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Intact inhibitory control processes in abstinent drug abusers (I): A functional neuroimaging study in former cocaine addicts

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Abstract

Neuroimaging studies in current cocaine dependent (CD) individuals consistently reveal cortical hypoactivity across regions of the response inhibition circuit (RIC). Dysregulation of this critical executive network is hypothesized to account for the lack of inhibitory control that is a hallmark of the addictive phenotype, and chronic abuse is believed to compound the issue. A crucial question is whether deficits in this circuit persist after drug cessation, and whether recovery of this system will be seen after extended periods of abstinence, a question with implications for treatment course and outcome. Utilizing functional magnetic resonance imaging (fMRI), we examined activation in nodes of the RIC in abstinent CD individuals ($n = 27$) and non-using controls ($n = 45$) while they performed a motor response inhibition task. In contrast to current

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users, these abstinent individuals, despite extended histories of chronic cocaine-abuse (average duration of use = 8.2 years), performed the task just as efficiently as non-users. In line with these behavioral findings, no evidence for between-group differences in activation of the RIC was found and instead, robust activations were apparent in both groups within the well-characterized nodes of the RIC. Similarly, our complementary Electroencephalography (EEG) investigation also showed an absence of behavioral and electrophysiological deficits in abstinent drug abusers. These results are consistent with an amelioration of neurobiological deficits in inhibitory circuitry following drug cessation, and could help explain how long-term abstinence is maintained. Finally, regression analyses revealed a significant association between level of activation in the right insula with inhibition success and increased abstinence duration in the CD cohort suggesting that this region may be integral to successful recovery from cocaine addiction.

Keywords

Abstinence; Cocaine; fMRI; Insula; Recovery; Response inhibition

1. Introduction

Current theories of addiction posit that deficits in inhibitory control play a major role in the development of addiction and the propensity to relapse (Everitt et al., 2008). The inability to inhibit an undesired behavior is one of the more significant facets of drug dependence (Lyvers, 2000) and diagnostic evaluations of drug addiction typically contain questions pertaining to the ability to inhibit behaviors with known negative consequences (DSM-IV). Although inhibitory control is considered a multi-faceted construct (Evenden, 1999), cocaine addicts display deficits on various measures of inhibitory control including impaired response inhibition (Fillmore and Rush, 2002; Verdejo-Garcia et al., 2007), impulsive choice (Coffey et al., 2003) and poor decision making (Monterosso et al., 2001). Most tasks measuring inhibitory control fall into paradigms that are broadly measuring either impulsive choice or impulsive responding. Measures of both constructs suggest that inhibitory control is involved in the acquisition and escalation/dysregulation phases of drug use (Perry and Carroll, 2008).

Neuroimaging studies conducted on current cocaine dependent (CD) users have shown that reduced inhibitory control is associated with neurobiological deficits in both prefrontal inhibitory control and insular regions. Kaufman et al. (2003), utilizing a Go/No-Go task, found that on successful inhibitions of a prepotent response, current cocaine users displayed hypoactivity in the right anterior cingulate and right insula, suggesting that these regions may be responsible for the weakened inhibitory control associated with cocaine dependence. These results were replicated in a study utilizing the same task with additional cortical hypoactivations observed in the right inferior parietal lobule and right middle frontal gyrus of current CD individuals (Garavan et al., 2008). Hester and Garavan (2004) examined current CD users on a Go/No-Go task with increased working memory demands and found that current users had poorer inhibitory performance compared to non-using controls that were associated with reduced activation in the anterior cingulate cortex and right prefrontal cortex. Supporting evidence for inhibitory control deficits comes from other paradigms and

other modalities. For example, using a “Counting” Stroop task, Barros-Loscertales et al. (2011) showed decreased activation of the right inferior frontal gyrus in current CD users compared to non-using controls when responding to incongruent stimuli. Utilizing diffusion tensor imaging in current CD individuals, Moeller et al. (2005) found that white matter integrity in the anterior corpus callosum was reduced in CD individuals and negatively correlated with behavioral measures of inhibitory control. Finally, Ersche et al. (2011) found that gray matter volumes in the insulae of current CD individuals were reduced compared to non-using controls and that reduced GM in the insulae of current users was correlated with greater impairments in behavioral measures of inattention as measured by the Stop Signal and Rapid Visual Information Processing Task. Although there is some uncertainty in specifying the exact cognitive process that underlies the cocaine users inhibitory control deficits (Li et al., 2008, 2006b), collectively, these results provide strong evidence that reduced inhibitory control in current users can be characterized by neurobiological deficits in prefrontal regions.

There is a clear imperative to determine whether deficits of inhibitory control ameliorate after the discontinuation of cocaine use. Improvement in inhibitory control accompanying continued abstinence could suggest that successful recovery from cocaine addiction is facilitated by increased inhibitory control. An investigation of two groups of recently abstinent CD patients (1 vs. 4 weeks) showed no differences on the “Impulse” subset of questions from the Difficulties in Emotion Regulation Scale. However, both abstinence groups showed poorer inhibitory control relative to non-using controls (Fox et al., 2007). Another study utilizing the Behavioral Assessment of the Dysexecutive Syndrome scale found that abstinent CD patients (mean abstinence of 25 weeks) exhibited inhibitory control deficits when compared to non-using controls (Verdejo-Garcia et al., 2007). These results suggest that deficits in inhibitory control may persist after the cessation of cocaine use. However, self-report measures of impulse control have limitations (Perry and Carroll, 2008) and consequently, neurobiological investigations of inhibitory control might be valuable in providing an objective measure of inhibitory deficits and their potential amelioration in abstinent CD individuals.

To date, only two neuroimaging studies have examined motor response inhibition in abstinent CD individuals. Li et al. (2008) looked at response inhibition in abstinent CD males ($n = 15$) utilizing a stop-signal task and examined activity patterns in the rostral anterior cingulate cortex and the dorsal medial frontal cortex. The authors found decreased activity in the rostral anterior cingulate in the CD group and theorized that this effect was responsible for inhibitory control deficits in CD individuals. The specific duration of abstinence was not reported in this study (although participants were at least 2 weeks post cessation), so one outstanding question is the length of abstinence that is required for the amelioration of cortical hypoactivity. Connolly et al. (2012) utilized a Go/No-Go motor response inhibition task to examine cortical activations in abstinent CD individuals who had attained either shorter ($n = 9$; average duration = 2.4 weeks) or longer ($n = 9$; average duration = 69 weeks) periods of abstinence. This investigation found that both the short- and long-term abstinence groups displayed greater cortical activity than drug naïve controls when performing a successful motor response inhibition in multiple nodes of the canonical

response inhibition circuit (RIC). The RIC has been identified as including the right middle and inferior frontal gyri, right inferior parietal lobule, bilateral insula and the midline cingulate and pre-SMA (Chen et al., 2009; Chevrier et al., 2007; Dodds et al., 2011; Fassbender et al., 2009, 2004; Garavan et al., 2006, 2008, 1999; Hampshire et al., 2010; Hester and Garavan, 2004; Kaufman et al., 2003; Konishi et al., 1999; Leung and Cai, 2007; Li et al., 2006a; Xue et al., 2008). These findings were paralleled by the absence of behavioral differences between the abstinent groups and the non-using controls, a finding suggestive of recovery of function. Thus, the finding of normalized inhibitory performance in tandem with increased cortical activity in inhibitory control areas in this study would appear to point to a period of major recovery within the RIC after drug cessation.

Because of the contradictory results from investigations of motor response inhibition in abstinent CD individuals, it remains unresolved whether there are enduring deficits in inhibitory control after extended cessation of drug use. These contradictory results may be due to the different motor response inhibition tasks that were used (Swick et al., 2011) or the relatively small sample sizes in both studies. Here, using a cross-sectional design, we examined a larger cohort of abstinent CD individuals with large variation in their durations of abstinence. As part of a multi-methodological approach to this issue, we also performed a parallel event-related potential (ERP) investigation in a second cohort of abstinent drug abusers and non-using controls (Morie et al., 2014). Comparisons between a non-using control population and abstinent patients, as well as within the abstinent patient group allowed us to test for cortical activation differences related to previous cocaine use and to assess if these differences changed with abstinence duration.

2. Methods

2.1. Subjects

Twenty-seven abstinent cocaine patients were recruited from in-patient addiction treatment centers located in New York State and 45 controls were recruited through the Volunteer Recruitment Pool at the Nathan S. Kline Institute for Psychiatric Research. It should be noted that the participants in our complementary EEG study constituted an almost completely separate cohort with only two patients and six controls participating in both EEG and fMRI studies. All 27 patients received a primary Axis I diagnosis of Cocaine Dependence and underwent random urine toxicology testing for cocaine and other abusable substances (alcohol, opiates, amphetamines, cannabinoids, phencyclidine, barbiturates, and benzodiazepines) at least twice a week to monitor continued abstinence. Abstinence was also confirmed by a New York State accredited substance abuse counselor with whom the patient met on a weekly basis. Abstinent patients were clean for an average of 32.3 weeks (Minimum = 0.87 weeks, Maximum = 100 weeks; SD = 23.9). It should be noted that the minimum duration of abstinence was only found in one participant and that the 14 patients with the shortest duration of abstinence had an average of 13.4 weeks of cocaine cessation. Exclusion criteria for patients and controls were as follows: 1) Any DSM-IV, Axis I diagnosis (excluding dependence or a past diagnosis of depression caused by CD for patients) based on the Structured Clinical Interview for the DSM-IV (SCID); 2) Head trauma resulting in loss of consciousness for longer than 30 min; 3) Presence of any past or

current brain pathology; 4) A diagnosis of HIV; 5) The presence of any contraindications to an MRI; 6) Age above 55 years and below 19 years; 7) Presence of WM hyperintensities (only one patient was excluded from the analysis because of clinically significant WM hyperintensities). Because of the high rates of comorbidity of alcohol and drug abuse among the patient population, patients were not excluded if they had abused other drugs or alcohol prior to the onset of their cocaine abstinence (5 individuals had comorbid alcohol dependence and 8 individuals had comorbid heroin dependence). None of the patients were currently using any amount of alcohol or drugs and through self-report all but two individuals reported having a previous relapse. Years of drug use were recorded during the initial SCID interviews. Controls were excluded if they had any major Axis 1 disorder and/or current or past alcohol/drug dependence diagnosis based on a SCID for the DSM-IV. The study received Institutional Review Board approval at the Nathan S. Kline Institute for Psychiatric Research. All participants were screened for contraindications for MRI and signed an informed consent document administered by HIPAA-certified staff.

The comparison samples of patients and controls consisted of 27 patients (3 women) and 45 controls (10 women) (see Table 1). The patients and controls did not differ in age (37.8 ± 7.8 , 38.1 ± 10.6 , $t(70) = -0.10$; $p = 0.92$) but patients had fewer years of education (12.9 ± 1.4 , 13.7 ± 1.7 , $t(70) = -2.01$; $p = 0.05$).

2.2. Stimuli and tasks

All participants completed a Go/No-Go motor response inhibition task, while being scanned, that consisted of a series of pictures depicting neutral scenes from the International Affective Picture System (IAPS) (Lang et al., 1997). This same task was also employed in our EEG investigation. The IAPS is a large set of standardized photographs that are rated with regard to their tendency to evoke an emotional response in the viewer. From this set, 158 neutral pictures were chosen with a mean emotional valence and arousal of 5.2 and 3.5 respectively, on a scale from 1 to 9. All stimuli subtended 8.6° horizontally 6.5° vertically of visual angle. Stimuli were delivered to a monitor in the magnet for a duration of 800 ms and were separated by a blank screen presented for 200 ms. Participants were instructed to quickly press a button at the onset of each stimulus (Go trials) and to withhold a response in instances when a stimulus was repeated (No-Go trials). Stimuli were presented pseudorandomly in three blocks with each block containing 180 trials. Within each block, 22 trials (12%) were No-Go trials. The high proportion of Go trials renders the quick button press to the occurrence of a stimulus to be the prepotent response. The withholding of a button press to stimulus repetition therefore required the recruitment of inhibitory neural mechanisms.

2.3. Image acquisition

MRI scans were performed in a 1.5T Siemens Vision system (Erlangen, Germany) at the Center for Advanced Brain Imaging (CABI) at the Nathan S. Kline Institute. Functional scans were acquired in three runs of 103 volumes utilizing a T2-weighted echo-planar sequence (TR/TE = 2000/50 ms, flip angle = 85° , 5 mm slice thickness, 224 mm FOV, 64×64 matrix, pixel size = $3.5 \times 3.5 \text{ mm}^2$, no gap). Twenty-two axial slices were obtained parallel to the AC-PC plane. Structural images were acquired utilizing a T1-weighted

magnetization-prepared rapid gradient echo (MPRAGE) (TR/TE = 11.6/4.9 ms, flip angle = 8°, 172 slices, 1.2 mm slice thickness, 307 mm FOV, 256 × 256 matrix, pixel size = 1.2 × 1.2 mm², no gap).

2.4. Image processing

The functional and anatomical data were pre-processed and analyzed using Brain Voyager (QX 2.3, Maastricht, The Netherlands) running in Windows XP environment. Functional scans were pre-processed by performing a slice scan time correction, 3D motion correction and high pass temporal filtering. Functional scans were excluded if they displayed >2 mm of motion in a given plane. For the patients, one participant was excluded from the analyses because of too much motion while one participant had two runs excluded and two participants each had one run excluded. For the controls, one participant was excluded because of too much motion. One participant had two runs excluded while four participants each had one run excluded. The T1-weighted anatomical slices were normalized into Talairach space and coregistered with the functional time courses. The resulting volumetric time courses were then spatially smoothed using a 6 mm full-width at half-maximum (FWHM) Gaussian kernel.

2.5. Analysis strategy

In this event-related design, successful inhibitions to No-Go trials (STOPS) and unsuccessful inhibitions (ERRORS) served as regressors of interest. These regressors were convolved with a two-gamma-variate hemodynamic response function and subjected to a first-level analysis using a fixed effects general linear model (GLM). For our analyses, we chose to only examine STOPS activation as the task did not result in sufficient numbers of ERRORS to provide for a meaningful comparison between STOPS and ERRORS.

Because we were most interested in examining cortical activations associated with inhibitory control, we first identified regions-of-interest (ROI) previously implicated as part of the RIC network within the task-defined map. This procedure consisted of identifying centers of mass based upon peak voxel activations and then confirming that the centers of mass fell within the canonical RIC. A review of the imaging literature on response inhibition processes utilizing similar motor response inhibition tasks identified the right middle and inferior frontal gyri, right inferior parietal lobule, bilateral insula and the midline cingulate and pre-SMA as canonical nodes of the RIC (Chen et al., 2009; Chevrier et al., 2007; Dodds et al., 2011; Fassbender et al., 2009, 2004; Garavan et al., 2006, 2008, 1999; Hampshire et al., 2010; Hester and Garavan, 2004; Kaufman et al., 2003; Konishi et al., 1999; Leung and Cai, 2007; Li et al., 2006a; Xue et al., 2008). The peak activations within each of these regions were identified and then served as the center of a 13 mm³ (2197 voxels) cubic ROI (see Fig. 1).

For each ROI, *t*-tests were performed between all patients and all controls utilizing the average ROI activation for each participant. This analysis was performed within Brain Voyager and utilized a contrast of STOPS >0 (0 = Baseline activation levels). Because this analysis utilized the average ROI activation for each individual as the independent variable and was not a voxelwise comparison, there was no correction for multiple comparisons.

Additionally, we did not perform an ROI-level correction as this would have resulted in a more stringent alpha-level and made a null-result more likely.

Next, we conducted a whole-brain voxelwise comparison between patients and controls to investigate whether there were any activation differences between the two groups in any regions of the brain. A voxelwise *t*-test was performed between groups (False Discovery Rate (FDR); $q = 0.05$) utilizing a *t*-test contrast of STOPS >0 and a cluster threshold of at least four contiguous voxels. In addition, a more liberal uncorrected voxelwise *t*-test ($p = 0.001$; 4 voxel threshold) was also inspected.

To ensure that any failure to find between-group differences from the previous whole-brain analysis was not due to the requirement to correct for multiple tests, we next restricted the group difference analysis to a mask of task-activated areas. This mask was created by collapsing all patients and control into one group and thresholding the contrast of STOPS >0 (FDR; $q = 0.05$) (anatomical resolution) (see Fig. 1). A voxelwise *t*-test on STOP activation was then performed between groups (FDR; $q = 0.05$; cluster threshold of at least four contiguous voxels) within this mask.

Finally, a linear regression approach was utilized to investigate whether duration of abstinence was predictive of brain responses within the RIC. For this analysis, we extracted the mean beta-weights for each of the ROIs. These beta-weights are the mean activation value of the contrast STOPS >0 within the ROI for each individual that were utilized in our between groups ROI analyses. These values were then entered into PASW Statistics Version 20 (SPSS, Inc., 2009, Chicago, IL) as a dependent variable in a linear regression with duration of abstinence, years of cocaine use, age and total number of STOPS as independent variables. A similar linear regression was conducted only on non-using controls utilizing total number of STOPS and age as the independent variables if they were found to be a significant predictor of ROI activation in a patient only regression.

3. Results

3.1. Behavioral results

Overall, abstinent patients did not display any significant behavioral differences from controls in terms of task performance (see Table 1). Patients did not differ from controls in the percentage of correct STOPS (0.75 ± 0.19 , 0.76 ± 0.19 , respectively, $t(70) = -0.35$; $p = 0.72$), total number of STOPS (48.8 ± 12.0 , 50.4 ± 12.5 , respectively, $t(70) = -0.56$; $p = 0.58$) and total number of ERRORS (13.3 ± 8.7 , 11.2 ± 9.6 , respectively, $t(70) = 0.97$; $p = 0.34$) committed. Patients also did not differ from controls in reaction time for correct responses (HITS) (386 ± 57 , 399 ± 60.8 , respectively, $t(70) = -0.90$; $p = 0.37$) or ERRORS (355.6 ± 116 , 347.8 ± 66.3 , respectively, $t(68) = 0.36$; $p = 0.72$). We also conducted a signal detection analysis to better examine individual differences in response patterns. Utilizing the d' values from the signal detection analysis, there were no significant differences between patients and controls in d' values (3.52 ± 1 , 3.58 ± 1.1 , respectively, $t(70) = -0.22$; $p = 0.83$). d' is computed by taking into account the probability of correctly responding to targets when a target is present and the probability of incorrectly initiating a response in the absence of a target (Green and Swets, 1966). For the patients, a linear regression was performed with total

STOPS as the dependent variable and duration of abstinence, years of cocaine use and age as the independent variables. None of the independent variables were significant predictors of total number of correct STOPS.

3.2. Abstinent patients vs. controls

The main focus of this study was to investigate if individuals who were abstaining from cocaine use would display cortical hypoactivations in the RIC when compared to non-using controls. For the ROI analysis, abstinent patients did not differ from controls within any of the seven ROIs utilizing a threshold of $p < 0.05$ (see Table 2). Abstinent patients did not differ from controls in the right insula ($t(70) = -0.17$; $p = 0.86$), right inferior frontal gyrus/middle frontal gyrus ($t(70) = 0.28$; $p = 0.78$), right inferior parietal lobule/precuneus ($t(70) = -0.85$; $p = 0.40$), right inferior frontal gyrus ($t(70) = -0.13$; $p = 0.89$), left pre-supplementary motor area/cingulate ($t(70) = 0.42$; $p = 0.68$), left precentral gyrus ($t(70) = -1.17$; $p = 0.24$) and left insula ($t(70) = 0.51$; $p = 0.61$).

In the whole-brain analysis, no regions differed between patients and controls at a threshold of $p < 0.05$, corrected for multiple comparisons using the FDR method. For the analysis of abstinent patients vs. controls, restricted to a mask of regions activated by the contrast of Stops > 0 , no regions differed between groups at a threshold of $p < 0.05$, corrected for multiple comparisons using the FDR method. The uncorrected whole-brain voxelwise analysis between groups showed that patients displayed higher activation than controls in the right superior temporal gyrus ($p < 0.001$; cluster threshold of at least four contiguous voxels).

3.3. Duration of abstinence

To examine if cortical activations within the RIC were predictive of duration of abstinence, response success, age or years of cocaine use a linear regression was conducted utilizing the beta-weights from each of the predefined ROIs as the dependent variables. The regressions included total number of STOPS, duration of abstinence, years of cocaine use and age as independent variables in the linear regression and found that greater activation of the right insula was predicted by both greater duration of abstinence ($p = 0.01$) and total number of STOPS ($p = 0.0001$) (see Fig. 2). We repeated this analysis excluding the participant with the shortest duration of abstinence (0.87 weeks) and found that greater duration of abstinence and total number of STOPS continued to be predictive of greater right insula activation. A similar regression was conducted in the controls using total number of STOPS and age as independent variables. For the controls, right insula activation was not predicted by total number of STOPS ($p = 0.12$).

4. Discussion

Our current investigation of inhibitory control in abstinent CD individuals revealed an absence of cortical activation differences in the RIC as compared to non-using controls. Additionally, duration of abstinence did not appear to be a major contributing factor to the present results since response success was not a significant predictor of length of abstinence and the patients performed the task just as successfully as the healthy controls. Participants

in our complementary EEG study also completed the same Go/No-Go task and similarly displayed no differences in behavioral or electrophysiological activity relating to inhibitory control (Morie et al., 2014). Both of these studies contradict previous investigations of motor response inhibition in current CD individuals showing cortical hypoactivations in the RIC when compared to non-using controls (Garavan et al., 2008; Kaufman et al., 2003), monitoring and inhibitory deficits in current drug abusers, evidenced by N2 and P3 amplitude reductions (Sokhadze et al., 2008; Yang et al., 2009), and deficits in monitoring ability (Franken et al., 2007). Utilizing two different methodologies and two virtually discrete cohorts (with an overlap of only two patients and six controls) both studies independently provide evidence suggestive of a recovery of inhibitory control within this population occurring over a time frame of weeks to months rather than years. Supporting this hypothesis, we have also observed evidence of recovery within white matter tracts of abstinent CD individuals utilizing diffusion tensor imaging (Bell et al., 2011). Similarly, Hanlon et al., 2011 observed reduced gray and white matter in current CD individuals when compared to both non-using control and abstinent CD individuals. However, because of this study's cross-sectional design, it is impossible to determine whether the abstinent patients' similarity of cortical activations in the RIC to non-using controls is definitively a result of recovery of function. It could be that this specific cohort was unique in that they did not display cortical hypoactivations in the RIC during cocaine dependence.

Our findings were not fully in line with prior investigations of abstinent CD individuals which have shown both hypo and hyperactivations in the RIC circuit when compared to non-using controls. Li et al. (2008) found that abstinent CD individuals showed cortical hypoactivations in the rostral anterior cingulate cortex when performing a motor response inhibition task. The authors do not list the abstinence duration of their cohort so it is possible that the participants in the study were only very recently abstinent in contrast to our cohort where our 14 abstinent users with the shortest time clean had an average duration of abstinence of 13.4 weeks. Therefore, our patient group may be further along in terms of abstinence duration which could be indicative of a strengthening of the RIC so that continued abstinence is possible. It is also possible that these two different outcomes were a result of the different types of motor response inhibition tasks that were used in each investigation. While Li et al. (2008) used a stop-signal task, the investigation we conducted utilized a Go/No-Go motor response inhibition task. A recent quantitative meta-analysis has shown that while these two tasks have significant overlap in the cortical regions they activate, Go/No-Go tasks produced greater activation in the frontoparietal control network than stop-signal tasks (Swick et al., 2011). Results from our investigation also differed somewhat from those of Connolly et al. (2012) in which both short (2.4 weeks) and long (69 weeks) duration abstinent patients displayed hyperactivations in the RIC relative to non-using controls. It is not clear why our cohort also did not display cortical hyperactivations, however, both studies are consistent in that they do not show the cortical hypoactivity of the RIC that is typical of current users.

The absence of performance and activation differences in abstinent CD abusers is especially notable given the robust evidence of inhibitory control deficits in cocaine addiction. These deficits are hypothesized to be partly responsible for the switch from single to daily drug usage (acquisition stage), and the switch from controlled to compulsive drug intake (Perry

and Carroll, 2008). Evidence supporting this model comes from Ersche et al. (2012) who showed that siblings of stimulant dependent individuals exhibited significantly decreased levels of inhibitory control when compared to non-using controls suggesting that deficits in inhibitory control precede substance dependence. Furthermore, rats that are rated as low in inhibitory control are more likely to escalate their initial drug-taking (Dalley et al., 2007) and develop compulsive drug-taking despite punishment (Belin et al., 2008) than rats rated as high in inhibitory control. It is also hypothesized that chronic drug use may result in structural and functional changes in cortical control areas which may then result in decreased inhibitory control (Dalley et al., 2011; Perry and Carroll, 2008). Regardless of the mechanism, there is general agreement that deficits in inhibitory control constitute a significant facet of drug dependence and that continued problems with inhibitory control could constitute a risk factor for relapse if not addressed. Based upon this, a goal of drug addiction treatment could be to increase the levels of inhibitory control in CD individuals. It has been shown that reduced inhibitory skills are associated with worse cocaine treatment outcomes (Aharonovich et al., 2006; Brewer et al., 2008; Streeter et al., 2008). Specifically, Moeller et al. (2001) showed that CD individuals who scored low on measures of inhibitory control were more likely to drop out of drug treatment and relapse to cocaine use. The abstinent users who participated in our study were all recruited from in-patient addiction treatment centers and were required to attend meetings with counselors at least 3 times a week. Additionally, most of the patients included in the study had achieved relatively long periods of abstinence during which they were receiving constant counseling on how to deal with their urges to use drugs again. Therefore, it is possible that because the cohort of former users in the current investigation was receiving intensive treatment that involved counseling on restraining urges, they possessed strengthened cognitive control mechanisms. These strengthened cognitive control mechanisms could explain why they do not display the typical hypoactivations associated with current cocaine dependence. One interpretation of these results is that increased duration of cocaine abstinence results in dynamic neurobiological changes that enable extended abstinence. Therefore, the period of abstinence in this cohort coupled with environmental seclusion may have resulted in an increased ability to inhibit behaviors which was then represented by a normalization of cortical activations in the RIC.

Although the results showed no differences between abstinent patients and controls in cortical activation of the RIC, we did find evidence of individual differences in cortical functioning within the right anterior insula of abstinent patients specifically relating to duration of abstinence and response success. It was observed that when STOPS occurred, increased cortical activation of the right anterior insula was predictive of increased response success and increased duration of abstinence. Interestingly, right insula activation in controls was not predicted by response success suggesting that this effect may be specific to recovering cocaine addicts. Evidence suggests that the anterior insular cortex plays an important role in maintaining drug use. Naqvi et al. (2007) showed that lesions of the anterior insulae were associated with the abrupt cessation of nicotine intake in dependent individuals. The authors speculated that this relationship was due to an association between this region and the urge to smoke cigarettes, consistent with this region's role in interoceptive processes (Craig, 2009). This would suggest that continued drug use, despite

aversive consequences, may be related to subjective drug urges and cravings mediated by anterior insular function. Our observation of inhibition-related increases in right anterior insula activation that correlate positively with the duration of abstinence might therefore provide a window into the restoration of functions that are unrelated to drug use. It will be interesting to determine in future research if the normal cognitive functioning of this brain region might provide a biomarker of recovery from addiction. It has been proposed that the anterior insular cortex is a critical component of a cognitive control system called the salience network. This network is theorized to consist of both the anterior cingulate cortex and the anterior insulae, with the primary function being to choose between competing external and/or internal stimuli in order to guide behavior (Seeley et al., 2007). It is hypothesized that within the salience network, the anterior insular cortex functions to first identify relevant stimuli from a wide array of choices. Once the stimulus is identified, the anterior insulae is then responsible for engaging higher-order processes that are related to processing the task at hand, and at the same time attenuating cognitive networks that are not conducive to task-related processing (Menon and Uddin, 2010). It is possible that greater engagement of the right anterior insula during motor response inhibition signifies a more active cognitive control system in that individual. We can speculate then that greater right insula activation is related to an increased ability to identify relevant stimuli that then need to be inhibited and that this effect could be responsible for longer durations of abstinence. However, whether this insula effect is responsible for, or is a result of, increased abstinence cannot be determined by this experimental design. Future investigations should be conducted to clarify the precise role this region plays in maintaining cocaine abstinence.

There are specific limitations in the present study that need to be acknowledged. Because of this study's cross-sectional design, it is impossible to determine if the absence of cortical deficits in abstinent CD individuals are due to a recovery of inhibitory deficits, or if they reflect pre-existing differences between patients. As stated previously, Ersche et al. (2012) showed that non-using individuals displayed similar cognitive deficits as their drugdependent siblings. Unfortunately, we did not collect family history information in this study. Therefore, it is possible that the absence of cortical activation differences between the groups may be due to similar family backgrounds. Additionally, this study employed a 1.5T magnet which is not as powerful as a 3T magnet. However, multiple studies examining response inhibition in current and abstinent cocaine addicts have also employed 1.5T magnets (Connolly et al., 2012; Garavan et al., 2008; Kaufman et al., 2003). It also needs to be pointed out that this study was conducted predominantly in male participants and that in view of this; appropriate care should be taken in generalizing these results to abstinent female CD patients.

4.1. Conclusions

Our relatively large sample of abstinent CD individuals and non-using controls provides evidence that individuals receiving intensive in-patient treatment for their addiction do not display the cortical hypoactivations in the RIC observed in current CD individuals. Furthermore, the right anterior insula was identified as a potentially important node of the RIC for response success and maintaining abstinence, a region that is hypothesized to be crucial for initiating cognitive control processes. Complementing these findings, we also

observed similar electrophysiological and behavioral results in a separate cohort of abstinent drug abusers (Morie et al., 2014). Although speculative, these results seem to provide evidence that intensive in-patient treatment may result in cortical normalization within the RIC and that right anterior insula activation reflects a continued strengthening of the cognitive control mechanisms that then helps the user to maintain abstinence.

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Fig. 1.

Brain regions that were activated utilizing a *t*-test contrast of Stops >0 (false discovery rate corrected; $q = 0.05$) (anatomical resolution) in patients and controls ($N = 72$). Images are in radiological orientation. Figure only shows positive activations. These activations were utilized to perform a between groups analysis restricted to a mask of task-activated regions. Black boxes show the size of the cubic ROIs within the brain activation map in each respective plane with the white lines intersecting at the peak activation which served as the center of each ROI.

Fig. 2.

Scatterplots showing the relationships between right insula activation and duration of abstinence ($r^2 = 0.66$; $p = 0.01$) (1) and the total number of STOPS ($r^2 = 0.66$; $p = 0.0001$) (2) for patients only. Duration of abstinence is in weeks.

Table 1

Participant demographics.

All patients vs. All controls	Group		<i>p</i>
	CD (<i>N</i> = 27)	Controls (<i>N</i> = 45)	
Age (years)	37.8 (7.8)	38.1 (10.6)	0.92
Years of education	12.9 (1.4)	13.7 (1.7)	0.05 ^a
Sex (male/female)	24/3	35/10	0.24 ^b
% Correct STOPS	75% (19%)	76% (19%)	0.72
Total STOPS	48.1 (12.0)	50.4 (12.5)	0.58
Total ERRORS	13.3 (8.7)	11.2 (9.6)	0.34
HITS RT ^c	386 (57)	399 (61)	0.37
ERRORS RT ^c	356 (116)	348 (66)	0.72
<i>d'</i>	3.5 (1.0)	3.6(1.1)	0.83

^a Significant between patients and controls.^b Pearson's chi-square significance level.^c RT = Reaction Time in milliseconds.

Table 2

Talairach coordinates of ROIs.

Cluster	Anatomical region	Talairach coordinate			Cluster size	<i>t</i> -Value	<u>P vs C^a</u>
		<i>X</i>	<i>Y</i>	<i>Z</i>			<i>p</i> -Value ^b
1	R. anterior insula	27	19	6	2197	4.90	0.86
2	R inferior/middle frontal gyrus	44	9	30	2197	5.97	0.78
3	R. inferior parietal lobule	25	-61	34	2197	5.75	0.40
4	R. inferior frontal gyrus	35	19	15	2197	4.92	0.89
5	L. preSMA/cingulate	-9	4	48	2197	4.54	0.68
6	L. precentral gyrus	-46	-2	30	2197	5.08	0.24
7	L. anterior insula	-31	19	7	2197	5.30	0.61

^aP vs C refers to Patients vs. Controls.^bp-Values are results from t-tests between patients and controls in each ROI.