Modern Psychological Studies

Volume 23 | Number 2 Article 5

2018

Will d-amphetamine's effect on impulsive choice be consistent when the environmental context changes by using decreasing delays to reinforcement?

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Abstract

Impulsivity (choosing a smaller, more immediate reward over a larger, more delayed reward) and substance abuse are positively correlated. It is important to understand how factors like delay to reward and drug effects determine impulsive choice, which can be studied using animal models. This study evaluated impulsive choice in rats, where delays to the larger reward (three food pellets) were presented in decreasing order versus one food pellet delivered immediately. Then, effects of *d*-amphetamine were assessed. It was found that in three of four rats, *d*-amphetamine increased impulsive choice when the larger option was presented with decreasing delays. This effect is contrary to what has generally been found with increasing delays. Thus, environmental context can influence drug effects on impulsive choice.

Keywords: d-Amphetamine, impulsivity, choice, delay discounting, delay order, rat, self-control

Will *d*-Amphetamine's Effect on Impulsive Choice be Consistent When the Environmental Context Changes by Using Decreasing Delays to Reinforcement?

Impulsivity has been discovered to be associated with multiple problem behaviors. One of these problem behaviors is substance abuse. Individuals who abuse substances tend to opt for the immediate drug high rather than prosocial, deferred reinforcers (Bickel, Odum, & Madden, 1999). In technical terms, a reward is more often referred to as a "reinforcer," so that term will be used henceforth. People who abuse substances display greater impulsive tendencies and lower self-control than those who do not. Research into determinants ("causes") of impulsive behavior has included studying "delay discounting" in animal models. In delay-discounting studies, subjects are given a choice between a smaller, sooner reinforcer (the impulsive option) and a larger, later reinforcer (the self-control option). Of interest is how the delay duration to the larger outcome affects this choice. It has been found that *d*-amphetamine and other stimulant drugs, which are often used to treat various medical conditions in humans, e.g., attention-deficit/hyperactivity disorder (ADHD), can increase self-control, i.e., decrease impulsive choice, in animal models when administered in controlled doses. However, the majority of this basic research on drug effects and delay discounting has been completed using increasing (progressively longer) delays to the larger reinforcer rather than decreasing (progressively shorter) delays. Therefore, there is a need to extend the generality of the finding that *d*-amphetamine increases self-control choice in a different environmental context (i.e., the order the delays are presented). More specifically, in this study, the purpose was to evaluate impulsive choice when using decreasing delays to the larger reinforcer. A second purpose was to assess effects of *d*-amphetamine on impulsive choice.

Literature Review

Impulse-control disorders are distinguished by an individual's inability to withstand an urge to engage in a behavior that is detrimental to his/her overall health or other individuals (Petry, 2001). Problems, such as pathological gambling, obesity, recurring aggression, and substance abuse, can arise from a lack of impulse control. Impulsivity can be operationally defined as choosing the smaller, more immediate reinforcer (reward) rather than the larger, more delayed reinforcer. The converse of impulsivity is self-control. These are widely accepted operational definitions that allow for manipulation of two key variables, reinforcer amount and reinforcer delay, in a laboratory setting using a delay-discounting task.

In standard delay-discounting tasks, the participants or subjects have a choice between a smaller, more immediate reinforcer and a larger, delayed reinforcer. For example, the participants may have a choice between $10 now and $100 in a week. The larger reinforcer will be chosen if its delay to delivery is fairly short. In this hypothetical case, the $100 will most likely be chosen when the participants only have to wait a week for it. However, when the delay to delivery increases, e.g., to one year, then the choice switches to the smaller, more immediate reinforcer. In other words, if the participants have to wait a year for the $100, their choice is likely to switch to receiving the $10 immediately. Thus, the delay has devalued the larger reinforcer to a point below that of the smaller reinforcer, i.e., the larger reinforcer has been discounted as a result of the delay. In general, as the delay to the larger reinforcer increases, choice for that option will decrease and the inverse response, i.e., choosing the smaller, more immediate reinforcer, increases. In an experimental context, systematically varying the delays

across blocks of trials allows for a within-session determination of delay discounting, which, with shorter delays, is ideal for studying effects of drugs.

In delay-discounting research, dependent measures may include percent larger-reinforcer choice, the indifference point, and area under the curve (AUC). Percent larger-reinforcer choice is the percent of total trials at a specific delay when the delayed, larger reinforcer was chosen and is plotted as a function of the delay to the larger reinforcer to construct delay-discounting functions (percent larger-reinforcer choice is calculated separately for each delay duration). Interpolating the delay from delay-discounting functions where choice is 50% for each alternative, yields the indifference point. The indifference point occurs when choice for the larger, delayed reinforcer and smaller, immediate reinforcer are the same and indicates that the value of both reinforcers are equal (the preference is equal). AUC specifies the total area under the delay-discounting function. If the reinforcer is discounted faster (the value of the larger, delayed reinforcer is decreased), the steeper the discounting function will be and the smaller AUC there will be. Fewer percent larger-reinforcer choices, shorter indifference points, and smaller AUC all indicate greater delay discounting (impulsive choice) and are described in more detail in the Data Analysis section. These dependent variables allow for comparison of delay discounting under different environmental and drug conditions.

Research has shown that substance use/abuse (and other impulse-control disorders) and increased delay discounting are positively correlated. For example, Kollins (2003) conducted a study involving 47 students at Western Michigan University. Participants completed a survey regarding their substance-use history. Then, they participated in a hypothetical choice task using a delay-discounting method similar to the one with money presented earlier. The participants were presented with various hypothetical choices between a larger, delayed amount of money

and a smaller, more immediate amount of money. The findings demonstrated that students with self-reported patterns of substance use demonstrated higher rates of discounting/impulsivity.

In a similar study with smokers, non-smokers, and ex-smokers (Bickel et al., 1999), the participants' impulsivity was tested by evaluating their rates of discounting with hypothetical monetary reinforcers. Before beginning the delay-discounting assessment, the participants completed the Eysenck Personality Questionnaire and segments of the Wechsler Adult Intelligence Scale to estimate their IQ. Then, they were given the delay-discounting assessment. The ex-smokers and non-smokers had a choice between different amounts of money, whereas, the smokers had a choice between different amounts of money and cigarettes. Smokers were required to smoke before the tests to avoid a skew in the data due to nicotine withdrawal, as well as take a scheduled cigarette break after the first test. It was discovered that smokers were more likely to discount the reinforcer at a more rapid rate than the ex-smokers and non-smokers (Bickel et al., 1999).

In addition, Allen, Moeller, Rhoades, and Cherek (1998) conducted a study where impulsivity was assessed by comparing behavioral and self-report measures of participants with a past history of drug dependence versus those without one. The participants were required to make choices between smaller, more immediate reinforcers and larger, delayed reinforcers. The individuals with a drug history made more impulsive choices as indicated by the finding that their mean indifference point was nearly half that of participants without a drug history (Allen et al., 1998).

Common to all of the above studies is that the delays to the larger reinforcer were presented in an ascending order, i.e., the delays got progressively longer across the choice tests. What happens, however, when the delays are presented in descending (decreasing) order? The

order of delay presentation may affect baseline rates of delay discounting. For example, when delays were delivered in ascending order in a study with genetically different rats conducted by Fox, Hand, and Reilly (2008), both groups (spontaneously hypersensitive rats [SHRs] and Wistar Kyoto rats [WKYs]) primarily chose the larger, delayed reinforcer when it was delayed between 0 and 6 s. Then at 12-s and 24-s delays, the SHR's choice for larger, delayed reinforcers decreased while the WKYs choice remained relatively the same. When the order of presentation was switched to descending order, however, both groups chose fewer larger, delayed reinforcers across all delays (Fox et al., 2008). This study not only reveals strain (genetic) differences in impulsivity, but also that impulsive choice increased when the delay order was descending.

During baseline training in an experiment with rats by Slezak and Anderson (2009), it was observed that the overall choice in both ascending-delay-order and descending-delay-order sessions was for the larger reinforcer when there was no delay between a lever press and a three food-pellet (the larger reinforcer) presentation (the alternate choice was one food pellet also with no delay to presentation). However, when delays were added and presented in an ascending order, there was a predominant pattern of decreased choice of the larger reinforcer as delays increased. The pattern of decreasing larger-reinforcer choice was also shown in the descending delay presentations although there were a few aberrations. It was also observed that AUC was greater (indicating more self-control) in the ascending delay presentations than in the descending presentations.

Research suggests that baseline differences in impulsive choice (delay discounting) may alter effects of stimulant drugs on impulsive choice (Huskinson, Krebs, & Anderson, 2012; Krebs & Anderson, 2012). The majority of studies that have investigated effects of *d*-amphetamine have utilized ascending delay presentation (e.g., Huskinson et al., 2012; Slezak &

Anderson, 2011; Slezak, Krebs, & Anderson, 2012). However, since the order of delay presentation may affect baseline delay discounting, drug effects may also be affected. Therefore, it is necessary to further examine whether effects of *d*-amphetamine (i.e., decreases in delay discounting) will remain the same when the delay sequence is presented in descending order. Some work, e.g., Maguire et al., 2014, Tanno, et al., 2014, has examined this issue, but in a different context. Thus, more research needs to be conducted.

It is vital to determine the influence stimulant drugs, like *d*-amphetamine, have on impulsivity. These drugs have been shown both to increase and decrease impulsivity, depending on factors like the environmental context. Thus, more research is needed to learn about the role of environmental context on this drug-behavior interaction. Investigating the relation between stimulant drugs and impulsivity may help to improve treatment and prevention of addiction and relapse to these types of drugs in at-risk populations (Perry & Carroll, 2008). Controlled doses of *d*-amphetamine have been used as treatment for people with ADHD, which has an impulse-control component. Due to the mixed findings of effects of *d*-amphetamine and impulsive behavior, and the role of the environmental context, the present study was designed to evaluate the drug's effects on delay discounting in a relatively novel context (decreasing delays) and compare them to those in a more established context (increasing delays). It was hypothesized that impulsive choice would be similar to what has been reported in prior literature with increasing delays to the larger reinforcer, and that *d*-amphetamine would reduce impulsive choice.

Method

Subjects

Four Sprague-Dawley male rats used in a prior laboratory class for undergraduate students functioned as the subjects. Subjects were housed in a colony room in the Life Sciences Building at West Virginia University (WVU). Subject body weights were monitored and allowed to change over the study's time period to permit for standard growth and development. Food restriction was enforced for about 22 h before each experimental session to help establish the food pellets as reinforcers during the choice tests. The colony room was kept at 21-27°C. A 12-hour reverse light/dark cycle was implemented. The housing and experimental procedures were approved by the WVU Animal Care and Use Committee.

Apparatus

Experimental sessions were conducted in eight standard operant-conditioning chambers for rats, each enclosed in a melamine sound-attenuating cubicle (Med Associates, VT). Each chamber contained a working area of 30.5 cm by 24.1 cm by 21.0 cm, a grid floor, and a 45-mg pellet dispenser with a pellet receptacle centered between two standard retractable response levers, which were 11.5 cm apart from each other, required at least 0.25 N for a response to be recorded, were 4.8 cm wide, protruded 1.9 cm into the chamber, and were elevated 8 cm from the grid floor. Two 28-V stimulus lights of 2.5 cm in diameter were approximately 7 cm above each lever. Each chamber had a 28-V houselight on the wall opposite the wall containing operandum, and a ventilation fan to circulate air and to mask extraneous noise. Equipment was interfaced to a computer and routines were programmed and conducted with MedPC-IV (Med Associates, VT).

Procedure

The rats were experimentally experienced from a WVU Psychology class. Therefore no feeder training was necessary. However, they had only experience pressing one lever. Procedures

involved alternating-lever training to establish responding on both levers, which was necessary for rats to make one of two choices during the delay-discounting task.

Initial Training

At the beginning of the alternating-lever sessions, the houselight was turned on to indicate the start of the session, the left lever was extended into the chamber, and the light above the left lever was turned on to signal to the rat that the left lever is extended. After every left lever press, a food pellet was presented. Once the fifth food pellet was presented, the left lever was retracted and the light above was turned off. Then, the right lever was extended into the chamber and the light above it was turned on to signal to the rat that the right lever is extended. After every right lever press, a food pellet was presented. Once the fifth food pellet was presented, the right lever was retracted and the light above was turned off. This alternation of levers gave the rats experience pressing both levers. These sessions ended after a total of 40 food pellets were delivered. This phase of the study lasted until rats were reliably pressing both levers.

Delay-Discounting Procedure

A discrete-trials choice procedure began after alternating-lever training. The procedure was similar to the one originally developed by Evenden and Ryan (1996). Every session contained five blocks of eight trials, two forced-choice trials followed by six free-choice trials. The trials began every 100 s. Forced-choice trials revealed the outcome associated with pressing each lever. In the first forced-choice trial, the right and left lever were randomly selected by the computer. The session started with a programmed 10-min black-out phase where the chamber was dark and the levers were retracted. After the blackout phase, the houselight was illuminated,

one randomly selected lever was extended into the chamber, and the light above it was turned on to commence the first trial. If the lever selected was associated with the presentation of one food pellet, then one pellet was presented immediately after the lever press. Afterward, the houselight was turned off and the chamber remained dark for the rest of the trial. On the other hand, if the selected lever was associated with delivery of three food pellets, then the houselight remained on during the delay for that block, and afterward, three food pellets were presented. The second forced-choice trial was the same procedure except it presented the lever that was not previously selected. Forced-choice trials revealed the outcome associated with pressing each lever, i.e., gave the rat experience with the different outcomes, before assessing choice. In the first forced-choice trial, the right and left lever were randomly selected by the computer, each lever's association with the large or small reinforcer remained the same for each rat throughout the study. In the occasion of an absence of a lever press within 30 s of the start of the trial, the lever was retracted and both the light and houselight was turned off. The chamber remained dark for the rest of the trial (70 s) and an omission was noted.

The remaining six trials in each block were free-choice trials. Both levers extended into the chamber simultaneously, and both the houselight and the lever lights were turned on at the start of every trial. A press on either lever had the same result as a press on that lever during the forced-choice trials in that block. If a lever press did not occur within 30 s of the start of the trial, the same steps occurred as it would if a lever press did not occur in the forced-choice trials. The levers retracted and both the light and houselight turned off. The chamber remained dark for the rest of the trial and an omission was noted.

Rats were exposed to descending delay sequences delivered across five blocks within a session. The delay sequence started at 40, 20, 10, 5, 0 s, but was adjusted to 60, 40, 20, 10, 0 s to

avoid ceiling (all self-control responding) effects. The sessions were conducted five days a week (Mon-Fri) for a minimum of 30 sessions, until at least an average of 80% choice was for the larger reinforcer when the delays to both outcomes were 0-s delays (the last block), no more than an average of 50% for the larger reinforcer when it was delayed the longest (the first block), and there were no increasing or decreasing trends in total number of larger-reinforcer choices across the last three days.

Drug Administration

d-Amphetamine obtained from Sigma-Aldrich (St. Louis, MO, USA) was dissolved in 0.9% sodium chloride and was injected in a volume of 1.0 ml/kg. Saline (the vehicle control) or *d*-amphetamine (0.1, 0.3, 0.56, and 1.0 mg/kg) was administered via intraperitoneal (*i.p.*) injections immediately prior to the session on Tuesdays and Fridays, if choice during the control session (the day before an injection) was within baseline range. All four rats received all doses at least twice.

Data Analysis

Percent larger-reinforcer choice was the principal dependent variable and was calculated by dividing the number of trials in which the larger reinforcer chosen by the total number of trials in which any choice was made at each delay duration. Percent larger-reinforcer choice was plotted on the y-axis as a function of the delay to the larger reinforcer to construct delay-discounting functions. AUC (a measure of impulsivity that takes into account all delays within sessions) was calculated using a formula similar to the one described by Myerson, Green, and Warusawitharana (2001) following study termination. AUC was calculated based on the average percent larger-reinforcer choice data for individual rats following each dose. The formula consisted of adding the area of the trapezoids that were shaped when vertical lines were drawn

from every normalized delay value to the attained percent choice at every delay. Once summed, the area of the trapezoids was divided by the whole area of the graph. Steeper functions resulted in lower AUCs, indicating greater delay discounting/impulsivity. Indifference points were interpolated by fitting a logistic equation to delay-discounting functions for individual rats and assessing at what delay duration choice was for the larger reinforcer 50% of the time. Percent of larger-reinforcer choices, AUC, and indifference points were averaged together for all four rats at each dose of *d*-amphetamine and were compared to average saline and baseline values to assess any increases or decreases in delay discounting. AUC and indifference-point data were further analyzed by using repeated-measures ANOVA because all rats received all drug doses, and Bonferroni post-hoc comparisons as needed. Values were statistically significant if $p < 0.05$.

Results

Baseline

Percent larger-reinforcer choice systematically decreased when delays were longer. When the delay for the larger reinforcer was 60 s, mean percent choice for the larger reinforcer was 18.1%. When the delay for the larger reinforcer was 40 s, mean percent choice for the larger reinforcer was 31.5%. When the delay for the larger reinforcer was 20 s, mean percent choice for the larger reinforcer was 60.3%. When the delay for the larger reinforcer was 10 s, mean percent choice for the larger reinforcer was 87.5%. Lastly, when both delays (for the smaller and larger outcomes) were 0 s, mean percent choice for the larger reinforcer was 93.9%. Thus, delay discounting (more larger-reinforcer choice at short delays to delivery and less at long delays to delivery) was observed in individual subjects, as well as in the group mean data, with decreasing delay presentation.

Saline

Similar to the baseline condition, when saline/placebo was administered, mean percent larger-reinforcer choice systematically decreased when delays were longer (see Figure 1, closed circles). The mean percent larger-reinforcer choice was 18.7% when the delay for the larger-reinforcer was 60 s, 29.0% when the delay for the larger-reinforcer was 40 s, 61.6% when the delay for the larger-reinforcer was 20 s, 91.2% when the delay for the larger-reinforcer was 10 s, and 94.1% when both delays were 0 s. Therefore, the injection procedure alone did not have a significant effect on choice, i.e., injection data were similar to the control/no-injection data.

d-Amphetamine Effects

Figure 1 shows mean percent larger-reinforcer choice for various doses of *d*-amphetamine. *d*-Amphetamine dose dependently decreased larger-reinforcer choice (increased impulsivity) in three of four rats. (Responding was suppressed at 1.0 mg/kg, therefore, those data have been omitted.) These findings are supported by a main effect of dose on average AUC, $F(4,12) = 9.97$, $p = .003$ (see Figure 2), as well as average indifference points, $F(4,12) = 9.92$, $p = .001$. Post-hoc comparisons using Bonferroni adjustments revealed that mean AUC was significantly reduced following 0.56 mg/kg *d*-amphetamine compared to saline/placebo administration, ($p = .014$), which indicates greater impulsive choice. Similarly, mean indifference points were significantly reduced following 0.56 mg/kg *d*-amphetamine compared to saline/placebo administration ($p = .023$), which indicates greater impulsive choice (data not shown). No other doses produced a statistically significant effect on AUC or indifference points when compared to saline vehicle.

Discussion

When comparing the general findings from prior research using increasing delays (e.g., Slezak & Anderson, 2009; Huskinson et al., 2012; Slezak & Anderson, 2011; Slezak, Krebs, &

Anderson, 2012) versus findings from the present study using decreasing delays, similar delay discounting was observed under control and saline conditions. However, *d*-amphetamine increased delay discounting/impulsive choice when the delays were presented in a decreasing order, which is contrary to much prior research with increasing delay presentation (but see Maguire et al., 2014, Tanno et al., 2014 for exceptions). In the Huskinson et al. (2012) study and the Slezak and Anderson (2011) study, self-control choice increased in rats following stimulant drug (caffeine and methylphenidate) administration. In other words, impulsive choice decreased. This was not the case in the present study, as impulsive choice increased following *d*-amphetamine administration.

There have been mixed findings in research on effects of stimulants on larger-reinforcer choice, however. In a study conducted by Slezak and Anderson (2009), both increasing and decreasing delays were used and the percentage of larger-reinforcer choice decreased for both. Specifically, the mean percent larger-reinforcer choice decreased 48% at increasing delays and 71% at decreasing delays from saline to 1.7 mg/kg *d*-amphetamine. This finding was similar to what occurred in the present study, in which, at the highest dose (0.56 mg/kg *d*-amphetamine), percent choice for the larger-reinforcer in the last block (0 s) was 64% percent and in the first block (60 s), percent choice for the larger-reinforcer was 0%. In both studies, percent larger-reinforcer choice after administration of *d*-amphetamine decreased significantly compared to when increasing delays were utilized. Clearly, more research into the variables that determine what effects *d*-amphetamine has on impulsive choice needs to be conducted.

Using four subjects in the present study served as a limitation. However, because a single-subject research design was used, each rat was tested individually and in-depth. Essentially, the study was replicated four times (once for each rat) which, based on prior

literature in this field, was likely to be sufficient. Second, this experiment only tested impulsive choice when delays were in decreasing order. There was no direct comparison to increasing delays, thus, the reliance on prior literature, which contains some procedural differences, was a limitation.

This study does add to existing literature and demonstrates that environmental context (the order delays are presented) can have an influence on effects of *d*-amphetamine on delay discounting/impulsivity. On a broader scale, this finding contributes to the body of evidence in behavioral pharmacology that environmental context is a major determinant of drug effects. There are other factors that impact impulsive choice, such as genetic and neurochemical factors (Huskinson et al., 2012). In the future, to expand on this study, it would be constructive to investigate effects of other drugs (e.g., cocaine, heroin) as well as effects of a random order of delay presentation to the larger reward (e.g., 40, 10, 0, 20, 60 s) in different strains of rats. Due to social relevance, there is a need to understand the varied conditions under which impulsive choice is observed and how drugs affect such behavior.

Acknowledgements

I (EJ) am tremendously grateful for the WVU McNair Scholars Program and Dr. Betty Mei for supporting me and giving me numerous opportunities. I would also like to express my appreciation to Dr. Karen Anderson and the WVU Psychology Department for project support, financial and otherwise. In addition, doctoral student Marissa Turturici was extremely generous with her time and aid in the laboratory.

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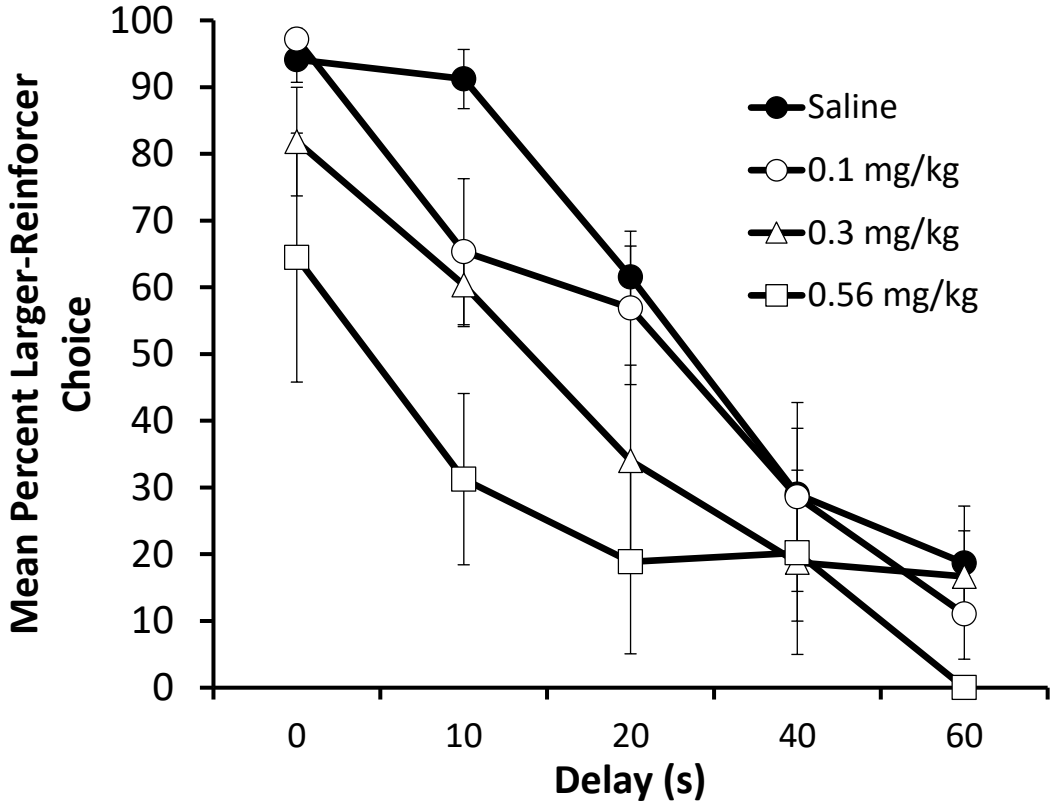

Figure 1. Mean percent larger-reinforcer choice during control conditions (saline/placebo) and doses of *d*-amphetamine (mg/kg) plotted as a function of reinforcer delay. (The smaller-reinforcer choice is the converse of larger-reinforcer choice.) Note that to facilitate comparison with prior literature using increasing delays, the delays here are also presented in ascending order. However, all delays in the present study were presented in descending order where 60 s was the first block and 0 s was the last block. Each data path represents the mean (n= 4 rats). Error bars represent standard error of the mean.

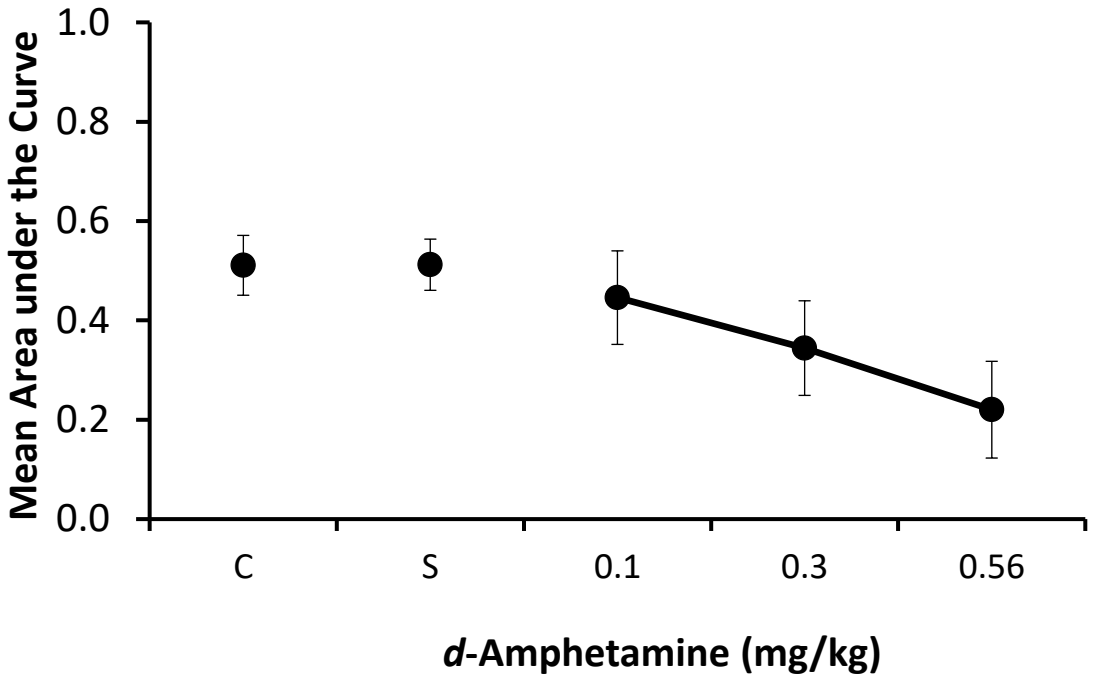

Figure 2. Mean AUC plotted as a function of control/no injection ("C"), saline ("S"), or *d*-amphetamine dose. Smaller AUC indicate greater impulsive choice. Each data point represents the mean (n= 4 rats). Error bars represent standard error of the mean.