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Doubling down: increased risk-taking behavior following a loss by individuals with cocaine use disorder is associated with striatal and anterior cingulate dysfunction

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Abstract

Background—Cocaine use disorders (CUDs) have been associated with increased risk-taking behavior. Neuroimaging studies have suggested that altered activity in reward and decision-making circuitry may underlie cocaine user's heightened risk-taking. It remains unclear if this behavior is driven by greater reward salience, lack of appreciation of danger, or another deficit in risk-related processing.

Methods—Twenty-nine CUD participants and forty healthy comparison participants completed the Risky Gains Task during a functional magnetic resonance imaging scan. During the Risky Gains Task, participants choose between a safe option for a small, guaranteed monetary reward and risky options with larger rewards but also the chance to lose money. Frequency of risky choice overall and following a win versus a loss were compared. Neural activity during the decision and outcome phase were examined using linear mixed effects models.

Results—Although the groups did not differ in overall risk-taking frequency, the CUD group chose a risky option more often following a loss. Neuroimaging analyses revealed that the comparison group showed increasing activity in the bilateral ventral striatum as they chose higher-

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value, risky options, but the CUD group failed to show this increase. During the outcome phase, the CUD group showed a greater decrease in bilateral striatal activity relative to the comparison group when losing the large amount, and this response was correlated with risk-taking frequency after a loss.

Conclusions—The brains of CUD individuals are hypersensitive to losses, leading to increased risk-taking behaviors, and this may help explain why these individuals take drugs despite aversive outcomes.

Keywords

Cocaine dependence; neuroimaging; reward; striatum; fMRI; error signal

Introduction

Despite the risk of substantial negative legal, medical and psychosocial outcomes (1, 2), cocaine remains one of the most widely used illicit drugs in the United States and Europe (3). The National Epidemiologic Survey on Alcohol and Related Conditions showed that approximately one in five individuals who try cocaine will subsequently develop a cocaine use disorder (CUD; i.e., abuse or dependence) (4). Recent research has revealed individuals with CUDs are more likely than controls to make hasty decisions resulting in personal harm, and that this poor decision-making may be related to disruptions in striatal and frontal brain regions (5-8). Further, prenatal exposure to cocaine increases the likelihood that adolescent males will be high risk-takers (9), suggesting that cocaine may directly influence risk-taking behavior. It remains unclear if the differences in risk-taking among cocaine users relative to control groups result from an inappropriate assessment of the probability of negative outcomes, a lack of appreciation for the harm that may result from their decisions, or another risk processing deficit.

Risk-taking, according to the economic definition, is when an individual chooses an option with a greater level of uncertainty (10). Several studies have examined neural and behavioral differences between cocaine users and controls during risk-taking tasks (11). Behavioral evidence has been mixed, with some studies finding elevated risk-taking relative to controls among cocaine users in laboratory tasks (12-14), and some finding no difference or even reduced risk-taking (15). The mixed findings may reflect the heterogeneity of the tasks used to probe risky behavior, where some tasks focus on learning to avoid disadvantageous options, while others examine cognitive biases or attempt to disentangle uncertainty from value (16-18). One neuroimaging study compared a CUD group to a control group when choosing between options with varying degrees of certainty on a gambling task. Although the groups chose the risky options with a similar frequency, the CUD group showed greater activity in the lateral orbitofrontal cortex during risky decision-making, but reduced activity in the dorsolateral prefrontal cortex (PFC) (8). In another study, a cocaine-using group of poly-substance abusers showed reduced ventromedial PFC activity relative to a control group during risk-taking, yet similar levels of risk-taking (19). Substance dependent individuals who use cocaine also exhibited greater striatal activity and reduced dorsal anterior cingulate cortex (ACC) activity relative to a control group during risky decisions with the potential to earn money (20). In sum, the literature suggests altered processing of

risk in the PFC, ACC, and striatum in individuals with CUDs, but this suggestion is largely based on cocaine users who did not have a primary diagnosis of a CUD.

The present study assessed the neural correlates of risk-taking and examined behavioral differences between individuals with CUDs and healthy volunteers using the Risky Gains Task (RGT; 21) during functional magnetic resonance imaging (fMRI). The RGT allows participants to earn money by choosing between safe and risky options. Previous studies using this task have shown that it recruits insula and ACC activity (21, 22) and that stimulant users take risks more frequently than control groups (23-25). The goal of this study was to determine whether altered risk-taking is associated with cocaine misuse. We hypothesized that individuals with a CUD would make more risky decisions relative to a control group. We further hypothesized that the behavioral differences would be related to neural activity in the striatum and ventral frontal cortex.

Methods and Materials

Participants

Thirty-two participants (4 female) with a primary diagnosis of cocaine dependence were recruited through 28-day inpatient treatment programs at the San Diego Veterans Affairs Medical Center and Scripps Green Hospital (La Jolla, CA). All participants had ceased using cocaine for a median of 30 days prior to participation (range: 10-121) and were randomly screened for the presence of drugs throughout the programs. Semi-structured clinical interviews revealed that no subjects were experiencing symptoms of withdrawal during neuroimaging sessions. Four participants were excluded from the final sample because of poor neuroimaging data quality.

Forty healthy, age-matched control participants (14 female) were recruited through internet ads, fliers, and local newspapers in the San Diego area. Eligible control participants endorsed (1) no lifetime history of DSM-IV Axis I disorders; (2) no lifetime history of DSM-IV substance dependence; and (3) no current drug or alcohol related problems or intoxication as confirmed by toxicology screen. Participants were informed that the study was examining behavior and brain characteristics related to stimulant dependence. Written informed consent was obtained from all participants after study procedures were fully explained.

Lifetime DSM-IV Axis I diagnoses, including substance abuse and dependence, and Axis II diagnoses were assessed using the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) (26), which allows for quantification of lifetime drug use. Diagnoses were based on consensus meetings with a clinician specialized in substance use disorders and study personnel. The following were exclusion criteria for all groups: (1) anti-social personality disorder; (2) current (past 6 months) Axis I panic disorder, social phobia, post-traumatic stress disorder, major depressive disorder; (3) lifetime bipolar disorder, schizophrenia, and obsessive compulsive disorder; (4) current severe medical disorders requiring inpatient treatment or frequent medical visits; (5) use of medications that affect the hemodynamic response within the past 30 days (e.g., antihypertensives); (6) current positive

urine toxicology test; and (7) history of head injuries with loss of consciousness for longer than 5 minutes.

During evaluation, participants (32 CUD, 34 control) performed the North American Adult Reading Test (27) to provide a measure of verbal intelligence (VIQ). Three control participants performed the Wechsler Test of Adult Reading (28) to provide a VIQ index. Scores from both tests were transformed to create a standardized VIQ score. Three control participants performed neither test and have no index for VIQ.

Risky Gains Task

The RGT has been used in a number of prior studies (21, 25). A schematic (Supplemental Figure S1) and information about neuroimaging analysis of the task is provided in the Supplemental Materials. The goal of the RGT was to earn as much money as possible. Participants selected one of three options—20¢, 40¢, or 80¢—on each of 96 trials. Each option appeared on the screen for 1s in ascending order, and if the participant pressed the button when the option was shown, she received that amount. Participants were told 20¢ was the safe option (guaranteed gain of 20¢) and 40¢ and 80¢ were risky options (choosing 40¢ or 80¢ resulted in a chance of either gaining or losing 40¢ or 80¢, respectively). Thus, although participants could gain more money by waiting until the 40¢ or 80¢ options appeared, they also risked losing. All trials lasted 3.5s regardless of which option was chosen. The participant received feedback (sound and a stimulus on the screen) as soon as an option was chosen or a loss was incurred, and the visual feedback remained on the screen until the trial was over. Thus, if the participant planned to wait for the 80¢ option but lost at 40¢, she would not get to press the button for the 80¢ option. Participants were given no information about the probabilities of winning or losing, but the number of loss trials (–40¢ and –80¢) was set so that choosing the same option on each trial would earn the same final payment. That is, choosing 20¢ each trial garnered a total of \$19.20, as did choosing 40¢ or 80¢ on each trial, so choosing risky versus safe provided no inherent advantage. Subjects were not informed of how many choices they would make or how long the task would last.

Behavioral analysis

The frequency of safe and risky choices were dependent upon each other, because choosing safe on a given trial necessarily precluded choosing a risky option. Thus, to avoid violating the statistical assumption that observations are independent, a single variable, the frequency of high risk choices, was chosen as the dependent variable of interest. Frequencies for each group were compared using an independent t-test. Trials were counted as high-risk if the participant pressed the button during the 80¢ option or if the participant lost when trying for 80¢. Frequency of high risk choices was also compared as a function of previous outcome to determine if losing or winning affected rates of subsequent risk-taking. A two-way repeated measures ANOVA examined frequency of risky choices to test for a main effect of group (CUD, control), condition (post-win, post-loss), and a group-by-condition interaction.

fMRI group analysis

A linear mixed-effects (LME) analysis was conducted using R statistical software (www.cran.org, version 3.2.2) using the *nlme* package. The decision and outcome phases

were analyzed separately. For the decision phase, group (CUD, control) and decision (20, 40, 80) were fixed effects in the model and individual participants were treated as random effects. LME analysis examined the main effects of decision and group, as well as examining a group-by-decision interaction effect. For the outcome phase, LME analysis examined the main effects of outcome (−80, −40, +20, +40, +80) and group, as well as examining a group-by-outcome interaction effect. Analyses were performed voxel-wise across the entire brain and results were converted to AFNI's BRIK format and returned to AFNI software (29) for significance testing. To preserve family-wise error, a volume-threshold adjustment was made for significant activation based on the results of AFNI's 3dClustSim program. For the main effect of task, *a priori* significance of $p < .001$ in a volume of 4 voxels (256 μL) resulted in an *a posteriori* significance of $p < .01$. For the group-by-decision interaction, *a priori* significance of $p < .05$ in a volume of 9 voxels (576 μL) resulted in an *a posteriori* significance of $p < .05$. Although ideally the same model tested in the behavioral analysis would be tested (post-win versus post-loss risk-taking), the current task was not designed with adequate power based on the number of events of each type during the RGT.

A second analysis was restricted to a mask that included the striatum, insula, and ACC, regions chosen based on *a priori* hypotheses and established as active during the RGT. The mask was based on the Talairach Daemon atlas. A volume threshold adjustment for significant activation was performed based on the results of 3dClustSim (*a priori* two-tailed $p < .05$ cluster size thresholds: ACC: 384 μL , insula: 320 μL , striatum: 256 μL). Center-of-mass coordinates are reported in Talairach space (x, y, z) and labeled using Talairach Daemon software (30).

Exploratory analysis: robust regressions

To explore the implications of brain activation identified by LME analysis, Huber robust regressions (31) were performed in R software using the *robustbase* package. Robust regressions were used because they are less sensitive to outliers than traditional parametric methods. In just the CUD participants, frequency of risky choices following a loss was compared to PSC during a large loss (−80¢). Another regression examined the relationship between log-transformed number of lifetime cocaine uses and days since last cocaine use versus PSC during a risky choice. To examine the role of potential covariates, another Huber regression examined the relationship between PSC during a risky choice and alcoholic drinks per week, cigarettes smoked per day, verbal IQ, and age. Family-wise error was preserved using a volume-threshold adjustment, as described above in *fMRI group analysis*.

Results

Demographics

The CUD group was significantly older, had fewer years of education, and a lower verbal IQ than the control group (see Table 1). The mean IQ for the CUD group (103.8) was near the normative average of 100, whereas the mean IQ for the control group (112.1) was nearly a standard deviation above average. The CUD group smoked and used substances (e.g., marijuana, cocaine) significantly more than the control group ($p < .001$). To assess the

influence of demographic and clinical differences on the behavioral and neuroimaging results, these variables were examined as correlates of the primary dependent variables (i.e. risk-taking and neuroimaging signal).

Behavioral Data

There was no difference between groups for frequency of risky decisions ($p = .36$). However, when trials were analyzed by whether they followed a win or a loss, there was a group-by-condition interaction for frequency of risky decisions ($F_{1,65} = 4.3$, $p = .04$, partial $\eta^2 = .06$; Figure 1). After a loss, CUD participants were more likely than control subjects to choose a high risk option (CUD: $M = 0.36$, $SEM = 0.05$; Control: $M = 0.26$, $SEM = 0.04$). There was no difference in behavior between the groups after a win (CUD: $M = 0.30$, $SEM = 0.03$; Control: $M = 0.27$, $SEM = 0.03$). There was no significant correlation between risk-taking overall or risk-taking post-loss with age, verbal IQ, gender, alcoholic drinks per week, or cigarettes per day (all $ps > .05$).

Imaging Data

Decision main effect: whole brain analysis—Across both groups, participants showed greater activity in the bilateral anterior insula and right dorsal ACC as a proportion of risk (Supplemental Table S1). That is, participants showed the least activity for 20¢ decisions and the most for decisions to try for 80¢. As this has been reported in previous studies of this task (21), these results will not be considered further here.

Group by decision interaction: whole brain analysis—There was a significant group by decision-type interaction for activity in the right ventral striatum (see Figure 2). Specifically, the control group showed increasing activity in proportion to potential for higher value, but the CUD group failed to scale striatal activity with potential monetary value. The control group showed the highest activity for an 80¢ decision, whereas the CUD group showed similar activity for all decisions. A complete list of regions with a group-by-decision interaction is listed in Table 2.

Group by outcome interaction: whole brain analysis—There was a significant group by outcome interaction in the bilateral ventral striatum (see Figure 3). The CUD group showed a greater decrease in activity relative to the control group following a loss of 80¢. Both groups showed more activity after winning 80¢ relative to losing 80¢. A complete list of regions with a group-by-outcome interaction is listed in Table 3.

Group main effect for decision and outcome phase: whole brain analysis—For the decision phase, there were main effects of group in the middle temporal gyrus (see Supplemental Table S2). For the outcome phase, there were main effects of group in the middle and superior temporal gyri and several other regions (see Supplemental Table S3).

Exploratory analyses

Group by decision interaction: Region-of-interest analysis—There was a group by decision interaction in the left ventral striatum, where the control group showed increased activity during a decision for 80¢ but the CUD group did not. A group by decision

interaction in the dorsal anterior cingulate cortex revealed that the CUD group showed less activity during a safe choice, but greater activity during a risky choice. The control group showed the opposite pattern, with high activity during a safe choice but lower activity during a risky choice (Figure 2).

Brain-Behavior Relationships—Among CUD participants, greater frequency of risky choices post-loss was associated with lower ventral striatal activity during notification of a large loss (Figure 4).

Brain-Clinical Characteristics Relationships—Among participants with a CUD, there was a relationship between lifetime cocaine use and activity during a risky decision in a cluster centered in the right medial frontal gyrus that extended into the dorso-rostral ACC; individuals with higher numbers of lifetime cocaine uses had greater activity. Time since last use of cocaine and dorsal ACC activity during a risky decision were also related, where individuals who had been abstinent longer had more activity (see Supplemental Figure S2). There was no relationship between striatal or ACC activity with age, verbal IQ, cigarette use, or alcohol use.

Discussion

This investigation addressed the question whether individuals with CUD show risk-related neural processing differences. While CUD participants did not take more risks than control subjects overall, they were more likely to engage in high-risk options after experiencing a loss. The neuroimaging results altered processing of risky decisions among the CUD participants in the dorsal ACC and ventral striatum. Further, CUD participants had an exaggerated decrease in ventral striatal activity following a loss, which correlated with risk-taking behavior after a loss. ACC activity during risky decision-making correlated with cocaine use, suggesting that neural processing of risk may be directly related to substance use. These results are consistent with the hypothesis that altered neural processing of risk contributes to CUDs.

These results substantiate previous behavioral studies showing that stimulant using individuals display altered risk-taking behavior relative to controls (18, 23, 32). In other studies using the RGT, a non-dependent group of stimulant users chose a risky option more often than stimulant-naïve young adults, although they did not differ in risk-taking following a loss (23). However, methamphetamine-dependent individuals did not differ from a control group in overall risk-taking, but did take risks at a greater rate following a loss (25). In the present study, CUD participants increased their frequency of risk-taking following a loss, and this behavior pattern more closely resembles the methamphetamine-dependent group than non-dependent stimulant users.

Altered risk-taking among cocaine users could reflect a variety of deficits in risk processing. Since the individuals with CUDs did not take more risks overall, it suggests they did not differ from the control group in their probability assessment. Further, since they did not take more risks following a win, it suggests they were not more motivated by reward. This corroborates a previous study that showed that individuals with a CUD relative to controls

were less sensitive to gradients of monetary value, since over half of the cocaine abusers rated both \$10 and \$1,000 as a 9 out of 10 on a scale of subjective monetary value (33). The neural results showed that control participants had increasing striatal activity as they decided for options with the potential for higher gain, but the CUD participants failed to show this increase, further suggesting that they were not more motivated by value.

Instead, there are several plausible explanations for why CUD participants increased their risk-taking behavior following a loss. First, they may exhibit the gambler's fallacy (34) to a greater extent than controls, where they mistakenly believe that a loss on a given trial indicates that the likelihood of a loss on the next trial will be lower. Thus, CUD participants take a second risk because they discount the probability of losing twice. Alternatively, studies have shown that people will generally avoid risk when choosing between a sure gain of \$500 or a gamble with a 50% chance at winning \$1,000 and a 50% chance at winning \$0; however, if the choice is between a sure loss of \$500 or a gamble with a 50% chance of losing \$1,000 and a 50% chance of losing nothing, people generally prefer the gamble (35). In the context of this study, controls may view the decision as a gamble for a win regardless of whether they won or lost previously. The CUD participants, however, may frame their post-loss choices as a risk to offset a loss, thereby explaining their increase in risk-taking frequency. This is consistent with problematic cocaine use patterns, where individuals achieve a brief euphoric state through drug use, but after the reinforcing effects wear off they use again to regain their lost euphoria (36). Our results suggest that patterns of problematic cocaine use may reflect a general decision-making pattern of impulsively taking risks to compensate for a heightened aversion to loss.

One role of dopaminergic neurons that project from the ventral tegmental area to the ventral striatum is to predict the arrival of a reward (37-39). Whereas these neurons initially fire at the receipt of an unexpected reward, they eventually adapt to fire when a cue appears that predicts the reward's arrival. When the cue appears but the reward fails to arrive, these neurons' firing rates diminish; this has been interpreted as a signal of prediction error (40). The present results of reduced striatal activity by all participants following a high-value loss could reflect a signal of prediction error since participants expected to win when choosing the high-risk option. The CUD participants show substantially less activity relative to controls, potentially signifying greater prediction error. Further, the CUD participants with the least ventral striatal activity during a large loss were most likely to take a subsequent risk, further supporting the notion that sensitivity to loss may drive risk-taking. Combined with the striatal activity pattern from the decision phase, individuals with CUDs may ignore the possibility of a loss when choosing the high-risk option, but then experience greater distress when they lose, which motivates them to seek risk again.

A region-of-interest analysis also showed differences between groups in anterior cingulate cortex activity. Previous research has suggested that the dorsal anterior cingulate, which is commonly active in risk-taking tasks (41), integrates signals for pain, negative affect, and cognitive control via reciprocal connectivity with the ventral striatum, amygdala, and lateral columns of the periaqueductal gray (42). This could suggest that dorsal anterior cingulate activity signals danger, and would explain why control participants avoided risk when cingulate activity was high but chose risky options when activity was low. This might

suggest that for participants with CUDs, the dorsal ACC may fail to integrate immediate outcomes into a running prediction of what will happen for each option, which leads to repeatedly choosing options that have negative consequences.

This study has a number of limitations. This was a cross-sectional study, so this data cannot indicate whether neural differences preceded cocaine use, were caused by it, or whether a third factor caused both neural differences and susceptibility to CUD. Second, the participants with CUDs were recruited primarily through a Veterans Affairs hospital and may not represent individuals with CUDs in the general population. The RGT is not designed to temporally separate neural activity related to decisions versus outcome since there was no jitter between one phase and the next, which could be addressed in future studies. Similarly, while we were able to analyze the behavior as a function of previous outcome (post-win versus post-loss), the same analysis was not possible with the imaging data because there were not enough events of each type (e.g. post-loss 80¢ choice) to generate reliable regressors. This represents an opportunity for future studies to determine whether participants with CUDs show different neural activity relative to a control group during post-loss decision-making.

Finally, the clinical group differed from the control group on a number of factors, including age, gender, verbal IQ, smoking status. Although the study design attempted to control for these factors by recruiting participants based solely on their diagnosis, we cannot rule out that these factors contributed to the observed effects. Nonetheless, these factors were examined as potential covariates for the behavioral findings, but none were significant. Similarly, none of these factors were associated with striatal activity based on robust regressions. Although the groups differed with respect to proportion of females, the sample size was insufficient to perform a proper gender analysis. The RGT has not been previously studied with respect to gender, so it will be important for future studies to address the role of gender on risk-taking, especially as it relates to substance use. Based on these analyses, we believe the best interpretation of the behavioral and neural differences is that they are correlates of CUDs rather than a result of demographic differences between groups.

We have provided evidence that increased risk-taking following a loss and altered neural activity in the striatum and dorsal anterior cingulate during risky decision-making are correlates of CUDs. We interpret the findings as evidence that individuals with a CUD experience excessively reduced striatal activity following a loss that drives them to take further risks to regain their lost reward. Future research should determine whether these risk-taking differences could serve as clinically useful biomarkers. For example, altered risk-related processing may serve as a marker of relapse likelihood for individuals with CUDs who are seeking treatment, as has been seen for other stimulant use disorders (24, 43). These results contribute to our understanding of CUDs and suggest a mechanism that underlies this destructive disorder.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Participants with a cocaine use disorder (CUD) did not differ from controls in their frequency of choosing the 40 and 80 cent options in trials following a win. The CUD group did, however, select the 80 cent option more frequently than controls on trials following a loss. This suggests that CUD participants do not take more risks than controls overall, but take more risks specifically following a loss. Error bars represent standard error of the mean.

Figure 2.

The top panel shows a significant cluster from the whole-brain analysis of the decision-phase for the group-by-condition interaction contrast. The control group's activity in the right ventral striatum increased in proportion to value, where a safe decision (20¢) elicited the least and a high risk decision (80¢) elicited the most activity. The participants with a cocaine use disorder (CUD) failed to show an increase for the high risk decisions, possibly indicating failure to appreciate differences in monetary value. In the middle panel, the same pattern was observed in the left ventral striatum. This cluster was identified using a region-of-interest approach focusing on the striatum, insula, and anterior cingulate cortex. The bottom panel showed a significant group-by-decision interaction in the left dorsal anterior

cingulate, as identified in the region-of-interest analysis. In this cluster, control participants showed greater activity when they chose to avoid risk, but less activity when they chose a risky option. The CUD group showed increasing activity when they chose risky options. Error bars represent standard error of the mean.

Figure 3.

These graphs show a significant group-by-outcome interaction in the bilateral ventral striatum. The most pronounced difference appears in the processing of a large loss (−80¢). The participants with a cocaine use disorder shows a greater reduction in striatal activity during a large loss relative to the control group. This may represent a prediction error signal. Error bars represent standard error of the mean.

Figure 4.

This graph shows a significant relationship between frequency of risk-taking following a loss and neural activity during notification of a large loss in a cluster containing the ventral striatum and part of the subgenual anterior cingulate. This may suggest that prediction error signal from the striatum when a loss is experienced drives further risk-taking.

Table 1

Group Characteristics

	CUD (N=32)		CTL (N=40)		df	t/ χ^2	p
	Mean or n	SD or %	Mean or n	SD or %			
Demographics							
Age (in years)	44.21	9.16	35.60	11.58	66.44	3.44	.001
Education (in years)	13.52	1.99	14.93	1.67	67	-3.185	.002
Verbal IQ	103.79	10.24	112.08 [*]	9.47	63	-3.38	.001
Female	4	13.79%	14	35.00%	1	3.92	.048
Caucasian	7	21.88%	22	55.00%	1	6.57	.010
African American	17	53.13%	5	12.50%	1	16.47	<.001
Hispanic	4	12.50%	3	7.50%	1	.730	.393
Co-Morbid Diagnoses							
Regular Smoker Past Year	16	57.10	2	5.00	1	23.01	<.001
Alcohol Dependence	8	27.60	0	--	1	12.48	<.001
Lifetime Alcohol Abuse	14	43.75	10	25.00	1	.219	.640
Current Alcohol Abuse	8	25.00	2	5.00	1	2.33	.127
Cannabis Dependence	3	10.30	0	--	1	4.33	.038
Opioid Dependence	1	3.40	0	--	1	1.40	.237
Drug Use							
Lifetime Cocaine Use	15626.50	22027.07	6.00	8.65			
Lifetime Crack Use	14140.29	18103.48	--				
Lifetime Methamphetamine Use	1840.17	3241.97	4.50	.71			
Lifetime Cannabis Use	15101.20	22258.80	56.81	191.09			
Number of Alcoholic Drinks per Week	12.50	14.82	3.57	4.45			
Cigarettes per Day Past Year	13.69	5.44	.5 ^{**}	--			

Note: CUD = cocaine dependent subjects. CTL = healthy comparison subjects.

Lifetime Use = total number of individual sessions of drug use throughout lifetime.

n=36

^{**} One CTL subject was a regular smoker at a rate of approximately 20 cigarettes per week.

^{*} Equal variances not assumed.

Table 2

fMRI Results for Group-by-Decision interaction: whole brain analysis

Volume (μL)	x	y	z	L/R	Area	BA	F
1344	18	-97	-1	R	Cuneus	18	4.38
1280	10	13	0	R	Caudate	25	4.72
576	61	-27	-1	R	Middle Temporal Gyrus	21	4.33
576	-4	44	43	L	Superior Frontal Gyrus	8	4.60
576	32	-27	58	R	Precentral Gyrus	4	3.51

Note: Coordinates reflect center of mass.

Table 3

fMRI Results for Group by Outcome Interaction: whole brain analysis

Volume (μL)	x	y	z	L/R	Area	BA	F
3008	18	11	6	R	Lentiform Nucleus		3.45
2176	52	22	19	R	Inferior Frontal Gyrus	45	3.52
1600	-35	12	3	L	Insula	13	3.44
1536	55	3	27	R	Precentral Gyrus	6	3.61
1472	-19	10	3	L	Lentiform Nucleus		2.96
1344	-44	-5	41	L	Precentral Gyrus	6	2.83
1152	41	-4	43	R	Precentral Gyrus	6	3.10
960	62	-30	0	R	Middle Temporal Gyrus	21	2.90
896	-20	-71	37	L	Precuneus	7	3.48
768	-4	22	-15	L	Medial Frontal Gyrus	25	2.99
768	36	26	-7	R	Inferior Frontal Gyrus	47	2.91
768	5	-90	16	R	Cuneus	18	3.02
768	-8	54	31	L	Superior Frontal Gyrus	9	3.14
768	28	-75	31	R	Cuneus	19	2.88
768	37	4	49	R	Middle Frontal Gyrus	6	3.06
640	-12	-10	10	L	Thalamus		3.13

Note: Coordinates reflect center of mass.