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ORIGINAL INVESTIGATION

Discrepant effects of acute cocaine on impulsive choice (delay discounting) in female rats during an increasing- and adjusting-delay procedure

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Abstract
Rationale The relationship between impulsive choice and cocaine use in humans has been well established, although the causal role between these variables is complex. To disentangle this relationship, studies using rats have focused on how acute or chronic cocaine alters impulsive choice. A predominance of studies has focused on chronic cocaine regimens, but few have assessed acute cocaine's effects on impulsive choice.
Objective The current study assessed if acute cocaine administrations alter delay discounting of rats in two common impulsive choice procedures.
Method Baseline delay discounting rates were determined in female rats using both an increasing- and adjusting-delay procedure. Once stable, a range of acute cocaine injections (2, 5, and 15 mg/kg i.p.) was administered prior to both procedures.
Results Baseline delay discounting rates were positively correlated between the increasing- and adjusting-delay procedures. Acute administrations of cocaine produced a dose-dependent decrease in preference for the large alternative in the increasing-delay procedure but had no effect in the adjusting-delay procedure.
Conclusions The concordance of delay discounting rates across the two choice procedures suggests that both quantify the same underlying components of impulsive choice. However, manipulations that disrupt large alternative preference may not be readily detected under the adjusting-delay procedure unless control conditions are employed.

Keywords Acute cocaine · Adjusting-delay · Delay discounting · Female · Increasing-delay · Impulsivity · Rats

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Introduction

Acute psychostimulant use (e.g., cocaine, amphetamine) has been tied to an increased prevalence of adverse behaviors (e.g., aggression, criminal acts, risky sexual, and drug use practices; Colfax et al. 2005; Hoaken and Stewart 2003). One common causal link among these adverse behaviors is an increase in impulsive choice or a preference for small, immediate outcomes over larger, delayed ones (de Wit 2009; Yi et al. 2010). A mechanism thought to underlie this phenomenon is that drugs like cocaine increase the rate of delay discounting, whereby the value of larger, delayed outcomes are discounted (devalued) at a much steeper rate, such that imposing a previously tolerated delay now shifts preference to the small, immediate alternative (for a review, see Madden and Bickel 2010).

Assessing the acute effects of cocaine on delay discounting in humans is complicated by ethical considerations, thus much research has focused on the long-term use of cocaine. In these studies, chronic cocaine users (e.g., currently using cocaine eight times per month, but sober during testing) have been shown to discount monetary outcomes at a higher rate than healthy non-drug using controls (Coffey et al. 2003; Heil et al. 2006; Kirby and Petry 2004). These results suggest that chronic cocaine use alone can increase delay discounting rates. Previous epidemiological evidence by Colfax et al. (2005), however, found the likelihood of risky, impulsive sexual and drug use behavior increased when individuals were under the acute influence of cocaine. Thus, acute cocaine may also increase discounting rates. As mentioned, examining this in humans is difficult; a solution is to model it in animals.

Several animal models of impulsive choice have been developed that can assess the acute effects of cocaine on delay discounting within a single session. These procedures

quantify discounting rates within one session by presenting several delays to the large alternative across successive trial blocks. Two procedures are commonly employed.

In the increasing-delay (ID) procedure, developed by Evenden and Ryan (1996), rats choose between a small, immediate (one pellet immediately) and large, delayed alternative (three pellets after T seconds). At the start of the session, the delay to the large alternative is 0 s and as the session progresses, the delay is increased across blocks of choice trials. The result forms a delay gradient, where preference for the large alternative is high without a delay and progressively decreases as delays increase. A steepening of this gradient (increased discounting) indicates an increase in impulsive choice.

In the adjusting-delay (AD) procedure, developed by Mazur (1987), rats choose between a small, more immediate and a larger, delayed alternative. Across trial blocks, the delay to the large alternative is adjusted based on choices to obtain an indifference point or a mean adjusted delay (MAD) value that causes indifference between the small, immediate and larger, delayed alternative. A decrease in the MAD value (increased discounting) indicates an increase in impulsive choice.

One difference between the ID and AD procedure is the determination of large alternative preference. In the ID procedure, preference for the large alternative is established prior to implementing delays, whereas in the AD procedure, preference for the large alternative typically is assumed and never explicitly examined. This procedural difference is an important point of divergence between the procedures.

In animals, both the ID and AD procedures have been employed to assess the impact of cocaine on delay discounting in rats (see reviews by Stein and Madden 2013; Setlow et al. 2009; Yi et al. 2010). Studies have examined the short-term behavioral effects of cocaine within both an acute and chronic dosing regimen. In an acute regimen, cocaine decreased discounting rates in an ID procedure (Winstanley et al. 2007), whereas in a chronic regimen, cocaine increased discounting rates in both AD (Logue et al. 1992) and ID procedures (Dandy and Gatch 2009). The disparity in the short-term behavioral effects of cocaine may be due to an interaction with the chronic dosing regimen. Indeed, when cocaine was administered to avoid the short-term behavioral effects, chronically experimenter- or self-administered cocaine (e.g., repeatedly for 9+ days) also increased discounting rates in the ID procedure (Broos et al. 2012; Dandy and Gatch 2009; Hernandez et al. 2013; Mendez et al. 2010; Mitchell et al. 2014; Paine et al. 2003; Roesch et al. 2007; Simon et al. 2007; but see Winstanley et al. 2007). Similar to the human studies, these findings suggest that chronic cocaine alone is sufficient to increase discounting rates in an ID procedure. Thus, to date, only one study (Winstanley et al. 2007) has examined the short-term effect of cocaine on delay discounting under an acute regimen, and the results were contrary to the chronic literature, suggesting that additional research is necessary.

To further explore this topic, the present study employed both AD and ID procedures. The use of two choice procedures was prompted by a discussion in Stein and Madden (2013) on the sensitivity of different choice procedures to examine pharmacological interventions. Specifically, they note that large alternative preference is assessed without a delay in the ID procedure, which is typically not done in the AD procedure. Consequently, a drug manipulation that disrupts large alternative preference, causing choice indifference, would be observed in the ID procedure (e.g., Madden et al. 2010), but would be missed in the AD procedure since MAD values would remain stable due to the choice indifference. An initial step to test this hypothesis is to determine if measures of discounting are related across the AD and ID procedures. Indeed, a very recent follow-up study by Craig et al. (2014) showed that discounting rates in male rats were positively correlated between these procedures. The main purposes of the present study were to 1) extend the findings to female rats and determine whether discounting rates across the ID and AD procedures were related and 2) determine if acute doses of cocaine produce concordant changes in delay discounting within the ID and AD choice procedures.

Method

Subjects Twenty 80-day-old female Wistar rats (Harlan Inc, Indianapolis, IN) weighing 229–288 g served as subjects (estrous cycles were not monitored). Females were used in this initial study since it complements previous research by Craig et al. (2014) that employed males, supports the NIH aim to expand use of females in research, and because female rats are more vulnerable to drug abuse (Anker and Carroll 2011). Upon arrival, rats were group housed in standard polycarbonate home-cages with ad libitum food and water access for a week. Once the study began, rats were singly housed in polycarbonate tubs with ad libitum water access, and they were fed 16 g of chow (minus pellets earned in session) ~1.5 h following experimental sessions (1530 hours) to maintain weights at ~85 % of free-feeding body weight. Rats were housed in a climate controlled room (24 °C) with a 12-h light-dark cycle (lights on at 0600). The experimental protocol (1008A87755) was approved by the University of Minnesota Institutional Animal Care and Use Committee, and the research was conducted in accordance with the Principles of Laboratory Animal Care (National Research Council 2011).

Apparatus Sessions were conducted daily in customized octagonal experimental chambers containing two levers, each with LED lights directly above and a houselight to provide general illumination. Between the levers, a food hopper delivered sweetened sucrose pellets (Bio-Serv® pellets #F0021). A

computer running Windows XP® and Med-PC IV® software orchestrated experimental sessions and recorded data.

Drugs Cocaine HCl was supplied by the National Institute of Drug Abuse (Research Triangle Institute, Research Triangle Park, NC). Cocaine was diluted in 0.9 % NaCl (saline) to a concentration of 8 mg/ml and then refrigerated. Injections (1.875 ml/kg) of saline and cocaine (2, 5, 15 mg/kg) were administered i.p. 30 min prior to experimental sessions. The range of cocaine doses was approximately evenly spaced on a logarithmic scale and included a high dose shown to alter impulsive choice (e.g., 15 mg/kg; Logue et al. 1992; Winstanley et al. 2007) and two lower doses shown to be behaviorally active in our laboratory.

Delay discounting sessions Rats were tested in two sessions per day (~9 AM and ~1 PM). Initially, rats were trained to respond on both levers under an independent concurrent variable-interval 15 s schedule during 45-min sessions. Once lever pressing produced >50 reinforcers in the AM and PM sessions, rats began the delay discounting procedures.

In the AM session, rats performed on an ID procedure (see Evenden and Ryan 1996). Sessions consisted of five blocks of two sample trials followed by ten choice trials. The start of either trial type was signaled by the illumination of the houselight and the light(s) above the active lever(s). Across the two sample trials, rats were exposed to both choice alternatives in random order. If the left lever was activated, a response on that lever produced one pellet immediately. If the right lever was activated, a response on that lever produced three pellets after a delay of T-s during which the stimulus light above the lever flashed at 2 Hz. Choice trials, where both levers were active, allowed rats to choose between the immediate and delayed alternatives. During the first block, the delay to the large alternative was 0 s, and it increased across successive trial blocks (3, 6, 12, and 24 s). Trials were separated with a 45-s compensating inter-trial interval (ITI) that ensured equal trial spacing regardless of the alternative chosen. Sessions terminated following completion of all trials or 60-min, which ever occurred first. Changes in delay gradient shape were quantified in two ways depending on the analysis. First, the acute effects of cocaine on impulsive choice were assessed using the area-under-the-curve (AUC; see Myerson et al. 2001) method, where a decrease in AUC indicated an increase in impulsive choice. Second, to obtain individual delay discounting rates (i.e., k) to compare to the AD procedure, delay gradients were fit with a slightly modified hyperbolic discounting equation (Fox et al. 2008):

$$Y = \frac{A}{1 + kD} \quad (1)$$

where Y equals the mean proportion of large alternative choices, A is equal to the proportion of large choices at the 0-s delay, D is the delay value, and k is a free parameter that reflects the rate of discounting due to delay.

In the PM session, rats performed on an AD procedure (see Mazur 1988). Sessions consisted of 16 blocks of two sample trials followed by two choice trials. The start of each trial type was signaled just as it was in the ID procedure (by the houselight and lever light[s]), and a response on the left lever resulted in one pellet immediately, whereas a response on the right lever resulted in three pellets following a delay of T-s. At the start of the first session, the large alternative delay was 2 s. Following each choice trial block, the delay to the large alternative was decreased 1 s if both choices were to the small alternative (min. 2-s delay), and the delay was increased 1 s if both choices were to the large alterative (max. 35-s delay). No change in delay occurred if there was a response to both alternatives. All trials were separated by an ITI where all lights were extinguished. The length of the ITI was reduced by the length of the experienced delay on the previous trial to ensure all trials were presented every 45 s. Sessions terminated following completion of all trials or 60 min, whichever occurred first. Each subsequent session began with the last adjusted delay value from the previous session. The main dependent measure of impulsivity was the MAD value across the 16 trial blocks of the session and a decrease in the MAD value indicates an increase in impulsivity. To determine rates of delay discounting (i.e., k) to compare the ID procedure, the stable MAD values were inserted into Mazur's (1987) hyperbolic discounting equation:

$$V = \frac{A}{1 + kD} \quad (2)$$

where V is the discounted value (e.g., 1) of a choice alternative amount (A; e.g., 3) when delivered following a delay (D) with k reflecting the rate of discounting.

Experimental design After performance on the ID and AD procedures had stabilized (minimum of 28 sessions, a length of time known to produce stable gradients for the ID procedure [Robinson et al. 2009; Simon et al. 2009]), acute injections of cocaine were administered. Stability was assessed visually and quantified in different ways for both procedures. In the ID procedure, rats were assessed for large alternative preference at the 0-s delay (>85 % choices to the large alternative) and stable gradients whereby the proportion of large alternative choices decreased as a function of increasing delay each session across the last six sessions (trend was assessed visually across three consecutive sets of 2-day average gradients). In the AD procedure, rats were assessed for stability across the last six sessions of baseline using a slightly modified version of the stability criteria outlined by Mazur (1988): the mean proportion of large alternative choices in the final three and preceding three sessions deviated from the six-

session mean by <10 %, and there was no visually apparent trend observed across the final six sessions.

Once both procedures were stable, saline (S) and then a descending order of cocaine doses were administered (15, 5, and 2 mg/kg, i.p.) 30 min prior to experimental sessions. Cocaine doses were each assessed in 2-day test blocks, each block separated by at least three non-drug baseline sessions. During each test block, cocaine was administered once daily 30 min prior to either the ID or AD procedure. To counterbalance the procedure (ID or AD) of the initial injection at each dose-testing block, rats were split into two equal groups based on ID AUC (e.g., half the rats received injections prior to the ID on day 1 and then prior to the AD on day 2, while the other rats were injected in the opposite order). Groups were rotated through each testing block, and no order effects were observed.

The initial baseline MAD values and ID gradients were calculated using the six stable sessions prior to the start of injections. To provide a reference for changes in MAD values across injections, the average of the last three baseline days around the 2 and 5 mg/kg doses was averaged and included in the data presented. Delay gradients from the ID procedure were stable across all baselines separating injections and therefore are not included in the data presented.

Data analysis Differences in MAD following saline control and drug administrations were analyzed using a repeated measures one-way ANOVA (GraphPad Prism 5.0a for Mac, San Diego, CA). Changes from saline in the proportion of large alternative choices at each delay for each cocaine dose were analyzed using a repeated measures two-way ANOVA (Drug X Delay; GB Stat, Dynamic Microsystems, Inc, Silver Springs, MD). Significantly different gradients were analyzed post hoc using Tukey's LSD protected *t* test to determine significant changes in impulsive choice at each delay value. The 15 mg/kg dose of cocaine disrupted behavior (e.g., stereotypy and anorexic behaviors are common following such large doses of cocaine), which resulted in some missing data points, mainly at the 24-s delay. Similar to previous research (e.g., Evenden and Ryan 1996), these missing data points were replaced with group mean values to conduct statistical analysis. The AUC calculations and Pearson's correlational coefficients between various measures were assessed using GraphPad Prism (5.0a) for Mac. To quantify the percent change in baseline AUC (decrease in large preference) across the cocaine dosing conditions, AUCs of the cocaine gradients were calculated using the baseline proportion of large choices at the 0-s delay.

Results

The baseline measures of impulsive choice (*k*) in the ID and AD procedures (Fig. 1) were significantly positively correlated, $r(20)=.69$, $p<0.01$ (since *k* tends to be positively skewed, the natural log of the *k* values were plotted), which indicates the two procedures measured a similar construct underlying delay discounting in rats. In relative terms, however, the natural log transform values of *k* were about eight times smaller in the ID procedure than the AD procedure, indicating rats maintained significantly steeper discounting rates in the AD procedure ($t(19)=14.94$, $p<0.05$).

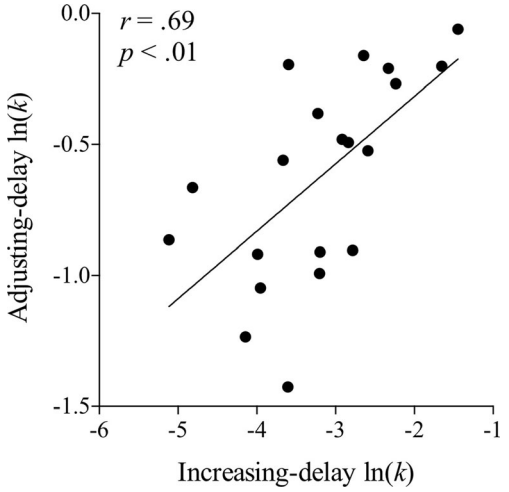

Fig. 1 The *line graph* depicts the relation between measures of delay discounting rates (*k*), after natural log transformation, in the ID procedure and AD procedure. Average baseline delay discounting rates were significantly ($p<.01$) positively correlated between the two procedures (natural log transformation removes the positive skew in *k*)

Acute doses of cocaine prior to the AD procedure did not systematically alter MAD values (Fig. 2a). According to a repeated measures one-way ANOVA comparing vehicle and all drug days, there was no significant main effect of drug across treatment conditions. Although not significant, there was a small reduction in MAD following the 2 mg/kg cocaine dose. This slight reduction in MAD, however, persisted in the 3 days of baseline that followed (last bar) suggesting this non-significant MAD reduction may not have been due to the acute cocaine injection.

The slight reduction in MAD following the 2 mg/kg dose of cocaine prompted an investigation in the change in MAD values across the first half of trial blocks, since this is when the peak drug effect would have occurred (this analysis was also prompted by the ID results—see below). A linear regression of adjusting-delay values across the first eight delay adjustments (i.e., the first half of the session) resulted in no significant trend in MAD values for the 2, 5, and 15 mg/kg doses of cocaine. This consistency in MAD adjustments supports the conclusion that acute cocaine did not systematically alter impulsive choice in the first half of the AD procedure.

Previous research has reported that the acute drug effects can interact with baseline levels of impulsive choice (see Kayir et al. 2014; Kolokotroni et al. 2014; Perry and Carroll 2008; Setlow et al. 2009). To investigate this relationship, the

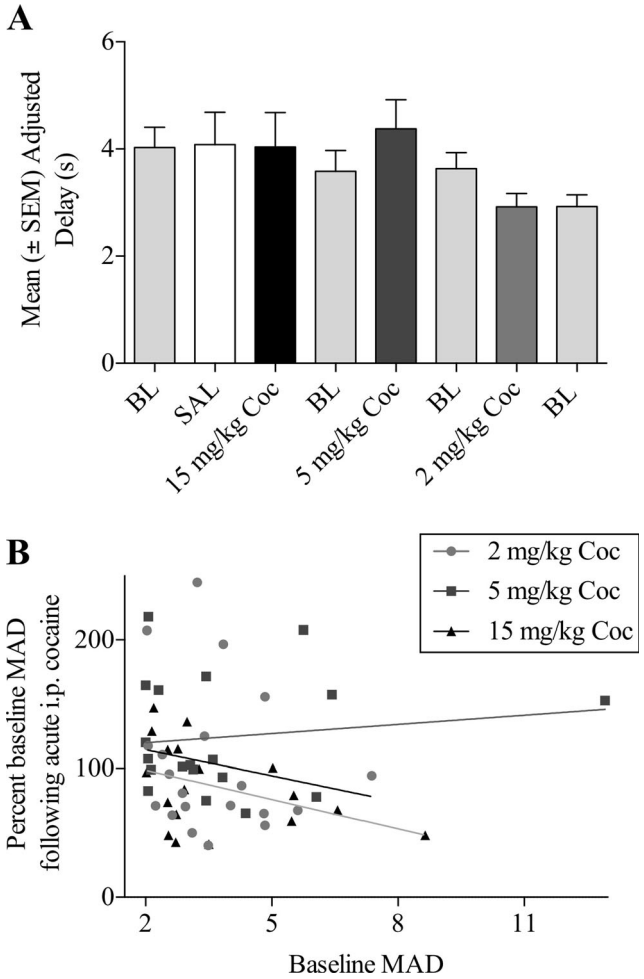

Fig. 2 The *top bar graph* (**a**) shows mean (±SEM) MAD values in the AD procedure during baseline (*light gray bar*) and following acute i.p. injections of saline (*white bar*) or cocaine doses (*darker gray bars*) that occurred 30-min prior to sessions. The *bottom dot plot* (**b**) graphs the percent change in baseline MAD following the injections of 2 (*circles*), 5 (*squares*), and 15 mg/kg of cocaine (*triangles*)

percent change in MAD scores was plotted as a function of the baseline MAD preceding each cocaine dose (Fig. 2b). There was no significant relationship between baseline MAD values and the percentage change in MAD following the 2, 5, and 15 mg/kg doses of cocaine. Even at the higher baseline MAD levels, there was not a systematic change in MAD values following any dose of cocaine. Taken together, these data suggest that larger baseline MAD levels did not predispose rats to be less sensitive to the acute effects of cocaine on impulsive choice within an adjusting-delay procedure.

Acute effects of i.p. cocaine in the ID procedure are presented in Fig. 3. The left column of graphs (A, C, and E) shows the proportion of large alternative choices across delays to that alternative. In general, preference for the large alternative decreased linearly with increases in delay, indicating rats were sensitive to the increase in delay across trial blocks. Acute injections of saline produced delay gradients that overlapped the baseline gradients (not presented), whereas cocaine dose dependently decreased preference for the large alternative at most of the shorter delays ($F[12, 228]=6.94$, $p<0.05$). A post hoc comparison yielded significant decreases in the proportion of large choices at all but the 24-s delay after 2 mg/kg (Fig. 3a: closed circles; $F[1, 39=7.71$, $p<0.05$) and 5 mg/kg dose of cocaine (Fig. 3c: closed squares; $F[1, 39=18.66$, $p<0.05$), and all but the 12 and 24-s delay for the 15 mg/kg (Fig. 3e: closed triangles; dose: $F[1, 39]=17.89$, $p<0.05$) dose of cocaine.

Similar to the AD procedure, baseline level of impulsive choice was examined to determine if it predicted the acute effect of cocaine. To accomplish this, the percent change in AUC from baseline following 2, 5, and 15 mg/kg doses of cocaine (Fig. 3b, d, and f, respectively) were plotted as a function of baseline AUC. At the 2 mg/kg dose of cocaine (Fig. 3b), there was a significant positive relationship [$r(20)=.56$, $p<0.05$] between the percentage change from baseline AUC when graphed as a function of baseline AUC, suggesting steeper baseline rates of delay discounting, indicate a vulnerability to the acute effects of cocaine on impulsive choice. Similar but nonsignificant findings were also observed at the 15 mg/kg dose of cocaine.

Discussion

The concordance of delay discounting rates (k) between the AD and ID procedures (Fig. 1) suggests that both quantify the same underlying construct of impulsive choice in female rats. These findings extend a recent study by Craig et al. (2014) who found the same positive correlation between these procedures, but in male rats. Indeed, related pigeon research has demonstrated that discounting rates determined via an adjusting-amount and -delay procedure were also positively correlated (Green et al. 2007). When combined, the present results suggest these impulsive choice procedures, each of which can assess the acute drug effects on impulsive choice in a single session, produce concordant measures of delay discounting rates in animals. As hypothesized by Craig et al. (2014) and demonstrated in the present study, however, acute drug effects can produce conflicting results between these two choice procedures (see Stein and Madden 2013 for a review of issues).

In the ID procedure, acute administration of cocaine dose dependently decreased preference for the larger, delayed alternative (Fig. 3) until choice indifference occurred at the highest dose (for similar findings see Dandy and Gatch 2009; Madden et al. 2010). In the AD procedure, increasing doses of cocaine had no systematic effect on impulsive choice (Fig. 2). The discrepant effect of acute cocaine was likely due to the lack of a standard protocol to explicitly assess large alternative preference in the AD procedure.

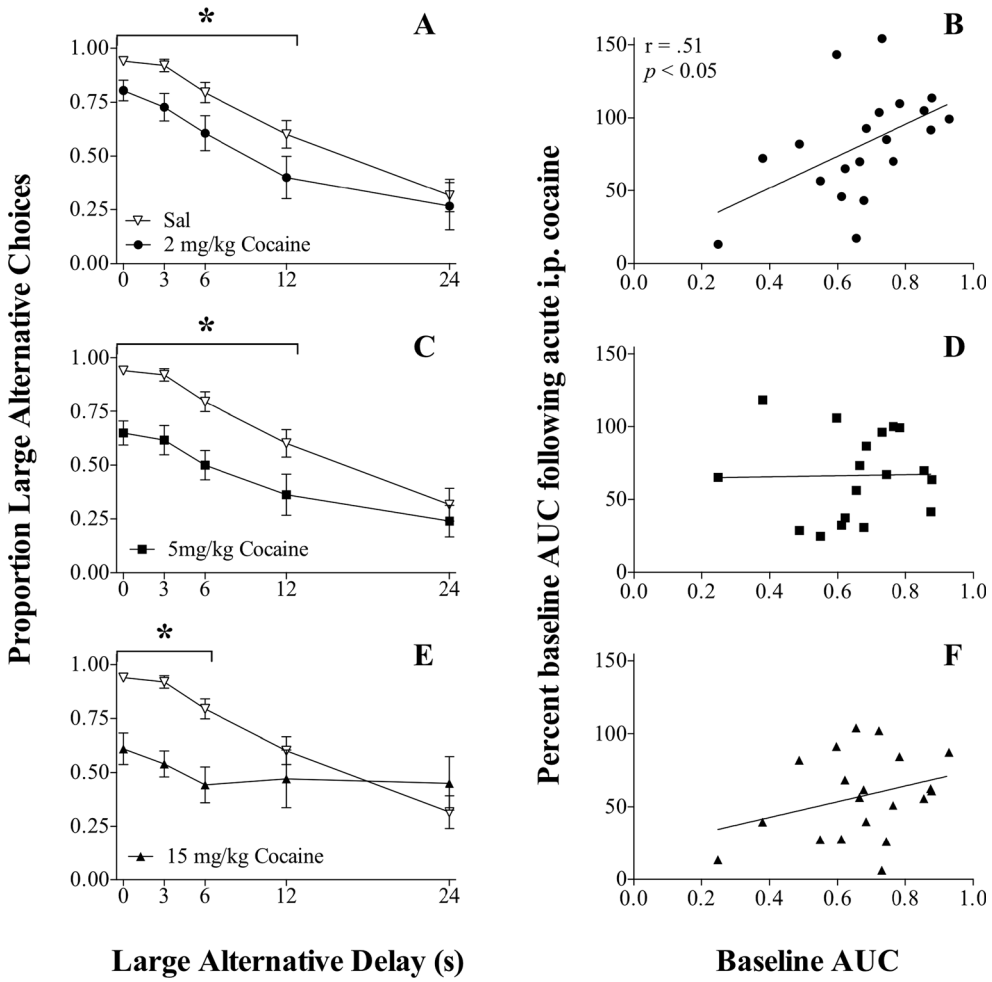

Fig. 3 The *left column* presents mean (±SEM) proportion of large alternative choices in the ID procedure as a function of large alternative delay following acute i.p. injections of saline (*open triangles*) and 2 mg/kg (*circles*; **a**; *$p<0.05$), 5 mg/kg (*squares*; **c**; *$p<0.05$), and 15 mg/kg of cocaine (*closed triangles*; **e**; *$p<0.05$). The *right column* plots the percentage change in baseline AUC as a function of baseline AUC following acute i.p. injections of 2 mg/kg (*circles*; **b**), 5 mg/kg (*squares*; **d**), and 15 mg/kg of cocaine (*closed triangles*; **f**). Note: Cocaine AUC calculations were normalized to the baseline proportion of large alternative choices with a 0-s delay

Evidence to support this conclusion can be derived from the complete disruption of large alternative preference at the 15 mg/kg dose during the ID procedure (Fig. 3e), which essentially produced choice behavior that appeared random. Random choice behavior in the AD procedure would not be distinguished from indifference produced by the large alternative delay, since in neither case would the MAD change systematically. Thus in the AD procedure, it would be difficult to determine if a manipulation had no effect on impulsive choice or if it completely degraded large alternative preference via some mechanism such as disruption in stimulus control exerted by the large alternative lever (see Branch and Dearing 1982) or diminished reinforcer magnitude sensitivity (Dandy and Gatch 2009; but see Roesch et al. 2007).

Mechanism aside, the disruption of large alternative preference in the ID procedure makes it difficult to interpret how cocaine altered impulsive choice. Typically, an increase in the rate of discounting, as measured by k (or AUC), is the preferred metric to conclude a manipulation increased impulsive choice (Mazur 1988). The present findings are in contrast to those of Winstanley et al. (2007) that showed acute doses of cocaine (7.5 and 15 mg/kg; i.p.) decreased impulsive choice in male rats responding in an ID procedure. Several procedural differences could explain the discrepant findings to the Winstanley studies (e.g., subject sex; duration of training; length of larger, later delays; surgical history). For example, the disparity could be due to a sex difference in impulsive choice or a sex difference in the acute effects of cocaine on impulsive choice. However, previous research (Perry et al. 2007, 2008) mostly revealed no sex differences in impulsive choice between male and female Wistar rats in an AD procedure, which leaves open the possibility of a sex difference in sensitivity to the acute effects of cocaine. Indeed, a review by Anker and Carroll (2011) highlighted that female rats appear to be more sensitive to cocaine as they exceeded males across all phases of the drug abuse process (e.g., acquisition, escalation, extinction, and reinstatement), suggesting a potential sex difference in the acute effects of cocaine on impulsive choice.

It was observed that a steeper baseline rate of delay discounting enhanced the acute, disruptive effects of cocaine. In Fig. 3b, the percent change in baseline AUC (non-normalized) at the 2 mg/kg dose was positively related to baseline rates of delay discounting. This relationship indicates

that more impulsive rats were more sensitive to the acute, behaviorally disruptive effects of cocaine on large alternative preference. Indeed, this is similar to recent research demonstrating that steeper baseline rates of discounting predicted stronger acute, impulsivity increasing effects of another stimulant, nicotine (e.g., Kayir et al. 2014; Kolokotroni et al. 2014). The present findings add to previous results from our lab showing that steeper discounting also predicts acquisition of cocaine self-administration (Perry et al. 2005, 2008), escalation of cocaine intake with extended access (Anker et al. 2009), and subsequent reinstatement of cocaine-seeking behavior in male and/or female rats (Perry et al. 2008). More broadly, given that cocaine users tend to be steeper discounters than nonusers (e.g., Coffey et al. 2003; Heil et al. 2006; Kirby and Petry 2004), perhaps this feeds an autotrophic cycle of drug use and increased instances of adverse, impulsive behaviors like those reported in the epidemiological study by Colfax et al. (2005).

The current results suggest that even if acute cocaine does not alter discounting rates, it could still increase instances of impulsive, risky behavior in humans (e.g., Colfax et al. 2005). For example, in the ID procedure, cocaine decreased large alternative preference and produced a parallel downward shift in the delay gradient until choice indifference occurred at the highest dose. Technically, this produced shallower discounting across increasing dose; however, it also produced an increase in the number of small alternative choices. In generalizing these findings to humans, it may be that the acute effects of cocaine cause a disruption in large alternative preference, resulting in an individual making more impulsive choices under conditions where they were predominately self-controlled.

Two points about the present data should be noted. First, the relatively low MAD values made it important to determine whether floor effects altered our interpretation. To examine this, the percent change in MAD values was analyzed (Fig. 2b) and even rats with relatively larger MAD values showed no systematic change in impulsive choice at any dose of cocaine. These results suggest that floor effects, while occasionally present in some rats, did not obscure the acute effects of cocaine in the AD procedure.

Second, the order of the two procedures was not counterbalanced, which leaves open the possibility that the absence of an acute effect of cocaine in the AD procedure was due to time of the day or having performed in the ID procedure earlier in the day. The former possibility seems unlikely, as an examination of the pharmacokinetics of cocaine by Baird and Gauvin (2000) revealed no difference in cocaine elimination rates across a 24-h period (0100, 0700, 1300, and 1900 hours). Additionally, the anorexic effects of acute cocaine did not appear to substantially suppress motivation for food in the AD procedure; across increasing dose, there was a slight reduction in trials completed, but this reduction was similar to that observed in the ID procedure. Taken together, it seems unlikely that the acute effects of cocaine were altered due to the timing of the experimental procedures.

In conclusion, acute cocaine exposure produced discrepant effects on impulsive choice across the procedures employed. In the ID procedure, acute cocaine produced a dose-dependent decrease in large alternative preference; whereas, in the AD procedure cocaine had no systematic effect. Indeed, such a disruption would not be expected in the AD procedure since it does not typically contain a control condition to assess preference for the large alternative. Therefore, results indicate that the traditional AD procedure may be less sensitive than the ID procedure for assessing acute drug effects on impulsive choice in animals. Looking ahead, researchers should be mindful that the disruption of large alternative preference might not be apparent under choice procedures that employ a titration methodology (e.g., adjusting-amount or -delay) unless proper control conditions are in place.

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