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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 users' 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 40 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 phases was 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 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, Error signal, fMRI, Neuroimaging, Reward, Striatum

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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 that individuals with CUDs are more likely than control subjects 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 male individuals 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 control subjects during risk-taking tasks (11). Behavioral evidence has been mixed, with some studies finding elevated risk taking relative to control subjects 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 with 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 (8). In another study, a cocaine-using group of polysubstance abusers showed reduced ventromedial prefrontal cortex activity relative to a control group during risk-taking yet similar levels of risk-taking (19). Substance-dependent individuals who used 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 prefrontal cortex, 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. 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 (four females) 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 before participation (range: 10–121) and were randomly screened for the presence of drugs throughout the programs. Semistructured 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 participants) 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 (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) antisocial personality disorder; 2) current (past 6 months) Axis I panic disorder, social phobia, posttraumatic stress disorder, and 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 within the past 30 days that affect the hemodynamic response (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 subjects) 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 had 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 are provided in the Supplement. The goal of the RGT was to earn as much money as possible. Participants selected one of three options—$0.20, $0.40, or $0.80—on each of 96 trials. Each option appeared on the screen for 1 second in ascending order, and if the participant pressed the button when the option was shown, she received that amount. Participants were told $0.20 was the safe option (guaranteed gain of $0.20) and $0.40 and $0.80 were risky options (choosing $0.40 or $0.80 resulted in a chance of either gaining or losing $0.40 or $0.80, respectively). Thus, although participants could gain more money by waiting until the $0.40 or $0.80 options appeared, they also risked losing. All trials lasted 3.5 seconds 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 $0.80 option but lost at $0.40, she would not get to press the button for the $0.80 option. Participants were given no information about the probabilities of winning or losing, but the number of loss trials (−$0.40 and −$0.80) was set so that choosing the same option on each trial would earn the same final payment. That is, choosing $0.20 on each trial garnered a total of $19.20, as did choosing $0.40 or $0.80 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 frequencies 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