HHS Public Access

Author manuscript

Brain Imaging Behav. Author manuscript; available in PMC 2015 March 01.

Published in final edited form as:

Brain Imaging Behav. 2014 March ; 8(1): 87–96. doi:10.1007/s11682-013-9247-y.

Error processing in current and former cocaine users

Brian C. Castelluccio[1,2], **Shashwath A. Meda**[1], **Christine E. Muska**[1], **Michael C. Stevens**[1,3], and **Godfrey D. Pearlson**[1,3]

[1]Olin Neuropsychiatry Research Center, Institute of Living, Hartford Hospital, Hartford, Connecticut, USA

[2]University of Connecticut, Department of Psychology, Storrs, Connecticut, USA

[3]Yale University, Departments of Psychiatry and Neurobiology, New Haven, Connecticut, USA

Abstract

Deficits in response inhibition and error processing can result in maladaptive behavior, including failure to use past mistakes to inform present decisions. A specific deficit in inhibiting a prepotent response represents one aspect of impulsivity and is a prominent feature of addictive behaviors in general, including cocaine abuse/dependence. Brain regions implicated in cognitive control exhibit reduced activation in cocaine abusers. The purposes of the present investigation were (1) to identify neural differences associated with error processing in current and former cocaine-dependent individuals compared to healthy controls and (2) to determine whether former, long-term abstinent cocaine users showed similar differences compared with current users. The present study used an fMRI Go/No-Go task to investigate differences in BOLD response to correct rejections and false alarms between current cocaine users (n=30), former cocaine users (n=29), and healthy controls (n=35). Impulsivity trait measures were also assessed and compared with BOLD activity. Nineteen regions of interest previously implicated in errors of disinhibition were queried. There were no group differences in the correct rejections condition, but both current and former users exhibited increased BOLD response relative to controls for false alarms. In current users, the pregenual cingulate gyrus and left angular/supramarginal gyri overactivated. In former users, the right middle frontal/precentral gyri, right inferior parietal lobule, and left angular/supramarginal gyri overactivated. Overall, our results support a hypothesis that neural activity in former users differs more from healthy controls than that of current users due to cognitive compensation that facilitates abstinence.

Keywords

inhibition; cocaine; fMRI; cingulate; drug abuse; abstinence

Corresponding Author: Brian Castelluccio, brian.castelluccio@uconn.edu.

Olin Neuropsychiatric Research Center, Institute of Living, 200 Retreat Avenue, Whitehall Building, Hartford, CT 06106

Conflict of Interest Statement

The authors declare that they have no conflict of interest.

Introduction

Response inhibition and error processing are crucial features allied with executive function that help facilitate social behaviors and promote adaptability in managing simple and complex demands of daily life (Menon, Adleman, White, Glover, & Reiss, 2001). Deficits in these abilities can result in maladaptive behavior, including impulsive tendencies and failure to use past mistakes to inform present decisions (Botvinick, Cohen, & Carter, 2004).

In humans, an ability to inhibit response to prepotent stimuli is frequently measured using Go/No-Go and Stop Signal tasks (Rubia et al., 2001). Go/No-Go is a classic response inhibition task, where a prepotent bias towards fast responding to 'Go' stimuli increases the difficulty of withholding a response to 'No-Go' stimuli. Because the task causes subjects to commit errors of disinhibition, fMRI Go/No-Go tasks can be used to study error processing brain network function. Neural circuitry implicated in error processing during Go/No-Go tasks comprises multiple brain regions, including premotor areas, left lateral prefrontal cortex, inferior frontal gyrus (IFG), striatum, inferior parietal, temporal and occipital regions, bilateral insular cortex and both rostral and dorsal anterior cingulate cortex (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Decary & Richer, 1995; Drewe, 1975; Eagle & Robbins, 2003; Iverson & Mishkin, 1970; Watanabe, 1986). These regions are also found to show functional connectivity during successful response inhibition and error commission (Stevens, Kiehl, Pearlson, & Calhoun, 2009).

Error commission and failure of response inhibition in general are associated with functional impairments in anterior cingulate cortex (ACC) and lateral frontal cortex (Mathalon, Whitfield, & Ford, 2003). Theoretical models suggest that an important role of the ACC is to detect conflicts between competing neural systems (e.g. 'stop' and 'go' networks) and recruit dorsolateral prefrontal cortex to resolve the conflicts (Carter & van Veen, 2007). Because of this role, ACC is relevant to choosing between alternatives and error avoidance; it is engaged for decision making processes during which errors are likely to occur (Magno, Foxe, Molholm, Robertson, & Garavan, 2006). Accordingly, ACC activity is associated with a variety of situations involving response conflict (Braver, Barch, Gray, Molfese, & Snyder, 2001; Carter, 1998). Thus, ACC can be conceptualized as a neural substrate of both error processing and response inhibition, two allied executive processes.

Frequent error commission in the form of deficits in inhibiting a prepotent response represents one aspect of impulsivity. Disinhibition is a lack of restraint putatively driven by deficits in the cognitive control system and is a prominent feature of addictive behaviors in general, including cocaine abuse/dependence (Kaufman, Ross, Stein, & Garavan, 2003). Adaptive inhibitory functions are notably diminished in the brains of cocaine users (Fillmore & Rush, 2002). Functional MRI investigation reveals reduced ACC activity related to both commission of errors and successful inhibition of a prepotent response in cocaine users compared to controls during a Go/No-Go task, where behaviorally cocaine users committed more errors (Kaufman et al., 2003). This suggests a role for ACC in both error processing and inhibitory control. Additionally, electroencephalography reveals reduced error-related negativity in cocaine users compared to healthy individuals in an Eriksen flanker task, suggesting deficits in error recognition (Franken, Van Strien, Franzek, & Van de Wetering,

2007). Substance abuse populations characterized by impulsivity have difficulty in inhibiting responses to No-Go stimuli (Chamberlain & Sahakian, 2007). Cocaine abusers have dysfunction in error processing and response inhibition. They also demonstrate atypical activity in a brain region implicated in both of these cognitive domains, the ACC.

Drug abuse in general, and cocaine abuse in particular, is hypothesized to lead to a condition in which substance use "hijacks" the brain's reward, motivation, memory, and control circuits such that they no longer function properly even after the drug has left the body (Volkow, Fowler, & Wang, 2003). Thus, rather than only acting acutely on the brain, abused substances may cause enduring changes in brain function that persist after cessation of use (Volkow et al., 1992). Altered neuromodulator receptor activity secondary to elevated stimulation levels from cocaine may lead to impaired cognitive control and other processes in cocaine abusers (Goldstein & Volkow, 2002). Evidence that such factors influence activation in ACC and other key cognitive control regions is beginning to emerge from fMRI studies. For example, in an imaging study of the cognitive control of 23-day abstinent cocaine abusers, using a Stroop task, weekly cocaine use prior to abstinence correlated negatively with activity in the rostral ACC and right lateral prefrontal cortex (Bolla et al., 2004). Complicating the study of this chronic effect of cocaine use on brain structure and function, cocaine dependence has also been linked to pre-existing personality traits believed to represent vulnerabilities to addiction. For instance, impulsivity traits have been implicated in both facilitating drug abuse and resulting from drug abuse (De Wit, 2009). One aim of the present work was to address the relationship between measures of trait-based impulsivity and neural activity related to error processing and inhibitory control in current and former cocaine users.

Despite evidence supporting a relationship between cocaine use, deficient error processing, and impulsive behavior, the temporal direction of this association is unknown. Existing cognitive deficits may influence individuals to abuse cocaine, or cognitive deficits may result from cocaine abuse, or both, warranting further study of these factors. Preclinical data suggest that genetic susceptibility for weak inhibitory control confers greater likelihood of cocaine use behavior (Cervantes, Laughlin, & Jentsch, 2013). Other investigations in mice indicate that cocaine use induces substantial neuroanatomical changes, which may be responsible for some drug-related behaviors (Wheeler et al., 2013). Some animal researchers have asserted that brief, circumscribed cocaine use directly causes impulsive behavior that persists long after cessation of use (Mendez, Simon, Hart, Mitchell, & Nation, 2011). In a clinical study of treatment-seeking cocaine users, Luo et al. (2013) observed that decreased activation of the dorsal ACC during processing of errors in an fMRI task predicted shorter time to relapse. This provides further evidence for the two theories articulated prior; cocaine use may produce dysfunctional neural circuitry and maladaptive behavior, or existing atypical neural circuitry may predispose an individual to cocaine use and lack of inhibitory control.

The purposes of the present investigation were (1) to identify neural differences associated with error processing in current and former cocaine-dependent individuals during performance of an fMRI Go/No-Go task compared to healthy controls in whom impulsivity had been assessed using a variety of approaches, and (2) to determine whether former, long-

term abstinent cocaine users showed similar differences compared with current users. We hypothesized that activation patterns in drug users would be associated with specific impulsivity measures. Further, we hypothesized that findings would have implications for achievement and maintenance of abstinence.

Methods

Subjects

Participants all signed written consents prior to participating, and the protocols were approved by both Hartford Hospital and Yale institutional review boards. Subjects were screened for drug history using Time Line Follow Back assessment and assessed for current and lifetime psychiatric diagnoses using the Structured Clinical Interview for DSM-IV-TR (First, Spitzer, Gibbon, & Williams, 2002; Sobell & Sobell, 1992). Subjects reported no lifetime history of brain injury causing loss of consciousness greater than 10 minutes, and did not have significant CNS neurologic illness or DSM-IV current Axis I psychiatric diagnoses, with the exception of two former cocaine users with past opioid dependence and seven current cocaine users with current comorbid opioid dependence. Subjects with estimated full-scale IQ less than 70 and pregnant women by urine screening were excluded (Wechsler, 1997).

Current cocaine users were identified as individuals who used cocaine at least twice in the week prior to the day of the participation and ten times in the last month and had positive urine for cocaine metabolites on the day of testing, indicating last use occurred between 36 and six hours prior. Former users were identified as individuals who reported not using cocaine or any other drug of abuse for at least six months prior to the study date and had negative urine for toxicological screening for cocaine, marijuana or opiates, (except for opioids in the case of the methadone-using subjects mentioned above). Individuals taking any prescribed psychoactive drugs (including antidepressants) were excluded. Healthy controls were excluded based on the same criteria, including any lifetime diagnosis of an Axis I disorder, with the exception of past major depression. Originally, 154 total participants were recruited. After exclusion of subjects due to inability to complete the scan session, excessive motion in the scanner, and group matching, the study groups included 30 current cocaine users, 29 former cocaine users, and 35 healthy controls. Complete demographic and cocaine use data are provided in Table 1. Study groups did not differ by age (F=2.408, p=0.096) or sex (χ^2=3.303, p=0.192).

Impulsivity scoring

In a previous study that included, but was not limited to many subjects in the current study, domains for multiple behavioral and self-report of impulsivity and related constructs were examined in subjects from a variety of substance abuse, at-risk and healthy control groups (Meda et al., 2009). Five widely-used, reliable and valid self-report questionnaires were used: (i) the Behavioral Inhibition/Activation System (BIS/BAS), (ii) the Barratt Impulsivity Scale (BIS-11), (iii) the Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ), (iv) the Sensation Seeking Scale (SSS Form V), and (v) the Padua Inventory (Carver & White, 1994; Patton, Stanford, & Barratt, 1995; Sanavio, 1988; Torrubia, Ávila,

Moltó, & Caseras, 2001; Zuckerman & Neeb, 1979). In additional, two computer-based behavioral laboratory tests were used: (i) the Balloon Analog Risk Task (BART) and (ii) the Experiential Discounting Task (EDT) (Lejuez et al., 2002; Reynolds & Schiffbauer, 2004). Each of these testing instruments was described previously in detail (Meda et al., 2009).

The current study made use of factor loading scores to represent impulsivity traits that were calculated via principal component analysis of these measures, described fully in (Meda et al., 2009). In that prior study, the factor corresponding to 'Self-Reported Compulsivity and Reward-Punishment Sensitivity' (Factor 2) differed most significantly between healthy controls and an At-Risk/Addicted (ARA) group, which included current and former cocaine dependent subjects as well as subjects with dense family histories of alcoholism. The questionnaires/tests which loaded significantly on Factor 2 were the SPSRQ (Punishment and Reward subscores) and the Padua Inventory. A second factor that differed significantly between controls and the ARA group was Factor 3, 'Self-Reported Impulsivity.' The questionnaires/tests which loaded significantly on Factor 3 were the Barratt Impulsivity Scale (BIS-11, Attentional, Motor and Non-planning impulsiveness subscores) and the Zuckerman Sensation Seeking Scale (SSS Form V).

For Factor 1, 'Self-Reported Behavioral Activation', Factor 4, 'Behavioral Temporal Discounting', and Factor 5, 'Behavioral Risk Taking' the ARA group was not significantly different from controls. The three BAS scores (Drive, Fun and Reward), EDT/BIS scores, and BART scores, loaded significantly on these three factors respectively (Meda et al., 2009).

Go/No-Go fMRI task

Participants performed an fMRI Go/No-Go task, as described in our prior publications (Stevens, Kiehl, et al., 2009; Stevens, Kiehl, Pearlson, & Calhoun, 2007; Stevens, Skudlarski, Pearlson, & Calhoun, 2009). They were instructed to respond by pressing a button with their right index finger as quickly and as accurately as possible every time an "X" (Go stimulus, 85%) appeared and to withhold this prepotent response to the letter "K" (No-Go stimulus, 15%). Each stimulus was presented for 50 milliseconds, and the presentation order of the "X"s and "K"s was random, except that two "K"s were never presented sequentially. The inter-stimulus interval varied randomly between three possibilities: 750 ms, 1750 ms, and 2750 ms. Stimuli were displayed on an LCD projector (SHARP XG-P25X) outside the scanner room, which the subjects saw via a mirror attached to the head coil of the MRI scanner. Each participant performed a block of 10 practice trials before the beginning of the scanning session to ensure that instructions were understood. Both reaction time and accuracy were emphasized. The task was administered in two runs of 246 trials each lasting seven minutes and 21 seconds, and a break of approximately one minute was given between runs. The total task length was approximately 15 minutes and 42 seconds. There are four possible response scenarios: the subject presses the button when "X" appears (correct hit), the subject does not press the button when "X" appears (miss), the subject presses the button when "K" appears (false alarm error), or the subject does not press the button when "K" appears (correct rejection).

Imaging protocol

Subjects were scanned with a 3 Tesla Siemens Allegra MRI scanner (Erlangen, Germany) at the Olin Neuropsychiatry Research Center at the Institute of Living in Hartford, CT. Functional data were acquired using an echo-planar sequence with the following imaging parameters: repeat time (TR) = 1500 ms, echo time (TE) = 27 ms, field of view = 22 cm, flip angle = 70°, acquisition matrix = 64 × 64, voxel size = 3.44 × 3.44, slice thickness = 5 mm, number of slices = 29, with inferior to superior slice acquisition order. The scanner was equipped with 40 mT/m gradients and a standard quadrature head coil. Six hundred EPI volumes were collected for each subject across two runs. Six dummy scans were acquired at the beginning of each run to allow the signal to equilibrate. Scanning was automatically triggered by the paradigm. Padded cushions were used to minimize head movement during scanning.

Data analysis and statistics

In-scanner reaction times to Go stimuli and No-Go errors were analyzed as behavioral measures for the Go/No-Go task, and groups were compared using one-way ANOVA tests. While the Go/No-Go paradigm employed in the present study was not designed for analysis of accuracy data, false alarm error percentages were also compared for group differences. Average reaction times to correct “X” hits or incorrect “K” errors were the most appropriate behavioral metric for in-scanner task performance.

All functional imaging data were preprocessed and analyzed using SPM5 software (Wellcome Department of Cognitive Neurology, London, UK). Slice timing correction was performed using the center slice as the reference. A high-pass filter with a cutoff period of 128 seconds was used to correct for linear trends. Motion correction was conducted using INRIAlign (Freire, Roche, & Mangin, 2002). Each subject’s translational and rotational movement were examined for excessive head motion. In cases of excessive motion, defined as 5 mm of translational or 3 degrees of rotational motion, deviant volumes were corrected by interpolating the nearest “unrepaired” volumes with the ArtRepair toolbox in SPM5 (Mazaika et al., unpublished data). Any subjects that required more than 20% of their time series to be corrected were not included in the analysis. Images were then spatially normalized to standard Montreal Neurological Institute (MNI) space. After spatial normalization, images were spatially smoothed with an 8 mm full width half-maximum Gaussian kernel.

Functional region-of-interest (ROI) masks with radii of 10 millimeters were created using *a priori* regions of interest coordinates, which were drawn from a prior fMRI Go/No-Go study that employed this task (Stevens, Kiehl, et al., 2009). Nineteen regions, each of which has been shown to exhibit a significant increase in hemodynamic activity correlated with either correct rejects or false alarms, were hypothesized to be relevant and examined (Table 2). For each subject, for each condition of interest (correct rejections and false alarms), a unique predictor time series was generated using stimulus event times logged during the experiment. Predictors were convolved with a gamma hemodynamic response function, and each voxel’s time course was analyzed with reference to the predictors using a general linear model approach. Contrasts were generated to determine significant regional BOLD signal

change during trials where responses to No-Go stimuli were accurately withheld (correct rejections) and where errors were committed (false alarms), both estimated relative to an implicit baseline. These contrasts were used within a SPM5 ANOVA model that compared the neural activity of the three subject groups in the correct rejections domain, and a separate, identical design was used to compare corresponding false alarm related activity. Because the analysis was based on *a priori* ROIs, an uncorrected significance level of 0.01 was accepted for the ANOVA. For ROIs that had significant F tests ($p<0.01$, uncorrected), *post hoc* t-tests were used for pairwise comparisons between groups. Family wise error (FWE) correction ($p<0.05$) was used as a threshold of significance values in the *post hoc* t-tests. Small volume correction at the voxel level was employed for all analyses.

Post hoc regression analyses were conducted to test whether any of the regions that were positive for group differences were significantly correlated with duration of abstinence in former users, and duration of cocaine use in former or current users. These analyses attempted to address the question of causality in cocaine-related neural dysfunction. As described in Meda et al., a factor analysis on the thirteen impulsivity trait measures collected for each subject was conducted (2009). Regressions were then used to examine hemodynamic activity in ROIs for correlation with factor scores on those factors that differed significantly between cocaine groups and healthy controls. The purpose of probing for correlations between factor loading scores and BOLD activity was to align trait-based conceptualizations of impulsivity with neural activation patterns. An uncorrected significance level of 0.01 was used as a threshold for all regression analyses.

Results

Behavioral results

One-way ANOVA comparisons yielded no significant differences between groups in mean reaction times (RT's) to either Go ($F=0.199$; $p=0.820$) or to No-Go stimuli ($F=0.157$; $p=0.855$). Additionally, there were no significant group differences in false alarm error percentage ($F=2.372$; $p=0.099$). See Table 3.

Impulsivity and related constructs

A one-way ANOVA with Bonferroni correction performed on the impulsivity trait factor scores produced in Meda et al. (2009) for these participants revealed significant group differences for Factor 2, 'Self-Reported Compulsivity and Reward-Punishment Sensitivity' ($F = 9.715$, $df = 143$, $p = 0.0001$ and for Factor 3, 'Self-Reported Impulsivity' ($F=10.167$, $df=143$, $p=0.00007$). There was no significant difference between the groups for Factors 1, 4 or 5 (see Methods section for a description of these factors). Post-hoc analyses with Bonferroni correction revealed that the healthy control group scored significantly lower on Factor 2 than the former cocaine users group ($p=0.00008$) and that healthy controls scored significantly lower on Factor 3 than both the former ($p=0.0008$) and the current cocaine users groups ($p=0.0008$), i.e. less impulsive in both cases.

Functional MRI results

Neither cocaine group showed significant differences from controls in activity associated with correct rejections in the ROIs tested. However, for false alarms, current cocaine users exhibited significant overactivation in two *a priori* ROIs, and former cocaine users exhibited significant overactivation in three *a priori* ROIs compared to controls. These regions are shown in Table 2. While significant group differences existed for the variables 'number of alcoholic drinks per week' and 'number of cigarettes per day,' including these variables as covariates in the imaging analysis did not change the results. When functional imaging analyses were covaried for 'years smoking', IQ, and 'years of education,' variables for which group differences were observed, (and the latter 2 of which were significantly correlated) the results changed minimally but trends were preserved.

A regression analysis conducted on the current cocaine users group revealed no significant effect of duration of cocaine use on BOLD activity associated with false alarms in either of the regions in which current users overactivated relative to controls. Regression analyses conducted on the former cocaine users group revealed a positive correlation between hemodynamic activity associated with false alarms and duration of cocaine use in the left angular/supramarginal gyri (p=0.001; Table 4).

In current users, false alarm BOLD activity correlated negatively with scores on impulsivity trait factor 3 in the pregenual cingulate gyrus (p=0.008; Table 5). In former users, false alarm BOLD activity was negatively correlated with score on impulsivity factor 2 in the right middle frontal/precentral gyri (p=0.001; Table 6) and right inferior parietal lobule (p=0.002; Table 6). It was positively correlated with score on impulsivity factor 3 in the right middle frontal/ precentral gyri (p=0.010; Table 6).

Discussion

The principal findings of this study were that two distinct cocaine user groups exhibited significantly increased BOLD activity relative to healthy controls in several *a priori* regions of interest during commission of false alarm errors in the Go/No-Go task. For current users, these regions were the pregenual cingulate gyrus and the left angular/supramarginal gyri. For former users, these regions were the right middle frontal/precentral gyri, right inferior parietal lobule, and the left angular/supramarginal gyri. There were no significant behavioral differences between the three groups in reaction time to Go stimuli or to No-Go stimuli. Differences were only manifest in functional activity.

As expected, the cocaine use groups had higher scores on specific factors representing trait-based conceptualizations of impulsivity. Interestingly, BOLD activity associated with false alarms in current users was negatively correlated with scores on factor 3, 'Self-Reported Impulsivity,' in the pregenual cingulate gyrus. This indicates that, among current users, higher degrees of self-reported impulsivity are connected to less error-related neural response in this region. Not surprisingly, current cocaine users with higher levels of behavioral impulsivity have lower levels of neural activity associated with error commission. In former users, false alarm related BOLD activity in the right middle frontal/ precentral gyri and right inferior parietal lobule was negatively correlated with scores on

factor 2, 'Self-Reported Compulsivity and Reward-Punishment Sensitivity,' Activity in the right middle frontal/ precentral gyri was positively correlated with scores on factor 3. It appears that, in former users, higher scores on trait-based impulsivity measures can predict less or greater neural activity associated with error commission.

Duration of previous cocaine use in former users was positively correlated with BOLD activity in the left angular/ supramarginal gyri. Thus, longer term past cocaine use predicted greater neural response to error commission in this region. This suggests that activity in this region of the parietal lobe is increased by prolonged cocaine use, and we speculate that this area is part of a network that compensates for cocaine-related functional deficits more generally.

Our results indicate that neural activity related to error processing in current cocaine users is less different from healthy controls than neural activity related to error processing in former cocaine users. These data are consistent with a hypothesis of cocaine dependence in which brain responses in current users appear less abnormal than in former users because use of the drug normalizes their usually atypical neural responses to errors toward that of healthy controls. Additionally, former users in the present study had used significantly more cocaine per day than current users in the study (U=434; p=0.018). The difference in amount of cocaine used may account for some of the BOLD differences between these groups, and it may support the initial hypothesis that drug consumption itself drives neural abnormalities. Setting aside abstinence, increased amount of average daily cocaine use correlates with increased deviation from healthy controls.

Increased regional BOLD activation seen in the former users may in part reflect cognitive strategies that were developed in order to achieve and maintain abstinence from cocaine use. These strategies, either learned in therapy or otherwise, possibly decrease individuals' cravings, desires, and/or impulsivity so as to increase their likelihood of resisting cocaine use. During commission of false alarm errors in the Go/No-Go task, the cognitive mechanisms that aid in maintenance of abstinence may become active in order to mark the events in such a way as to prevent future impulsive errors. Use of cocaine can be seen as a result of impulsivity; despite bearing negative consequences, it is a desirable choice for cocaine-dependent individuals. Being able to withhold responding in error to the prepotent stimulus in the Go/No-Go task may represent a learned neural mechanism that has allowed former users to establish and maintain abstinence.

An alternative explanation involves a pre-existing inherent advantage among former compared to current users toward achieving abstinence. Some cocaine users may have underlying neural differences that allow them to discontinue use more easily than others. These individuals may compose the former user group in the present study. The features that allow for relative ease of abstinence might manifest themselves in response to false alarm errors by activating brain regions to a greater extent than in healthy controls or non-abstinent cocaine users. Having an enhanced regional BOLD response to impulsive errors in task-relevant brain regions might be advantageous to individuals trying to discontinue use of an addictive drug.

The differences in BOLD activation in the cocaine groups were observed only in the false alarm and not in the correct reject condition. When presented with a No-Go stimulus, a subject has two options: to respond or to withhold response. By responding, the subject commits an impulsive false alarm error; by withholding, the subject correctly rejects the stimulus and successfully avoids an error. Cognitive activity associated with correct rejections relies on a "stop" network, whereas activity associated with false alarm errors relies on a "go" network. Given the overactivation of brain regions in both cocaine groups relative to healthy controls in only the false alarm condition, we conclude that the "go" network is the neural basis for differences between the groups.

Previous studies have associated cocaine dependence with neural hypoactivation in frontal areas related to executive control functions (Beveridge, Gill, Hanlon, & Porrino, 2008; Bolla, Cadet, & London, 1998; Garavan & Hester, 2007; Li et al., 2008). We speculate that our findings in former users support a model of abstinence in which recovery from cocaine dependence relies upon hyperactivation of neural resources involved in cognitive control over impulsive behaviors. This hyperactivation is necessary to outcompete the effects of cocaine use-related hypoactivity, and cocaine dependent individuals who exhibit the proper patterns of hyperactivation are able to override cocaine-related damage and deficits in order to become abstinent. Some recent research on drug use supports our results. Former cigarette smokers exhibit greater BOLD response than healthy controls in several regions during error processing in a Go/No-Go task (Nestor, McCabe, Jones, Clancy, & Garavan, 2011). Abstinent former marijuana users exhibit greater BOLD response than healthy controls during inhibition in a Go/No-Go task (Tapert et al., 2007). Taken together with data from other studies, our results may point to a neural hyperactivation trend in abstinent drug users.

A primary advantage of the current study is that we examined a distinct, well-characterized former cocaine abuse population in addition to a current cocaine abuse group, a comparison that has not been previously published. Additionally, the former users were abstinent for relatively long periods; while the minimum was 6 months, some of the subjects had maintained abstinence periods as long as 20 years. The study also has the advantage of relatively large subject groups.

Limitations of the study include difficulties matching groups demographically, reliance on subjects' self-reports for cocaine use and abstinence information, and the inclusion of several subjects with co-morbid opioid dependence, (two former and seven current users). Repeating the analyses without these subjects yielded the same results as when they were included. Information on amount of use for current and former users, duration of use for current and former users, and duration of abstinence for the former users relied on self-reports based on Time Line Follow Back methods. Additionally, among both cocaine use groups there was a wide range of weekly usage, duration of use, and onset of use; we acknowledge that these differences may impact neural effects of the drug, although conversely it represents a spectrum of naturalistic drug use. In the case of current users, a necessary admixture of subjects with and without current acute cocaine effects may have added variance that may have obscured differences from controls.

This study should serve as a stimulus for further investigation of the neural activity of former cocaine abusers. It would be useful to perform a longitudinal study on former users from the present study who successfully maintain abstinence in order to investigate whether their BOLD activity during the fMRI Go/No-Go task ever approaches that of healthy individuals. The unique neuropsychiatric status of individuals who have overcome addiction demands further inquiry. The anomalous neurocognitive functioning of these individuals presents a rich area for research into the nature of recovery from addiction and the associated neuroplasticity.

Acknowledgments

Funding for this study was provided by the National Institute on Drug Abuse by grant RO1 DA020709 to G. Pearlson.

References

Aron AR, Fletcher PC, Bullmore ET, Sahakian BJ, Robbins TW. Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. Nature Neuroscience. 2003; 6(2):115–6.

Beveridge TJR, Gill KE, Hanlon CA, Porrino LJ. Review. Parallel studies of cocaine-related neural and cognitive impairment in humans and monkeys. Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences. 2008; 363(1507):3257–66.

Bolla KI, Cadet J-L, London ED. The Neuropsychiatry of Chronic Cocaine Abuse. The Journal of Neuropsychiatry and Clinical Neurosciences. 1998; 10(3):280–289. [PubMed: 9706535]

Bolla KI, Ernst M, Kiehl K, Mouratidis M, Eldreth D, Contoreggi C, Matochik J, et al. Prefrontal cortical dysfunction in abstinent cocaine abusers. The Journal of Neuropsychiatry and Clinical Neurosciences. 2004; 16(4):456–64. [PubMed: 15616172]

Botvinick MM, Cohen JD, Carter CS. Conflict monitoring and anterior cingulate cortex: an update. Trends in Cognitive Sciences. 2004; 8(12):539–46. [PubMed: 15556023]

Braver TS, Barch DM, Gray JR, Molfese DL, Snyder A. Anterior cingulate cortex and response conflict: effects of frequency, inhibition and errors. Cerebral Cortex. 2001; 11(9):825–36. [PubMed: 11532888]

Carter CS. Anterior Cingulate Cortex, Error Detection, and the Online Monitoring of Performance. Science. 1998; 280(5364):747–749. [PubMed: 9563953]

Carter CS, Van Veen V. Anterior cingulate cortex and conflict detection: an update of theory and data. Cognitive, Affective & Behavioral Neuroscience. 2007; 7(4):367–79.

Carver CS, White TL. Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: The BIS/BAS Scales. Journal of Personality and Social Psychology. 1994; 67:319–333.

Cervantes MC, Laughlin RE, Jentsch JD. Cocaine self-administration behavior in inbred mouse lines segregating different capacities for inhibitory control. Psychopharmacology. 2013 in press.

Chamberlain SR, Sahakian BJ. The neuropsychiatry of impulsivity. Current Opinion in Psychiatry. 2007; 20(3):255–61. [PubMed: 17415079]

De Wit H. Impulsivity as a determinant and consequence of drug use: a review of underlying processes. Addiction Biology. 2009; 14(1):22–31. [PubMed: 18855805]

Decary A, Richer F. Response selection deficits in frontal excisions. Neuropsychologia. 1995; 33(10): 1243–1253. [PubMed: 8552227]

Drewe EA. Go-no go learning after frontal lobe lesions in humans. Cortex. 1975; 11:8–16. [PubMed: 1149469]

Eagle DM, Robbins TW. Inhibitory Control in Rats Performing a Stop-Signal Reaction-Time Task: Effects of Lesions of the Medial Striatum and d-Amphetamine. Behavioral Neuroscience. 2003; 117:1302–1317. [PubMed: 14674849]

Fillmore MT, Rush CR. Impaired inhibitory control of behavior in chronic cocaine users. Drug and Alcohol Dependence. 2002; 66(3):265–273. [PubMed: 12062461]

First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition (SCID-I/P). Biometrics Research: New York State Psychiatric Institute; New York: 2002.

Franken IHA, Van Strien JW, Franzek EJ, Van de Wetering BJ. Error-processing deficits in patients with cocaine dependence. Biological Psychology. 2007; 75(1):45–51. [PubMed: 17196732]

Freire L, Roche A, Mangin JF. What is the best similarity measure for motion correction in fMRI time series? IEEE Transactions on Medical Imaging. 2002; 21(5):470–84. [PubMed: 12071618]

Garavan H, Hester R. The role of cognitive control in cocaine dependence. Neuropsychology Review. 2007; 17(3):337–45. [PubMed: 17680368]

Goldstein RZ, Volkow ND. Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. The American Journal of Psychiatry. 2002; 159(10):1642–52. [PubMed: 12359667]

Iverson SD, Mishkin M. Perseverative interference in monkeys following selective lesions of the inferior prefrontal convexity. Experimental Brain Research. 1970; 11:376–386. [PubMed: 4993199]

Kaufman JN, Ross TJ, Stein E. a, Garavan H. Cingulate hypoactivity in cocaine users during a GO-NOGO task as revealed by event-related functional magnetic resonance imaging. The Journal of Neuroscience. 2003; 23(21):7839–43. [PubMed: 12944513]

Lejuez CW, Read JP, Kahler CW, Richards JB, Ramsey SE, Stuart GL, Strong DR, et al. Evaluation of a behavioral measure of risk taking: The Balloon Analogue Risk Task (BART). Journal of Experimental Psychology: Applied. 2002; 8:75–84. [PubMed: 12075692]

Li CR, Huang C, Yan P, Bhagwagar Z, Milivojevic V, Sinha R. Neural correlates of impulse control during stop signal inhibition in cocaine-dependent men. Neuropsychopharmacology. 2008; 33(8): 1798–806. [PubMed: 17895916]

Luo X, Zhang S, Hu S, Bednarski SR, Erdman E, Farr OM, Hong K-I, et al. Error processing and gender-shared and -specific neural predictors of relapse in cocaine dependence. Brain. 2013; 136:1231–44. [PubMed: 23485852]

Magno E, Foxe JJ, Molholm S, Robertson IH, Garavan H. The anterior cingulate and error avoidance. The Journal of Neuroscience. 2006; 26(18):4769–73. [PubMed: 16672649]

Mathalon DH, Whitfield SL, Ford JM. Anatomy of an error: ERP and fMRI. Biological Psychology. 2003; 64(1-2):119–141. [PubMed: 14602358]

Meda SA, Stevens MC, Potenza MN, Pittman B, Gueorguieva R, Andrews MM, Thomas AD, et al. Investigating the behavioral and self-report constructs of impulsivity domains using principal component analysis. Behavioural Pharmacology. 2009; 20(5-6):390–9. [PubMed: 19724194]

Mendez IA, Simon NW, Hart N, Mitchell MR, Nation JR. Impulsive Choice in a Delay Discounting Task. Behavioral Neuroscience. 2011; 124(4):470–477. [PubMed: 20695646]

Menon V, Adleman NE, White CD, Glover GH, Reiss AL. Error-related brain activation during a Go/NoGo response inhibition task. Human Brain Mapping. 2001; 12(3):131–43. [PubMed: 11170305]

Nestor L, McCabe E, Jones J, Clancy L, Garavan H. Differences in “bottom-up” and “top-down” neural activity in current and former cigarette smokers: Evidence for neural substrates which may promote nicotine abstinence through increased cognitive control. NeuroImage. 2011; 56(4):2258–75. [PubMed: 21440645]

Patton JH, Stanford MS, Barratt ES. Factor structure of the Barratt impulsiveness scale. Journal of Clinical Psychology. 1995; 51(6):768–74. [PubMed: 8778124]

Reynolds B, Schiffbauer R. Measuring state changes in human delay discounting: an experiential discounting task. Behavioural Processes. 2004; 67(3):343–56. [PubMed: 15518985]

Rubia K, Russell T, Overmeyer S, Brammer MJ, Bullmore ET, Sharma T, Simmons A, et al. Mapping motor inhibition: conjunctive brain activations across different versions of go/no-go and stop tasks. NeuroImage. 2001; 13(2):250–61. [PubMed: 11162266]

Sanavio E. Obsessions and compulsions: The Padua inventory. Behaviour Research and Therapy. 1988; 26(2):169–177. [PubMed: 3365207]

Sobell, LC.; Sobell, MB. Timeline follow-back: A technique for assessing self-reported alcohol consumption. In: Litten, R.; Allen, J., editors. Measuring Alcohol Consumption: Psychosocial and Biochemical Methods. Humana Press; Totowa, NJ: 1992. p. 41-72.

Stevens MC, Kiehl K. a, Pearlson GD, Calhoun VD. Brain network dynamics during error commission. Human Brain Mapping. 2009; 30(1):24–37. [PubMed: 17979124]

Stevens MC, Kiehl KA, Pearlson GD, Calhoun VD. Functional neural networks underlying response inhibition in adolescents and adults. Behavioural Brain Research. 2007; 181(1):12–22. [PubMed: 17467816]

Stevens MC, Skudlarski P, Pearlson GD, Calhoun VD. Age-related cognitive gains are mediated by the effects of white matter development on brain network integration. NeuroImage. 2009; 48(4): 738–746. [PubMed: 19577651]

Tapert SF, Schweinsburg AD, Drummond SPA, Paulus MP, Brown SA, Yang TT, Frank LR. Functional MRI of inhibitory processing in abstinent adolescent marijuana users. Psychopharmacology. 2007; 194(2):173–83. [PubMed: 17558500]

Torrubia R, Ávila C, Moltó J, Caseras X. The Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ) as a measure of Gray's anxiety and impulsivity dimensions. Personality and Individual Differences. 2001; 31(6):837–862.

Volkow ND, Fowler JS, Wang G-J. The addicted human brain: insights from imaging studies. The Journal of Clinical Investigation. 2003; 111(10):1444–51. [PubMed: 12750391]

Volkow ND, Hitzemann R, Wang GJ, Fowler JS, Wolf AP, Dewey SL, Handlesman L. Long-term frontal brain metabolic changes in cocaine abusers. Synapse. 1992; 11(3):184–90. [PubMed: 1636149]

Watanabe M. Prefrontal unit activity during delayed conditional Go/No-go discrimination in the monkey. II. Relation to Go and No-go responses. Brain Research. 1986; 382(1):15–27. [PubMed: 3768673]

Wechsler, D. Wechsler Adult Intelligence Scale. 3rd Edition. Psychological Corporation; San Antonio, TX: 1997.

Wheeler AL, Lerch JP, Chakravarty MM, Friedel M, Sled JG, Fletcher PJ, Josselyn SA, et al. Adolescent cocaine exposure causes enduring macroscale changes in mouse brain structure. The Journal of Neuroscience. 2013; 33(5):1797–803a. [PubMed: 23365219]

Zuckerman M, Neeb M. Sensation seeking and psychopathology. Psychiatry Research. 1979; 1(3): 255–264. [PubMed: 298353]

Table 1

Demographic and drug use data for current cocaine users, former cocaine users, and healthy controls. Both descriptive and inferential statistics are provided. Seven of the current users had comorbid opioid dependence. Two of the former users had past comorbid opioid dependence. Values reported are *M (SD)*, except where otherwise noted.

M=Male; F=Female; W=White; B=Black; H=Hispanic; A=Asian; X=Mixed; O=Other

	Current Users (n=30)	Former Users (n=29)	Healthy Controls (n=35)	Group Comparison
Age	37.6 (7.3)	40.3 (6.4)	35.8 (10.0)	$F(2,91)=2.408$ $p=0.096$
Age range	21 - 45	22 - 50	21 - 58	--
IQ	92.9 (16.5)	94.8 (17.0)	110.3 (16.7)	$F(2,82)=9.159$ $p=0.0003$ H>F ($p=0.003$) H>C ($p=0.001$)
Sex (%M/F)	60.0 / 40.0	75.9 / 24.1	54.3 / 45.7	$\chi^2(2)=3.303$ $p=0.192$
Race/Ethnicity (%W/B/H/A/X/O)	57.1/0/11.4/2.9/0/28.6	37.9/31.0/17.2/0/3.5/10.3	46.7/43.3/6.7/0/0/3.3	$\chi^2(10)=28.071$ $p=0.002$
Years of Education	12.4 (1.9)	13.0 (1.7)	15.6 (2.4)	$F(2,80)=20.025$ $p<0.0001$ H>F ($p<0.0001$) F>C ($p<0.0001$)
Handedness (% right/left/ambidextrous)	96.6 / 3.4 / 0	81.5 / 0 / 18.5	94.4 / 0 / 5.6	$\chi^2(4)=8.047$ $p=0.090$
Number of Alcoholic Drinks/ Week	10.3 (15.1)	2.7 (7.3)	3.8 (4.9)	$H(2)=11.792$ $p=0.003$ H>F ($p=0.011$) C>F ($p=0.002$)
Percent Smokers	86.2	71.4	9.4	$\chi^2(2)=41.179$ $p<0.0001$
Number of Cigarettes/ Day	9.4 (7.1)	7.6 (8.3)	1.2 (4.3)	$H(2)=33.122$ $p<0.001$ F>H ($p<0.0001$) C>H ($p<0.0001$)
Years Smoking	13.3 (8.8)	13.3 (11.3)	1.3 (5.2)	$H(2)=33.312$ $p<0.001$ F>H ($p<0.0001$) C>H ($p<0.0001$)
Duration of Cocaine Use (months)	196.4 (103.7)	152.8 (96.3)	--	--
Amount of Cocaine Used (USD/day)	$206.00 ($311.00)	$897.00 ($1474.00)	--	$U=434$ $p=0.018$
Duration of Cocaine Abstinence (months)	--	51.2 (76.8)	--	--

Table 2

Regions of Interest. Anatomical names, Brodmann areas, and MNI coordinates for spherical ROI centers are listed. *F* statistics and uncorrected significance levels with threshold at p=0.01 are provided for three-way group comparison. For ROIs with significant *F* statistics, *T* statistics and small volume corrected FWE significance values ($p<0.05$) are provided for two contrasts. The first contrast, C>H, shows areas that have increased hemodynamic activity correlated with false alarms in the current cocaine group relative to the healthy control group. The second contrast, F>H, shows areas that have increased hemodynamic activity correlated with false alarms in the former cocaine group relative to the healthy control group. *P* values marked N.S. do not pass the significance threshold. Cluster size in number of voxels (k) is shown for significant between groups comparisons.

Region	Brodmann Areas	x	y	z	3-way comparison		C > H			F > H		
					$F_{(2,91)}$	$p_{uncorr.}$	$T_{(91)}$	p_{fwe}	k	$T_{(91)}$	p_{fwe}	k
Anterior cingulate gyrus (RCZ)	24, 32	3	33	27	3.73	N.S.						
Anterior cingulate gyrus (CCZ)	24, 32	−6	9	42	3.05	N.S.						
Cingulate gyrus	24	−6	−21	39	4.20	N.S.						
L middle frontal/precentral gyri	9, 6	−42	0	42	3.03	N.S.						
R middle frontal/precentral gyri	9, 6	51	12	30	5.77	0.004	1.90	N.S.		3.29	0.015	105
L superior/middle frontal gyri	9, 10	−30	45	30	1.72	N.S.						
R superior/middle frontal gyri	9, 10	33	45	24	4.26	N.S.						
L anterior insula	13, 47	−36	6	−3	2.07	N.S.						
R anterior insula	13, 47	39	21	−3	1.27	N.S.						
L inferior parietal lobule	40	−51	−39	39	4.41	N.S.						
R inferior parietal lobule	40	57	−39	36	5.38	0.006	1.72	N.S.		3.23	0.024	107
Posterior cingulate/cuneus	30, 19	0	−66	0	4.55	N.S.						
Cingulate gyrus (pregenual)	25	3	9	−9	4.97	0.009	3.12	0.027	29	1.69	N.S.	
Medial frontal gyrus	9, 10	−3	48	15	4.76	N.S.						
L angular/supramarginal gyri	40	−54	−60	33	5.53	0.005	3.06	0.020	69	2.86	0.032	39
R inferior parietal lobule, supramarginal gyrus	40	57	−54	24	2.41	N.S.						
R superior/middle temporal gyri, parahippocampal gyrus, inferior frontal gyrus, amygdala, hippocampus, insula	21, 22, 38, 13, 47	−36	18	−15	3.97	N.S.						
L superior/middle temporal gyri, parahippocampal gyrus, inferior frontal gyrus, amygdala,	21, 22, 38, 13, 47	51	6	−15	1.90	N.S.						

Region	Brodmann Areas	x	y	z	3-way comparison		C > H			F > H		
					$F_{(2,91)}$	$p_{uncorr.}$	$T_{(91)}$	p_{fwe}	k	$T_{(91)}$	p_{fwe}	k
hippocampus, insula												
L cerebellum	N.A.	−24	−54	−21	2.63	N.S.						

Table 3

Behavioral data, including mean reaction times to Go stimuli (correct hits) and No-Go stimuli (false alarms) in milliseconds (*SD*) and mean false alarm error percentage (*SD*). There are no significant differences between groups in reaction time to Go stimuli (F=0.199; p=0.820), reaction time to No-Go stimuli (F=0.157; p=0.855), or error percentage (F=2.372; p=0.099).

	Go RT	No-Go RT	Error Percent
Current users	414.2 (57.6)	347.2 (42.6)	23.9 (11.0)
Former users	415.5 (66.1)	353.0 (38.7)	24.9 (10.3)
Healthy controls	407.4 (61.2)	353.4 (59.2)	30.0 (13.2)

Table 4

BOLD activity in the three *a priori* regions in which former cocaine users overactivated relative to healthy controls during false alarms was regressed onto duration of cocaine use and duration of abstinence. Results are shown for models of both positive and negative relationships. The symbol -- indicates that the analysis had no results.

Regions	Brodmann Areas	Duration of Use Positive		Duration of Use Negative		Abstinence Positive		Abstinence Negative	
		T_{27}	p	T_{27}	p	T_{27}	p	T_{27}	p
R middle frontal/precentral gyri	9, 6	1.08	0.135	0.61	0.240	1.21	0.112	1.79	0.042
R inferior parietal lobule	40	1.02	0.147	1.93	0.032	1.41	0.081	1.19	0.114
L angular/supramarginal gyri	40	3.26	0.001	--	--	0.35	0.306	2.39	0.012

Table 5

BOLD activity in the two *a priori* regions in which current cocaine users overactivated relative to healthy controls during false alarms was regressed onto scores on impulsivity trait factor 3. Results are shown for models of both positive and negative relationships.

Regions	Brodmann Areas	Factor 3 Positive		Factor 3 Negative	
		T_{28}	p	T_{28}	p
Cingulate gyrus (pregenual)	25	−0.14	0.427	2.58	0.008
L angular/supramarginal gyri	40	1.15	0.121	1.79	0.041

Table 6

BOLD activity in the three *a priori* regions in which former cocaine users overactivated relative to healthy controls during false alarms was regressed onto scores on impulsivity trait factors 2 and 3. Results are shown for models of both positive and negative relationships.

Regions	Brodmann Areas	Factor 2 Positive		Factor 2 Negative		Factor 3 Positive		Factor 3 Negative	
		T_{27}	p	T_{27}	p	T_{27}	p	T_{27}	p
R middle frontal/precentral gyri	9, 6	0.71	0.216	3.49	0.001	2.46	0.010	−0.09	0.414
R inferior parietal lobule	40	−1.15	0.581	3.13	0.002	1.85	0.037	1.08	0.134
L angular/supramarginal gyri	40	1.07	0.137	1.22	0.110	0.15	0.356	1.35	0.089