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The impact of *d*-amphetamine on resistance to extinction (RTE) in a single schedule preparation

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The impact of *d*-amphetamine on resistance to extinction (RTE) in a single-schedule preparation

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Abstract

Some researchers have suggested that the discrepancy in findings between studies of resistance-to-extinction that use single-schedules and those that use multiple-schedules is the result of increased discriminability between training and extinction conditions in the single-schedule preparation, masking the true relation between reinforcer density and resistance to extinction. Because *d*-amphetamine has been shown to interfere with stimulus control in a number of preparations, the current study examined the effects of *d*-amphetamine on rats' lever-pressing in the context of a single-schedule resistance-to-extinction preparation. During training, doses of *d*-amphetamine or vehicle were administered 15 min prior to sessions in which the delivery of reinforcers occurred according to variable-interval 10-s, 90-s, or 240-s schedules. A 2-hr extinction session followed the 50-min training sessions, which occurred 5-7 days per week for each rat for at least 15 sessions. Pre-session injections of *d*-amphetamine resulted in higher resistance to extinction across all training schedules than pre-session injections of vehicle did, but *d*-amphetamine did not change the direction of the relation between reinforcer density and resistance to extinction. I discuss the results in a context that emphasizes the commonalities between resistance to extinction procedures completed in discrete trials and free-operant contexts with the hope of bridging the gap between these two bodies of literature.

The impact of *d*-amphetamine on resistance to extinction (RTE) in a single-schedule preparation

Investigations of resistance to extinction (RTE) using multiple-schedule preparations have shown that there is a positive relation between RTE and the density of reinforcement during training (Nevin, 2003; Nevin, Mandell & Atak, 1983). However, studies of RTE using single-schedule preparations (Cohen, Riley & Weigle, 1993, Shull & Grimes, 2006) have not replicated this result. Some researchers have suggested that the discrepancy in findings occurs because the training and extinction (EXT) conditions are more discriminable from each other in the single-schedule preparations than in the multiple-schedule preparations, masking the true relation between reinforcer density and RTE. This view is supported by work showing a positive relation between reinforcer density and RTE in a single-schedule procedure when the discriminability between training and EXT is accounted for mathematically (Shull & Grimes, 2006). Researchers have yet to explore whether experimental manipulations that reduce stimulus control would also reveal the positive relation between reinforcer density and RTE.

Pharmacological agents affect a variety of basic behavior processes, and experimental manipulations involving drugs can serve as a powerful means to study basic behavioral phenomenon (Branch, 2006). Thus, an experimental manipulation using a behaviorally active compound that impacts stimulus control should help characterize and analyze the behavioral processes underlying RTE in a single-schedule preparation. Because *d*-amphetamine disrupts stimulus control of free-operant behavior under a variety of conditions (Götestam, 1977; Laties, Wood & Rees, 1981; Nielsen & Appel, 1985; Wiley,

Compton & Golden, 2000), I will examine the effects of *d*-amphetamine on RTE in the context of a single-schedule preparation.

The partial reinforcement effect

Throughout the history of the experimental analysis of behavior, there has been disagreement about which training regimens will result in responding that is more persistent during subsequent periods of EXT. Early work suggested that continuously reinforced (CRF) behavior is less resistant to EXT than partially reinforced (PRF) behavior (Boren, 1961; Jenkins, McFann & Clayton, 1950; Jenkins & Rigby, 1950). Jenkins and Rigby assessed RTE after training with intermittent reinforcement or continuous reinforcement. They trained rats to lever-press for water according to a fixed-interval (FI) 2-min schedule, a FI 1-min schedule, and a CRF schedule. Once responding was stable, three 1-hr EXT sessions followed. The researchers used the number of responses during EXT as the primary index of RTE. The results showed that rats in the intermittent reinforcement groups made approximately 40% more lever presses than rats in the CRF group, leading the researchers to conclude that PRF results in greater RTE than CRF. This phenomenon, originally report by Skinner (1938), lead to a great deal of interest by learning theorists of the time after the publication of a landmark study by Humphreys (1939). Ultimately designated the partial reinforcement effect (PRE, or partial reinforcement extinction effect PREE; Katz, 1957), has been replicated many times, over a range of situations (Cohen et al., 1993; Leonard, 1975; Prados, Sanza & Artigas, 2008; Rescorla, 1999).

Cohen et al. (1993) investigated the conditions that produce the PREE. Specifically, these researchers were interested in revealing the relation between reinforcer

density in various PRF arrangements and RTE. The researchers trained 28 rats to lever-press according to various FI, fixed-ratio (FR), variable-interval (VI) and variable-ratio (VR) schedules of reinforcement. During the FI conditions, rats were trained to lever-press according to three different schedules of reinforcement in four different conditions: FI 30-s, FI 60-s, FI 120-s, and FI 30-s. During the FR conditions, rats were trained to lever-press according to three different schedules of reinforcement in four different conditions: FR 40, FR 80, FR 160, and FR 40. During the VI conditions, rats were trained to lever-press according to three different schedules of reinforcement in four different conditions: VI 30-s, VI 60-s, VI 120-s and VI 30-s. During the VR conditions, rats were trained to lever-press according to three different schedules of reinforcement in four different conditions: VR 40, VR 80, VR 160, and VR 40. For each of these schedule conditions, after responding was stable, the researchers imposed three 1-hr EXT sessions. The researchers calculated baseline response rates by dividing the total number of responses in a session by the duration of the session and RTE by dividing response rate during EXT by response rate during baseline. Across all PRF variations, RTE increased as the density of reinforcers decreased. In other words, the relation between reinforcer density and RTE appeared negative.

Despite the fact that the PREE is well-documented, it does not occur under all conditions (Nevin, 1974; Nevin et al., 1983; Nevin, 1988). For example, Nevin (1974) investigated RTE in pigeons using a multiple-schedule arrangement. The red and green keys signaling a VI 6-min and VI 2-min schedule of reinforcement, respectively, alternated regularly during each session. A 5.5 hr EXT session occurred once responding was stable. Response rates during the EXT condition were higher relative to baseline

rates when the green key was illuminated than when the red key was illuminated. Thus, in contrast to the many studies documenting the PREE, these data suggest a positive correlation between RTE and density of reinforcement used in training.

Nevin and colleagues (Cohen et al., 1993; Nevin, 1974; Nevin et al., 1983) have argued that EXT is only one of many ways to disrupt operant behavior and that examinations of RTE are a special case of the more general concept of resistance to change (RTC), which can be understood in terms of behavioral momentum theory (BMT; Nevin & Grace, 2000). BMT uses a metaphor derived from mechanics to account for the conditions that affect the extent to which an operant is resistant to changes in the environment. In physics, momentum is the product of velocity and mass, and the following formula describes the change in velocity of a moving object that is confronted by a contact force:

$$\Delta v = F/m \qquad (1)$$

where v represents velocity, F represents force, and m represents the object's mass. The expression shows that the extent to which the velocity of a moving object will change is proportional to the external contact force applied and inversely proportional to the mass of the moving object. For example, if the same external force we applied to a bowling ball and to a ping pong ball that were both moving at the same velocity, the velocity of the bowling ball would be less impacted than the velocity of the ping pong ball because the bowling ball has greater mass than the ping pong ball. By analogy, the behavioral momentum equation is:

$$\log (B_x/B_o) = f(x/m) \qquad (2)$$

where F is replaced by x and Δv is replaced by log B_x/B_o. Applied to behavioral change, the equation shows that change in responding, with response rate during baseline (B_o.) and disruption (B_x) represented as logarithms is related directly to x, which represents the value of some procedural change and is related inversely to m, which represents behavioral mass and has been shown to depend on a power function of the density of reinforcement maintaining responding (Nevin & Grace, 2000; Nevin, Tota, Torquato, & Shull, 1990). Because it is unlikely that a simple proportional relation between the value of procedural change and reinforcer density hold for behavioral change, this more general form of the equation shows that behavior change is a function, f, of this proportion, to be discovered for each type of procedural change.

Given the same procedural change, behavior reinforced according to rich schedules of reinforcement will engender more persistent responding than behavior reinforced according to lean schedules of reinforcement. For example, consider an individual trained to respond on a multiple VI 10-s VI 240-s schedule of reinforcement. If EXT is imposed, the response rate correlated with the VI 10-s schedule should be less impacted than the response rate correlated with the VI 240-s schedule. Typical experiments measuring RTC are arranged similarly to the procedures in the Nevin (1974) study described above. Subjects emit responses for access to a reinforcer, and once responding is stable in all components of the multiple-schedule, the researcher manipulates the experimental setting by imposing a disruptor such as pre-session feeding, response-independent access to reinforcers, or EXT. Consistent with the behavioral momentum equation described above, RTC is determined by examining the rate of responding following the introduction of the disruptor relative to the rate of responding

during stable performance under the preceding reinforcement conditions in each component of the schedule. The resulting positive relation between reinforcer density in the different components of the multiple-schedule and RTC accounts not only for data resulting from EXT as a disruptor but also for data involving other disruptors such as pre-session feeding and access to response-independent reinforcement (Cohen et al., 1993; Nevin, 1974).

One factor that may contribute to the inconsistent findings regarding RTE and studies in the PREE literature is the differential discriminability of transitioning from a period of reinforcement to EXT (Cohen et al., 1993; Nevin, 1988; Shull & Grimes, 2006) across the different procedures. EXT procedures have two characteristics that contribute to the amount of change EXT introduces on steady-state behavior. First, EXT removes the response-reinforcer contingency. Second, because the reinforcer density is a property of the stimulus context, the fact that no reinforcer deliveries occur during EXT alters the stimulus context. These two characteristics of EXT contribute to the disruptive force of EXT; in other words, together they contribute to x in *Equation 2* described above.

In a single-schedule arrangement, moving from a CRF, or a relatively rich schedule, to EXT is more discriminable than moving from a PRF, or relatively lean schedule, to EXT. Thus, one could say that EXT following CRF has more force than EXT following PRF. In experiments that revealed a negative relation between reinforcer density during training and subsequent RTE (Cohen et al., 1993; Shull& Grimes, 2006) responding during EXT typically was examined following training on a single-schedule of reinforcement; a situation where the transition from reinforcement to nonreinforcement is much more discriminable following richer reinforcement schedules than following

leaner reinforcement schedules. In experiments that revealed a positive relation between RTE and the reinforcer density (Nevin, 1974), responding during EXT typically was examined following exposure to a multiple-schedule with differing reinforcer densities in each component. As suggested by Nevin and Grace (1999), in the multiple-schedule arrangement, the discriminability of the transition from reinforcement to nonreinforcement for each schedule component is affected by the discriminability of the change in rate of reinforcement in that component as well as the discriminability of the change in the overall average rate of reinforcement across all components. Because this second aspect of discriminability is common to the components of the multiple schedule during the EXT test sessions, its contribution to the discriminability of each component reduces the differential discriminability between the components when the two are compared (Shull & Grimes). That is, the force of EXT following relatively rich and relatively lean schedules in a multiple-schedule arrangement is closer to equal. Obviously, this common aspect of discriminability does exist for single-schedule arrangements. However, consistent with this explanation, Shull and Grimes (2006) incorporated a mathematical correction to account for and equalize the discriminability factor in single-schedule procedures and showed that when applied a positive relation between RTE and the reinforcer density of the maintaining schedule was revealed (specific details about the mathematical correction appear below). This finding suggests that other methods of reducing differential discriminability between PRF schedules and EXT might yield similar findings.

Amphetamine

Research has shown that amphetamine disrupts stimulus control over free-operant behavior under a variety of conditions (Götestam, 1977; Laties, Wood & Rees, 1981; Wiley, Compton & Golden, 2000). Laties, et al. (1981) conducted an experiment in which they trained rats to respond for milk according to a fixed consecutive number (FCN) schedule of reinforcement that required them to press one lever at least eight times in a row before pressing another lever one time to earn a reinforcer. Training either occurred in the presence of an illuminated house light or in the presence of an illuminated houselight supplemented with a compound tone-cue light discriminative stimulus. After responding was stable, the researchers administered pre-session injections of 0.0 mg/kg (saline), 0.1 mg/kg, 0.3 mg/kg, 1.0 mg/kg, 1.7 mg/kg or 3.0 mg/kg of *d*-amphetamine and measured the number of correct responses, the conditional probability of switching from one lever to the other, and response rate. Under baseline conditions, the rats responded correctly (i.e., produced at least 8 consecutive responses on one lever before pressing the other lever) 90% of the time on average in the presence of a compound discriminative stimulus and only 50% of the time on average when only the houselight was present, suggesting weaker stimulus control in the houselight-only condition. When *d*-amphetamine was administered, doses of 1.0 mg/kg or more reduced correct responding, and this effect was more pronounced when stimulus control was weak and the houselight-only signaled the schedule. Analysis of the conditional probability data revealed that, at all doses, the rats tended to switch correctly when the compound discriminative stimulus was present more so than when it was not. Overall response rates did not differ across discriminative stimulus conditions suggesting that accuracy of responding, and not ability

to respond, was impaired by *d*-amphetamine. Taken together, these data provide evidence that amphetamine interferes with responding under weak stimulus control.

Experiments conducted by Weiner and colleagues demonstrating that amphetamine attenuated the PREE in rats running a maze (Weiner, Bercovitz, Lubow & Feldon, 1985; Weiner, Feldon & Bercovitz, 1986) suggest an additional reason to study the effects of amphetamine on RTE following single-schedule training. Weiner et al. (1985) had rats run a straight alley once a day and reinforced completing the maze on either a CRF or PRF schedule. They found that rats exposed to chronic injections of amphetamine during the acquisition phase of the experiment did not show the PREE that is typically observed in this preparation. Feldon and Weiner (1992) replicated these findings, showing that chronic amphetamine administered during training attenuated the PREE when EXT followed food-reinforced lever-pressing in a discrete-trials procedure. Based on these results, the researchers suggested that when a training regimen including instances of behavior that are not reinforced (i.e., PRF) is established under the influence of amphetamine, stimulus control during later periods of nonreinforcement (i.e., EXT) is disrupted. Thus, it is reasonable to suggest that amphetamine might attenuate the discriminability of moving from intermittent reinforcement to EXT in single-schedule, free-operant preparations, as well.

According to Nevin (1988), the experimental results documenting a negative relation between reinforcer density and subsequent RTE are a product of procedures that promote discriminability of transitioning from reinforcement to nonreinforcement. Equating discriminability across different schedules by using a multiple-schedule procedure, or accounting for discriminability mathematically (Shull & Grimes, 2006),

reveals a positive relation between RTE and reinforcer density. Based on the results of Weiner and colleagues (Weiner et al., 1985), it seems possible that amphetamine can accomplish pharmacologically what these other procedures do through using particular methods or computations, respectively. The current study will investigate this possibility by administering injections of amphetamine prior to each session in a single-schedule RTE procedure.

Method

Subjects

The subjects were 14 experimentally naive male Sprague-Dawley rats that were individually housed in plastic cages (23cm x 20.5cm) kept in a colony room illuminated from 8:00 a.m. to 8:00 p.m. on a 12-hr light-dark cycle, at a temperature of 21^{O}C - 27^{O}C and at a humidity of 45% - 55%. When water and saccharin solution were used during an interim stage of pretraining (sessions 8 - 17), rats had free access to water in the home cage for the 5 hrs that followed each training session. For the first 7 days and every day after session 18, which included only food pellet deliveries, they had continuous access to water in the home cage and were maintained on a controlled food regimen of 10 - 12 g per day delivered in the form of 45mg pellets (Bio-Serv, Frenchtown, NJ; TestDiet®, Richmond, IN) earned during experimental sessions and Harlan (Madison, WI) rodent diet (8604) delivered about 1 hr after each session.

Apparatus

The experiment was conducted in Med-Associates (Georgia, VT) rat operant chambers (ENV-008CT) situated in a ventilated, sound and light attenuated cubicle. Each operant chamber contained two retractable response levers (ENV-112CM) that were located on the front wall evenly spaced on either side of an opening through which pellet and liquid reinforcer delivery occurred. A houselight was located at the top center of the back wall of the operant chamber, and below it, across from the feeder opening, was a third retractable lever that was not used in the current study. Above each lever were three colored LED stimulus lights (red, yellow, and green, left to right). A 4.0 KHz (80 db) speaker, controlled by a Med Associates Audio Stimulus Generator (ANL-926),

was located on the front wall of the chamber above the pellet dispenser. A computer using MED-PC IV software programming controlled the operant chambers.

Procedure

General Procedure. Training sessions occurred 5 - 7 days a week throughout the study. Fifteen min prior to each session, each rat received an i.p. injection of *d*-amphetamine or saline and was placed in the operant chamber. Each session began with the illumination of the houselight. Each training session ended after 50 min or the delivery of 250 reinforcers, whichever came first. At the end of each session, any extended the levers were retracted, and the houselight was extinguished.

Pretraining. All pretraining sessions lasted for 50 minutes or until 250 reinforcers were delivered. Fifteen minutes prior to each session, which began with the illumination of the houselight, each rat was injected with .3 ml of saline and placed in the chamber. Prior to the first session, the food receptacle was baited with 25 pellets; however, the levers remained retracted and no additional food pellets were delivered. For the next two sessions, the food receptacle in each chamber again was baited with 25 pellets prior to the session, and the levers remained retracted; however, one pellet was delivered according to a random time 30-s schedule throughout the session. A 2000 Hz tone occurred for 500-ms concurrently with each pellet delivery. The next four sessions involved an autotraining procedure such that prior to each pellet delivery, one of the two front levers (counterbalanced across rats) extended in the chamber and the three LEDs above the extended lever were illuminated. If the rat did not press the lever within 10 s, the lever was retracted, a pellet was delivered, and the three LEDs extinguished. If the rat pressed the lever within 10 s, the lever was retracted, the pellet was delivered and the

LEDs extinguished. After 10 lever presses, an operant contingency was in place such that the rat had to press the lever in order for food delivery to occur. All but one rat learned to press the lever using this procedure. That rat was dropped from the protocol. For the remaining 11 rats, during sessions 8 - 10, .01 cc of water followed each lever press. Because the number of responses emitted during sessions 8 - 10 declined steadily, a 17% w/v saccharine solution was used instead of water during sessions 11 and 12. Beginning with session 12, the procedure changed to a free-operant CRF procedure. Each session began when the lever extended into the chamber and the three LEDs illuminated. At the end of each session, the lever retracted, and the three LEDs extinguished. Because response rates declined over the next five sessions, beginning with session 18, I reinstituted food delivery as the consequence for lever-pressing. After 4 days of CRF for food pellets, all 11 rats demonstrated proficient lever-pressing.

For one rat, R-1-17, who began the procedure 7 days after the others, training consisted of 2 days of autotraining sessions with pellets, 3 days of autotraining sessions with water, and 2 days of autotraining sessions with saccharine solution. Sessions 8-12 included the CRF procedure with saccharine solution and because his responding declined over these sessions, during session 13, the autotraining procedure was reinstituted using food pellets and during session 14, food pellets were delivered according to a continuous schedule of reinforcement. After these two sessions, R-1-17 demonstrated proficient lever-pressing.

Rat R-1-13 received one day of autotraining 7 days after the others began the procedure but did not press the lever during this session. He was reintroduced to the study when the other rats were completing the second condition and was trained to lever

press by completing 9 CRF sessions with a food pellet delivered contingent on each lever press.

Resistance to Extinction. During the training phase, when the session began, the house light was illuminated, the target lever was extended into the chamber, and the LED lights above the lever were illuminated. During each session, .45 mg food pellet reinforcers were delivered contingent on lever-pressing according to a variable interval (VI) schedule that provided a roughly constant probability of reinforcement (Fleshler & Hoffman, 1962). There were three training conditions: VI 10 s, VI 90 s and VI 240 s. Due to time constraints, each rat completed only two of three training conditions. Within each training condition, there were two phases: *d*-amphetamine dissolved in saline (0.9% sodium chloride) and vehicle (saline only). Each rat received 3.2 mg/kg of *d*-amphetamine at the beginning of the first drug phase. If responding was not maintained following administration of this dose, the dose was reduced to 1.0 mg/kg of *d*-amphetamine. Table 1 shows the dose of *d*-amphetamine used with each rat as well as the training conditions each completed and the order in which they occurred. Within each phase of each condition, VI training for each rat continued for at least 15 sessions (Shull & Grimes, 2006) and was followed by one 2-hr EXT session

Results

As is customary in single-schedule RTE studies (Cohen et al., 1993; Nevin, 1988), I quantified RTE as the response rate during EXT (B_x) expressed as a proportion of the response rate during the last five sessions of the immediately preceding baseline training condition (B_0). B_x/B_0 values between 0.0 and 1.0 indicate lower response rates during EXT than during training with higher values representing higher RTE. A B_x/B_0 value of 1.0 indicates the same response rate during EXT, or complete RTE.

Figure 1 shows RTE represented as the mean (+*SD*) B_x/B_0 as a function of training schedule during each condition. In the vehicle phase, the rats showed higher RTE when trained under the leaner schedules. In the *d*-amphetamine phases, there was not a monotonic relation between RTE and training schedule. RTE was 1.37 in the VI 90-s condition, RTE was 1.25 in the VI 240-s condition, and 1.37 in the VI 10-s condition. For all training schedule conditions, RTE was higher during the *d*-amphetamine phases compared to the vehicle phase.

Figures 2 - 4 shows B_x/B_0 for each individual rat as a function of training schedule during each drug phase. During the vehicle phases, a visual analysis of the B_x/B_0 values revealed 6 of the 11 rats showed a PREE: 2 of the 5 rats (R-1-2 and R-1-8) that experienced the VI 10-s and VI 90-s training conditions, 3 of the 4 rats (R-1-4, R-1-10 and R-1-17) that experienced the VI 10-s, and VI 240-s schedule training conditions and 1 of the 2 rats (1-3) that experienced VI 10-s and VI 90-s training conditions. During the *d*-amphetamine phases, 9 out of the 11 rats showed a PREE; the 2 rats (R-1-10 and R-1-17) that did not show a PREE in the *d*-amphetamine phases were both trained on VI 10-s and VI 240-s.

In order to examine the relation between RTE and reinforcer density in a manner consistent with previous literature that discusses BMT (e.g., Shull & Grimes, 2006), Figure 3 displays RTE values for individual rats as a function of reinforcers earned per minute during training under vehicle and *d*-amphetamine phases. The curve in each graph represents the best-fit function describing the data using the a behavioral momentum following equation with the value of the disruptor, *x*, number of extinction sessions, augmented to account for the contingency reduction and discriminability facets of EXT as follows (Nevin & Grace, 2000, Equation 17; Shull & Grimes, Equation 1):

$$\log (B_x/B_0) = -x\ (c + dr)/r^a$$

where the right side of the equation is negative because the disruptive force decreases behavior, r^a represents the strengthening effect of the baseline training schedule with a reinforcer density of r, x represents the number of EXT sessions, *c* represents the effects of removing the contingency during EXT, *d* represents the change in the stimulus context when transitioning from training with reinforcer density *r* to EXT. As noted by Shull and Grimes, this equation is a representation of RTE that accounts for the opposing effects of reinforcer density during training and the discriminability of transitioning from that reinforcer density to EXT.

Because each rat experienced only two training schedule conditions, the functions were fit, using SigmaPlot® 10, across rats represent the three training schedule conditions. For these fits, *x* was set as 1 because there was one EXT session conducted following each training condition. The free parameters, *c* and *d*, were constrained to a value between 0 and 1 and the free parameter *a* was left unconstrained. Table 2 displays the values of all three free parameters as well as a measure of the variance accounted for

by each function. Figure 3 shows, regardless of drug condition, a negative relation between RTE and density of reinforcement in the current procedure. For the vehicle condition, the function generally fit the data well although there was more variability at higher reinforcer densities. For the 1.0 mg/kg *d*-amphetamine condition, the function generally fit the data well except for two outliers at the lowest reinforcer densities. For the 3.2 mg/kg condition, the function generally fit the data well except for a single outlier at the low reinforcer density values. The functions were generally flat and slightly curvilinear across all values of reinforcer densities for the vehicle phase and for rats that received 1.0 mg/kg *d*-amphetamine (top and middle panels), whereas the functions shows a marked curvilinear relation with a steep decline at the highest reinforcer densities in the *d*-amphetamine phase for rats that received 3.2 mg/kg (bottom panel).

Discussion

The current investigation examined how *d*-amphetamine influenced RTE in a single-schedule preparation. Consistent with previous research (Feldon & Weiner, 1989), RTE was higher in conditions that included pre-session injections of *d*-amphetamine than during conditions that included pre-session injections of vehicle. Also consistent with previous research (Cohen, 1993; Shull & Grimes, 2006), there was a negative relation between reinforcer density during training and subsequent RTE. Inconsistent with my initial prediction, the direction of this relation did not differ during conditions with pre-session injections of *d*-amphetamine.

At first, these results seem inconsistent with the findings of Weiner et al. (1985), who reported that *dl*-amphetamine reduced RTE and eliminated the PREE for rats responding according to a PRF schedule in a one-trial-per day discrete trials procedure. However, subsequent investigations by Weiner and colleagues have shown that numerous procedural variables moderate the effects of *d*-amphetamine on RTE and PREE. For example, Feldon et al. (1989) investigated the impact of amphetamine on RTE in a multitrial discrete trials procedure with short intertrial intervals (ITI). During the weeklong training phase, they trained rats to run in a straight alley for food pellets delivered according to either a CRF or PRF schedule. The procedure included 6 daily trials with an ITI of 5 min or 3 daily trials with an ITI of 20 min following a pre-session injection of *d*-amphetamine. Unlike the results from the one-trial per day procedure (Weiner et al., 1985), pre-session injections of *d*-amphetamine did not eliminate the PREE in this multitrial procedure. These results are consistent with the results of the current study in that *d*-amphetamine did not abolish the PREE.

According to Feldon, Weiner, and colleagues (Feldon, Bercovitz & Weiner, 1989; Feldon & Weiner, 1989) the PREE develops under conditions in which an animal has to respond during periods that include some reinforced responses and other nonreinforced responses. As a result, responding comes under the stimulus control of nonreinforcement. However, Feldon et al. and Feldon and Weiner (1989) argued that the type of stimulus control differs as a function of the length of the ITI and that this is the source of *d*-amphetamine's differential effects across procedures. With long ITIs, such as the 24 hrs that intervene between the trials in the one-trial per day procedures, stimulus control develops as a result of reinforced responses that occur in the context of cues (e.g., the apparatus) that through respondent conditioning have become conditioned stimuli that signal the absence of reinforcement. They suggested that *d*-amphetamine disrupts the formation of the PREE under these conditions by interfering with the respondent conditioning of the contextual cues. In contrast, they argue that with the relatively short ITIs in procedures that include multiple trials per day, stimulus control develops as a result of reinforced responses that occur following immediately preceding periods of nonreinforcement in a way that is not mediated by respondent conditioning and thus is not affected by *d*-amphetamine. To the extent that the context-mediated stimulus control is weaker than the more direct stimulus control by nonreinforcement as Feldon et al. (1989) argued, their findings are consistent with other work showing that *d*-amphetamine disrupts behavior under relatively weak stimulus control more so than behavior under relatively strong stimulus control (Laties et al., 1981).

With respect to the current investigation, Feldon et al.'s (1989) account of the stimulus control that develops in the multitrial discrete trial procedure with short ITIs can

be extended to free-operant procedures using VI schedules. A VI schedule is one in which the first response made after a variable amount of time passes is followed by a reinforcer. That is, responses maintained by VI schedules are reinforced in the context of the immediately preceding interval; a temporally extended period during which any responses that occur are not reinforced. Consequently, the amount of time that passes between each reinforcer delivery can become a discriminative stimulus for emitting many responses that do not each individually earn a reinforcer. Despite the differences between discrete trial procedures and free-operant procedures, if the nature of the stimulus control that develops under both procedures is similar, it is reasonable to expect that *d*-amphetamine would have similar effects on the resulting stimulus control and, as a result, have a similar impact on the PREE under these two types of procedures. Additionally, this argument can be extended to other conditions where behavior under relatively weak vs. relative strong stimulus control would determine the extent to which *d*-amphetamine could influence behavior.

It is reasonable to suggest that behavior maintained by relatively lean VI schedules is likely to be under weaker stimulus control than behavior maintained by relatively rich VI schedules because animals must respond during longer periods of nonreinforcement under lean VI schedules compared to rich VI schedules. That is, the relative strength of the stimulus control exerted by the stimulus conditions of a VI schedule is determined by the interreinforcement intervals (IRIs). Consequently, there should be a systematic relation between the density of reinforcement for the schedules in question and the extent to which *d*-amphetamine will impact the discriminability between a given training schedule and EXT. With respect to the current study, the discrimination

between EXT and the two leaner schedules should be more disrupted by *d*-amphetamine than behavior trained according to the VI 10-s schedule. Consistent with this proposition, pre-session injections of *d*-amphetamine resulted in complete RTE for rats during the VI 90-s and VI 240-s but not for rats in the VI 10-s condition. Unfortunately, the limited range of schedules included in the current study precludes a convincing conclusion. To investigate this idea, future studies testing the effects of *d*-amphetamine on RTE should use schedules leaner than VI 240-s and richer than VI 10-s. This would extend the findings of Weiner et al. (1985) and Feldon et al. (1989) into a free-operant context and provide a parametric analysis of the extent to which the effects of *d*-amphetamine depend upon the different IRIs associated with different densities of reinforcement

RTE is a product of the opposing effects of the density of reinforcement on the strengthening of behavior and the discriminability of the transition from training to EXT (Nevin, 1988; Nevin & Grace, 2000; Shull & Grimes, 2006). That is, a higher reinforcer density increases RTE by strengthening behavior but decreases RTE by making the transition between conditions more discriminable. They proposed that the discriminability of the transition from training to EXT is particularly salient in single-schedule preparations and that this accounts for the fact that the positive relation between reinforcer density and RTE is not evident in studies involving those preparations (Cohen et al., 1993; Shull & Grimes, 2006). In order to account for the discriminability of the transition from training to EXT, Shull and Grimes (2006) calculated the mean IRI of the last five training sessions and used it as a measure of the number of reinforces that an animal would have received during the EXT session and incorporated it into their measure of RTE. In this way, they mathematically equated the effects of the density of

reinforcement on the discriminability of the transition into EXT allowing the positive relation between reinforcer density and RTE that characterizes the behavior strengthening effects predicted by BMT to be revealed. Following their reasoning, the fact that I did not observe a positive relation between RTE and density of reinforcement, suggests that *d*-amphetamine did not eliminate the differential discriminability of transitioning from training to EXT for the different VI schedules as I predicted it would. I based my prediction, in part, on the work of Weiner et al. (1985) who investigated the PREE using a one-trial per day procedure. However, as described above, the single-schedule VI preparations used in BMT research are more comparable to the multitrial procedures used by Feldon and Weiner (1989) and Feldon et al. (1989) in which *d*-amphetamine did not disrupt stimulus control. Viewed in this way, the current findings are not surprising and are consistent with a general explanation of the development of RTE that is applicable to both discrete trials and free-operant procedures.

Determining the best-fit functions for the current data using Shull and Grime's (2006) Equation 1 provides additional information about the effects of *d*-amphetamine on RTE. The parameter values for the best-fit function for the vehicle condition were similar to those documented by Shull and Grimes. The variance accounted for in this condition was much lower than the values documented by Shull and Grimes probably due to the fact that I fit the function to data obtained from all of the rats, whereas Shull and Grimes fit the function to data from individual rats. Also similar to Shull and Grimes, the *c* parameter value was zero for all conditions. The *d* parameter value, which represents the discriminability of the transition from reinforcement to EXT, decreased as the dose of *d*-amphetamine increased in the current study as did the *a* parameter value, which

represents sensitivity to effects of reinforcer density. As Shull and Grimes noted, interpretations based on applications of this formula should be approached with caution because its use has not been replicated. Nonetheless, one can consider these findings preliminary evidence that *d*-amphetamine alters the discriminability of the transition from reinforcement to EXT and sensitivity to reinforcer density, which warrants further exploration.

Thus far, I have interpreted the results in terms of the impact of *d*-amphetamine on stimulus control. However, it is also possible that the general stimulant properties of *d*-amphetamine affected responding in the current study. For example, one possible explanation for a general increase in RTE during conditions with pre-session injections of *d*-amphetamine may be that *d*-amphetamine caused response perseveration (Evenden & Robbins, 1982). Future studies should attend to the pattern of the changes in responding during EXT (e.g., the beginning of the session vs. the end of the session) to determine if the observed RTE under drug conditions results from the direct drug effects. In addition, continuing EXT sessions until responding is extinguished and comparing how long it takes for this to occur could provide an indication of the extent to which response perseveration is impacting these results.

Another feature of the current study worth noting is that I used different doses of *d*-amphetamine for different animals, which might have complicated the results. Originally, I had intended to use a dose of 3.2 mg/kg of *d*-amphetamine; however, using a dose of 1.0 mg/kg for some rats was necessary in order to accomplish two objectives. First, I wanted to use a dose of *d*-amphetamine that has been shown to be behaviorally active in previous literature. Second, I needed to use a dose of *d*-amphetamine that

allowed for responding to be maintained during the protocol. Because some rats failed to respond following the administration of the 3.2 mg/kg dose, I used a lower behaviorally active dose for those rats. Although I cannot be sure, it is possible that the rats requiring the lower dose experienced anorexic effects of *d*-amphetamine at the 3.2 mg/kg dose. Previous research has shown that the anorexic effects of *d*-amphetamine occur at a dose of 0.5 mg/kg and higher (Babbini, Gaiardi & Bartoletti, 1977). Originally, I had planned to avoid problems associated with the anorexic effects of *d*-amphetamine by using water as a reinforcer. However, for unknown reasons, lever-pressing was not maintained while using water as a reinforcer, and time constraints did not permit me to pursue this option further.

The fact that responding during the VI training may not have been stable before moving to EXT is another element of the current study that limits the generalizability of my conclusions. Based on previous literature showing that protocols similar to the current one produce stable responding after 15 sessions (Shull & Grimes, 2006), this is when EXT sessions occurred. However, there is no guarantee that response rates were stable, and the data from the current study show that the response rates for individual sessions during the last five sessions of each training condition were as much as 100% below and 390% above the mean for those five sessions, depending on the condition. Future studies of this type would benefit from applying a stability criterion, such as requiring each rat's response rate during the last 5 sessions of training to be within 5% of its average response rate for those sessions, without showing any upward or downward trend.

Originally, I had hoped to use *d*-amphetamine to disrupt stimulus control in a single-schedule RTE procedure as a means to unmask the positive relation between reinforcer density and RTE. According to these data, administering a pre-session injection of *d*-amphetamine does not impact RTE in a single-schedule procedure in this way. However, this study makes an important contribution in that it helps fill a gap in the RTE literature by showing commonalities in two distinct bodies of research on RTE and the PREE: those done in the context of discrete trial procedures and those done in the context of free-operant procedures. Interpreting the data from the current study from a perspective that highlights the role of stimulus control by periods of nonreinforcement helps to characterize the type of stimulus control that mediates behavior in single-schedule RTE procedures as well as discrete trial procedures. In addition, such investigations may help in fully understanding the discriminability confound in single-schedule RTE procedures. In this way, these data extend the findings of Feldon, Weiner, and colleagues (Feldon et al., 1989; Feldon & Weiner, 1989) to a free-operant procedure and, consequently, help integrate RTE research done using discrete trial procedures and free-operant procedures.

Table 1

Order of conditions

Rat ID	Condition 1	Condition 2	Condition 3	Condition 4
R-1-1	VI 10-s	VI 10-s	VI 240-s	VI 240-s
	Vehicle	*d*-amphetamine*	Vehicle	*d*-amphetamine*
R-1-2	VI 90-s	VI 90-s	VI 10-s	VI 10-s
	Vehicle	*d*-amphetamine*	Vehicle	*d*-amphetamine*
R-1-3	VI 240-s	VI 240-s	VI 90-s	VI 90-s
	Vehicle	*d*-amphetamine**	Vehicle	*d*-amphetamine*
R-1-4	VI 10-s	VI 10-s	VI 240-s	VI 240-s
	Vehicle	*d*-amphetamine*	Vehicle	*d*-amphetamine**
R-1-5	VI 90-s	VI 90-s	VI 10-s	VI 10-s
	Vehicle	*d*-amphetamine**	Vehicle	*d*-amphetamine**
R-1-6	VI 240-s	VI 240-s	VI 90-s	VI 90-s
	Vehicle	*d*-amphetamine**	Vehicle	*d*-amphetamine*
R-1-8	VI 90-s	VI 90-s	VI 10-s	VI 10-s
	d-amphetamine*	Vehicle	*d*-amphetamine**	Vehicle
R-1-9	VI 10-s	VI 10-s	VI 90-s	VI 90-s
	d-amphetamine**	Vehicle	*d*-amphetamine**	Vehicle
R-1-10	VI 10-s	VI 10-s	VI 240-s	VI 240-s
	d-amphetamine**	Vehicle	*d*-amphetamine**	Vehicle
R-1-11	VI 10-s	VI 10-s	VI 90-s	VI 90-s
	d-amphetamine**	Vehicle	*d*-amphetamine**	Vehicle
R-1-17	VI 240-s	VI 240-s	VI 10-s	VI 10-s
	d-amphetamine*	Vehicle	*d*-amphetamine**	Vehicle
R-1-13	VI 240-s	VI 240-s		
	d-amphetamine*	Vehicle		
R-1-7	VI-10			
	d-amphetamine*			

Note. *1.0 mg/kg; **3.2 mg/kg

Table 2

Best fitting free parameters and proportion of variance accounted for

Condition	R^2	c	d	a
Vehicle	.2976	.0000	.7093	.8687
d-amphetamine (1.0 mg/kg)	.4689	.0000	.2140	.3377
d-amphetamine (3.2 mg/kg)	.2707	.0000	.0057	-1.745

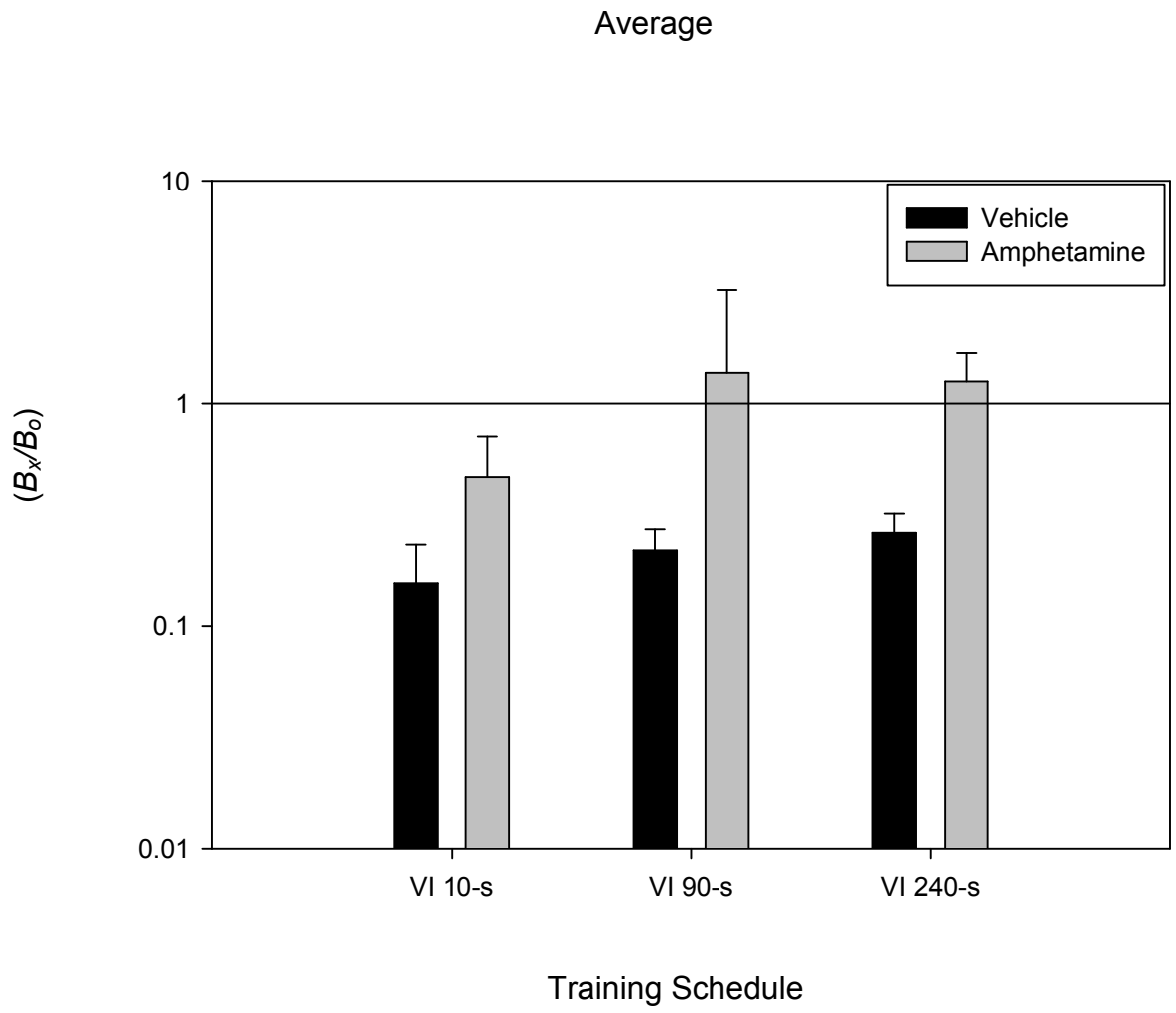

Figure 1: Shows the average B_x/B_0 (+*SD*) as a function of each schedule and drug condition.

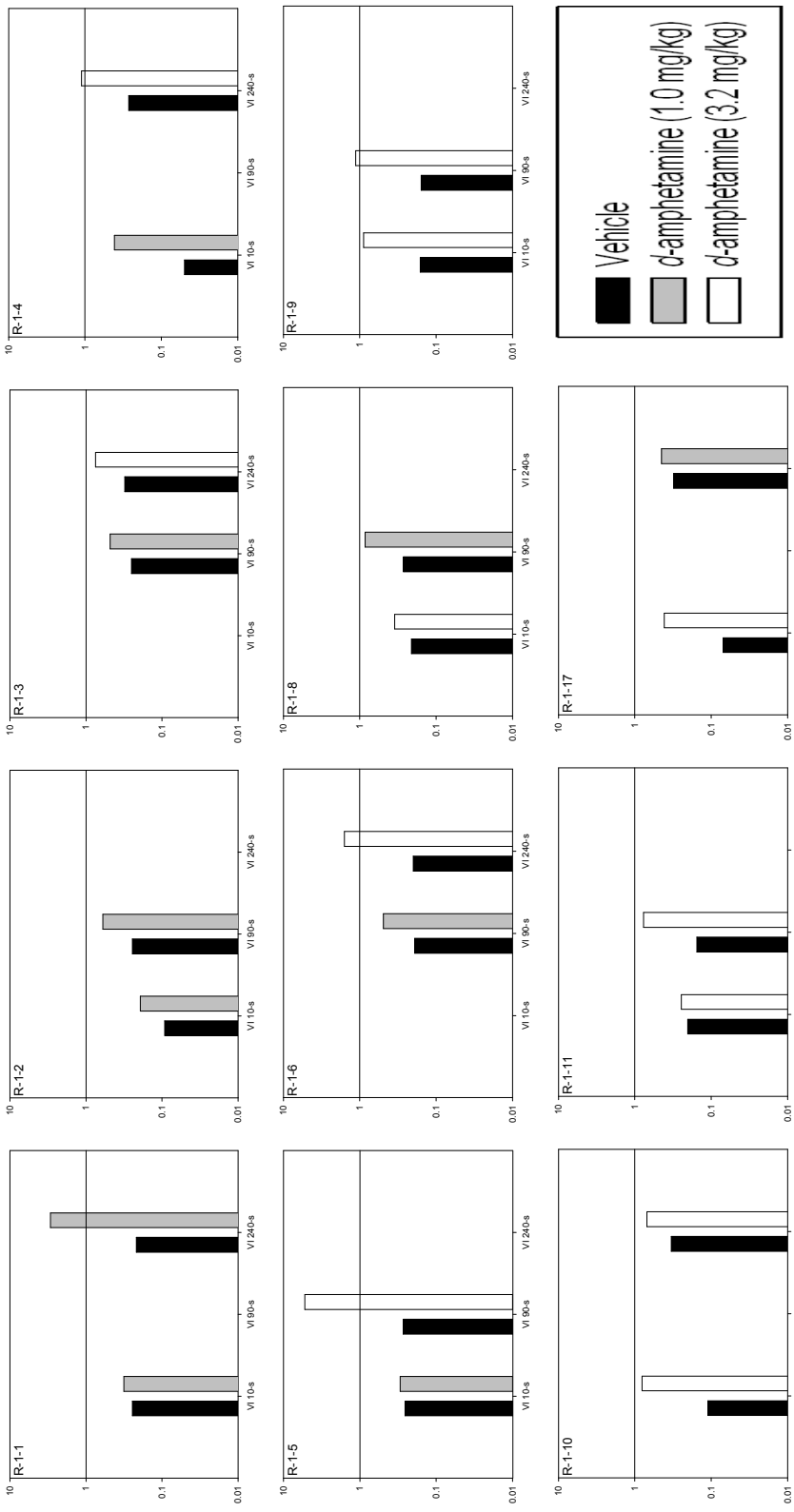

Figure 2: Shows the individual B_x/B_0 as a function of training schedule for each drug phase.

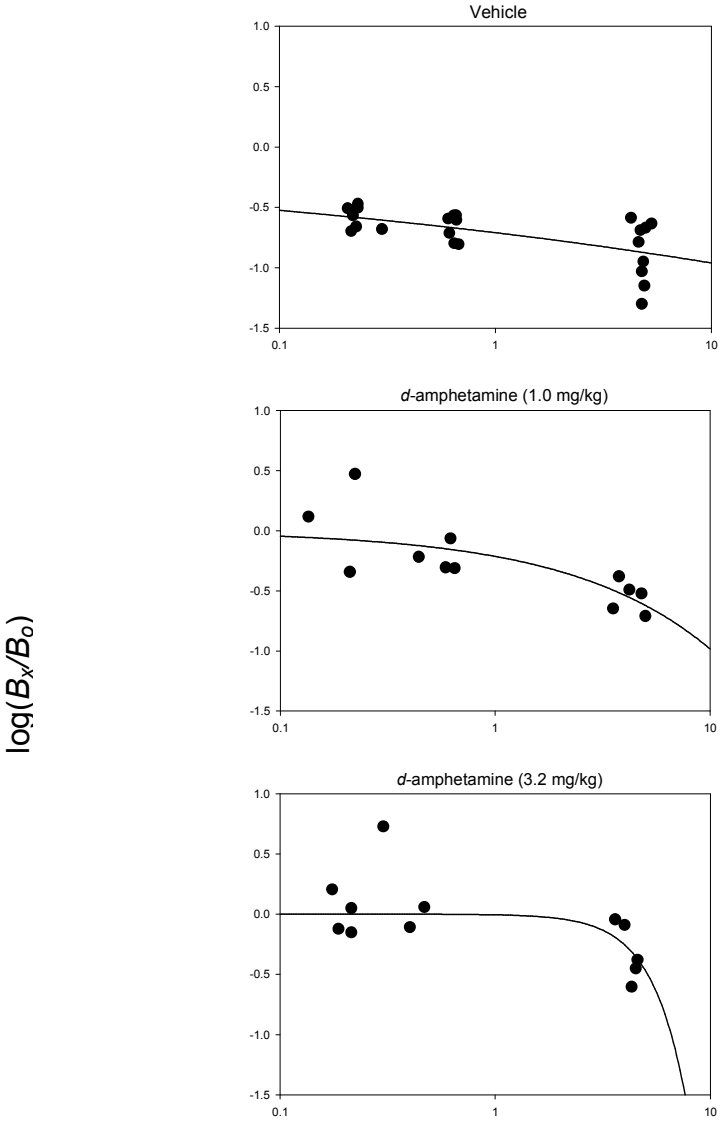

Figure 3. B_x/B_0 for each rat as a function of the number of reinforcers earned per minute during training.

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