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Effects of *d*-amphetamine and MK-801 on impulsive choice: modulation by schedule of reinforcement and delay length

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Abstract

Procedural modifications can modulate drug effects in delay discounting, such as signaling the delay to reinforcement and altering the order in which delays are presented. Although the schedule of reinforcement can alter the rate at which animals discount a reinforcer, research has not determined if animals trained on different schedules of reinforcement are differentially affected by pharmacological manipulations. Similarly, research has not determined if using different delays to reinforcement can modulate drug effects in delay discounting. Male Sprague Dawley rats (n = 36) were split into four groups and were trained in a delay-discounting procedure. The schedule of reinforcement (fixed ratio [FR] 1 vs. FR 10) and delays to reinforcement (0, 5, 10, 20, and 50 s vs. 0, 10, 30, 60, 100 s) were manipulated for each group. Following behavioral training, rats were treated with *d*-amphetamine (0, 0.25, 0.5, and 1.0 mg/kg) and MK-801 (0, 0.03, and 0.06 mg/kg). Results showed that amphetamine decreased impulsive choice when a FR 1 schedule was used, but only when the short delay sequence was used. Conversely, amphetamine decreased impulsive choice when a FR 10 schedule was used, but only when rats were trained on the long delay sequence. MK-801 decreased impulsive choice in rats trained on a FR 1 schedule, regardless of delay sequence, but did not alter choice in rats trained on a FR 10 schedule. These results show that schedule of reinforcement and delay length can modulate drug effects in delay discounting.

Keywords

Impulsive choice; delay discounting; schedule of reinforcement; delay length; amphetamine; MK-801

1. Introduction

Elucidating the neurochemical underpinnings of impulsive choice is important as we can identify ways to treat those that have disorders characterized by excessive impulsivity (e.g.,

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attention-deficit/hyperactivity disorder, substance use disorders). To this end, the contribution of the dopaminergic system to delay discounting has been heavily studied [1–21], although the glutamatergic system has received considerable attention during the past few years [4, 19, 22–30]. The neurochemical basis of impulsive choice has often been examined using delay-discounting procedures. Evenden and Ryan [31] developed a discounting procedure that is most commonly used in behavioral pharmacology studies. In this procedure, subjects are allowed to choose between a large magnitude reinforcer (typically 3-5 food pellets, depending on the experiment) and a small magnitude reinforcer (typically 1 food pellet). Across blocks of trials, the delay to the large magnitude reinforcer is increased. Animals that are classified as low impulsive, or as exerting high self control, will continue to respond for the large magnitude reinforcer as the delay to reinforcement continues to increase. To determine the contribution of neurotransmitter systems to impulsive choice, subjects receive acute injections of a drug of interest.

One challenge to elucidating the neurochemical underpinnings of impulsive choice is that certain procedural modifications can alter the effects of pharmacological manipulations on choice. For example, using a cue to signal delay to reinforcement alters the effects of *d*-amphetamine in delay discounting; specifically, when no signal is used, amphetamine decreases choice for the large magnitude reinforcer, whereas amphetamine *increases* choice when a signal is used [2]. Additionally, changing the order in which delays are presented can modulate drug effects in delay discounting. Amphetamine [9, 13] and methylphenidate [13] increase responding for the large magnitude reinforcer when the delays increase across the session but decrease responding when the delays decrease across the session. Finally, reinforcement magnitude can modulate drug effects. Specifically, amphetamine does not alter impulsive choice in rats that make a choice between a 1-pellet reinforcer and a 3-pellet reinforcer, but it increases impulsive choice in rats that make a choice between a 2-pellet reinforcer and a 6-pellet reinforcer [5].

In addition to the procedural manipulations described above, another procedural factor that may modulate drug effects in delay discounting is the schedule of reinforcement. Historically, behavioral pharmacology studies have primarily used a fixed ratio (FR) 1 schedule of reinforcement in discounting procedures [see 32 for a review]. Relying exclusively on FR 1 schedules of reinforcement can be problematic because they may not fully capture real-world decision making. Not all behaviors are reinforced on FR 1 schedules, such as going to work. Related to discounting, animals trained on a leaner schedule of reinforcement choose a large, delayed reinforcer more frequently compared to animals trained on a FR 1 schedule of reinforcement [33]. Concerning drug effects on discounting, MK-801, a glutamate N-methyl-D-aspartate (NMDA) receptor uncompetitive antagonist, increases choice for the large magnitude reinforcer when a FR 1 schedule is used [27] but does not affect impulsive choice when a FR 10 schedule is used [28]. The results of these two studies cannot necessarily be used to make the assertion that the schedule of reinforcement modulates drug effects in delay discounting. First, these studies were conducted at different times in different laboratories. Second, the delay lengths used in each study differed (0, 5, 10, 20, 50 s vs. 0, 10, 30, 60, 100 s). Thus, delay length, not schedule of reinforcement, may have accounted for the discrepancies across these studies.

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The goal of the current study was to further elucidate how procedural manipulations can alter drug effects in a delay-discounting procedure. We tested four separate groups of rats. The first group of rats (FR 1/short delay group) was trained on a FR 1 schedule of reinforcement and was exposed to a short delay sequence (0-50 s). The second group (FR 10/short delay group) was trained on a FR 10 schedule of reinforcement and was exposed to the same short delay sequence as the first group. The third and fourth groups (FR 1/long delay and FR 10/long delay groups) were similar to the first two, with the exception that they were exposed to a long delay sequence (0-100 s). Following training, rats received injections of amphetamine and MK-801. Amphetamine was chosen because it is commonly used in experiments assessing how parametric manipulations alter drug effects on discounting [2, 9, 13]. MK-801 was also chosen because our laboratory has primarily focused on the contribution of the glutamatergic system to impulsive choice, and we have found contradictory evidence concerning the effects of this drug on discounting [27–28].

2. Materials and methods

2.1. Animals

Thirty-six adult, male Sprague Dawley rats were obtained from Envigo (Indianapolis, IN; weighing between 200-224 g upon arrival). They were acclimated to an animal housing room and handled for six days before any behavioral testing began. The housing room was maintained on a 12:12-h cycle (lights on at 700 h), and rats were tested in the light phase (approximately 1100-1600 h). Rats were individually housed in clear plastic cages (30 cm wide × 24.6 cm high × 41.2 cm long) with a wire top lid to hold food and a plastic external bottle top to hold two water bottles. Each cage contained one plastic nylon bone. Rats had *ad libitum* access to water but were restricted to 15 g of food each day. Rats were immediately fed following completion of each session.

2.2. Drugs

D-amphetamine sulfate and (+)-MK-801 hydrogen maleate (Sigma, St. Louis, MO) were prepared in sterile 0.9% NaCl (saline) and injected in a volume of 1 ml/kg. All injections were delivered subcutaneously (s.c.). The doses were calculated based on salt weight.

2.3. Apparatus

Nine operant-conditioning chambers (28 × 21 × 21 cm; ENV-008; MED Associates, St. Albans, VT) located inside sound attenuating chambers (ENV-018M; MED Associates) were used. The front and back walls of the chambers were made of aluminum, while the side walls were made of Plexiglas. There was a recessed food tray (5 × 4.2 cm) located 2 cm above the floor in the bottom-center of the front wall and was located between the retractable levers. Each lever (4.8 × 0.55 × 1.9 cm) was located 2.1 cm above the floor and required a force of 0.245 N to depress. An infrared photobeam was used to record head entries into the food tray. A 28-V white stimulus light (2.54 cm diameter) was located 6 cm above each response lever. A 28-V white house light was mounted in the center of the back wall of the chamber. All responses and scheduled consequences were recorded and controlled by a computer interface. A computer controlled the experimental session using Med-V software.

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2.4. Procedure

For 2-3 sessions, rats received magazine training, in which 20 food pellets (45 mg dustless precision pellets; product F0021; Bio-Serv, Frenchtown, NJ) were non-contingently delivered into the food tray according to a variable-time 30 s schedule of reinforcement. Once subjects ate all of the food during a two-day period, they were given lever-press training, which lasted 4-24 sessions. Some rats needed 24 sessions due to a technical issue that occurred with the equipment, which prevented them from receiving reinforcement when they pressed the lever. Each session began with illumination of the house light. A head entry into the food tray resulted in presentation of one lever; each lever was presented pseudo-randomly, with no more than two consecutive presentations of the same lever. A response on the extended lever (FR 1) resulted in the following events: extinguishment of the house light, retraction of the lever, and delivery of one food pellet. After a 5-s intertrial interval (ITI), the house light was illuminated. Each lever-press training session ended after a rat earned 40 reinforcers or after 30 min, whichever came first. When a subject was able to complete all 40 trials for two consecutive sessions, they were given magnitude discrimination training.

Rats received 4-5 sessions of magnitude discrimination training. Similar to lever-press training, each session consisted of 40 trials, and the beginning of each trial was signaled by illumination of the house light. A head entry into the food tray extended one of the levers (the order of presentation between the two levers was pseudo-randomized, with no more than two consecutive presentations of the same lever). Completing the response requirement resulted in the following events: extinguishment of the house light, retraction of the lever, and delivery of reinforcement (one lever was associated with immediate delivery of one pellet, whereas the other lever was associated with immediate delivery of four pellets; the lever associated with the large magnitude reinforcer was counterbalanced across rats). If an animal failed to respond within 20 s, the lever was retracted, the light was extinguished, and the trial was scored as an omission. Each trial lasted 30 s. Because each trial lasted 30 s, the ITI was variable. For example, if an animal completed the response requirement within 5 s, there was a 25-s ITI; if an animal completed the trial within 15 s, there was a 15-s ITI. For half of the rats, the response requirement was a FR 1 for each magnitude discrimination training session. For half of the rats, the response requirement increased across each magnitude discrimination training session to a terminal FR 10 (FR 1, FR 3, FR 5, and FR 10; the schedule of reinforcement increased after each session). For magnitude discrimination training, there were no strict stability criteria. Most rats trained on the FR 1 schedule completed all 40 trials by the end of training; however, for rats trained on the FR 10 schedule of reinforcement, omissions increased as the FR requirement increased. Because we wanted the number of training sessions to be similar across rats trained on the FR 1 and FR 10 schedules, we did not want to administer too many additional training sessions during this phase of the experiment.

Discounting sessions consisted of 5 blocks of 9 trials. The first 4 trials in a block were forced-choice trials, in which only one lever was randomly presented (no more than two consecutive presentations of the same lever). The remaining trials were free-choice trials, in which both levers were extended. Each trial began with illumination of one of several stimuli (first block of trials: house light; second block: house light and left stimulus light; third

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block: house light and right stimulus light; fourth block: house light and both stimulus lights; fifth block: both stimulus lights only). As in reward magnitude discrimination training, completing the response requirement on one lever always resulted in immediate delivery of one food pellet. A response on the other lever resulted in delayed delivery of 4 pellets. For subjects trained on the FR 10 schedule of reinforcement, they had to emit 10 responses on a single lever to end the trial (e.g., if a subject responded on the left lever four times and then responded on the right lever six times, this would not end the trial; the animal would need to respond on the right lever an additional four times). The delay to delivery of the large magnitude reinforcer increased across blocks of trials for all rats. Rats were divided into four groups. For one group, the delays to the large magnitude reinforcer were 0, 5, 10, 20, and 50 s, and responses were reinforced according to a FR 1 schedule of reinforcement (FR 1/short delay group). For one group, the delays were 0-50 s, but responses were reinforced according to a FR 10 schedule of reinforcement (FR 10/short delay group). The final two groups were similar to the first two, with the exception that the delays to reinforcement were 0, 10, 30, 60, and 100 s (FR 1/long delay and FR 10/long delay groups). Following completion of the response requirement on either lever, all stimulus lights were extinguished, the levers were retracted, and reinforcement (either one pellet or four pellets) was delivered. The levers remained retracted during the ITI. If a response was not made within 20 s, the trial was scored as an omission, which resulted in the levers retracting and the house light being extinguished for the remainder of the trial. To compensate for the delay to the large magnitude reinforcer, the length of each trial increased across blocks of trials (for short delay sequence: 30, 35, 40, 50, and 80 s; for long delay sequence: 30, 40, 60, 90, and 130 s). Regardless if the subject responded for the large magnitude reinforcer or the small magnitude reinforcer, each trial lasted the same amount of time. Because each trial lasted the same amount of time, the ITI depended on how quickly each subject completed the response requirement (similar to magnitude discrimination training).

Baseline training was considered completed when (1) all subjects showed a typical discounting function (i.e., rats consistently choose the large magnitude reinforcer at the 0-s delay and then switched their choice to the small magnitude reinforcer as the delay increased) and (2) there were no increasing or decreasing trends across a 3-day period. Following behavioral training (41 sessions for rats trained on the FR 10 schedule of reinforcement; 44 sessions for rats trained on the FR 1 schedule of reinforcement), rats were treated with amphetamine (0, 0.25, 0.5, and 1.0 mg/kg). Initially, rats received saline and the two highest doses of amphetamine (in a randomized order). Due to the high number of omissions observed with each dose (particularly for rats trained on the FR 10 schedule), we tested the 0.25 mg/kg dose. Three days after being treated with the 0.25 mg/kg dose of amphetamine, rats began receiving MK-801 injections. Rats were tested with MK-801 (0, 0.03, and 0.06 mg/kg). Each dose of amphetamine and MK-801 was administered 15 min before each session, and each injection was administered every 3-5 days. The doses and pre-session treatment time (15 min) were based on previous studies [1, 14, 23, 27–28]. Rats were trained as normal on sessions in which they did not receive an injection, and the experimenters visually inspected each subject’s data to ensure discounting returned to baseline levels before receiving the next dose.

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2.5. Statistical Analyses

2.5.1. Baseline data.—To determine if omissions differed across rats trained on the FR 1 and FR 10 schedules, a Mann-Whitney U test was conducted. Similarly, to determine if omissions differed across rats trained on the short delay sequence and the long delay sequence, a separate Mann-Whitney U test was conducted. Statistical significance was defined as $p < .05$.

For discounting data, we fit an exponential model to the raw data in order to derive two parameter estimates. The exponential model is defined by the equation $V = Ae^{-kD}$, where V is the subjective value of the reinforcer, A is the intercept and refers to discriminability of reinforcer magnitude (i.e., how much the animal prefers the large reinforcer relative to the small reinforcer when they are both available immediately), e is Euler's number, k is the slope of the discounting function (i.e., measure of impulsive choice), and D is the delay to delivery of the large reinforcer. Although hyperbolic discounting is typically preferred over the exponential model due to its ability to account for preference reversals [see 34 for a discussion], it is important to note that hyperbolic functions are often used to describe discounting that occurs in the adjusting delay procedure [e.g., 35]. In the adjusting delay procedure, animals often make choices between two delayed reinforcers. In cases in which subjects choose between an immediate reinforcer and a delayed reinforcer (as in the current experiment), some have argued that the exponential function better describes discounting [36–37]. Related to this point, in our experience, exponential functions provide a better fit of the data when the Evenden and Ryan [31] procedure is used, particularly when modeling drug effects on discounting. In the current experiment, hyperbolic and exponential functions provided a good fit of baseline data (median R^2 for hyperbolic function = .974; median R^2 for exponential function = .984). When examining Bayesian Information Criteria (BIC), there is not much difference between the two models (BIC for hyperbolic function = 39.751; BIC for exponential function = 44.078; note: lower BICs indicate better model fit). However, when fitting discounting functions following drug administration, the exponential function provides a superior fit to the data. For example, for the amphetamine analyses, the BIC for the hyperbolic function is 324.585, whereas the BIC for the exponential function is 201.232 (for MK-801 data, the BICs are 112.032 and 93.792, respectively). Additionally, the variability associated with the hyperbolic function is exceedingly high compared to the exponential function. For the hyperbolic function, the standard error of the mean for each condition ranges from 0.003-0.818 following amphetamine administration. However, the standard error ranges from just 0.022-0.080 when the exponential model is used. A similar trend is observed for the MK-801 data (range of .045-1.102 for hyperbolic function and range of .022-.111 for exponential function). For these reasons, we tend to fit exponential functions to our discounting data.

The exponential function was fit to individual subject data via nonlinear mixed effects (NLME) modeling using the NLME package in *R* [38]. The NLME models defined A and k as free parameters, Delay as a fixed, continuous within-subjects variable, Delay Type and Schedule as fixed, nominal between-subjects variables, and Subject as a random factor. Specifically, the A and k parameter estimates were allowed to vary across subjects. Contrasts

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were conducted using the emmeans package in *R* [39]. *P* values were adjusted using the Tukey method. Statistical significance was defined as $p < .05$.

2.5.2. Drug effects.—Several nonparametric tests were conducted to determine drug effects on omissions. To compare omissions (averaged across each drug dose) across rats trained on the FR 1 schedule and the FR 10 schedule, a Mann-Whitney U test was conducted. To determine if omissions (averaged across each drug dose) differed as a function of delay type, a separate Mann-Whitney U test was conducted. Several Friedman tests were conducted to determine if each drug significantly altered omissions. The first Friedman test determined if amphetamine/MK-801 increased omissions (averaged across each condition). Four separate Friedman tests were conducted for each condition. Durbin-Conover post hoc tests were used when the results of Friedman test were statistically significant. Statistical significance was defined as $p < .05$ for the Mann-Whitney U tests and the first Friedman test described above. For the Friedman tests that were conducted for each individual condition, statistical significance was defined as $p < .0125$ to control for Type I error.

To determine how amphetamine/MK-801 altered performance in delay discounting, we fit the exponential discounting function to individual subjects via NLME modeling using the NLME package in *R* [38]. The NLME models defined A and k as free parameters, Delay as a fixed, continuous within-subjects variable, Dose as a fixed, nominal within-subjects variable, Delay Type and Schedule as fixed, nominal between-subjects variables, and Subject as a random factor, with the A and k parameter estimates being allowed to vary across subjects. Contrasts were conducted using the emmeans package in *R* [39]. *P* values were adjusted using the Tukey method. Statistical significance was defined as $p < .05$.

3. Results

3.1. Baseline Data

3.1.1. Omissions.—Figure 1a shows the total number of omissions during free-choice trials across each condition. Rats trained on the short delay sequence had more omissions relative to rats trained on the long delay sequence, $U = 57.500$, $p < .001$. Rats trained on the FR 10 schedule of reinforcement had more omissions relative to rats trained on the FR 1 schedule of reinforcement, $U = 92.000$, $p = .024$.

3.1.2. Discounting.—Figure 1b shows the raw proportion of responses for the large magnitude reinforcer across each condition. Rats showed no differences in their discriminability of reinforcer magnitude as a function of the FR ratio or delays chosen (i.e., A parameter estimates obtained from the exponential discounting function did not differ across conditions), all F's ≤ 0.664, all p's ≥ .417 (Fig. 1c). Rats trained on the FR 10 schedule of reinforcement, regardless of delay length, showed decreased impulsive choice relative to rats trained on the FR 1 schedule of reinforcement (i.e., lower k values), $F(1, 133) = 23.115$, $p < .001$ (Fig. 1d). There was no significant main effect of Delay Type, $F(1, 133) = 0.722$, $p = .397$, nor a significant Delay Type × Schedule interaction, $F(1, 133) = 0.104$, $p = .747$.

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3.2. Drug Effects on Discounting Performance

3.2.1. Omissions.—Figure 2 shows omissions following administration of amphetamine (Fig. 2a) and MK-801 (Fig. 2b). Overall, amphetamine (0.5 and 1.0 mg/kg) significantly increased omissions (averaged across each condition), $\chi^2(3) = 43.500$, $p < .001$. Rats trained on the short delay sequence had more omissions following amphetamine relative to rats trained on the long delay sequence, $U = 60.500$, $p = .001$. Rats trained on the FR 10 schedule had more omissions (even following saline administration) relative to rats trained on the FR 1 schedule, $U = 71.500$, $p = .004$. Amphetamine (0.5 and 1.0 mg/kg) significantly increased omissions for rats in each condition, all χ^2 values ≥ 17.524, all p values ≤ .001. Additionally, the lowest dose of amphetamine (0.25 mg/kg) significantly increased omissions in rats in the FR 10/short delay group.

MK-801 (0.06 mg/kg) significantly increased omissions (averaged across each condition), $\chi^2(2) = 9.447$, $p = .009$. Rats trained on the short delay sequence had more omissions following MK-801 administration relative to rats trained on the long delay sequence, $U = 82.00$, $p = .011$. Rats trained on the FR 10 schedule had more omissions (even following saline administration) relative to rats trained on the FR 1 schedule, $U = 48.500$, $p < .001$. When examining each individual condition, MK-801 (0.06 mg/kg) increased omissions in the FR 10/long delay group, $\chi^2(2) = 13.714$, $p = .001$; all other χ^2values ≤ 4.000, all other p values ≥ .135.

3.2.2. Discounting.—Figure 3 shows the raw proportion of responses for the large magnitude reinforcer following amphetamine administration. Because the highest dose of amphetamine (1.0 mg/kg) completely suppressed behavior in most of the rats tested, this dose was excluded from the NLME analyses, and the data from this dose are not presented in Figure 3 or in Figure 4. Following amphetamine administration, NLME analyses revealed that rats trained on the long delay sequence (0-100 s) had larger A parameter estimates compared to rats trained on the short delay sequence (0-50 s), $F(1, 423) = 4.341$, $p = .038$. Additionally, there was a significant Delay Type × Schedule × Dose interaction, $F(2, 423) = 3.172$, $p = .043$. This interaction may be explained by the finding that amphetamine decreased A parameter estimates in the FR 1/short delay group, whereas A parameter estimates tended to increase for the FR 10/short delay group; however, these results were reversed in rats trained on the long delay sequence (Fig. 4a).

Results of the NLME analyses revealed that rats trained on the FR 10 schedule had lower k parameter estimates (i.e., showed less discounting) compared to rats trained on the FR 1 schedule, $F(1, 423) = 22.534$, $p < .001$, and that amphetamine decreased k parameter estimates, $F(2, 423), = 8.030$, $p < .001$. There were also significant Delay Type × Dose, $F(2, 423) = 4.995$, $p = .007$, Schedule × Dose, $F(2, 423) = 6.224$, $p = .002$, and Delay Type × Schedule × Dose, $F(2, 423) = 7.038$, $p = .001$, interactions (Fig. 4b). Amphetamine decreased k parameter estimates in the FR 1/short delay group without altering k parameter estimates in the FR 10/short delay group. However, amphetamine decreased k parameter estimates in the FR 10/long delay group without altering k parameter estimates in the FR 1/long delay group. Amphetamine decreased k parameter estimates to a greater extent in the FR 1/short delay group relative to the FR 10/long delay group.

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Figure 5 shows the raw proportion of responses for the large magnitude reinforcer following MK-801 administration. NLME analyses revealed that MK-801 decreased *A* parameter estimates, $F(2, 462) = 4.353$, $p = .013$ (Fig. 6a). Concerning *k* parameter estimates, rats trained on the FR 10 schedule had decreased *k* parameter estimates relative to rats trained on the FR 1 schedule, $F(1, 462) = 18.996$, $p < .001$, and MK-801 decreased *k* parameter estimates, $F(2, 462) = 13.044$, $p < .001$. There was also a Schedule × Dose interaction, $F(2, 462) = 12.424$, $p < .001$. Rats trained on the FR 1 schedule of reinforcement had decreased *k* parameter estimates following administration of MK-801 (0.06 mg/kg), whereas MK-801 did not alter *k* parameter estimates in rats trained on the FR 10 schedule (Fig. 6b).

4. Discussion

Understanding how neurotransmitter systems control impulsive choice can be difficult as previous research has shown that certain procedural manipulations (e.g., signaling the delay to reinforcement, increasing/decreasing the delays to reinforcement, reinforcer magnitude) can alter how acute drug administration affects impulsive choice in delay discounting [2, 5, 9, 13, 29–30]. The results of the current study extend the existing literature by showing that two additional procedural manipulations can modulate drug effects in delay discounting. Specifically, amphetamine decreased delay discounting when a FR 1 schedule was used, but only when the short delay sequence (0-50 s) was used. Conversely, amphetamine decreased delay discounting when a FR 10 schedule was used, but only when rats were trained on the long delay sequence (0-100 s). MK-801 decreased discounting in rats trained on a FR 1 schedule, regardless of delay sequence, but did not alter discounting in rats trained on a FR 10 schedule.

In an effort to increase discriminability across blocks of trials, we used different stimuli to signal each block (e.g., house light alone, left and right stimulus lights, etc.). One potential concern is that two blocks of trials (second and third) used just one of the stimulus lights (left stimulus light for the second block; right stimulus light for the third block). Thus, the use of these stimulus lights may have biased subjects' responding in the discounting task. If this were the case, one would expect to observe increased responses for the large magnitude reinforcer in rats that received this alternative after responding on the left lever during the second block; conversely, responses should be higher for rats that experienced the large alternative after responding on the right lever during the third block of trials. However, this was not observed in the current experiment. Thus, we are not concerned that the ways in which the blocks were scheduled biased animals' responding. Future studies can use blinking lights and/or tones to better signal each trial block.

The finding that rats trained on a FR 10 schedule showed decreased impulsive choice relative to rats trained on a FR 1 schedule is consistent with a previous report [33]. In addition to responding more for the large magnitude reinforcer, rats trained on the FR 10 schedule of reinforcement had more omissions relative to rats trained on the FR 1 schedule of reinforcement. This finding is not completely surprising as animals needed to complete more responses on the lever before expiration of the limited hold (in this experiment, 20 s). What was somewhat surprising is that rats trained on the short delay sequence had more omissions relative to rats trained on the long delay sequence, with this effect being more

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noticeable for subjects trained on the FR 10 schedule of reinforcement. It is unlikely that the increased omissions observed in these groups are due to a combination of shorter trial lengths and satiation. Even though the trials are shorter compared to the long delay groups (0-80 s vs. 0-130 s), subjects had at least 10 s to consume their food before the start of the next trial. Furthermore, in our previous work using a delay sequence of 0-50 s [27], we observed few omissions (near 0).

Although we cannot fully explain the increased omissions observed in the short delay groups, we found that amphetamine increased choice for the large magnitude reinforcer (i.e., decreased *k* parameter estimates) in rats trained on a FR 1 schedule, but only when the short delay sequence was used. This finding is consistent with previous reports that use shorter delay sequences (0-40 s or 0-60 s) [14, 40–44; but see 31, 45]. A novel contribution of this study is the finding that amphetamine does not affect delay discounting in rats trained on a FR 1 schedule when the delay lengths are increased, although amphetamine decreases impulsive choice when a FR 10 schedule is used in conjunction with the long delay sequence. The differential effects observed following amphetamine administration in the FR 1/short delay and the FR 10/short delay groups may be due, at least in part, to baseline differences in discounting. Rats trained on the FR 1 schedule under the short delay sequence had higher basal levels of impulsive choice relative to rats trained on the FR 10 schedule under the short delay sequence. Therefore, observing significant decreases in impulsive choice following amphetamine administration in the FR 10/short delay group may have been precluded by their low baseline levels of impulsivity. Previous studies have observed that the effects of amphetamine are dependent on baseline differences in impulsive choice [5, 12, 46].

The argument that the differential results observed across FR 1/short delay and FR 10/short delay groups is explained by baseline differences is somewhat contradicted by the findings observed with the long delay groups. Not only did amphetamine increase choice for the large magnitude reinforcer in FR 1/short delay rats, it increased choice for this alternative in FR 10/long delay rats (albeit the magnitude of this effect was larger for the FR 1/short delay group). If baseline differences accounted for the differential effects observed across groups, one would expect to see decreased impulsive choice in both groups trained on the FR 1 schedule of reinforcement (regardless of delay length). Interestingly, Barbelivien et al. [40] found that amphetamine did not affect impulsive choice in rats characterized as high impulsive or as low impulsive; instead, amphetamine only affected discounting in rats that had “medium” levels of impulsive choice, thus providing an additional argument against the idea that the current results are merely due to baseline differences in impulsive choice. Overall, these results suggest that schedule of reinforcement and delay length can interact with one another to modulate how drugs influence choice.

Similar to previous research, MK-801 decreased impulsive choice when a FR 1 schedule of reinforcement was used [23, 27], but failed to alter discounting when a FR 10 schedule was used [28]. Although the current results are similar to previous reports, one inconsistency is that we did not observe a significant alteration in impulsive choice following the 0.03 mg/kg dose as previously observed [23, 27]. Unlike previous studies, we did not include a lower dose (e.g., 0.01 mg/kg) because this dose typically does not alter discounting [23, 27–28].

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By only including two doses of MK-801, this may have altered how rats responded to the 0.03 mg/kg dose in the current experiment. Another potential explanation for the null effects observed with MK-801 (0.03 mg/kg) is that each subject received injections of amphetamine before being tested with MK-801. Exposure to amphetamine may have altered rats' sensitivity to MK-801. Despite this minor limitation, we still show that schedule of reinforcement is an important modulator of drug effects on impulsive choice. Although baseline differences may not adequately account for the differential effects observed with amphetamine, this explanation appears to account for the effects observed with MK-801. Because rats trained on the FR 10 schedule of reinforcement have lower basal levels of impulsive choice (regardless of delay length), it may have been difficult to see further decreases in impulsive choice in these rats. There is some evidence that baseline differences can alter how NMDA receptor ligands alter impulsive choice. Cottone et al. [22] found that ketamine, an uncompetitive NDMA receptor antagonist, increases impulsive choice in low-impulsive rats but has no effect on high-impulsive rats.

One major caveat of the study needs to be acknowledged. Due to the large number of omissions (particularly following amphetamine administration), we conducted a supplementary analysis examining the number of omitted forced-choice and free-choice trials across individual blocks of trials. If animals omitted a large number of forced-choice trials following amphetamine administration, this would imply that drug-induced changes in behavior may reflect alterations in perseveration, as opposed to alterations in impulsive choice. When examining the FR 1/short delay and FR 10/long delay groups (the two groups that showed significant decreases in impulsive choice following amphetamine administration), subjects omitted 55% and 72% of all forced-choice trials, respectively. Because these subjects omitted more than half of the forced-choice trials, this provides support for the argument that amphetamine merely increased perseverative responding, as subjects were unlikely to respond on one of the levers during force-choice trials during a given block of trials. The argument that amphetamine increases perseverative responding in discounting is consistent with past studies [9, 13]. Interestingly, when examining the FR 1/short delay and FR 1/long delay groups following MK-801 administration (the two groups that showed decreased impulsive choice following MK-801 administration), we found that subjects omitted just 31% and 4% of all forced-choice trials, respectively. Thus, the changes in responding observed following MK-801 administration may not be entirely explained by increased perseveration.

A few additional limitations to the study are worth mentioning. In an effort to minimize the number of variables in the current study, we did not include a condition in which the delays to reinforcement decreased across the study, and we did not include a condition in which we signaled the delay to reinforcement. Although changing these parameters is known to modulate drug effects in discounting [2, 9, 13, 29–30], research has not examined how these parameters interact with schedule of reinforcement and/or delay length to modulate drug effects in this procedure. Furthermore, we did not examine sex differences and/or strain differences. Although sex differences have not been observed at baseline in the Evenden and Ryan [31] procedure [3], female rats are more sensitive to the effects of acute amphetamine administration relative to male rats [3]. Also, when considering strain differences, previous research has shown that amphetamine does not affect discounting in spontaneously

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hypertensive rats (SHR), but increases impulsive choice in Wistar Kyoto rats [47]. Future work can examine how procedural manipulations, such as schedule of reinforcement and delay length, interact with biological variables (e.g., sex, strain) to alter how drugs affect impulsive choice. Future studies can also determine how procedural manipulations alter drug effects in other discounting procedures, such as probability discounting [e.g., 29, 48] or the risky decision task [49].

The results of the current study further highlight the difficulties of elucidating the exact neurochemical underpinnings of impulsive choice. The effects of amphetamine and MK-801 were dependent on which schedule of reinforcement was used and/or how long the delays to reinforcement were. These findings, in conjunction with others examining how signaling the delay to reinforcement [2] or altering the order in which delays are presented [9, 13, 29–30], lead to the question, “what is the most appropriate way of designing the Evenden and Ryan [31] discounting procedure?” Historically, studies using this procedure have used a FR 1 schedule of reinforcement, have systematically increased the delays to reinforcement, and have used a delay range of 0-40 s or 0-60 s. Considering that modifying these parameters can drastically alter how pharmacological manipulations affect behavior in this task, future studies may want to consider including one or more of these procedural manipulations to better determine how a drug affects impulsive choice. Realistically, a study cannot include every possible combination of manipulations (e.g., short delay sequence with a FR 1 schedule in which the delays decrease across the session vs. long delay sequence with a FR 10 schedule in which the delay to reinforcement is signaled, etc.), but one may want to keep these parameters in mind when designing a discounting study. If one expects a drug to increase impulsive choice, using a FR 1 schedule of reinforcement in which the delays to reinforcement increase across the session may preclude one from observing such effect, as this arrangement can produce steep discounting. If the goal is to identify how a drug alters choice, these procedural parameters can be altered across individual subjects to ensure that basal levels of discounting are not too shallow or not too steep. For example, Anderson and colleagues often adjust the delay length for individual subjects to prevent floor and ceiling effects in discounting [33, 50–51]. In conclusion, the results of the current experiment extend the literature by showing that the schedule of reinforcement and delay length can modulate drug effects in delay discounting.

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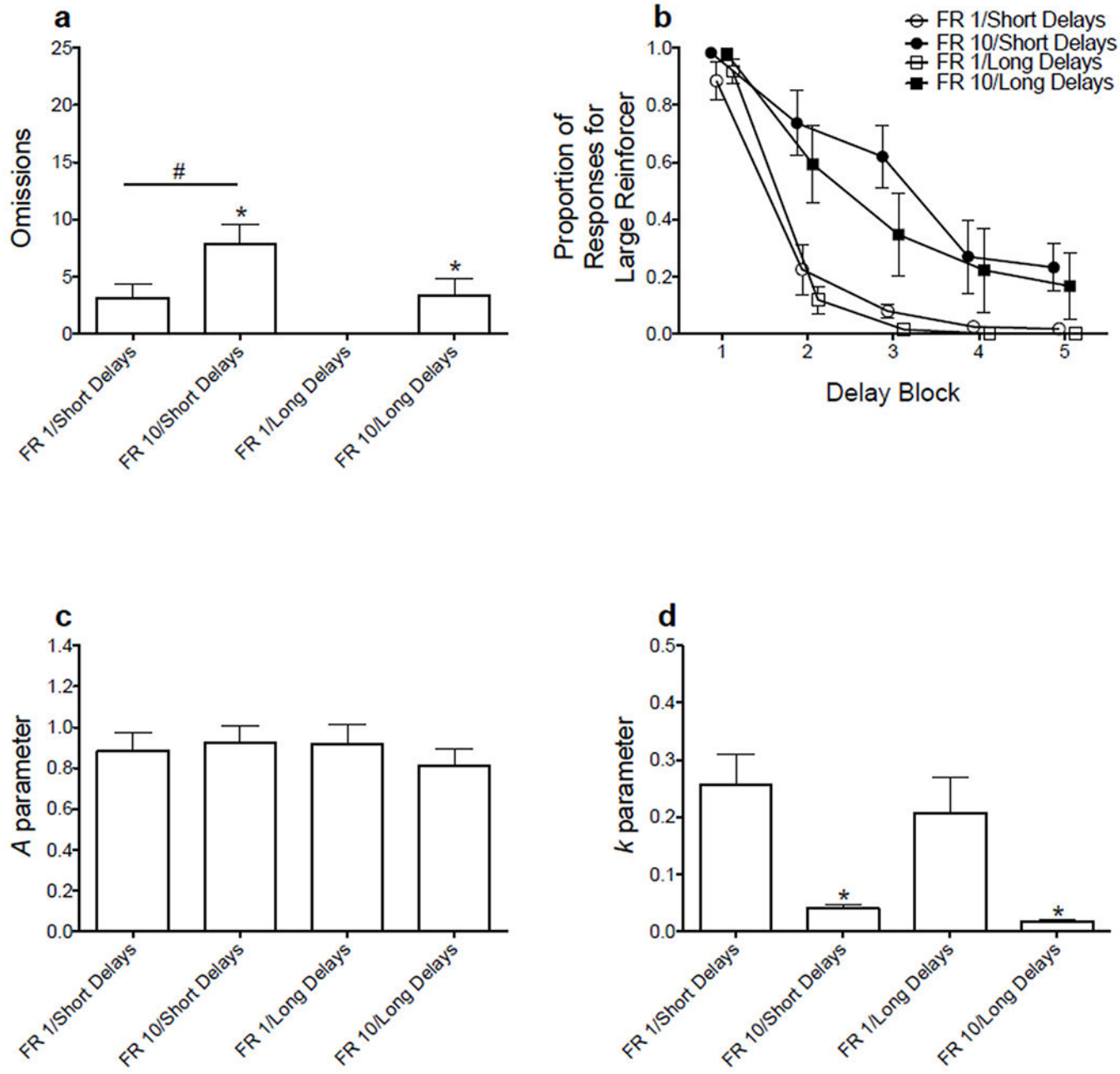

Figure 1.

(**a**) Mean (±SEM) omissions during free-choice trials. (**b**) Mean (±SEM) proportion of responses for the large magnitude reinforcer at the end of baseline training for each condition. (**c**) Mean (±SEM) *A* parameter estimates (i.e., choice for the large magnitude reinforcer when its delivery is immediate). (**d**) Mean (±SEM) *k* parameter estimates (i.e., impulsive choice). #$p < .05$, relative to rats trained on the long delay sequence. *$p < .05$, relative to rats trained on a FR 1 schedule of reinforcement.

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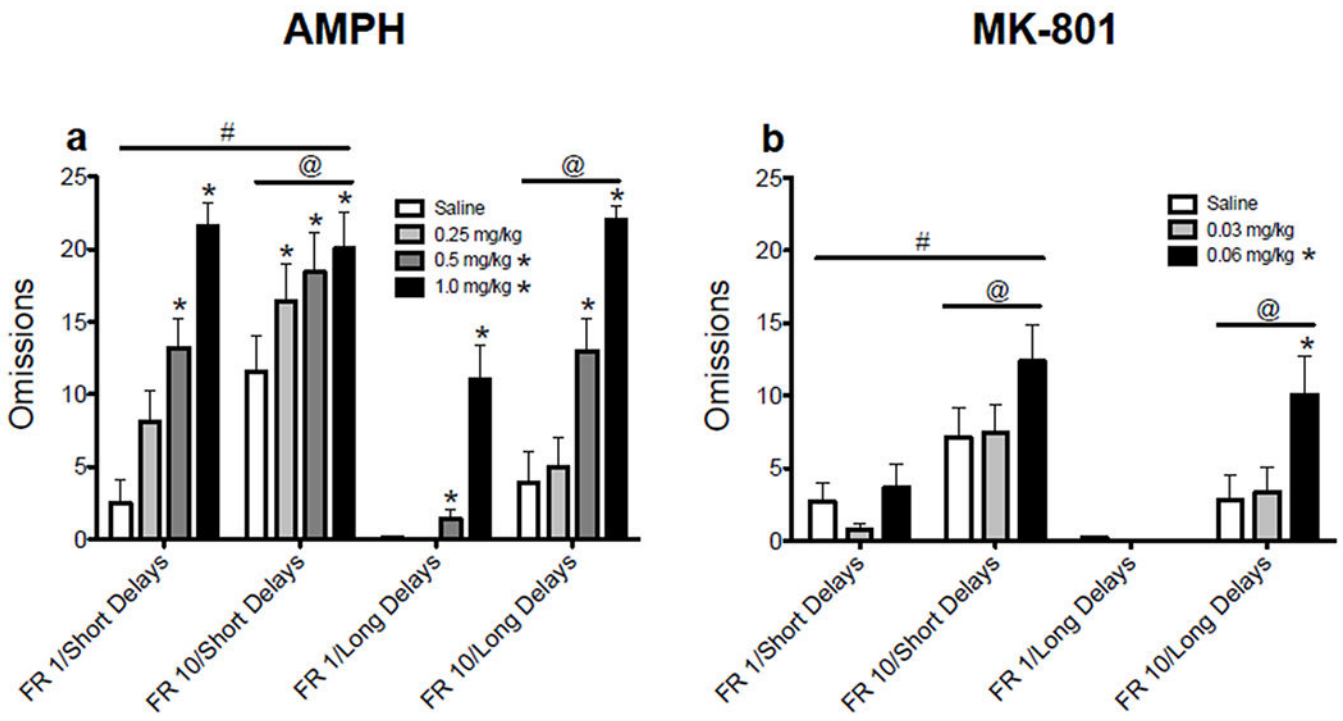

Figure 2.

Mean (±SEM) omissions following administration of amphetamine (**a**) and MK-801 (**b**). #$p < .05$, relative to rats trained on the long delay sequence. @$p < .05$, relative to rats trained on a FR 1 schedule of reinforcement. *$p < .05$, relative to vehicle.

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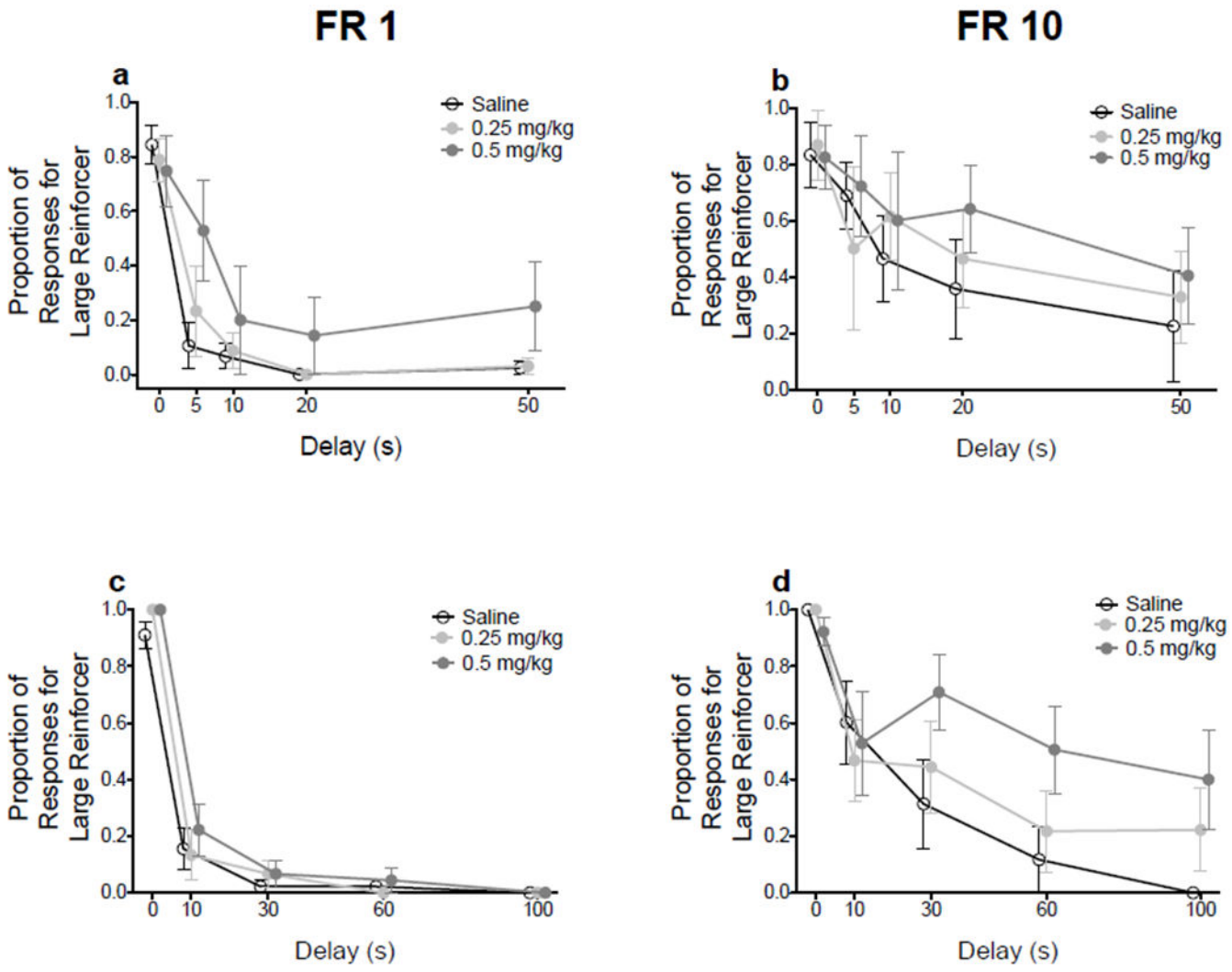

Figure 3.

Mean (±SEM) proportion of responses for the large magnitude reinforcer following amphetamine administration. Graphs in the left column represent rats trained on the FR 1 schedule of reinforcement. Graphs in the right column represent rats trained on the FR 10 schedule of reinforcement. Graphs in the top row represent rats trained on the short delay sequence. Graphs in the bottom row represent rats trained on the long delay sequence.

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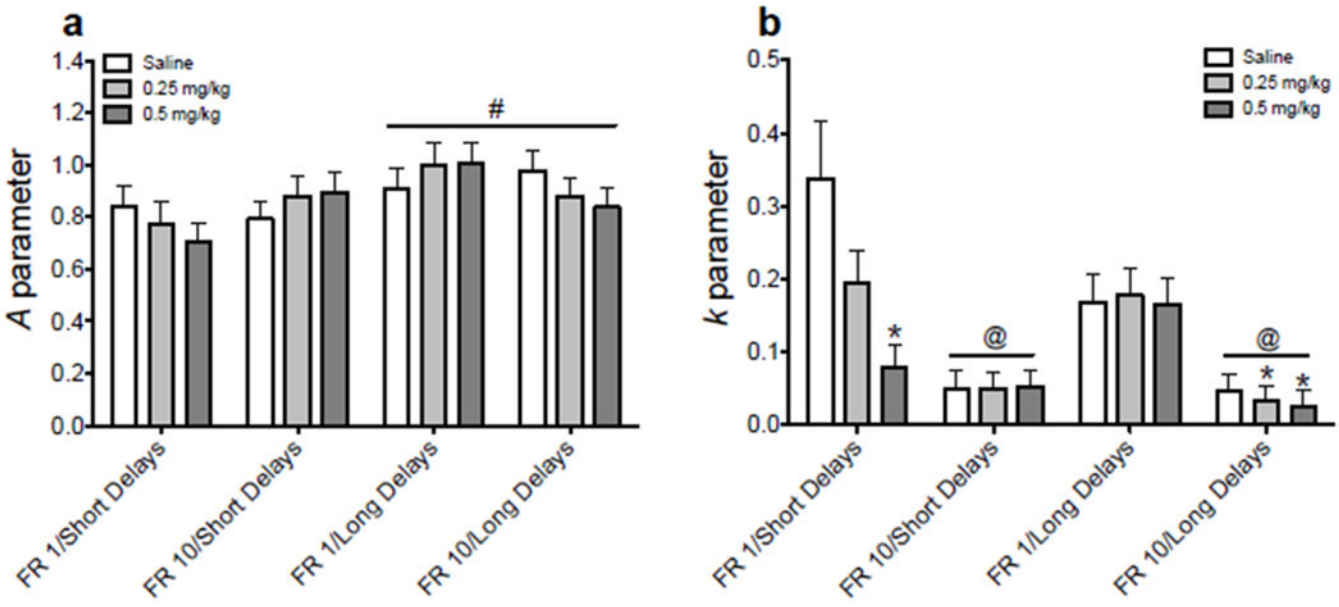

Figure 4.

Mean (±SEM) *A* parameter (**a**) and *k* parameter (**b**) estimates following amphetamine administration. #$p < .05$, relative to rats trained on the long delay sequence. @$p < .05$, relative to rats trained on a FR 1 schedule of reinforcement. *$p < .05$, relative to vehicle.

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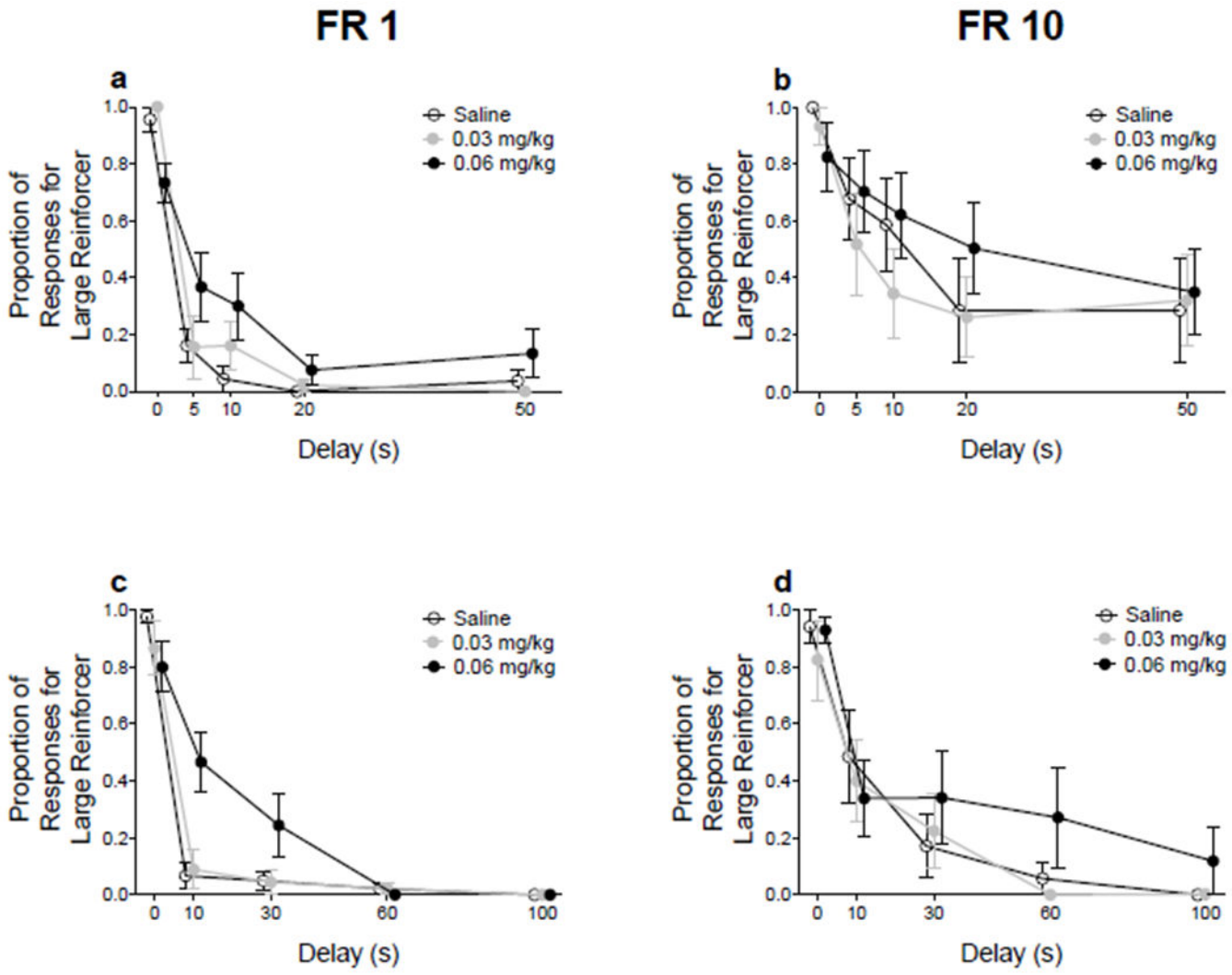

Figure 5.

Mean (±SEM) proportion of responses for the large magnitude reinforcer following MK-801 administration. Graphs in the left column represent rats trained on the FR 1 schedule of reinforcement. Graphs in the right column represent rats trained on the FR 10 schedule of reinforcement. Graphs in the top row represent rats trained on the short delay sequence. Graphs in the bottom row represent rats trained on the long delay sequence.

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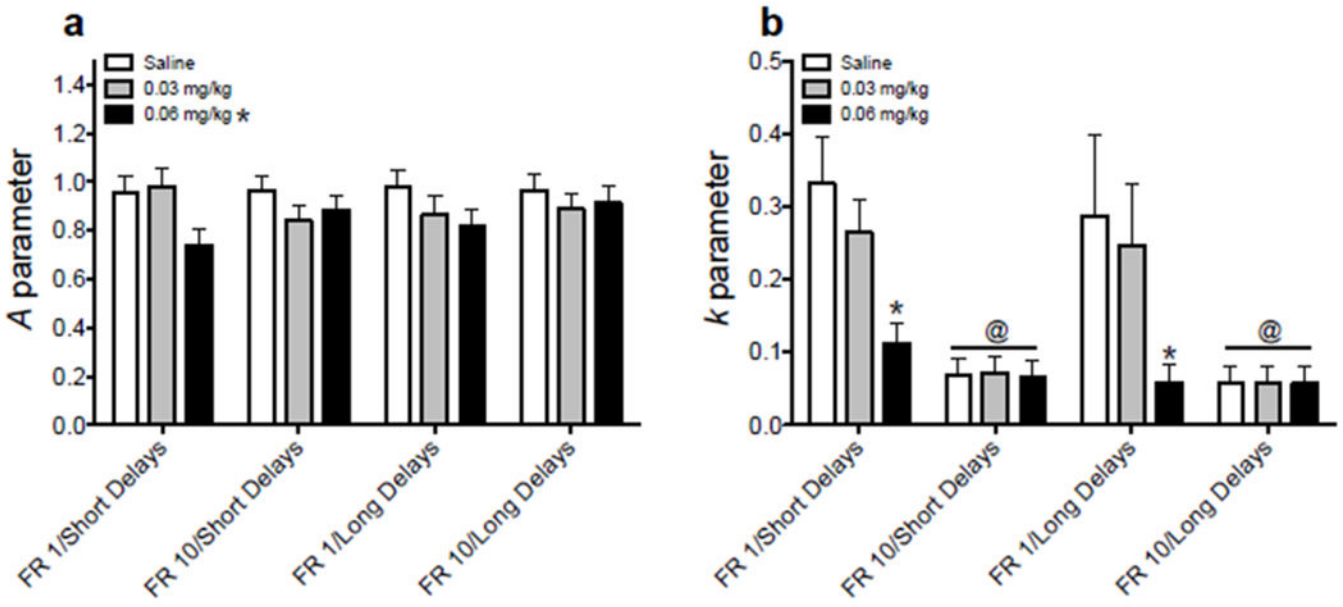

Figure 6.

Mean (±SEM) *A* parameter (**a**) and *k* parameter (**b**) estimates following MK-801 administration. @$p < .05$, relative to rats trained on a FR 1 schedule of reinforcement. *$p < .05$, relative to vehicle.