Published in final edited form as:

Behav Neurosci. 2010 August ; 124(4): 470–477. doi:10.1037/a0020458.

Self-Administered Cocaine Causes Long-Lasting Increases in Impulsive Choice in a Delay Discounting Task

Ian A. Mendez,

Department of Psychology, Texas A&M University

Nicholas W. Simon,

Department of Psychology, Texas A&M University

Nigel Hart,

Department of Psychology, Texas A&M University

Marci R. Mitchell,

Department of Psychology, Texas A&M University

Jack R. Nation,

Department of Psychology, Texas A&M University

Paul J. Wellman, and

Department of Psychology and Faculty of Neuroscience, Texas A&M University

Barry Setlow

Department of Psychology and Faculty of Neuroscience, Texas A&M University

Abstract

Cocaine use is associated with high levels of impulsive choice (preference for immediate over delayed rewards), but it is not clear whether cocaine use causes elevated impulsive choice, or whether elevated impulsive choice is solely a predisposing factor for cocaine use. This study examined the effects of prior cocaine self-administration on rats performing a delay discounting task commonly used to measure impulsive choice. Male Long-Evans rats were implanted with intravenous catheters, and following recovery, were trained to self-administer 30 mg/kg/day cocaine HCl (approx. 0.5 mg/kg/infusion) for 14 consecutive days (a control group received yoked intravenous saline infusions). Following three weeks of withdrawal, all rats were food-restricted and began training on the delay discounting task in standard operant chambers. On each trial, rats were given a choice between two levers. A press on one lever delivered a small food reward immediately, and a press on the other delivered a large food reward after a variable delay period. Rats that self-administered cocaine displayed greater impulsive choice (enhanced preference for the small immediate over the large delayed reward, as reflected by shorter indifference points) compared to controls, but were no different from controls on a “probabilistic discounting” task in which they chose between small certain and large uncertain rewards. These data suggest that self-administered cocaine can cause lasting elevations in impulsive choice, and that the high levels of impulsive choice observed in human cocaine users may be due in part to long-term effects of cocaine on brain function.

Keywords

cocaine; impulsivity; delay discounting; choice; addiction

Alterations in decision-making processes have been reported in users of a range of addictive drugs, including heroin, nicotine, alcohol, and cocaine (Kalivas & Duffy, 1989; Bechara, 2005; Reynolds, 2006; de Wit, 2009). Such decision-making deficits are particularly evident in laboratory tests of temporal, or delay discounting in which subjects choose between rewards of different magnitudes that are available after different delays (e.g., choices between a small immediate vs. a large delayed reward). All individuals decrease their preference for the large reward as the delay to its delivery increases (i.e., the delay discounts the subjective value of the large reward), and this pattern of decision-making is often referred to as “impulsive choice” (Rachlin & Green, 1972; Ainslie, 1975). However, the rate at which this preference decreases is steeper in drug-users compared to control subjects (Vuchinich & Simpson, 1998; Mitchell, 1999; Coffey, Gudleski, Saladin, & Brady, 2003; Kirby & Petry, 2004; Reynolds, 2006).

Despite considerable evidence for the existence of elevated impulsive choice in drug users, it is difficult to determine whether this elevation is caused by preexisting elevations in impulsive choice that render individuals more likely to initiate or continue drug use (e.g., by increasing choice of the immediate rewards of drug use over the delayed, presumably larger rewards associated with abstinence) or by the effects of chronic drug use itself on brain function (Dawes, Tarter, & Kirisci, 1997; Bickel, Odum, & Madden, 1999; Monterosso, Ehrman, Napier, O’Brien, & Childress, 2001; Kirby & Petry, 2004; Bechara, 2005; Garavan & Stout, 2005; Heil, Johnson, Higgins, & Bickel, 2006; de Wit, 2009). Such distinctions are possible in animal models, however, which have provided evidence for both accounts (Richards, Sabol, & de Wit, 1999; Dallery & Locey, 2005; Mitchell, Reeves, Li, & Phillips, 2006; Diergaarde et al., 2008—see Perry & Carroll, 2008) for recent review. These data are particularly strong in the case of cocaine, for which there is evidence that animals displaying high levels of impulsive choice acquire and escalate self-administration more rapidly than low impulsive choice cohorts (Perry, Larson, German, Madden, & Carroll, 2005; Anker, Perry, Gliddon, & Carroll, 2009). There is also considerable evidence that chronic cocaine exposure in animals can cause long-lasting elevations in impulsive choice, suggesting that cocaine itself may play a causal role in the elevated impulsive choice observed in users of this drug (Logue et al., 1992; Paine, Dringenberg, & Olmstead, 2003; Roesch, Takahashi, Gugs, Bissonette, & Schoenbaum, 2007; Simon, Mendez, & Setlow, 2007; Anker, Zlebnik, Gliddon, & Carroll, 2009; Dandy & Gatch, 2009; see Setlow, Mendez, Mitchell, & Simon, 2009 for review). However, with one exception, animals in these studies were exposed to cocaine passively (i.e., through experimenter-administered injections). Self-administration, usually intravenous, is considered to be the best currently available model of human patterns of drug use, and self-administered cocaine can have strikingly different effects than experimenter-administered cocaine on several behavioral and neurobiological outcomes (McFarland, Lapish, & Kalivas, 2003; Miguens et al., 2008). It is therefore important to determine whether self-administered cocaine causes lasting elevations in impulsive choice similar to those observed with experimenter-administered cocaine.

The primary goal of this study was to determine how chronic self-administered cocaine affects impulsive choice, using an experimental design identical to that shown previously to be sensitive to the effects of experimenter-administered cocaine (Simon et al., 2007) to allow direct comparison between the two routes of administration. Based on our previous findings, we expected that self-administered cocaine would increase impulsive choice. An additional goal of this study was to determine how this same cocaine self-administration regimen affects performance in another decision-making task designed to assess decision-making under conditions of uncertainty, the “probabilistic discounting” task.

Methods

Subjects

The subjects were 20 male Long-Evans rats weighing 250–275 g upon arrival (Charles River Laboratories, Raleigh, NC). Rats were housed individually in a climate-controlled vivarium (25°C) in the Department of Psychology at Texas A&M University. Rats had food and water available ad lib (except as noted below) and were tested during the light cycle of a 12-hour light/dark schedule (lights on 0800–2000). All animal procedures were conducted according to the “Principles of Laboratory Animal Care” (National Academy of Sciences) and met all NIH and institutional animal care and use guidelines. Rats were allowed to acclimate to vivarium conditions for at least one week after arrival before procedures began.

Apparatus

Cocaine self-administration—Cocaine self-administration was conducted in 12 identical standard rat test chambers (30.5 × 25.4 × 30.5 cm, Coulbourn Instruments, Whitehall, PA) housed in sound-attenuating cubicles. Each chamber was equipped with two response levers and a stimulus light located above each lever. Twenty ml syringes mounted on infusion pumps (Razel Scientific Instruments; Stamford, CT) were used for i.v. drug delivery to rats in each test chamber. The system was interfaced with two computers, each running custom-made software to control drug delivery and record data from six of the chambers.

Delay and probabilistic discounting tasks—Testing in the discounting tasks was conducted in eight identical standard rat test chambers (30.5 × 25.4 × 30.5 cm, Coulbourn Instruments, Whitehall, PA) with metal front and back walls, transparent Plexiglas side walls, and a floor composed of steel rods (0.4 cm in diameter) spaced 1.1 cm apart. Each test chamber was housed in a sound attenuating cubicle, and equipped with a recessed food pellet delivery trough fitted with a photobeam to detect head entries and a 1.12 W lamp to illuminate the food trough. This trough, into which the 45 mg grain-based food pellet rewards (PJAI, Test Diet; Richmond, IN) were delivered, was located 2 cm above the floor in the center of the front wall. Two retractable levers were located to the left and right of the food delivery trough, 11 cm above the floor. Experiments were controlled, and data were collected, by a computer interfaced with the behavioral test chambers and equipped with Graphic State 3.01 software (Coulbourn Instruments).

Surgical Procedures

Rats were anesthetized using a combination of ketamine (80 mg/kg) and xylazine (20 mg/kg). Using sterile techniques, a catheter consisting of 0.51-mm ID Silastic tubing (coated with heparin to minimize occlusion) was inserted into the right jugular vein and sutured to muscle tissue in the area of the vein. The catheter was passed subcutaneously through the body using an 11-ga stainless steel tube as a guide, and attached to a back mount cannula connector pedestal (Plastics One, Roanoke, VA). This plastic pedestal consisted of a threaded cylindrical top on a base molded around a stainless steel tube that projected upward, and was passed through a small incision in the skin over the scapulae. Rats were allowed at least 7 days of recovery from surgery prior to commencing cocaine self-administration. During this recovery period, antibiotic ointment was applied to the incision sites, and the catheters were infused daily with 0.1 ml of a sterile saline solution containing heparin (1.25 U/μl) and ampicillin (200 mg/ml) to prevent infection and the formation of clots and fibroids (Nation, Smith, & Bratton, 2004; Wellman, Nation, & Davis, 2007).

Behavioral Procedures

Cocaine self-administration—During self-administration sessions, the back mount cannula connector accommodated a spring leash, through which the catheter was threaded. Attaching to the cannula connector at one end, the other end of the leash was connected to a single fluid channel swivel. The swivel design permitted an interlock with a connecting arm located above the behavioral test chamber. The arm allowed for free movement and delivery of intravenous cocaine or saline vehicle solutions in the test chamber. A catheter ran from the top of the fluid swivel to the syringe mounted on the infusion pump.

Self-administration was conducted using a master-yoke design, such that each “master” rat that underwent i.v. cocaine self-administration procedures had a “yoked” rat run simultaneously that received i.v. infusions of saline on the same schedule. For the master (cocaine) rats, only the left lever was active, such that a press resulted in delivery of 0.16 ml of cocaine solution (0.5 mg/kg/infusion) delivered over 6 seconds. A press of the right lever for the master rats and a press of either lever for the yoked rats had no programmed consequences. During these self-administration shaping sessions cocaine rats were food-restricted to 15 g of food per day, which resulted in a decrease in body weight to 85% of free-feeding weight. This food restriction procedure was used to motivate acquisition of cocaine self-administration (Campbell & Carroll, 2001; Campbell, Morgan, & Carroll, 2002; Nation et al., 2004). Self-administration began with shaping sessions in which food paste (standard rat chow and water) was placed on the active lever and used to train master rats to lever press for drug delivery on an FR1 schedule. Initially, rats were shaped in 2-hr daily sessions until a criterion of 30 lever presses was met. A second shaping stage required rats to meet a criterion of 60 lever presses on an FR2 schedule during a 2-hr session. Once criterion for the second shaping stage was achieved, cocaine rats were returned to free feeding and began self-administration sessions, which were also set on an FR2 delivery schedule. During each of these 14 sessions, rats were allowed to self-administer a total of 60 infusions. A session ended (for both the master and yoked rat) when this 60 infusion limit (total of 30 mg/kg cocaine) was reached. This dose and procedure were chosen to mimic, as closely as possible in a self-administration setting, the dose of experimenter-administered cocaine we found previously to cause long-lasting increases in impulsive choice in the delay discounting task (Simon et al., 2007). Following the last self-administration session, rats remained in their home cages undisturbed for 3 weeks (with ad lib food and water), followed by commencement of the delay discounting task.

Delay discounting task—The procedures for the delay discounting task have been described previously (Evenden & Ryan, 1996; Simon et al., 2007). Prior to the start of behavioral testing, rats were reduced to 85% of their free-feeding weight over the course of 1 week, and were maintained as such throughout the duration of the delay discounting task. In order to maintain the rats at 85% of their free feeding weight during the task, rats were limited to 15 g of food per day (in addition to their food rewards earned during the task).

On the day before the start of behavioral testing, each rat was given five 45 mg food pellets in its home cage to reduce neophobia to the food reward used in the task. The task began with a 64 min session of magazine training consisting of 38 deliveries of a single food pellet with an intertrial interval (ITI) of 100 ± 40 s. On the following day, rats were shaped to press a single lever (either left or right, counterbalanced across groups; the other was retracted during this phase of training) in order to receive a single food pellet. Once they reached a criterion of 50 lever presses during a 30-min session, they were shaped to press the opposite lever using the same schedule and criterion.

Following completion of lever press shaping, both levers were retracted, and rats were shaped to nose poke into the food trough during simultaneous illumination of the trough light and a 1.12 W house light. When a nose poke occurred, a single lever was extended, and a lever press

resulted in immediate delivery of a single food pellet. Immediately following the lever press, the house and trough lights were extinguished and the lever was retracted. The left and right levers were presented an equal number of times, with no more than two consecutive presentations of the same lever. Rats were trained to a criterion of at least 60 successful trials in an hour with an ITI of 40 ± 10 s, after which testing on the delay discounting task began.

Each session in the delay discounting task consisted of 5 blocks of 12 trials each. Within each session, each of the 100-s trials began with a 10-s illumination of the food trough and house lights. A nose poke into the food trough during this time extinguished the food trough light and triggered extension of either a single lever (forced trials) or of both levers simultaneously (choice trials). Trials on which rats failed to nosepoke during this time window were scored as omissions. A press on one lever (either left or right, counterbalanced across groups) resulted in delivery of a single food pellet immediately following the lever press. A press on the other lever resulted in delivery of four food pellets after varying delays. Levers remained extended for 10 s, and failures to press either lever within this window were scored as omissions. Once either lever was pressed, both levers were retracted and the house light was extinguished until food delivery. Food delivery was accompanied by reillumination of both lights, which were again extinguished upon entry to the food trough for food collection or after 10 s, whichever occurred sooner. Each of the five 12-trial blocks in a session began with two forced trials (one for each lever), followed by 10 choice trials. During the first 12-trial block, the delay to the large reward was set at 0 s. In subsequent 12-trial blocks, the delay to the large reward increased to 10, 20, 40, and 60 s. Because trials were of fixed duration, reward choice did not influence the rapidity of progress through the trials (i.e., choice of the small immediate reward did not result in more or sooner choice opportunities). Thus, choice of the large delayed reward was, from an objective perspective, an “optimal” choice, as it resulted in more food delivery over the course of a session.

The percentage of trials on which rats chose the large reward lever (number of large reward lever choices/total responses) was calculated for each block as an indicator of reward preference (Simon et al., 2010; Simon et al., 2007). Rats were tested in the delay discounting task for 40 daily sessions, at which point stable responding was observed across the final 5 sessions (36–40). Stable responding was defined by the absence of a main effect or interaction involving session in a repeated measures analysis of variance (ANOVA), accompanied by a significant main effect of trial block (Cardinal, Robbins, & Everitt, 2000; Simon et al., 2007).

Probabilistic discounting task—Immediately after completion of the delay discounting task, the rats were tested in an additional decision-making task designed to determine the degree to which probability of reward omission discounted reward value (Cardinal & Howes, 2005; Floresco & Whelan, 2009). The parameters of this task were similar to the delay discounting task, except that the large reward was reduced to 3 food pellets and the sessions were 60 min in duration and consisted of 8 forced choice trials (to allow complete sampling of the reward probabilities in each block) followed by 10 free choice trials. During the first block of trials, the large reward was delivered with 100% probability. During each of the four subsequent blocks, the probability of large reward delivery was systematically decreased (75, 50, 25, 0%). There were no delays associated with either reward. Rats were tested in this task for 15 daily sessions, at which point stable responding was observed across the final 5 sessions (11–15).

Data Analyses

Comparison of self-administration across sessions was conducted using a paired *t* test. Analyses of stable performance in the decision-making tasks were conducted using a two-factor repeated measures ANOVA (trial block $\times$ test session). Stable performance was defined as a main effect of trial block with no main effects or interactions involving test session.

Comparisons between drug groups in the delay and probabilistic discounting tasks were conducted using two-factor repeated measures ANOVA (drug condition $\times$ trial block). Indifference point (the point at which the large reward was chosen 50% of the time) in the delay discounting task was calculated for each subject using a linear regression model constructed from the data points across the 5 trial blocks, and subsequently compared using an unpaired t test (Diller, Saunders, & Anderson, 2008; Winstanley, Dalley, Theobald, & Robbins, 2004). Relationships between self-administration during the 1st hour of the session (number of infusions earned), performance in the delay discounting task, and performance in the probabilistic discounting task were evaluated using bivariate Pearson's correlations. For all analyses, p values less than .05 were considered significant.

Results

Two rats in the yoked saline control group died prior to or during behavioral testing, and their data were excluded from analysis.

Cocaine self-administration

Because the self-administration sessions consisted of a fixed number of cocaine infusions, changes in the total number of infusions/session across sessions could not be evaluated. However, the number of infusions earned in the first hour of Sessions 1 and 14 was recorded to determine whether the rats displayed any evidence of an escalated rate of cocaine self-administration (Ahmed & Koob, 1998). Although the mean number of infusions earned in the first hour did increase from Session 1 (12.9) to Session 14 (17.6), this difference did not reach statistical significance (paired t test, $t_{(8)} = 1.32$, ns).

Delay discounting

Rats required between 4 and 8 sessions to complete the shaping protocol for the delay discounting task, with cocaine and yoked saline control rats requiring similar numbers of sessions (cocaine = 5.70, yoked = 5.63, $t_{(16)} = .08$, ns). Furthermore, both the cocaine and yoked groups of rats achieved stable responding across the last 5 sessions of testing in the delay discounting task (Sessions 36–40), represented by a main effect of trial block ($F_s > 36.72$, $ps < .01$), but no main effects or interactions involving session ($F_s < 1.79$, ns). A further comparison between the two groups of performance across the last 20 sessions using a three-factor ANOVA (Session $\times$ trial block $\times$ drug condition) revealed no interactions involving drug condition ($F_s < 1.20$, ns), suggesting that cocaine self-administration did not alter the rate at which rats achieved stable performance in the delay discounting task. One rat in the cocaine group omitted a large number of choice trials in the delay discounting task (26.4% omissions, which was >2 SD outside the group mean of 5.2%), and his data were excluded from all subsequent analyses. There were otherwise no group differences in number of omissions, either with or without this rat included ($ts < .73$, ns).

Data collapsed across Sessions 36–40 in the delay discounting task (during which stable performance was observed; Cardinal et al., 2000; Simon et al., 2007) are shown in Figure 1A, and suggested that preference for the large reward decreased as the delay to its delivery increased (i.e., the delay discounted the value of the large reward), and that such discounting was greater in the cocaine self-administration group. An ANOVA revealed a main effect of trial block, such that large reward preference declined significantly with increasing delays, $F_{(4, 60)} = 83.12$, $p < .01$, but the main effect of drug condition did not quite reach significance, $F_{(1, 15)} = 3.92$, $p = .07$, nor was there a significant interaction between trial block and drug condition, $F_{(4, 60)} = 1.44$, ns . As an additional measure of performance on the delay discounting task we calculated indifference points for each animal (the delay at which there is 50% preference for the large reward). A t test comparing these indifference points revealed that the

cocaine self-administration group had a significantly lower indifference point than the saline control group, $t_{(16)} = 2.30$, $p < .05$, providing evidence for significantly greater discounting of delayed rewards in the cocaine group (Figure 1B). In our previous work, we observed that chronic cocaine-treated rats spent significantly less time performing nose pokes into the food trough during the delay periods prior to food delivery, suggesting possible decreased anticipation of reward delivery (Simon et al., 2007); however, there was neither a main effect nor interaction involving drug condition on this measure in the current experiment, $F_s < .70$, *ns*.

Probabilistic discounting

Because of its similarity to the delay discounting task, no additional shaping was needed for rats to acquire the probabilistic discounting task. Both cocaine and yoked groups achieved stable responding across the last 5 sessions (11–15) of testing in the probabilistic discounting task, represented by a lack of main effect or interaction involving session ($F_s < 1.24$, *ns*), and a main effect of trial block ($F_s > 59.18$, $p_s < .01$). Data collapsed across Sessions 11–15 are shown in Figure 2. Rats appeared to reduce their preference for the large reward as its probability of omission increased (i.e., the value of the large reward was discounted by decreasing probabilities of its delivery), but there were no apparent differences between drug conditions. This impression was confirmed by the results of a two-factor ANOVA, in which there was a main effect of trial block, such that rats' preference for the large reward declined as the probability of its delivery decreased, $F_{(4, 68)} = 72.69$, $p < .01$, but no main effect or interactions involving drug condition ($F_s > .58$, *ns*).

Correlations among measures

There were no significant Pearson's correlations among any of the measures of cocaine self-administration (number of infusions during the first hour of self-administration Sessions 1 and 14, and percent change in this number), and performance on the delay or probabilistic discounting tasks ($r_s < .64$, *ns*).

Discussion

Results from this study show that self-administered cocaine can cause a long-lasting (at least 3 months) increase in preference for small immediate over large delayed rewards (increased impulsive choice). These observations are similar to findings in human cocaine users, suggesting that the increased impulsive choice in this population may be due, at least in part, to lasting effects of the cocaine itself (Heil et al., 2006; Kirby & Petry, 2004; Monterosso et al., 2001). The results of this study are also consistent with previous work in rodents showing that chronic experimenter-administered cocaine can cause elevated impulsive choice, and in combination with our previous findings using experimenter-administered cocaine (Simon et al., 2007), they suggest that the route of administration is less of a critical factor than the amount of cocaine intake (Dandy & Gatch, 2009; Setlow et al., 2009). A recent paper by Anker, Zlebnik et al. (2009) reported that prior cocaine self-administration experience caused an increase in impulsive choice in a delay discounting task when rats were tested immediately following cocaine cessation (this effect was specific to a subset of rats that displayed low levels of impulsive choice prior to cocaine experience). The present results extend these findings by showing that self-administered cocaine-induced elevations in impulsive choice can persist several months after cocaine cessation.

It is important to note that cocaine's effects in the present study were not likely due to altered acquisition of the delay discounting task. Not only was there no effect of cocaine self-administration experience on the number of sessions required to learn the task, but two studies have now shown that rats pretrained in the delay discounting task prior to chronic cocaine

administration still show elevated impulsive choice during withdrawal (Anker, Zlebnik et al., 2009; Dandy & Gatch, 2009). Additionally, the effects of cocaine did not appear to result from changes in reward magnitude detection or motivation to obtain rewards, as cocaine rats chose the large reward at the same rate as yoked controls during the first block of trials in which there was no delay. It is possible that the elevated impulsive choice in cocaine rats was due to effects on time perception; indeed, a recent study identified some degree of impaired timing in cocaine/methamphetamine users (Wittmann, Leland, Churan, & Paulus, 2007). Future studies will determine whether chronic cocaine in this model causes alterations in time perception.

A novel finding of this study was that cocaine self-administration did not affect choice behavior in the probabilistic discounting task, which was similar in structure to the delay discounting task, but in which the value of the large reward was “discounted” by decreasing probability of its delivery across trial blocks. These findings suggest a dissociation between the effects of chronic cocaine on probabilistic and delay discounting in rats, which is supported by findings in human cocaine users showing no correlation between performance on delay and probabilistic decision-making tasks (Monterosso et al., 2001), as well as by data in rats showing no correlations between performance on these two tasks (Simon, Gilbert, Mayse, Bizon, & Setlow, 2009). Furthermore, the dissociation between the effects of chronic cocaine in these two tasks suggests that the elevated impulsive choice in the delay discounting task was due primarily to cocaine’s effects on factors specific to temporal decision-making, rather than on general factors such as increases in incentive motivation, changes in sensitivity to reward magnitude, or discriminative ability, although it is possible that the longer withdrawal time at which rats were tested in the probabilistic discounting task may have reduced cocaine’s effects (Deroche, Le Moal, & Piazza, 1999; Klein, Gehrke, Green, Zentall, & Bardo, 2007; Mendez et al., 2008; Roesch et al., 2007). Interestingly, the opposite pattern of effects in these two decision-making tasks has been observed following several weeks of withdrawal from chronic experimenter-administered amphetamine, which has no effect on delay discounting but increases choice of the large uncertain reward in the probabilistic discounting task (Floresco & Whelan, 2009; Stanis, Marquez Avila, White, & Gulley, 2008)—note that although increases in impulsive choice have been observed during chronic amphetamine administration, these effects do not endure for more than a few days of withdrawal (Gipson & Bardo, 2009). Although the mechanism of this apparent double dissociation between the effects of chronic cocaine and amphetamine is not clear, it is consistent with other evidence for dissociations between cognitive disruptions produced by exposure to these two drugs, as well as with evidence for different neural substrates for delay and probabilistic discounting performance (Cardinal, 2006; Floresco, St Onge, Ghods-Sharifi, & Winstanley, 2008).

Anker, Perry et al. (2009) recently showed that rats with preexisting high levels of impulsive choice displayed greater escalation of cocaine self-administration than low-impulsive cohorts. In the current experiment, there was no significant escalation of cocaine self-administration during the 1st hour of the sessions (Mantsch, Yuferov, Mathieu-Kia, Ho, & Kreek, 2004), although the self-administration protocol used (a fixed number of infusions) may not have been optimal for observing such escalation. This lack of escalation may explain why no relationships were observed between changes in cocaine self-administration patterns and impulsive choice in the delay discounting task. It remains to be seen whether variations in self-administered cocaine intake result in different effects on impulsive choice, although there is some evidence for a dose-dependent effect of experimenter-administered cocaine on impulsive choice (Dandy & Gatch, 2009).

A network of cortico-basal ganglia structures (including prefrontal cortex, ventral striatum, amygdala, and subthalamic nucleus) is involved in discounting of delayed rewards (Cardinal, 2006; Floresco et al., 2008; Hariri et al., 2006; McClure, Laibson, Lowenstein, & Cohen, 2004; Uslaner & Robinson, 2006; Winstanley, Theobald, Cardinal, & Robbins, 2004). Chronic

cocaine administration has been shown in animal studies to cause long-lasting neuroadaptations within these structures (Ferrario et al., 2005; Kalivas & Volkow, 2005; Nestler, 2004; Winstanley et al., 2007), and thus it is likely that such alterations may account for cocaine's lasting effects on impulsive choice observed here and by others (Anker, Zlebnik et al., 2009; Simon et al., 2007; Stalnaker, Takahashi, Roesch, & Schoenbaum, 2009). It is not clear which of these neuroadaptations might be critical for cocaine-induced changes in impulsive choice, but it is possible that they involve dysregulation of dopamine signaling, as a) this neurotransmitter system strongly modulates impulsive choice (Cardinal et al., 2000; van Gaalen, van Koten, Schoffelmeer, & Vanderschuren, 2006); b) chronic cocaine causes alterations in dopamine neurotransmission within structures implicated in discounting of delayed rewards (Goto & Grace, 2005; Kalivas & Duffy, 1989; Little, Patel, Clark, & Butts, 1996); and c) the ability of drugs acting on the dopaminergic system to modulate impulsive choice is altered following chronic cocaine administration (Setlow et al., 2009; Winstanley et al., 2007). Further work is necessary, however, to determine the causal links between cocaine-induced neuroadaptations and increases in impulsive choice.

Acknowledgments

We thank the Drug Supply Program at NIDA for kindly providing cocaine HCl, Dr. Aaron Taylor for statistical consultation, and Colin Vokes for technical assistance. Supported by MH65728 (I. A. M., N. H.), DA023331 (N. W. S.), DA013188 (P. J. W., J. R. N.), and DA024671 (B. S.) from the National Institutes of Health. This paper is dedicated to the memory of our colleague, mentor, and friend, Dr. Jack R. Nation, who passed away before the experiments were completed.

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Figure 1.

Effects of prior cocaine self-administration on performance in the delay discounting task. A) Preference for the large delayed reward decreased as a function of delay in both groups. B) In the delay discounting task, there was a significant decrease in the indifference points of the cocaine rats compared to yoked saline controls. * $p < .05$.

Figure 2. Effects of prior cocaine self-administration on performance in the probabilistic discounting task. Rats that self-administered cocaine did not differ from yoked saline controls.