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Impulsivity and drugs of abuse: a juice-reinforced operant procedure for determining within-session delay discounting functions in rhesus monkeys

David R. Maguire, Jun-Xu Li*, and Charles P. France

Departments of Pharmacology (DRM, J-XL, CPF) and Psychiatry (CPF), the University of Texas Health Science Center at San Antonio, San Antonio, Texas

Abstract

Introduction—Impulsivity is a behavioral trait that is thought to contribute to a variety of disorders, including drug abuse. Efficient, sensitive procedures are needed for studying drug effects on impulsivity (e.g., delay discounting) in nonhumans.

Methods—Three monkeys responded under an operant choice procedure whereby responses on one lever resulted in immediate delivery of 0.15 ml of juice [Hawaiian Punch®]) and responses on another lever resulted in delivery of 0.75 ml of juice, either immediately or after a delay (3.75–40 s). The delay to the larger reinforcer increased within-session across discrete blocks allowing for generation of delay-discounting functions within sessions.

Results—Without delay, monkeys chose the larger reinforcer nearly exclusively. With increasing delay, monkeys progressively switched their choice from the larger to the smaller reinforcer in a delay-dependent manner. In 2 monkeys, acute administration of morphine (0.1 and 0.32 mg/kg) or ketamine (0.1 and 0.32 mg/kg) but not diazepam (0.1–1.0 mg/kg) dose-dependently shifted the delay-discounting functions to the left, indicating increased discounting. In one monkey, daily morphine treatment (0.32 mg/kg/day, 3-hr pretreatment) produced a rapid, sustained leftward shift in the delay-discounting function; the curve returned to the pre-drug position 6 days after discontinuation of treatment.

Discussion—This delay discounting procedure is sensitive to both behavioral and pharmacological manipulations and appears to be particularly sensitive to chronic drug treatment and drug withdrawal. Given the importance of drug dependence and withdrawal in the initiation, maintenance of, and relapse to drug taking, this procedure should be useful to study one aspect of this process.

Keywords

delay discounting; juice; methods; morphine; opioid; rhesus monkey

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Corresponding author: Charles P France, Department of Pharmacology, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, Texas, USA, 78229-3900, 210 567 6969 (Voice), 210 567 0104 (Fax), france@uthscsa.edu.

*Current address: Department of Pharmacology and Toxicology, University of Buffalo, the State University of New York, Buffalo, NY, USA 14214

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Impulsivity is associated with a number of high risk behaviors, including substance abuse. One common feature of impulsivity is the tendency to choose an immediately available reinforcer over a delayed reinforcer, even when the delayed reinforcer is much larger in magnitude. This behavioral process, whereby the effectiveness of a reinforcer decreases (i.e., discounted) as a hyperbolic function of the delay to its presentation (Mazur, 1987; Myerson & Green, 1995; Rachlin & Raineri, 1992), has been termed delay discounting and differences in the degree of delay discounting appear to be related to certain behavioral patterns. In a typical delay discounting procedure, subjects chose between a smaller reinforcer delivered immediately and a larger reinforcer delivered either immediately or after a delay (Ainslie, 1975; Rachlin, 1974). Under such a procedure, choice for the larger reinforcer is inversely related to the delay to its presentation. The decrease in choice of the larger reinforcer is interpreted as the delay-dependent decrease of the relative value of the larger delayed reinforcer as compared to the smaller immediately available reinforcer. Changes in the steepness of the delay-discounting function are thought to reflect differences in discounting. For example, current drug users discount delayed reinforcers more rapidly than individuals who have never used drugs or those who are drug abstinent (e.g., see reviews by Bickel & Marsch, 2001; Perry & Carroll, 2008; Yi et al., 2009), suggesting that delay discounting might be an important process underlying drug abuse (see Bickel et al, 2012).

A number of studies have examined the effects of acute drug treatment on delay discounting (see de Wit & Mitchell, 2009; Perry & Carroll, 2008 for recent reviews). Many commonly abused drugs (e.g., nicotine, alcohol, cocaine, and opioids) can increase delay discounting, supporting the view that increased discounting might be a consequence of drug use. Other studies have examined whether discounting is a predisposing factor for drug use. For example, more rapid delay discounting in rats can predict increased self-administration of cocaine (Anker et al., 2009; Belin et al., 2008; Dalley et al., 2007; Perry et al., 2008), methylphenidate (Marusich & Bardo 2009), and alcohol (Oberlin et al., 2009; Poulos et al., 1995), suggesting that increased discounting might also contribute to the initiation and maintenance of drug abuse (although see Schippers et al., 2012).

Drug abuse is a behavioral pattern associated with repeated (chronic) drug taking over extended periods of time. Thus, studies on the effects of chronic drug administration are necessary to fully understand how changes in discounting might influence drug abuse. Relatively few studies have examined the effects of chronic drug treatment or discontinuation of chronic treatment on discounting, although the limited data that are available suggest that discounting can be increased by chronic drug treatment as well (e.g., Setlow et al., 2009 for a review; Harvey-Lewis et al., 2012). There are a number of challenges to studying the effects of chronic drug treatment and discontinuation of treatment on delay discounting in the preclinical laboratory, including the following: 1) extended training is often necessary to establish stable baseline performance; 2) extended drug treatment is often necessary to establish stable drug effects (e.g., tolerance, dependence); 3) discontinuation-induced changes in behavior can persist for many days or weeks; 4) depending on the particular procedure, generating a complete delay discounting function might require many sessions; and 5) the species that are commonly used to study delay discounting (e.g., rats) have a relatively short lifespan. Moreover, ethical, safety, and cost considerations preclude such chronic dosing studies in humans.

Several laboratories have examined delay-discounting in nonhuman primates (e.g., Anderson & Woolverton, 2003; Carroll et al., 2009; Freeman et al., 2009, 2012; Hamilton et al., 2012; Jedema et al., 2010; Kim et al., 2008, 2009; Newman et al., 2008; Tobin et al., 1996; Woolverton & Anderson, 2006; Woolverton et al., 2007) although few studies have examined repeated (chronic) drug treatment or used a procedure that allows determination of

delay-discounting functions within a single session. Within-session determination of delay functions would facilitate efficient determination of discounting at specific time points (e.g., after acute drug administration) as well as evaluation of changes in discounting across time (e.g., during chronic drug administration or after discontinuation of drug administration). The goal of this study was to develop a delay-discounting procedure in rhesus monkeys (a species with a relatively long [>20 years] lifespan) that would allow determination of delay functions within a single session. A preferred drink (Hawaiian Punch[®]) was used to maintain responding because the magnitude of this reinforcer (i.e., volume) is easily varied and controlled. Because monkeys were trained successfully under this procedure, the effects of several drugs of abuse (e.g., morphine), that have been reported to alter delay discounting under other conditions (Kieres et al., 2004; Floresco et al., 2008), were examined for their effects on delay discounting for juice.

Methods

Subjects

Three adult rhesus monkeys (*Macaca mulatta*), two female (VE and NK) and one male (OP), were used in this study. Their body weight (7–9 kg) was maintained by post-session feeding (Harlan Teklad, High Protein Monkey Diet, Madison, WI, USA) in the home cages. Monkeys also received fresh fruit and peanuts daily. Access to water was available for 4 hours daily beginning immediately after training sessions (i.e., 20-hour fluid restriction); during sessions monkeys could respond to receive juice (Hawaiian Punch[®]) as described below. Subjects were housed individually in a colony room and were maintained under a 14/10-hour light/dark cycle (lights on at 0600). Animals used in these studies were maintained in accordance with the Institutional Animal Care and Use Committee, The University of Texas Health Science Center at San Antonio, and the 1996 Guide for the Care and Use of Laboratory Animals (Institute of Laboratory Animals Resources on Life Sciences, National Research Council, National Academy of Sciences).

Apparatus

Monkeys were seated in commercially available primate chairs (Model R001, Primate Products, Miami, FL) that were placed in sound-attenuating operant chambers containing two response levers. Located above each lever were circular, translucent disks that could be trans-illuminated either green or white. The custom-made juice delivery system included a liquid reservoir, a solenoid valve, and a clear soft PVC tube. The solenoid valve was controlled by software that also controlled all other experimental events (Med-PC IV software, Med Associates, Inc., East Fairfield, VT). The PVC tube delivered the juice and was protected by a steel tube assembled on the primate chair; placement of the tube was adjusted so as to be immediately adjacent to the mouth of the monkey such that the monkey could easily contact and drink from the end of the tube. Extraneous sounds were masked by white noise and an exhaust fan. Experimental events were arranged and data were recorded by an interface (Med Associates, Inc., East Fairfield, VT) connected to a PC computer running Med-PC IV software.

Behavioral procedure

Initially monkeys were trained to press on either of two levers for delivery of banana-flavored food pellets (300 mg; Bio-Serv, Frenchtown, NJ). During this training period, monkeys were also trained after daily sessions to drink juice from a drinking tube. After responding for pellets occurred reliably (i.e., monkeys received 100 pellets within a 1-hour session for at least 3 consecutive sessions), the reinforcer was changed to small volumes (0.15–0.75 ml) of juice. Monkeys rapidly learned to drink juice through the PVC tube.

The procedure used in the current study was similar to the procedure described by Evenden and Ryan (1996) for generating within-session delay functions in rats. Sessions consisted of five 14-min blocks. Each block began with 2 forced trials followed by 10 choice trials. During a forced trial a light over one of the levers was illuminated and a response on that lever delivered the reinforcer (0.15 ml of juice immediately or 0.75 ml of juice either immediately or after a delay) that was associated with that lever during subsequent choice trials in that block. During the second choice trial the light over the other lever was illuminated and a response on that lever delivered the alternate reinforcer (i.e., that was not available during the first forced trial) that was associated with that lever during subsequent choice trials in that block. The order of presentation of forced trials was the same for each block within a daily session but changed quasi-randomly across sessions with the constraint that the same order could not occur for more than two consecutive sessions. During choice trials lights were illuminated over both levers and a response on either lever produced a reinforcer. During forced and choice trials, the first response on an active lever immediately extinguished the green light(s) and illuminated the white center light until juice delivery. For all three monkeys, responses on the left lever resulted in illumination of the white center light for 0.5 s followed by immediate delivery of 0.15 ml of juice; responses on the right lever resulted in illumination of the white center light for 0.5 to 40 s (depending on the monkey and arranged delay) followed by the delivery of 0.75 ml of juice. Following the delivery of juice was a timeout period that lasted for a variable period (equal to 60 s minus the delay) that was adjusted so that the period of time between the end of one response period and the beginning of the subsequent response period was always the same. During the timeout period, all lights were off and responding had no programmed consequence. Each response period lasted for a maximum of 15 s (limit hold); if a response on the active lever did not occur during that time, the green light(s) was (were) extinguished, and a 60-s timeout period was initiated. Sessions were conducted daily at approximately the same time and lasted 70 min.

Upon implementation of the delay procedure a logarithmic series of delays was introduced. For monkey VE the series was 0, 3.75, 7.5, 15, and 30 s, and for monkeys NK and OP the series was 0, 5, 10, 20, and 40 s. These series were determined empirically for individual monkeys in order to generate conditions where there was a progressive switch in responding from the lever associated with 0.15 ml juice to the lever associated with 0.75 ml of juice over the 5 blocks. Delays were presented in ascending order each session with one delay per block; the first block never included a delay (i.e., either reinforcer was available for immediate delivery).

Sessions without any delay in all 5 blocks were conducted every 5 to 7 sessions to confirm that switching within sessions was due to delay and not to other (e.g., temporal) factors. No-delay sessions, with both reinforcers available immediately after a response, occurred daily until responding for the larger reinforcer in the last block of the session (previously associated with the longest delay) was greater than 80%. Delays were re-introduced in the next daily session.

Pharmacological procedure

After responding was stable with delays, the effects of morphine, ketamine, and diazepam were assessed by administering a single dose of a drug 15 min prior to the start of the session. Saline was administered prior to other sessions including, but not limited to, sessions immediately preceding a drug test session. Doses of each drug were assessed in a non-systematic order and under the constraint that at least one non-drug (saline) session intervened between successive drug administrations. A drug test did not occur if the delay curve generated during the immediately preceding session did not fall within the 95%

confidence intervals (95% CI) of the delay curve determined under baseline conditions prior to commencement of drug testing.

The effect of daily morphine administration was assessed in one monkey (VE) by administering 0.32 mg/kg morphine once daily 3 hours prior to daily sessions. Daily administration of morphine continued for 22 sessions, after which daily morphine injections were replaced with daily saline injections.

Data analysis

For each session the total number of trials completed and the percentage of responses emitted on the lever associated with the larger reinforcer were recorded. The percentage of responding for the larger reinforcer was used to construct delay-response curves. The mean ($\pm$ 95% CI) delay-response curves observed in all sessions immediately preceding test sessions served as a control for any drug effects. If the response curve determined after the administration of drug fell outside of the 95% CI of the control curves, the effect of drug on delay was considered to be significantly different from control.

Drugs

The drugs used in this study were morphine sulfate (The Research Technology Branch, National Institute on Drug Abuse, Rockville, MD, USA), ketamine hydrochloride (Burns Veterinary Supply, Farmers Branch, TX, USA), and diazepam (Sigma Chemical, St. Louis, MO, USA). Morphine was dissolved in sterile water. Ketamine was obtained in a commercially prepared solution and diluted with saline to the appropriate concentrations. Diazepam was dissolved in a vehicle comprising 50% ethanol and 50% Emulphor then diluted with saline for specific concentrations. All drugs were administered subcutaneously in a volume of 0.2 to 0.8 ml, and pretreatment times were either 15 min or 3 hr, depending on the experimental conditions.

Results

A total of 300 and 267 training sessions were conducted with monkeys NK and VE, respectively, prior to drug testing; a total of 324 sessions were conducted with OP before being removed from the study (i.e., not tested with drugs). Across those training sessions there was no delay in effect for 98, 81, and 147 training sessions for monkeys NK, VE, and OP, respectively. Figure 1 shows the mean ($\pm$ 95% CI) percent responding for the larger reinforcer as a function of delay averaged across 10 sessions with delays that immediately preceded (circles) or followed (inverted triangles) sessions without delays (diamonds). All monkeys responded more than 80% on the lever associated with the larger reinforcer during the first block when both reinforcers were available immediately. As the delay to the larger reinforcer increased, responding for the larger reinforcer decreased (to 30, 10, and 20 % for VE, NK, and OP, respectively, in the last block; Figure 1) and responding for the smaller reinforcer increased accordingly. When delays were removed for all blocks (diamonds) monkeys responded predominantly on the lever associated with the larger reinforcer in all blocks. The average number (range) of no-delay sessions that were required for monkeys to satisfy the criterion of responding at least 80% on the lever associated with the large reinforcer during the last block were 2.1 (1–14), 1.6 (1–4), and 3.5 (1–17) for monkeys NK, VE, and OP, respectively. During the first session in which the delays were reinstated (triangles), responding for the larger reinforcer again decreased as a function of delay to the larger reinforcer with the resulting delay functions closely approximating the initial delay function for individual monkeys.

Administration of 0.32 mg/kg morphine 15 min prior to the session shifted the delay-response curve leftward in both monkeys (Figure 2). Monkeys responded more than 80% for the larger reinforcer during the first block when there was no delay; however, responding for the larger reinforcer decreased and responding for the smaller reinforcer increased in blocks with delay after the administration of 0.32 mg/kg morphine. A smaller dose of morphine (0.1 mg/kg) had no apparent effect on the delay-response curve. Neither dose of morphine significantly affected the number of trials completed in the session, as compared with control (saline) performance in these monkeys (Table 1).

Administration of ketamine 15 min prior to the session also shifted the delay-response curves to the left in both monkeys (Figure 3). Monkeys responded more than 80% for the larger reinforcer during the first block when there was no delay; however, responding for the larger reinforcer decreased and responding for the smaller reinforcer increased in blocks with delay after the administration of 0.1 or 0.32 mg/kg ketamine. Administration of diazepam 15-min prior to the session did not appear to change the delay function in either monkey (Figure 4), up to doses that markedly decreased the number of trials completed in both monkeys (Table 1).

The effects of daily morphine treatment and discontinuation of daily treatment were assessed in monkey VE. A dose of 0.32 mg/kg of morphine administered 15 minutes before the session shifted the delay-response curve leftward; in contrast, there was no apparent effect on the delay curve when the same dose was administered 3 hours prior to the session (Figure 5, left panel). Although 0.32 mg/kg of morphine 3 hours prior to the session had no apparent effect on the delay function (diamonds, left and center panels, Figure 5), when that dose was administered daily it shifted the delay function to the left (Figure 5, center panel). The center panel of Figure 5 shows that on days 7, 16, and 22 of once daily treatment with 0.32 mg/kg of morphine the delay function was shifted leftward with this monkey responding predominantly on the lever associated with the smaller reinforcer at all delay values. Under control conditions (i.e., no morphine treatment) this monkey responded predominantly on the lever associated with the larger reinforcer at all delay values except 30 seconds. During the first block for all sessions when there was no delay for either reinforcer, this monkey continued to respond predominantly for the larger reinforcer (Figure 5, data points above "0", center panel). Two days after the discontinuation of daily morphine treatment the delay-response curve remained shifted to the left (Figure 5, right panel, inverted triangles); however, 4 days later (i.e., 6 days after discontinuation of treatment) the curve had shifted to the right and was similar to the control curve determined prior to morphine treatment.

Discussion

This study developed a procedure for studying delay discounting in rhesus monkeys responding under a concurrent schedule of juice presentation with responding on one lever resulting in delivery of a small amount (0.15 ml) of juice and responding on a second lever resulting in delivery of a larger amount (0.75 ml) of juice. Responding under this procedure was sensitive to both reinforcer delay and to reinforcer amount, as evidenced by both within- and across-session changes in responding. During the first block of sessions, when both reinforcers were available immediately after a response, all monkeys responded predominantly on the lever associated with the larger amount of juice; however, as the delay to the larger reinforcer increased, responding for the larger reinforcer decreased and responding for the smaller reinforcer increased. When the delay to the larger reinforcer was removed for the entire session, monkeys responded on the lever associated with the larger reinforcer in all blocks within 1 to 3 sessions. The rapid adjustment in response allocation suggests that the within-session pattern of switching from responding on one lever to

responding on the other was a function of delay and not simply due to the passage of time or number of blocks. When the delays were reinstated for the larger reinforcer, the delay function re-emerged rapidly and often with a single session. The patterns of responding observed in the current study with rhesus monkeys closely resemble those obtained in rats using a similar procedure (e.g., Evenden & Ryan, 1996). Therefore, the current procedure, adapted for rhesus monkeys, appears to produce stable and sensitive performance that is under the control of the experimentally relevant variables (i.e., reinforcer delay and amount).

This procedure was developed with a small number of subjects which, under some conditions, might be expected to limit the generality of these results; however, one purpose for developing this procedure was to generate stable delay functions within a single session so as to facilitate studies that require frequent assessment of drug effects over long periods of time. Within-subject designs of this type allow for comparison of effects during each phase of an experiment with comparison to baseline responding for individual subjects. Multiple replications of delay functions within and among subjects increases confidence that the observed results will generalize to a broader set of subjects and conditions.

The role of delay discounting in drug abuse has received considerable attention (see Bickel et al., 2012) and procedures similar to the one developed in this study have allowed investigators to assess (within-session) the effects of various factors on discounting (see de Wit & Mitchell, 2009; Perry & Carroll, 2008 for recent reviews). Results of this study demonstrate that reliable within-session delay functions can be determined repeatedly in monkeys over long periods of time. Moreover, those delay functions were sensitive to the effects of drug administered acutely or repeatedly. Studying dosing conditions that model human drug abuse can require many months of treatment and testing. Moreover, substantial periods of training are often required to establish stable performance with choice procedures and delay. Together with the relatively long lifespan of monkeys in the laboratory, these results indicate that procedures such as the one described in this paper will be especially useful for studying the consequences of long-term drug treatment, dependence, tolerance, and withdrawal on delay discounting, a widely studied index of impulsivity.

Once the procedure was established and shown to be sensitive to delay, several drugs were examined for their ability to alter delay functions. Acute administration of the mu opioid receptor agonist morphine shifted the delay function leftward in both monkeys by decreasing responding for the larger reinforcer only in components associated with a delay to the larger reinforcer, suggesting it increased sensitivity to reinforcer delay and thus increased delay discounting. These data are consistent with previous work in rodents indicating that acute administration of morphine increases delay discounting (e.g., Kieres et al., 2004; Pattij et al., 2009; Pitts & McKinney, 2005). Acute administration of the NMDA receptor antagonist ketamine also shifted the delay curve leftward without altering responding for the larger reinforcer in the first (no-delay) block (e.g., Floresco et al., 2008). The benzodiazepine diazepam failed to systematically alter the delay function up to doses that produced general behavioral disruptions, consistent with results in humans showing that benzodiazepines do not reliably alter impulsivity (Acheson et al., 2006; Reynolds et al., 2004).

Most drug abuse involves repeated (often daily) drug administration necessitating the development of procedures that can be used to examine long-term drug treatment on measures of impulsivity. Daily treatment with an initially ineffective dose of morphine (0.32 mg/kg administered 3 hr prior to the session) resulted in a leftward shift in the delay curve that persisted for the duration of chronic treatment (22 days). Within a week after chronic treatment was discontinued, the curve shifted back to the original baseline position. These data showing that repeated administration of an otherwise ineffective dose of an opioid

receptor agonist (morphine) enhance discounting, support the view that chronic exposure to drugs increases discounting, impulsivity, and the risk for continued drug use (e.g., prescription opioids). These data are commensurate with other reports from rats showing that repeated treatment with opioid receptor agonists is associated with increased discounting (e.g., Harvey-Lewis et al., 2012; Schippers et al., 2012).

One striking finding of the current study is that this delay discounting procedure appears to be very sensitive to morphine. A dose of 0.32 mg/kg morphine has few, if any, behavioral effects (e.g., antinociception, discriminative stimulus effects, decreased respiration) in rhesus monkeys (Gerak et al., 1998; Li et al., 2008a, b), although this dose of morphine can increase scratching (Ko et al., 2003). In the current study, acute treatment with 0.32 mg/kg morphine markedly shifted the delay discounting function leftward in both monkeys studied, demonstrating that this procedure is sensitive to morphine. Thus, this procedure may offer a sensitive method to study one aspect (increased delay discounting) of opioid effects that has not been rigorously examined but which might be particularly relevant to recent increases in the abuse of prescription opioids. Another interesting finding is that repeated morphine treatment, at a dose that acutely does not alter the delay discounting function, markedly shifted the discounting curve leftward. This effect is not likely due to the accumulation of drug across days since even a 10-fold larger dose of morphine (3.2 mg/kg) lasts for not more than 6 hours (France, unpublished observation). This effect of morphine is also reversible because 6 days after the discontinuation of daily treatment the discounting curve returned to its pre-treatment position. Thus, this procedure may be particularly useful for examining temporal changes in the discounting function during and after repeated drug treatment, and consequently, may be useful to begin to understand the consequence of prolonged drug treatment and withdrawal.

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References

- Acheson A, Reynolds B, Richards JB, de Wit H. Diazepam impairs behavioral inhibition but not delay discounting or risk taking in healthy adults. *Exp Clin Psychopharmacol.* 2006; 14:190–198. [PubMed: 16756423]
- Ainslie G. Specious reward: a behavioral theory of impulsiveness and impulse control. *Psychol Bull.* 1975; 82:463–496. [PubMed: 1099599]
- Anderson KG, Woolverton WL. Effects of dose and infusion delay on cocaine self-administration choice in rhesus monkeys. *Psychopharmacology (Berl).* 2003; 167:424–430. [PubMed: 12690423]
- Anker JJ, Perry JL, Gliddon LA, Carroll ME. Impulsivity predicts the escalation of cocaine self-administration in rats. *Pharmacol Biochem Behav.* 2009; 93:343–348. [PubMed: 19490925]
- Bickel WK, Marsch LA. Toward a behavioral economic understanding of drug dependence: delay discounting processes. *Addiction.* 2001; 96:73–86. [PubMed: 11177521]
- Bickel WK, Jarmolowicz DP, Mueller ET, Koffarnus MN, Gatchalian KM. Excessive discounting of delayed reinforcers as a trans-disease process contributing to addiction and other disease-related vulnerabilities: emerging evidence. *Pharmacol Ther.* 2012; 134:287–297. [PubMed: 22387232]
- Carroll ME, Mach JL, La Nasa RM, Newman JL. Impulsivity as a behavioral measure of withdrawal of orally delivered PCP and nondrug rewards in male and female monkeys. *Psychopharmacology (Berl).* 2009; 207:85–98. [PubMed: 19697013]
- Dalley JW, Fryer TD, Brichard L, Robinson ES, Theobald DEH, Laane K, Pena Y. Nucleus accumbens D2/3 receptors predict trait impulsivity and cocaine reinforcement. *Science.* 2007; 315:1267–1270. [PubMed: 17332411]

- de Wit, H.; Mitchell, SH. Drug effects on delay discounting. In: Madden, GJ.; Bickel, WK., editors. *Impulsivity: the behavioral and neurological science of discounting*. Washington, DC: American Psychological Association; 2009. p. 213-242.
- Evenden JL, Ryan CN. The pharmacology of impulsive behaviour in rats: the effects of drugs on response choice with varying delays of reinforcement. *Psychopharmacology (Berl)*. 1996; 128:161–170. [PubMed: 8956377]
- Floresco SB, Tse MTL, Ghods-Sharifi S. Dopaminergic and glutamatergic regulation of effort- and delay-based decision making. *Neuropsychopharmacology*. 2008; 33:1966–1979. [PubMed: 17805307]
- Freeman KB, Green L, Myerson J, Woolverton WL. Delay discounting of saccharin in rhesus monkeys. *Behav Processes*. 2009; 82:214–218. [PubMed: 19540317]
- Freeman KB, Nonnemacher JE, Green L, Myerson J, Woolverton WL. Delay discounting in rhesus monkeys: equivalent discounting of more and less preferred sucrose solutions. *Learn Behav*. 2012; 40:54–60. [PubMed: 21870212]
- Gerak LR, Brandt MR, France CP. Studies on benzodiazepines and opioids administered alone and in combination in rhesus monkeys: ventilation and drug discrimination. *Psychopharmacology (Berl)*. 1998; 137:164–174. [PubMed: 9630003]
- Hamilton LR, Czoty PW, Nader MA. Behavioral characterization of adult male and female rhesus monkeys exposed to cocaine throughout gestation. *Psychopharmacology (Berl)*. 2011; 213:799–808. [PubMed: 20959969]
- Harvey-Lewis C, Perdrizet J, Franklin KBJ. The effect of morphine dependence on impulsive choice in rats. *Psychopharmacology (Berl)*. 2012; 1007/s00213-012-2738-5
- Kieres AK, Hausknecht KA, Farrar AM, Acheson A, de Wit H, Richards JB. Effects of morphine and naltrexone on impulsive decision making in rats. *Psychopharmacology*. 2004; 173:167–174. [PubMed: 14752586]
- Ko MC, Lee H, Song MS, Sobczyk-Kojiro K, Mosberg HI, Kishoika S, Naughton NN. Activation of κ -opioid receptors inhibits pruritus evoked by subcutaneous or intrathecal administration of morphine in monkeys. *J Pharmacol Exp Ther*. 2003; 305:173–179. [PubMed: 12649366]
- Li JX, McMahon LR, France CP. Comparison of naltrexone, 6 α -naltrexol, and 6 β -naltrexol in morphine-dependent and in nondependent rhesus monkeys. *Psychopharmacology (Berl)*. 2008a; 195:479–486. [PubMed: 17874317]
- Li J-X, McMahon LR, Gerak LR, Becker GL, France CP. Interactions between Delta(9)-tetrahydrocannabinol and mu opioid receptor agonists in rhesus monkeys: discrimination and antinociception. *Psychopharmacology (Berl)*. 2008b; 199:199–208. [PubMed: 18470505]
- Mazur, JE. An adjusting procedure for studying delayed reinforcement. In: Commons, ML.; Mazur, JE.; Nevin, JA.; Rachlin, H., editors. *Quantitative analyses of behavior: the effect of delay and of intervening events on reinforcement value*. Vol. 5. Hillsdale, NJ: Erlbaum; 1987. p. 55-73.
- Marusich JA, Bardo MT. Differences in impulsivity on a delay discounting task predict self-administration of a low unit dose of methylphenidate in rats. *Behav Pharmacol*. 2009; 20:447–454. [PubMed: 19696657]
- Myerson J, Green L. Discounting of delayed rewards: models of individual choice. *J Exp Anal Behav*. 1995; 64:263–276. [PubMed: 16812772]
- Newman JL, Perry JL, Carroll ME. Effects of altering reinforcer magnitude and reinforcement schedule on phencyclidine (PCP) self-administration in monkeys using an adjusting delay task. *Pharmacol Biochem Behav*. 2008; 90:778–786. [PubMed: 18582491]
- Oberlin BG, Grahame NJ. High-alcohol preferring mice are more impulsive than low-alcohol preferring mice as measured in the delay discounting task. *Alcohol Clin Exp Res*. 2009; 33:1294–1303. [PubMed: 19389183]
- Pattij T, Schetters D, Janssen MCW, Wiskerke J, Schoffelmeer AN. Acute effects of morphine on distinct forms of impulsive behavior in rats. *Psychopharmacology (Berl)*. 2009; 205:489–502. [PubMed: 19436995]
- Perry JL, Nelson SE, Carroll ME. Impulsive choice as a predictor of acquisition of IV cocaine self-administration and reinstatement of cocaine-seeking behavior in male and female rats. *Exp Clin Psychopharmacol*. 2008; 16:165–177. [PubMed: 18489020]

- Perry JL, Carroll ME. The role of impulsive behavior in drug abuse. *Psychopharmacology (Berl)*. 2008; 200:1–26. [PubMed: 18600315]
- Pitts RC, McKinney AP. Effects of methylphenidate and morphine on delay-discount functions obtained within sessions. *J Exp Anal Behav*. 2005; 83:297–314. [PubMed: 16047609]
- Poulos CX, Le AD, Parker JL. Impulsivity predicts individual susceptibility to high levels of alcohol self-administration. *Behav Pharmacol*. 1995; 6:810–814. [PubMed: 11224384]
- Rachlin H. Self-control. *Behaviorism*. 1974; 2:94–107.
- Rachlin, H.; Raineri, A. A behavioral view of irrationality, impulsiveness, and selfishness. In: Loewenstein, GF.; Elster, J., editors. *Choice over time*. New York: Russell Sage Foundation; 1992. p. 93-118.
- Reynolds B, Richards JB, Dassinger M, de Wit H. Therapeutic doses of diazepam do not alter impulsive behavior in humans. *Pharmacol Biochem Behav*. 2004; 79:17–24. [PubMed: 15388279]
- Schippers MC, Binnekade R, Schoffeleer ANM, Pattij T, De Vries TJ. Unidirectional relationship between heroin self-administration and impulsive decision-making in rats. *Psychopharmacology (Berl)*. 2012; 219:443–452. [PubMed: 21887498]
- Setlow B, Mendez IA, Mitchell MR, Simon NW. Effects of chronic administration of drugs of abuse on impulsive choice (delay discounting) in animal models. *Behav Pharmacol*. 2009; 20:380–389. [PubMed: 19667970]
- Tobin H, Logue AW, Chelonis JJ, Ackerman KT, May JG. Self-control in the monkey *macaca fascicularis*. *Learn Behav*. 1996; 24:168–174.
- Woolverton WL, Anderson KG. Effects of delay to reinforcement on the choice between cocaine and food in rhesus monkeys. *Psychopharmacology (Berl)*. 2006; 186:99–106. [PubMed: 16568283]
- Woolverton WL, Myerson J, Green L. Delay discounting of cocaine by rhesus monkeys. *Exp Clin Psychopharmacol*. 2007; 15:238–244. [PubMed: 17563210]
- Yi, R.; Mitchell, SH.; Bickel, WK. Delay discounting and substance abuse. In: Madden, GJ.; Bickel, WK., editors. *Impulsivity: the behavioral and neurological science of discounting*. Washington, DC: American Psychological Association; 2009. p. 191-211.

Figure 1.

Delay discounting functions obtained prior to (circles), during (diamonds), and after (inverted triangles) sessions with no delay. The mean ($\pm$ 95% CI) percent responding for the larger reinforcer (ordinate) is plotted as a function of delay (s) to the larger reinforcer (abscissa). Data were averaged across 10 sessions for three monkeys.

Figure 2.

Delay functions for two monkeys that received pre-session injections of saline (circles), 0.1 mg/kg (inverted triangles), or 0.32 mg/kg (triangles) morphine. See Figure 1 for other details.

Figure 3.

Delay functions for two monkeys that received pre-session injections of saline (circles), 0.1 mg/kg (inverted triangles), or 0.32 mg/kg (triangles) ketamine. See Figure 1 for other details.

Figure 4.

Delay functions for two monkeys that received pre-session injections of saline (circles), 0.1 mg/kg (inverted triangles), 0.32 mg/kg (triangles), or 1.0 mg/kg (diamonds) diazepam. See Figure 1 for other details.

Figure 5.

Effects of morphine on delay functions in VE before, during, and after daily morphine treatment. Left panel: effects of 0.32 mg/kg of morphine administered 15 min or 3 hours prior to the session. Center panel: delay functions determined on days 1, 7, 16, and 22 of treatment with 0.32 mg/kg/day of morphine administered 3 hours prior to sessions. Right panel: delay functions determined 2 days and 6 days after discontinuation of daily morphine administration. See Figure 1 for other details.

Table 1

Trials completed per session

Monkey	Baseline [*]	<u>Morphine (mg/kg)</u>		<u>Ketamine (mg/kg)</u>		<u>Diazepam (mg/kg)</u>	
		0.1	0.32	0.1	0.32	0.1	0.32
VE	50 ^{**}	50	50	50	50	50	49
NK	43.4 (36.9–46.8)	46	50	34	42	***	30

* The values under “Baseline” represent the mean number of trials completed during control sessions. The 95% confidence interval surrounding the mean is shown in parentheses for monkey NK.

** Monkey VE completed all trials during baseline sessions; confidence limits were not calculated.

*** This dose of diazepam was not tested in monkey NK.