)				
MoneyWon	5483.8 (1589.1)	5291.7 (1776.2)	0.44 [a]	.664
Nicotine packs/year, mean (SD)	1.74 (6.5)	12.65 (14.6)	-4.26[a]	< .001*

[a]Values obtained by t-test.
[b]Values obtained by χ^2 test.
*Value significant at α level of $p < .05$.

Table 3. Clinical characteristics of cocaine-addicted subjects by relapse confirmation.

	Self-reported + UDS (*n* = 26)	Missing (*n* = 9)	Non-Relapsers (*n* = 10)	T-Stat	*p*-Value
Gender, *n* (%)				3.27[b]	.352
Male	23	8	8		
Female	3	1	2		
Age, mean (SD) (years)	43.35 (7.3)	46 (5.8)	39.8 (8.1)	1.78[a]	.182
Race, *n* (%)				9.59[b]	.143
Caucasian	5	0	5		
African-American	19	9	4		
Hispanic	2	0	1		
Education, mean (SD) (years)	12.2 (1.7)	12.4 (1.9)	13.8 (2.4)	2.71[a]	.078
WTAR FSIQ, mean (SD)	92.3 (9.1)	88 (7.6)	96.3 (8.6)	2.17[a]	.128
BIS total, mean (SD)	68.2 (5.8)	72.1 (8.9)	68.3 (5.7)	1.29[a]	.287
RRT, mean (SD), money won	5305.8 (1800)	5016.7 (1867)	5502.5 (1788.6)	.172[a]	.842
CCQ total, mean (SD)	2.45 (0.9)	2.44 (0.8)	2.32 (0.4)	.108[a]	.898
Cocaine Use, mean (SD)					
Days used in past 90 days	67.9 (25.1)	70.3 (26.7)	56.4 (32.1)	.806	.453
$ used in past 90 days	6401.7 (4809.1)	10,276.7 (8408.2)	5373 (4831.5)	2.05	.141
Days used in lifetime	3017.4 (1798.7)	3906.8 (2303.5)	2100.4 (1706.9)	2.18	.126
Lifetime $ spent	396,393.8 (315797.9)	627,186.8 (710610.4)*	125,251.9 (90975.5)*	3.83	.030*

[a]Values obtained by t-test.
[b]Values obtained by χ^2 test.
*Value significant at α level of $p < .05$.

Table 4. Clinical characteristics of the patient subgroups.

	Short-term Relapse (n = 22)	Long-Term Relapse (n = 23)	T-Stat	p-Value
Gender, *n* (%)			.003[b]	.953
Male	19 (86)	20 (87)		
Female	3 (14)	3 (13)		
Age, mean (SD) (years)	43.7 (7.4)	42.5 (7.4)	.524[a]	.603
Race, *n* (%)			.311[b]	.856
Caucasian	5 (23)	5 (22)		
African-American	16 (73)	16 (69)		
Hispanic	1 (4)	2 (9)		
Education, mean (SD) (years)	12 (1.8)	13.2 (2)	-2.15[a]	.038*
WTAR FSIQ, mean (SD)	92.2 (9.2)	92.4 (8.9)	-.056[a]	-.153
BIS total, mean (SD)	68.3 (6.9)	69.7 (6.2)	-.707[a]	.484
CCQ total, mean (SD)	2.6 (.88)	2.2 (.62)	1.82[a]	.076
RRT, mean (SD)				
MoneyWon	5729.6 (1602.9)	4872.8 (1866)	1.65[a]	.106
Nicotine packs/year, mean (SD)	16.3 (14.6)	9.13 (14.0)	1.69[a]	.098
Cocaine Use, mean (SD)				
Days used in previous 90 days	66.4 (27.2)	65.3 (27.3)	.141[a]	.888
$ used in previous 90 days	6248.4 (5339.2)	7617.4 (6275.5)	-.787[a]	.436
Days used in lifetime	3230.6 (2217.6)	2762.8 (1642.1)	.807[a]	.424
Lifetime $ spent on cocaine	478529.2 (550205.1)	290252.1 (219216.3)	1.52[a]	.136

[a]Values obtained by t-test.
[b]Values obtained by χ^2 test.
*Value significant at α level of $p < .05$.

Table 5. Regions of Interest by predictor strength and identifying contrast.

Rank per SCDFC	ROI	Identifying Contrast	Secondary Contrast
2.08	Left Insula	Increase on LossRev-WinAcq	Increase on LossRev
-1.81	Left OFC	Increase on LossRev-WinAcq	Increase on LossRev
-1.05	Paracingulate	Increase on LossRev-WinAcq	Increase on LossRev + Decrease on WinAcq
.841	Right DLPFC2	Increase on LossRev-WinAcq	Decrease on WinAcq
-.832	Left Amygdala	Increase on WinAcq	NA
.680	Right OFC	Increase on LossRev-WinAcq	Increase on LossRev
-.626	Right DLPFC1	Increase on LossRev-WinAcq	Decrease on WinAcq
.525	Right Amygdala	Increase on WinAcq	NA
.496	Precuneus	Decrease on LossRev-WinAcq	Decrease on LossRev
.480	Left Hippocampus	Increase on WinAcq	NA

Note: Regions of interest obtained from voxel-level inference analysis (P = 0.15) and included in final relapse prediction model. SCDC = Standardized Canonical Discriminant Function Coefficients; NA = not applicable due to ROI activation occurring in single contrast; LossRev = large loss following a change in contingencies (unexpected loss); WinAcq = large win following correct choice of the "good shape" (expected win).

Table 6. Mean percentage signal change results for patient subgroups.

	# of Voxels	x	y	z	ST Relapse (*N*=22)*	LT Relapse (*N*=23)*	*F*	*p*-value
Left Amygdala	75	-24	-2	-18	.115 (.13)	.120 (.11)	.026	.872
Right Amygdala	118	26	0	-18	.118 (.11)	.129 (.10)	.128	.722
Right DLPFC1	10	30	48	22	.159 (.16)	.109 (.16)	1.088	.303
Right DLPFC2	10	38	38	26	.106 (.15)	.134 (.17)	.320	.574
Left Hippocampus	316	-26	-30	-10	.089 (.04)	.094 (.05)	.116	.735
Left OFC	165	-36	20	-14	.167 (.16)	.174 (.15)	.018	.893
Right OFC	120	36	22	-10	.119 (.14)	.157 (.13)	.928	.341
Left Insula	139	-36	18	-4	.113 (.15)	.181 (.15)	2.344	.133
Paracingulate	602	2	20	44	.196 (.20)	.168 (.17)	.254	.617
Precuneus	494	-4	-58	16	-.146 (.11)	-.123 (.12)	.493	.487

*Values provided are means with standard deviations; ST = short-term; LT = long-term
Note: x, y, z coordinates are provided for the mass center.

Table 7. Discriminant function analysis group membership predictions.

		Predicted Group Membership		
		ST Relapse	*LT Relapse*	*N*
Original Grouped Cases[a]				
	ST Relapse	16 (72.7)	6 (27.3)	22
	LT Relapse	3 (13.0)	20 (87.0)	23
Cross-validated Grouped Cases[b]				
	ST Relapse	16 (72.7)	6 (27.3)	22
	LT Relapse	7 (30.4)	16 (69.6)	23

a. 80.0% of original grouped cases correctly classified.

b. 71.1% of cross-validated grouped cases correctly classified.

Note: ST = short-term relapse; LT = long-term relapse

Figure 1. Experimental design of the Response Reversal Task (RRT). Stimulus presentation (left panel): the two fractals (S+ and S-) alternate in their positions (right and left) in a pseudorandom order. Subjects have 3 seconds to choose the S+ or S- fractal. Feedback presentation (middle panel): money won or lost in response to the stimulus choice is presented at the top of the screen (win in green, loss in red), and a bar depicting the current total money won or lost is presented as a bar at the bottom of the screen. The feedback presentation is displayed for a total of 3 seconds. An inter-stimulus fixation cross (right panel) is presented on the screen for 2, 4, or 6 seconds (jittered).

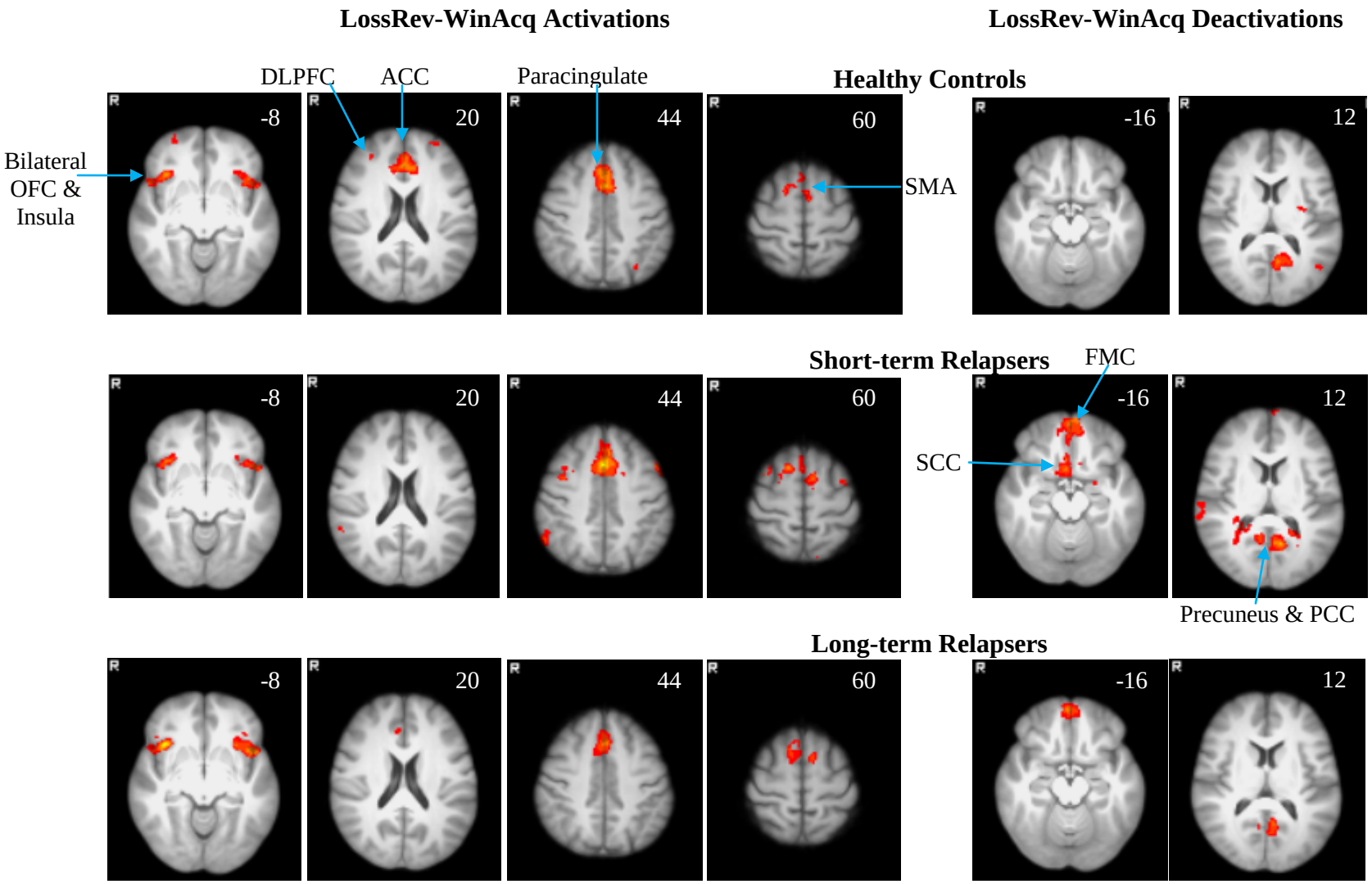
LossRev-WinAcq Activations
LossRev-WinAcq Deactivations
Healthy Controls
DLPFC
ACC
Paracingulate
Bilateral OFC & Insula
SMA
-8
20
44
60
-16
12
Short-term Relapsers
FMC
SCC
Precuneus & PCC
Long-term Relapsers

Figure 2. Group activation changes using original cluster-level inference analysis. Z statistic images were thresholded using clusters determined by Z > 2.3 and a (corrected) cluster significance threshold of P = 0.05. Rows display images by group: healthy controls, short-term relapsers, and long-term relapsers. Images on left depict activations during the LossRev-WinAcq comparisons. Note, DLPFC and ACC are largely not visible across groups with these parameters. Images to the right display deactivations during the LossRev-WinAcq contrast that are primarily accounted for by deactivations during the LossRev only contrast. Amygdala, hippocampus, and temporal cortex activations are not present in these contrasts. MNI coordinates (Z axis) noted in the upper right corner of each image. R = right; OFC = orbitofrontal cortex; DLPFC = dorsolateral prefrontal cortex; ACC = anterior cingulate cortex; SMA = supplementary motor area; FMC = frontal medial cortex; SCC = subcallosal cortex; posterior cingulate cortex.

SECTION 2

APPENDIX A

Additional Background

According to statistics produced by the Substance Abuse and Mental Health Services Administration (SAMHSA), 4.8 million Americans aged 12 and older in 2009 had abused cocaine in some form, and an estimated 2.65 million persons aged 12 or older received treatment for a cocaine use disorder (SAMHSA, 2010). In 2009, one million emergency room visits involved an illicit drug and 422,896 of these visits involved cocaine (SAMHSA, 2010). Cocaine users are at risk of cardiovascular complications, respiratory failure, strokes, and seizures (Allred & Ewer, 1981; Guerot, et al., 2002; Levine, et al., 1987; Majlesi, et al., 2010; O'Leary & Hancox, 2010). They are also at risk for sexually transmitted diseases and HIV infection (de Azevedo, Botega, & Guimaraes, 2007). Further, individuals with cocaine dependence frequently exhibit transient depressive symptoms that meet symptomatic and duration criteria for Major Depressive Disorder, particularly during the withdrawal period (DSM-IV, 2000; Kilbey, et al., 1992). Cocaine intoxicated individuals may also display delusions and hallucinations that resemble a psychotic disorder (Kuzenko, et al., 2011) or impulsive behavior and sleep deficits resembling bipolar disorder (Dell'Osso, et al., 2011; Swann, 2010). Moreover, chronic cocaine users often experience periods of anxiety or panic symptoms that may persist following abstinence (Han, et al., 2010; Louie, Lannon, & Ketter, 1989; Santucci & Rosario, 2010).

In addition to the physical and mental health related consequences, cocaine use has an effect on communities and the workplace. Cocaine dependent individuals may resort to illegal means for securing funds to foster their use, such as theft, prostitution, or drug dealing.

Adolescents engaged in cocaine use are more likely to skip school and display poorer academic performance (O'Malley, Johnston, & Bachman, 1985; D. E. Smith, Schwartz, & Martin, 1989). Cocaine dependent employees are more likely to change jobs frequently, be late or absent from work, produce less, become involved in workplace accidents, and to file workers' compensation claims (SAMHSA, 2010). Thus, cocaine dependence is an individual and societal problem requiring intervention.

Prevention and treatment programs have provided limited success at reducing the prevalence of this problem (Aharonovich, Nunes, & Hasin, 2003; Dutra, et al., 2008). As a result, research efforts in the past couple decades have shifted their focus towards psychological, biological, and neurological factors that either contribute to the development of addiction or to the persistence of the disorder. Concurrent advances in measurement capabilities, such as structural and functional neuroimaging techniques, have provided the opportunity to further investigate these factors. Research has revealed that long-term cocaine use could cause persistent neural deficits and that these deficits endure following a brief period of abstinence (Beatty, Katzung, Moreland, & Nixon, 1995; Browndyke, et al., 2004; Di Sclafani, Tolou-Shams, Price, & Fein, 2002). The orbitofrontal cortex (OFC), an area of the brain implicated in decision-making and inhibition, is one such area shown to have alterations in functioning following cocaine dependence (Bolla, et al., 2003; Calu, et al., 2007; Fillmore & Rush, 2006; Schoenbaum, et al., 2004; Schoenbaum & Shaham, 2008; Volkow & Fowler, 2000; Volkow, et al., 1993). Cocaine dependence has also been associated with neuropsychological abnormalities in decision-making, executive functioning, impulsivity, visuoperception, psychomotor speed, and manual dexterity (Beatty, et al., 1995; Bechara & Martin, 2004; Browndyke, et al., 2004; A.

Verdejo-Garcia & Perez-Garcia, 2007). While it is clear that cocaine use can affect neurological functioning, the potential impact of these deficits on maintaining abstinence is still unclear.

While studies have shown changes in OFC activation and impaired decision-making in addicted populations, there have been few studies examining the ability of these measures to predict relapse. Further, treatment outcome studies have found that individuals with elevated baseline levels of impulsivity remain in treatment a shorter period of time (Moeller et al., 2001). However, a limitation of these studies is that additional information regarding the underlying mechanisms involved and data about relapse following discharge is not provided. Further investigation is needed to determine the relevance of impaired decision-making in cocaine-addicted individuals, as well as, if and how potential differences in neural activation during decision-making are related to relapse. Understanding whether cocaine-addicted individuals with impaired decision-making return to use sooner than their less-impaired peers and whether prospective relapse can be predicted by observed deficits in neural activation (i.e., in the OFC), could help inform psychological and pharmacological interventions for substance dependent individuals.

Cocaine Dynamics

Preparations and Routes of Administration

Cocaine (benzoylmethylecgonine) is derived from the leaves of the Erythroxylon plant, a tree or shrub native to western South America. The dried coca leaves are dissolved in a solution of kerosene, alkaline bases, potassium permanganate, and sulfuric acid to produce coca paste (Lowinson, 1997). Coca paste can be treated with hydrochloric acid to become cocaine hydrochloride, a fine, white powder. This compound can be administered intranasal (i.e.,

"snorted") or it can be dissolved in water or saline and administered intravenously. Cocaine alkaloid (a.k.a., "freebase" or "crack" cocaine) is an odorless, colorless, crystalline substance created by a mixture of bases with paste. Cocaine alkaloid has a melting point of 98º C, which converts the substance to a stable vapor for inhalation (Prakash & Das, 1993). Crack cocaine is the most popular form of cocaine due to its accessibility and inexpensiveness (Boghdadi & Henning, 1997). It is made by dissolving cocaine hydrochloride in water, mixed with baking soda, and heated. The byproduct is a soft mass that becomes hard ("rock") when dry. The most common routes of administration include oral (onset of effects within 1 hour; duration of several hours), intranasal (3-5 minute onset; 45-60 minutes duration), intravenous (1-2 minute onset; 10-20 minute duration), and inhalation (30 second onset; 5-10 minute duration); however, cocaine can also be administered topically as a local anesthetic (Preti, 2006).

Pharmacology

Cocaine is a stimulant drug that typically increases alertness, energy, and motor activity, generates feelings of euphoria, and enhances sensations of competence and sexual ability, as well as feelings of paranoia, restlessness, and anxiety at higher doses (Preti, 2006). Physiological changes are also induced with cocaine administration, such as tachycardia and hypertension. The primary means by which cocaine prompts these pharmacological actions is to block the reuptake of certain neurotransmitters into presynaptic nerve terminals (Benowitz, 1993; Prakash & Das, 1993). Considerable evidence emerged early on suggesting that the reinforcing effects of cocaine derived from the blocking of dopamine reuptake (Kuhar, Ritz, & Boja, 1991). However, pharmacological studies found that dopaminergic medications were not effective for reducing the euphoric effects and self-administration of cocaine (Kuhar, et al., 1991). Subsequent theories

maintained that dopaminergic mechanisms were involved in the initiation of drug use, but posited that other mechanisms were likely contributing to dependence and craving. Thus, current theory holds that cocaine blocks the reuptake of dopamine, serotonin, and norepinephrine into presynaptic nerve terminals; thus, increasing the norepinephrine, serotonin, and dopamine-mediated effects in the central and peripheral nervous systems. For example, dopamine increases in the nucleus accumbens (NAcc) are associated with the euphoric effects and drug-seeking behavior that follows exposure to conditioned drug-related cues (P. E. Phillips, Stuber, Heien, Wightman, & Carelli, 2003; Yun, Nicola, & Fields, 2004). Further, these dopamine responses are moderated by glutamatergic projections from the frontal cortex and limbic areas, including the ventral tegmental area (VTA) (Taber, Das, & Fibiger, 1995; You, Wang, Zitzman, Azari, & Wise, 2007), orbitofrontal cortex (OFC) (E. T. Rolls, 1996), the amygdala and ventral hippocampus (Grace, Floresco, Goto, & Lodge, 2007). Disrupted synaptic functioning of the frontal regions may contribute to the impaired control over drug taking that characterizes drug addiction.

Dependence Criteria

Cocaine dependence is defined as a disorder resulting from persistent use of cocaine despite significant impairment or distress in psychosocial functioning (DSM-IV, 2000). Associated symptoms include tolerance, withdrawal, consumption of increased amounts or over longer time periods than intended, inability to control use, excessive time spent in drug related efforts, reduction in important social, occupational or recreational activities due to use, and continued use despite awareness of associated physical or psychological problems. Due in part to its euphoric effects and short half-life, individuals using cocaine can develop dependence after

a relatively short period of experimentation, particularly when smoking and intravenous methods are the preferred routes of administration (Boghdadi & Henning, 1997). Withdrawal effects, such as decreased energy, limited ability to experience pleasure, dysphoria, and reduced interest in the environment, are considered mild in comparison to other substance use disorders, and thus, do not contribute much to the addictive nature of cocaine (Lowinson, 1997). Underlying biological and neurological changes are believed to occur during this process from use to dependence that creates a perceived need for cocaine despite apparent negative consequences.

Treatment Approaches and Outcomes

Proposed interventions for treating substance dependence typically focus on addressing ambivalence or motivation to abstain, development of more appropriate and adaptive coping strategies (according to social learning theory), changing reinforcement contingencies, affect management, improving interpersonal functioning, enhancing social supports, and compliance with pharmacotherapy (K. M. Carroll, 1997). Treatment approaches have been moderately effective at helping individuals stop abusing drugs and lead more productive lives. In a review of 27 randomized controlled trials of psychosocial interventions for cocaine and psychostimulant related disorders, cognitive-behavioral therapy (CBT) interventions were most effective at reducing dropouts from treatment and cocaine use (Knapp, Soares, Farrel, & Lima, 2007). Behavioral interventions were also found to be preferable to clinical management, usual care, information and referral. In these types of treatment, individuals receive psychoeducation about the relapse process and learn to identify internal (e.g., thoughts or emotions) and external (e.g., triggers/cues) precipitants of drug urges, to engage in lifestyles changes that increase healthy behaviors and decrease exposure to situations with drug associations, and to prevent relapse

following a lapse or slip (K. M. Carroll, 2005). Intensive interventions and CBT with some form of contingency management (CM) appear to demonstrate the most benefits. Examination of controlled clinical trials of CBT interventions with and without CM (34 studies and 2,340 participants) revealed that interventions utilizing both CBT and CM had the highest effect sizes followed by CM only interventions with substance dependent individuals (Dutra, et al., 2008). Approximately 31% of the population examined achieved clinically significant abstinence post-treatment and about 32% of participants remained abstinent during the study period; however, another third of subjects (35.4% across conditions; 42.0% cocaine patients) dropped out of treatment and a significant portion of the participants were unable to retain abstinence post-treatment. Further, employment-based reinforcement programs with abstinence-contingent employment programs help maintain long-term abstinence; however, the effects of these programs tend to dissipate over time once the contingency program is discontinued (DeFulio & Silverman, 2011).

Participation in 12-step programs concurrently with professional treatment programs is often recommended. Twelve-step programs (e.g., Alcoholics or Narcotics Anonymous) focus on abstinence, fellowship at meetings, and working through outlined steps. Compared with individuals who participate in professional treatment only, individuals who participate in professional treatment and 12-step programs are more likely to achieve remission (Moos & Moos, 2005). Additionally, higher probability of remission at 16 months was associated with longer duration in a 12-step program, whereas abstinence lapses and relapses were associated with shorter duration in a 12-step program. Thus, while clinical interventions consistently offer

benefits for treating cocaine dependence, they are not sufficient for securing treatment retention or maintaining long-term abstinence.

Approximately 70% of individuals (18 cocaine dependent patients) in a CBT treatment program prematurely discontinued treatment, completing an average of six sessions compared to an average of ten sessions in treatment completers, and early discontinuation was associated with poorer cognitive functioning (i.e., attention, mental reasoning, and spatial processing), sustained substance use, and relapse (Aharonovich, Nunes, & Hasin, 2003). Treatment retention is a consistent problem within substance abuse treatment, but it is not unique to CBT. Cocaine dependent individuals often do not adhere to medication regimens and medical protocols related to comorbid disorders or health concerns (Cregler & Mark, 1986; Nyenwe et al., 2007). Further, successful treatment retention may be hindered by brain alterations suggestive of mild cognitive impairments (Aharonovich, et al., 2006). It stands to reason that if one has cognitive impairment he or she may not benefit from a treatment that focuses on cognitions, and thus, may be more vulnerable to relapse if this is the only treatment provided. Therapeutic interventions will continue to be only moderately effective until underlying biological and neurological deficits are identified and addressed, which may require an individually tailored and multidisciplinary treatment approach.

Currently available pharmacotherapies for drug dependence may facilitate detoxification and treatment of coexisting disorders, but are not sufficient for stabilizing or maintaining abstinence from cocaine use or improving treatment retention (K. M. Carroll, 1997; de Lima, de Oliveira Soares, Reisser, & Farrell, 2002; Preti, 2006; Rilling & Adinoff, 2006) . For instance, clinical use of antidepressants (M. S. Lima, Reisser, Soares, & Farrell, 2003), carbamazepine (A.

R. Lima, Lima, Soares, & Farrell, 2002), or dopamine agonists (Soares, Lima, Reisser, & Farrell, 2003) as stand-alone treatments for cocaine abuse has not been supported. Glutamatergic and GABAergic agents are believed to be moderately effective at reducing the associated euphoria and at alleviating cue-induced craving (Dackis, 2004). Additionally, preclinical studies suggest that several types of compounds (e.g., dopamine D1-like receptor agonists, dopamine D3 antagonist, and cannabinoid CB1 receptor antagonist) are effective at reducing reinstatement induced by cocaine cues, discrete cues, and stress; however, these compounds still need to be proven efficacious in human clinical trials and across types of relapse (Shaham, Shalev, Lu, De Wit, & Stewart, 2003). Over the past couple decades, anti-cocaine vaccinations have been developed and tested; however, these are not ready for distribution (Kinsey, Kosten, & Orson, 2010). While the future of vaccinations seems promising, use of this intervention may not be the most economical option as it will likely require booster shots to maintain the desired levels of anti-cocaine antibodies and will need to be offered in conjunction with other interventions (e.g., rehabilitation and psychotherapy) to foster remission. At this time, the most promising strategy for facilitating recovering and maintaining abstinence appears to be a combination of addiction treatment medications with psychotherapeutic interventions that are tailored to each individual's drug abuse pattern (e.g., type of use; route; alone or with other substances) and co-occurring medical, psychiatric, and social problems.

Previous Relapse Perspectives

By the current definition, substance use disorders are marked by chronic relapsing events. Relapse rates for stimulant dependent individuals within a year of seeking treatment vary between 50 and 65 percent (Sinha, et al., 2006). Relapse is defined as a return of symptomatic

behavior following a period of improvement (*Merriam-Webster's collegiate dictionary*, 2003), and is considered a multi-determined process with psychosocial, biological, and neurological components. Psychosocial factors contributing to relapse have been well studied over the past few decades. Several intrapersonal determinants of relapse have been identified including self-efficacy, outcome expectancies, motivation, coping resources, negative emotional states, response to treatment, and physiological factors (e.g., cravings, urges, and withdrawal), as well as, environmental (e.g., drug associated discrete and contextual cues) and social factors predicting relapse (Brownell, Marlatt, Lichtenstein, & Wilson, 1986; K.M. Carroll & Rawson, 2005; Shaham, et al., 2003; Sinha, et al., 2006). For example, sense of purpose in life (e.g., power, material possessions, family) prior to entering treatment was examined as a predictor of response to a 30-day treatment program, and was found to significantly predict better treatment outcomes for relapse and frequency of cocaine use (via positive urine drug screens and collateral report) in the 6-month period following treatment (Martin, MacKinnon, Johnson, & Rohsenow, 2011). Additionally, urge to use cocaine has been found to be predictive of the amount spent on cocaine in the first 3-months following a residential treatment program, and these urges were found to be more intense preceding a relapse rather than a close encounter (Rohsenow, Martin, Eaton, & Monti, 2007). Further, clinical symptoms, such as trauma history, depressive and anxiety symptoms, stress, and comorbid psychiatric disorders, have been thoroughly investigated and are considered common reasons cited for relapse (McKay, Rutherford, Alterman, Cacciola, & Kaplan, 1995; Sinha, et al., 2006). For example, current major depression predicted crack cocaine use at follow-up for women in drug court (Johnson et al., 2011). Additionally, exposure to stress leads to the reinstatement of drug seeking behavior and increases relapse susceptibility

in dependent individuals (Shaham, et al., 2003; Sinha, 2008). Numerous psychological theories have been posited that incorporate these factors into explanations of relapse processes: classical and instrumental conditioning, trait theories, self-regulatory theories, cognitive appraisal model, social learning theories, and self-efficacy and outcome expectancy models (Brandon, Vidrine, & Litvin, 2007; Collins, Parks, & Marlatt, 1985; Connors, Maisto, & Donovan, 1996).

While these theories and individual factors are relevant and informative, associated treatment options are insufficient given high relapse rates. Therefore, more recent investigations have targeted associated biological and neurological changes, resulting from exposure to substances that are believed to maintain addiction and increase risk of relapse. Without an understanding of both the predisposing factors and neurobiological changes that take place, clinical implications of this research will be limited. Investigations into the biological responses involved in drug relapse have examined alterations in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system in cocaine-addicted individuals. For example, Sinha and colleagues (2006) conducted an experiment in which 49 cocaine-addicted subjects were exposed to three guided imagery sessions with either a stress situation, drug cue, or relaxation script while measures of HPA axis responses and physiological responses (blood pressure and pulse) were measured. The findings from this study indicated the idea that greater stress-induced, rather than drug cue-induced, cocaine craving predicted a shorter time to first use. However, stress-induced corticotrophin and cortisol levels were not associated with time to relapse, but were associated with average quantity of cocaine consumed per occasion in the 90 days following treatment. The authors suggest that the association between consumption and the biological response may be evidence of an inability to control intake after initiation of use.

Another study explored the ability of brain-derived neurotropic factor (BDNF) to serve as a biomarker of relapse risk in cocaine dependent individuals (D'Sa, Fox, Hong, Dileone, & Sinha, 2011). Cocaine dependent individuals demonstrated higher serum BDNF levels compared to healthy controls with the cocaine dependent group means being 28% to 56% higher than control group means. Additionally, two-thirds of the cocaine dependent participants (23 of 35) in this study relapsed to cocaine use prior to the end of the 90 day follow-up period, and these individuals were found to significantly differ ($p < .04$) in serum BDNF levels from the non-relapsing cocaine dependent patients. Higher levels of serum BDNF were significantly predictive of shorter time to cocaine relapse, as well as greater quantities of cocaine used and greater number of days of cocaine use over a 90-day follow-up period (D'Sa, et al., 2011). These studies represent prospective studies noting previously undocumented associations between biological markers and relapse outcome measures, and require replication and further elucidation to confirm their role in the relapse process and treatment design.

Neural Alterations in Cocaine Addiction

Neurocognitive Aspects of Relapse

Novel investigations are also exploring the influence of neurocognitive deficits and neural dysfunction on cocaine relapse risk. Chronic cocaine abusing individuals have repeatedly demonstrated impairments on several neuropsychological measures following a relatively brief period of abstinence (e.g., two to six weeks), including problem-solving, perceptual motor speed and spatial processing, learning, immediate and delayed memory, attention, abstract reasoning, cognitive flexibility, verbal knowledge, and executive functioning (Beatty, et al., 1995; Browndyke, et al., 2004; Cunha, Nicastri, de Andrade, & Bolla, 2010; Di Sclafani, et al., 2002;

Goldstein et al., 2004; Jovanovski, Erb, & Zakzanis, 2005; A. Verdejo-Garcia, et al., 2006). In persons suffering from cocaine addiction, reductions in inhibitory control were found relative to controls (Fillmore & Rush, 2002) and heroin users (Bornovalova, Daughters, Hernandez, Richards, & Lejuez, 2005; A. J. Verdejo-Garcia, Perales, & Perez-Garcia, 2007), heightened impulsivity was found relative to controls ($p < .01$)(Coffey, et al., 2003; Wittmann, Leland, Churan, & Paulus, 2007), and impulsivity was related to the severity of cocaine abuse, the severity of cocaine withdrawal, and the likelihood of poor treatment retention (Moeller, et al., 2001). Further, neurocognitive scores in the domains of attention, memory, spatial ability, speed, accuracy, global cognitive functioning, and global reasoning have been shown to be significantly lower in treatment non-completers relative to treatment completers (effect size range of .59 to .87) (Aharonovich, et al., 2006).

Some variability appears across neurocognitive studies in the specific types of deficits observed; however, there is little question that neurocognitive impairments are present. Effect sizes are generally large (range of 0.49 to 1.29) for analyses showing significant group differences in neurocognitive performance (Browndyke, et al., 2004; Goldstein, et al., 2004). Comparability of findings across studies is challenged by differences in sample sizes, intensity and duration of drug use, length of abstinence, the neuropsychological battery employed, group definition (e.g., cocaine use only, 'substance dependent', or polysubstance use), and the comparative group used (e.g., healthy control group present; normative data only). For example, Beatty and colleagues (1995) combined visual perception, perceptual motor speed, and attention into one skill domain measured by the Trail Making Test forms A and B (Reitan & Wolfson, 1993) and two subtests from the WAIS-R (Block Design and Digit Symbol) (Wechsler, 1981).

Based on subject performance on these measures, the authors concluded that the cocaine-addicted sample displayed motor speed deficits relative to healthy controls. However, Browndyke and colleagues (2004) did not find a motor speed deficit utilizing finger-tapping test (Reitan & Wolfson, 1993), but did find significant group differences (p = .016) on the Trail Making Test (forms A and B), which they identified as a measure of graphomotor skills and executive functioning. In addition, neuropsychological impairment in individuals with current cocaine use disorders appears relatively mild, meaning they are within one standard deviation of control group performance (Goldstein, et al., 2004; Woicik et al., 2009) or within the low average to average performance levels relative to age- and education-matched norms (Browndyke, et al., 2004). Further, neuropsychological performance is typically inversely related to the amount of cocaine used (i.e., greater use associated with poorer performance) (Bolla, Rothman, & Cadet, 1999; Di Sclafani, et al., 2002), and the intensity of cocaine use (grams per week) may be more strongly related to neurobehavioral performance than frequency or duration of cocaine use (Bolla, et al., 1999). For example, one study found no group differences (cocaine group versus non-drug using group) on Wisconsin Card Sorting Test (WCST) (Heaton, 1993) performance; however, a dose-related effect was noted - the more cocaine use reported the lower the performance on this measure. Finally, the extent to which these cognitive impairments persist is currently unclear with preliminary evidence suggesting that deficits persist at 6-months abstinence with some improvement found in immediate memory (Di Sclafani, et al., 2002; Strickland, et al., 1993).

Decision-making and Relapse

Of particular relevance to the current study are potential deficits in decision-making that seem to characterize substance dependent individuals and the association between these deficits and one's tendency to relapse. Focusing on decision-making impairments has overt clinical relevance based on these reported neurocognitive deficits and anecdotal accounts from cocaine addicted individuals. Decision-making refers to a deliberate, conscious process in which an individual evaluates the potential positive and negative consequences of a choice before coming to a conclusion (Bechara, 2005). Temporal delay allows for reflection on the choice and planning for future action. Intact decision-making is relevant to maintaining one's determination to abstain from substances in a community treatment setting where there is less structure and more environmental temptations (Passetti, et al., 2011). However, cocaine abusers generally display poorer performances on tests of decision making [e.g., the Gambling Task (Bechara, et al., 1994)], particularly those tests requiring evaluation of future consequences in the presence of immediate gains (Grant, et al., 2000). Further, many of the treatment approaches proposed to treat cocaine dependence address faulty decision-making and cognitions (e.g., CBT); however the success of these interventions may be hindered by the individual's decision-making abilities and potentially the effectiveness of brain regions normally supporting these activities. Designing interventions focused on decision-making deficits in cocaine-dependent individuals would benefit from identification of brain regions involved in these deficits and an understanding of how disruptions in these areas are associated with a tendency to relapse.

Assessments of Decision-Making in Cocaine Addiction

Decision-making typically encompasses two major processes. First, assessment of risk and delay requires consideration of the value of the potential reward or punishment, the duration

of the time period before the selected outcome is received, and the probability that the outcome will occur (Monterosso, Ehrman, Napier, O'Brien, & Childress, 2001). Theoretically, relapse results from the selection of choices associated with the immediate benefits of intoxication, even if those choices are coupled with negative future consequences (e.g., loss of job, home, or relationships) (Bechara & Damasio, 2002). Two common tests of delay and risk are the Delayed Discounting Procedure (DDP) (Bickel, Odum, & Madden, 1999) and the Gambling Task (GT) (Bechara, et al., 1998). The DDP offers smaller-sooner rewards relative to larger-later rewards, typically using real or hypothetical money. Studies utilizing DDP have demonstrated that persons addicted to cocaine repeatedly choose smaller, immediate monetary rewards over larger, delayed monetary rewards and tend to discount the monetary reward more rapidly over time than controls ($p < .01$) (Coffey, et al., 2003; Kirby & Petry, 2004). Cocaine-addicted individuals also discount cocaine rewards at a higher rate than monetary rewards (Coffey, et al., 2003). The GT involves choosing between decks of cards offering high payments with higher penalties or decks offering low payments with lower penalties, which is the more optimal, long-term strategy. Substance abuse patients are more likely than controls to choose large immediate rewards despite the risk of higher losses (Bartzokis, et al., 2000; Bechara, et al., 2001; Grant, et al., 2000). For example, Bechara (2004) found that 11% of healthy controls and 61% of substance dependent individuals (8 of 17 alcohol use, 3 of 8 cocaine use, and 14 of 16 methamphetamine use individuals) opted for choices with high immediate gains despite higher future losses. However, significant differences in performance are not always found. For example, Adinoff and collaborators (2003) found that cocaine addicted individuals did not differ in GT performance from healthy controls, and others have found that significant differences in group performance

emerge across the various blocks of the task (Bechara & Martin, 2004; M. Ernst et al., 2003) suggesting a need to analyze multiple components of the behavioral performance to better characterize potential impairments.

Response reversal is the second major decision-making process and occurs due to changing response contingencies, such as amount of reward, type of outcome (e.g., reward to punishment), or time it takes to receive the reward. Once the contingencies change, a person must consider the positive and negative qualities of potential responses followed by a decision to either continue or change their current pattern of responding. For example, cocaine use is typically highly rewarding initially due to the euphoric effects and has little apparent costs (may not initially be detrimental to health or functioning). However, over time the highly pleasurable effects of cocaine use dissipate and multiple negative consequences emerge, such as legal, health, and social problems. The cocaine dependent individual's persistent use despite these negative consequences suggests difficulties in the response reversal aspect of decision-making. Preclinical studies also suggest that chronic cocaine exposure (14 daily injections of cocaine) results in impairments in reversal learning, even following a two week period of abstinence (Krueger, et al., 2009). Further, clinical studies provide convincing evidence for response perseveration in cocaine users (significantly more errors, $p < .001$) to previously rewarding stimuli following a change in contingencies on a probabilistic reversal-learning task compared with controls, amphetamine users, opiate users, and ex-drug users (Ersche, et al., 2008).

The Wisconsin Card Sorting Test (WCST) (Heaton, 1993) is a traditional test of response reversal and mental flexibility. Performance on this task has been variable (Hoff et al., 1996; Jovanovski, et al., 2005) within cocaine abusing populations, with some studies finding poorer

performance than healthy controls (Beatty, et al., 1995; Cunha, et al., 2010; Dolan, Bechara, & Nathan, 2008; Woicik et al., 2011) and other studies finding no difference (Grant, et al., 2000; A. Verdejo-Garcia & Perez-Garcia, 2007). Inconsistency in these findings may be related to differences in abstinence periods and outcome variables examined (e.g., perseverations versus categories completed), as well as dose-related effects (inverse association) of cocaine on WCST performance (Bolla, et al., 1999). Additionally, Woicik and colleagues (2011) examined a subset of WCST higher performing cocaine addicted subjects whose scores were comparable to control subjects and looked at the block-by-block performance of these individuals. The authors found that these cocaine addicted subjects still exhibited more perseveration when they were first asked to sort based on a previous sorting rule (the initial task-set switch; $p < .05$). Further, ecologically valid tests of functioning may be more discriminative than traditional measures at detecting cognitive impairments in a cocaine dependent population. For example, Verdejo-Garcia and Perez-Garcia (2007) found that substance dependent individuals (64.9% cocaine use) performed significantly poorer than controls on 5 of 6 subtests of the Behavioural Assessment of the Dysexecutive Syndrome (BADS; effect sizes = 0.53 to 1.30) (Wilson, Alderman, Burgess, Ernslie, & Evans, 1996), an ecologically valid measure of executive function, but did not perform significantly different than controls on the WCST. The authors also found that performance on the BADS predicted everyday problems related to apathy, disinhibition, and executive dysfunction, whereas, WCST performance did not.

O'Doherty and colleagues (2003) established a reversal task in which subjects have to choose a stimulus from two unfamiliar fractal patterns and switch their response to the other stimulus when contingencies change. Subjects receive feedback regarding the correctness of the

chosen stimulus by a monetary loss or win. Damage to the OFC in humans produces deficits in the ability to perform this task, such that subjects perseverate to the previously rewarded response. While this task has been administered to healthy subjects and individuals with OFC lesions, it has not been used to assess the neural functioning in drug abuse subjects. However, the O'Doherty et al. paradigm offers several advantages: reversals do not occur until after mastery of the contingency, there are multiple reversals in the task, use of more salient rewards and punishments (variable monetary values), and independent assessment of brain activation to reward and punishment. Due to its use of monetary feedback (versus "right/wrong" feedback in the WCST), the O'Doherty response reversal task may be more ecologically valid and effective at eliciting decision-making processes in the study participants, particularly the cocaine use group, who invest considerable time and effort in pursuits to gain money to obtain cocaine, and demographically similar healthy groups that may consist of individuals with lower socioeconomic status. Thus, this task will be administered within the scanner environment to generate decision-making processes for observation. However, the WCST will also be examined to help clarify the discrepant literature, expand the literature by determining its ability to predict relapse, and to serve as a behavioral measure of decision-making (due to training of the RRT prior to scanning).

Neural Correlates of Relapse

Imaging Techniques

Following the realization that cocaine-addicted individuals were performing abnormally on measures of neuropsychological functioning, investigators began to focus their efforts on identifying alterations in neural processes and neural correlates of these functional changes.

Functional neuroimaging measures metabolic changes to allow for identification of brain regions associated with specific cognitive processes and mapping of brain activations associated with these processes. The most common functional neuroimaging techniques include single photon emission computed tomography (SPECT), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI). SPECT is a nuclear medicine technique that uses radionuclides (i.e., those that emit a single photon with each radioactive decay event) and a computer-aided gamma camera to take cross-sectional images through the body (Katz & Groskin, 1998). PET imaging is another form of nuclear medicine using cyclotron-produced positron emitters and a special camera to detect the photon reactions (Katz & Groskin, 1998). These nuclear medicine techniques provide fairly good spatial resolution (SPECT is poorer than PET), but are limited by the invasiveness of radioactive injections, expense of using radioactive isotopes, limited accessibility of equipment (for PET), and the slowness of image acquisition (Huettel, Song, & McCarthy, 2009; Katz & Groskin, 1998). In contrast, fMRI is less invasive, provides excellent temporal resolution (one image every few seconds), uses the body's natural physiology to measure change (no ionizing radiation), allows for multiplanar imaging (axial, coronal, sagittal, and oblique), and provides good anatomic detail. Functional MRI typically measures changes in blood oxygenation levels over time and is based on the principles of magnetic resonance imaging (MRI). MRI scanners use electromagnetic waves or radiofrequency pulses to cause hydrogen nuclei of protons in the body tissues to resonate to varying degrees, generating a signal that is emitted back to the scanner (Huettel, et al., 2009; Katz & Groskin, 1998). The generated signal depends on the tissue properties (different tissues relax at different rates) and the magnet settings. Functional MRI utilizes special coils that allow more rapid

acquisition of images, and thus, allows for measurement of more rapidly occurring bodily processes. For example, changes in blood oxygenation levels occur quickly following neuronal activity, granting localization of brain activity by seconds and within millimeters of its origin. Activation is determined by changes in the total amount of deoxygenated hemoglobin measured in that region (Huettel, et al., 2009). This bold-oxygenation-level-dependent (BOLD) contrast is the technique most often utilized in fMRI.

Neural Structures

The orbitofrontal cortex is an area of the brain often implicated in decision-making studies (Bechara, 2001; Berlin, et al., 2004; Hornak et al., 2004; Matsuo et al., 2009), although the anatomy of the human OFC varies considerably between individuals, particularly in the more lateral and anterior aspects of the region creating a challenge for functional imaging research (Kringelbach & Rolls, 2004). The OFC is located on the ventral surface of the prefrontal cortex and receives inputs from all of the sensory modalities: visual, taste, olfactory, somatosensory, and auditory (E. T. Rolls, 2004). Additionally, the OFC receives extensive inputs from the amygdala and cingulate cortex, has reciprocal connections with other prefrontal areas and motor areas, and receives indirect information via projections from the mediodorsal thalamic nucleus pars magnocellularis (Kringelbach & Rolls, 2004; Ongur & Price, 2000). Projections from the OFC extend to temporal lobe areas (e.g., inferior temporal cortex, amygdala, and entorhinal cortex), cingulate cortex, preoptic region, lateral hypothalamus, ventral tegmental area, and to the head of the caudate nucleus (E.T. Rolls, 1999). Conclusions from animal studies and functional imaging studies are that the OFC is involved in the changing and relative reward value of many unlearned or primary reinforcers (e.g., taste and tactile stimuli) and many learned or

secondary reinforcers (e.g., olfactory and visual stimuli), as well as in the learning and reversing of associations between these secondary and primary reinforcers, and in controlling and correcting reward-related and punishment-related behavior (E. T. Rolls, 2004). Individuals with OFC lesions exhibit difficulties in the mediation of behaviors and cognitive processes necessary for the regulation of planning, including emotional and social functioning, decision-making, reversal learning, and mental flexibility (Adinoff, et al., 2003; Bechara, et al., 2001; Berlin, et al., 2004; Hornak, et al., 2003; Volkow & Fowler, 2000). In the presence of such lesions, established behaviors are not altered in response to a reversal of reward contingencies (Hornak, et al., 2004) and decision-making does not appropriately reflect long-term consequences (Bechara, 2001). Further, a morphometry study in healthy individuals found that smaller gray matter volumes of the bilateral OFC predicted higher scores on a self-report measure of impulsivity [Barratt Impulsivity Scale (BIS-11)] (Matsuo, et al., 2009) and it was suggested that greater engagement of the right OFC is needed to maintain behavioral inhibition in impulsive individuals (Horn, Dolan, Elliott, Deakin, & Woodruff, 2003).

With respect to substance-dependent individuals, decreased regional cerebral blood flow (rCBF) and glucose utilization is observed in abstinent cocaine, methamphetamine, and alcohol-addicted subjects (Adinoff, et al., 2001; Volkow et al., 2001; Volkow, et al., 1993; Volkow, Hitzemann, Wang, Fowler, Burr, et al., 1992), lower medial (Fillmore & Rush, 2006; Franklin, et al., 2002) and right lateral (Fillmore & Rush, 2006) OFC gray matter tissue density has been reported in cocaine-addicted subjects relative to healthy controls, and increased OFC activation is exhibited during a decision-making task (Bolla, et al., 2003) and drug craving (Bonson et al., 2002; Wang et al., 1999). Preclinical studies also show that cocaine-treated rats exhibit identical

deficits to rats with OFC lesions, particularly the inability to exhibit response latency during discrimination learning, impairment in rapid reversal learning, and delayed discounting (Calu, et al., 2007; Schoenbaum, et al., 2004). Thus, OFC alterations in cocaine-addicted individuals may help account for the inability to evaluate, plan for, and select appropriate choices that contributes to relapse.

Apart from the OFC, several other brain areas have been directly or indirectly implicated in decision-making processes. Ghahremani and colleagues (2010) agree that the lateral OFC is involved in identifying changes in "stimulus-response contingencies" and revising these associations by inhibiting conditioned responses to allow formation of new associations. However, they go a step further by proposing an interaction between the OFC and the right inferior frontal gyrus (IFG) and the dorsal anterior cingulate cortex (ACC), regions believed to use these associations to direct appropriate actions. The ACC is involved in emotional and cognitive processing through two major anatomical subdivisions, the dorsal cognitive division and the ventral affective division (Hersh, Mulgrew, Van Kirk, & Kranzler, 1999). The affective subdivision has extensive connections with the amygdala and periaqueductal grey, nucleus accumbens, hypothalamus, anterior insula, hippocampus and orbitofrontal cortex, and is involved in conditioned emotional learning, and assigning emotional salience to internal and external stimuli (Hersh, et al., 1999; Swann, et al., 2004). The cognitive subdivision has reciprocal connections with the lateral prefrontal cortex, parietal cortex, and premotor and supplementary motor areas, and is involved in multiple functions, such as modulation of attention or executive functions by influencing sensory or response selection (Carter, Botvinick, & Cohen, 1999; Hersh, et al., 1999; Vogt, Finch, & Olson, 1992). Cocaine-dependent individuals relative to

healthy controls typically demonstrate ACC hypoactivation on functional MRI during emotionally salient cognitive tasks (Goldstein et al., 2009) and emotionally neutral cognitive tasks (Li et al., 2008). Positive relationships between ACC functioning and measures associated with decision-making ability, such as delayed discounting tasks (Meade, Lowen, MacLean, Key, & Lukas, 2011), gambling task (Adinoff, et al., 2003), and Go/No-Go response inhibition task performance (Hester & Garavan, 2004) have also been found in cocaine dependent individuals.

The inferior frontal gyrus is located within the frontal cortex superior to the central sulcus, and has primarily been implicated in the mediation of response inhibition, particularly the right IFG (A. R. Aron, Robbins, & Poldrack, 2004; Bossert, Ghitza, Lu, Epstein, & Shaham, 2005; Gorelick et al., 2008). Metabolic decreases in the right IFG during purposeful inhibition of craving to cocaine cues suggest that this region may also be worth investigating for its role in decision-making (Volkow, et al., 2010).

Neural Changes in Cocaine Addiction

Human neuroimaging studies documenting chronic cocaine-related brain changes have found variations in gray matter volume, D2 receptor and dopamine transmission, regional cerebral blood flow, and metabolic changes. Structurally, cocaine dependence has been linked to reductions in grey matter concentrations in multiple cortical areas relative to controls, including the ventromedial OFC, ACC, anteroventral insular, and superior temporal cortices ($p < .01$) with the average grey matter reductions in a region ranging from 5% to 11% (Franklin, et al., 2002). Grey matter density was also significantly reduced ($p < 0.004$) in a 20-day abstinent cocaine group versus a non-drug using group in the right infragenual and perigenual regions of the ACC, right lateral prefrontal and right medial orbitofrontal cortices, and the whole right lobar region of

the prefrontal cortex (Fillmore & Rush, 2006). Similarly, prefrontal cortex gray matter volume was also reduced in a six-week abstinent substance dependent sample (cocaine only and cocaine and alcohol dependent subjects) relative to normal controls ($p < 0.01$), with group membership accounting for 10% of the variance (Fein, et al., 2002). Additionally, Ersche et al. (2011) found significant reductions in OFC grey matter volume that were associated with cocaine-related compulsivity ($p \sim 0.002$), caudate enlargement that was associated with significant attentional impairments in cocaine users ($p \sim 0.002$), and associations between longer periods of cocaine use and greater grey matter reductions in the anterior and middle cingulate gyrus, middle frontal cortex (orbital part), rectus gyrus, supplementary motor area, superior temporal gyrus, insula, cerebellum, and left caudate ($p < 0.001$). Another study found significantly lower gray matter volumes in the bilateral premotor cortex, right orbitofrontal cortex, bilateral temporal cortex, left thalamus, and bilateral cerebellum in a cocaine-dependent group relative to a healthy comparison group, and the reductions in bilateral cerebellar grey matter volumes were shown to be inversely related to years of cocaine use and measures of executive function (e.g., Trails B time and Stroop interference time) (Sim, et al., 2007). These studies helped identify associations between structural brain abnormalities, neurocognitive performance, and cocaine dependence. Further, Rando and colleagues (2011) have explored the association between these changes and relapse variables within an alcohol dependent population, and found that smaller medial frontal and parietal-occipital grey matter volumes were each predictive of shorter time to any alcohol use and to heavy drinking relapse. However, there are no known studies linking these alterations with relapse in a cocaine dependent population.

Cerebral metabolic and neurotransmitter receptor availability changes have also been noted with cocaine dependence. Chronic cocaine abusers have exhibited reduced frontal glucose metabolism compared with healthy controls, and these metabolic reductions endured for three to four months of abstinence and were correlated with the dose and the years of cocaine use (Volkow, Hitzemann, Wang, Fowler, Wolf, et al., 1992). Similarly, another placebo-controlled study found that the acute effects of cocaine in polydrug abusers were associated with euphoria and significant decrements in cerebral glucose metabolism (5% to 26%) in 26 of 29 brain regions, including neocortical areas, basal ganglia, portions of the hippocampal formation, thalamus, and midbrain (London, et al., 1990). Additionally, polysubstance abusers have been found to show a steeper anterior-posterior gradient and lower absolute regional cerebral glucose metabolism in the lateral occipital gyrus, with a trend towards similar effects in other posterior areas (Stapleton et al., 1995). Reductions in metabolic activity have also been linked to decreases in receptor levels. For example, striatal dopamine response or receptor availability was found to be significantly lower in cocaine abusers during early (up to 1 month since last cocaine use) and protracted (up to four months since last cocaine use) withdrawal in comparison to normal subjects (Martinez, et al., 2009; Volkow, et al., 1993; Volkow et al., 1999). Further, these lower levels of striatal D2 receptors were found to be associated with lower metabolism in the OFC and ACC in cocaine-addicted subjects (Goldstein & Volkow, 2002). However, there has been no evidence of the association between these metabolic changes and relapse factors in a cocaine dependent population. Alternatively, pre-treatment elevations in regional mu-opioid receptor binding in the anterior cingulate, medial and middle frontal, middle temporal, and sub-lobar insular gyri were associated with shorter periods of cocaine abstinence during treatment

among adults with cocaine use disorders in an outpatient setting (Ghitza et al., 2010). These same individuals showed pretreatment elevations of mu-opioid receptor binding in the medial and middle frontal gyri that were associated with greater cocaine use. Gorelick and colleagues (2008) found that increased mu-opioid receptor binding in frontal and temporal cortex at one and twelve weeks abstinence was associated with time to relapse after discharge from an inpatient treatment program. These findings suggest that alterations in both mu-opioid receptor binding and glucose metabolism could serve as predictive markers of relapse and response to treatment; however, the mechanisms mediating these relationships have not been fully elaborated.

Cocaine dependence has also been linked to alterations in cerebral blood flow. Chronic cocaine abusers have displayed cerebral hypoperfusion in the frontal, periventricular, and temporal-parietal cortex (Browndyke, et al., 2004; Strickland, et al., 1993), including the bilateral orbitofrontal cortex (Adinoff, et al., 2001). Ernst and colleagues (2000) found increased resting cerebral blood flow (rCBF) in the frontal white matter (p = .02) and globus pallidus (p = .05) and decreased rCBF in the putamen (p = .04) and the temporal cortex (p = .02) of abstinent (average of about 11 months) cocaine users relative to healthy controls. Another study found focal perfusion abnormalities in polydrug users (all met current criteria for cocaine abuse/dependence) relative to an older control group in the inferior parietal cortex (16/18 patients), temporal cortex (15/18 patients), anterofrontal cortex (14/18 patients), and basal ganglia (11/18 patients) (Holman et al., 1991). These authors also found abnormalities in neuropsychological test performance between groups, but were unable to investigate associations between these deficits and perfusion abnormalities given their small sample size (18 patients; 15 controls). Few studies have examined the relationship between cocaine-induced perfusion

abnormalities and cognitive functioning. Browndyke and colleagues (2004) found significant deficits in motor speed and complex attention in cocaine-addicted individuals with higher abnormal perfusion severity. Additionally, increased rCBF in the anterior cingulate and dorsolateral prefrontal cortex was found to be significantly related to better decision making performance (Adinoff, et al., 2003). While changes in cerebral blood flow have been identified in cocaine dependent individuals and have been associated with some neurocognitive abilities (Adinoff, et al., 2003; Browndyke, et al., 2004), the implications of these changes in blood flow in relapse risk have not been elucidated.

Neural Changes during Decision-Making

Alterations in neural activity have also been found during decision-making tasks in cocaine dependent individuals compared with healthy controls. When the Gambling Task was administered to acutely abstinent (mean of 5 days) cocaine-dependent patients following completion of a resting SPECT scan, better Gambling Task performance was negatively correlated with blood flow in the anterior cingulate gyrus and the middle, medial, and superior frontal gyri (corrected $p < .0001$) (Tucker, et al., 2004). Alternatively, Adinoff and colleagues (2003) found that the anterior cingulate and dorsolateral prefrontal cortex showed higher resting rCBF in subjects with higher gambling task scores than those with low scores, accounting for 44% of the variance in scores across groups . This association maintained irrespective of drug history, meaning that healthy control individuals and cocaine dependent individuals display an association between decreased perfusion and poorer task performance. Differences in these study findings could be attributed to differing periods of abstinence (about five days in Tucker study and 21 to 55 days in Adinoff study) and the use of a healthy control comparison group

(Adinoff study). Regardless, these studies suggest an association between anterior cingulate functioning and decision-making ability that may be altered in at least a subset of chronic cocaine users. Utilizing PET during the Gambling Task, others have found that 25-day abstinent cocaine abusers display greater activation in the right OFC and less activation in the right dorsolateral prefrontal cortex and left medial prefrontal cortex compared to controls (Bolla, et al., 2003). Better gambling task performance was associated with greater right OFC activation in both groups (positive correlation; $p < .001$). Again, this study suggests that decision-making activates neural regions in cocaine-addicted subjects that deviate from the activation pattern seen in healthy controls. However, there are no known studies linking neural changes during decision-making with measures of relapse (e.g., time to first use) in a cocaine dependent population.

Neural Associations with Relapse

The literature examining the relationship between neural activity and relapse in a cocaine dependent population is scarce. Historically, studies have focused on treatment retention and the duration these deficits persist. Paralleling advances in neuroimaging techniques, early explorations of the relationship between neural deficits and relapse have begun in substance use populations. For example, Paulus, Tapert, and Schuckit (2005) investigated treatment-seeking methamphetamine dependent males three to four weeks after cessation of drug use utilizing fMRI during a simple two-choice prediction task. In this study, relapse data was obtained at a one-year follow-up contact and defined as the time to first use (any use of methamphetamine). The authors found that fMRI activation patterns in the right insular, posterior cingulate, and temporal cortex predicted about 91% of subjects who did not relapse and about 94% of subjects

who did relapse. The combination of right middle frontal gyrus, middle temporal gyrus, and posterior cingulate activation was considered to best predict time to relapse ($p < .01$). This investigation demonstrated for the first time the possibility of using functional neuroimaging to predict relapse in individuals with methamphetamine addiction. However, the sample utilized did not also meet criteria for cocaine dependence or another substance use disorder, and thus, it is unclear how these findings generalize to other substance use disorders apart from methamphetamine dependence. Further, brain activation (fMRI) during drug cue exposure has been associated with vulnerability to treatment dropout and relapse to cocaine use (urine drug testing) (Kosten, et al., 2006). Specifically, greater activation in the posterior cingulate, extending dorsally to the boundary of the anterior cingulate, was found in relapsers compared to non-relapsers during the first 30 seconds of cue exposure (i.e., videotape of a man smoking cocaine), suggesting more active engagement in viewing the drug cue stimuli. The authors proposed that the posterior cingulate operates below conscious awareness to initiate habitual behavior upon exposure to a drug cue. This study was one of the first to show an association between neural activation during drug-cue exposure and relapse to cocaine use. However, it focuses on drug cue exposure and does not explore the more upper level cognitive process of decision making. Additionally, differences in alcohol cue-induced activation in the putamen, anterior cingulate, and medial prefrontal cortex were found between alcohol dependent individuals and healthy controls, and these differences appeared most prominent in individuals who relapsed to alcohol use during a three-month post-treatment follow-up period (Grusser et al., 2004). Medial prefrontal cortex cue-induced activation but not craving severity was associated with subsequent amount of alcohol intake. Again, this study demonstrates the potential

importance of considering brain activation as a means of better understanding prospective relapse risk in a substance dependent population. While none of these studies focused on decision-making, alterations in activation, or a cocaine dependent population, they opened the door for investigations into neural correlates of relapse and helped identify brain areas for further investigation.

APPENDIX B

Hypotheses

Aim I: Determine if neural changes during a decision-making task are present in abstinent cocaine-addicted subjects relative to controls. Decision-making will be elicited with the Response Reversal Task (RRT).

> **Hypothesis I**: Cocaine-addicted subjects will exhibit decreased neural activation following a change in contingencies during the response reversal task. Alterations in activation will be defined relative to activation in the control subjects, and are projected to occur in the orbitofrontal cortex, cingulate cortex, insular cortex, frontal gyri (inferior, superior, middle, and medial), the striatum, amygdala, hippocampus, and temporal gyri (middle and superior).

Aim II: Determine whether the BOLD response during a decision-making task can be used to predict relapse in cocaine-dependent individuals.

> **Hypothesis II**: Identified alterations in activation in cocaine-addicted subjects relative to controls will 1) differentiate relapsers from non-relapsers and 2) predict time to relapse. Healthy control subjects and non-relapsing individuals will show more activation in the OFC, cingulate cortex, insula, frontal gyri, amygdala, hippocampus, and temporal gyri relative to relapsing individuals. Activation alterations in these brain areas will also predict time to relapse (short-term versus long-term) in those subjects who relapse.

Aim III: A) Determine whether performance on a standardized neurocognitive measure of decision-making, the Wisconsin Card Sorting Test (WCST), can be used to predict relapse in a

cocaine-dependent sample. B) Construct a predictive model of cocaine relapse that incorporates neuroimaging, neurocognitive measures of decision-making, or a combination of these methods.

Hypothesis III: A) Poorer performance on the WCST will be associated with a briefer time to relapse. B) Measures of neural activation during response reversal will contribute more specificity for predicting individuals who relapse than neurocognitive measures of decision-making alone.

APPENDIX C

Treatment Center Descriptions

The Dallas VA Medical Center's Substance Abuse Program is a thirty bed residential program with 24-hours a day staffing and is locked down after hours. Individuals first requiring detoxification or hospitalizations for acute psychiatric disturbances are treated on the acute psychiatric unit at the VAMC prior to entering the substance abuse program. Patients of the program participate in a three week intensive substance abuse treatment program that endorses the disease model of addiction and endorses abstinence as the desired outcome. Curriculum-based instruction addresses coping and decision-making skills, relapse prevention, prevocational and vocational skills, social skills, and symptom management. Homeward Bound, Inc. is a community mental health and substance use disorder treatment provider in for the Dallas/Fort Worth Metroplex. Homeward Bound is a multi-modality program that offers an acute care inpatient detoxification program, intensive residential treatment, and intensive and supportive outpatient services. The program at Homeward Bound emphasizes education and counseling, formulation of new thinking, an experience of sobriety and a commitment to change, as well as integration of materials from 12-step programs. Nexus Recovery Center, Inc. provides drug and alcohol abuse treatment for disadvantaged women, including women with children and adolescent girls. Nexus offers an intensive inpatient program, as well as, intensive and supportive outpatient services and a detoxification program. In addition to substance abuse treatment, Nexus offers their patients parenting classes, family education and counseling, life skills training, and on-site childcare. Nexus psycho-educational group sessions cover a wide range of topics from alcohol and drug education to stress management and trauma coping skills.

It is expected that the duration of treatment stay for all participants will range from two to four weeks or until completion of all baseline assessments for this study. This time frame will provide a period during which patients will remain in a controlled environment where their abstinence can be verified and to allow for resolution of cocaine withdrawal. Since each treatment program varies to some degree in the services provided, recruitment site or treatment facility will be explored as a potential confound in analyses. Similarly, length of treatment stay is expected to vary slightly within our cocaine dependent group, and thus, length of treatment stay will also be explored as a potential confound in analyses.

APPENDIX D

Measure Description

Listed below are the measures administered to participants in chronological order.

Demographics and some clinical history was obtained via interview-assisted questionnaire, including age, gender, ethnicity, height, weight, BMI, handedness, marital and dependent information, education history, employment history, recent alcohol, caffeine, and nicotine consumption, personal and family medical history, family substance use history, and personal diagnosis history. Additionally, an assessment of traumatic brain injury was completed with all subjects that solicited information pertaining to various means of injury to the head or neck (e.g., motor vehicle accident or fall), as well as questions about loss of consciousness (i.e., presence, duration, and quantity). Individuals were excluded from participation if they reported a head injury with loss of consciousness lasting several hours or more, persistent symptoms associated with the head injury (e.g., nausea, vomiting, dizziness, and memory loss), subsequent imaging with abnormalities, or multiple head injuries with loss of consciousness. Contact information for the client and a collateral person was also obtained to assist with the follow-up process. Demographic and screening information obtained were examined for group differences and associations with dependent measures.

Structured Clinical Interview for the DSM-IV-TR Axis I Disorders (SCID-I) (First, 2007). The SCID-I is a standardized and structured assessment tool widely used and accepted for the accurate diagnosis of past and current Axis I psychiatric disorders. Initial diagnosis of cocaine dependence was provided by the treatment facility and confirmed through the administration of

this measure. Information regarding age of onset for cocaine dependence was obtained in this interview.

Wechsler Test of Adult Reading (WTAR) (Wechsler, 2001). The WTAR provides an estimate of premorbid intellectual functioning of adults aged 16-89. It is based on a reading-recognition paradigm in which the subject must read and pronounce words with irregular pronunciations; knowledge of word meaning is not required, but correct reading of the words correlates well with IQ. The word list contains 50 words, and the task is discontinued upon completion of the list or with 12 incorrect consecutive pronunciations. The WTAR was developed and normed with the *Wechsler Adult Intelligence Scale–Third Edition,* allowing for direct comparison between predicted and actual intelligence. Normative scores were based on a nationally representative, stratified sample. The WTAR has excellent internal consistency (.90 to .97) and test-retest reliability (.90 to .94) (Wechsler, 2001). The WTAR also demonstrates convergent and discriminant validity, as well as, serves as a stout estimate of intelligence even when suboptimal effort is given on the task (Bechara, et al., 1994). The WTAR was used as an estimation of intelligence and was considered as a possible covariate for between-group comparisons.

Timeline Follow-Back (TLFB) (L. C. Sobell, Brown, Leo, & Sobell, 1996). The TLFB is an assessment tool that uses a calendar and other memory aids to gather retrospective estimates of an individual's daily substance use over a specified period of time. The TLFB was conducted as a patient interview, and provided information regarding the amount of cocaine used and the number of days of cocaine use over the patient's lifetime and within the last ninety days prior to entering treatment. The lifetime portion of the measure traced the individual's cocaine

consumption behavior from the age of first regular use (at least once a month) until 90 days prior to last use. Information was recorded regarding the quantity (dollar amount consumed), frequency (e.g., days per week, month, or year), route of use (e.g., snorting, smoking, or intravenously), and associated life events (e.g., divorce, starting a job, or incarceration). The ninety day portion of the measure utilized monthly calendars to help the individual trace their most recent daily use. Information was also gathered regarding maximum cocaine use on any one day during their lifetime and on any one day during the last 90 days. Data gathered with this measure was used to help describe the sample studied and was considered as a possible covariate within analyses. Patient self-reported drug consumption using this method generally has high test-retest reliability, convergent and discriminant validity with other measures, agreement with collateral reports of patients' substance use, and agreement with patients' urine drug tests (Ehrman & Robbins, 1994; Fals-Stewart, O'Farrell, Freitas, McFarlin, & Rutigliano, 2000; Hersh, et al., 1999).

Barratt Impulsiveness Scale 11 (BIS-11) (Patton, Stanford, & Barratt, 1995). The BIS-11 is a self-report, paper-and-pencil instrument designed to assess the complex personality construct of impulsiveness. The questionnaire consists of 30 items answered on a four-point scale (Rarely/Never, Occasionally, Often, Almost Always/Always). Responses are scored 1 through 4 with 4 indicating the most impulsive response. Heightened levels of impulsiveness are reflected in higher total scores. Scores are also available for three domains: Attentional impulsiveness (AI), Motor impulsiveness (MI), and Non-planning impulsiveness (NP). AI evaluates actions precipitated by lack of attention; it can be exacerbated in anxious situations. MI evaluates hyperactivity due to need of movement, which is exacerbated by stress. NP evaluates attitudes

and conclusions precipitated by lack of reflection. Higher BIS-11 scores are often found for cocaine dependent adults relative to controls (Lane et al, 2007; Lejuez et al 2007; Allen et al 1998), and are associated with poorer treatment retention (Moeller, et al., 2001). Therefore, this measure was included to control for impulsivity as a potential confound and for exploratory analyses. The BIS-11 is highly correlated with similar self-report measures (convergent validity) of impulsiveness, and demonstrates good internal consistency (Cronbach's $\alpha = 0.83$) and test-retest reliability (Spearman's Rho = 0.83) (Stanford, et al., 2009).

Cocaine Craving Questionnaire-Brief (CCQ) (Tiffany, Singleton, Haertzen, & Henningfield, 1993). The CCQ was administered to cocaine dependent subjects to assess their subjective experience of craving. Due to the strong association in the literature between craving and return to use, the assessment of craving was being used here for inclusion in future analyses as a potential confound. The CCQ-Brief is a 10-item self-report measure that asks subjects to evaluate their craving on a seven-point visual analogue scale. The subject darkens the circle corresponding to their degree of agreement or disagreement with the statement; closeness to one end or the other indicating strength of disagreement or agreement. A total score was obtained by averaging all items. The CCQ-Brief has demonstrated good convergent validity with other measures of current cocaine craving and strong internal consistency (alpha = .90) (Sussner et al., 2006).

Wisconsin Card Sorting Test (WCST) (Heaton, 1993). The WCST is generally considered a measure of executive function due to its reported sensitivity to frontal lobe dysfunction. As such, the WCST is believed to assess the following frontal lobe functions: strategic planning, organized searching, utilizing environmental feedback to shift cognitive sets,

directing behavior toward achieving a goal, and modulating impulsive responding. The WCST consists of four stimulus cards and 128 response cards depicting figures of various forms (crosses, circles, triangles, or stars), colors (red, blue, yellow, or green), and numbers of figures (one, two, three, or four). Each response card can be matched to a stimulus card on one, or a combination, of these three stimulus parameters. The matching principles change throughout the test, and thus, subjects must figure out the matching principle and modify their responses based on feedback (e.g., correct versus incorrect). The computerized Version 3 of the test was used, which has demonstrated general equivalence with the manual version of the task (Artiola i Fortuny & Heaton, 1996). Primary outcome variables from this measure included number of perseverative responses and total errors (Barcelo & Knight, 2002); however, categories completed and failure to maintain set (FMS) were also obtained.

APPENDIX E

Additional Data Analyses and Results

Group differences on WCST perseverative responses, total error scores, categories completed, and failure to maintain set (FMS) were assessed with multivariate analysis of variance (MANOVA), followed by post-hoc ANOVAs. Bonferroni correction was used to assess statistical significance for the four outcome variables ($p = .01$). Seven cocaine-addicted individuals from the original sample were not included in these analyses, as computer malfunction prevented completion of the WCST. No significant differences were found between cocaine-addicted and healthy control subjects on WCST performance (Table 8). It is worth noting that cocaine-addicted subjects exhibited low average error t-scores; whereas, the healthy controls obtained error t-scores within the Average range. Thirteen percent of controls performed in the impaired range on error t-scores and perseverative t-scores, as denoted by a t-score of less than 40; whereas, 37 percent and 33 percent of patients scored in the impaired range on error t-scores and perseverative t-scores, respectively. When all individuals regardless of completion of the RRT were included in a MANOVA, it was found that patient and control groups differed significantly on errors t-score [$F(1, 70) = 4.56$, $p = .036$]; however, this difference was not present between patient subgroups and disappeared when WTAR FSIQ was included as a covariate in the analysis [$F(1, 68) = 1.31$, $p = .256$]. Similarly, groups based on short-term and long-term relapse did not show significant differences on WCST performance variables (Table 9). It is also worth noting that the short-term relapsing group scored low average on perseveration t-scores; whereas the long-term relapsing group exhibited perseveration t-scores within the Average range. Thirty-six percent of short-term relapsers performed in the

impaired range on error t-scores and perseverative t-scores, as denoted by a t-score of less than 40; whereas, 35 percent and 22 percent of long-term relapsers scored in the impaired range on error t-scores and perseverative t-scores, respectively. Further, WCST scores of patients who did not successfully complete training on the RRT were compared with those who completed the RRT, and no significant difference was found between these groups on WCST performance (Table 10). Finally, correlations investigating the relationship between WCST variables and neural activation in the ten ROIs, RRT performance measured by 'money won,' and time-to-relapse were not significant at a $p < .05$.

WCST was administered outside of the scanner environment and without prior training to provide a behavioral measure of decision-making abilities. Consistent with previous findings, the current results lacked significant differences in WCST performance between cocaine-dependent and healthy control subjects (Cunha, et al., 2010; Grant, et al., 2000; A. Verdejo-Garcia & Perez-Garcia, 2007). Failure to find significant results between groups on the WCST could be related to a diluting of the data based on the variables selected, as they may not best demonstrate response reversal. For example, Woicik and colleagues (2011) examined a subset of higher WCST performing cocaine addicted subjects whose scores were comparable to control subjects and looked at the block-by-block performance of these individuals. The authors found that these higher performing cocaine addicted subjects still exhibited more perseveration when they were first asked to sort based on a previous sorting rule (the initial task-set switch; $p < .05$).

In addition, it is possible that decision-making deficits may decrease with increased abstinence from cocaine use resulting in no apparent difference in inter-group performance. However, this sample of cocaine-addicted subjects displayed high relapse rates suggesting some

impairment in cognitive abilities that is not being captured by their WCST performance. Further, cocaine-addicted subjects performed more poorly on this task, and on some measures of performance, scored below average compared to the control group's average performance. Thus, it is possible that the WCST is not sensitive enough to detect group differences in an abstinent patient sample. It has been proposed that significant differences in decision-making performance could be found with use of a more ecologically valid measure than traditional decision-making tasks, such as the WCST. For example, Verdejo-Garcia and Perez-Garcia (2007) found that substance dependent individuals (64.9% cocaine use) performed significantly poorer than controls on five of six subtests of the Behavioural Assessment of the Dysexecutive Syndrome (BADS; effect sizes = 0.53 to 1.30) (Wilson, et al., 1996), an ecologically valid measure of executive function, but did not perform significantly different than controls on the WCST. The authors also found that performance on the BADS predicted everyday problems related to apathy, disinhibition, and executive dysfunction, whereas, WCST performance did not. Grant, Contoreggi, and London (2000) also found that a sample of 30 polysubstance abusers (28/30 reported cocaine abuse) performed more poorly on the Gambling Task than 24 control subjects, but did not differ from control subjects on the WCST.

Hypothesis Three

Linear discriminant function analysis (F_{enter}: $P<.05$) was conducted to predict whether a cocaine-addicted individual relapsed in the short-term versus long-term following acute inpatient substance abuse treatment based on their decision-making abilities as measured with the WCST. Predictor variables were errors t-score, perseverative responses t-score, categories completed, and FMS. Significant mean differences were not observed for any of the predictors on time-to-

relapse. The discriminant function revealed no significant association between groups and all predictors (Wilks' λ=.92, χ^2=2.83, *p*=.59), accounting for 8% of between group variability. The cross-validated classification showed that overall 50.0% of patients were correctly classified. Long-term relapsers were classified with better accuracy than short-term relapsers (Table 11).

Mean percentage BOLD signal change for the ten previously identified ROIs and WCST scores (errors t-score, perseverative responses t-score, categories completed, and FMS) were added as independent variables to the prediction model to assess whether the combination of variables improved classification rates. The discriminant function revealed no significant associations between groups and all predictors (Wilks' λ=.52, χ^2=19.15, *p*=.159), accounting for 48% of the variance between groups. The cross-validated classification showed that overall 63.2% were classified correctly into short-term and long-term relapse groups. Again, long-term relapsers were classified with better accuracy than short-term relapsers (Table 12).

The classification model utilizing WCST performance to predict cocaine relapse failed to show classification probabilities better than those found by chance. Further, the model was improved with the addition of neural activation data; however, the cross-validated classification probabilities did not exceed those obtained by use of neuroimaging data alone to predict cocaine relapse.

APPENDIX F

Additional Tables and Figures

Table 8. Means and standard deviations for WCST variables across subjects.

	Healthy Controls (n = 23)	Cocaine-Dependent (n = 38)	F	p-Value
Errors T-score	47.2 (9.7)	43.11 (11.1)	2.11	.152
Perseverative Responses T-Score	48.7 (11.0)	45 (13.3)	1.26	.267
Categories Completed	5.4 (1.4)	4.8 (1.6)	2.26	.139
FMS	.52 (.85)	.79 (1.2)	0.87	.356

Table 9. Means and standard deviations of WCST variables for the patient subgroups.

	Short-term Relapsers (n = 17)	Long-term Relapsers (n = 21)	F	p-Value
Errors T-score	41.0 (10.8)	44.81 (11.3)	-1.05	.299
Perseverative Responses T-Score	42.8 (14.9)	46.8 (11.9)	-.933	.357
Categories Completed	4.7 (1.5)	4.9 (1.7)	-.290	.774
FMS	.94 (1.3)	.67 (1.2)	.690	.495

Table 10. Means and standard deviations of WCST variables for patient RRT subgroups.

	No RRT Group (n = 7)	RRT Group (n = 38)	t	p-Value
Errors T-score	39.9 (10.14)	43.11 (11.1)	0.72	.475
Perseverative Responses T-Score	42.6 (8.6)	45.0 (13.3)	0.46	.645
Categories Completed	3.9 (2.7)	4.8 (1.6)	1.27	.211
FMS	.86 (1.1)	.79 (1.2)	.138	.891

Table 11. Discriminant analysis group membership predictions with WCST scores.

	Predicted Group Membership		
	ST Relapse	*LT Relapse*	*N*
Original Grouped Cases[a], count (%)			
ST Relapse	9 (52.9)	8 (47.1)	17
LT Relapse	6 (28.6)	15 (71.4)	21
Cross-validated Grouped Cases[b], count (%)			
ST Relapse	5 (29.4)	12 (70.6)	17
LT Relapse	7 (33.3)	14 (66.7)	21

a. 63.2% of original grouped cases correctly classified.

b. 50.0% of cross-validated grouped cases correctly classified.

*Note: ST = short-term relapse; LT = long-term relapse

Table 12. Group membership predictions with WCST scores and activation changes.

	Predicted Group Membership		
	ST Relapse	*LT Relapse*	*N*
Original Grouped Cases[a], count (%)			
ST Relapse	14 (82.4)	3 (17.6)	17
LT Relapse	3 (14.3)	18 (85.7)	21
Cross-validated Grouped Cases[b], count (%)			
ST Relapse	9 (52.9)	8 (47.1)	17
LT Relapse	6 (28.6)	15 (71.4)	21

a. 84.2% of original grouped cases correctly classified.

b. 63.2% of cross-validated grouped cases correctly classified.

*Note: ST = short-term relapse; LT = long-term relapse

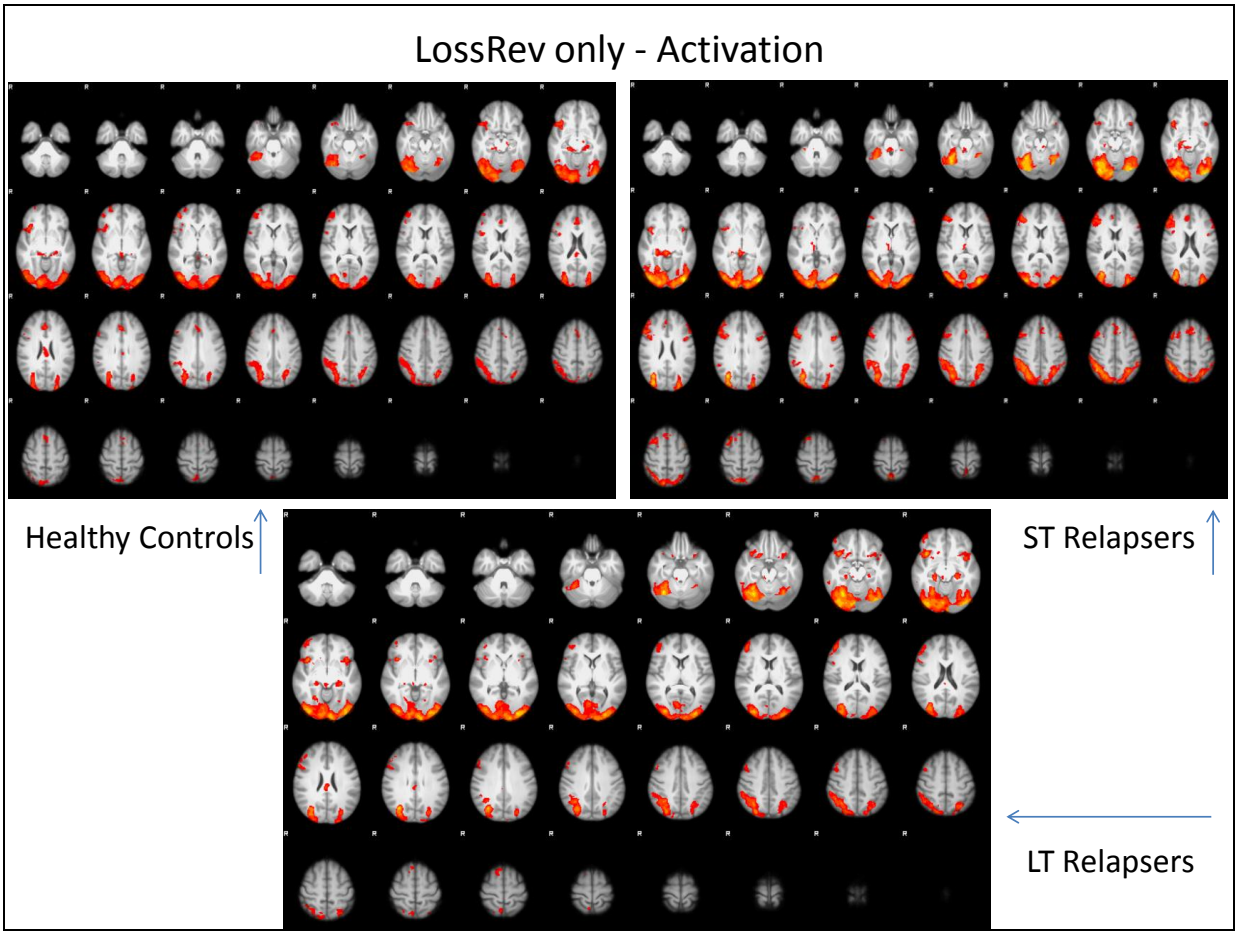

Figure 3. Group activation patterns during LossRev to baseline contrast using original cluster-level inference analysis. Z statistic images were thresholded using clusters determined by Z > 2.3 and a (corrected) cluster significance threshold of P = 0.05.

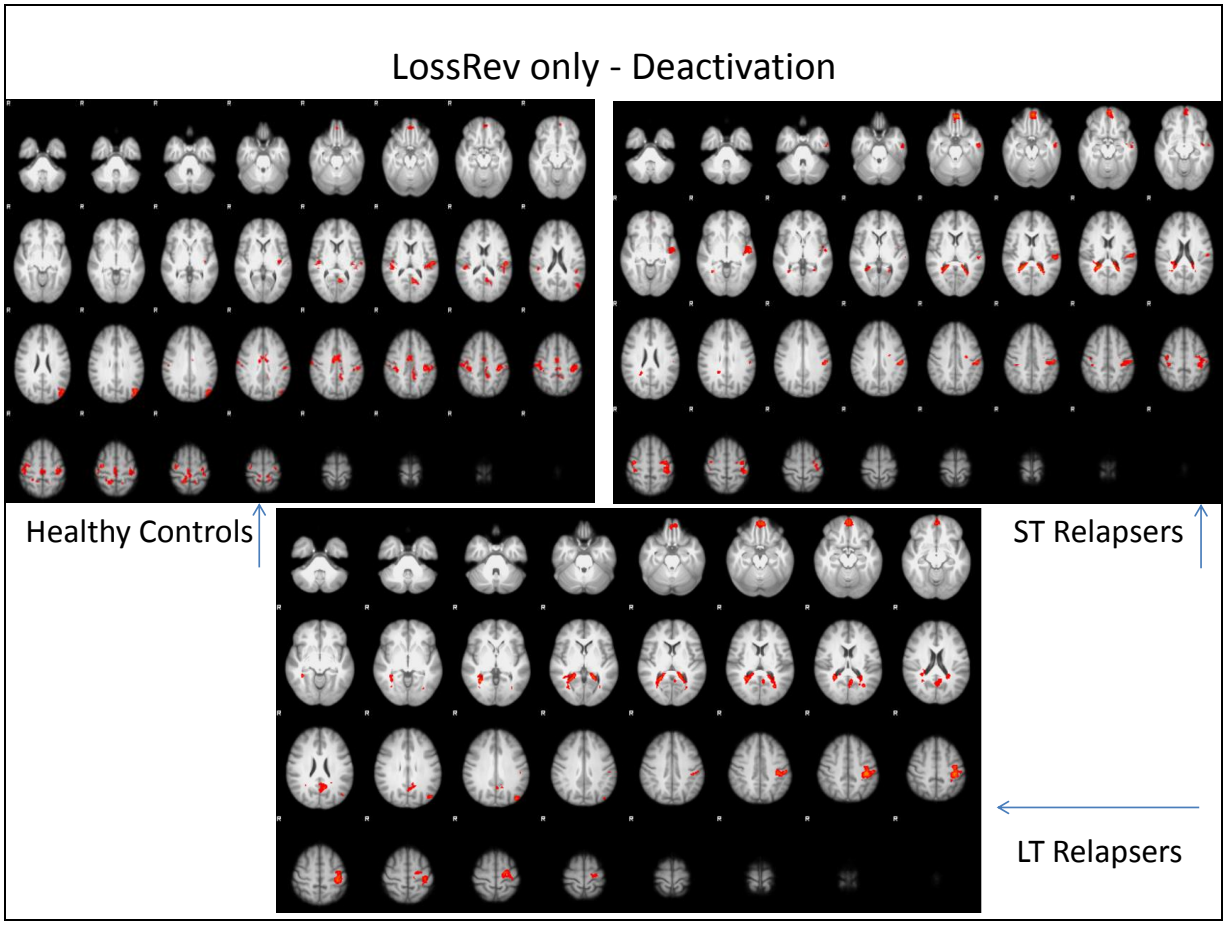

Figure 4. Group deactivation patterns during LossRev to baseline contrast using original cluster-level inference analysis. Z statistic images were thresholded using clusters determined by Z > 2.3 and a (corrected) cluster significance threshold of P = 0.05.

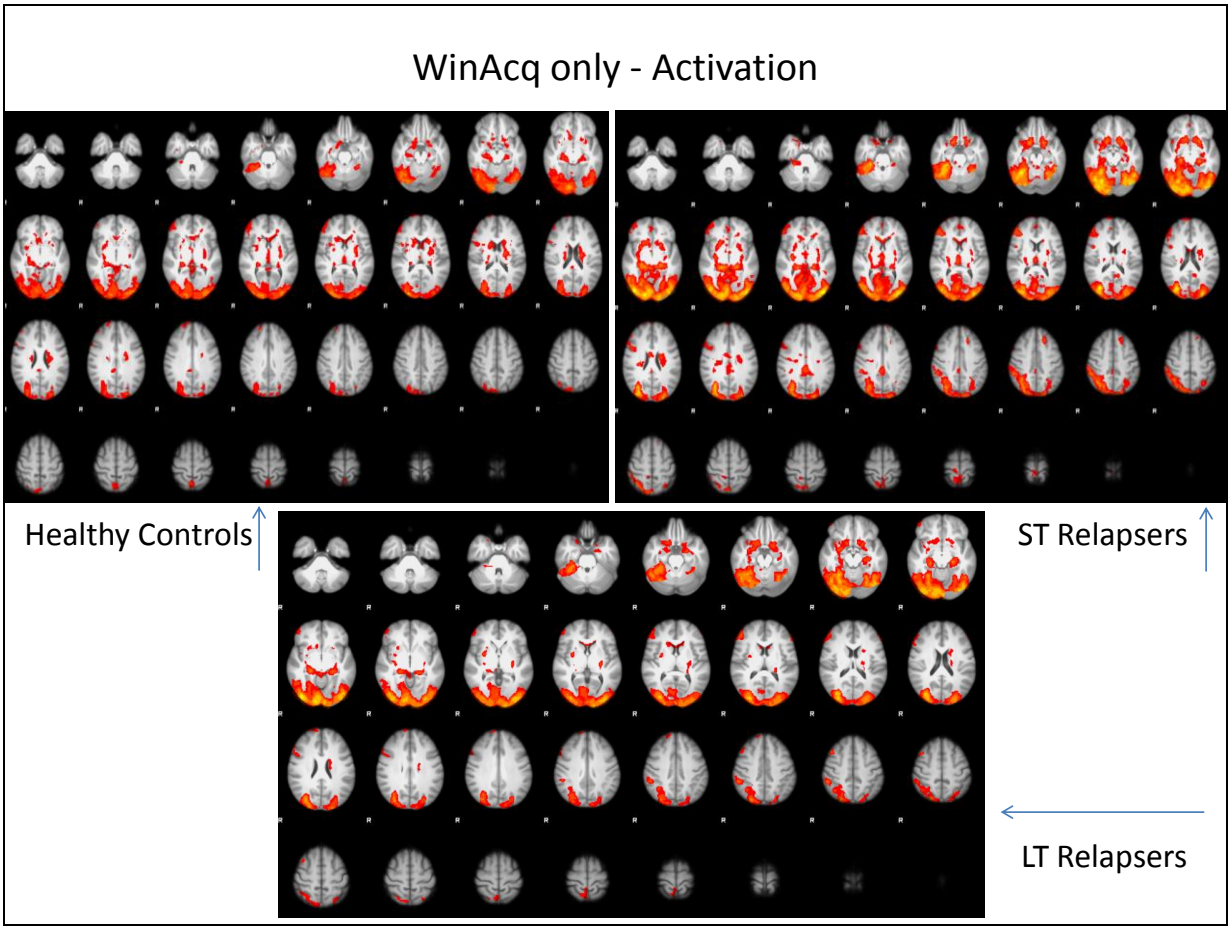

Figure 5. Group activation patterns during WinAcq to baseline contrast using original cluster-level inference analysis. Z statistic images were thresholded using clusters determined by Z > 2.3 and a (corrected) cluster significance threshold of P = 0.05.

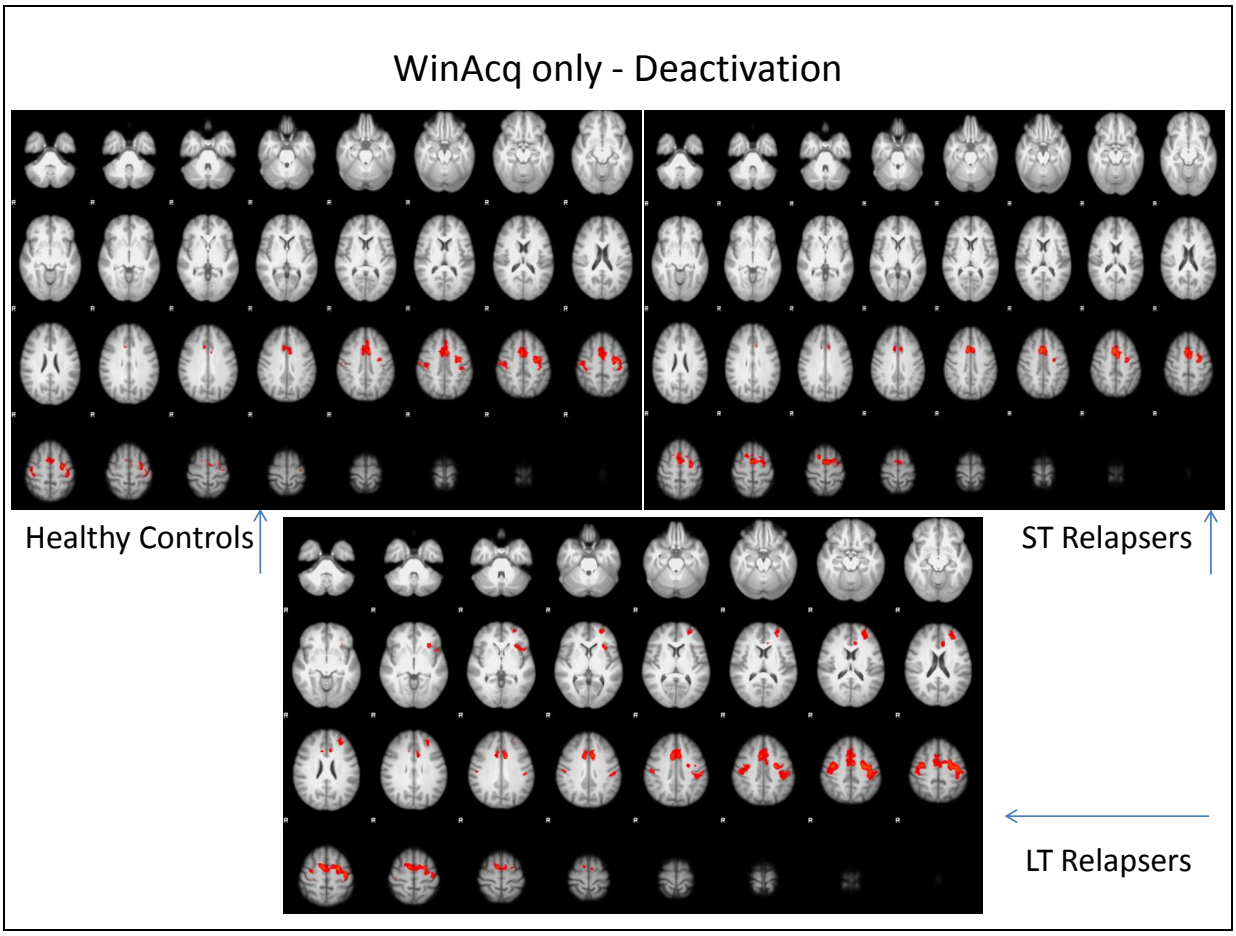

Figure 6. Group deactivation patterns during WinAcq to baseline contrast using original cluster-level inference analysis. Z statistic images were thresholded using clusters determined by Z > 2.3 and a (corrected) cluster significance threshold of P = 0.05.

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