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Effects of acute and repeated administration of caffeine on temporal discounting in rats

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Abstract

Delay to presentation is one variable that can weaken the reinforcing efficacy of an outcome in a choice situation and drugs have been shown to modify such choices. A growing body of literature has examined effects of stimulant drugs on temporal (delay) discounting, but effects of caffeine, the most widely used stimulant in the world, have not previously been assessed. In the present experiment, effects of caffeine (administered acutely and repeatedly) on temporal discounting were analyzed. Male Sprague–Dawley rats ($n=7$) chose between a single food pellet delivered immediately after a lever press and three food pellets delivered after a delay. The delay to the three pellets increased within each session, from 0 to 16 s. High doses of caffeine increased large-reinforcer choice relative to control conditions. With repeated caffeine exposure, percent choice for the large reinforcer decreased relative to acute administration, but was still greater than pre-drug baseline. Following withdrawal of drug administration, choice returned to levels seen during pre-drug baseline. Reintroduction of caffeine increased the percent choice for a larger, delayed reinforcer to near acute levels. The results from the present study are consistent with previous research in which stimulant drugs have decreased temporal (delay) discounting.

Keywords: Caffeine; Choice; Delay discounting; Impulsivity; Rat; Stimulant; Temporal discounting

1. Introduction

In general, as the delay to reinforcer presentation increases, the subjective value of the reinforcer decreases. Value is often defined in terms of response allocation to alternatives correlated with reinforcers. The decrease in value with increasing delay is known as delay or temporal discounting (cf. Mazur, 1987) and has been demonstrated with both human and nonhuman animals. As the natural environment is often filled with competing reinforcers of different magnitudes and occurring at different delays, choice between delayed and immediate reinforcers is of both conceptual and practical interest.

Choice has been studied extensively in situations in which an organism must select between two quantitatively different, but qualitatively similar reinforcers, such as two amounts of money, drugs, or food (see Green and Myerson, 2004, for a review). Such differential choices can be operationally defined as "self-controlled" or "impulsive" (Ainslie, 1974). Typically, the "self-controlled" choice consists of the selection of a larger, delayed reinforcer to the exclusion of a smaller, more immediate reinforcer. "Impulsive" choice is defined as the selection of a smaller reinforcer to the exclusion of a larger, delayed reinforcer. When the delay to the presentation of both reinforcers is relatively short, more responses are typically allocated to the alternative correlated with the larger reinforcer. As delay to the larger reinforcer is increased, responding switches to favor the smaller, more immediate reinforcer. Through systematic manipulation of delay to reinforcer delivery, it is possible to determine to what extent an individual discounts delayed consequences.

Increased rates of impulsive choice (delay discounting) have been implicated in a number of clinically relevant disorders or conditions, such as drug abuse, attention-deficit hyperactivity disorder (ADHD), pathological gambling, suicide, and others (American Psychiatric Association, 2000). A number of studies

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have demonstrated increased rates of delay discounting among drug abusers relative to non-abusers (cf. Bickel et al., 1999; Coffey et al., 2003; Kirby and Petry, 2004). Thus, there is a well-established correlation between "impulsivity" or delay discounting and substance abuse. For example, Kirby and Petry (2004) demonstrated that heroin and cocaine abusers discounted delayed rewards more quickly than non-substance-abusing controls. Moeller and Dougherty (2002) suggest that impulsivity plays a critical role in the both the onset and continuation of substance abuse. Perry et al. (2005) found that "high impulsive" rats acquired cocaine self-administration more rapidly than "low impulsive" rats (as determined by a delay-discounting procedure), suggesting that greater levels of impulsivity may precede substance abuse. However, more work needs to be conducted to better elucidate the relation between impulsive choice (increased delay discounting) and drug taking, and how drugs affect such choice. An understanding of the factors that contribute to increased impulsive choice may result in the development of effective treatments for impulse-control disorders such as drug abuse.

Evenden and Ryan (1996) developed a procedure to test effects of drugs (e.g., *d*-amphetamine, diazepam, and imipramine) on delay discounting of food reinforcers. In this experiment, rats were presented with a choice between a single food pellet delivered immediately following a lever press and three or five food pellets delivered after a longer delay following a response on the other lever. Sessions were organized in blocks of trials in which the delay to the large reinforcer progressively increased (between 0.5 and 60 s), and the delay to the single food pellet remained constant (0 s). This procedure provides data that allow the researcher to generate temporal-discounting functions within a single experimental session. The generation of within-session discounting functions allows for the rapid evaluation of drug effects. These methods were used as the basis for the present study.

In many cases, stimulant drugs have been shown to decrease impulsive choice (cf. Cardinal et al., 2000; Pietras et al., 2003; Pitts and McKenney, 2005; Wade et al., 2000; Winstanley et al., 2003, 2005). However, it should be noted that there are some studies in which stimulants increased impulsive choice (e.g., Charrier and Thiebot, 1996; Evenden and Ryan 1996; Flora and Dietze, 1993; Logue et al., 1992) or had no effect on large-reinforcer choice (e.g., Bizot et al., 1988). When characterizing the body of work in the area, it is important to acknowledge the inconsistent results and attempt to understand the factors that may lead to these discrepancies. A better examination of the procedural and subject variables that determine differential drug effects is certainly warranted.

Given that stimulant drugs are often used to decrease rates of impulsive behavior, as in the treatment of ADHD, it is important to clarify the relation between stimulant drugs and impulsive choice. One way to clarify this relation is to examine effects of another exemplar stimulant. Although effects of other stimulant drugs have been evaluated in delay-discounting procedures, caffeine has not been tested previously in this experimental preparation.

Caffeine is considered the world's most widely used stimulant. It is readily available in a variety of forms, and is legally obtained, in contrast with other stimulants such as cocaine and amphetamine (Daly and Fredholm, 1998; Fisone et al., 2004). The widespread use of caffeine necessitates a better understanding of its behavioral effects on impulsive choice. Moderate caffeine consumption has been shown to increase alertness and arousal (Daly and Fredholm, 1998; Flora and Dietze, 1993; Smith, 2002). Repeated caffeine use has been associated with the use of other drugs and has also been shown to potentiate the discriminative-stimulus effects of other stimulants (Gasior et al., 2000, 2002). Additionally, repeated consumption of caffeine may modify psychomotor effects of other drugs, including amphetamine, cocaine, and nicotine (Cauli and Morelli, 2005). Daly and Fredholm (1998) suggested that caffeine may be considered a model drug of abuse, due to its wide usage and its relation to other drugs. A better understanding of the effects of this commonly used stimulant on delay discounting is needed.

The reinforcing properties of psychomotor stimulants such as caffeine have been well documented (Berridge, 2006; Daly and Fredholm, 1998; Gasior et al., 2000; Mumford and Holtzman, 1991; Rothman et al., 2001). Caffeine and other stimulants (e.g., amphetamine, methylphenidate, and methamphetamine) share similar neural pathways of action, which suggests that their effects on impulsive choice may be related (Berridge, 2006; Holtzman, 1987; Rothman et al., 2001; van Gaalen et al., 2006; Winstanley et al., 2005). An analysis of effects of caffeine on delay discounting may help to clarify physiological processes that underlie impulsive behavior. For example, if caffeine has similar effects as other stimulants and shares neurochemical mechanisms, this would suggest that the neurological mechanisms are implicated in the behavioral effects. If the mechanism of the drugs is the same, however, and behavioral effects are different, other variables must be implicated to resolve the discrepant outcomes.

The reinforcing and psychomotor effects of caffeine (along with other stimulants) are mediated by monoamine (e.g., dopamine, norepinephrine) neurotransmitter systems in the brain (Cardinal et al., 2000; Fredholm et al., 1999). Caffeine acts via a negative modulatory pathway by directly antagonizing adenosine A_1 and A_{2A} receptors, resulting in enhanced dopamine and norepinephrine transmission in the nucleus accumbens (Cauli and Morelli, 2005; Cardinal, 2006; Cardinal et al., 2001; Daly and Fredholm, 1998; Everitt and Wolf, 2002). Data suggest that caffeine increases monoamine neurotransmitter turnover and induces reinforcing effects through mesolimbic reward pathways in the brain (Berridge, 2006; Cardinal et al., 2001; Fredholm et al., 1999; Kuczenski and Segal, 2001; Rothman et al., 2001). Disruption of this pathway through dopamine receptor blockage can reduce the reinforcing effects of caffeine (Jain and Holtzman, 2005). Furthermore, dopaminergic and noradrenergic transmission may be involved with impulsive choice and reinforcer value (Arnsten, 2006; Cardinal, 2006; Cardinal et al., 2000; Cardinal et al., 2001; van Gaalen et al., 2006). That is, lower levels of dopamine have been associated with steeper rates of delay discounting (i.e., increased impulsive choice) (cf. Cardinal, 2006). In general, drugs that increase the levels of dopamine (e.g., stimulants) have been demonstrated to increase levels of self-controlled behavior (cf. Cardinal et al., 2000; Winstanley et al., 2003, 2005).

Flora and Dietze (1993) examined effects of caffeine on impulsive choice in a maze-running experiment. In one arm of the maze, rats received a single food pellet immediately. In the other arm of the maze, rats received six food pellets following a delay of 15 s. Flora and Dietze found that when rats were allowed access to caffeinated water before running in the maze, they became more likely to choose the impulsive outcome than when they had access to water without caffeine. The present study differs in several significant ways from Flora and Dietze. Specifically, the present study used lever pressing instead of maze running as the operant. Furthermore, the drugs were orally self-administered in the Flora and Dietze study, but the drug was injected by the experimenter in the present study. The researcher-controlled administration of the drug may allow for greater control of the dosing and time course of the drug. Also, Flora and Dietze held the delay to the presentation of the larger reinforcer constant at a single value. In the present study, a number of different delays to the presentation of the reinforcer were presented within an experimental session, rather than a fixed delay.

The present study was designed to evaluate effects of acute and repeated administration of caffeine on temporal discounting in male Sprague–Dawley rats using a procedure based on the work of Evenden and Ryan (1996). Acute dosing of caffeine was conducted to determine effects of a wide range of doses. Chronic (repeated) dosing was used to assess potential for behavioral change following repeated exposure to the drug (i.e., tolerance or sensitization). The assessment of chronic effects may also increase the external validity of the manipulation, as caffeine is frequently consumed on a daily basis. Although caffeine is a widely self-administered drug and there is an interest in the effects of stimulants on delay discounting, effects of caffeine have not previously been assessed in a discrete-trials delay-discounting procedure.

2. Methods

2.1. Animals

Seven male Sprague–Dawley rats (Hilltop Lab Animals, Inc., Scottdale, PA) served as subjects. Subjects were 22 months of age at the start of drug testing. Each subject had participated in previous operant studies but was drug naïve at the time of this study. Two of the rats had experience with variable-ratio (VR) schedules of reinforcement and five had experience with differential-reinforcement-of-low-rates (DRL) schedules before exposure to the delay-discounting task. Subjects performed similarly on the choice procedure from the beginning of the delay-discounting task (see Results), indicating no clear effects of their different behavioral histories. Water was available continuously in the home cage and subjects were fed 15 g of rat chow 30 min after each session, resulting in approximately 23 h of food deprivation before the start of each experimental session. Subjects were housed individually under a 12-h reversed light/dark cycle. The procedures used were part of a protocol approved by the Animal Care and Use Committee of West Virginia University.

2.2. Drugs

Anhydrous caffeine (Sigma, St. Louis, MO) was dissolved in saline to an injection volume 1.0 mg/ml and was administered via intraperitoneal (i.p.) injection (1.0 ml/kg) immediately before the subjects were placed into the experimental chamber. Behavioral testing began 10 min later.

2.3. Apparatus

Seven standard two-lever operant-conditioning chambers for rats measuring 30.5 cm × 24.1 cm × 21.0 cm in size with metal floor bars 1.9 cm apart were used. The levers were 4.8 cm wide, entering 1.9 cm into the chamber, requiring a force of 0.25 N. Levers were located 11.5 cm apart and 8 cm above the chamber floor. Forty-five milligram food pellets were delivered by a modular pellet dispenser into a pellet receptacle located between levers. A 28-V houselight was centered at the top of the wall opposite the levers in each chamber. Two 28-V stimulus lights were located 7 cm above the levers covered in 2.5 cm diameter translucent caps. Each chamber was enclosed in a sound-attenuating box (Med Associates, VT). A ventilation fan in each compartment masked extraneous noise. All chambers were controlled by an IBM©-compatible computer in an adjacent room using MedPC-IV© (Med Associates, VT) software.

2.4. General procedure

Prior to the start of this study, subjects were initially trained to acquire lever pressing and were subsequently used in procedures involving VR and DRL schedules of reinforcement. At the start of the current experiment, subjects had approximately 75 sessions of experience with a discrete-trials choice procedure (similar to the procedure used by Evenden and Ryan, 1996) in which they chose between a single food pellet delivered immediately and three food pellets delivered after varying delays. This extended history with the delay-discounting procedure is different from the procedure used by Evenden and Ryan (1996) in that these authors began testing drugs after 12 sessions. After approximately 75 sessions of the exposure to the delay-discounting procedure, choice was determined to be stable based on visual inspection and verified by the criterion of less than a two-response difference at each block between sessions for the last five sessions.

Each session began with a 10-min blackout period to permit subjects to acclimate to the experimental environment and to allow any administered drug to become active. Experimental sessions consisted of five blocks of eight trials, each containing two forced-choice trials and six free-choice trials. In the first trial, the light above a randomly selected lever was illuminated and a press on that lever resulted in the light extinguishing and one of the programmed outcomes (e.g., delivery of a single, immediate food pellet). In the second forced-choice trial, the other lever light was illuminated and a press on that lever resulted in the other outcome (e.g., three food pellets delivered after a delay). The forced-choice trials preceded the free-choice trials in order to expose subjects to both contingencies before

allowing them to choose between them. Trials started every 100 s, resulting in variable intertrial intervals (ITI) across blocks (depending on the delay value programmed). During ITIs, no stimuli were illuminated in the chamber. If no lever press occurred within 30 s of trial onset, the lever light and houselight were extinguished, and no food was delivered. Such trials were counted as omissions and were excluded from analysis.

Following two forced-choice trials, the remainder of a block included six free-choice trials in which the subject could choose between either one food pellet delivered immediately or three food pellets delivered after the same delay as in the preceding forced-choice trial. Both lever lights were illuminated and a single press of either lever resulted in the delivery of one of the two consequences. Each consequence (single pellet or three pellets) remained correlated with a single lever for the duration of the experiment, and the lever associated with the three-pellet alternative was counterbalanced across subjects. The completion of two forced-choice and six free-choice trials constituted a block. In subsequent blocks within each session, the delay to presentation of the three-pellet alternative systematically increased. Delay values in each of the five blocks were 0, 2, 4, 8, and 16 s, respectively. Sessions were conducted Monday through Friday. On Wednesdays, delays to the presentation of the three food pellets were maintained at 0 s in all blocks. These probe sessions were conducted to assess preference for the larger reinforcer and to demonstrate that behavior was sensitive to reinforcer amount. If choice for the larger reinforcer in the free-choice trials was at least five (out of six) responses in each block, subjects returned to the delay conditions during the next experimental session. If subjects selected the larger reinforcer less than five times in any one block during the 0-s probe sessions, they experienced the 0-s delay probe procedure for additional sessions until this criterion was met. The delay (baseline) condition was in effect until responding across blocks was considered stable by visual inspection of the data and a minimum of 83% (5/6) of responses in the first block were allocated to the lever correlated with the large reinforcer.

2.5. Acute caffeine administration

Once stable baseline responding was established, acute drug administration began. Saline was administered via intraperitoneal (i.p.) injection immediately before the 10-min blackout period. Injections occurred every Tuesday and Friday, given that two conditions were met: (1) subjects met the criterion on 0-s probe sessions on Wednesday, and (2) subjects chose the larger reinforcer five or more times in the first (0-s) block of the relevant control day (Monday or Thursday). Subjects received at least three administrations of saline before caffeine administration began. Caffeine doses of 10.0, 17.0, and 30.0 mg/kg and saline were tested in either an increasing or decreasing order, counterbalanced across subjects, and all subjects received each dose at least twice. No differences were observed between subjects receiving increasing or decreasing dosing regimens. A third administration was given if choice for the larger reinforcer in the two previous sessions varied by more than 33% (two responses) in one or more blocks of trials. A maximum of three acute administrations was required for behavior to stabilize (i.e., not vary more than 33% from the average of the three determinations). After the acute dose–response function was generated, repeated (chronic) administration of 30.0 mg/kg caffeine began.

2.6. Repeated (chronic) caffeine administration and withdrawal

In this phase, sessions were conducted 7 days per week. Caffeine (30.0 mg/kg) was administered immediately before experimental sessions via i.p. injection. This dose was chosen because it produced the largest behavioral effect during the acute administration phase. Following at least 15 sessions with repeated caffeine exposure, stability of responding was evaluated. Once subjects showed variability of less than three choices within each block over two or three sessions, caffeine administration was terminated and subjects were given daily saline injections for a minimum of ten sessions. The number of sessions of repeated administration of caffeine and saline is presented for each subject in Table 1. As a final experimental manipulation, all subjects received administrations of 30.0 mg/kg caffeine for three consecutive sessions.

2.7. Data analysis

The primary dependent measure was percent choice for the large reinforcer, which was observed across a series of increasing delay values within each session. From this measure, indifference points and area under the curve (AUC) were derived. Caffeine dose–response functions were generated for percent choice of the larger reinforcer across increasing delays in each session block. Functions were fitted to the data using logistic regression, and indifference points (the delay value at which percent choice for each alternative was 50%) were interpolated based on these functions. Statistical analysis of the mean differences in indifference points between conditions (when data from all sessions from both acute and repeated administration were included) was conducted using paired *t*-tests with a significance level of 0.05.

Area under the curve (AUC) was derived by calculating the area of trapezoids that were formed by drawing vertical lines from each obtained percent choice to the *x*-axis. The areas of these trapezoids were summed and this total was divided by the full possible area of the graph (e.g., 1600). Whereas indifference points are interpolated from a function that was fitted to the

Table 1
The number of administrations of repeated 30.0 mg/kg caffeine and saline, by subject number

Subject	30.0 CAFF	Saline
S30-1	23	13
S30-3	16	18
S20-4	16	19
S30-5	21	12
S20-6	16	15
S30-7	15	18
S30-8	15	19

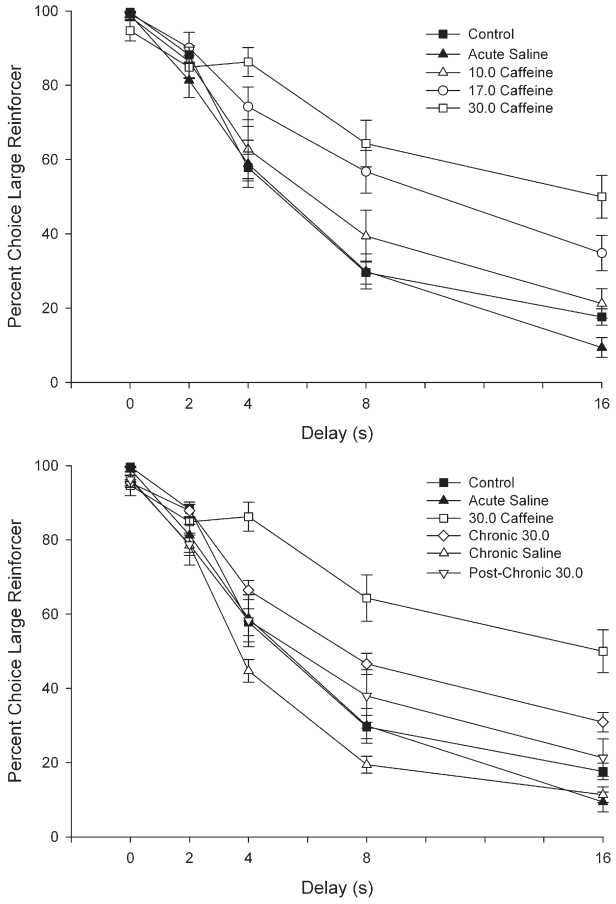

Fig. 1. Group mean ($n=7$) delay-discounting functions for percent choice of the larger (i.e., three-pellet) alternative across increasing delay blocks. Error bars represent standard error of the mean (SEM). The top panel depicts all data from acute caffeine administration and the bottom panel depicts all data from chronic caffeine administration.

data, AUC is derived from the obtained choice. This measure was included as a supplement to the indifference point, since AUC is based on the observed percent choice and indifference points are further removed from the raw data, i.e., are based on a fitted function.

3. Results

No significant differences were observed between rats with histories of VR and DRL responding at any point during the study, so data were combined across all subjects. Mean data presented are generally representative of individual-subject data. Data from individual subjects are presented in the Appendix A. Percent choice for the larger reinforcer decreased as delay to presentation increased (Fig. 1, upper panel, filled squares) for all subjects. Caffeine administration resulted in dose-dependent increases in percent choice for the larger reinforcer. This corresponds to less steep delay-discounting functions relative to control values (Fig. 1, upper panel, open symbols), higher indifference points (Table 2), and larger area under the curve (Fig. 2) measurements.

On non-drug (i.e., control) days, performance was generally consistent with pre-drug baseline performance. If performance was disrupted in the 0-s block of trials on a control day, drug was not given on the following day and the aberrant session was, therefore, not included as a control day. Control data are averaged across all control sessions within the experiment. Mean control indifference points ($M=5.08$ s, SEM=1.92) did not differ significantly from those of saline ($M=4.02$ s, SEM=1.51), $t(6)=1.13$, $p=0.30$, but AUC measurements were statistically different, $t(6)=3.69$, $p=0.01$. Acute saline was used to compare subsequent drug conditions.

Acute caffeine administration resulted in increases in mean indifference points (Table 2), corresponding with an increase in mean percent large-reinforcer choice (Fig. 1, top panel, open symbols). The observed increases occurred in a dose-dependent fashion (also see Tables 2 and 3). Although percent choice in the 10.0 mg/kg caffeine condition increased, indifference points ($M=4.62$ s, SEM=1.75) were not significantly different from saline, $t(6)=-1.90$, $p=0.11$, and this was also found to be true of the AUC comparison, $t(6)=-2.17$, $p=0.72$. However, following administration of 17.0 mg/kg caffeine ($M=12.08$ s, SEM=5.63), there was a statistically significant increase relative to saline for indifference points, $t(6)=-5.50$, $p<0.01$, and AUC, $t(6)=-4.58$, $p<0.01$. Similarly, indifference points

Table 2
Indifference points (i.e., the delay value at which the one- and three-pellet alternatives were equal in value), in seconds, are presented for each subject ($n=7$) in each condition

Subject	Control		Acute saline		CAFF 10.0		CAFF 17.0		CAFF 30.0		Chronic CAFF 30.0		Chronic saline		Post-chronic 30.0	
S30-1	4.70	0.92	4.99	0.96	10.36	0.97	10.63	0.95	16.56	0.73	10.17	0.92	5.08	0.94	7.15	0.97
S30-3	6.21	0.96	7.71	0.99	7.98	0.89	12.29	0.95	16.12	0.92	5.58	0.97	3.30	0.98	3.67	0.87
S20-4	6.92	0.96	6.51	0.99	3.60	0.94	10.27	0.91	17.89	0.72	7.39	0.95	3.77	0.98	8.01	0.95
S30-5	1.96	0.99	1.69	0.98	2.61	0.94	3.98	0.86	12.48	0.56	3.70	0.83	1.43	0.99	2.00	0.90
S20-6	5.12	0.97	3.94	0.96	12.13	0.99	12.59	0.94	13.12	0.94	15.29	0.93	5.92	0.98	6.97	0.90
S30-7	17.31	0.99	13.37	0.99	15.51	0.99	22.99	0.57	14.32	0.87	24.20	0.97	12.08	0.79	17.72	0.93
S30-8	3.00	0.99	2.01	0.99	6.59	0.99	11.81	0.89	15.19	0.67	13.48	0.73	3.31	0.84	6.96	0.94
Mean	6.46		5.75		8.39		12.08*		15.10*		11.40*		4.87		7.50	
SEM	1.92		1.52		1.75		2.13		0.73		2.65		1.3		1.89	

Indifference points were interpolated based on curves fitted to the data. Rows include indifference points calculated based on average performance during each condition. The right column under each condition contains R^2 values for the functions from which the indifference points were interpolated. Mean and SEM are presented for each condition. Asterisks indicate values that are significantly different from saline at the 0.05 level. CAFF refers to caffeine and doses are presented as mg/kg.

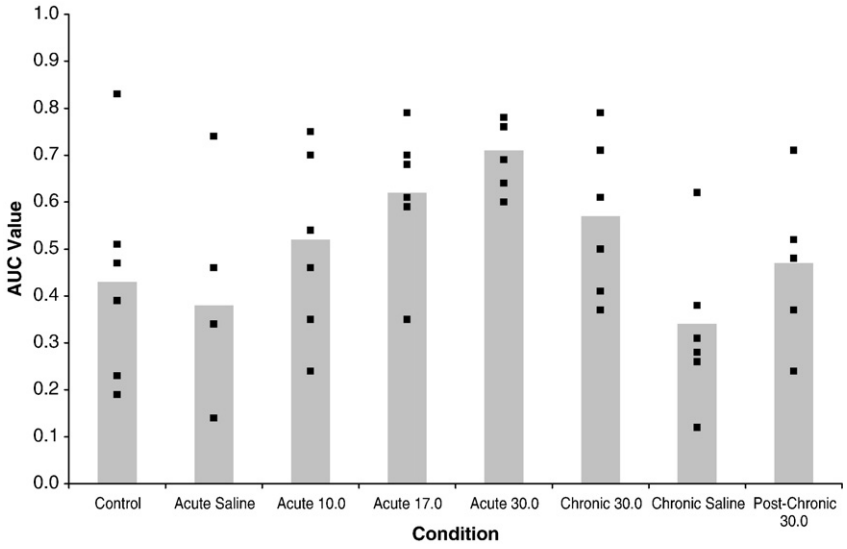

Fig. 2. Area under the curve (AUC), by subject and condition. AUC was determined by dividing the group-average delay-discounting function into trapezoids, summing the area of these trapezoids, and dividing this sum by the total graph area. The gray bars represent the group mean value in each condition, and the black squares represent individual-subject data. Caffeine doses are presented as mg/kg.

for the 30.0 mg/kg caffeine (M=15.10 s, SEM=1.93) were significantly higher than saline values, $t(6)=-2.66$, $p<0.05$, and AUC again reflected this increase, $t(6)=-2.65$, $p<0.05$.

After repeated administration of 30.0 mg/kg caffeine, percent choice for the larger reinforcer decreased relative to acute 30.0 mg/kg administration for five subjects and increased for two subjects, as indicated by both indifference points and area under the curve. Individual and group mean indifference points are shown in Table 2 and individual and group mean AUC data are displayed in Fig. 2. Although repeated administration of the 30.0 mg/kg dose resulted in an overall decrease in indifference points (M=11.40 s, SEM=2.65) relative to acute 30.0 mg/kg, there was still a statistically significant increase in indifference points relative to when acute saline was administered, $t(6)=-2.66$, $p<0.05$, and AUC, $t(6)=-2.65$, $p<0.05$ (see also the bottom panel of Fig. 1). Mean indifference points following 30.0 mg/kg acute caffeine did not differ significantly from repeated 30.0 mg/kg caffeine, $t(6)=1.28$, $p=0.25$ and neither did AUC values, $t(6)=2.11$, $p=0.08$.

An analysis of the time course of the changes between acute and chronic administration is presented in Table 3. In this table, AUC is presented for the first 15 sessions of repeated 30.0 mg/kg caffeine administration. Analysis of the time course yields mixed results. However, most changes that were observed (relative to acute administration) occurred within the first five sessions. For two subjects (S30-1, S30-3) there is a general decreasing trend in AUC between session 1 and session 15. For one subject (S30-4) no clear change is observed. For four subjects (S30-5, S20-6, S30-7, S30-8) there is a general increasing trend from the first to fifteenth session. The increasing trend is also reflected in the average AUC for each block of five sessions, as shown in the right-most column of the table.

Following repeated exposure to 30.0 mg/kg caffeine, repeated saline administration (M=5.17 s, SEM=1.23) resulted in a decrease in percent choice for the larger reinforcer across delays below the control levels (Fig. 1, bottom panel, open upright triangles and closed squares). The indifference points following repeated saline were not significantly different from acute saline values, $t(6)=0.90$, $p=0.40$, and neither were AUC, $t(6)=0.99$, $p=0.36$. Re-administration of 30.0 mg/kg caffeine for three sessions resulted in a slight recovery of the effect of repeatedly administered caffeine (Fig. 1, bottom panel, open downward triangles). In this condition, there was an increase in large-reinforcer choice relative to saline, but the percent choice was not as high as in the chronic-administration phase. This effect was not significantly different from saline as indexed by indifference points, $t(6)=-1.54$, $p=0.18$, and AUC, $t(6)=-1.71$, $p=0.14$. However, there were statistically significant differences obtained between indifference points, $t(6)=3.19$, $p<0.01$, and AUCs, $t=3.360$, $p<0.02$, when comparing repeated administration of 30.0 mg/kg caffeine and post-chronic administration of 30.0 mg/kg caffeine, with higher indifference points obtained in the chronic-dosing phase. During some sessions near the end of the post-chronic administration of 30.0 mg/kg caffeine, a few rats failed to respond and those trials were counted as omissions and not included in data analysis. Overall, however, there were very few omissions throughout the study.

Table 3
Time-series analysis of chronic caffeine administration, by subjects

Sessions	S30-1	S30-3	S20-4	S30-5	S20-6	S30-7	S30-8	Mean	SEM
1 to 5	0.57	0.52	0.52	0.33	0.62	0.67	0.51	0.53	0.04
6 to 10	0.55	0.41	0.50	0.34	0.75	0.91	0.71	0.60	0.07
11 to 15	0.51	0.34	0.50	0.53	0.79	0.90	0.70	0.61	0.07

The area under the curve (AUC) measurement is presented for the first 15 sessions of repeated 30.0 mg/kg caffeine administration, for all subjects. Mean and SEM are also presented.

4. Discussion

Temporal discounting was observed in the present study. As the delay to the large reinforcer increased, the percentage of responses allocated to that alternative systematically decreased. When caffeine was administered acutely, dose-dependent increases in percent choice for the large reinforcer were observed. These increases are consistent with effects of other stimulant drugs, such as amphetamine and methylphenidate, which are often prescribed to treat ADHD (Arnsten, 2006; Richards et al., 1999; van Gaalen et al., 2006). Thus, the results of the present study add further support to the finding that the administration of stimulants decreases impulsive choice. It is important to note, however, there have been some studies in which stimulants have been shown to increase impulsive choice (cf. Evenden and Ryan, 1996; Flora and Dietze, 1993; Logue et al., 1992). Some differences between the present study and these other studies include the presence of stimuli during the blackout (e.g., flashing light), the type of task (lever pressing vs. maze running) and the history of the subjects (e.g., number of sessions). Future work may be aimed at identifying variables related to procedures, subjects, and drugs that are responsible for the inconsistent results.

The present study is the first to assess effects of caffeine in an animal model of delay discounting. Given the widespread use of caffeine among humans, this is an important contribution to the existing literature. In studies with human subjects, moderate doses of caffeine have been shown to increase arousal, improve subjective mood, and increase concentration (Daly and Fredholm, 1998; Fredholm et al., 1999; Juliano and Griffiths, 2004). Smith et al. (2006) suggested that the improvements in mood caused by caffeine occurred across groups of caffeine users and nonusers, independent of their withdrawal status. Other stimulants, such as amphetamine, have similar subjective positive effects on mood and arousal (de Wit et al., 2002). State of arousal has been linked to impulsive choice, with low arousal associated with increased impulsive behavior (Fredholm et al., 1999). Delay-discounting patterns may be subject to variability in state (e.g., subjective mood, arousal). For example, sleep-deprived (i.e., less aroused) participants discount the value of potential rewards more than non-sleep-deprived participants (Reynolds and Schiffbauer, 2004). Using animal models instead of human participants allows for more direct and less complicated evaluation of behavioral effects of drugs. For, with constant environments, it may be assumed that the state of the subjects will be relatively stable across testing sessions through the constant values of the light/dark cycle, temperature, and food deprivation. However, the human analogue of the present study has not yet been conducted and may be of value. Replication with humans would add to the external validity of the present study and may enhance the understanding of the behavioral effects of commonly used stimulants. Understanding these effects may help elucidate the mechanisms of action of caffeine and reveal the mechanisms that govern impulsive choice.

In the present study, effects of repeated administration of caffeine were also examined. The repeated administration of the drug may increase the external validity of the manipulation, as caffeine is often consumed daily by humans. Juliano and Griffiths (2004) noted that repeated caffeine use can lead to subjective, physiological, and behavioral tolerance effects in humans, as indicated by diminished effects following repeated administration. In the present study, repeated caffeine administration resulted in a significant increase in large-reinforcer choice relative to non-drug and saline conditions, as indexed by indifference points, but not AUC. The magnitude of the effect was not as pronounced as when acute doses were administered (e.g., mean indifference points and AUC values were lower in the repeated-administration condition than in the acute-administration condition). Percent choice for the larger reinforcer remained higher than control levels throughout 15 sessions of repeated caffeine administration, but it is not clear if an extended period of daily administration would have resulted in a complete return to baseline. The attenuation of caffeine effects may reflect the development of tolerance. For a complete analysis of tolerance, which may lead to a better understanding of the effects observed, a second dose–response function should be derived following repeated exposure to caffeine. Future work could explicitly evaluate the development of tolerance through replication of the present procedure.

The unsystematic results of the time-series analysis suggest that effects of repeated exposure to caffeine were not consistent, underscoring the importance of considering individual differences when evaluating drug effects. Interestingly, Cauli and Morelli (2005) noted that repeated administration of comparable doses of caffeine (15–30 mg/kg) via an oral route of administration was not sufficient for the development of tolerance to locomotor effects of the drug. Thus, route of administration of the drug may be an important variable to consider when making cross-study comparisons. When Kirch et al. (1990) repeatedly administered relatively high doses (25 mg/kg and 50 mg/kg) of caffeine to rats using i.p. injections (as in the present study), increased levels of dopamine and serotonin were observed in the striatum. At a lower dose (10 mg/kg), no significant changes in monoamine levels were observed. The findings of Kirch and colleagues map on to the findings of the present experiment: there were no changes in large-reinforcer choice when the lowest dose was administered, but higher doses resulted in increased large-reinforcer choice. This is consistent with the body of literature suggesting that lower levels of serotonin and dopamine are correlated with increased levels of impulsive choice (cf. Cardinal, 2006; van Gaalen et al., 2006). When caffeine was administered repeatedly in the present study, tolerance may have been observed for some subjects, as indicated by differences in choice between acute and chronic caffeine conditions. The possible emergence of tolerance in the present study may imply that the effects of caffeine on impulsive choice in humans would also change following repeated drug administration. Additional research is required to determine if such tolerance would also occur in human subjects in a similar experimental procedure.

Although the results of the present study are consistent with those of Kirch et al. (1990), it is important to note that the results obtained in the present study are not consistent with the results of Flora and Dietze (1993), in which effects of caffeine were

evaluated on impulsive choice in a maze-running paradigm. As noted in the introduction of this paper, there are several important differences between the present study and the work of Flora and Dietze (i.e., response class, route of administration, delay conditions). The procedural differences may be sufficient to explain the inconsistencies of the outcome. Because there are inconsistencies in the literature, however, replication may be warranted. This replication may identify conditions under which stimulants increase or decrease impulsive choice, possibly illuminating neurochemical (e.g., dopaminergic, serotonergic involvement) and behavioral (e.g., sensitivity to reinforcer amount and delay) mechanisms of action.

Withdrawal from repeated caffeine use can cause headache, fatigue, anxiety, and decreased performance on cognitive tasks in humans (Fredholm et al., 1999). In nonhuman animals, caffeine withdrawal can result in reduced levels of locomotor activity and operant behavior, as well as sleep disruption (Nehlig, 1999). The severity of withdrawal symptoms is generally related to the dose that had been administered repeatedly. In the present study, no physiological signs of withdrawal were measured, but termination of caffeine administration resulted in a return to pre-drug levels of choice (e.g., no differences were observed between acute and repeated saline indifference points). The recovery of pre-drug choice when the drug was removed suggests that the observed increases in large-reinforcer choice were, in fact, due to the drug administration, and not historical or maturational variables. Furthermore, the observed recovery suggests that despite the possible development of tolerance during the repeated-dosing phase, no long-term changes in behavior occurred in the absence of the drug. Additional research may be conducted to determine if there are physiological correlates to changes in impulsive choice when caffeine withdrawal occurs.

Following the withdrawal phase, caffeine was briefly re-administered at the previously repeated dose (30.0 mg/kg). The increase in percent large-reinforcer choice was again observed, but did not equal that after acute administration of the same dose, indicating the possible persistence of any tolerance that may have developed. It is unclear whether increasing the number of sessions during which saline was administered would have diminished any such tolerance as indicated by a return to acute-administration choice patterns.

The increase in self-controlled choice suggests that the mechanism of action of caffeine may be common to other drugs of abuse that increase self-controlled choice, such as amphetamine or cocaine (cf. Wade et al., 2000; Winstanley et al., 2003). Caffeine increases monoamine neurotransmitter turnover and its reinforcing effects are mediated through mesolimbic reward pathways in the brain (Berridge, 2006; Cardinal et al., 2001; Fredholm et al., 1999; Kuczenski and Segal, 2001; Rothman et al., 2001). Disruption of this pathway through dopamine receptor blockade can reduce the reinforcing effects of caffeine (Jain and Holtzman, 2005). Dopaminergic and noradrenergic transmission have been implicated in studies of impulsive choice and reinforcer value (Arnsten, 2006; Cardinal et al., 2000; Cardinal et al., 2001; Cardinal, 2006; van Gaalen et al., 2006). Despite this link to the mesolimbic reward pathways, caffeine does not preferentially affect structures within the brain, suggesting that it has an atypical mechanism of action (Cauli and Morelli, 2005). Testing an adenosine agonist or dopamine antagonist in conjunction with caffeine (an adenosine antagonist) may clarify the physiological mechanism of action underlying the behavioral effects observed in the present study. Additional research could examine effects of caffeine in combination with other common drugs of abuse (e.g., nicotine, ethanol) to increase the external validity of this preparation, as humans commonly consume multiple drugs at once.

Although the present discussion has been framed in terms of effects of caffeine on temporal discounting, alternative explanations for the present results should also be considered. For example, it is possible that caffeine administration enhanced discrimination between the two alternatives (cf. Hewlett and Smith, 2007; Kohler et al., 2006), increasing sensitivity to reinforcer amount. This seems more likely than the converse, because if the converse of this was true (i.e., caffeine disrupted discrimination between the alternatives), the delay-discounting functions would have flattened to indifference (e.g., 50% responding on each alternative), which was not observed. It is also possible that caffeine administration resulted in perseverative responding on the lever associated with the large reinforcer. Stereotypical behavior has been observed following the administration of some stimulants. As stereotypical behavior may occur with head movement, sniffing, or other behaviors (cf. Frantz et al., 2007), the extent to which this stereotypy extends to lever pressing in the present experiment is unknown, and was not evaluated in the present study. As a final consideration, it is possible that caffeine (stimulant) administration increased conditioned reinforcing effects of stimuli in the experimental setting (cf. Everitt and Wolf, 2002; Pietras et al., 2003; Pitts and McKenney, 2005). However, in the present study, there were no stimuli presented during the delay, i.e., the houselight remained illuminated and the lever lights were extinguished following a lever press. While it is possible that the houselight gained some properties of conditioned reinforcement, this possibility is unlikely and was not directly assessed.

In the present study, effects of acute and repeated administration of caffeine were assessed on temporal discounting in rats. When caffeine was administered acutely, the percent choice for the large reinforcer increased in a dose-dependent fashion. When administered repeatedly, the effects of caffeine on impulsive choice were attenuated for some subjects, suggesting the possible development of behavioral tolerance. However, tolerance was not directly assessed. During the repeated saline-administration (withdrawal) phase, choice returned to baseline levels. Following withdrawal, the repeated dose was administered again for three sessions. In this condition, large-reinforcer choice increased, but the magnitude of the change was not as great as during the acute phase. The present results add additional support to the finding that administration of stimulant drugs (including caffeine) generally decreases impulsive choice.

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Appendix A

Mean and standard error of the mean (SEM) percent choice for the large reinforcer, organized by subject, delay, and condition

Condition	Delay (s)	Subject							Mean	SEM
		S30-1	S30-3	S20-4	S30-5	S20-6	S30-7	S30-8		
Baseline	0	98.79	100.00	100.00	98.30	100.00	100.00	98.30	99.34	0.32
	2	88.07	98.30	92.36	53.30	94.42	100.00	53.30	82.82	7.76
	4	45.14	48.40	47.18	13.40	41.75	91.63	13.40	42.99	9.96
	8	25.07	25.00	25.73	15.00	23.58	85.38	15.00	30.68	9.29
	16	10.64	10.10	10.73	8.30	11.25	45.75	8.30	15.01	5.14
Control	0	98.79	100.00	100.00	100.00	100.00	100.00	98.58	99.62	0.24
	2	88.07	93.20	98.79	47.46	98.58	98.79	81.92	86.69	6.97
	4	45.14	69.90	82.14	5.15	66.75	92.79	18.17	54.29	12.40
	8	25.07	30.00	34.57	1.31	12.58	86.79	2.83	27.29	11.01
	16	10.64	14.40	15.50	7.69	12.67	57.29	2.83	17.29	6.86
Saline	0	93.20	100.00	100.00	100.00	100.00	100.00	100.00	99.03	0.97
	2	86.60	89.00	93.20	33.25	91.50	100.00	50.00	77.65	9.61
	4	53.40	83.33	80.00	8.50	45.75	90.00	5.67	52.38	12.17
	8	23.40	38.67	30.00	4.25	16.75	80.00	0.00	27.58	10.14
	16	10.20	5.67	6.80	0.00	4.25	33.40	0.00	8.62	4.35
10.0 Acute	0	88.67	100.00	100.00	100.00	100.00	100.00	100.00	98.38	1.62
	2	89.00	91.50	83.33	61.00	100.00	100.00	89.00	87.69	5.01
	4	77.67	58.00	39.00	22.00	91.50	94.33	77.67	65.74	10.30
	8	55.67	50.00	11.33	16.67	75.00	72.00	33.33	44.86	9.56
	16	28.00	17.00	16.67	0.00	25.00	50.00	5.67	20.33	6.20
17.0 Acute	0	100.00	100.00	100.00	100.00	100.00	100.00	94.33	99.19	0.81
	2	100.00	100.00	94.33	61.00	100.00	100.00	77.67	90.43	5.80
	4	83.50	83.50	72.00	44.67	94.33	83.33	66.67	75.43	6.14
	8	58.50	66.50	55.33	22.33	66.33	72.33	61.00	57.47	6.24
	16	25.00	33.00	28.00	16.67	33.33	72.00	38.67	35.24	6.68
30.0 Acute	0	94.33	100.00	100.00	83.33	100.00	83.33	100.00	94.43	2.97
	2	83.33	83.50	94.33	88.67	83.33	89.00	67.00	84.17	3.25
	4	94.33	91.50	100.00	61.00	88.67	72.33	88.67	85.21	5.16
	8	61.00	83.50	66.33	44.33	66.67	55.67	83.33	65.83	5.36
	16	55.67	50.00	61.00	50.00	39.00	50.00	44.33	50.00	2.70
30.0 Chronic	0	96.30	100.00	97.88	95.19	95.75	90.24	91.57	95.28	1.29
	2	96.30	95.00	92.63	68.24	92.56	87.29	84.69	88.10	3.66
	4	74.52	62.65	66.56	39.71	82.14	87.15	62.85	67.94	5.91
	8	53.61	24.53	43.88	19.05	67.86	78.23	56.38	49.08	8.18
	16	27.61	6.00	13.56	23.10	50.00	68.00	48.54	33.83	8.42
Saline chronic	0	96.08	95.06	97.37	93.08	92.86	99.00	97.32	95.82	0.87
	2	84.46	74.81	84.95	26.33	90.43	97.06	82.32	77.19	8.87
	4	59.00	34.24	42.21	5.67	66.43	83.29	30.68	45.93	9.75
	8	20.69	11.76	12.32	5.67	28.57	49.06	8.84	19.56	5.72
	16	16.77	4.00	5.56	0.00	9.57	41.06	3.53	11.50	5.32
Post-chronic 30.0	0	94.33	100.00	100.00	100.00	94.33	89.00	100.00	96.81	1.65
	2	94.33	88.67	72.33	44.67	78.00	83.33	83.33	77.71	6.13
	4	66.67	39.00	77.67	16.67	72.00	88.67	66.67	61.05	9.36
	8	44.33	22.33	50.00	16.67	33.33	72.00	39.00	39.67	6.98
	16	5.67	16.67	11.00	11.00	22.33	55.67	16.67	19.86	6.30

Caffeine doses are presented as mg/kg.

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