NEURAL ACTIVITY DURING THE STOP SIGNAL TASK, A DISINBITION TASK, PREDICTS RELAPSE IN COCAINE DEPENDENT PARTICIPANTS

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ACKNOWLEDGEMENTS

My deepest gratitude is to my mentor, Dr. Bryon Adinoff, for his guidance and generosity in time, patience, knowledge, and resources. I have learned tremendous information about addiction and will continue to study this interest field of psychiatry during residency. This priceless research experience has taught me the research process and the critical thinking and decision-making involved. Further, I would like to thank Dr. Spence for explaining discriminant analysis and for his patience responding to multiple statistical questions. I am indebted to Thomas Harris, the FSL guru, who helped define imaging parameters, created brain images and analyzed group differences, among other things, that made the project possible. Many thanks are offered to Bryan Jester and Jacquelyn Braud who taught me so much about the project, helped me understand the data and patiently answered my many questions. Lastly, many thanks go to my friends and family. My journey through medical school and accomplishments could not have been possible without their love and support.

May 2013

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by

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DISSERTATION

Presented to the Faculty of the Medical School
The University of Texas Southwestern Medical Center at Dallas
In Partial Fulfillment of the Requirements
For the Degree of

DOCTOR OF MEDICINE WITH DISTINCTION IN RESEARCH

The University of Texas Southwestern Medical Center at Dallas
Dallas, TX

ABSTRACT

NEURAL ACTIVITY DURING THE STOP SIGNAL TASK, A DISINBITION TASK, PREDICTS RELAPSE IN COCAINE DEPENDENT PARTICIPANTS

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Background: Relapse is a prevalent phenomenon in addiction. Impaired inhibitory control is associated with relapse and is a significant predictor of cocaine use and treatment retention.

Objective: Functional magnetic resonance imaging (fMRI) was used to examine the association between BOLD response during the Stop Signal Task (SST, a measure of inhibitory control), and time to relapse in cocaine-dependent patients.

Methods: Forty-nine 2-4 weeks abstinent cocaine-dependent participants were assessed and then followed weekly for up to 26 weeks as outpatients. Relapse was defined as any use of cocaine during the follow up period. The patients were categorized into 27 individuals in the relapse group (relapsed within 30 days) and 22 in the non-relapse group (did not relapse at 30 days). BOLD response during successful inhibition ("StopSuccess") during SST was compared between groups ($z>2.3$, $p=0.05$). Regions of interest (ROIs) were also identified using mean percent BOLD signal change in the combined patient group. Percent BOLD change values were calculated within the significantly activated voxels during StopSuccess (voxel-based analysis, $P = 0.15$). Identified clusters were used in discriminant analysis through the Statistical Product and Service Solutions software to predict group membership.

Results: Consistent with our hypothesis, the study found BOLD changes during the SST that were able to predict those who relapse from those who did not. Specifically, the left lateral occipital cortex exhibited greater BOLD activation in the relapse group than the non-relapse group. On the other hand, the relapse group had lower BOLD activation in the left lateral orbitofrontal cortex and left anterior insula. Using discriminant analysis, these two regions of interest were able to classify 76.9% of individuals into their respective groups correctly with cross-validation.

Conclusion: The left lateral occipital cortex, left lateral orbitofrontal cortex and left anterior insula can be used to identify those at risk of relapse and offer insights into mechanisms of relapse.

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PRIOR PUBLICATIONS & PRESENTATIONS

PRESENTATIONS:

Vo Lan Chi. "Neural Activity During the Stop Signal Task, a Disinhibition Task, Predicts Relapse in Cocaine-Dependent Patients." 51st Annual Medical Student Research Forum. University of Texas Southwestern Medical Center. Dallas, Texas. January 22, 2013.

Vo Lan Chi. "Neural Activity During the Stop Signal Task, a Disinhibition Task, Predicts Relapse in Cocaine-Dependent Patients." Texas Research Society on Alcoholism, 23rd Annual Scientific Meeting. Hilton Austin Airport, Austin, Texas. February 22, 2013.

Vo Lan Chi. "Neural Activity During the Stop Signal Task, a Disinhibition Task, Predicts Relapse in Cocaine-Dependent Patients." MD with Distinction in Research Thesis Presentation. University of Texas Southwestern Medical Center. Dallas, Texas. March 27, 2013.

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INTRODUCTION

Cocaine addiction is a chronic relapsing disorder, with up to seventy-five percent (Adinoff et al., 2007) of drug dependent patients return to active substance use within one year following treatment. In one study with cocaine-addicted individuals, 65% of its sample reported using cocaine during the 90 days follow-up phase (Sinha, Garcia, Paliwal, Kreek, & Rounsaville, 2006). Impaired inhibitory control plays a role in ongoing drug use and relapse (Newton, De La Garza, Kalechstein, Tziortzis, & Jacobsen, 2009), and is significant predictor of cocaine use and treatment retention (Moeller et al., 2001).

Impulsive behaviors are observed in a wide range of psychiatric disorders, including substance use disorder. There is a relationship between impulsivity and the development of substance abuse in at-risk children (Caspi, Moffitt, Newman, & Silva, 1996; Cloninger, Sigvardsson, & Bohman, 1988; Dawes, Tarter, & Kirisci, 1997; Giancola, Martin, Tarter, Pelham, & Moss, 1996) and impulsivity measures have consistently been found to be higher in substance-abusing populations than in controls (Ball, Carroll, Babor, & Rounsaville, 1995; Bechara, 2005; Cloninger, Sigvardsson, Przybeck, & Svrakic, 1995; M.T. Fillmore & Rush, 2002; Patton, Barnes, & Murray, 1997). However, the exact manner in which impulsivity is related to the pathology of substance abuse has yet to be clearly determined.

Disinhibition, a component of impulsivity and the focus of this study, refers to the inability to suppress or inhibit previously reinforced behaviors that are no longer working to the person's advantage (Adinoff, Rilling et al. 2007). Numerous neurocognitive and behavioral tasks have been developed to identify the inhibitory processes that underlie self-control disorders. Both the Stop Signal Task (SST) and Go/No-Go measure disinhibition. However, the Go/No-Go measures other cognitive functions such as decision-making, response competition/response

selection, conflict monitoring, and the detection of rare stimuli (Rubia, Smith, Brammer, & Taylor, 2003). The SST is a specific measure of inhibitory control, in that it measures the ability to withhold at the last minute an already triggered response (Rubia et al., 2003). The SST is designed around a model of cognitive control, which postulates that the ability to inhibit an action is determined by competing activating/inhibiting processes that are elicited by cues to activate or inhibit a response (M.T. Fillmore & Rush, 2002). It is thought that the task replicates everyday situations in which a behavior needs to be inhibited unexpectedly (Rubia et al., 2003). The SST, therefore, may offer unique advantages as a relatively specific measure of an individual's ability to inhibit a pre-potent action (M.T. Fillmore & Rush, 2002).

The technological advances in neuroimaging allow fMRI to be increasingly used to identify neural mechanisms that may be related to impulsive characteristics in individuals suffering from addiction. In persons suffering from cocaine addiction, reductions in inhibitory control were found relative to controls (M.T. Fillmore & Rush, 2002), and heightened impulsivity was found relative to controls (Coffey, Gudleski, Saladin, & Brady, 2003; Wittmann, Leland, Churan, & Paulus, 2007). Impulsivity was found related to the severity of cocaine abuse, the severity of cocaine withdrawal, and the likelihood of poor treatment retention(Moeller et al., 2001).

There are shared neurological abnormalities associated with impulsivity and cocaine addiction. Regions of the prefrontal cortex, including the anterior cingulate cortex (ACC), right dorsal lateral prefrontal cortex and the orbitofrontal cortex (OFC), have consistently been shown to be associated with impaired inhibitory control and cocaine dependence (Goldstein & Volkow, 2011). Li et al (2008) found relative hypoactivation of the rostral ACC, an area involved in the control of stop signal inhibition, during SST performance in cocaine-addicted males compared to

healthy controls. (Li et al., 2008). These findings are consistent with two studies that found cingulate hypoactivation, as well as presupplementary motor and insula hypoactivity (Kaufman, Ross, Stein, & Garavan, 2003) and right prefrontal cortices hypoactivation (Hester & Garavan, 2004) using the Go-No-Go task in cocaine dependent individuals. A pattern emerged in which the dorsal ACC is hypoactive during these inhibitory control tasks, and this hypoactivity was mostly associated with impaired performance, particularly with shorter abstinence durations (Goldstein & Volkow, 2011). Chronic cocaine abuse has been linked with cerebral hypoperfusion in the bilateral OFC, which was correlated with impulsivity (Adinoff et al., 2001; Browndyke et al., 2004; Strickland et al., 1993).

Structural imaging studies have shown reduced PFC grey matter density or thickness across addiction populations (up to 20% loss) (Goldstein & Volkow, 2011). For example, 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, 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; M. T. Fillmore & Rush, 2006; Franklin et al., 2002; Sim et al., 2007). Despite some conflicting results, most studies in individuals who are addicted to cocaine, methamphetamine, heroin and nicotine report similar PFC grey matter reductions — which are most evident in the DLPFC, ACC and orbitofrontal cortex (OFC) — that are associated with longer duration or increased severity of drug use (Goldstein & Volkow, 2011).

Several studies have used fMRI to correlate with treatment, craving measures and relapse in drug dependent individuals. Neural activity during a simple two-choice prediction task was able to predict relapse in methamphetamine dependent individuals. The study found that fMRI

activation patterns in the right insular, posterior cingulate, and temporal cortex predicted 91% of those who did not relapse and 94% of those who relapse (Paulus, Tapert et al. 2005). Drug-cued brain activation were able to predict relapse in alcohol (Grusser et al., 2004), nicotine (McClernon et al., 2007) and cocaine (Kosten, Scanley et al. 2004, Brewer, Worhunsky et al. 2008) dependent patients, and those activations were better predictor than subjective craving measures (Brewer, Worhunsky, Carroll, Rounsaville, & Potenza, 2008; Grusser et al., 2004; T.R. Kosten et al., 2004). Kosten et al. found their worse treatment effectiveness score correlated with BOLD activation in the left precentral, superior temporal, and posterior cingulate cortices and right middle temporal and lingual cortices in cocaine dependent individuals. The left posterior cingulated cortices activation was able to distinguished eight individuals who did not relapse from nine individuals who relapsed (T. R. Kosten et al., 2006).

The present study used an fMRI SST disinhibition task to examine BOLD response in cocaine-addicted subjects as a means of prospectively predicting relapse to cocaine use. It aimed to identify disinhibition deficits and neural changes associated with relapse in cocaine-addicted subjects. It was hypothesized that the BOLD changes in cocaine-addicted individuals would be able to differentiate those who relapse from those who do not. These neural differences would contribute to further understanding of the neural deficit associated with relapse and subsequently help to identify those at high risk of relapse. It has the potential to help tailor treatment for those at high risk of relapse.

METHOD

Research Participants

Cocaine-addicted volunteers were recruited from residential treatment programs at the Veteran Affairs Medical Center, Homeward Bound Inc., and Nexus Recovery Center. The duration of treatment stay for all participants ranged from 2 to 4 weeks. All volunteers gave written informed consent prior to enrollment and were compensated for their time upon completion of study procedures. Participants 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)(DSM-IV, 2000; 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) (Sobell & Sobell, 1978). Participants were excluded if they met criteria for active Axis I affective, anxiety or psychotic disorder, organic brain syndrome, major medical illness or neurological disorder. Participants did not take any psychoactive medications, had no fMRI contraindications, and successfully completed the SST training. 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]) were administered during the first and second weeks of inpatient

treatment. Neuroimaging procedures occurred between the two and four weeks of abstinence. Patients were then discharged to a non-structured environment and followed up twice weekly.

Follow Up

Patients were followed up twice weekly, once by phone and once as an in-person clinic visit, for up to 24 weeks to obtain return to use information. At each in office visits, urine drug screen was obtained. 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, 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. A total of 49 men and women were classified into two different participant groups: the relapsed (=27; participants who relapsed within 30 days post-treatment) and non-relapsed (n=22; participants who did not relapse within 30 days).

fMRI Task

The SST was given during fMRI. The task is modeled after the Rubia, et al. study (Rubia et al., 2003). Subjects wore goggles that displayed the stimuli - right, left and upward facing arrow – (Figure 1) and held a control allowing them to push a button with either of their thumbs. Subjects responded while the stimulus was being displayed in the goggles. The go-signal was an arrow pointing either right or left, with 5000ms of duration each that appear on screen with a mean interstimulus interview of 1.8 seconds. Arrows pointing right directed the subject to push the button with their right thumb, and arrows pointing left directed the subject to push the button with their left thumb. The stop-signal was an arrow facing upward. When participants saw this upward arrow, they were instructed not to push any button for the previous go-signal. Once a go-signal is display, the participant must wait for the stop-signal. If the participant did not press any go-button (left or right arrow) and there was an upward arrow immediately after the go-signal (right or left arrow), then the participant has successfully stopped ("StopSuccess"). If the participant did press on a go-signal and then there was a stop-signal immediately after the go-signal, than the participant has failed to stop ("StopFailure"). The stop stimulus (20% of the trial) appeared exactly 250ms after the go-signal. The time interval of 250 ms between go-signal and stop-signal onsets changes according to each subject's performance. It becomes 50 ms longer after a successful stop making it harder to inhibit, and 50 ms shorter after a stop failure, making it easier to inhibit. Thus, the tracking algorithm assured that the task is equally challenging and

difficult for each individual, providing approximately 50% stop success and 50% stop failure trials.

Seventy-four stop trials (37 of them appearing after a left arrow and 37 appearing after a right arrow) were pseudo-randomly interspersed with 288 go trials and at least three repetition times apart from each other to allow adequate separation of the hemodynamic response. Since the algorithm of the task design assured that subjects fail half of all stop events, stop success and failure events control each other for low frequency, as they result in relatively equal frequencies at the end of the task.

fMRI Scan Acquisition

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. 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, 0.94 mm in-plane resolution (FOV = 256 mm x 256 mm, 256 x 256 matrix, 1 x 1 x 1 mm resolution)] were obtained in 160 sagittal slices to facilitate localization of fMRI activation. During the SST, 384 whole brain frames of T2-weighted EPI sequence images were obtained [36, 3.0-mm contiguous transverse slices from inferior to superior, 3.25 x 3.25 x 3.0 mm resolution].

fMRI Analysis

fMRI analysis was conducted through the use of FEAT (fMRI Expert Analysis Tool), which is part of FSL (FMRIB's Software Library, www.fmrib.ox.ac. Uk/fsl). FSL is an image analysis and statistical tool for use with fMRI, MRI, and diffusion tensor imaging. Pre-statistical processing will include slice-timing correction using Fourier-space time-series phase-shifting; motion correction using MCFLIRT; non-brain removal using BET; spatial smoothing using a Gaussian kernal of FWHM 5mm; mean-based intensity normalization of all volumes by the same factor; and highpass temporal filtering (Gaussian-weighted LSF straight line fitting, with sigma =30.0 seconds). Time-series statistical analyses were carried out using FEAT with local autocorrelation correction.

The initial analysis paired time points within the SST with co-occurring changes in BOLD response for each trial of the task for each individual. Responses to baseline go trials were subtracted from the stop success trials and stop failure trials to control for brain activation related to motor execution. This study specifically analysized 500ms immediate after the upward stop signal is display, at the moment of which participants realize their StopFailure or StopSuccess. During StopFailure, this moment would correlates to when the participants think "Opps." This analysis is not like the analysis done in the Rubia et al. study, in which they considered the whole 1.8s duration including go and stop-signals (Rubia et al., 2003).

Neural activations in participants were assessed utilizing an exploratory analysis of significant voxels. Within FEAT, a two level analysis was conducted. Primary exploratory variables included in the general linear model at first-level analysis were StopSuccess and StopFailure and discards with four contrasts: StopSuccess only, StopFailure only, StopSuccess-StopFailure, and StopFailure-StopSuccess. Total Stop Signal Reaction Time (SSRT) for each

participant was considered as a nuisance variable in the analysis to control for individual differences in impulsive responding. It can be calculated by subtracting the average stop signal delay at which subjects achieved 50% of inhibition from the average reaction time to go signals (Rubia et al., 2003). The SSRT is the time required for a subject to cancel the movement after seeing the stop signal, and a longer SSRT indicates poor response inhibition.

Higher-level analysis was carried out using FLAME (FMRIB's Local Analysis of Mixed Effects) to derive group differences (relapse and nonrelapse) in activation for each of the four contrasts. The present study focused on the group differences in the StopSuccess only, with the assumption that neural activation during StopSuccess could show adaptive neural processes that prevented cocaine dependent individual from relapse.

Clinically relevant areas of activation were further investigated by interrogating first-level FEAT results using FEATquery, a tool in FSL, which reports %BOLD signal changes at the subject level. 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 $P = 0.05$. Clusters less than five voxels in size were excluded. Functional clusters were named by the Harvard-Oxford Cortical Structural Atlas, which is an atlas based on population probability maps of cortical and subcortical structural areas. Clusters were binarized to make regions of interest (ROI) masks. FEATquery used these masks to calculate mean %BOLD change within the voxels of the masks for each subject. These values were then input into the Statistical Packages for the Social Sciences, version 19.0 (SPSS, Inc. Chicago, IL) for statistical analysis.

Statistical Analysis

Non-imaging data was analyzed using the SPSS software (SPSS Inc. Chicago, IL). One-way ANOVA were used to explore group differences in demographic variables, WTAR full scale IQ, total BIS-11 scores, and SST SSRT scores. Group differences were deemed significant at $p < 0.05$.

Linear discriminant function analysis was conducted to predict whether a cocaine-addicted individual would fall within the relapse group or the non-relapse group. The categorical groups (relapse versus non-relapse) were used as dependent measures while the mean % BOLD signal change in the identified ROIs as the independent measure. The discriminant analysis produced a percentage of individuals predicted correctly into group memberships with two values, the original and cross-validated. The cross validation is a classification that successively classified all cases but one to develop a discriminant function and then categorize the case that was left out. This process is repeated with each case left out in turn. This cross validation produces a more reliable function and more honest presentation of the power of the discriminant function than that provided by the original classifications (Burns & Burns, 2009).

RESULTS

Clinical Characteristics

One-way analyses of variance (ANOVAs) showed no group differences between the two groups in demographic information, substance abuse history, intellectual functioning (WTAR), impulsivity (Barrett Impulsivity Scale-11 [BIS-11]), and SSRT (Table 1).

Functional Neuroimaging Characteristics

Similar to previous studies that investigated impulsivity during neuroimaging, changes in activation were noted in multiple cortical and subcortical areas. Clinically significant regions of interest (ROIs) during SST StopSuccess were derived from the analysis of all participants (n=49) with participants' mean and corrected voxel significance threshold of $p<0.05$ (Table 2). These regions were the left and right OFC and anterior insular cortex, anterior cingulate cortex, brainstem and left putamen. The lateral OFC and anterior insular cortex are two areas were considered as one region of interest. Figure 2 displays areas of significant activation during StopSuccess in the two participant groups, the relapse and the non-relapse. The left lateral occipital cortex was the only significant difference in BOLD activation between the relapse and non-relapse group (Figure 3), with greater activation in the relapse group than the non-relapse group. Unlike the other regions, the left lateral occipital cortex region of interest was derived from the analysis of the relapse group greater than non-relapse group contrast.

Neuroimaging and Relapse Findings

The final six clusters of ROIs used in statistical analysis were the left and right OFC and anterior insular cortex, anterior cingulate cortex, brainstem, left putamen and left lateral occipital

cortex (Table 2). Mean percent BOLD signal change data was extracted from each of the ROIs and included in the discriminant function analysis as predictor variables.

Discriminant analysis was conducted to predict whether a cocaine-addicted individual would fall within the relapse group or the non-relapse group. The areas of differences between relapse and non-relapse individuals are used as the independent measure and relapse status as the dependent measure. The standardized canonical discriminant function coefficients stemming from this analysis, which provide an index of the importance of each predictor (Burns & Burns, 2009), were utilized to focus the selection of ROIs to the strongest set of predictors for inclusion in a subsequent discriminant analysis. The discriminant analysis revealed that the left lateral occipital cortex and the left lateral OFC and anterior insular cortex BOLD response best predicted group membership for participants. The discriminant function of the analysis was highly significant (Wilk's $\lambda = 0.523$, $\chi 2 = 29.776$, $p < .001$). The cross-validated classification showed the two ROIs correctly predicted 21 out of 27 (77.8%) individuals who relapsed and 18 out of 22 (81.8%) individuals who did not relapse (Table 3). The overall cross-validated classification is 79.6% correct.

DISCUSSION

By utilizing changes in the BOLD response during a disinhibition task to predict cocaine relapse, this study identified disinhibition neural changes associated with relapse in cocaine-addicted subjects. Consistent with our first hypothesis, the study found BOLD changes during the SST that were able to predict those who relapse from those who did not. Specifically, the left lateral occipital cortex exhibited greater BOLD activation in the relapse group than the non-relapse group. On the other hand, the relapse group had lower BOLD activation in the left lateral OFC cortex & anterior insula. Using discriminant analysis, these two regions of interest were able to classify 76.9% of individuals into their respective groups correctly with cross-validation.

Several studies have used fMRI to successfully predict relapse in drug dependent patients. Neural activity during a simple two-choice prediction task were able to predict relapse, using the same discriminant analysis approach as the present study, in methamphetamine dependent individuals (Paulus, Tapert, & Schuckit, 2005). Paulus et al. assessed forty-six treatment-seeking methamphetamine dependent males three to four weeks after cessation of drug underwent fMRI during performance of a simple two-choice prediction task. The relapse data was obtained at a one-year follow-up contact and defined as the time to first 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 80 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 ($p < .01$). Paulus et al found activation in the right inferior frontal gyrus and anterior insula to be higher in the non-relapse. In the present study, the right OFC and anterior insula was analyzed as a ROI but had lower contribution as a predictor of group classification than the left OFC and

anterior insular ROI. The posterior cingulate and middle temporal cortex were not considered in the discriminant analysis in the present study. As the sample was limited to methamphetamine-dependent subjects, it is unknown if these findings generalize to other substance use disorders. During an fMRI Stroop task conducted prior to treatment initiation, the contrast of incongruent versus congruent conditions showed activation involving the OFC and insula (Brewer et al., 2008). The right putamen, left posterior cortex and left ventromedial prefrontal cortex involving the medial OFC correlated with longer duration of self-reported abstinence. Although it is the lateral OFC in the present study that was able to predict relapse group membership, the repetition involvement of OFC in predicting relapse points to its importance. The numerous differences between these studies, including drug of dependence, nature of the task, intervention and outcome measures may explain the differing areas of activation reported in the previous studies compared to the present study.

Orbitofrontal Cortex and Anterior Insula

Co-activation of the OFC and anterior insula is often found (Brooks, Nurmikko, Bimson, Singh, & Roberts, 2002; Craig, 2002; O'Doherty, Critchley, Deichmann, & Dolan, 2003). In multiple studies, the anterior insular cortex was found activated in association with subjective feelings, self recognition, error awareness, feeling of knowing and heartbeat awareness (Craig, 2009; Ghahremani, Monterosso, Jentsch, Bilder, & Poldrack, 2010). The only feature that was common to all of these studies was that they engage the awareness of the subjects and it was accepted that the anterior insula engenders human awareness.

The lateral OFC is believed to have a role in contingency re-evaluation (Ghahremani et al., 2010; Hampshire, Chaudhry, Owen, & Roberts, 2012). Contingency re-evaluation is best

explained with studies utilizing a reversal learning task, which is a classic measure of behavioral flexibility. Reversal learning tasks provides a context to test participants' capacity to change previously acquired behavior when environmental rules change. Gahremani et al. One study isolated reversal- related brain activation independent of cognitive control processes invoked during initial learning and found the lateral OFC to be more activated during reversal than acquisition (Ghahremani, Monterosso, Jentsch, Bilder, & Poldrack; Ghahremani et al., 2010). Several studies using reversal learning task found the lateral OFC to be involved in affecting change at the point of reversal by overriding the previously rewarded and routine response (Ghahremani et al.; O'Doherty et al., 2003). The lateral OFC role in contingency re-evaluation is further supported by lesion studies in rodents, nonhuman primates and human imaging studies. (Murray, O'Doherty, & Schoenbaum, 2007; Nahum, Ptak, Leemann, & Schnider, 2009; Ragozzino, 2007; Schoenbaum). OFC lesions in men are associated with a tendency to keep behaving according to one set of beliefs even when it is clear from environmental feedback that those predictions no longer reflect the reality of the situation (Schnider, 2003).

Taken together, the anterior insula activates to engender conscious awareness of relevant information while the OFC cortex is responsible for the processing of contingency information relevant to adaptive behavior such that co-activation is necessary to effect a change in behavior. The present study found the non-relapse group with greater activation in the left lateral OFC and anterior insula, suggesting individuals who did not relapsed have better conscious awareness and ability to adapt when contingencies change. On the contrary, the relapse group may have impairment in their ability to adapt when feedback changes.

Occipital Cortex

The present study, along with other studies, suggested the visual cortex play a larger role in predicting relapse than previously thought. Grusser et al. found activation in the bilateral visual cortex and the medial frontal gyrus during alcohol-related versus neutral visual stimuli in alcoholics who subsequently relapsed versus control(Grusser et al., 2004). Kosten et al. presented videos of cocaine smoking to recently abstinent cocaine dependent subjects while acquiring BOLD fMRI (T.R. Kosten et al., 2004). Activation in the right lingual and right inferior occipital gyri showed significant correlations with treatment effectiveness. Interestingly, two brain areas showed activation differences between cue and baseline conditions for in the group of full sample of 17 cocaine-dependent subjects ($p<0.01$): the right temporal and left occipital. It is the left lateral occipital cortex in our study that was the only significant difference in activation between those who relapse and those who did not. The study designs of these two studies use drug-related distracters, which the present did not. That may explain why brain regions activated in these studies are not the exact regions that this present study found. The trend of visual cortex activation in relapse studies is noteworthy and the role of the visual cortex in relapse should be further studied.

The role occipital cortex activation in cocaine-dependent patients remains unclear. It is suggested that hyperactivation in the occipital cortex in cocaine-dependent individual reflect increased visual cortical processing(de Fockert, Rees, Frith, & Lavie, 2001; Hester & Garavan, 2009; Nelissen et al., 2012). Compared to controls, cocaine abusers showed hyperactivation in occipital cortices during a visuospatial task (Tomasi et al., 2007). The present study showed the relapse group has greater activation in the lateral occipital cortex compared to control. Given that performance on the task is equally maintained between the two groups, greater activation in

lateral occipital cortex to maintain performance may signify an underlying abnormality in attention of the relapse group.

Occipital Cortex and Orbitofrontal Cortex

There is a complex and poorly understood relationship between the occipital cortex with the OFC cortex. Several studies have suggested that the OFC cortex plays a role in mediating the ability of drug-associated cues to motivate drug-seeking behavior. For instance, an intact OFC is required for cocaine-associated stimuli to act as conditioned reinforcers and for conditioned cues to guide instrumental responses. Nelissen and colleagues used fMRI to look at the conditioned effects of cocaine on rhesus monkey through classical conditioning by pairing a red visual shape, the conditioning stimulus, with a noncontingent cocaine infusion (Nelissen et al., 2012). Functional MRI sessions without cocaine infusions were interspersed with conditioning sessions with cocaine. Differences between fMRI activity evoked by the red shape and a green control shape in the absence of cocaine were measured at different stages during the conditioning process. To assess the behavioral preference of the monkey in a task-unconstrained manner, a free-choice gaze preference paradigm was given after each conditioning session, during which both the red and green shape were simultaneously presented on the screen. The OFC, ventrolateral prefrontal cortex, and the occipital cortex showed increased activity during the conditioning process. While the OFC decrease to or below baseline after the conditioning process, activity in the early visual processing, V2 area of the occipital cortex, remain elevated above the preconditioning baseline and correlated significantly with gaze preference of the monkey for the conditioned red shape. It was suggested that fMRI activity in early visual cortex is biased in favor of more valuable stimuli. (Serences & Saproo, 2010; Shuler & Bear, 2006).

Although the lateral occipital cortex region is generally thought to be related to later visual progressing (V3 and beyond), the homology of the lateral occipital cortex brain areas in between human and monkey areas is uncertain (Larsson & Heeger, 2006). Studies have suggest there is feedback/feedforward complex interaction between early visual processing and the lateral occipital cortex (Koivisto, Railo, Revonsuo, Vanni, & Salminen-Vaparanta, 2011; Larsson & Heeger, 2006; Sayres & Grill-Spector, 2008; Shpaner, Molholm, Forde, & Foxe, 2013). Taken together, the OFC is important for establishing novel representations of stimulus valence with cocaine as the reinforcer, whereas complex visual processing in the lateral occipital cortex is involved in retaining these associations.

Attentional Bias

Cocaine user often have difficulty with disengaging attention from cocaine-related stimuli resulting in greater attentional bias (Hester & Garavan, 2009), which is a predictive of poorer outcomes during treatment (Carpenter, Schreiber, Church, & McDowell, 2006). As salience of a stimulus directs attention relatively automatically (Pessoa & Ungerleider, 2004), a greater level of cognitive control must be imposed to ignore the salient stimulus and instead attend to a less salient stimulus. Hester and colleagues examined the neural mechanisms underlying this attentional bias in cocaine users by varying working memory load to reflect the demands imposed by ruminative craving thoughts (Hester & Garavan, 2009). A given working memory task manipulated the requirement for selective attention by varying the background contents, cocaine-related or neutral. Cocaine users had significantly poorer attentional control under high working memory demands, suffering both increased response times and reduced recall accuracy, with this effect more pronounced for cocaine stimuli when compared to neutral

stimuli. This reflects poor cognitive control performance with increasing working memory load. Working memory is argued to play a critical role in actively maintaining attentional priorities, so that when greater load demands are placed, implementing these 'attentional priorities' suffers, and greater processing of irrelevant information occurs (Kane & Engle, 2003). During high working load, the presence of task-irrelevant cocaine stimuli was associated with increases in left occipital cortex activity in the cocaine users, consistent with increased visual processing of the irrelevant stimuli (Hester & Garavan, 2009). In addition, the cocaine stimuli were associated with increased right lateral OFC activation. Those individuals with higher levels of right prefrontal activity having lower levels of attentional bias, suggesting better cognitive disregard of cocaine-related stimuli.

Although, the present study did not use any drug-related distractors, the concept of greater visual processing of irrelevant stimuli fits with our results. The increase in occipital cortex in those who relapsed may reflect increase effort to process task-relevant stimuli. The present study showed those who relapsed had greater lateral occipital and lower lateral OFC cortex, suggesting the relapse group have difficulty modulating the neural mechanisms underlying the cognitive control that restrict the visual processing of task-irrelevant stimuli.

Hester et al. used the same cocaine-related and neutral stimuli as the abovementioned study in an emotional Stroop task, and demonstrated that cocaine users had a significant attentional bias for the cocaine-related stimuli equivalent to the non-drug-related incongruent-colour word stimuli (Hester, Dixon, & Garavan, 2006). Given this finding, the relationship between neural activity and behaviour may not be specific to drug-related stimuli, but may generalize to other stimuli that cocaine users find evocative or salient.

Correlations with StopSuccess

Our study suggested the occipital cortex has a role in processing and maintaining the saliency of stimuli, regardless of whether it is drug-related or not. In the present study, StopSuccess have more BOLD response than baseline go trials indicating it as a high salience stimulus. The increase in occipital activation during StopSuccess in those who relapse may be necessary in order to process and maintain StopSuccess as high salience for the SST, in which the performance is equal between the two groups. The non-relapse group may be able to process the StopSuccess signal as high salience more effectively, and thus did not need compensatory increase activation in the occipital cortex to maintain it as high salience. That was consistent with the abovementioned Nelissen study, in which monkeys had greater occipital activation even after the preference for cocaine was evident, suggesting the occipital activation is associated with maintaining cocaine as high salience (Nelissen et al., 2012).

In summary, the OFC and anterior insula attribute salience to stimuli, including StopSuccess, during SST while the occipital cortex retain and maintain its saliency. Those two integrated process is needed in order to prioritize attention. In the present study those who relapsed had lower OFC and anterior insula activation, reflecting deficit in cognitive control needed to disregard task-irrelevant stimuli. Those who relapse may also have attentional bias to task-unrelated stimuli, consistent with hyperactive occipital cortex processing of stimuli.

Clinical Implications

The present study's relapse group could possibly be helped by activities that enhance attention and processing of task relevant stimuli. One possible therapy is meditation. In recent years, meditation has been studied as a possible therapy to reduce craving.

Reduction in craving has show effective in maintaining abstinence, and thus the neural mechanism of craving should be further study. The mechanism behind craving may be connected to the mechanism affecting attention. It is well accepted that cocaine dependent individuals, compared to control, have higher baseline craving without drug-related cues. One of the strongest predictors of relapse to emerge in both pre-clinical and clinical research studies is craving (Anton, 1999; Breese, Sinha, & Heilig, 2011; Drummond, 2001; Marlatt, 1978; Shadel et al., 2011; Sinha & O'Malley, 1999), and many of the most effective psychotherapies for addiction have focused on reducing or managing substance craving. Bowen and colleagues conducted the first randomized-controlled trial evaluating the feasibility and initial efficacy of an 8-week outpatient Mindfulness-Based Relapse Prevention (MBRP) program as compared to treatment as usual (Bowen et al., 2009). Initial efficacy was supported by significantly lower rates of substance use in those who received MBRP as compared to those in treatment as usual over the 4-month post-intervention period. Additionally, MBRP participants demonstrated greater decreases in craving. It is unclear how MBRP may be effective in reducing substance craving. A secondary analysis conducted by the same group found the mindfulness factor, which comprised of interdependent process of acceptance, awareness and nonjudgment, to be significantly associated with treatment and predictive of the level of craving at the end of treatment. Higher levels of this factor could be a potential mechanism by which MBRP may influence craving. Importantly, acceptance, awareness, or nonjudgment did not independently mediate the association between MBRP and the level of craving following treatment, suggesting that the combination of the processes is necessary to produce changes in craving.

The meditation process requires awareness and processing of different external and internal stimuli but encourage the individual to not attribute saliency to these stimuli. Those who

meditate are encouraged to let go of all stimuli of sensory, affective and thoughts and engage in only self-awareness in the moment. A study looking at functional connectivity during meditation concluded that the complex act of meditation may involve attentional reorienting, self-monitoring, and affective regulation (Froeliger et al., 2012).

The present study's relapse group could possibly be helped by meditation through its components of awareness, acceptance, and nonjudgement. Awareness of stimuli is largely mediated by the anterior insula. The processing of task-relevant stimuli could be seen as acceptance of stimuli, which is mediated by the OFC. The concept of being nonjudgment requires that external and internal stimuli are not given any salience. Although the relapse group had higher visual occipital processing of stimuli, they had lower OFC and anterior insula activation correlating to lower awareness and processing of relevant stimuli for the SST. In other words, they are aware and accept stimuli, but are not able to effectively use the cognitive control of the OFC and anterior insula to suppress processing of irrelevant stimuli. Meditation in those who relapse could increase activation in the OFC and anterior insula, enabling better cognitive processing of task-relevant stimuli. That would allow more effective performance on the task. In short, meditation would be helpful in the relapse group because it decreases their hyperactivation of visual processing of task-irrelevant stimuli and direct their attention and awareness toward task-relevant stimuli. It would also help in decreasing attribution of cocaine as high salience and decrease craving through enabling disregard of cocaine-related stimuli.

Limitations, strengths, and future directions

There are several strengths to the present study design. The two participant groups matched well clinically. Sample sizes were 27 individuals of those who relapsed and 22 who did

not, which are reasonable for neuroimaging studies. The participant groups were carefully screen and patients did not have other active DSM Axis I disorder beside substance use, medical or neurological disorders, or were on psychotropic medications. The follow up period of six month is thorough, with twice-weekly contact, once by phone and once as an in-person clinic visit, and urine drug screen was obtained at each visit.

There are several limitations to the current findings. The inclusion/exclusion criteria may limit the generalizability of our findings since 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 disinhibition deficits, BOLD response, and substance use. Subjects who did not return from follow-up were counted as relapse, which can result in an overestimation of relapse count or an underestimation of the real time of relapse in those participants. Finally, the stop signal task used in the present study does not directly mimic real world situations or address how individuals exercise inhibitory control.

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 and inclusion of individuals with comorbid psychiatric disorders. Only StopSuccess was examined in the current analyses, while the SST provides multiple avenues for exploring disinhibition. Exploring other processes (StopSuccess, StopFailure) responsible for generating the changes in neural activation during SST may elucidate disinhibition correlation with relapse. 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, the current investigation demonstrates that functional neuroimaging may be useful for long-term clinical predictions in cocaine-dependence. Altered neural processes of disinhibition may play a critical role in relapse. Disinhibition is a complex construct incorporating multiple cognitive processes mediated by activity in the lateral OFC, anterior insula, brainstem, anterior cingulate, and lateral occipital cortex. Several of these neural substrates, the lateral OFC, anterior insula, and lateral occipital cortex were determined to be important predictors of cocaine relapse, correctly classifying 79.6% of individuals into relapse and non-relapse groups. Understanding the implication of the chance of relapse based on the activation and deactivation patterns in various ROIs may guide clinical practice, such as extending length of stay in inpatient treatment, providing more intensive individualized treatment throughout, or enrollment in a structured outpatient treatment following discharge. Better understanding of the neural processes of impulsivity and relapse may ultimately help to develop new treatment approaches that are targeted to increase patients' chances for long-term abstinence.

TABLES & FIGURES

Table 1. Characteristics of relapse and non-relapse participant groups

	Relapse		Non- Relpase		P-value*
Subjects	27		22		
Numbers of Males	24		20		
White	25.9%		18.2%		
Black	70.4%		77.3%		
Hispanic	3.7%		4.5%		
Right Handed	88.9%		86.4%		
Left Handed	7.4%		9.1%		
Ambidextrous	3.7%		4.5%		
	Mean	Std Deviation	Mean	Std Deviation	
Age (years)	44.3	6.3	42.4	7.7	0.398
Education (years)	12.0	1.9	12.9	1.7	0.085
WTAR_FSIQ	86.7	8.6	91.2	8.3	0.320
Stop Signal Task					
Stop Signal Reaction Time	237.8	172.0	155.5	113.4	0.077
Impulsivity Measures					
Stroop ColorWord TScores	48.7	9.0	48.7	9.4	0.994
Barrett Impulsivity Scale					
Nonplanning Impulsiveness	24.8	2.0	25.1	3.0	0.709
Motor Impulsiveness	22.2	3.5	22.1	4.2	0.958
Attentional Impulsiveness	16.1	2.7	16.1	2.5	0.941
Barret Impulsivity Score Total	63.0	6.2	63.3	7.7	0.892
Drug Use					
Days used in lifetime	3,311.4	2,355.6	2,917.6	1,497.4	0.500
Lifetime $ spent on cocaine	420,817.5	552,459.7	295,057.4	215,844.6	0.291
Days used previous 90 days	68.0	27.1	66.9	26.3	0.876
$ spent in previous 90 days	6,080.3	5,641.0	6,945.0	6,021.9	0.607

Table 1. Demographics, Stop Signal Task, Impulsivity Measures and Drug Use in the relapse and non-relapse groups. One-way analyses of variance showed no significant group differences. *Value significant at α level of $p < .05$.
WTAR_FSIQ= Wechsler Test of Adult Reading Estimated Full Scale IQ score
Stroop ColorWordTScores= reading color of the ink the words are printed in while ignoring the word
SSRT= Stop Signal Reaction Time; average response time minus the average delay

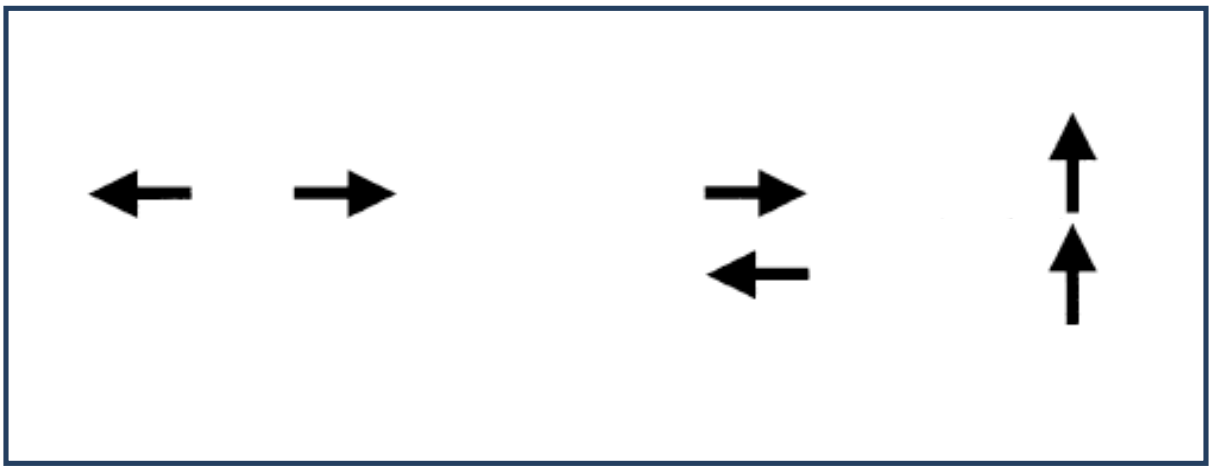

Figure 1. Schematic illustration of the stop signal task. The interval between horizontal (go signal) and vertical arrows (stop signal) in the stop trials becomes shorter/longer in steps of 50 ms depending on each subject's performance ensuring 50% of correctly inhibited and 50% failed stop trials for each subject.

Table 2. Clinically significant regions of interest during SST StopSuccess in cocaine-dependent participants

Side	Regions of Interest	Cluster size (voxels)	Voxel Z-value	Montreal Neurological Institute coordinate (mm)		
				x	y	z
Right	Lateral orbitofrontal & anterior insular cortex	460	7.24	34	22	-8
N/A	Anterior cingulate cortex	520	6.8	8	26	30
N/A	Brainstem	55	5.7	-4	-30	-10
Left	Lateral orbitofrontal & anterior insular cortex	351	6.73	-38	18	0
Left	Putamen	9	5.21	-18	14	-6
Left	Lateral occipital cortex*	657	4.46	-58	-66	-14

Table 2. Clinically significant regions of interest during SST stop success. *The left lateral occipital cortex region of interest were derived from the relapse group greater than non-relapse group contrast. All other regions were derived from analysis of all participants (n=49) with participants' mean and corrected voxel significance threshold of $p<0.05$.

Figure 2. BOLD response during SST stop success in relapse and non-relapse participants.

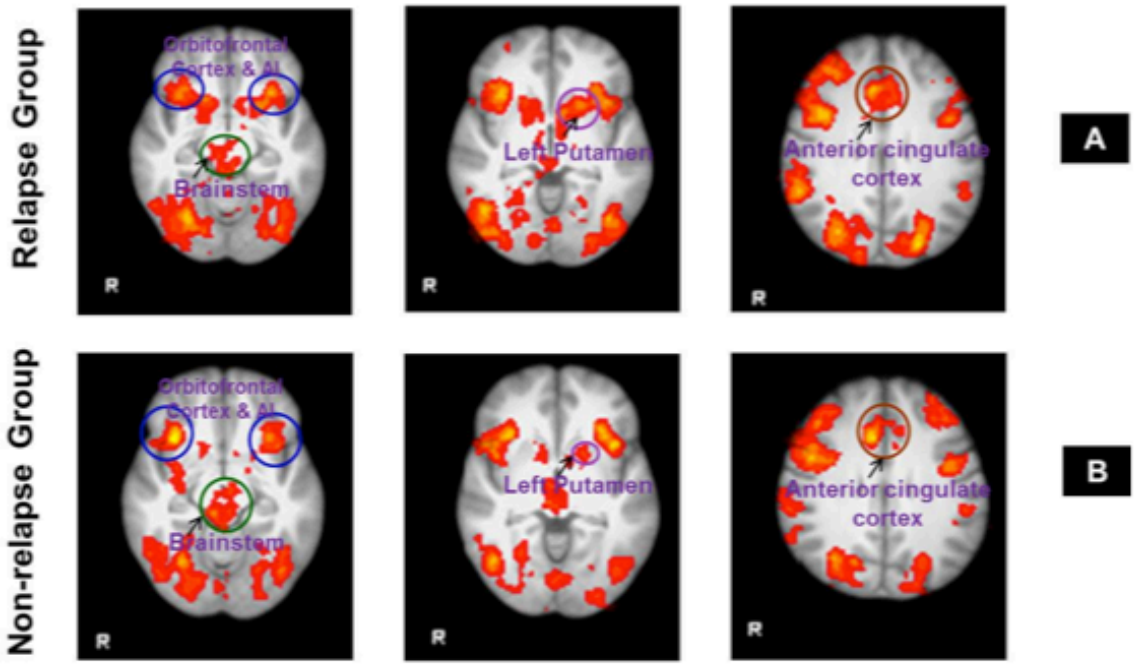

Figure 2. BOLD response during SST StopSuccess in relapse (n=27) and non-relapse (n=22, B) participant groups. The left and right lateral orbitofrontal cortex and anterior insula, left putamen, anterior cingulate cortex, and brainstem are clinically significant regions of interest that were further investigated (Z>2.3, P=0.05)

Figure 3. Differences in BOLD response between relapse and non-relapse participants groups.

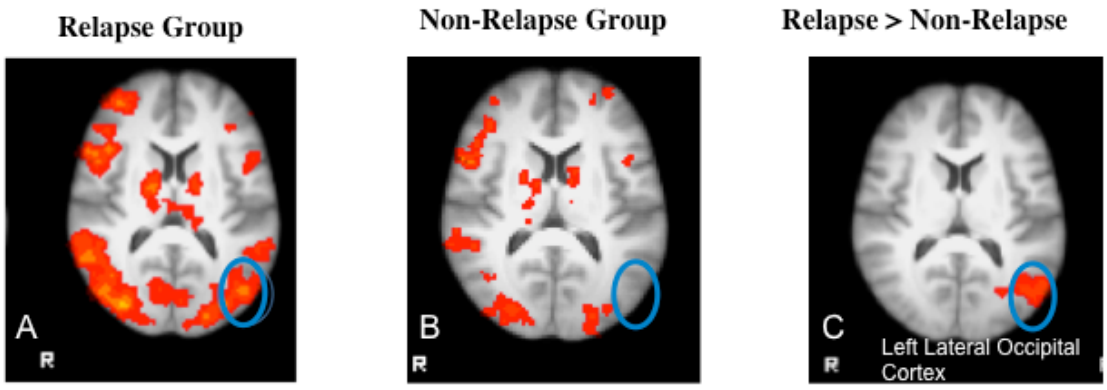

Figure 3. Difference in BOLD response during the SST stop success between cocaine-dependent patients who relapse (n=27, box A) and those who did not relapse (n=22, box B). Relapse group have greater activation in the left lateral occipital cortex (Z >2.3, P = 0.05).

REFERENCES

Adinoff, B., Devous, M. D., Best, S. M., George, M. S., Alexander, D., & Payne, K. (2001). Limbic responsiveness to procaine in cocaine-addicted subjects. *American Journal of Psychiatry, 158*(3), 390-398.

Adinoff, B., Rilling, L. M., Williams, M. J., Schreffler, E., Schepis, T. S., Rosvall, T., & Rao, U. (2007). Impulsivity, neural deficits, and the addictions: the "oops" factor in relapse. *J Addict Dis, 26 Suppl 1*, 25-39.

Ball, S.A., Carroll, K.M., Babor, T.F., & Rounsaville, B.J. (1995). Subtypes of cocaine abusers: Support for a Type AñType B distinction. *Journal of Consulting and Clinical Psychology, 63*(1), 115.

Bechara, Antoine. (2005). Decision making, impulse control and loss of willpower to resist drugs: a neurocognitive perspective. *Nature Neuroscience, 8*(11), 1458-1463. doi: 10.1038/nn1584

Bowen, S., Chawla, N., Collins, S. E., Witkiewitz, K., Hsu, S., Grow, J., . . . Marlatt, A. (2009). Mindfulness-based relapse prevention for substance use disorders: a pilot efficacy trial. *Subst Abus, 30*(4), 295-305. doi: 10.1080/08897070903250084

Brewer, J. A., Worhunsky, P. D., Carroll, K. M., Rounsaville, B. J., & Potenza, M. N. (2008). Pretreatment brain activation during stroop task is associated with outcomes in cocaine-dependent patients. *Biol Psychiatry, 64*(11), 998-1004. doi: 10.1016/j.biopsych.2008.05.024

Brooks, J. C., Nurmikko, T. J., Bimson, W. E., Singh, K. D., & Roberts, N. (2002). fMRI of thermal pain: effects of stimulus laterality and attention. *Neuroimage, 15*(2), 293-301. doi: 10.1006/nimg.2001.0974

S1053811901909747 [pii]

Browndyke, J. N., Tucker, K. A., Woods, S. P., Beauvals, J., Cohen, R. A., Gottschalk, P. C., & Kosten, T. R. (2004). Examining the effect of cerebral perfusion abnormality magnitude on cognitive performance in recently abstinent chronic cocaine abusers. *Journal of Neuroimaging, 14*(2), 162-169.

Burns, R. B., & Burns, R. A. (2009). *Discriminant Analysis Business Research Methods and Statistics using SPSS*. London: Sage Publications Ltd.

Carpenter, K. M., Schreiber, E., Church, S., & McDowell, D. (2006). Drug Stroop performance: relationships with primary substance of use and treatment outcome in a drug-dependent outpatient sample. *Addict Behav, 31*(1), 174-181. doi: 10.1016/j.addbeh.2005.04.012

Caspi, A., Moffitt, T.E., Newman, D.L., & Silva, P.A. (1996). Behavioral observations at age 3 years predict adult psychiatric disorders: Longitudinal evidence from a birth cohort. *Archives of General Psychiatry, 53*(11), 1033.

Cloninger, C. R., Sigvardsson, S., & Bohman, M. (1988). Childhood personality predicts alcohol abuse in young adults. *Alcohol Clin Exp Res, 12*(4), 494-505.

Cloninger, C. R., Sigvardsson, S., Przybeck, T. R., & Svrakic, D. M. (1995). Personality antecedents of alcoholism in a national area probability sample. *Eur Arch Psychiatry Clin Neurosci, 245*(4-5), 239-244.

Coffey, S. F., Gudleski, G. D., Saladin, M. E., & Brady, K. T. (2003). Impulsivity and rapid discounting of delayed hypothetical rewards in cocaine-dependent individuals. *Experimental and Clinical Psychopharmacology, 11*(1), 18-25.

Craig, A. D. (2002). How do you feel? Interoception: the sense of the physiological condition of the body. *Nat Rev Neurosci, 3*(8), 655-666.

Craig, A. D. (2009). How do you feel--now? The anterior insula and human awareness. *Nat Rev Neurosci, 10*(1), 59-70. doi: 10.1038/nrn2555

Dawes, M.A., Tarter, R.E., & Kirisci, L. (1997). Behavioral self-regulation: correlates and 2 year follow-ups for boys at risk for substance abuse. *Drug and Alcohol Dependence, 45*(3), 165-176.

de Fockert, J. W., Rees, G., Frith, C. D., & Lavie, N. (2001). The role of working memory in visual selective attention. *Science, 291*(5509), 1803-1806. doi: 10.1126/science.1056496 291/5509/1803 [pii]

DSM-IV, A. T. F. o. . (2000). *Diagnostic and statistical manual of mental disorders : DSM-IV-TR (4th edition, text revision ed.)*. Washington DC: American Psychiatric Association.

Ersche, K. D., Barnes, A., Jones, P. S., Morein-Zamir, S., Robbins, T. W., & Bullmore, E. T. (2011). Abnormal structure of frontostriatal brain systems is associated with aspects of impulsivity and compulsivity in cocaine dependence. *Brain, 134*(Pt 7), 2013-2024. doi: 10.1093/brain/awr138

Fein, G., Di Sclafani, V., & Meyerhoff, D. J. (2002). Prefrontal cortical volume reduction associated with frontal cortex function deficit in 6-week abstinent crack-cocaine dependent men. *Drug and Alcohol Dependence, 68*(1), 87-93.

Fillmore, M. T., & Rush, C. R. (2006). Polydrug abusers display impaired discrimination-reversal learning in a model of behavioural control. *J Psychopharmacol, 20*(1), 24-32. doi: 10.1177/0269881105057000

Fillmore, M.T., & Rush, C.R. (2002). Impaired inhibitory control of behavior in chronic cocaine users. *Drug and Alcohol Dependence, 66*(3), 265-273.

First, M. B. (2007). *Structured clinical interview for DSM-IV-TR axis I disorders : SCID-I*. Research ed. Biometrics Research Dept. New York State Psychiatric Institutute., New York, NY.

Franklin, T. R., Acton, P. D., Maldjian, J. A., Gray, J. D., Croft, J. R., Dackis, C. A., . . . Childress, A. R. (2002). Decreased gray matter concentration in the insular, orbitofrontal, cingulate, and temporal cortices of cocaine patients. *Biol Psychiatry, 51*(2), 134-142. doi: S0006322301012690 [pii]

Froeliger, B., Garland, E. L., Kozink, R. V., Modlin, L. A., Chen, N. K., McClernon, F. J., . . . Sobin, P. (2012). Meditation-State Functional Connectivity (msFC): Strengthening of the Dorsal Attention Network and Beyond. *Evid Based Complement Alternat Med, 2012*, 680407. doi: 10.1155/2012/680407

Ghahremani, D. G., Monterosso, J., Jentsch, J. D., Bilder, R. M., & Poldrack, R. A. Neural components underlying behavioral flexibility in human reversal learning. *Cereb Cortex, 20*(8), 1843-1852. doi: bhp247 [pii] 10.1093/cercor/bhp247

Ghahremani, D. G., Monterosso, J., Jentsch, J. D., Bilder, R. M., & Poldrack, R. A. (2010). Neural components underlying behavioral flexibility in human reversal learning. *Cereb Cortex, 20*(8), 1843-1852. doi: 10.1093/cercor/bhp247

Giancola, P. R., Martin, C. S., Tarter, R. E., Pelham, W. E., & Moss, H. B. (1996). Executive cognitive functioning and aggressive behavior in preadolescent boys at high risk for substance abuse/dependence. *Journal of Studies on Alcohol, 57*(4), 352-359.

Goldstein, R. Z., & Volkow, N. D. (2011). Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. *Nat Rev Neurosci, 12*(11), 652-669. doi: 10.1038/nrn3119

Grusser, S. M., Wrase, J., Klein, S., Hermann, D., Smolka, M. N., Ruf, M., . . . Heinz, A. (2004). Cue-induced activation of the striatum and medial prefrontal cortex is associated with subsequent relapse in abstinent alcoholics. *Psychopharmacology, 175*(3), 296-302.

Hampshire, A., Chaudhry, A. M., Owen, A. M., & Roberts, A. C. (2012). Dissociable roles for lateral orbitofrontal cortex and lateral prefrontal cortex during preference driven reversal learning. *Neuroimage, 59*(4), 4102-4112. doi: 10.1016/j.neuroimage.2011.10.072

Hester, R., Dixon, V., & Garavan, H. (2006). A consistent attentional bias for drug-related material in active cocaine users across word and picture versions of the emotional Stroop task. *Drug Alcohol Depend, 81*(3), 251-257. doi: 10.1016/j.drugalcdep.2005.07.002

Hester, R., & Garavan, H. (2004). Executive dysfunction in cocaine addiction: evidence for discordant frontal, cingulate, and cerebellar activity. *Journal of Neuroscience, 24*(49), 11017-11022.

Hester, R., & Garavan, H. (2009). Neural mechanisms underlying drug-related cue distraction in active cocaine users. *Pharmacol Biochem Behav, 93*(3), 270-277. doi: 10.1016/j.pbb.2008.12.009

Kane, Michael J., & Engle, Randall W. (2003). Working-memory capacity and the control of attention: The contributions of goal neglect, response competition, and task set to Stroop interference. *Journal of Experimental Psychology: General, 132*(1), 47-70. doi: 10.1037/0096-3445.132.1.47

Kaufman, J.N., Ross, T. J., Stein, E. A., & Garavan, H. (2003). Cingulate hypoactivity in cocaine users during a GO-NOGO task as revealed by event-related functional magnetic resonance imaging. *Journal of Neuroscience, 23*(21), 7839-7843.

Koivisto, M., Railo, H., Revonsuo, A., Vanni, S., & Salminen-Vaparanta, N. (2011). Recurrent processing in V1/V2 contributes to categorization of natural scenes. *J Neurosci, 31*(7), 2488-2492. doi: 10.1523/JNEUROSCI.3074-10.2011

Kosten, T. R., Scanley, B. E., Tucker, K. A., Oliveto, A., Prince, C., Sinha, R., . . . Wexler, B. E. (2006). Cue-induced brain activity changes and relapse in cocaine-dependent patients. *Neuropsychopharmacology, 31*(3), 644-650.

Kosten, T.R., Scanley, B., Tucker, K.A., Oliveto, A., Prince, C., Sinha, R., . . . Wexler, B. E. (2004). *Cue-Induced Brain Activity Changes and Treatment Outcome in Cocaine Dependent Patients.* Paper presented at the ACNP 43rd Annual Meeting, San Juan, Puerto Rico.

Larsson, J., & Heeger, D. J. (2006). Two retinotopic visual areas in human lateral occipital cortex. *J Neurosci, 26*(51), 13128-13142. doi: 10.1523/JNEUROSCI.1657-06.2006

Li, C. S., Huang, C., Yan, P., Bhagwagar, Z., Milivojevic, V., & Sinha, R. (2008). Neural correlates of impulse control during stop signal inhibition in cocaine-dependent men. *Neuropsychopharmacology, 33*(8), 1798-1806.

McClernon, F. J., Hiott, F. B., Liu, J., Salley, A. N., Behm, F. M., & Rose, J. E. (2007). Selectively reduced responses to smoking cues in amygdala following extinction-based smoking cessation: results of a preliminary functional magnetic resonance imaging study. *Addiction Biology, 12*(3-4), 503-512.

Moeller, F. G., Dougherty, D. M., Barratt, E. S., Schmitz, J. M., Swann, A. C., & Grabowski, J. (2001). The impact of impulsivity on cocaine use and retention in treatment. *Journal of Substance Abuse Treatment, 21*(4), 193-198.

Murray, E. A., O'Doherty, J. P., & Schoenbaum, G. (2007). What we know and do not know about the functions of the orbitofrontal cortex after 20 years of cross-species studies. *J Neurosci, 27*(31), 8166-8169. doi: 10.1523/JNEUROSCI.1556-07.2007

Nahum, L., Ptak, R., Leemann, B., & Schnider, A. (2009). Disorientation, confabulation, and extinction capacity: clues on how the brain creates reality. *Biol Psychiatry, 65*(11), 966-972. doi: 10.1016/j.biopsych.2009.01.007

Nelissen, K., Jarraya, B., Arsenault, J. T., Rosen, B. R., Wald, L. L., Mandeville, J. B., . . . Vanduffel, W. (2012). Neural correlates of the formation and retention of cocaine-induced stimulus-reward associations. *Biol Psychiatry, 72*(5), 422-428. doi: 10.1016/j.biopsych.2012.02.021

Newton, T. F., De La Garza, R., 2nd, Kalechstein, A. D., Tziortzis, D., & Jacobsen, C. A. (2009). Theories of addiction: methamphetamine users' explanations for continuing drug use and relapse. *American Journal on Addictions, 18*(4), 294-300. doi: 911211983 [pii]
10.1080/10550490902925920

O'Doherty, J., Critchley, H., Deichmann, R., & Dolan, R. J. (2003). Dissociating valence of outcome from behavioral control in human orbital and ventral prefrontal cortices. *Journal of Neuroscience, 23*(21), 7931-7939.

Patton, D., Barnes, G. E., & Murray, R. P. (1997). A personality typology of smokers. *Addict Behav, 22*(2), 269-273. doi: S0306-4603(96)00004-4 [pii]

Paulus, M. P., Tapert, S. F., & Schuckit, M. A. (2005). Neural activation patterns of methamphetamine-dependent subjects during decision making predict relapse. *Archives of General Psychiatry, 62*(7), 761-768.

Pessoa, Luiz, & Ungerleider, Leslie G. (2004). Neuroimaging studies of attention and the processing of emotion-laden stimuli. *144*, 171-182. doi: 10.1016/s0079-6123(03)14412-3

Ragozzino, M. E. (2007). The contribution of the medial prefrontal cortex, orbitofrontal cortex, and dorsomedial striatum to behavioral flexibility. *Ann N Y Acad Sci, 1121*, 355-375. doi: 10.1196/annals.1401.013

Rubia, K., Smith, A. B., Brammer, M. J., & Taylor, E. (2003). Right inferior prefrontal cortex mediates response inhibition while mesial prefrontal cortex is responsible for error detection. *Neuroimage, 20*(1), 351-358.

Sayres, R., & Grill-Spector, K. (2008). Relating retinotopic and object-selective responses in human lateral occipital cortex. *J Neurophysiol, 100*(1), 249-267. doi: 10.1152/jn.01383.2007

Schnider, A. (2003). Spontaneous confabulation and the adaptation of thought to ongoing reality. *Nat Rev Neurosci, 4*(8), 662-671. doi: 10.1038/nrn1179

Schoenbaum, Geoffrey; Nugent, Summer L.; Saddoris, Michael P.; Setlow, Barrr.

Serences, J. T., & Saproo, S. (2010). Population response profiles in early visual cortex are biased in favor of more valuable stimuli. *J Neurophysiol, 104*(1), 76-87. doi: 10.1152/jn.01090.2009

Shpaner, M., Molholm, S., Forde, E., & Foxe, J. J. (2013). Disambiguating the roles of area V1 and the lateral occipital complex (LOC) in contour integration. *Neuroimage, 69*, 146-156. doi: 10.1016/j.neuroimage.2012.11.023

Shuler, M. G., & Bear, M. F. (2006). Reward timing in the primary visual cortex. *Science, 311*(5767), 1606-1609. doi: 10.1126/science.1123513

Sim, M. E., Lyoo, I. K., Streeter, C. C., Covell, J., Sarid-Segal, O., Ciraulo, D. A., . . . Renshaw, P. F. (2007). Cerebellar gray matter volume correlates with duration of cocaine use in cocaine-dependent subjects. *Neuropsychopharmacology, 32*(10), 2229-2237. doi: 10.1038/sj.npp.1301346

Sinha, R., Garcia, M., Paliwal, P., Kreek, M. J., & Rounsaville, B. J. (2006). Stress-induced cocaine craving and hypothalamic-pituitary-adrenal responses are predictive of cocaine relapse outcomes. *Archives of General Psychiatry, 63*(3), 324-331.

Sobell, M. B., & Sobell, L. C. (1978). *Behavioral treatment of alcohol problems*. New York: Plenum Press.

Strickland, T. L., Mena, I., Villanueva-Meyer, J., Miller, B. L., Cummings, J., Mehringer, C. M., . . . Myers, H. (1993). Cerebral perfusion and neuropsychological consequences of chronic cocaine use. *Journal of Neuropsychiatry and Clinical Neurosciences, 5*(4), 419-427.

Tomasi, D., Goldstein, R. Z., Telang, F., Maloney, T., Alia-Klein, N., Caparelli, E. C., & Volkow, N. D. (2007). Thalamo-cortical dysfunction in cocaine abusers: implications in attention and perception. *Psychiatry Res, 155*(3), 189-201. doi: 10.1016/j.pscychresns.2007.03.002

Wittmann, M., Leland, D. S., Churan, J., & Paulus, M. P. (2007). Impaired time perception and motor timing in stimulant-dependent subjects. *Drug and Alcohol Dependence, 90*(2-3), 183-192.