HHS Public Access

Author manuscript

Exp Clin Psychopharmacol. Author manuscript; available in PMC 2017 December 01.

Published in final edited form as:

Exp Clin Psychopharmacol. 2016 December ; 24(6): 456–463. doi:10.1037/pha0000098.

SHALLOW DISCOUNTING OF DELAYED COCAINE BY MALE RHESUS MONKEYS WHEN IMMEDIATE FOOD IS THE CHOICE ALTERNATIVE

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Abstract

Huskinson et al. (2015) recently examined delay discounting in monkeys choosing between an immediate drug (cocaine) reinforcer and a delayed nondrug (food) reinforcer. The present experiment examined the reverse situation: choice between immediate nondrug (food) and delayed drug (cocaine) reinforcers. Whereas the former choice situation exemplifies drug abuse from a delay-discounting perspective, our interest in the latter choice situation is derived from the observation that drug abusers, who characteristically are associated with impulsive choice, typically must devote considerable time to procuring drugs, often at the expense of immediate nondrug alternatives. Accordingly, we analyzed three male rhesus monkeys' choices between immediate food and delayed cocaine (0.1 and 0.2 mg/kg/injection) using a hyperbolic model that allowed us to compare discounting rates between qualitatively different reinforcers. Choice of immediate food increased with food amount, and choice functions generally shifted leftward as delay to cocaine increased, indicating a decrease in the subjective value of cocaine. Compared to our previous delay-discounting experiment with immediate cocaine versus delayed food, both doses of delayed cocaine were discounted at a shallow rate. The present results demonstrate that rhesus monkeys will tolerate relatively long delays in an immediate-food versus delayed-drug situation, suggesting that in inter-temporal choices between cocaine and food, the subjective value of cocaine is less affected by the delay until reinforcement than is the subjective value of delayed food. More generally, the present findings suggest that although drug abusers may choose impulsively when immediate drug reinforcement is available, they exercise self-control in the acquisition of a highly preferred, delayed drug reinforcer.

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Portions of these data were presented at the 76th Annual Meeting for the College on Problems of Drug Dependence in June 2014 and at the annual meeting of the International Study Group Investigating Drugs as Reinforcers (ISGIDAR) in June 2016.

Keywords

Choice; Cocaine; Delay Discounting; Rhesus Monkey; Self-administration

Introduction

In the study of delay discounting, self-control has been defined as choice of a larger, more delayed reinforcer over a smaller, more immediate one, whereas impulsive choice has been defined as choice of the smaller, more immediate reinforcer. The concept of delay discounting has proven to be important for understanding drug abuse, and drug abusers have been conceptualized as impulsive because they choose the more immediate reinforcing effects of drugs over more delayed, nondrug alternative reinforcers such as health, employment, or interpersonal relationships (for reviews, see Perry and Carroll, 2008; Yi, Mitchell, and Bickel, 2010). The delay-discounting literature is replete with studies of the discounting of nondrug reinforcers (e.g., food) in nonhuman animals. Such studies have generated useful information, but they do not capture the most critical choice faced repeatedly by drug abusers – the choice to take (or not take) a drug.

In a previous experiment targeting such choices, Huskinson, Woolverton, Green, Myerson, and Freeman (2015) examined the discounting of a delayed food reinforcer by rhesus monkeys when the immediate alternative was cocaine, and compared it to the discounting of delayed food when the immediate alternative also was food. Notably, delayed food was discounted more steeply when cocaine was the immediate alternative than when food was the immediate alternative. These findings suggest that impulsive choice, as defined by choice between immediate and delayed reinforcers, is not a static construct, but rather may vary in degree within the same subject depending on whether or not at least one option is drug delivery.

Much less is known about choices involving drug reinforcers when the drug is the delayed reinforcer and the nondrug alternative is the immediate one. In this situation, where choice is between immediate food and delayed drug, choosing the drug could be seen, perhaps paradoxically, as the self-controlled choice and food as the impulsive choice. Despite the apparent paradox, situations in which the choice is between an immediate nondrug reinforcer and a delayed drug reinforcer are important to study because drug abuse is not simply a matter of choosing immediate drug reinforcers over delayed nondrug reinforcers. Certainly, choice between immediate drug and delayed nondrug reinforcers represents an ecologically relevant model that captures one significant aspect of drug abuse. However, drug abuse also involves situations in which individuals choose more delayed drug reinforcers over more immediate nondrug ones, and importantly, drug abusers devote considerable time and effort to procuring drugs, yet this situation has received virtually no discussion in the literature on discounting in humans (cf. Bickel, Landes, Christensen, Jackson, Jones, Kurth-Nelson, et al., 2011).

Choice between immediate food and delayed drug delivery has been examined in a small number of experiments with nonhuman animals. As expected, delaying delivery of a drug reinforcer increased choice of the immediate food alternative and decreased choice of the

drug (i.e., remifentanil, a mu-opioid receptor agonist: Maguire, Gerak, and France, 2013; cocaine: Woolverton and Anderson, 2006), but unfortunately, these experiments were not conducted in a way that made it possible to compare rates of discounting across different reinforcers, choice situations, or experiments. However, there is a way to make such comparisons. Several decades of research indicate that the effect of delay on the value of a reinforcer is well described by a hyperboloid discounting function (for a review, see Green and Myerson, 2004), and a discounting framework based on the hyperboloid model does allow for such comparisons. According to this framework, the decrease in the value of a reinforcer as the delay to its delivery increases is given by

$$V = A/(1+k\mathrm{D})^{s}, \quad (1)$$

where V is the present value of the delayed alternative, A is the magnitude of the delayed alternative, k is a parameter that reflects the rate of discounting, and D is the delay to reinforcer delivery. The scaling parameter s is typically unnecessary for describing choice by nonhuman animals (for a review, see Vanderveldt, Oliveira, and Green, 2016). In which case s is set equal to 1, and Eq. 1 reduces to a simple hyperbola (Mazur, 1987). Larger k values indicate steeper discounting or more impulsive choice, and smaller k values may be described as indicating more self-control.

The discounting framework has been applied to monkeys' choice between immediate drug versus delayed drug delivery (i.e., remifentanil: Maguire, Gerak, and France, 2016; cocaine: Woolverton, Myerson, and Green, 2007), as well as to monkeys' choice between immediate and delayed nondrug reinforcers (Freeman, Green, Myerson, and Woolverton, 2009; Freeman, Nonnemacher, Green, Myerson, and Woolverton, 2012) and, in one recent study, to choice between immediate drug delivery and a delayed food reinforcer (Huskinson et al., 2015). The observed k values were smaller (indicating shallower discounting reflective of more self-controlled choice) when the choice was between immediate and delayed cocaine or immediate and delayed food than when the choice was between immediate cocaine and delayed food (see Table 1 for k values across studies). Taken together, these results raise the possibility that how steeply delayed reinforcers are discounted depends on whether choice is between the same type of reinforcer or whether choice is between different reinforcers. To date, the only arrangement of cocaine and food that has not been examined from a discounting perspective is choice between immediate food and delayed cocaine. The results from this choice situation could have important implications for our understanding of drug abuse, especially when considered in light of the time and effort that drug abusers devote to the pursuit of eventually obtaining drug effects at the expense of immediately available, nondrug alternatives.

Importantly, Bickel and colleagues (2011) have examined delay discounting of all four possible arrangements of hypothetical money and cocaine in human participants (i.e., immediate versus delayed money, immediate versus delayed cocaine, immediate cocaine versus delayed money, and immediate money versus delayed cocaine). The rank order of k values in their study from smallest (or most self-controlled) to largest (or most impulsive) was money versus money, immediate cocaine versus delayed money, cocaine versus cocaine,

and immediate money versus delayed cocaine. When focusing on choice between drug and nondrug reinforcers, obtained *k* values were significantly smaller with immediate cocaine versus delayed money than with immediate money versus delayed cocaine. That is, Bickel et al.'s participants were more self-controlled in the situation with immediate cocaine and delayed money, a result opposite to that found with rhesus monkeys for whom choice between immediate cocaine and delayed food was the most impulsive.

In order to explicate the role of the nature of the choice situation in determining how monkeys choose between immediate and delayed outcomes, the current experiment examined discounting of delayed drug (cocaine) reinforcers by male rhesus monkeys when the immediate alternative was a nondrug (food) reinforcer. Hyperbolic discounting functions were used to assess rates of discounting in order to allow comparisons between conditions in the current experiment as well as comparisons between the current experiment and previous studies with monkeys in which the discounting framework was applied.

Method

All animal-use procedures were approved by the University of Mississippi Medical Center's Institutional Animal Care and Use Committee and were conducted in accordance with the National Research Council's Guide for Care and Use of Laboratory Animals (8^{th} edition, 2011).

Subjects and Apparatus

Three male rhesus monkeys (*Macaca mulatta*) served as subjects. They were experimentally naïve at the beginning of the experiment. The monkeys were maintained at healthy body weights determined by close collaboration with veterinary staff. Weights were maintained by food provided during the session (i.e., food pellets delivered for one of the choice alternatives) as well as by supplemental feeding (Teklad 25% Monkey Diet, Harlan/Teklad, Madison, WI). Daily supplemental feedings occurred post-session at least 30 minutes following the final choice. Subject weights ranged from 8.95 to10.0 kg at the beginning of the experiment. Fresh fruit and forage (e.g., dried fruit and nuts) were provided daily, and a multivitamin was given three times per week. Subjects were given unlimited access to water. Lights were maintained on a 16/8-h light/dark cycle, with lights on at 0600 h.

The monkeys were fitted with a mesh jacket and tether (Lomir Biomedical, Malone, NY) that attached to the rear wall of the experimental cubicle (1.0 m^3, Plaslabs, Lansing, MI). A single response lever (custom designed and fabricated, see Huskinson et al., 2015, for details) could be moved to the left or right. There was a set of four lights, two white and two red, aligned vertically on either side of the response lever. A feeder was mounted on the outside of the cubicle door and delivered 1-g very berry pellets (Bio-Serv) at a rate of one pellet per 0.5 s. Drug infusions, 10 s in duration, were delivered by a peristaltic infusion pump (Cole-Parmer, Chicago, IL). A Macintosh computer with custom interface and software controlled experimental events and recorded data.

Surgery

Each monkey had a single-lumen catheter implanted intravenously as described previously (e.g., Huskinson et al., 2015). Monkeys were given atropine sulfate (0.04 mg/kg, i.m.) and ketamine hydrochloride (10 mg/kg, i.m.) followed by inhaled isoflurane. A silicon catheter was implanted into a major vein with the tip terminating near the right atrium. The distal end of the catheter was passed subcutaneously to the mid-scapular region, where it exited the subject's back and then was threaded through the tether and connected to a swivel (Lomir Biomedical, Inc., Malone, NY). A chewable antibiotic (Kefzol; Eli Lilly & Company, Indianapolis, IN) was given (22.2 mg/kg) twice daily for seven days to prevent infection. If a catheter became nonfunctional, it was removed, and the subject was removed from the experiment for 1–2 weeks until a new catheter was implanted. The catheter was filled with 40 units/ml heparinized-saline between sessions to prevent clotting at the catheter tip.

Procedure

The procedure was similar to previous delay-discounting studies from our laboratory (Freeman et al., 2009; 2012; Huskinson et al., 2015; Woolverton et al., 2007). Sessions were conducted daily, beginning at 11:00 a.m. Each session began with two sampling trials, one for each kind of reinforcer. The purpose of the sample trials was to ensure that subjects experienced the contingencies for that session, more specifically, which direction of lever movement was associated with an immediate amount of food (1–16 pellets/delivery), and which direction was associated with a delayed amount of cocaine (0.1 or 0.2 mg/kg/injection, in separate conditions). Which reinforcer was available on the first sample trial was determined randomly and was signaled by illumination of the corresponding set of white lever lights.

The sample trials were followed by eight choice trials during which both sets of white lever lights were illuminated. On all trials, five consecutive lever responses to one side (FR 5) had to occur to result in reinforcer delivery. Responses to either side reset the FR contingency on the other side. Following completion of the FR 5 on one side, the corresponding set of white lights was darkened, and if a delay was programmed, the red lights on that side flashed throughout the delay. After the delay, or immediately after completion of the FR 5 when the delay was 0 s, the red lights were illuminated for 10 s during reinforcer delivery. Following reinforcer delivery, all lever lights were darkened during a timeout period. The next trial always began 30 min after initiation of the preceding reinforcer delivery to ensure that reinforcement rate did not co-vary with delay. Responses during delays, reinforcer deliveries, and timeouts were recorded but had no programmed consequences.

Separate choice functions (percent choice of immediate food as a function of the number of food pellets, which varied from 1 to 16) were established for different delays (which ranged between 0 and 720 s) and cocaine dosages (either 0.1 or 0.2 mg/kg/injection). Subjects MR4321M and RQ7733 experienced the 0.1 mg/kg/injection condition first and the 0.2 mg/kg/injection condition second. Subject RQ7715 completed some delay conditions with 0.2 mg/kg/injections first. However, because it was difficult to obtain complete choice functions that ranged from 20–80% food choice with this larger dose in some delay conditions, RQ7715 was switched to the 0.1 mg/kg/injection condition for approximately

one third of the delay conditions, and then returned to the larger-dose condition. RQ7715 then was returned to the smaller-dose conditions to finish all of the delay conditions.

Within each dose condition, food magnitudes and delays were examined in an irregular order within and between monkeys. Each delay condition was in effect until choice was stable according to the following criteria: 1) completion of all sample and choice trials in three consecutive sessions, 2) the number of trials on which the immediate food reinforcer was chosen did not differ from the running three-session mean by more than one trial for three consecutive sessions, and 3) there was no upward or downward trend across the three sessions. Once choice was stable, the sides associated with the cocaine and food reinforcers were reversed, and stable choice was re-determined.

Data Analysis

For each delay condition, we calculated the mean percentage of trials on which immediate food was chosen in the last three sessions of each pairing (and its reversal) of lever-directions with food and cocaine. A separate choice function (i.e., percent choice of immediate food as a function of number of immediate food pellets per delivery) was calculated for each delay with the goal of obtaining functions with choices that ranged from 20–80% food choice in order to obtain indifference points. Although in many of the conditions with shorter delays, food choice did not exceed 50% with the largest food amount tested (16 pellets/delivery), a larger number of pellets/delivery was not tested because satiation was observed with this amount when it was chosen at higher percentages.

In delay-discounting experiments where a hyperbolic framework is used, indifference points are plotted as a function of delay (D), and A in equation 1 is typically the amount of the delayed reinforcer (e.g., Green, Myerson, Shah, Estle, and Holt, 2007; Woolverton et al, 2007). When the immediate and delayed choice alternatives are the same type of reinforcer, setting A equal to the amount of the delayed reinforcer reflects the fact that when $D = 0$, the immediate and delayed reinforcers may be assumed to be equivalent in value, and thus A is also equal to the amount of the immediate reinforcer when $D = 0$. When choice is between different types of reinforcers, A may be set equal either to the amount of immediate reinforcer when the choice is between the two alternatives both delivered immediately and the two reinforcers are chosen equally often (i.e., the indifference point) or to the relative size of the to-be-delayed reinforcer at indifference (i.e., the normalized indifference point, expressed as a proportion or percentage of the other reinforcer; Huskinson et al., 2015). Because the indifference point at the 0-s delay could not be calculated for all subjects, A in equation 1 was estimated by allowing it to vary as a free parameter.

For the delays at which complete choice functions were obtained, the amount of immediate food that predicted 50% choice between immediate food and delayed cocaine (i.e., the indifference point) was estimated by log-transforming the x-axis in the choice functions and fitting a logistic function (GraphPad Software 6.0). In all cases, (normalized) indifference points were expressed as percentages of the estimated value of A for individual subjects. This was done to facilitate comparisons between the two cocaine magnitude conditions in the current study as well as between the current and previous data sets. Importantly, normalizing indifference points in this manner did not change estimates of k or R^2 values.

Drugs

Cocaine hydrochloride was provided by the National Institute on Drug Abuse (Rockville, MD). Solutions were prepared using 0.9% saline. Doses are expressed as the salt forms of the drugs.

Results

Figure 1 shows choice functions obtained for each of the three monkeys at each dose of cocaine (0.1 mg/kg/injection, left column; 0.2 mg/kg/injection, right column). For all three subjects, food choice did not increase above 50% with the largest amount of food tested (16 pellets/delivery) at the 0-s delay, nor in some cases, at the 30-, 60-, and 120-s delays. When choice functions did increase above 0%, choice of immediate food was generally an increasing function of amount at both cocaine doses. However, there were some exceptions to this general finding (e.g., RQ7715 at 240-s delay with 0.1 mg/kg/injection of cocaine). As the delay to cocaine delivery increased, choice functions tended to shift leftward, and progressively smaller amounts of food were chosen over delayed cocaine. Exceptions to this general pattern were most apparent with the larger dose of cocaine.

Figure 2 shows the normalized value of cocaine as a function of the delay to its delivery for each subject at both doses. As the delay to the 0.1 (left column) or 0.2 (right column) mg/kg/injection of cocaine increased, indifference points decreased (i.e., value of the delayed reinforcer was a decreasing function of delay to its receipt). Overall, the data in Figure 2 were fairly well described by a simple hyperbola (mean R^2 = .83, median R^2 = .85, range R^2 = 0.71–0.90). Figure 2 also presents the estimated values of A that were used to normalize indifference points as well as the k values for each subject at each dose. For two of three subjects (MR4321M and RQ7733), A was larger for the larger dose of cocaine, indicating that a larger number of food pellets was subjectively equal to the larger dose of cocaine. This relation was reversed for RQ7715, although it is to be noted that this subject experienced the doses of cocaine in a different order than the other subjects (see Procedure). Obtained k values for the 0.1 (median k = 0.028, range = 0.010–0.028) and 0.2 (median k = 0.009, range = 0.004–0.019) mg/kg/injections of cocaine were similar to previous experiments with food versus food and cocaine versus cocaine choice, but were much smaller than k values obtained with immediate cocaine versus delayed food (see Table 1).

Discussion

As expected, and consistent with previous delay-discounting findings, the value of delayed cocaine decreased as the delay to its delivery increased, and the obtained discounting functions for delayed cocaine were well described by the hyperbolic equation (e.g., Mazur, 1987; Woolverton et al., 2007). Importantly, discounting of delayed cocaine injections was shallow compared to previous experiments with rhesus monkeys in which choice was between immediate cocaine and delayed food. Subjects in the present study tolerated relatively long delays to cocaine delivery, often choosing it over immediate food. Comparison of monkeys' discounting rates in the present study (median k = 0.015) and previous experiments with food and cocaine (see Table 1) reveals that discount rates are similar across different combinations of immediate and delayed food and cocaine with the

important exception that when immediate cocaine is pitted against delayed food, discount rates are relatively steep.

Taken together, these findings lead to three important conclusions. First, discounting rates for delayed reinforcers may differ depending on both the type of reinforcer immediately available and the type of reinforcer available after a delay. Caution should be exercised when making assumptions about discounting rates for a given reinforcer type (e.g., cocaine) based on results from a single choice situation (e.g., choice between immediate cocaine and delayed food). Second, the finding that delayed cocaine is apparently discounted at a relatively shallow rate regardless of the immediate alternative has important implications for our understanding of drug abuse and why drug abusers often devote substantial time and effort to obtaining drugs. Drug abusers may not always be impulsive (i.e., they are apparently able to tolerate delays to drug delivery). Like the monkeys in the present study, drug abusers may exercise self-control in the acquisition of highly preferred yet delayed drug reinforcers. Finally, our results with immediate food and delayed cocaine are similar to discounting with immediate food and delayed food (Huskinson et al., 2015). This suggests that when neither option is cocaine, rhesus monkeys are also able to tolerate relatively long delays to delivery of a nondrug reinforcer. Of course, making cocaine an unavailable option for human drug abusers may not be possible.

Our finding of shallow discounting of a delayed drug reinforcer by rhesus monkeys is in contrast to previous reports with drug-dependent human participants that show steep discounting of hypothetical drugs relative to the rate at which drug-dependent individuals discount hypothetical money (e.g., Bickel, Odum, and Madden, 1999; Bickel et al., 2011; Coffey, Gudleski, Saladin, and Brady, 2003; Madden, Petry, Badger, and Bickel, 1997). There are many procedural differences that likely could account for this difference between the results of human and monkey experiments. In experiments with rhesus monkeys, the reinforcers are actually delivered to the subjects on multiple trials and until choice is stable. Hypothetical outcomes are generally presented to human participants with fewer choice trials, and often with much larger amounts delivered after longer delays (e.g., days, months, or years). Perhaps drug-dependent individuals would discount actual deliveries of cocaine similar to our rhesus monkeys. Indeed, there is evidence that human participants discount actual deliveries of a juice reinforcer at rates similar to discounting of food and liquid reinforcers in nonhuman primates (Freeman et al., 2012; Huskinson et al., 2015; Jimura, Myerson, Hilgard, Braver, and Green, 2009).

An alternative hypothesis is that human participants would discount actual cocaine and hypothetical cocaine at the same rate, and thus, that human participants discount delayed cocaine more impulsively than rhesus monkeys. It also is possible that the difference in delay discounting observed between humans and monkeys is due to the type of nondrug reinforcer examined in each case. For rhesus monkeys, food or liquid is usually the nondrug reinforcer whereas in studies with human participants, hypothetical money is the usual nondrug reinforcer. Money can be used to obtain a wide variety of reinforcers, including food and drugs, and may be discounted differently than food or drugs as a result of its fungibility. A reinforcer with similar characteristics as money does not exist for rhesus monkeys.

It is important to note, however, that our results are consistent with previous laboratory examinations of cocaine versus money or food choice in human participants and rhesus monkeys that have demonstrated similar difficulties in disrupting cocaine choice (e.g., Foltin, Haney, Rubin, Reed, Vadhan, Balter, and Evans, 2015; Nader and Woolverton, 1991; 1992; Negus, 2003). These experiments did not manipulate the delay to cocaine delivery as in the current experiment, but similar results were obtained. For example, increasing the number of responses required (presses on a space bar for human participants and lever presses for rhesus monkeys) or the amount of money (humans) or food pellets (monkeys) had minimal effects (Foltin et al., 2015). In other studies, large response requirements (i.e., 480 responses) and food amounts (i.e., 16 pellets) were necessary to consistently decrease monkeys' cocaine choice (Nader and Woolverton, 1991; 1992).

Another possible explanation for the obtained outcomes is that the level of food restriction in the current experiment was relatively mild. It is to be noted, however, that with rats, deprivation level has no effect on delay discounting of immediate versus delayed water deliveries (Richards, Mitchell, de Wit, and Seiden, 1997; Wade, de Wit, and Richards, 2000) or immediate versus delayed food pellets (Cardinal, Robbins, and Everitt, 2000). In experiments that did not directly assess discounting, moreover, there is no consistent effect of deprivation level on choice of a smaller, more immediate food amount (e.g., Eisenberger, Masterson, and Lowman, 1982; Ho, Wogar, Bradshaw, and Szabadi, 1997). In our previous experiment with immediate food versus delayed food, discounting of delayed food also was relatively shallow, and the food regimen for those subjects was the same as that in the present study (Huskinson et al., 2015). This suggests that the food pellets were sufficiently reinforcing that the monkeys tolerated similar delays to reinforcer delivery. To our knowledge, the effects of food restriction on delay discounting of food and cocaine have not been examined, and thus it remains possible that we would have obtained different results with severely food restricted animals.

On a related note, when interpreting behavior that involves the delivery of cocaine or other stimulants, it also is important to consider cocaine's ability to reduce an organism's appetite as an alternative explanation for the obtained outcomes. Because cocaine is a known appetite suppressant, it is possible that cocaine decreased the reinforcing effectiveness of food, and thus reduced food choice. Notably, previous reports have shown that cocaine and *d*-amphetamine administration can reduce operant responding maintained by food in rhesus monkeys (Glowa and Fantegrossi, 1997; Negus and Mello, 2003a; 2003b; Panlilio, Goldberg, Gilman, Jufer, Cone, and Schindler, 1998). In experiments that have examined effects of cocaine on such behavior, the sessions and timeouts were relatively brief and resulted in relatively large amounts of cocaine intake compared to those possible in the current experiment (Glowa and Fantegrossi, 1997; Panlilio et al., 1998). Doses that resulted in similar intake to the current experiment did not alter food-maintained responding (Glowa and Fantegrossi, 1997). In addition, tolerance to effects of *d*-amphetamine on food-maintained responding generally develops within days (Negus and Mello, 2003a; 2003b). Because the rhesus monkeys in the current experiment received cocaine for several months, and each trial was separated by 30 min, any effect of appetite suppression likely would have been limited to the initial training period (i.e., before tests were conducted).

In the majority of delay-discounting experiments conducted with nonhuman animals, the magnitude of the delayed reinforcer does not affect discounting rate (e.g., Freeman et al., 2009; 2012; for a review, see Vanderveldt et al., 2016). In contrast, human participants choosing between hypothetical outcomes reliably discount larger delayed amounts less steeply than smaller ones (e.g., Green, Myerson, and McFadden, 1997; for a review, see Green and Myerson, 2004). Similarly, the k values in the current experiment were smaller when the delayed cocaine reinforcer was a 0.2 mg/kg/injection than when it was a 0.1 mg/kg/injection. However, given the large amount of data indicating an absence of a magnitude effect with nonhuman subjects, including rhesus monkeys choosing between nondrug reinforcers, data from more subjects will be needed before concluding that monkeys discount larger doses of cocaine less steeply than smaller doses,

In addition, it may be noted that while A was larger in the 0.2 mg/kg/injection condition than in the 0.1 mg/kg/injection condition for two monkeys, the opposite was true for monkey RQ7715. This latter result is peculiar because, as noted previously, A represents the amount of the immediate reinforcer when $D = 0$, indicating that, for this monkey, the higher cocaine dose is predicted to be subjectively equivalent to a smaller amount of food than is the lower dose. This obviously is the opposite of what would be expected, but it should be noted that this subject experienced the larger dose prior to the smaller dose, the other other two subjects experienced the larger dose last, raising the possibility of an order effect in the results for the A parameter.

Future studies are clearly needed to determine whether the present findings generalize to other drugs within the stimulant class (e.g., methamphetamine) as well as to drugs from other drug classes (e.g., opioids). Maguire and colleagues (2016) recently examined delay discounting of remifentanil, an ultra-short acting mu-opioid agonist, in a drug versus drug choice situation. As with cocaine, rhesus monkeys showed relatively shallow discounting of delayed remifentanil, with ks ranging from 0.004–0.008 (median $k = 0.008$). These results suggest that remifentanil, and perhaps other mu-opioid agonists, are discounted similarly to delayed cocaine, although it will be important to determine whether this similarity extends to choices between nondrug and drug reinforcers.

Drug abuse is often conceptualized in terms of impulsive choice of more immediate drug effects over more delayed nondrug alternatives. Contrary to what might be expected given the classification of substance abuse as an impulse-control disorder, however, drug-dependent individuals allocate significant resources to the time-consuming procurement of drugs, often at the expense of immediate nondrug alternatives. We believe the most important finding in this experiment was that discounting of a delayed drug reinforcer, cocaine, was much shallower when the immediate alternative was food than that previously observed in the reverse situation with immediate cocaine and delayed food (Huskinson et al., 2015). This finding demonstrates that rhesus monkeys wait a relatively long time when the delayed outcome is the delivery of a drug reinforcer. More generally, our findings suggest that drug abusers may exercise self-control in the acquisition of delayed drug reinforcers. Future research is needed to determine whether similar effects occur with other drugs of abuse and with drug combinations that are commonly co-abused. Evaluation of the discounting of delayed outcomes may hold promise for the discovery and development of

novel treatments that ideally would reduce choice of delayed as well as immediate drug reinforcers and increase choice of nondrug alternatives.

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Public Significance Statement

Previous reports suggest that drug abusers choose impulsively when drugs are immediately available. The present results demonstrate that rhesus monkeys are relatively self-controlled when choosing between immediate food and delayed cocaine delivery. These results suggest that drug abusers can exercise self-control in pursuit of a highly preferred, delayed drug reinforcer.

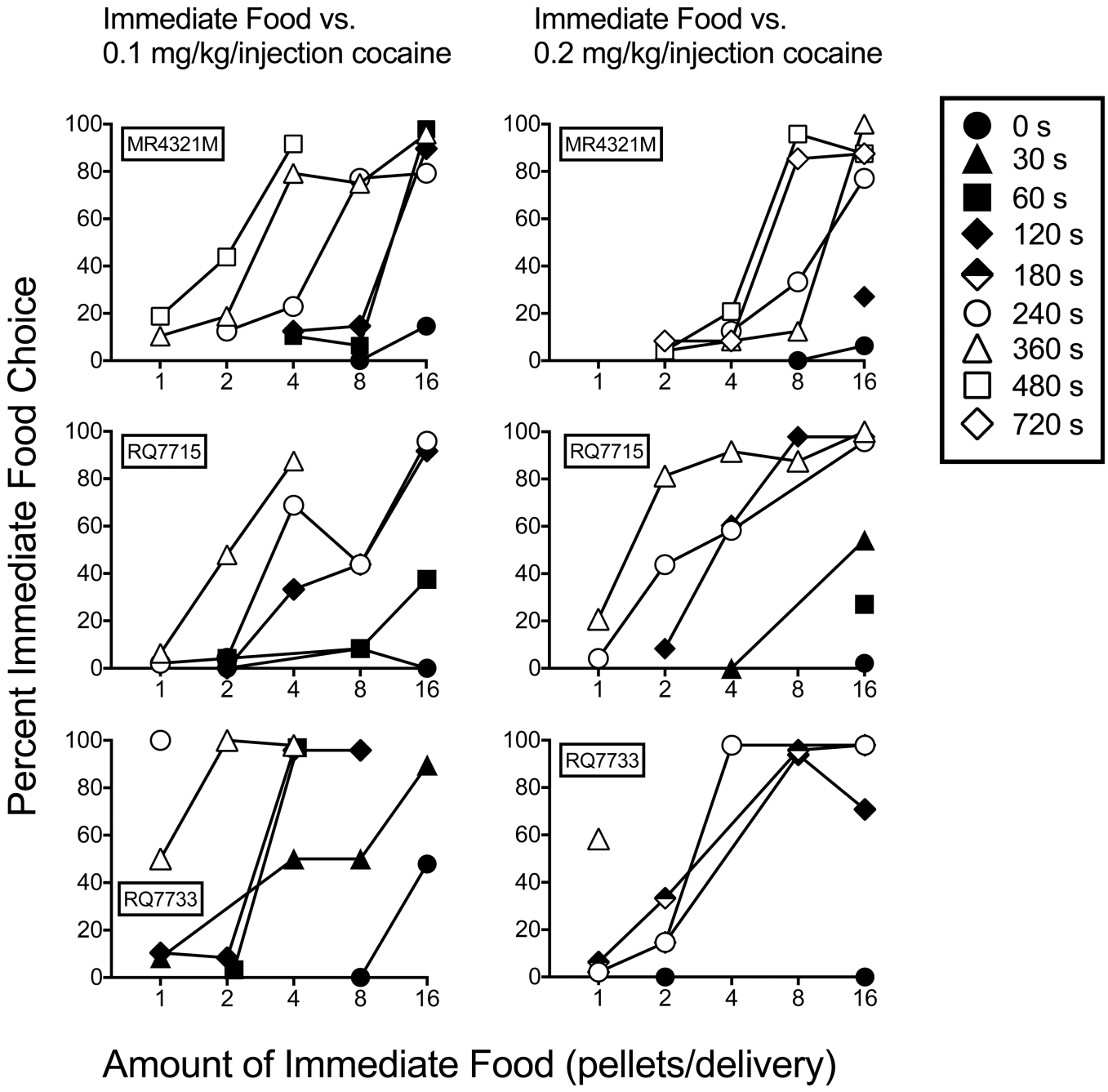

Figure 1.

Mean percent immediate food choice as a function of the immediate amount of food (1–16 pellets/delivery). The delayed amount of cocaine was 0.1 (left column) or 0.2 (right column) mg/kg/injection. Each data point is the average of the initial-lever pairing and its reversal, and each choice function represents a different delay (0–720 s) to the 0.1 or 0.2 mg/kg/injection alternatives.

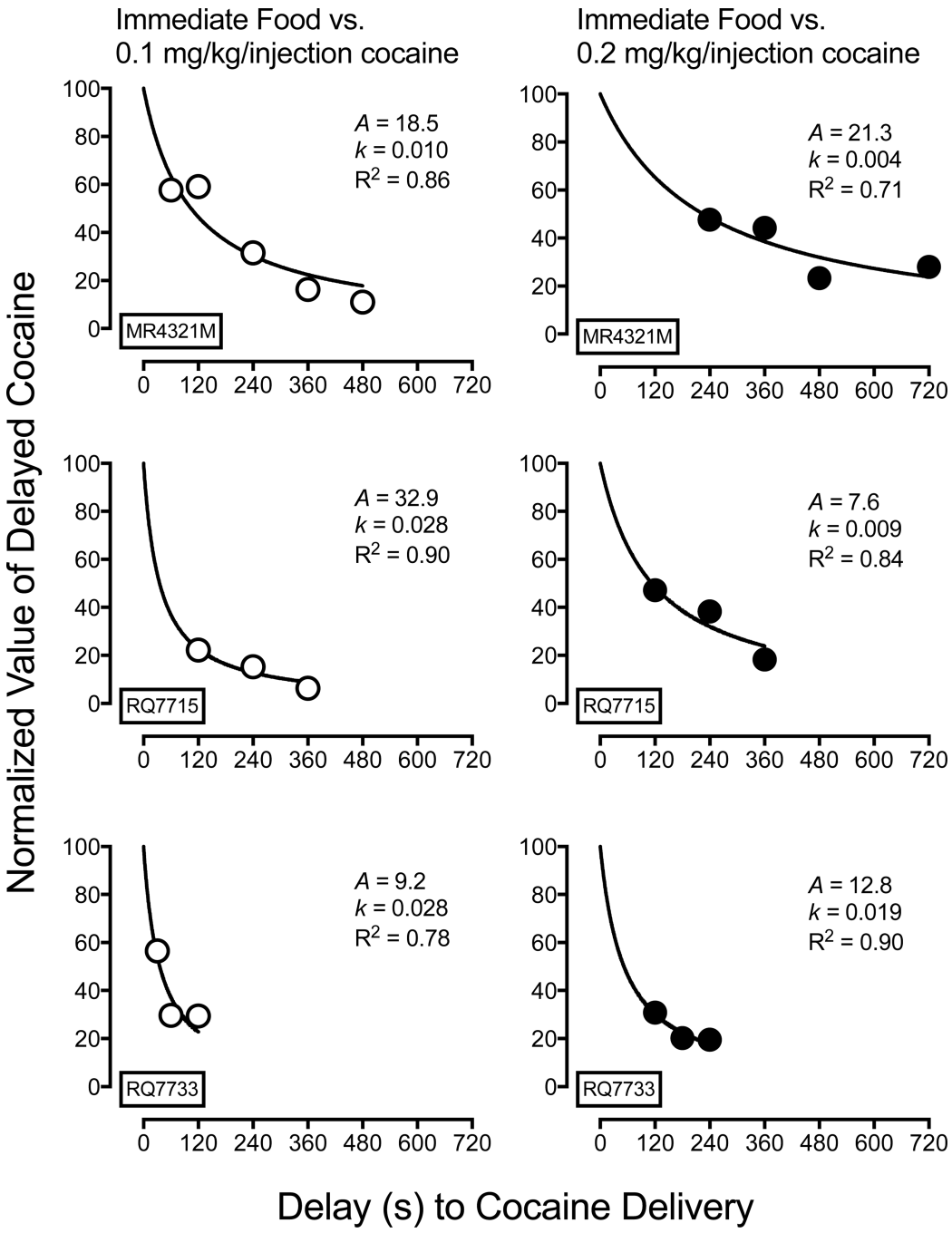

Figure 2.

Normalized value of delayed cocaine injections as a function of the delay (s) to cocaine delivery when choice was between immediate food (1–16 pellets/delivery) and 0.1 (left column) or 0.2 (right column) mg/kg/injection of cocaine. These data were derived from choice functions shown in Figure 1. Each panel shows *A, k*, and R^2 values for individual subjects in each condition.

Table 1

Median *k* values (ranges in parentheses) for rhesus monkey in discounting experiments with food and cocaine reinforcers. For the immediate options, the table provides the range of food amounts or cocaine dosages that were tested; for the delayed options, the fixed, delayed amount or dosage is provided. Blank cells indicate combinations that have not been tested.

	Median *k* value (Range)			
	Delayed Food 4 pellets	**Delayed Food 8 pellets**	**Delayed Cocaine 0.1 mg/kg/injection**	**Delayed Cocaine 0.2 mg/kg/injection**
Immediate Food 1–16 pellets/delivery	0.014[a] (0.010–0.058)	---	0.028[c] (0.010–0.028)	0.009[c] (0.004–0.019)
Immediate Cocaine 0.003–0.4 mg/kg/injection	0.055[a] (0.033–0.827)	0.190[a] (0.035–0.290)	---	0.008[b] (0.002–0.078)

[a] Huskinson et al. (2015)

[b] Woolverton et al. (2007)

[c] Present experiment