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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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 magnetic resonance imaging monetary incentive delay task (MIDT) to investigate reward-loss neural response differences among 42 current cocaine users, 35 former cocaine users, and 47 healthy subjects who 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 activation pattern, except for loss outcome, where former compared with current cocaine users activated ventral tegmental area more robustly. We also found regional prefrontal activation differences during loss anticipation between cocaine-using groups. Both groups of cocaine users scored higher than control subjects on impulsivity, compulsivity and reward-punishment sensitivity factors. In addition, impulsivity-related factors correlated positively with activation in amygdala and negatively with anterior cingulate activation during loss anticipation.

Conclusions: Compared with healthy subjects, both former and current users displayed abnormal brain activation patterns during MIDT performance. Both cocaine groups differed similarly from healthy subjects, but differences between former and current users were localized to the ventral tegmental area 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 users suggest that these tendencies and relationships may pre-exist cocaine addiction.

Key Words: Addiction, cocaine, impulsivity, monetary incentive delay task, monetary loss, monetary reward

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 allostatis (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 nonaddicted adults report diverse rewards processing activations in the nucleus accumbens, ventral tegmental area, amygdala, insula, orbitofrontal cortex, anterior cingulate and dorsolateral prefrontal cortices, hippocampus/parahippocampal 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 control subjects 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), blood oxygen level–dependent (BOLD) responses during reward processing in substance abuse/dependence have been associated with poor cognitive control, impulsive/

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compulsive behavior, and novelty seeking, factors that may signify 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 functional magnetic resonance imaging (fMRI) MIDT (31) to quantify brain activation during prospect, anticipation, and outcome 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 preselected 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 preselected 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); and 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 those 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 predrug functional status in the former users.

Methods and Materials

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 the 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 advertisements, and outpatient drug treatment programs. All participants provided informed written consent approved by Hartford Hospital and Yale University Institutional Review Boards.

A time line followback questionnaire (36) was used to quantify drug consumption amounts. Current and former cocaine users either currently or formerly (respectively) met criteria for DSM-

Table 1. Group Demographics, Cocaine Use, and In-Scanner Behavior

	Healthy Subjects	Current Cocaine Users	Former Cocaine Users	Chi-Square/ANOVA F Value/$p_{uncorrected} < .05$
Prospect/Anticipation Reward/Punishment				
Group *n*	47	42	35	–
Age (years ± SD)	34.61 ± 9.02	38.52 ± 7.07	38.48 ± 7.58	3.44/.035
Women	44%	42%	26%	1.99/ns
Outcome Punishment				
Group *n*	19	17	18	–
Age (years ± SD)	32.58 ± 8.14	39.82 ± 6.20	41.11 ± 5.91	8.32/.001
Women	36%	47%	22%	2.40/ns
Outcome Reward				
Group *n*	46	24	24	–
Age (years ± SD)	34.70 ± 9.11	39.08 ± 6.81	39.38 ± 6.76	3.75/.027
Women	41%	37%	29%	.99/ns
Demographics for Full Sample				
Caucasians	81%	53%	51%	–
Education (years ± SD)	16.46 ± 2.16	12.40 ± 1.45	13.34 ± 1.64	61.76/3.26e-19
Beck Depression Inventory II	4.05 ± 2.72	11.67 ± 9.28	9.25 ± 8.04	13.48/5.17e-6
WAIS-II information	11.28 ± 1.85	8.97 ± 2.84	9.28 ± 3.54	9.18/1.93e-4
WAIS-II block design	11.57 ± 3.17	9.21 ± 5.82	9.94 ± 3.08	3.63/.029
Cocaine Use Information				
Duration of use (months ± SD)[a]	NA	402 ± 1408	143 ± 101	1.08/ns
Amount used (weeks ± SD, USD)[a]	NA	$289 ± 350	$699 ± 805	−2.83/.007
Abstinence duration (months ± SD)[a]	NA	NA	46±73	–
Urine test for cocaine (positive/negative)	0/47	30/12	0/35	–
In-Scanner Behavior				
Mean RT loss (msec)	297	333	390	1.22/ns
Mean RT nonloss (msec)	250	270	273	1.22/ns
Mean RT win (msec)	258	271	280	1.30/ns
Mean RT nonwin (msec)	298	326	367	1.30/ns
Hit rate loss	31.52%	30.90%	36.36%	–
Hit rate nonloss	68.46%	69.04%	63.63%	–
Hit rate win	68.08%	70.86%	65.45%	–
Hit rate nonwin	31.91%	20.09%	34.54%	–
Total average earnings (USD)	$25.40	$27.54	$20.11	1.39/ns

ANOVA, analysis of variance; NA, not applicable; ns, nonsignificant; RT, reaction time; USD, United States dollars; WAIS-II, Wechsler Adult Intelligence Scale II.

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