Published in final edited form as:
Addiction. 2014 December ; 109(12): 2062–2070. doi:10.1111/add.12666.

The relationship between years of cocaine use and brain activation to cocaine and response inhibition cues

James J. Prisciandaro, Ph.D., **Jane E. Joseph, Ph.D.**, **Hugh Myrick, M.D.**, **Aimee L. McRae-Clark, Pharm.D.**, **Scott Henderson, B.A.**, **James Pfeifer, B.A.**, and **Kathleen T. Brady, M.D. Ph.D.**
Medical University of South Carolina; Department of Psychiatry and Behavioral Sciences; Clinical Neuroscience Division; 67 President Street, MSC861; Charleston, SC 29425

Abstract

Aims—Functional Magnetic Resonance Imaging research has attempted to elucidate the neurobehavioral underpinnings of cocaine dependence by evaluating differences in brain activation to cocaine and response inhibition cues between cocaine dependent individuals and controls. Less research has investigated associations between task-related brain activation and cocaine use characteristics; the present study was designed to address this gap in the literature.

Design—Cross-sectional.

Setting—The Center for Brain Imaging at the Medical University of South Carolina.

Participants—51 cocaine users (41 dependent).

Measurements—Brain activation to cocaine-cue exposure and go no-go tasks in six a priori selected brain regions of interest and cocaine use characteristics (i.e., cocaine dependence status, years of cocaine use, cocaine use in the past 90 days) assessed via standardized interviews.

Findings—Participants demonstrated elevated activation to cocaine (bilateral ventral striatum, dorsal caudate, amygdala; mean F=19.00, mean $p<.001$) and response inhibition (bilateral anterior cingulate, insula, inferior frontal gyrus; mean F=7.01, mean $p=.02$) cues in all hypothesized brain regions. Years of cocaine use was associated with task-related brain activation, with more years of cocaine use associated with greater activation to cocaine cues in right (F=7.97,$p=.01$) and left (F=5.47,$p=.02$) ventral striatum and greater activation to response inhibition cues in left insula (F=5.10,$p=.03$) and inferior frontal gyrus (F=4.12,p=.05) controlling for age, cocaine dependence status, and cocaine use in the past 90 days.

Conclusions—Years of cocaine use may be more centrally related to cocaine cue and response inhibition brain activation as compared to cocaine dependence diagnosis or amount of recent use.

Keywords

fMRI; cue; go no-go; years of use; cocaine; response inhibition

The authors declare no financial interests or conflicts of interest.

INTRODUCTION

Cocaine use is a major public health concern. The 2011 National Survey on Drug Use and Health reported that approximately 1.4 million Americans actively use cocaine (1). These numbers are especially concerning because cocaine use is consistently associated with substantially increased mortality (2), psychiatric illness (3), functional impairment (4), and criminal behavior (5).

Over the past 20 years, human functional magnetic resonance imaging (fMRI) research has attempted to elucidate the neurobehavioral underpinnings of cocaine dependence. This research has largely focused on two core characteristics of cocaine dependence: cue reactivity and impulsivity. During self-administration of cocaine, spatially and temporally associated stimuli (e.g., paraphernalia) gain incentive salience via classical conditioning; reactivity to such stimuli is believed to play a key role in maintenance and relapse to cocaine-seeking and taking behavior (6). Recent meta-analyses have demonstrated that cocaine cues activate a variety of reward-related brain structures including the ventral striatum, dorsal caudate, and amygdala in individuals with cocaine dependence (7, 8). Impulsivity, broadly defined as the tendency to act without forethought, has been shown to be associated with both acquisition and relapse to problematic cocaine use (9, 10). Human functional neuroimaging research has demonstrated that individuals with cocaine dependence show less anterior cingulate (ACC) activation to response inhibition cues (i.e., stimuli that indicate one should inhibit a prepotent response) relative to healthy controls (11–13). Furthermore, neuroimaging research has repeatedly supported the importance of the inferior frontal gyrus and insula in response inhibition (14).

Although a substantial number of functional neuroimaging studies have investigated differences between individuals with cocaine dependence and healthy controls in terms of neural activation to cocaine and response inhibition cues, we are not aware of studies that have examined associations between cocaine use characteristics (e.g., years of use, recent use, dependence severity) and neural activation to cocaine and inhibition cues. However, non-imaging research has supported associations between cocaine use severity (15), duration of cocaine use (16), and cognitive impairments, and a number of volumetric imaging studies have supported associations between duration of cocaine use and gray matter loss (17, 18). The present study simultaneously investigated associations between a variety of cocaine use characteristics and brain activation to cocaine and response inhibition cues in cocaine using individuals.

METHOD

Participants

Forty-one individuals meeting DSM-IV criteria for current Cocaine Dependence were recruited from a clinical trial involving 71 participants (19). Of the 30 trial participants who did not participate in the fMRI study, approximately half were not interested whereas the other half were excluded due to ferrous implants or claustrophobia. All procedures in the present report were conducted prior to entry into the intervention trial. Because most participants (81%) reported using cocaine for >10 years, and because the range of possible

associations between cocaine use characteristics and brain activation to cues would be predictably attenuated if only cocaine users with extensive use histories were evaluated (20), we concurrently recruited an additional 10 cocaine users with less extensive use histories through advertisements. These additional participants reported using cocaine within the past 3 months but never met DSM-IV criteria for Cocaine Dependence. Exclusionary criteria for all participants included medications for addiction, major medical (e.g., diabetes) and psychiatric conditions (e.g., schizophrenia), pregnancy or nursing, ferrous metal implants or pacemakers, left-handedness, and DSM-IV criteria for non-cocaine substance dependence (except caffeine, nicotine, marijuana, or alcohol) within 60 days of the study. All participants were required to maintain ≥72 hours of abstinence from alcohol and all drugs of abuse prior to the scanning appointment as confirmed by breathalyzer, urine drug screen (UDS), and self report. All procedures were performed in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki, with approval from the Medical University of South Carolina Institutional Review Board.

Procedure

Potential participants completed the Substance Use Disorders module of the Structured Clinical Interview for DSM-IV (SCID) (21) and the Mini International Neuropsychiatric Interview (MINI) (22). Cocaine use in the preceding three months was assessed using the Timeline Follow-back method (23). Once all inclusion and no exclusion criteria were met, participants were scheduled for an fMRI visit within one-week.

Cocaine cue-reactivity paradigm

The present investigation utilized a visual cocaine cue-reactivity fMRI paradigm (24). In this paradigm, subjects view pictures of cocaine and cocaine-related objects (e.g., crack pipe), neutral objects (e.g., furniture), and blurry, visual control images that lack object recognition over six 120-second sets. Each 120-second set contains three 30-second image blocks (cocaine images, neutral objects, visual control images), containing five pictures displayed for 4.8 seconds each, and one 30 second rest block. During the final 6-seconds of each block, participants are asked to rate their craving, from zero (“none”) to four (“severe”), using a handpad. Participants’ craving scores are computed by taking their average rating following cocaine blocks and subtracting from it their average rating following neutral object blocks. Blocks within sets and stimuli within blocks are presented in pseudorandom order.

Response inhibition (i.e., go no-go) task

The go no-go task consists of 20 blocks, lasting 26.25 seconds each; 10 go no-go blocks alternate with 10 rest (i.e., fixation-cross) blocks. During go no-go blocks, participants are presented with 21 letters, one at a time, for 250 milliseconds each, followed by 1 second interstimulus intervals (i.e., black screen). They are instructed to press a button on their handpad as soon as they see a letter other than “X,” but to withhold a response if they see the letter “X;” "X" is presented 20% of the time, on average. Presentation order of letters in go no-go blocks is randomized to remove confounding effects due to the overlap of hemodynamic responses.

Image acquisition

MRI scans were performed in a Siemens 3.0T Trio (Erlangen, Germany) MR scanner with a 12-channel head coil. Following localizer and anatomical scans, the cue reactivity and go no-go scans were acquired with approximate AC-PC alignment using an echo-planar gradient-echo pulse sequence (TR = 2200 ms, TE = 35 ms, flip angle = 90%). Each brain volume consisted of 36 transverse slices (64 × 64 matrix, 3.0 mm thickness, no gap). Voxel size was 3 mm^{3}.

Region of Interest (ROI) definitions

Given that study hypotheses were anatomically specific, ROI analyses were used in place of whole-brain analyses. A relatively small number of focal brain regions (3 per task) were selected to help control the experimentwise alpha level. Each selected brain region was represented by separate right and left hemispheric ROIs. For the cocaine cue-reactivity paradigm, ROIs were created for the ventral striatum (i.e., nucleus accumbens and the ventromedial portions of the caudate nucleus and putamen), dorsal caudate nucleus, and amygdala (7, 8); see Figure 1 for ROI locations. Unfortunately, available anatomical atlases do not include ROIs for ventral and dorsal striatum; as such the following strategy was used to isolate the nucleus accumbens and ventromedial caudate nucleus (i.e., ventral striatum) from the dorsal caudate nucleus. For the ventral striatum, two 10 mm spherical ROIs were created centered on the nucleus accumbens, at Montreal Neurological Institute (MNI) coordinates 12,15,-6 (right) and -12,15,-6 (left) (25). Dorsal caudate ROIs were created by subtracting the above described ventral striatal ROIs from the caudate nucleus ROIs provided by the Automated Anatomical Labeling (AAL) atlas incorporated in MarsBaR (26). For the go no-go task, all ROIs were defined via the AAL atlas in MarsBaR. Specifically, ROI masks were created for the anterior cingulate gyrus (ACC), insula, and inferior frontal gyrus [pars opercularis] (14); see Figure 2 for ROI locations.

Image analysis

fMRI analyses were conducted using Statistical Parametric Mapping software 8 (SPM8, The Wellcome Department of Cognitive Neurology, London) and the MarsBaR SPM8 toolbox (26). Preprocessing was conducted separately for each fMRI task. All volumes within a task run were realigned to the first volume. Images were stereotactically normalized into a standard space, with a resolution of 3 mm^3 voxels using an MNI template. Data were smoothed with an isotropic 8 mm Gaussian kernel and were high-pass filtered (cue exposure paradigm cut-off period = 240s; go no-go task cut-off period = 128s). Following preprocessing, region of interest fMRI data were analyzed separately for each task within a general linear model (GLM) mixed effects framework. First, within-task data from individual participants was analyzed via fixed-effects GLM at the whole-brain level, with cocaine cue blocks modeled as a box-car function, and go and no-go responses modeled as single impulse functions specified by time of onset from the beginning of the run, both convolved with the standard canonical hemodynamic response function. Six movement parameters were included as covariates to control for the influence of residual head motion. First-level analyses were conducted separately for each task. For the cue exposure paradigm, each block type (cocaine images, neutral objects, visual control images, cross-hair) was

represented by a separate regressor and a contrast map of cocaine pictures minus neutral objects was created for each participant. For the go no-go task, all block (task, rest) and event (correct go trial, correct no-go trial, omission error, commission error) types were represented by separate regressors. A contrast map of no-go trials (i.e., correct no-go trial or commission error) minus go trials (i.e., correct go trial or omission error) was created for each participant; the no-go minus go trials contrast was selected to represent response inhibition because it is the most commonly used contrast in go no-go studies (14). Participants' task-specific contrast values were then averaged within each relevant brain region of interest such that each ROI was represented by a single contrast value. These subject-specific contrast values were extracted for second-level (between-subjects) analysis in IBM SPSS Statistics 20.0 software (IBM Corp, Armonk, NY). First, we performed separate GLMs (analogous to one-sample t-tests) on participants' cocaine minus neutral image and no-go minus go contrast values to evaluate whether cocaine and no-go cues significantly activated the a priori hypothesized brain regions of interest. Second, we performed GLMs (analogous to ANCOVA or multiple regression models) with age, cocaine dependence diagnostic status (i.e., meeting vs. not meeting DSM diagnostic criteria for cocaine dependence), years of cocaine use, and percent days cocaine use in the past 90 days predicting participants' cocaine minus neutral and no-go minus go contrast values, respectively. Quadratic terms were included for continuous predictors (i.e., years of cocaine use, percent days cocaine use), and all continuous predictors were centered prior to analysis. Because each statistical model was evaluated on 6 dependent variables (i.e., two hemispheric variants of three brain regions), a corrected alpha level of $p < 0.01$ was adopted for all statistical tests. In addition to the above ROI analyses, traditional whole-brain analyses were conducted and results of these analyses are presented in Supplementary Figures 1–4.

Behavioral data analysis

Two separate GLMs with subjective craving to cocaine versus neutral cues during the cocaine cue paradigm and number of commission errors during the go no-go task as dependent variables and age, cocaine dependence diagnostic status, years of cocaine use (and its quadratic term), and percent days cocaine use in the past 90 days (and its quadratic term) as predictors, were estimated.

RESULTS

Participant characteristics

Fifty-one participants (41 cocaine dependent, 37 male, 35 African-American) were scanned. Twenty of these participants reported primarily using powder cocaine whereas 28 participants reported primarily using crack cocaine. Eight participants met criteria for alcohol dependence, and two participants met criteria for marijuana dependence, at the time of the study. Ten participants had positive marijuana urine drug screens at the study appointment but denied marijuana use in the preceding 72 hours. Four participants reported taking antidepressant medications, and three participants met DSM criteria for current Axis I disorders, including social phobia, agoraphobia, dysthymic disorder, and ADHD. Of cocaine dependent participants, individuals reported a mean age of cocaine dependence onset of 30.0

years (SD = 9.0). Most participants were not married (n = 44) and were unemployed (n = 43). On average, participants were 41.1 years of age (SD = 12.2) and had used cocaine for 14.7 years (SD = 9.0). Participants reported using cocaine an average of 32.4% of days (SD = 24.2%) in the 90 days preceding the study; median time since last cocaine use was 25 days. Post-hoc analyses demonstrated that Axis I disorders (including marijuana and alcohol dependence), psychiatric medications, race, gender, and method of cocaine administration were not associated with task-related brain activation in any of the evaluated brain regions of interest (all ps > 0.10). Two participants were excluded from analyses involving the cocaine cue exposure paradigm due to excessive head motion (i.e., ≥ 3 mm/degrees in any direction. Four participants were excluded from analyses involving the go no-go task due to excessive head motion, five were excluded due to invalid behavioral data (> 1/3 omission errors [n = 4], 100% commission errors [n = 1]), and one additional participant did not complete the go no-go task. Finally, one additional cocaine user was excluded from analyses because they experienced a claustrophobic reaction midway through one of the functional runs. In sum, 48 participants were available for cocaine cue task analyses and 40 participants were available for go no-go analyses.

Cocaine cue-reactivity paradigm

Participants reported more subjective craving following cocaine versus neutral pictures (t[47]=9.22, p < 0.001). Brain activation to cocaine cues was significantly higher than activation to neutral cues in bilateral ventral striatum, dorsal caudate, and amygdala at the corrected (i.e., p < 0.01) alpha level (Table 1). The proportion of shared variance between subjective craving and brain activation to cues did not exceed 10% in any ROI (mean r = 0.23, mean p = 0.16). Controlling for covariates, the linear effect of years of use was significant in right ventral striatum at the corrected alpha level and in left ventral striatum at the uncorrected (i.e., p < 0.05) alpha level; specifically, *greater* years of use were associated with increased activation to cocaine cues in the ventral striatum (Table 2). None of the evaluated quadratic terms were significantly associated with task-related activation in any brain region. Younger age was associated with increased activation to cocaine cues in the amygdala (right: F=5.23,p=0.03; left: F=8.57,p=0.01); age was not significantly associated with activation in any other regions. Significant effects remained when non-dependent cocaine users were removed from the sample. Years of cocaine use was not significantly associated with subjective craving to cocaine minus neutral cues (F = 2.23, p = 0.12).

Response inhibition (i.e., go no-go) task

Total number of commission errors was inversely correlated with activation to no-go cues in the right insula (r = −0.35, p = 0.03). Across participants, activation to no-go cues was significantly higher than activation to go cues in left insula and right inferior frontal gyrus (pars opercularis) at the corrected (i.e., p < 0.01) alpha level and in right insula, left inferior frontal gyrus, and bilateral anterior cingulate gyrus at the uncorrected (i.e., p < 0.05) alpha level (Table 1). Controlling for covariates, the linear effect of years of use was significant in left insula and inferior frontal gyrus at the uncorrected alpha level (Table 2); specifically, *increased* years of use were associated with increased activation to no-go cues in left insula and inferior frontal gyrus. Neither age nor any of the evaluated quadratic terms were significantly associated with task-related activation in any brain region. Significant effects

remained when non-dependent cocaine users were removed from the sample. Years of cocaine use was not significantly associated with commission errors ($F = 0.82$, $p = 0.45$).

DISCUSSION

The present study used fMRI to examine associations between cocaine use characteristics and regional brain activation to cocaine and response inhibition cues in cocaine users. As expected, participants demonstrated elevated activation to both cocaine (ventral striatum, dorsal caudate, amygdala, as well as occipital cortex, inferior frontal gyrus, anterior and posterior cingulate, orbitofrontal cortex, hippocampus, thalamus in whole-brain analyses) and response inhibition (ACC, insula, inferior frontal gyrus, as well as putamen in whole-brain analyses) cues in all hypothesized brain regions.

Among evaluated cocaine use characteristics, only years of cocaine use was associated with brain activation to cocaine and response inhibition cues. Regarding cocaine cue reactivity, more years of cocaine use were associated with greater activation to cocaine cues in ventral striatum in both primary ROI and supplementary whole-brain analyses. This finding is consistent with a recent study that demonstrated associations between increased years of alcohol consumption and increased ventral striatum activation to alcohol cues in alcohol-dependent individuals (27). This finding is also compatible with the incentive salience theory of addiction, in that individuals with a more extensive cocaine use history, and therefore a more extensive drug cue learning history, would be expected to have a more robust neural reactivity to a wider variety of cocaine cues (28).

Conversely, the lack of observed association between cocaine dependence status and dorsal caudate activation to cocaine cues in the present study could be interpreted as inconsistent with research demonstrating greater dorsal striatal activation to alcohol cues in heavy versus light drinkers (29). These findings may also suggest that "trait-like" facets of cocaine abuse severity (e.g., years of use) may be stronger determinants of brain activation to cues relative to "state-like" facets of severity (e.g., recent use, subjective craving) (30). Although the present study included relatively few non-dependent users, providing non-optimal power for evaluating associations between dependence status and cue activation, our number of non-dependent cocaine users was the same as Vollstadt-Klein and colleagues' (29) number of light drinkers. Potential explanations for this discrepancy in findings include the fact that different substance using populations were investigated.

In addition to associations between years of cocaine use and ventral striatum activation to cocaine cues, we also found significant associations between years of cocaine use and activation to response inhibition cues. Specifically, more years of use were associated with increased activation to no-go cues in left inferior frontal gyrus (pars opercularis) and left insula. It is important to note that these associations were only significant at the uncorrected (i.e., $p < 0.05$) alpha level and, as such, should be considered tentative until replicated. Although past research has emphasized the role of the right inferior frontal gyrus in response inhibition (31), a number of studies have since demonstrated bilateral activation of the inferior frontal gyrus to response inhibition cues (32, 33). Similarly, although the insula has not been emphasized in the response inhibition literature, a recent meta-analysis

demonstrated that insula is central to the brain's response to inhibition cues (14). Interestingly, *increased* activation to no-go cues was associated with increased years of cocaine use in both the inferior frontal gyrus and the insula. Given there was no association between task performance and years of use, the direction of the obtained association supports previous findings that increased activation to inhibition cues may represent a compensatory mechanism designed to mitigate drug-related impairments in substance-dependent individuals (34). In contrast to these findings, there was no association between years of use and ACC activation to inhibition cues. Given that ACC hypoactivation has been the focus of response inhibition research in cocaine dependence, our lack of demonstrated associations between cocaine use characteristics and ACC activation to inhibition cues may be viewed as unexpected. However, patterns of brain activation that distinguish cocaine-dependent individuals and healthy controls may not be the same as those that distinguish cocaine-using individuals with more versus less years of use.

Cocaine dependence status and recent cocaine use were not associated with brain activation to cocaine and response inhibition cues. These results may suggest that years of cocaine use may be more centrally or uniquely related to cocaine cue and response inhibition brain activation relative to cocaine dependence status and recent use. Given the cross-sectional nature of the present study, it is unclear whether our findings reflect the accumulation of neurological insults resulting from chronic cocaine use or, alternatively, an association with other, potentially premorbid, characteristics (e.g., impulsivity); longitudinal research is needed to make such distinctions.

Although brain reactivity to cocaine and response inhibition cues was associated with years of cocaine use in the present study, behavioral analogues of these responses (subjective craving, commission errors) were not. Furthermore, subjective craving was minimally associated with brain activation to cocaine cues. Dissociation between neurobiological and behavioral markers is common in the neuroimaging literature (30).

The above conclusions should be evaluated in light of study limitations. First, as noted above, although the sample size for the present study was moderate-large relative to most fMRI investigations, it was still relatively small. The maximum number of participants possible was recruited given budgetary constraints. Results should be considered preliminary until replicated in larger samples. Second, as mentioned previously, the present study was a cross-sectional comparison of cocaine users with varying years of use. Third, the cocaine cue paradigm was administered prior to the response inhibition task in all participants. Although this fixed task ordering could have produced order-effects, this concern was mitigated by two factors: 1) task order was distributed across years of use and 2) our data suggested that the cocaine cue task did not induce enduring increases in craving. These limitations notwithstanding, the present study contributes to the literature by demonstrating associations between years of cocaine use and brain activation to cocaine and response inhibition cues in cocaine using individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Declarations of Interest

Funding for this study was provided by NIH grants F32 DA032250 (Prisciandaro) and R01 DA023188 (Brady); the NIH had no further role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

REFERENCES

1. SAMHSA. Results from the 2011 National Survey on Drug Use and Health: Summary of National Findings. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2012.
2. SAMHSA. Drug Abuse Warning Network, 2008: Area Profiles of Drug-Related Mortality. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2010.
3. Conway KP, Compton W, Stinson FS, Grant BF. Lifetime comorbidity of DSM-IV mood and anxiety disorders and specific drug use disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. The Journal of clinical psychiatry. 2006; 67:247–257. [PubMed: 16566620]
4. Lozano OM, Domingo-Salvany A, Martinez-Alonso M, Brugal MT, Alonso J, de la Fuente L. Health-related quality of life in young cocaine users and associated factors, Quality of life research: an international journal of quality of life aspects of treatment. care and rehabilitation. 2008; 17:977–985.
5. ONDCP. ADAM II 2008 Annual Report: Arrestee Drug Abuse Monitoring Program II. Washington, DC: Office of National Drug Control Policy; 2009.
6. Everitt BJ, Robbins TW. Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. Nature neuroscience. 2005; 8:1481–1489.
7. Kuhn S, Gallinat J. Common biology of craving across legal and illegal drugs - a quantitative meta-analysis of cue-reactivity brain response. The European journal of neuroscience. 2011; 33:1318–1326. [PubMed: 21261758]
8. Chase HW, Eickhoff SB, Laird AR, Hogarth L. The neural basis of drug stimulus processing and craving: an activation likelihood estimation meta-analysis. Biological psychiatry. 2011; 70:785–793. [PubMed: 21757184]
9. Belin D, Mar AC, Dalley JW, Robbins TW, Everitt BJ. High impulsivity predicts the switch to compulsive cocaine-taking. Science. 2008; 320:1352–1355. [PubMed: 18535246]
10. Economidou D, Pelloux Y, Robbins TW, Dalley JW, Everitt BJ. High impulsivity predicts relapse to cocaine-seeking after punishment-induced abstinence. Biological psychiatry. 2009; 65:851–856. [PubMed: 19181308]
11. Kaufman JN, Ross TJ, Stein EA, 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: the official journal of the Society for Neuroscience. 2003; 23:7839–7843. [PubMed: 12944513]
12. Hester R, Garavan H. Executive dysfunction in cocaine addiction: evidence for discordant frontal, cingulate, and cerebellar activity. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2004; 24:11017–11022. [PubMed: 15590917]
13. Li CS, Huang C, Yan P, Bhagwagar Z, Milivojevic V, Sinha R. Neural correlates of impulse control during stop signal inhibition in cocaine-dependent men. Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology. 2008; 33:1798–1806. [PubMed: 17895916]
14. Swick D, Ashley V, Turken U. Are the neural correlates of stopping and not going identical? Quantitative meta-analysis of two response inhibition tasks. NeuroImage. 2011; 56:1655–1665. [PubMed: 21376819]
15. Ersche K, Bullmore E, Craig K, Shabbir S, Abbott S, Muller U, et al. Influence of compulsivity of drug use on dopaminergic modulation of attentional bias in stimulant dependence. Arch Gen Psychiatry. 2010; 67:632–644. [PubMed: 20530013]

16. Vonmoos M, Hulka L, Preller K, Jenni D, Baumgartner M, Stohler R, et al. Cognitive dysfunctions in recreational and dependent cocaine users: role of attention-deficit hyperactivity disorder, craving and early age at onset. BJ Psych. in press.
17. Sim M, Lyoo I, Streeter C, Covell J, Sarid-segal O, Ciraulo D, et al. Cerebellar gray matter volume correlates with duration of cocaine use in cocaine-dependent subjects. Neuropsychopharmacology. 2007; 32:2229–2237. [PubMed: 17299505]
18. Ersche K, Barnes A, Jones P, Morein-zamir S, Robbins T, Bullmore E. Abnormal structure of frontostriatal brain systems is associated with aspects of impulsivity and compulsivity in cocaine dependence. Brain. 2011; 134:2013–2024. [PubMed: 21690575]
19. Santa Ana EJ, Prisciandaro JJ, Shaftman SR, Saladin ME, McRae AL, Brady KT. Effect of D-cycloserine and cue exposure therapy on physiological and subjective craving in cocaine dependence. 2012
20. Hunter, JE.; Schmidt, F. Methods of meta-analysis: Correcting error and bias in research findings. Newbury Park, CA: Sage; 1990.
21. First, M.; Spitzer, R.; Gibbon, M.; Williams, J. Research Version, Patient Edition. New York: New York State Psychiatric Institute; 1996. Structured Clinical Interview for DSM-!V Axis I Disorders.
22. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. The Journal of clinical psychiatry. 1998; 59(Suppl 20):22–33. quiz 34–57. [PubMed: 9881538]
23. Sobell, LC.; Sobell, MB. Timeline followback user's guide: a calendar method for assessing alcohol and drug use. Toronto: Addiction Research Foundation; 1996.
24. Prisciandaro JJ, McRae AL, Myrick H, Henderson S, Brady KT. Brain activation to cocaine cues and motivation/treatment status. Addict Biol. in press.
25. Schacht JP, Anton RF, Myrick H. Functional neuroimaging studies of alcohol cue reactivity: a quantitative meta-analysis and systematic review. Addict Biol. 2013; 18:121–133. [PubMed: 22574861]
26. Brett, M.; Anton, J-L.; Valabregue, R.; Poline, J-B. Region of interest analysis using an SPM toolbox [abstract]; 8th International Conference on Functional Mapping of the Human Brain; Sendai, Japan. 2002.
27. Claus ED, Ewing SW, Filbey FM, Sabbineni A, Hutchison KE. Identifying neurobiological phenotypes associated with alcohol use disorder severity. Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology. 2011; 36:2086–2096. [PubMed: 21677649]
28. Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain research Brain research reviews. 1998; 28:309–369. [PubMed: 9858756]
29. Vollstadt-Klein S, Wichert S, Rabinstein J, Buhler M, Klein O, Ende G, et al. Initial, habitual and compulsive alcohol use is characterized by a shift of cue processing from ventral to dorsal striatum. Addiction. 2010; 105:1741–1749. [PubMed: 20670348]
30. Carter BL, Tiffany ST. Meta-analysis of cue-reactivity in addiction research. Addiction. 1999; 94:327–340. [PubMed: 10605857]
31. Aron AR, Durston S, Eagle DM, Logan GD, Stinear CM, Stuphorn V. Converging evidence for a fronto-basal-ganglia network for inhibitory control of action and cognition. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2007; 27:11860–11864. [PubMed: 17978025]
32. Cai W, Leung HC. Cortical activity during manual response inhibition guided by color and orientation cues. Brain research. 2009; 1261:20–28. [PubMed: 19401178]
33. Li CS, Huang C, Constable RT, Sinha R. Imaging response inhibition in a stop-signal task: neural correlates independent of signal monitoring and post-response processing. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2006; 26:186–192. [PubMed: 16399686]
34. Harding IH, Solowij N, Harrison BJ, Takagi M, Lorenzetti V, Lubman DI, et al. Functional connectivity in brain networks underlying cognitive control in chronic cannabis users.

Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2012; 37:1923–1933. [PubMed: 22534625]

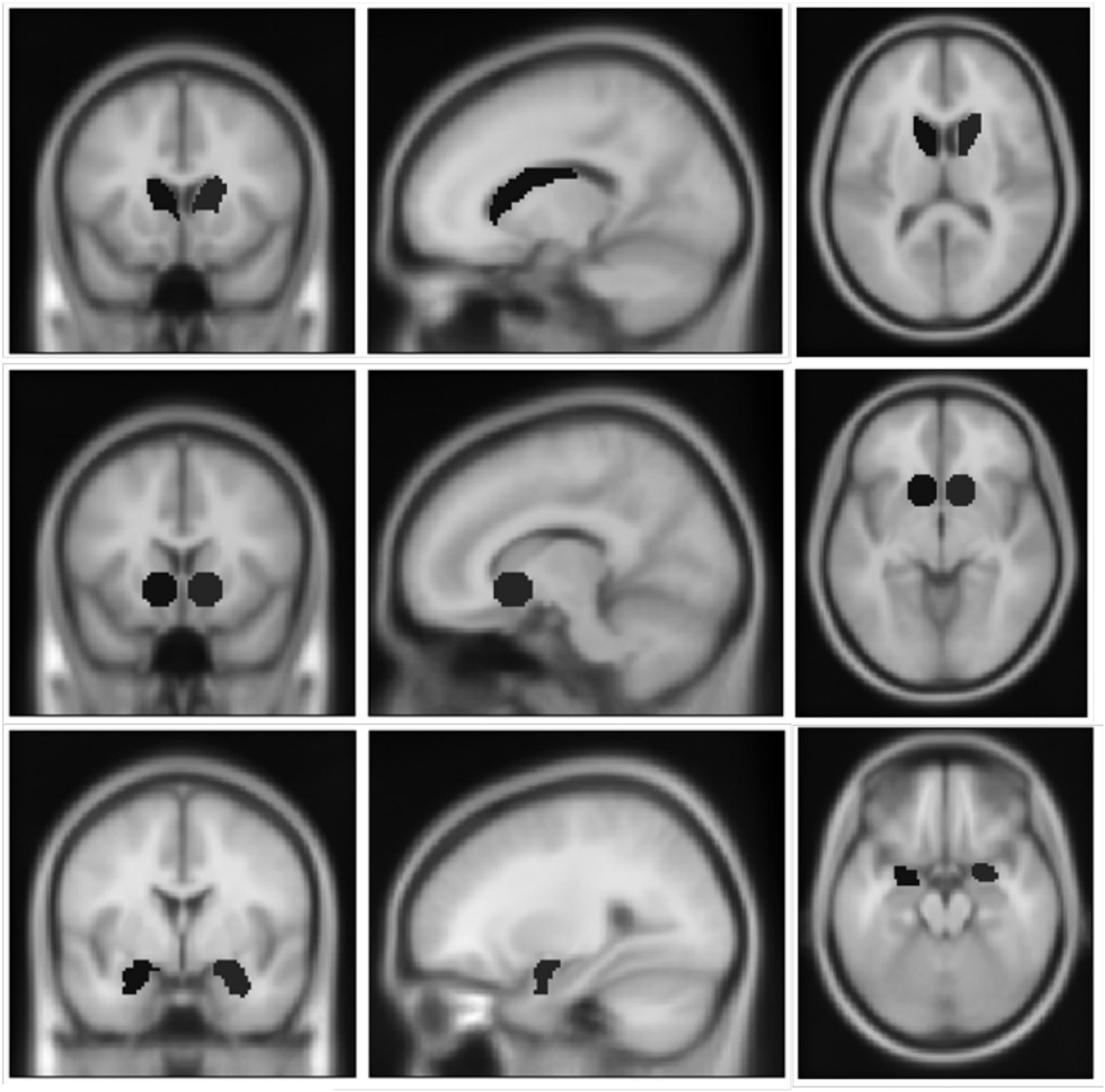

Figure 1.
Region of interest locations for the cocaine cue-reactivity paradigm: Dorsal caudate nuclei (top panel), ventral striatum (middle panel), and amygdala (bottom panel).

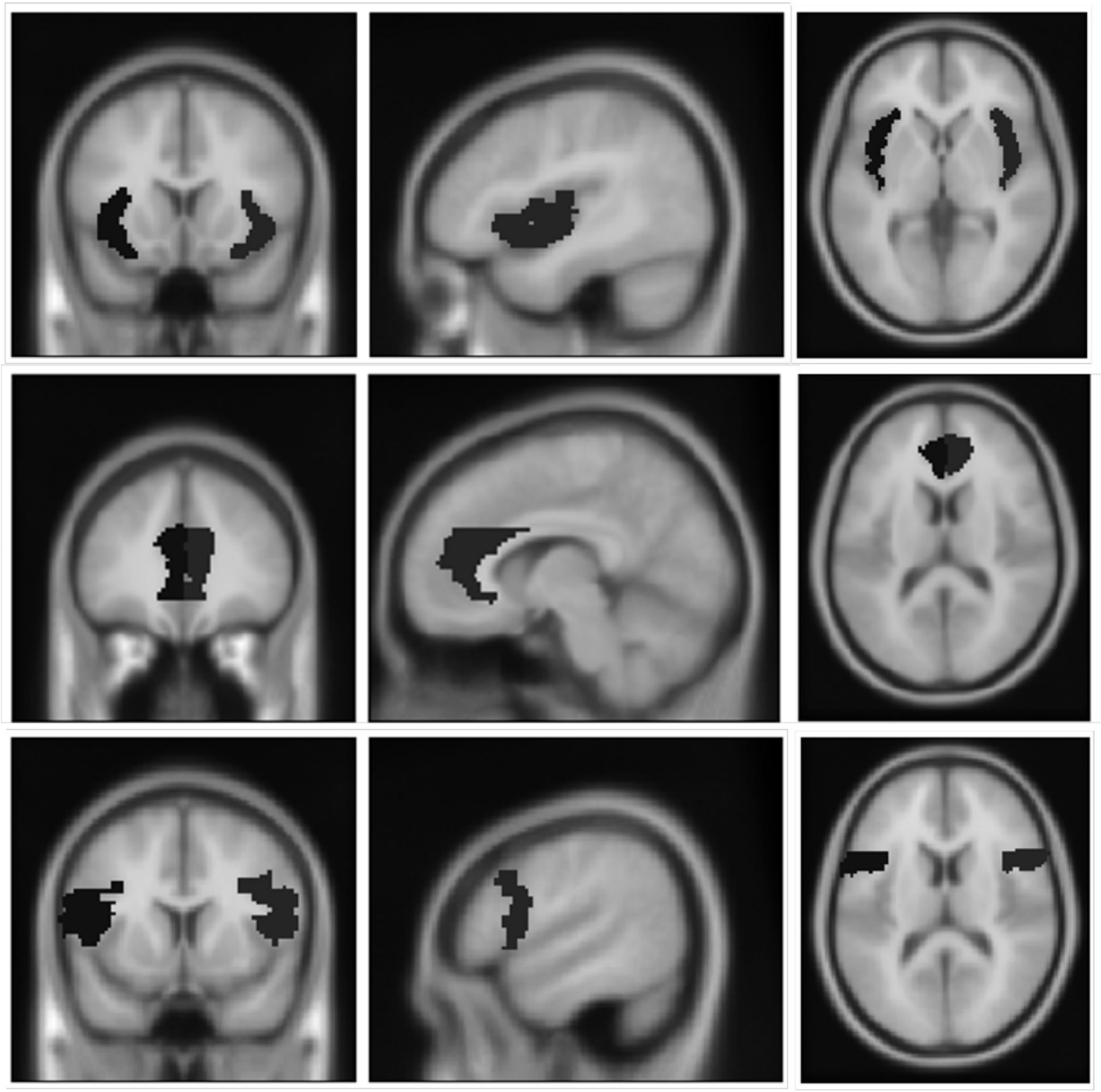

Figure 2.
Region of interest locations for the go no-go task: Insula (top panel), anterior cingulate gyrus (middle panel), and inferior frontal gyrus, pars opercularis (bottom panel)

Table 1

One sample (i.e., intercept only) multivariate general linear models evaluating mean activation to cues across subjects (n = 48)

Contrast	Brain Region	Hem.	F
Cocaine vs. Neutral	Ventral Striatum		
		Right	10.91*
		Left	13.90*
	Dorsal Caudate		
		Right	21.99*
		Left	17.72*
	Amygdala		
		Right	22.49*
		Left	26.97*
No-go vs. Go	Insula		
		Right	4.40†
		Left	7.61*
	Anterior Cingulate		
		Right	6.52†
		Left	5.17†
	Inferior Frontal Gyrus, Pars Opercularis		
		Right	12.89*
		Left	5.49†

Note: Hem. = Hemisphere.

† $p < 0.05$;

* $p < 0.01$

Table 2

Effects of cocaine use characteristics on brain activation to cocaine and no-go cues.

			F-Statistics		
Contrast	**Brain Region**	**Hemisphere**	**Cocaine Dependence**	**Years of Use**	**% Days Use**
Cocaine vs. Neutral	Ventral Striatum	Right	2.20	7.97*	0.10
		Left	2.70	5.47†	1.49
	Dorsal Caudate	Right	0.70	1.46	0.01
		Left	1.16	0.68	0.23
	Amygdala	Right	0.69	0.82	1.29
		Left	0.90	0.55	1.12
No-go vs. Go	Insula	Right	0.36	0.60	1.07
		Left	0.84	5.10†	1.23
	Anterior Cingulate	Right	1.20	1.78	0.81
		Left	2.33	2.66	0.81
	Inferior Frontal	Right	0.25	0.22	1.25
	Gyrus, Opercularis	Left	0.28	4.12†	0.73

Note: Linear effects of age and quadratic effects of years of use and % days use not shown; see Results for summaries of these effects.

† $p \leq 0.05$;

* $p \leq 0.01$.