Published in final edited form as:

Biol Psychiatry. 2013 October 1; 74(7): 529–537. doi:10.1016/j.biopsych.2013.04.029.

Robust Changes in Reward Circuitry during Reward Loss in Current and Former Cocaine Users during Performance of a Monetary Incentive Delay Task

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Abstract

Background—Abnormal function in reward circuitry in cocaine addiction could predate drug use as a risk factor, follow drug use as a consequence of substance-induced alterations, or both.

Methods—We used a functional MRI Monetary Incentive Delay Task (MIDT) to investigate reward-loss neural response differences among current cocaine users (N=42), former cocaine users (N=35) and healthy control subjects (N=47). Subjects also completed psychological measures and tasks related to impulsivity and reward.

Results—We found various reward processing-related group differences in several MIDT phases. Across task phases we found a “control>current user>former user” fMRI BOLD activation pattern, except for loss outcome, where former compared to current cocaine users activated ventral tegmental area (VTA) more robustly. We also found regional prefrontal activation differences during loss anticipation between cocaine-using groups. Both groups of cocaine users scored higher than controls on impulsivity, compulsivity and reward-punishment sensitivity factors. In addition,

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Disclosure/Conflicts of interest

Dr. Pearlson has consulted for Bristol-Myers Squibb.

Dr. Potenza has consulted for and advised Boehringer Ingelheim; has consulted for and has financial interests in Somaxon; has received research support from the National Institutes of Health, Veteran's Administration, Mohegan Sun Casino, the National Center for Responsible Gaming and its affiliated Institute for Research on Gambling Disorders, and Forest Laboratories, Ortho-McNeil, Oy-Control/Biotie and Glaxo-SmithKline pharmaceuticals; has participated in surveys, mailings or telephone consultations related to drug addiction, impulse control disorders or other health topics; has consulted for law offices and the federal public defender's office in issues related to impulse control disorders; provides clinical care in the Connecticut Department of Mental Health and Addiction Services Problem Gambling Services Program; has performed grant reviews for the National Institutes of Health and other agencies; has guest-edited journal sections; has given academic lectures in grand rounds, CME events and other clinical or scientific venues; and has generated books or book chapters for publishers of mental health texts.

All other authors report no biomedical financial interests or potential conflicts of interest.

impulsivity-related factors correlated positively with BOLD activation in amygdala and negatively with anterior cingulate activation during loss anticipation.

Conclusions—Compared to healthy subjects, both former and current cocaine users displayed abnormal brain activation patterns during MIDT performance. Both cocaine groups differed similarly from healthy controls, but differences between former and current cocaine users were localized to the VTA during loss outcome and to prefrontal regions during loss anticipation, suggesting that long-term cocaine abstinence does not normalize most reward circuit abnormalities. Elevated impulsivity-related factors that relate to loss processing in current and former cocaine users suggest that these tendencies and relationships may pre-exist cocaine addiction.

Keywords

Monetary incentive delay task; Cocaine; Monetary reward; Monetary loss; Impulsivity; Addiction

Introduction

Cocaine use may lead to compulsive drug-seeking and drug-taking behaviors, particularly in impulsive individuals (1). Cocaine administration influences nucleus accumbens function via dopamine neurons originating in the ventral tegmental area, thereby affecting extended reward networks involved in acquisition and reinforcement of drug-consumption behaviors (2). This mechanism may initiate self-reinforcement, where cocaine-provoked abnormalities in signaling of reward likelihood may increase the likelihood of future cocaine use.

Various hypotheses (3, 4) have been suggested to account for the relationship between reward system function and addiction: impulsivity (5), reward deficiency syndrome (6), incentive salience (7) and allostasis (8) models, each of which involve the interplay of reward and cognitive neural systems in the brain. Although research is only beginning to use functional neuroimaging to investigate the above hypotheses as related to addictions (4), the neurocircuitry underlying reward processing itself is well characterized (9, 10). Functional neuroimaging studies of addicted and non-addicted adults report diverse rewards processing activations in the nucleus accumbens, ventral tegmental area, amygdala, insula, orbito-frontal cortex, anterior cingulate and dorsolateral prefrontal cortices, hippocampus/para-hippocampal gyrus, ventral pallidum and lateral habenula (11-13).

A previous study using a monetary incentive delay task (MIDT) found in treatment-seeking cocaine-dependent patients versus controls elevated activation in regions within reward circuitry during reward anticipation and reward outcome, and this increased activation associated with poor treatment outcome (14). Similarly, cocaine users have shown increased activation in the anterior cingulate during craving suppression, inhibitory control and motivation enhancement during emotionally salient tasks (12).

Although these findings link neural correlates of reward processing to current cocaine use/dependence, the existence of long-term functional changes in reward circuitry related to cocaine use is less clear (4, 15, 16). One means to investigate this question is to compare former (long-term abstinent) and current cocaine users with never-drug-using healthy subjects, so that functional brain differences in former users would not be attributable to acute dependence, but to either pre-existing factors or cumulative, chronic drug effects (12, 14, 17). Such findings might indicate abstinence-related recovery of brain function (18). Investigating further, one can examine relationships between measured brain dysfunction and self-reported and behavioral tendencies (e.g., impulsivity) related to substance-use-disorder risk (1, 19-23). Previously (1, 24-28) BOLD responses during reward processing in substance abuse/dependence have been associated with poor cognitive-control, impulsive/

compulsive behavior and novelty-seeking, factors that may signify for drug-addiction. Thus, it is important to investigate a range of impulsivity- and compulsivity-related measures in current and former cocaine users.

This study used a modified version (14, 27, 29, 30) of the fMRI MIDT (31) to quantify brain activation during prospect (A1), anticipation (A2) and outcome (OC) phases for reward/loss trials. To our knowledge, no previous study has compared current and former cocaine users to examine reward circuitry during processing of monetary rewards and losses. We hypothesized that both current and former cocaine users would show significantly different activation patterns from healthy subjects and from each other in pre-selected regions of interest (ROI) during reward and loss processing. Specifically, we predicted the following based on prior studies. 1) Both current and former cocaine users would show less activation in pre-selected ROIs during reward/loss prospect and anticipation phases (12, 32). 2) During reward/loss outcome trials, current and former cocaine users would show increased activations in these ROIs (33). 3) Current and former users would score higher on impulsivity-related factor scores, which would correlate with BOLD activation in former and current users (14, 27, 28, 34, 35). Overall, we predicted that former user values would be intermediate between these of healthy subjects and current users, as long-term abstinence would promote recovery from acute drug “hijacking” of reward circuitry (15, 16) allowing restitution to pre-drug functional status in the former users.

Materials and Methods

Participants

We recruited healthy subjects (N=153), current cocaine users (N=43) and former cocaine users (N=35); of these, all cocaine-using subjects and 48 healthy subjects who best matched them demographically (age and sex) were included in analyses (Table 1). Table 1 lists demographics for MIDT outcome phases (analyzed in a slightly reduced sample) as described later. Participants were recruited by word of mouth, flyers, newspapers, online advertisement and outpatient drug treatment programs. All participants provided informed written consent approved by Hartford Hospital and Yale University Institutional Review Boards.

A Time-Line Follow-Back questionnaire (36) was used to quantify drug consumption amounts. Current and former cocaine users either currently or formerly (respectively) met criteria for DSM-IV-TR cocaine dependence. Drug use information (in either grams or financial amounts) was converted into dollars using the National Drug Intelligence Center information (www.justice.gov/ndic/pubs38/38661/cocaine.htm; Table 1). The amount of drugs used is an approximation, as it was self-reported. Current cocaine users were defined as individuals using cocaine at least twice a week prior to their day of participation and at least 10 times in the last month. Subjects were not informed of inclusion/exclusion criteria. All participants in the study required an observed urine test for cocaine on the day of screening. We included subjects who met criteria for current cocaine use via self-report (Table 1) and/or positive urine test. Former cocaine users were defined as individuals who had no self-reported cocaine or any other street drug six or more months prior to the study date and had negative urine toxicology screens for common drugs of abuse (Supplement 1: Table S1). Healthy subjects were excluded if they met lifetime DSM-IV criteria for substance abuse/dependence, except for nicotine dependence, or if their urine tested positive for recreational drugs on the day of testing. Twelve current cocaine users and eight former cocaine users had comorbid opioid use, as subject recruitment sources included an outpatient treatment program that provided methadone (Supplement 1: Table S1). General exclusionary criteria included a diagnosis of any current non-substance-related major psychiatric Axis I disorder as assessed by Structured Clinical Interview for DSM-IV-TR (SCID; (37)), major

physical illness, current or past history of central nervous system neurological disease, history of head trauma causing loss of consciousness >15 minutes, or ferromagnetic objects in the body.

Monetary Incentive Delay Task (MIDT)

FMRI was performed using an event-related MIDT (Figure 1), modified from the original design (38) as described (27) and used previously (14, 27, 29, 30). Detailed task description is included (see Supplement 1). Group-wise in-scanner behavior variables are reported (Table 1).

FMRI Image Analyses

FMRI data were acquired as described in Supplement 1.

Data Preparation

FMRI images were preprocessed using Statistical Parametric Mapping (SPM5 www.fil.ion.ucl.ac.uk/spm/software/spm5/), running in MATLAB 7.1 (MathWorks, Natick, Massachusetts) on a Linux platform. The first six images of each time series were removed to compensate for saturation effects. Images were realigned using INRIAAlign (39) and normalized to standard echo-planar-image template in Montreal-Neurological-Institute (MNI) space available in SPM5. We used a gaussian kernel of 8mm full-width half-maximum to smooth images after normalization. Data were re-sampled at 3×3×3mm.

FMRI Statistical Comparisons

For each participant, event onsets for each of the task conditions were convolved with the hemodynamic response function from SPM5. Both a main effect and temporal derivative were modeled. A 128sec high-pass filter was included in each model. To account for head motion > 1 voxel, separate regressors for each time-point identified by realignment as exceeding this threshold were specified to remove variance from each first-level model for that image. Four subjects moved > 3 voxels. One of those subjects had a very low correlation with the mean T map of all subjects; thus we excluded that subject from analyses.

Each subject had the following contrasts separately for \$0, \$1 and \$5 events modeled versus implicit baseline in 1st level fMRI analyses: 1) Prospect of loss; 2) Anticipation of loss; 3) Outcome receipt of loss; 4) Outcome receipt of non-loss; 5) Prospect of reward; 6) Anticipation of reward; 7) outcome receipt of reward; 8) Outcome receipt of non-reward. Few previous studies (40, 41) have successfully contrasted \$0 trials with reward and loss trials. We had few trials of \$0 reward and loss combined to use as a baseline and thus choose to use an implicit baseline.

To test the study hypotheses, we used random-effects, one-way SPM5 ANOVAs to compare healthy subjects and current and former cocaine users for prospect and anticipation of rewards and losses, and rewarding and losing outcomes in 20 *a priori* regions-of-interest (ROIs) (Supplement 1: Figure S1) selected based upon previous relevant MIDT neuroimaging research (11, 27, 29, 30, 38, 42, 43). The ROIs included: 1) amygdala, 2) anterior cingulate, 3) caudate, 4) insula, 5) mesial prefrontal cortex 6) orbito-frontal cortex, 7) hippocampus, 8) para-hippocampal gyrus, 9) nucleus accumbens, and 10) ventral tegmental area in left and right hemispheres individually. The ROI masks were created using the Wake Forest University Pickatlas utility in SPM (44) except for nucleus accumbens. The nucleus accumbens mask, coordinates and spatial locations were obtained from the Cerefy (45) and electronic Talairach-Tournoux brain atlases (46). This nucleus accumbens mask was further refined based on additional information (38, 47-50) and edited using MARINA

software (51). Anatomical location and spatial validity were verified by an imaging expert (GDP). We did not include non-win and non-lose trials in second-level outcome phase analyses in order to evaluate absolute effects related to reward or loss. As a result, the numbers of trials were reduced in the outcome phases. Thus, we combined \$5 and \$1 trials in across MIDT phases to avoid noise relating to fewer trials. For each condition, we first performed an ANOVA F-test and then study-group-wise comparisons using small volume corrections where the above-described ROIs were the small volumes. We report only effects surviving family-wise-error (FWE) correction of $p < 0.05$. We controlled for age, combined intelligence score, Beck Depression Index and race across task phases as potential confounds. We took mean of subjects' education, Wechsler-Adult-Intelligence-Scale information and block design test scores to gain degrees of freedom to account for combined intelligence score. Missing values of all variables were replaced by their group mean.

Impulsivity-related Post-hoc Analyses

Assessment instruments were those described in our previous studies (27, 28) and thus the same correlation matrix from the principal components analysis was used to determine impulsivity-related factor scores in the current study, as the majority of the current sample was a subset of the previous study sample (28). The resulting five factors were then compared using one-way ANOVAs to find group differences. To find correlations between the fMRI-activated brain regions and principal-components-analysis-derived factors, we used voxel-wise regression analysis for each MIDT condition in the full sample as in Table 1. Separate multiple regression models were used where the independent variables were those factors which significantly differed across all three groups and the dependent variables were data within each ROIs. We report only those ROIs showing significant differences in ANOVA main effects at a level of $P_{FWE} < 0.05$. Please see Supplement 1 for factor descriptions.

Results

One-sample t-test results for the full sample are listed in Tables S2 and S3 (see Supplement 1). We also report (x, y, z) MNI coordinates for each significant ROI peak voxel in this section.

Loss Prospect

In prospect (A1) of loss, right amygdala (30, -3, -21), anterior cingulate (6, 9, 27), right anterior cingulate (6, 9, 27), right hippocampus (30, -9, -24), bilateral para-hippocampal gyrus (-21, -12, -30; 12, -42, 0) and right ventral tegmental area (12, -15, -18) showed significant group differences (Supplement 1: Table S4; Figure 2). In post-hoc (t-statistical) analyses, current cocaine users less activated right amygdala (30, -3, -21), anterior cingulate (6, 9, 27), para-hippocampal gyrus (33, 0, -21) and ventral tegmental area (12, -15, -18) and former cocaine users also less activated right amygdala (30, -3, -21), right hippocampus (30, -9, -24), bilateral para-hippocampal gyrus (-21, -12, -27; 12, -42, 0), and right ventral tegmental area (12, -15, -18) compared to healthy subjects (Supplement 1: Table S5). We observed no differences between current and former cocaine users.

Loss Anticipation

In loss anticipation (A2), right insula (45, -15, 15) right Brodmann area (BA) 10 (42, 57, 6) and right para-hippocampal gyrus (30, -42, -15) showed significant activation differences (Supplement 1: Table S4; Figure 2). In post-hoc analyses, current cocaine users less activated right insula (45, -18, 21) and former cocaine users less activated right insula (45, -15, 15), right BA 10 (12, 63, 30) and right para-hippocampal gyrus (30, -60, -9) compared to

healthy subjects (Supplement 1: Table S5). Former users showed less activation in right BA 10 compared to current users.

Loss Outcome

In loss receipt (OC), right hippocampus (33, -30, -9) and left VTA (9, -6, -9) showed significant group differences (Supplement 1: Table S4; Figure 2). In post-hoc analyses, former cocaine users more activated right hippocampus (33, -30, -9) compared to healthy subjects (Supplement 1: Table S5). Greater left ventral tegmental area (-12, -9, -12) activation was observed in former cocaine users compared to current users. Figure 3 illustrates left ventral tegmental area effect sizes by subject group. Current cocaine users did not significantly differ from healthy subjects.

Reward Prospect

In reward prospect, right para-hippocampal gyrus showed group differences (Supplement 1: Table S4; Figure 2). In post-hoc analyses, current and former cocaine users less activated right para-hippocampal gyrus (21 -21 -24) compared to healthy subjects (Supplement 1: Table S5). We did not find differences between current and former cocaine users.

Reward Anticipation

We found no overall significant differences in main effects analyses.

Reward Outcome

We found no overall significant differences in the main effects analyses.

Impulsivity-Related Factor Analyses and Correlations

In a one-way ANOVA, Factor 2 'Self-Reported Compulsivity and Reward/Punishment Sensitivity' ($F=8.207$, $df=2$, $P_{\text{uncorrected}}=0.00045$; including the Padua Inventory (52) and the Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ) (53)) and Factor 3 'Self-Reported Impulsivity' ($F=8.261$, $df=2$, $P_{\text{uncorrected}}=0.00043$; including the Barratt Impulsiveness Scale (BIS -11) (54) and the Sensation-Seeking Scale (SSS Form V) (55)) differed significantly amongst groups. Post-hoc analyses demonstrated that current cocaine users scored higher ($P_{\text{Bonferroni}}=0.00028$) than healthy subjects while former cocaine users did not differ significantly from healthy subjects on factor 2 'Self-Reported Compulsivity and Reward/Punishment Sensitivity'. Both current ($P_{\text{Bonferroni}}=0.002$) and former cocaine users ($P_{\text{Bonferroni}}=0.004$) scored higher than healthy subjects on factor 3 'Self-Reported Impulsivity'. We found a positive correlation ($P_{\text{FWE}}=0.046$; 27, -9, -15) between right amygdala activation and factor 2 scores and negative correlation ($P_{\text{FWE}}=0.028$; 3, 9, 27) between right anterior cingulate activation and factor 2 scores also during loss anticipation in the full sample (Table 1). Figure 4A and 4B illustrates the correlation plots and respective brain rendering.

Although right nucleus accumbens ($p_{\text{uncorrected}}=0.035$; 12, 12, -9) and right insula ($p_{\text{uncorrected}}=0.019$; 48, 9, -3) activations during prospect of reward negatively correlated with abstinence duration in former users and left amygdala ($p_{\text{uncorrected}}=0.014$; -18, -3, -27) activation negatively correlated with abstinence duration during anticipation of reward, no correlations survived correction for multiple comparisons.

In order to further investigate relationship of significantly different impulsivity measures and on left ventral tegmental area BOLD activation, we calculated the mean of factor 2 scores for the full sample of 124 subjects, and we divided each groups into lower and higher factor-score groups based on these mean values. We then performed two-sample t-tests on

those groups' BOLD activation values in the left ventral tegmental area. The two-sample t-test between low and high impulsive subjects within former users revealed a significant difference ($t = 2.701$; $P = 0.016$) between the two groups' left ventral tegmental area BOLD responses. We illustrate the difference along with group-wise mean factor 2 & 3 values in Figure 4C, 4D, 4E. We found no significant difference when we divided groups based on factor 3 scores.

Discussion

The main goals of this study were to investigate neural correlates of monetary loss and reward processing in current and former cocaine users compared to healthy controls and to investigate their relationships with impulsivity-related measures. Specifically, we examined differences in BOLD activation patterns in current cocaine users, former cocaine users and healthy control subjects during reward and loss trials of a modified fMRI MIDT. As predicted, we found multiple fMRI-measured BOLD activation pattern differences across groups in various reward processing-related pre-selected ROIs. Overall we found less/more activation in both cocaine-using groups as compared to healthy subjects in various pre-selected reward-processing-related ROIs across MIDT phases.

Current and former cocaine users differed equally from healthy controls, but did not differ from each other except during the loss anticipation and outcome phases. During loss prospect, both cocaine-using groups showed less activation in amygdala, para-hippocampal gyrus and ventral tegmental area while current users additionally showed less activation in anterior cingulate and former users additionally showed less activation in hippocampus relative to healthy controls. This reduced activation in anterior cingulate in current users has been reported in a previous study (12) that associated anterior cingulate function with altered motivation and inhibition in cocaine users. This finding may represent failure to inhibit in current users during loss prospect. Consistent with previous studies (56-58) in rats and humans that report the hippocampus is sensitive to reward-loss, we also observed reduced hippocampal activation in former cocaine users during loss prospect and outcome. Another core region, the insula, activated less robustly in both cocaine-using groups compared to healthy controls during loss anticipation, a finding which may be associated with lower levels of attention and anxiety in cocaine users. During loss prospect phase, both cocaine-using groups showed lower amygdalar activation compared to healthy controls. The amygdala has been associated with emotional and motivational processing in general and cocaine cravings in cocaine dependence (59), and less amygdalar activation during loss prospect may reflect emotional/motivational abnormalities in cocaine users. A previous study (32) also revealed less activation in the amygdala, insula, orbito-frontal cortex, anterior cingulate and prefrontal cortex regions association with impaired motivation and self-control in current cocaine users during reward-processing-related trials.

Similar to a previous study examining individuals positive versus negative for alcoholism family history (27), we found that current and former cocaine users differed significantly compared to healthy controls on impulsivity factors 2 and 3. This prior study (27) also reported negative associations between nucleus accumbens BOLD activation during reward anticipation and factor 2 scores both in individuals family history positive and negative for alcoholism. In the current study, we found that in the full sample, impulsivity factor 2 measures correlated with right anterior cingulate BOLD signal change during loss anticipation in the right amygdala (positively) and anterior cingulate (negatively). This finding suggests that amygdala and anterior cingulate activation may be modulated by impulsivity measures. However, we did not find that BOLD activation of those regions differed significantly between groups during loss anticipation.

Differences between Cocaine-using Groups

Prefrontal cortical regions contribute importantly to emotion regulation and reward processing (60). A previous study of reward processing (32) reported prefrontal region differences in cocaine addiction. We found that former cocaine users activated BA 10 less compared to both current cocaine users and healthy controls during loss anticipation. The ventral tegmental area, an integral region for normal reward function, contains neural cell bodies of ascending mesocortical and mesolimbic dopamine systems. We found striking between-group differences in left ventral tegmental area activation during loss outcome. Former cocaine users showed more activation than current users in the ventral tegmental area during this phase. A possible explanation for these findings may be that past chronic cocaine use may have persistently or permanently altered neural structures engaged in reward-loss function (61) and cocaine use might “stabilize” their reward circuitry. However, longitudinal studies are needed to test directly this possibility.

Implications and Future Directions

We found no reward-punishment related differences between current and former cocaine users except during loss anticipation and outcome. Multiple factors may contribute to these findings. Significant reward-processing-related variability exists in the fMRI cocaine literature (4). In the current study, we assessed current cocaine users at different times following last drug use. As cocaine was not administered on site or in standard doses, different study subjects may have been on a spectrum between partial withdrawal and residual intoxication, and these clinical differences may not have been sufficiently obvious to have excluded their participation. It is also possible that current cocaine users were less motivated during the task and thus showed blunted responses across task phases, consistent with a recent study showing reduced motivation/attention in current cocaine users (62). However, we controlled for numbers of winning and losing trials in the outcome phase to minimize this possibility. Since participants were recruited from various community sources, it was not possible to gather consistently accurate information about prior treatment. Thus, we were unable to relate these variables to study findings. Current and former users also differed on estimated cocaine use. This may have accounted for analysis outcome differences, but we did not include this as a covariate in the model because it is a self-reported estimate rather than a true quantitative observation. In a post-hoc analysis, we included cocaine use as a covariate to the model and re-analyzed the data. The original results survived this correction, with the exception that the left VTA activation to loss outcome changed from $p=0.027$ to $p=0.054$. We also re-analyzed the subset of current sample omitting opioid users and replicated the majority of prior findings: however, some findings did not survive $p<0.05$ -FWE-correction criteria (Supplement 1: Tables S6 and S7), perhaps reflecting smaller sample sizes. Although we account for various types of motion using motion-censoring fMRI-analysis algorithms, we did not remove all time-series with head motion. However, we employed cut-offs for retention that are comparable to many published studies. Future studies should examine several critical variables that would better characterize cocaine-using subgroups including abstinence duration, amount of drug use and time of recovery. However, effective characterization will require a well controlled prospective study to ensure accurate data collection to avoid retrospective trial bias. Although we have published accurate and theoretically meaningful results before (27) with this version of MIDT, future studies should probably include longer version of this task or average 2 runs of the same task to avoid potential noise effects due to less trials. The neural underpinnings of reward- and loss-related processes (e.g., delay discounting) should also be examined prospectively.

Conclusions

Together, these findings suggest that current cocaine use (and/or possibly other variables related to differences between groups, such as those related to treatment-seeking status, impulsivity-related measures) may influence reward-processing circuits. From a clinical perspective, such direct influences could contribute to deficits in risk/reward decision-making observed in cocaine-dependent individuals and could contribute to continued cocaine use (63).

Consistent with a reward deficiency hypothesis, we observed less robust activation patterns in pre-selected ROIs during reward prospect, loss prospect, loss anticipation trials in both cocaine-using groups relative to control subjects. Contrary to our predication, former users showed relatively greater activation in hippocampus compared to healthy subjects and in ventral tegmental area as compared to current users during loss outcome. Another significant difference between former and current cocaine users was in left prefrontal cortex/ Brodmann area 10 during loss anticipation. Further studies should investigate the extent to which functional differences in former cocaine users reflect aspects of pre-existing features, exposure to cocaine, or recovery. We also found higher scores on impulsivity-related factors in cocaine users compared to healthy subjects. These findings suggest that certain impulsivity-related constructs may influence current cocaine use whereas others may persist during abstinence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was funded by NIDA grants # RO1 DA020709, RO1 DA020908, P20 DA027844 and NIAAA grant # RO1 P50-AA12870-05 and in part by the Connecticut Department of Mental Health and Addiction Services. This work was presented at the Society of Biological Psychiatry 66th annual Meeting, May 1-4, 2011, San Francisco, CA and at Organization for Human Brain Mapping 17th annual Meeting, June 26-30 2011, Quebec City, Canada.

We would like to acknowledge the late Dr. Daniel Hommer for help and encouragement in designing the MID task.

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Figure 1. Monetary Incentive Delay Task (MIDT) flow chart

A1=Prospect phase; A2=Anticipation phase; OC=Outcome phase; win=reward trials; lose=loss trials; Cue=Notification of trial type indicating winning or losing amounts; Target=button press; ITI=inter-trial interval.

Figure 2. Neural Correlates of Reward and Loss Processing in Current and Former Cocaine-users and Healthy Controls

Brain images show SPM results during monetary reward and loss trials in all subjects (Healthy subjects N= 47; Current cocaine users N= 42; Former cocaine users N= 35). Main-effect differences at a whole-brain level are overlaid on a T1 template brain provided by the FSL library using Mango software. The color bar shows the statistical F-contrast values ranging from 2 to 11 where red to yellow colors represent low to high values, respectively. Y coordinates of the corresponding image slices are noted towards the end of the figure. Left brain images are displayed on the left.

Figure 3. Activation in the Left Ventral Tegmental Area and Right Brodmann Area 10

Bar graphs illustrating the effect size $\pm$ SEM for the groups in the significantly different regions between current and former cocaine users. (A) Left ventral tegmental area during loss outcome: Here we see a “Former>Healthy>Current” pattern with current and former being significantly different (Healthy controls N = 19; Current cocaine users N= 17; Former cocaine users N= 18) (B) Right Brodmann area 10 during loss anticipation: Here we see a “Healthy>Current>Former” pattern with current and former being significantly different (Healthy Controls N=47; Current users N=42; Former users N=35). Statistical thresholds were $p<0.05$ uncorrected; cluster threshold =5. Bar graph was generated using rfxplot toolbox in SPM5 for the pre-selected ROI.

Figure 4. Impulsivity factors and fMRI activations

(A) Scatter plot of right amygdala activation correlation with impulsivity factor 2. Red transparent region show ROI. Activation is shown in yellow. (B) Scatter plot showing anterior cingulate and impulsivity factor 2 correlations. In respective brain rendering red transparent region show ROI and activation is shown in green. (C) Group mean of factor 2 (comprising the Padua Inventory and the Sensitivity to Punishment and Sensitivity to Reward Questionnaire) scores $\pm$ SEM. (D) Group mean of factor 3 (comprising the Barratt Impulsiveness Scale-11 and Zuckerman Sensation-Seeking Scale) scores $\pm$ SEM. (E) Mean of left ventral tegmental area BOLD response $\pm$ SEM in originally 3 groups now split into “low-impulsive” and “high-impulsive” groups based on a median split relative to the mean factor 2 score of the full sample.

Table 1
Group demographics, cocaine use and in-scanner behavior

	Healthy subjects	Current cocaine user	Former cocaine user	Chi-Square/ ANOVA F value/ $P_{uncorrected}$ <0.05
Prospect/Anticipation Reward/Punishment				
Group N	47	42	35	--
Age (Years $\pm$ SD)	34.61 $\pm$ 9.02	38.52 $\pm$ 7.07	38.48 $\pm$ 7.58	3.44/0.035
Women	44%	42%	26%	1.99/ns
Outcome Punishment				
Group N	19	17	18	--
Age (Years $\pm$ SD)	32.58 $\pm$ 8.14	39.82 $\pm$ 6.20	41.11 $\pm$ 5.91	8.32/0.001
Women	36%	47%	22%	2.40/ns
Outcome Reward				
Group N	46	24	24	--
Age (Years $\pm$ SD)	34.70 $\pm$ 9.11	39.08 $\pm$ 6.81	39.38 $\pm$ 6.76	3.75/0.027
Women	41%	37%	29%	0.99/ns
Demographics for full sample				
Caucasians	81%	53%	51%	--
Education (Years $\pm$ SD)	16.46 $\pm$ 2.16	12.40 $\pm$ 1.45	13.34 $\pm$ 1.64	61.76/3.26e-19
Beck Depression Inventory II	4.05 $\pm$ 2.72	11.67 $\pm$ 9.28	9.25 $\pm$ 8.04	13.48/5.17e-6
WAIS-II Information	11.28 $\pm$ 1.85	8.97 $\pm$ 2.84	9.28 $\pm$ 3.54	9.18/1.93e-4
WAIS-II Block design	11.57 $\pm$ 3.17	9.21 $\pm$ 5.82	9.94 $\pm$ 3.08	3.63/0.029
Cocaine use information				
*Duration of use (Months $\pm$ SD)	N/A	402 $\pm$ 1408	143 $\pm$ 101	1.08/ns
*Amount used (Weeks $\pm$ SD, USD)	N/A	\$289 $\pm$ 350	\$699 $\pm$ 805	-2.83/0.007
*Abstinence duration (Months $\pm$ SD)	N/A	N/A	46 $\pm$ 73	--
Urine test for cocaine (pos/neg)	0/47	30/12	0/35	--
In-scanner behavior				
Mean RT Loss (ms)	297	333	390	1.22/ns
Mean RT Non-loss (ms)	250	270	273	1.22/ns
Mean RT Win (ms)	258	271	280	1.30/ns
Mean RT Non-win (ms)	298	326	367	1.30/ns
Hit rate Loss	31.52%	30.90%	36.36%	--
Hit rate Non-Loss	68.46%	69.04%	63.63%	--
Hit Rate Win	68.08%	70.86%	65.45%	--
Hit Rate Non-Win	31.91%	20.09%	34.54%	--
Total average earnings (USD)	25.40	27.54	20.11	1.39/ns

RT=reaction time; WAIS-II=Wechsler Adult Intelligence Scale II

* This is a self-reported measurement and thus represents a best possible approximation.