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Intake-dependent effects of cocaine self-administration on impulsive choice in a delay discounting task

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Abstract

Cocaine use is associated with high levels of impulsive choice (greater discounting of delayed rewards) in humans, but the cause/effect relationships between cocaine use and impulsive choice are not fully understood. In previous work, we found that both experimenter- and self-administration of fixed quantities of cocaine caused lasting increases in impulsive choice in rats. The present study extended these findings by taking into account baseline impulsive choice prior to self-administration, and by allowing rats free access to cocaine. Male Long-Evans rats were trained in a delay discounting task in which they made discrete-trial choices between small immediate and large delayed food rewards. Half of the rats were then implanted with intravenous catheters and, following recovery, allowed to self-administer cocaine HCl (1.0 mg/kg/infusion) in 6 hour sessions over 14 days. Control rats orally self-administered a sucrose solution under similar conditions. Upon completion of self-administration training, rats remained abstinent for 3 weeks before retesting in the delay discounting task. Cocaine and control groups did not differ prior to self-administration, but afterward, the cocaine group showed greater impulsive choice (fewer choices of large, delayed rewards) than controls. Additional analyses revealed that the effects of cocaine on impulsive choice were intake-dependent; rats classified as “low intake” did not differ from controls, whereas rats classified as “high intake” were significantly more impulsive than both controls and their pre-cocaine baseline. These findings are consistent with the idea that cocaine-induced, pharmacologically based neural adaptations promote the development of impulsive decision making.

Keywords

Decision-making; impulsivity; cocaine; delay discounting; intertemporal choice; rat

Introduction

Cocaine users present with a range of neurocognitive deficits including prominent elevations in impulsivity. For example, cocaine-dependent patients show reliably greater impulsive choice in delay discounting tasks (i.e. greater preference for smaller, sooner rewards over larger, but delayed rewards) as well as greater impulsive action as measured by the Stop-Signal task (i.e. an inability to inhibit a prepotent response) than non-users (Bickel and Marsch, 2001, Fillmore and Rush, 2002, Coffey et al., 2003, Heil et al., 2006, Li et al., 2006, Colzato et al., 2007, Johnson, 2012, Moreno-Lopez et al., 2012). Importantly, impulsivity associated with cocaine use is evident even after protracted abstinence. For example, Heil et al. (2006) investigated impulsive choice using a delay discounting procedure and showed that there were no differences in impulsive choice between cocaine-abstinent and cocaine-dependent individuals, but that both of these groups were significantly more impulsive than control participants. These results suggest that greater impulsive choice in cocaine users does not solely depend on active cocaine use; however it is unclear if greater impulsive choice in these individuals is a preexisting condition or an enduring consequence of cocaine use.

Animal models have been used effectively to parse the cause-effect relationships between impulsivity and cocaine use. Using such models, several research groups have shown that in rats, high levels of both impulsive action and impulsive choice predict subsequent acquisition and escalation of cocaine self-administration (SA) (Perry et al., 2005, Dalley et al., 2007, Anker et al., 2009, Broos et al., 2012), suggesting that impulsivity could be a pre-disposing factor for human cocaine use. The effects of chronic cocaine on impulsivity in animal models have been less consistent. Chronic cocaine regimens (either experimenter- or self-administered) have been reported to increase, decrease, or have no effect on impulsive action in the stop-signal or 5-choice serial reaction time tasks (Paine et al., 2003, Dalley et al., 2005, Winstanley et al., 2009, Caprioli et al., 2013). In contrast, a preponderance of evidence suggests that these same cocaine regimens cause lasting increases in impulsive choice ((Paine et al., 2003, Winstanley et al., 2007, Anker et al., 2009, Dandy and Gatch, 2009, Zuo et al., 2012)– see (Setlow et al., 2009) for review). For example, previous work from our laboratory (Simon et al., 2007) showed that 14 days of i.p. cocaine administration (30 mg/kg/day) resulted in elevated preference for smaller immediate over larger, delayed rewards compared to vehicle-administered controls. This effect was evident 3 months after cocaine cessation, suggesting that cocaine exposure can cause long-lasting increases in impulsive choice. A follow-up experiment employing intravenous cocaine SA procedures yielded similar results. In this study, rats that self-administered 30 mg/kg/day cocaine for 14 days showed greater preference for small, immediate over large, delayed food rewards 3 months later, in comparison to control rats that received yoked saline infusions ((Mendez et al., 2010) – see also (Anker et al., 2009)).

The present study was designed to extend these prior findings in several ways. First, rats were pre-trained on the delay discounting task prior to SA, to provide a baseline measure of impulsive choice and to determine whether this index of trait impulsivity predicted cocaine SA. Second, rats were provided unlimited access to cocaine during 6 h sessions (without restrictions on the maximum number of infusions), to determine whether the amount of cocaine intake is a significant factor in altering impulsive choice. Third, control rats orally self-administered a sucrose solution, in order to control for possible effects of new instrumental learning *per se* on impulsive choice. Fourth, the response required for cocaine (or sucrose) SA (i.e., a nosepoke) differed from that required for food delivery in the delay discounting task (i.e., a lever press), in order to preempt response generalization across the two tasks.

Methods

Subjects

Male Long-Evans rats (n=36, weighing 275–300 g on arrival; Charles River Laboratories, Raleigh, NC) were individually housed and kept on a 12h light/dark cycle (lights on at 0700 hours) with free access to food and water except as noted. During behavioral testing in the delay discounting task, rats were maintained at 85% of their free-feeding weight, with allowances for growth. During cocaine or sucrose SA sessions, rats were fed 30 g of food/day (note that rats had free access to food and water in the week before and after surgery). All animal procedures were conducted from 0900–1800 during the light cycle (lights on 0700 – 1900) and were approved by the University of Florida Institutional Animal Care and Use Committee and followed NIH and APA guidelines.

Delay Discounting Apparatus

The delay discounting task was conducted in standard behavioral test chambers (Coulbourn Instruments, Whitehall, PA) housed within sound-attenuating isolation cubicles. Each chamber was 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, which was located 2 cm above the floor in the center of the front wall. Forty-five mg grain-based food pellets (PJAI, Test Diet, Richmond, IN) could be delivered into the food trough. Two retractable levers were located to the left and right of the food trough, 11 cm above the floor. A 1.12 W house light was mounted on the rear wall of the isolation cubicle. Locomotor activity was assessed throughout each session with an infrared activity monitor mounted on the ceiling of the test chamber. This monitor consisted of an array of infrared (body heat) detectors focused over the entire chamber. Movement in the chamber (in x, y, or z planes) was defined as a relative change in the infrared energy falling on the different detectors in the array. Test chambers were interfaced with a computer running Graphic State software (Coulbourn Instruments), which controlled programmed events and data collection.

Implantation of Intravenous Jugular Catheters

Rats were anesthetized using isoflurane gas. Using sterile techniques, a catheter was inserted into the right jugular vein and sutured to muscle tissue in the area of the vein. The catheter was then passed subcutaneously over the shoulder and attached to a back mounted cannula

connector pedestal. 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 5 days of recovery from surgery prior to commencing cocaine SA. During this recovery period, antibiotic ointment was applied to the incision sites, and catheters were flushed daily with heparinized saline and for the first seven days with an antibiotic solution to prevent occlusions (Nation et al., 2004, Wellman et al., 2007). Catheters were tested weekly for patency using an IV infusion of 0.1 ml propofol, which causes rapid but transient loss of muscle tone.

Self-Administration Apparatus

Self-administration procedures were conducted in 12 identical standard rat test chambers (30.5 × 25.4 × 30.5 cm, Coulbourn Instruments, Whitehall, PA) housed in sound-attenuating cubicles. These chambers were located in a separate room from that used for testing in the delay discounting task. Each chamber was equipped with two nosepoke holes located on the left and right side of the front wall, and which could be illuminated with a light located inside the hole. Twenty-ml syringes mounted on infusion pumps were used for IV drug delivery to rats in each test chamber. The syringes were connected via PE50 tubing to a fluid swivel and from there to a fluid line which mated to the back mounted connector pedestal. Each chamber was also equipped with a liquid dipper trough located in the center of the front wall. The chambers were interfaced with a computer running Graphic State software to control drug delivery and record data from each of the chambers. During SA sessions, only one of the two nosepoke holes (the “active” hole) was illuminated (the left/right position of the illuminated hole remained constant across all sessions).

Behavioral Procedures

Rats were tested in the behavioral procedures in the order in which they are described below in two separate cohorts, each with both cocaine and sucrose SA groups.

Shaping—Shaping procedures for the delay discounting task followed those used previously (Cardinal et al., 2000, Simon et al., 2007, Simon et al., 2009). Following training to respond at the food trough upon food delivery, rats were trained to press a single lever (either the left or right; the other lever was retracted during this phase of training) to receive a single food pellet. After reaching a criterion of 50 lever presses in 30 min, rats were then trained on the opposite lever to the same criterion. This was followed by further shaping sessions in which both levers were retracted and rats were trained to nose poke into the food trough during simultaneous illumination of the trough and house lights. When a nose poke occurred, a single lever was extended (left or right, pseudorandomly determined, such that each lever was presented once in every two-trial block), and a lever press resulted in immediate delivery of a single food pellet. Immediately following the lever press, the trough light was extinguished and the lever was retracted. Rats were trained to a criterion of 30 presses on each lever within 60 min.

Delay discounting task—A detailed description of this task is provided in (Mendez et al., 2010, Mitchell et al., 2012). Each 60-min session consisted of 5 blocks of 12 trials each. Each 60-s trial 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-choice trials) or of both levers simultaneously (free-choice trials). Trials on which rats failed to nose-poke during this 10-s window were scored as omissions. Each block consisted of 2 forced-choice trials followed by 10 free-choice trials. A press on one lever (either left or right, counterbalanced across subjects) resulted in one food pellet (the small reward) delivered immediately. A press on the other lever resulted in three food pellets (the large reward) delivered after a variable delay. Failure to press either lever within 10 s of their extension resulted in the levers being retracted and lights extinguished, and the trial was scored as an omission. Once either lever was pressed, both levers were retracted for the remainder of the trial. The delay duration increased between each block of trials (0, 4, 8, 16, 32 s), but remained constant within each block (Evenden and Ryan, 1996, Cardinal et al., 2000, Winstanley et al., 2003, Simon et al., 2007). In addition, the identity of the two levers (small and large reward) remained fixed across sessions. Following training to stability in the delay discounting task, rats were returned to ad lib feeding and divided into two groups (cocaine and sucrose SA), equated for baseline levels of impulsive choice.

Cocaine Self-Administration Group—Rats in the cocaine SA group (n=18) underwent surgery, followed by at least 5 days of recovery prior to beginning SA procedures. During cocaine SA sessions, nosepokes into the illuminated (active) nosepoke hole were reinforced on a fixed ratio 1 (FR1) schedule by delivery of cocaine HCl (1.0 mg/kg/infusion, Drug Supply Program, NIDA) in a volume of 0.16 ml over 6 s followed by a 20 s timeout period. Nosepokes at the non-illuminated (inactive) nosepoke hole were recorded but had no programmed consequences. The left/right positions of the active and inactive nosepoke holes were counterbalanced in relation to the left/right position of the large reward levers used in the delay discounting task, such that half the rats that had the large reward on the left side in the delay discounting task had the active nosepoke hole on the left, and half had it on the right (and the same for rats that had the large reward on the right on the delay discounting task). Cocaine SA sessions lasted for 6 h/d for 14 d.

Sucrose Self-Administration Group—Each rat in the sucrose SA control group (n=18) was matched to a cocaine SA rat based on baseline delay discounting performance (i.e. rats with similar discounting curves were paired together). Sucrose SA rats were trained to nosepoke on a FR1 schedule to obtain access to 40 μ l of a 20% sucrose solution via the liquid dipper on a schedule such that the number of sucrose reinforcers allowed to be earned by each rat was matched to the number earned by its partnered cocaine rat for each SA session (for example, if a cocaine rat received 30 cocaine infusions in a session, then its sucrose partner was allowed to self-administer only 30 sucrose deliveries in its session on that day). This procedure was designed to equate instrumental conditioning and number of reinforcer deliveries across the two groups for each of the 14 days of training.

Reassessment of Delay discounting Performance—Following 14 days of cocaine or sucrose SA, rats were left undisturbed in their home cages for 3 weeks to ensure drug washout before returning to the delay discounting task for retesting for an additional 20 sessions, at which point stable performance was evident.

Data Analysis

Raw data files were exported from Graphic State software and compiled using a custom macro written for Microsoft Excel (Dr. Jonathan Lifshitz, University of Kentucky). Statistical analyses were conducted in SPSS 20. To assess stability of performance in the delay discounting task, repeated measures ANOVAs were conducted on group data across 5 consecutive sessions. Stable performance was defined by the absence of a main effect of session, the absence of an interaction between session and delay, and the presence of a main effect of delay. Baseline locomotor activity in these tasks was measured by averaging activity (in arbitrary units) across all inter-trial interval (ITI) segments, in which no lights or levers were present. In all cases, p values less than 0.05 were considered significant, and error bars represent SEMs.

Results

Rats achieved stable performance in the delay discounting task in 25–30 sessions and were then assigned to cocaine or sucrose SA groups, matched for choice performance. Prior to SA experience, there were no differences in choice of the large, delayed reward between rats assigned to the cocaine and sucrose groups (two-factor ANOVA (group $\times$ delay), main effect of delay, $F_{(1, 34)} = 113.85$, $p < 0.001$; main effect of group, $F_{(1, 34)} = 0.17$, $p = 0.69$; group $\times$ delay interaction, $F_{(4, 136)} = 0.67$, $p = 0.62$; Figure 1A).

Following SA procedures, rats were returned to their home cages and were left undisturbed. After 3 weeks, they were again food restricted and retested in the delay discounting task for an additional 20 daily sessions. Final delay discounting performance was recorded during the last 5 test sessions (sessions 16–20, following a total of 6 weeks of abstinence from cocaine or sucrose SA) by which point performance was stable. A two-factor ANOVA (group $\times$ delay) conducted on data averaged across sessions 16–20 revealed significantly greater impulsive choice in the cocaine SA group compared to the sucrose SA group, particularly at longer delays (main effect of group, $F_{(1, 34)} = 3.01$, $p = 0.09$; main effect of delay, $F_{(4, 136)} = 133.95$, $p < 0.002$; group $\times$ delay interaction, $F_{(4, 136)} = 3.12$, $p = 0.02$; Figure 1B).

A primary goal of this experiment was to determine whether cumulative cocaine intake modulated the drug's effects on subsequent delay discounting. There was only a modest and non-significant correlation between cumulative cocaine intake and mean post-SA impulsive choice (Spearman's $\rho = -0.37$, $p = 0.13$); however, this comparison does not take into account potential interactions with delay or the sucrose SA control condition. To incorporate these variables into the analysis, rats in the cocaine SA group (along with their respective sucrose SA controls) were divided by median split into high ($n = 9$) and low ($n = 9$) cocaine intake groups. Mean cumulative cocaine intake was greater in the high intake group (mean $\pm$ SEM; 432 ± 191 mg) compared to the low intake group (51 ± 21 mg), although this difference did not quite reach statistical significance ($t_{(16)} = 2.10$, $p = 0.052$), likely because of the greater variance in the high intake group. A four-factor ANOVA (pre/post timepoint $\times$ cocaine/sucrose group $\times$ high/low intake $\times$ delay) revealed a main effect of pre/post timepoint, such that, across groups, rats showed significantly greater impulsive choice after SA compared to before ($F_{(1, 32)} = 27.44$, $p < 0.001$). In addition, there was an interaction

between pre/post timepoint and group, such that group differences in impulsive choice were greater post-SA than pre-SA ($F_{(1, 32)} = 4.81, p = 0.04$; compare Figures 1A and 1B). Post hoc comparisons revealed that despite the presence of a significant interaction between group and delay at the post-SA timepoint (Figure 1B; see above for statistical results), none of the differences reached significance at any of the delays. As an additional assessment of the effects of SA experience, we compared impulsive choice pre- vs. post-SA within each SA group. In the cocaine group, there were significant main effects of pre/post timepoint ($F_{(1, 17)} = 44.33, p < 0.001$), delay ($F_{(4, 68)} = 66.50, p < 0.001$) and a significant interaction between these two variables ($F_{(4, 69)} = 9.72, p < 0.001$). In the sucrose group, there was a significant main effect of delay ($F_{(4, 68)} = 73.00, p < 0.001$) and a significant interaction between delay and pre/post timepoint ($F_{(4, 69)} = 4.83, p = 0.002$), but the main effect of pre/post timepoint did not reach significance ($F_{(1, 17)} = 2.54, p = 0.13$). See Supplementary Materials for comparisons of pre- and post-SA performance on the same graphs.

The most important result to emerge from this four-factor ANOVA was a significant three-way interaction between pre/post timepoint, group, and high/low intake, suggesting that the effects of SA on the change in impulsive choice from pre- to post-SA differed as a function of intake ($F_{(1, 32)} = 7.91, p = 0.008$). To further investigate the sources of this interaction, follow-up comparisons were conducted separately in low and high cocaine intake rats (and their respective matched sucrose SA controls) using two- and three-factor ANOVAs. In low intake rats, impulsive choice increased from pre- to post-SA, but there were no main effects or interactions involving SA group, indicating that low cocaine intake had no effect on impulsive choice relative to low sucrose intake (main effect of delay, $F_{(4, 64)} = 54.88, p < 0.001$; main effect of pre/post timepoint, $F_{(1, 16)} = 27.29, p < 0.001$; main effect of group, $F_{(1, 16)} = 0.21, p = 0.66$; pre/post timepoint $\times$ delay interaction, $F_{(4, 64)} = 11.56, p < 0.001$; pre/post timepoint $\times$ group, $F_{(1, 16)} = 0.24, p = 0.63$; delay $\times$ group, $F_{(6, 64)} = 0.60, p = 0.66$; pre/post timepoint $\times$ delay $\times$ cocaine/sucrose group, $F_{(4, 64)} = 0.14, p = 0.97$; Figures 2A and 2B). Follow-up two-factor ANOVAs comparing pre- and post-SA timepoints in low intake rats within each group (see Supplementary Materials) revealed significant changes from pre- to post-SA in both the sucrose SA (main effect of delay, $F_{(4, 32)} = 30.63, p < 0.001$; main effect of pre/post timepoint, $F_{(1, 8)} = 12.12, p = 0.008$; pre/post timepoint $\times$ delay interaction, $F_{(4, 32)} = 8.26, p < 0.001$) and cocaine SA groups (main effect of delay, $F_{(4, 32)} = 25.79, p < 0.001$; main effect of pre/post timepoint, $F_{(1, 32)} = 17.17, p = 0.003$; pre/post timepoint $\times$ delay interaction, $F_{(4, 32)} = 4.53, p = 0.005$).

The same analyses conducted in high intake rats also revealed an increase in impulsive choice post-SA relative to pre-SA (main effect of delay, $F_{(4, 64)} = 78.99, p < 0.001$; main effect of pre/post timepoint, $F_{(1, 16)} = 6.34, p = 0.02$, pre/post timepoint $\times$ delay interaction, $F_{(4, 64)} = 5.21, p < 0.001$); however, unlike in low intake rats, there was a significant interaction between pre/post timepoint and group, indicating that the difference between cocaine and sucrose SA groups was greater at the post-SA compared to the pre-SA timepoint (pre/post timepoint $\times$ group interaction, $F_{(1, 16)} = 10.33, p = 0.005$; Figures 2C and 2D; in addition, main effect of group, $F_{(1, 16)} = 1.41, p = 0.25$; delay $\times$ group interaction, $F_{(4, 64)} = 1.575, p = 0.19$; pre/post timepoint $\times$ group $\times$ delay interaction, $F_{(4, 64)} = 3.34, p = 0.015$). Further comparisons within high intake rats at each timepoint confirmed these

effects, revealing no differences between groups pre-SA (two-factor ANOVA, group x delay, $F_s < 0.26$, $p_s > 0.90$; Figure 2C), but greater impulsive choice in the cocaine group compared to the sucrose control group post-SA, particularly at long delays (main effect of delay, $F_{(4, 64)} = 62.21$, $p < 0.001$; main effect of group, $F_{(1, 16)} = 4.40$, $p = 0.05$; group x delay interaction, $F_{(4, 64)} = 3.22$, $p = 0.02$, Figure 2D). Post-hoc comparisons between groups at each delay revealed a significant difference between groups only at the 8 s delay ($t_{(16)} = 2.27$, $p = 0.04$; Figure 2D). Follow-up two-factor ANOVAs comparing pre- and post-SA timepoints in high intake rats within each group (see Supplementary Materials) revealed no change from pre- to post-SA in the sucrose SA group (main effect of delay, $F_{(4, 32)} = 39.84$, $p < 0.001$; main effect of pre/post timepoint, $F_{(1, 8)} = 0.17$, $p = 0.69$; pre/post timepoint x delay interaction, $F_{(4, 32)} = 0.51$, $p = 0.73$) but a robust increase in impulsive choice from pre- to post-SA in the cocaine group (main effect of delay, $F_{(4, 32)} = 40.57$, $p < 0.001$; main effect of pre/post timepoint, $F_{(1, 32)} = 29.69$, $p = 0.001$; pre/post timepoint x delay interaction, $F_{(4, 32)} = 7.14$, $p < 0.001$). Post-hoc comparisons between pre/post timepoints at each delay in the high intake cocaine group revealed significant differences between timepoints at all but the 0 s delay ($t_{(8)} > 2.90$, $p_s < 0.02$).

Interestingly, despite the fact that impulsive choice was significantly increased following (high intake) cocaine SA, choice of the large, delayed reward in the delay discounting task pre- and post-SA was significantly (or near-significantly) correlated in all four groups, demonstrating the stability of performance on the delay discounting task across time (cocaine high intake: $r=0.89$; cocaine low intake: $r=0.94$; sucrose high intake: $r=0.61$; sucrose low intake: $r=0.80$; all $p_s < 0.01$ except for sucrose high intake group, $p = 0.08$).

In contrast to the effects of high cocaine intake on subsequent impulsive choice, there appeared to be no relationship between impulsive choice prior to SA and subsequent cocaine intake (Figure 3A). This relationship was assessed in three ways. First, a two-factor ANOVA (group X delay) comparing pre-SA impulsive choice in the high and low intake cocaine groups (designated as in Figure 2) revealed no main effects or interactions involving group (main effect of delay, $F_{(4, 64)} = 34.04$, $p < 0.001$; main effect of group, $F_{(1, 16)} = 0.39$, $p = 0.54$; group x delay interaction, $F_{(4, 64)} = 0.45$, $p = 0.77$). Similarly, there was no correlation between pre-SA impulsive choice (mean % choice of the large reward averaged across all 5 blocks of trials) and total cocaine intake (Spearman's $\rho = -0.25$, $p = 0.32$). Finally, a median split of the cocaine SA group based on pre-SA impulsive choice revealed no difference in cocaine intake between rats classified as having high and low pre-SA impulsive choice (two-factor ANOVA (group x self-administration session), main effect of session, $F_{(13, 208)} = 0.61$, $p = 0.84$; main effect of group, $F_{(1, 16)} = 0.59$, $p = 0.45$; group x delay interaction, $F_{(13, 208)} = 0.75$, $p = 0.71$; Figure 3B). In combination, these analyses indicate the absence of relationships between pre-SA, baseline levels of impulsive choice and cocaine intake in this cohort.

There were no differences in ITI locomotor activity during the delay discounting task between rats in the sucrose or cocaine SA groups (Table 1), either pre- or post-SA (pre: $t_{(34)} = 0.56$, $p = 0.58$; post: $t_{(34)} = 1.17$, $p = 0.25$). Locomotor activity did decrease from pre- to post-SA across all rats; however, this decrease was not modulated by group or intake factors (3-factor ANOVA (pre/post timepoint x group x high/low intake) main effect of pre/post

timepoint: $F_{(1,32)} = 9.73, p = 0.004$; pre/post x group: $F_{(1,32)} = 0.12, p = 0.73$, pre/post x intake: $F_{(1,32)} = 1.89, p = 0.18$, pre/post x group x intake: $F_{(1,32)} = 0.33, p = 0.57$). In addition, there were no correlations between pre- or post-SA locomotion and cumulative cocaine intake (Spearman's rho, pre = $-0.10, p = 0.71$.; post = $0.07, p = 0.78$). The numbers of omitted choice trials did not differ between groups, either as a function of drug or intake condition ($t_s < 1.90, p_s > 0.08$; Table 1).

Discussion

The goal of this study was to investigate potential bi-directional relationships between delay discounting (impulsive choice) and intravenous cocaine self-administration. There was no evidence that baseline (pre-drug) impulsive choice predicted subsequent cocaine intake; however, consistent with previous findings (Logue et al., 1992, Paine et al., 2003, Simon et al., 2007, Anker et al., 2009, Dandy and Gatch, 2009, Mendez et al., 2010, Zuo et al., 2012), cocaine SA caused an increase in impulsive choice which was present as long as 40 days post-cocaine and only present in rats with higher levels of cocaine intake. These data provide further evidence that cocaine administration can cause alterations in cognitive function – specifically an increase in impulsivity – and suggest that elevated impulsive choice in human cocaine users does not solely reflect differences in trait impulsivity.

The present findings of increased impulsive choice following cocaine SA are consistent with those from studies of human subjects, in which users of cocaine and other drugs of abuse display greater impulsive choice than non-users in decisions involving both hypothetical and actual drug and natural rewards (Madden et al., 1997, Bickel et al., 1999, Coffey et al., 2003, Kirby and Petry, 2004, Heil et al., 2006, Reynolds, 2006, Perry and Carroll, 2008, Bradford, 2010, Ersche et al., 2010). In addition, there is some evidence that the magnitude of cognitive deficits in cocaine users is associated with duration of cocaine use (which likely reflects cumulative intake - e.g., (Goldstein et al., 2004, Verdejo-Garcia and Perez-Garcia, 2007, Madoz-Gurpide et al., 2011, Fernandez-Serrano et al., 2012, Torres et al., 2013)). In combination with the present data showing increased impulsive choice only in high intake rats, these findings suggest that there is a threshold for cocaine's effects on impulsive choice, below which the drug may have little or no effect. Interestingly, similar intake-dependent effects were observed by Broos et al. (2012), who found that among rats displaying low baseline levels of impulsive choice, only those that self-administered more than 30 mg/kg/day cocaine became more impulsive. In contrast to the present findings, however, this increased impulsivity was only evident during the SA period, and returned to baseline after cessation of SA. The reasons for these different effects on impulsive choice of similar levels of cocaine intake are not clear. One possibility is that the effects of cocaine on impulsive choice require an "incubation period" such that they become more pronounced after several weeks of abstinence (e.g., Grimm et al., 2001), although there were also numerous methodological differences between the current study and that of Broos et al. (2012). Future experiments which systematically vary and compare cocaine intake variables will be useful for resolving this issue.

In human subjects, it is likely that some portion of the elevated impulsive choice in cocaine users can be attributed to a pre-existing condition (which could be expected to predispose

those individuals to drug use). There is limited evidence for such a contribution of pre-existing impulsive choice to subsequent drug use (e.g., (Audrain-McGovern et al., 2009)); however, because of the number of potentially confounding variables, such effects are difficult to identify unambiguously in human subjects. Fortunately, animal studies have provided clear evidence that individual differences in impulsive choice predict various measures of propensity for cocaine SA. For example, higher levels of impulsive choice can predict more rapid acquisition and escalation of cocaine SA (Perry et al., 2005, Anker et al., 2009), as well as greater persistence of cocaine seeking during extinction (Broos et al., 2012). Similar effects have been observed with other drugs of abuse (e.g., (Diergaarde et al., 2008, Marusich and Bardo, 2009)). No such relationships were observed in the present study (i.e., high and low cocaine intake rats did not differ in pre-existing levels of impulsive choice, and there were no relationships between measures of pre-existing impulsive choice and cocaine intake). The cocaine SA procedures employed, however, were designed to be comparable with cocaine administration parameters used previously in our laboratory (Simon et al., 2007, Mendez et al., 2010) rather than to maximize sensitivity to individual differences (e.g., by using low doses of cocaine under short-access conditions (Perry et al., 2005, Perry et al., 2007, Hu and Becker, 2008, Perry et al., 2008, Zhao and Becker, 2010)).

A previous study from our laboratory (Mendez et al., 2010) showed that impulsive choice was greater in rats with a history of cocaine SA compared to yoked intravenous saline administration. The present study expanded upon this prior work by dissecting the influence of baseline impulsive choice and of the pharmacological and conditioning factors associated with cocaine SA on delay discounting performance. First, training rats in the delay discounting task prior to SA (unlike in (Mendez et al., 2010)), allowed comparisons of the effects of cocaine SA not only to controls, but also to pre-SA baseline conditions. The fact that after SA, high intake rats in the cocaine group differed both from their baseline and their respective controls provides additional evidence that increased impulsive choice is related at least in part to the pharmacological effects of cocaine. Second, the use of the sucrose control group which had a similar behavioral history (i.e., operant responding for the same number of reinforcers) rules out the possibility that the increased impulsive choice in the cocaine SA group was due solely to the additional learning experience provided by cocaine SA. It should be noted that the cocaine SA group underwent catheter surgery as well, whereas the sucrose SA group did not. Stress and anesthetic exposure related to surgery may alter decision making processes, including delay discounting (Shafiei et al., 2012, Kimura et al., 2013). Importantly, however, the control group in the Mendez et al. (2010) study underwent catheter surgery, suggesting that surgical stress alone is not sufficient to increase impulsive choice. The fact that the low intake cocaine group in the present study also did not show increased impulsive choice provides further support for this contention. Third, the use of a different instrumental response during SA (nosepoking for cocaine or sucrose vs. lever pressing for food in the delay discounting task) helps to rule out the possibility that learning the instrumental response in one task interacted with learning or performance in the other. Finally, it is important to note that the cocaine-induced increase in impulsive choice was not likely due to a gross inability to discriminate between the large and small rewards. The cocaine SA group showed normal (near 100%) choice of the large reward at the 0 s delay, indicating intact reward preference. In addition, we have recently found that cocaine induces

the opposite effect on reward choice in rats tested in another decision making task (the Risky Decision-making Task). This task is very similar in design to the delay discounting task, except that the “cost” of the large reward is a risk of mild footshock accompanying the reward rather than a delay to its delivery. In this task, a cocaine SA regimen similar to that used here increased the subsequent choice of the large (risky) reward (Mitchell et al., 2014), indicating that cocaine’s effects on impulsive choice in the present study were likely not due to a gross reduction in preference for large rewards.

A recent study by Xie et al. (2012) investigated the effects of cocaine-paired contextual stimuli on impulsive decision-making by training rats on a delay discounting task, and then pairing experimenter-administered cocaine (15 mg/kg/day for 14 days) or saline vehicle with two distinct contexts. They found that rats exhibited greater impulsive choice in the cocaine-paired context compared to the saline-paired context, suggesting that cocaine-predictive environmental cues can influence the degree to which delayed rewards are discounted (although see (Broos et al., 2012)). In the present study, although the delay discounting task and SA procedures were conducted in different chambers in different rooms with distinct response manipulanda, there were still similarities between the testing environments (e.g., the same sizes and shapes of the test chambers). Hence, a contribution of the cocaine-paired context to the effects observed here cannot be ruled out entirely. Unlike in the Xie et al. (2012) study, however, both the cocaine and control (sucrose SA) groups in the present study experienced pairings of the SA context with reward, which might be expected to minimize differences in the influence of reward cues learned in the SA context on subsequent impulsive choice (e.g., it is possible that, aside from any pharmacological effects of cocaine, both sucrose- and cocaine-paired contextual cues influenced impulsive choice to a similar extent). In addition, there was no evidence for cocaine-induced increases in locomotor activity in the delay discounting task, as might be expected were cocaine-induced contextual conditioning to have generalized to the delay discounting task to a significant degree.

The fact that high and low cocaine intake rats did not differ in their degree of impulsive choice prior to cocaine SA suggests that cocaine intake (or the pharmacological effects of cocaine) was responsible for post-cocaine alterations in impulsive choice. Of course, it is not possible to rule out other innate factors in high intake rats that both predisposed them to greater cocaine intake and rendered them more susceptible to the effects of cocaine on impulsive choice. Notably, however, Dandy & Gatch (2009) showed that increases in impulsive choice resulting from repeated experimenter-administered cocaine were dose-dependent, such that whereas both 7.5 and 15 mg/kg/day (over 9 days) caused acute effects, only the 15 mg/kg/day dose resulted in elevated impulsive choice after cocaine administration was discontinued. Hence, as in the present study, these data provide support for both intake-dependent and lasting effects of cocaine on impulsive choice.

Consumption of sucrose solutions in rats can produce an “addiction-like” behavioral phenotype, which includes escalation of intake, naloxone-precipitated withdrawal symptoms, and changes in dopamine signaling (for review see (Avena et al., 2008)). Given that control rats in the present study were consuming sucrose, it is possible that such consequences of sucrose consumption caused alterations in impulsive choice. The study

design employed cannot rule out this possibility; however, the access conditions used in studies of addiction-like sucrose intake differ considerably from those used here (e.g., multiple hours of free access to a sucrose solution in the home cage, vs. several dozen 0.04 ml sucrose reinforcers available on an instrumental contingency). More importantly, even if sucrose SA conditions in the present study had effects on impulsive choice similar to those of cocaine, they would be predicted to be in the same direction as those of cocaine (i.e., also increasing impulsive choice), and hence such effects would bias *against* being able to detect any effects of cocaine. Thus, irrespective of whether sucrose SA produced effects on impulsive choice, the results provide support for pharmacological actions of cocaine on impulsive choice.

Despite considerable evidence for chronic cocaine-induced alterations in impulsive choice (as well as other aspects of cognition), the mechanisms by which cocaine exerts these effects remain unclear. Chronic cocaine causes lasting alterations in gene expression and electrophysiological properties of neurons in orbitofrontal cortex and nucleus accumbens (Freeman et al., 2001, Stalnaker et al., 2006, Takahashi et al., 2007, Winstanley, 2007, Winstanley et al., 2007, Stalnaker et al., 2009, Lucantonio et al., 2012, Regier et al., 2012, Besson et al., 2013), both of which have been strongly implicated in regulating impulsive choice (Mobini et al., 2002, McClure et al., 2004, Acheson et al., 2006, Bezzina et al., 2007, Roesch et al., 2007a, Bezzina et al., 2008, Ballard and Knutson, 2009, da Costa Araujo et al., 2009, Mariano et al., 2009, Galtress and Kirkpatrick, 2010, Zeeb et al., 2010, Mar et al., 2011, Diekhof et al., 2012, Valencia-Torres et al., 2012, Abela and Chudasama, 2013, Jo et al., 2013). In addition, we have recently shown that in cocaine-naïve rats, high levels of impulsive choice are associated with low levels of D2 dopamine receptor mRNA expression in the medial prefrontal cortex (mPFC) (Simon et al., 2013). Although reports are mixed regarding the contributions of mPFC to impulsive choice (Weissenborn et al., 1997, Cardinal et al., 2001, Dalley et al., 2004, Carli et al., 2006, Winstanley et al., 2006, Churchwell et al., 2009, Gill et al., 2010, Loos et al., 2010, Perry et al., 2011, Sripada et al., 2011, Li et al., 2013), chronic cocaine SA is reported to reduce mPFC D2 mRNA (Briand et al., 2008), suggesting that cocaine-induced alterations in mPFC dopamine signaling may contribute to increases in impulsive choice.

In summary, the present findings support the idea that chronic cocaine can cause lasting increases in impulsive choice. In combination with other data from animal studies showing that pre-existing high levels of impulsive choice predict some measures of cocaine (and other drug) SA (Perry et al., 2005, Anker et al., 2009, Broos et al., 2012) our findings suggest that elevated impulsive choice observed in chronic cocaine users may be both a contributing factor to and a consequence of drug use. It remains to be determined, however, whether the mechanisms by which pre-existing vs. drug-induced factors contribute to elevated impulsive choice differ (e.g., via effects on sensitivity to reinforcer magnitude vs. sensitivity to delays; (Roesch et al., 2007b, Locey and Dallery, 2009, 2011)). Future research employing animal models, particularly with cocaine SA procedures that are sensitive to individual differences in “addiction-like” behaviors (Deroche-Gamonet et al., 2004, Belin et al., 2008), will be important for elucidating these mechanisms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Cocaine Self-Administration Causes Long-Lasting Increases in Impulsive Choice

A) Before self-administration, rats' preference for the large reward varied as a function of the associated reward delay. On average, rats preferred the large reward when reward delay was short, but shifted their preference to the small, immediate reward as reward delay increased. There were no differences between the two groups prior to cocaine or sucrose self-administration. **B)** Six weeks after the last self-administration session, the cocaine self-administration group displayed significantly greater impulsive choice than sucrose self-administration controls. * = significant main effect or interaction involving self-administration group.

Figure 2. Cocaine-Induced Increases in Impulsive Choice Depend on the Amount of Cocaine Intake

A) Low intake rats in the cocaine and sucrose self-administration groups performed equivalently on the delay discounting task prior to self-administration. **B)** Following self-administration, low intake rats in the two groups did not differ, suggesting that low cocaine intake has no effect on impulsive choice. **C)** High intake rats in the cocaine and sucrose self-administration groups performed equivalently on the delay discounting task prior to self-administration. **D)** Following self-administration, however, high intake rats in the cocaine group displayed significantly greater impulsive choice compared to sucrose self-administering controls (as well as their pre-self-administration baseline), suggesting that high cocaine intake causes lasting increases in impulsive choice. * = significant main effect or interaction involving self-administration group. + = significant difference between groups at the indicated delay.

Figure 3. Cocaine Self-administration

A) Self-administered cocaine intake over the 14 sessions. **B)** Self-administered cocaine intake over the 14 sessions, split by high or low baseline level of impulsive choice (i.e., prior to self-administration).

Table 1

Trial omissions and inter-trial interval locomotor activity

Group	Pre-SA	Pre-SA	Post-SA	Post-SA
	Percentage of Choice Trials Omitted	Locomotion (Locomotor units/ITI)	Percentage of Choice Trials Omitted	Locomotion (Locomotor units/ITI)
Sucrose SA low	2.09 (0.70)	385.52 (76.60)	4.04 (1.37)	269.65 (61.74)
Cocaine SA low	0.67 (0.25)	423.06 (76.97)	4.53 (1.17)	294.88 (32.94)
Sucrose SA high	1.47 (0.76)	305.55 (38.05)	4.27 (1.58)	233.03 (25.37)
Cocaine SA high	4.18 (2.01)	336.28 (41.81)	7.33 (3.03)	314.17 (55.42)

Standard error of the mean is in parenthesis. Locomotion represents the average number of locomotor units for each inter-trial interval (ITI). SA = self-administration.