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Reinforcement magnitude modulation of rate dependent effects in pigeons and rats

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Abstract

Response rate can influence the behavioral effects of many drugs. Reinforcement magnitude may also influence drug effects. Further, reinforcement magnitude can influence rate-dependent effects. For example, in an earlier report, we showed that rate-dependent effects of two antidepressants depended on reinforcement magnitude. The ability of reinforcement magnitude to interact with rate-dependency has not been well characterized. It is not known whether our previous results are specific to antidepressants or generalize to other drug classes. Here, we further examine rate-magnitude interactions by studying effects of two stimulants (d-amphetamine [0.32-5.6 mg/kg] and cocaine [0.32-10 mg/kg]) and two sedatives (chlordiazepoxide [1.78-32 mg/kg] and pentobarbital [1.0-17.8 mg/kg]) in pigeons responding under a 3-component multiple fixed-interval (FI) 300-s schedule maintained by 2-, 4-, or 8-s of food access. We also examine the effects of d-amphetamine [0.32-3.2 mg/kg] and pentobarbital [1.8-10 mg/kg] in rats responding under a similar multiple FI300-s schedule maintained by 2- or 10- food pellet (45mg) delivery. In pigeons, cocaine and, to a lesser extent, chlordiazepoxide exerted rate-dependent effects that were diminished by increasing durations of food access. The relationship was less apparent for pentobarbital, and not present for d-amphetamine. In rats, rate-dependent effects of pentobarbital and d-amphetamine were not modulated by reinforcement magnitude. In conclusion, some drugs appear to exert rate-dependent effect which are diminished when reinforcement magnitude is relatively high. Subsequent analysis of the rate-dependency data suggest the effects of reinforcement magnitude may be due to a diminution of drug-induced increases in low-rate behavior that occurs early in the fixed-interval.

Keywords

chlordiazepoxide; pentobarbital; cocaine; d-amphetamine; rate-dependent; reinforcement magnitude; fixed-interval; pigeon; rat

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Introduction

The behavioral effects of many drugs can depend on the environmental circumstances present when they are assessed (Kelleher and Morse, 1968). Such “drug-behavior” interactions demonstrate that understanding drug action requires knowledge of the biological targets of the drug as well as the behavioral processes prevailing at the time of testing (e.g., Barrett, Thompson, and Dews, 1990). Perhaps one of the most studied drug-behavior interactions is rate dependency (Wenger and Dews, 1976). Descriptively, rate-dependency reflects the fact that the control rate of responding before drug administration is an important determinant of the behavioral effects of many drugs. In general, behavior maintained at low baseline rates of responding, such as those observed at the early portions of fixed-interval schedules or during a differential-reinforcement-of-low-rate (DRL) schedules, tends to be increased (or decreased less) by drugs compared with behavior maintained at higher baseline rates, such as those at the terminal portions of fixed-interval schedules, which tend to be decreased (Kelleher and Morse, 1968). The generality of rate-dependency is well established; stimulants such as cocaine and d-amphetamine and sedatives such as chlordiazepoxide and pentobarbital are well-documented examples (Kelleher and Morse, 1968; McMillan, 1973).

While rate-dependency has helped to characterize how properties of behavior can influence drug effects, rate-dependency itself may be influenced by other environmental variables. Identification of conditions that promote or modulate rate dependency is therefore important to understanding how baseline response rate impacts drug effects (Branch, 1984). One such variable that appears to be important in determining the rate-dependency of drug action is reinforcer magnitude. Lamb and Ginsburg (2008), for example, showed that rate-dependent drug effects of the antidepressants fluvoxamine and desipramine were diminished by increasing the reinforcement magnitude (*see also* Ginsburg and Lamb, 2008). Thus, with shorter food presentations and low doses of these drugs, low rates of responding were increased more than high rates of responding, resulting in a negative slope of the function relating log[drug effect as percent control of baseline rate] against log[baseline rate]. The steepness of the slope of this function was attenuated during components in which behavior was maintained by longer food presentations (Lamb and Ginsburg, 2008; Ginsburg and Lamb, 2008). These results provided evidence that the rate-dependent effects of some drugs could be influenced by reinforcement magnitude.

Similar results, in which behavioral disruption by a drug depends on the magnitude of the reinforcement that maintains the behavior, have been reported for another antidepressant, fluoxetine (Cohen, 1986), as well as for the antipsychotics haloperidol or clozapine (Harper, 1999a). However, drugs from other classes, including the sedative pentobarbital, and the stimulant d-amphetamine did not produce clear reinforcement magnitude-dependent behavioral disruptions (Cohen, 1986). Thus, there may be differences in the ability of drugs to disrupt behavior in a reinforcement magnitude-dependent manner that, in turn, depend on drug class.

The ability of reinforcement magnitude to modulate the rate-dependent effects of at least some drugs appears consistent with general theories of behavioral resistance to change (Nevin and Grace, 2000). Nevin and his collaborators (*see* Nevin, 2002) demonstrated that the greater the magnitude or frequency of reinforcement, the more resistant behavior is to disruption by prefeeding or extinction. Thus, in a multiple variable-interval schedule in which responding is maintained by differing amounts of food presentation, responding reinforced with the larger amount is more resistant to disruption by extinction or prefeeding (*see* Nevin and Grace, 2000). Nevin characterized this relationship as behavioral momentum. Behavioral momentum conceptualizes resistance to behavioral change as

analogous to the concept of momentum in physics. Response rate is likened to velocity while the resistance to change is akin to mass. In physics, momentum is the product of mass and velocity, and thus in behavioral momentum the relationship between the deceleration or acceleration of the behavior (i.e., its resistance to change) under the influence of the disruptive “force” provides a measure of the “mass” of the behavior. Thus, Nevin asserts that behavioral mass and therefore momentum increases with reinforcement magnitude based on his work showing that behavior under multiple variable-interval schedules is more resistant to disruption by prefeeding or extinction when maintained by greater reinforcement magnitudes (Nevin, 2002). In a similar manner, the blunted rate-dependent effects of antidepressants observed when behavior was maintained by larger, rather than smaller, reinforcer magnitudes may reflect increased resistance to change.

Rate-dependency has been alternatively interpreted as rate-constancy or the regression of response rate to a common level independent of the control response rate which results in a slope which approaches -1 (Gonzalez and Byrd, 1977). In this work, the authors state that as dose and effect of a drug increase, the slope of a rate-dependency regression becomes more negative and approaches -1. Decreasing reinforcer magnitude results in more negative rate-dependency slopes, without changing the y-intercept (Lamb and Ginsburg, 2008; Ginsburg and Lamb, 2008). Thus, this effect could be interpreted as consistent with decreasing reinforcer magnitude increasing disruptive drug effects, and consistent with resistance to change theories.

These earlier studies indicate that under certain conditions, reinforcement magnitude may influence rate-dependent effects of some drugs. The generality of this finding is important to the interpretation of at least two different lines of research. First, there is great interest in behavior maintained by different reinforcement magnitudes. For example, the relative choice of a large versus small reinforcing event depending on the delay to the large event (delay discounting) is an important measure of impulsivity, and the effects of various drugs on impulsive choice is a growing area of study. Similarly, there is a great interest in drug effects on responding maintained by qualitatively different reinforcing events (i.e. food versus drug). Such studies are increasingly common in the search for biological mechanisms responsible for drug abuse and addiction as well as in the search for potential treatments for addiction. The extent to which such drug effects could be impacted by quantitative differences in the maintaining event will influence the interpretation of these studies.

It is important to note, however, that resistance to change studies are conducted using multiple schedules, and the reinforcement conditions in alternative components can influence the behavioral effects of disruptors such as prefeeding or extinction as well as drug administration. Thus, the schedule arrangement may influence the generality of observed reinforcement-magnitude dependent drug effects. Grace, McLean, and Nevin (2003) demonstrated that resistance to change due to prefeeding or extinction during a component with a constant reinforcement rate varied inversely with reinforcement rate in the alternative component. Similarly, drug effects under fixed-intervals arranged within a multiple schedule can depend on the schedule programmed in alternative components, such as increasing the fixed-ratio during one component makes low-rate behaviors during a subsequent fixed-interval component more likely to increase following ethanol administration (Barrett and Stanley, 1980). Thus, behavior during an interval component under a multiple schedule may be influenced by conditions present in the other components. This interaction among schedule component conditions, resistance to change, and rate-dependent drug effects must be considered when interpreting results from similar studies.

The goal of the present study was to extend our earlier results by examining potential reinforcement magnitude modulation of rate-dependent effects of other drugs. We examined

the generality of the effects we observed by testing cocaine, d-amphetamine, chlórdiazepoxide, and pentobarbital in pigeons and d-amphetamine and pentobarbital in rats using the same procedures we previously used (Lamb and Ginsburg, 2008; Ginsburg and Lamb, 2008).

Methods

Subjects

All animals were housed individually under a 14/10 hour light/dark cycle and were tested during the light cycle. Experimental procedures were approved by the Institutional Animal Use and Care Committee of the University of Texas Health Science Center at San Antonio.

Pigeons—Five adult male White Carneau pigeons (Palmetto Pigeon Plant, Sumter, South Carolina, USA) served as subjects. Four subjects were tested following administration of all four drugs, and one additional bird (five total) was tested following d-amphetamine administration. Only three birds received the highest dose of cocaine tested (10 mg/kg). Pigeons were maintained at 80% of their free-feeding weights by supplementing food earned during the procedure with postsession food in their home cages. Pigeons had free access to water and grit while in their home cages. All pigeons had previously served as subjects, responding under the same procedure for at least 3 months prior to drug administration and had received acute doses of fluvoxamine and desipramine (Lamb and Ginsburg, 2008).

Rats—Eight adult male Lewis rats (Harlan Labs, Indianapolis, IN, USA) served as subjects. All eight were tested following d-amphetamine and six of these rats were tested following pentobarbital administration. Rats were maintained at approximately 330g by supplementing food earned during the procedure with 12-15g of rat chow postsession in their home cages. Rats had free access to water while in their home cages. Rats also had previously served as subjects, responding under the same procedure for over 8 months and had received acute doses of fluvoxamine and desipramine (Ginsburg and Lamb, 2008).

Apparatus

Pigeon studies were performed in Gerbrands G7410 test chambers (Alderston, Massachusetts, USA). The chambers were housed in a ventilated enclosure (Gerbrands G7211) to attenuate ambient light and sound. A white noise generator in the procedure room was also used to mask ambient sound. A clear house light was positioned above the chamber. Three response keys were distributed horizontally across one wall, however, only the key in the center of the wall was used for this experiment. The key could be illuminated with a red, white, or green light. A solenoid-operated hopper below the center key was used to deliver food (Purina Checkers, Purina Mills, St. Louis, MO, USA). Food availability was signaled by illumination of a light above the hopper. Experimental contingencies and data were controlled and collected by a computer using Med-PC IV software (WMPC, MedAssociates, Georgia, Vermont, USA).

Rat studies were conducted in commercially available chambers (Standard Rat Chamber, MedAssociates, Georgia, Vermont, USA) which are housed in light and sound attenuating enclosures (Med-Associates, Georgia, Vermont, USA). Chambers are equipped with two response levers, each located below a stimulus light, along one wall. A pellet magazine delivered food pellets (45-mg rat chow flavored pellets, Bio-Serv, Frenchtown, NJ, USA) into a hopper located between the two response levers. A clear light bulb was mounted above the chamber near the opposite wall. Experimental contingencies and data were controlled and collected by a computer using Med-PC IV software (Med-PC IV,

MedAssociates, Georgia, Vermont, USA). Pink noise was generated in the procedure room to attenuate ambient sound.

Pigeon procedure

Pigeons were trained to respond under a multiple fixed-interval (FI) 300-s schedule in which completion of the response requirement resulted in different durations of food access, depending on the component (Lamb and Ginsburg, 2008). Initiation of each FI component was signaled by illumination of the center key as well as the house light. Illumination of the center key with green, white, or red light signaled that the first key peck after the interval elapsed resulted in food presentation for 2-, 4-, or 8-s respectively. Each fixed-interval was followed by a 60-s limited hold; failure to respond during the limited hold ended the component. A 60-s timeout occurred between components regardless of whether the component ended with reinforcement or lapse of the limited hold. During the timeout, all lights in the chamber were turned off, and responses had no scheduled consequences. The order of FI components was randomized by choosing without replacement from a list of the six possible orders that the three components could occur. Each daily session provided four presentations of each component.

Rat procedure

Rats were initially trained to respond under a multiple fixed-interval (300-s) schedule as previously described (Ginsburg and Lamb, 2008). During one component of the schedule, completion of the response requirement on the active lever resulted in illumination of the house light and delivery of 2 food pellets separated by 1-s; in the other component, the alternate light was illuminated and the alternate lever was active, and completion of the response requirement resulted in illumination of the house light and delivery of 10 pellets. Beginning immediately (0-s), one pellet was delivered every second. The next interval began 10-s after completion of the response requirement in either component. A 10-s limited hold followed each component; failure to respond during this period resulted in immediate initiation of the subsequent component. The order of component presentation was randomized under a blocked design to ensure equal presentations of each component during each daily session, and to prevent unintentional clustering of the components. Each component was presented six times each day.

Drugs

Drug effects were determined following administration of varying doses on either Tuesday or Friday. Saline was administered on Thursdays and served as the control. Dose order was mixed among subjects such that the order in each subject was unique. A second determination of dose effects was achieved by reversing dose order for the first determination in each subject. Results of the two determinations at each dose were averaged for each subject. d-Amphetamine HCL (NIDA, Bethesda, MD, USA), pentobarbital Na (Sigma, St. Louis, MO, USA), and chlordiazepoxide HCL (Sigma, St. Louis, MO, USA) were each administered 15-min prior to the start of the session; cocaine HCL (NIDA, Bethesda, MD, USA) was administered 10-min prior to the session. All drugs were administered into the pectoral muscle in pigeons and intraperitoneally in rats. Doses were calculated based on the weight of the salt. Doses were tested at 1/4 log unit increments over the following range in pigeons: d-amphetamine [0.32-5.6 mg/kg], cocaine [0.32-10 mg/kg], chlordiazepoxide [1.78-32 mg/kg], and pentobarbital [1.0-17.8 mg/kg]. In rats, doses of 0.32, 1.0, and 3.2 mg/kg d-amphetamine and 1.8, 3.2, 5.6, and 10 mg/kg pentobarbital were tested.

Analysis

Dose effects across the entire fixed-interval

Drug effects were normalized for each subject to the average Thursday control rate for each reinforcement magnitude for that subject, and effects of each dose were expressed as percent of control. Normalized rate of responding for each magnitude of reinforcement was averaged for the group following each drug dose and plotted as a function of drug and dose. ED50s were only determined for drugs which produced a 50% reduction in responding for the group. ED50 data were then calculated for each reinforcement magnitude. For each subject, only doses that bracketed 50% of control responding were included in the regression, resulting in two points that constituted the portion of the dose-response function that included a 50% reduction. From these points, a linear regression was performed and the ED50 dose was interpolated. ED50 values for all subjects were then averaged, and confidence limits (95%) were then calculated from the standard deviation and sample size for the smallest reinforcement magnitude (2-s or 2-pellet) component. ED50 values for the other components were then compared with these confidence limits to assess whether they significantly differed from the ED50 for the smallest reinforcement condition.

Influence of reinforcement magnitude on rate-dependent drug effects

Only effects of doses that resulted in less than 80% reduction in average control rate of responding for the group were included in these analyses. This limit was set to prevent inclusion of doses for which too few subjects or too few points were present for reasonable interpretation. For each component, local response rates over ten consecutive tenths of the interval (30-s per bin) were calculated. Response rate during each bin following each dose was normalized to a percentage of the average saline control rate during the corresponding bin. Saline control rates were determined by averaging the response rates for each subject on the Thursdays of the weeks each drug was administered. Rate-dependent drug effects were assessed as described previously (Lamb and Ginsburg, 2008). Briefly, response rate during each 10th of the interval (bin) was calculated for each component for each subject. Bins in which the control response rate was less than 0.01 responses/s and dose effects that resulted in a response rate of zero were excluded from analysis. For each drug in each species, a linear mixed-effects regression (NLME package, R: a language and environment for statistical computing, Vienna, Austria) was performed. Linear-mixed effects models provide a linear regression that includes a “within-subjects” error term. This could be thought of as analogous to a within-subjects ANOVA. In the linear mixed-effects model, fixed-effects are parameters associated with repeatable levels of experimental factors (e.g. dose and reinforcement magnitude in the present study) and random effects are associated with individual experimental units (e.g. individual subjects). These random effects are associated with observations from the same (“within-subject”) classification factor, which allows a mixed-effects model to better represent the covariance structure induced by the classification factor (Pinheiro and Bates, 2000). For the present study, we used the model $\log_{10}(\text{drug rate} / \text{control rate} * 100) \sim \log_{10}(\text{control rate}) * \text{drug dose} * \text{reinforcement condition}$, with subject used as the repeated measure. An analysis of variance was performed on the resulting linear model, and assessed for interactions among the factors. Due to the presence of two- or three-way interactions for each analysis, further analyses were performed at each dose level under each control condition. For these analyses, the model used was $\log_{10}(\text{drug rate} / \text{control rate} * 100) \sim \log_{10}(\text{control rate})$, again with subject as the repeated measure. Confidence limits for the slopes during the 2-s or 2-pellet reinforcement conditions were calculated using the parameters derived from the model. The slopes for the different reinforcement conditions were compared with the 95% confidence limits of the slope for the smallest reinforcement condition (2-s or 2-pellets). Slopes that fell outside of this range were considered significantly different.

Results

Baseline Responding

Both rats and pigeons exhibited accelerating rates of responding typical of fixed-interval schedules. In fixed interval schedules, responding is maintained at low rates early in the interval and accelerates as time elapses (e.g., Ferster and Skinner, 1957). This is evident in quarter-life values (time into each fixed-interval at which ¼ of total responses are made, see Herrnstein and Morse, 1957). For pigeons, quarter-life values were $73.2 \pm 2.5\%$, $68.2 \pm 2.2\%$, and $67.4 \pm 2.9\%$ s (for 2-, 4-, and 8-s intervals, respectively). For rats, quarter-life values were $55.3 \pm 3.3\%$ and $39.7 \pm 5.9\%$ s (for 2- and 10-pellet intervals, respectively). Quarter-life values are greater than 25%, demonstrating that responding accelerated across each interval. Baseline rates of responding across each component were (mean $\pm$ S.E.M., resp/s): 0.58 ± 0.04 , 0.70 ± 0.04 , and 0.78 ± 0.04 in pigeons (2-, 4-, and 8-s, respectively) and 0.62 ± 0.07 and 1.42 ± 0.12 in rats (2- and 10-pellets, respectively)

Dose effects across the entire Fixed-Interval

All drugs dose-dependently decreased average response rate in both species, though the lowest dose of d-amphetamine (0.32 mg/kg) tested increased response rates in both components in rats (Fig.1 and Fig.2). In pigeons, ED50s generally did not differ among components (see Table 1). In rats, the ED50 following d-amphetamine during the 2-pellet condition was significantly greater than the ED50 for the 10-pellet component. This is likely due to the slight, but nonsignificant increase in response rate produced by 1 mg/kg d-amphetamine during the 2-pellet component relative to the slight but nonsignificant decrease in rate during the 10-pellet component for six of the eight rats. ED50 for pentobarbital in rats was not calculated as response rates for the group did not fall below 50% of the control rates following any dose.

Rate-dependency

Vehicle administration did not produce rate-dependent effects. Results of a mixed two-factor ANOVA did not reveal any interaction between log(control-rate) and reinforcement magnitude, nor main effects of either factor for either pigeons or rats.

All drugs exerted rate-dependent effects that depended in turn on dose. This is apparent in Fig. 3 for pigeons, and Table 2 for rats, where larger doses of each drug generally resulted in more negative (steeper) slopes. As shown for each drug in Fig. 3, rate-dependency slopes are less negative at lower doses than at higher doses, indicative of a dose-related increase in rate-dependency in pigeons. These same data are described in Table 2, as well as rate-dependency slopes for doses of d-amphetamine and pentobarbital in rats. Here again, the absolute value of rate-dependency slopes increases with increasing dose, indicating that rate-dependent effects are dose-related in rats as well.

Reinforcement magnitude effects on rate-dependency slopes

Cocaine and to a lesser extent chlordiazepoxide provided evidence consistent with reinforcement magnitude attenuating rate-dependent drug effects. Cocaine exerted rate-dependent effects that were modulated by reinforcement magnitude (see Table 2 and Fig. 3). A three way interaction among control response rate, reinforcement condition, and dose was present. ($F[12, 704]=2.0$, $p<0.05$). As shown in Fig. 3 and Table 2, slopes during the FI maintained by 8-s hopper time were significantly less negative (shallower) than those during the FI maintained by 2-s hopper time following 5 of the 7 doses tested (excepting 1.0, and 5.6 mg/kg). This indicates that the rate-dependent effects of cocaine were generally blunted by increased reinforcement magnitude.

Following chlordiazepoxide administration, a three-way interaction among control response rate, reinforcement condition, and dose was present ($F[10, 508]=8.5, p<0.05$). Subsequent analysis at each level of the reinforcement conditions revealed that responding for the 2-s grain presentation exhibited a negative slope indicative of rate-dependency even at the lowest dose tested (1.78 mg/kg), though the slope was not different from zero during the FI maintained by 8-s hopper time following 1.78 mg/kg chlordiazepoxide. As shown in Fig. 3 and Table 2, the rate-dependency slope during the FI maintained by 8-s hopper time was significantly less negative (shallower) than during the FI maintained by 2-s hopper time following a dose of 10 mg/kg. Thus, rate-dependent effects of this dose of chlordiazepoxide were blunted by increased reinforcement magnitude, though it should be noted that the rate-dependency slope was significantly steeper for the FI maintained by 8-s hopper time following a dose of 3.2 mg/kg. Doses of chlordiazepoxide greater than 10 mg/kg reduced average response rate by more than 80%, so those doses were not assessed for rate-dependent effects.

Only a weak case can be made for modulation of rate-dependent effects by reinforcement magnitude following pentobarbital. A three-way interaction among control rate, reinforcement condition, and dose was not significant in pigeons or rats. However, in pigeons, two-way interactions between control rate and dose or control rate and reinforcement condition were significant ($F[4, 539]=15.2$ and $F[2, 539]=6.1$, respectively, $p<0.05$). In pigeons, rate-dependency slope was shallower for the FI maintained by 8-s hopper time compared with the FI maintained by 2-s hopper time following only doses of 1.78 and 5.6 mg/kg (Fig. 3 and Table 2). This was not true following 1.0, 3.2, or 17.8 mg/kg, suggesting little or no modulation of rate-dependent effects of pentobarbital by reinforcer magnitude. In rats, a two way interaction was present between control rate and dose ($F[2, 449]=38.1, p<0.05$), but not between control rate and reinforcer magnitude. There was no dose of pentobarbital that resulted in rate-dependent effects that depend on reinforcement magnitude in rats (Table 2).

There was no evidence that rate-dependent effects of d-amphetamine are modulated by reinforcement magnitude. A three-way interaction among control rate, reinforcement condition, and dose was not significant in pigeons, but was significant in rats ($F[2, 449]=9.2, p<0.05$). In pigeons, a two-way interaction between control rate and dose was significant ($F[5, 689]=3.3, p<0.05$), but the interaction between control rate and reinforcement condition was not. The only condition exhibiting a slope difference between the FI maintained by 2-s and 8-s hopper times was following a dose of 3.2 mg/kg in pigeons. Following 3.2 mg/kg d-amphetamine, the slope during the FI maintained by 8-s hopper time was significantly steeper and than during the FI maintained by 2-s hopper time. However, this appears to be due to an aberrant point given that the slope during the FI maintained by 2-s hopper time following this dose is shallower than the slope following a lower dose of 1.78 mg/kg. In rats, there was also no evidence that rate-dependent effects of d-amphetamine were modulated by reinforcement magnitude. Indeed, as in pigeons, there was evidence of *greater* rate-dependent effects during the FI reinforced by 10-pellets compared with the FI maintained by 2-pellets following 1 mg/kg (Table 2).

Reinforcement magnitude effects on rate-dependency intercepts

In both pigeons and rats, there were few conditions in which there were significant differences among intercepts (i.e. the point at which the function intersects $\log[\text{control rate} = 1 \text{ resp/s}]$, or zero) that depended on reinforcement magnitude (Table 3). However, the array of statistically significant differences in intercept values is unsystematic, suggesting that they are not reliable.

Discussion

The results of the present study provide further evidence that reinforcement magnitude can influence rate-dependent effects of some drugs. However, such effects do not necessarily generalize to other drugs with similar pharmacological mechanisms. Thus, reinforcement magnitude modulation of rate-dependent effects appears to be of limited generality across drug classes. Further, the influence of reinforcement magnitude is predominantly exerted on low-rate behavior that occurs early in the interval as evidenced by differences in slopes but not intercepts (which reflect effects at control rates of $-\log(0)$ or 1 resp/s), and thus is unlikely to affect the results of most studies in which response rates are moderate or high. This represents important information for the interpretation of studies comparing drug treatment effects on behavior maintained by different magnitude or types of reinforcing events. As discussed below, reinforcement magnitude differences are unlikely to influence the results of most such studies, and can often be ruled out as an important consideration in their interpretation.

In the present study, reinforcement magnitude dependent modulation of rate-dependent drug effects was apparent in pigeons following cocaine and chlordiazepoxide administration. However, pentobarbital revealed only very weak reinforcement magnitude modulation of rate-dependent effects while d-amphetamine exerted none at all. In previous work in our laboratory, rate-dependent effects of antidepressants were similarly modulated by reinforcement magnitude in both pigeons and rats (Lamb and Ginsburg, 2008; Ginsburg and Lamb, 2008). These effects appear to generalize across rats and pigeons for antidepressants, and for amphetamine (in that rate-dependent effects were not influenced by reinforcement magnitude in either species). However, more examples from these and other classes need to be studied.

As described in the Introduction, the schedule arrangement can profoundly influence resistance to change due to disruptors such as prefeeding and extinction, as well as the rate-dependent effects of drugs (Barrett and Stanley, 1980; Grace et al., 2003). In a review of behavioral consequences of different reinforcement magnitudes, Bonem and Crossman (1988) note that reinforcement magnitude effects on behavioral disruption seen in multiple schedules are not seen in comparable simple schedules. In the same work, the authors also point out considerations based on the particular reinforcing event selected, so differences in the reinforcing event may influence results from other similar studies. Thus, the generality of our results across other schedule arrangements also remains unknown.

Taken together with our previous work and that of others, pharmacological disruption of overall response rate is not generally modulated by reinforcement magnitude (Cohen, 1986; Ginsburg and Lamb, 2008; Harper, 1999a; Lamb and Ginsburg, 2008; Lamb and Ginsburg, 2005). Thus by this broad, and commonly used metric, behavioral momentum does not appear to hold for drug disruption. However, when examined at a more molecular level, rate-dependent effects of some drugs do appear to be modulated by reinforcement magnitude, in a manner consistent with behavioral momentum theory. For drugs that demonstrated the effect, greater reinforcement magnitude resulted in more resistance of low-rate behavior to change. The net result of this was that the steepness of the rate dependency slope was blunted under greater reinforcement magnitude conditions, while intercepts (which represent effects at the relatively high control response rate of 1 resp/s) were not different among reinforcement conditions. Our findings are consistent with previous studies in which rate-dependent effects of fluvoxamine and desipramine were modulated by reinforcer magnitude, but only at lower control rates of responding (Lamb and Ginsburg, 2008), but contrast with work demonstrating that prefeeding or extinction differentially

disrupts peak response rate during a fixed-interval depending on reinforcer magnitude (Grace and Nevin, 2000).

Other research has indicated that, in contrast to overall response rate, the distribution of responding (timing) is reinforcement-magnitude-dependent (Doughty and Richards, 2002; Ludvig, Conover, and Shizgal, 2007). Specifically, greater reinforcer magnitudes tend to lead to responding earlier in the interval. This effect was evident in our results as response-rates did not differ among components, but quarter-life did. In our study, greater reinforcement magnitude was associated with lower quarter-life, indicating that responding began earlier in the intervals reinforced with a higher-magnitude, and later in those reinforced by a lower magnitude. Because intervals reinforced with a high-magnitude were most often followed by an interval reinforced with a relatively lower magnitude, these results are consistent with the conclusions of Ludvig et al., (2007) who conclude that reinforcement magnitude influences timing both by eliciting responding earlier in the interval through anticipatory responding, and by delaying responding in the subsequent interval through larger immediate after-effects.

Considered together, the net result is that increasing reinforcement magnitude can produce shifts in the timing of responses early in the interval, leading to higher local rates early in the interval, while not affecting peak rates late in the interval or overall rate across the interval. Further, the implication of these results is that reinforcement magnitude can influence the effect of some drugs on the relatively lower rates that occur early in the interval, perhaps because the underlying local response distribution and rate depends on the reinforcement magnitude. However, the relative influence of even dramatic differences in effects at low response rates contribute only slightly to the overall response rate across an entire fixed-interval, resulting in modest, inconsistent, or no apparent modulation of overall response rate by reinforcement magnitude following drug administration.

Modulation of rate-dependency by reinforcer magnitude was apparent following cocaine but not d-amphetamine in pigeons. Harper (1999b), similarly found no effect of d-amphetamine consistent with momentum. Harper suggested this was because of stimulus control deficits produced by amphetamine which might also account for results reported here. Previously we have shown that modulation of rate-dependency by reinforcer magnitude was consistent across two different antidepressants (Lamb and Ginsburg, 2008). Thus, this study provides limited support of generality of the effect within a drug class. Due to the limited amount of information available, one can only speculate about the reason for this apparent lack of generality within a drug class. One possibility is that the drugs which clearly exert rate-dependent effects that are modulated by reinforcement magnitude (fluvoxamine, desipramine, and cocaine) are voltage-dependent reuptake inhibitors. In contrast, d-amphetamine (despite acting at similar targets) is a voltage-independent neurotransmitter releaser and does not appear to exert this effect. Two drugs with more ambiguous results act as modulators of the same receptor, though at different sites. Thus, the way in which a drug exerts its pharmacological action may be more important to this effect than where that action is exerted. Considerably more data are necessary to confirm or refute this hypothesis.

In conclusion, the present study provides evidence that the rate-dependent effects of cocaine, possibly chlordiazepoxide, and perhaps pentobarbital decrease with increasing reinforcement magnitude, providing some limited support for the generality of our previous results with fluvoxamine and desipramine. In contrast, reinforcement magnitude did not alter rate-dependent effects of d-amphetamine. The reason reinforcement magnitude can influence rate-dependent effects of some, but not all, drugs is unclear. However, more generally, such modulation of rate-dependent effects is unlikely to influence the results or conclusions drawn from studies using procedures that generate moderate or high response

rates, typical of many studies in which drug effects on behaviors maintained by different reinforcing events are compared.

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Figure 1. Effects of cocaine, d-amphetamine, chlordiazepoxide, and pentobarbital on average overall response rate under a multiple fixed-interval 300-s schedule in pigeons for each interval (2-s, 4-s, or 8-s grain presentation) plotted against log(dose). Points represent the mean ($\pm$ S.E.M.) of four pigeons, except for d-amphetamine where $n=5$.

Figure 2.

Effects of d-amphetamine and pentobarbital on average overall response rate under a multiple fixed-interval 300-s schedule in rats for each interval (2-pellet or 10-pellet presentation) plotted against log(dose). Points represent the mean ($\pm$ S.E.M.) of eight or six rats (for d-amphetamine and pentobarbital, respectively).

Figure 3.

Regression of log(drug effects expressed as a percentage of control rate) against log(control rate) in pigeons showing data from each subject following administration of selected doses of each drug or vehicle during each interval. Responding during intervals which were maintained by 2-s (top row), 4-s (middle row), or 8-s (bottom row) hopper access are shown. Points represent mean data for a single bird coded by color. Values for regression slopes may be found in Table 2.

Table 1

ED50 for Test Compounds in Pigeons and Rats

Pigeons		
Hopper time	ED50	95% C.I.
Cocaine		
2-s	7.0	[5.2 - 8.9]
4-s	6.8	
8-s	6.0	
Chlordiazepoxide		
2-s	6.2	[1.5 - 10.9]
4-s	9.4	
8-s	8.5	
Pentobarbital		
2-s	11.2	[3.8 - 18.5]
4-s	13.7	
8-s	15.9	
Amphetamine		
2-s	3.4	[1.8 - 4.9]
4-s	2.6	
8-s	3.1	
Rats		
	ED50	95% C.I.
Pentobarbital	N.D.	N.D. - Not determined due to maximum group effect >50%
Amphetamine		
2-pellets	1.7	[1.5 - 1.9]
10-pellets	1.4	

Table 2

Slope for the regression of log[drug effect (as percent control rate)] against log[control rate]

Drug	Hopper Time (sec)	Pigeons					
		Dose (mg/kg)		Dose (mg/kg)		Dose (mg/kg)	
Chlordiazepoxide	2	1.8	3.2	5.6	10.0	1.8	3.2
	4	0.21	0.30	0.40	0.48	0.32	0.56
	8	0.07	0.10	0.19	0.28	0.32	10.0
Cocaine	2	0.18	0.43	0.39	0.46	0.50	0.84
	4	0.10	0.07	0.19	0.28	0.30	0.61
	8	0.03	0.08	0.38	0.22	0.30	0.40
Pentobarbital	2	0.07	0.31	0.25	0.43	0.64	0.77
	4	0.13	0.08	0.18	0.23	0.58	0.68
	8	0.23	0.17	0.28	0.23	0.70	0.65
Amphetamine	2	0.32	0.56	1.0	1.8	3.2	
	4	0.05	0.04	0.29	0.55	0.10	
	8	0.03	0.22	0.13	0.34	0.55	
		0.02	0.10	0.23	0.44	0.49	
Drug	Pellets delivered	Rats					
		Dose (mg/kg)		Dose (mg/kg)		Dose (mg/kg)	
Pentobarbital	2	1.8	3.2	5.6	10.0	1.8	3.2
	4	0.18	0.32	0.23	0.41	0.32	0.56
	8	0.22	0.36	0.20	0.55	0.32	10.0
Amphetamine	2	0.13	0.40	0.10	0.23	0.44	0.49
	4	0.16	0.67				

Underline – Significantly negative slope (indicative of rate-dependent effect)

Italic – Slope for 2-sec condition significantly different from 4-sec or 8-sec condition

Bold – Slope for 2-sec condition significantly MORE NEGATIVE than 4-sec or 8-sec condition

Table 3
Intercepts for the regression of log[drug effect (as percent control rate)] against log[control rate]

Pigeons				
Drug	Hopper Time (sec)	Dose (mg/kg)		
Chlordiazepoxide		1.8	3.2	5.6
				10.0
	2	1.85	1.65	1.70
	4	2.05	1.96	1.76
Cocaine	8	2.01	1.91	1.80
		0.32	0.56	1.0
			1.8	3.2
			5.6	10.0
Pentobarbital	2	2.02	1.97	2.01
			1.96	1.95
	4	2.06	2.07	2.03
			2.06	2.05
D-amphetamine	8	1.93	1.97	2.00
		1.0	1.8	3.2
			5.6	10.0
			17.8	
Rats	2	1.99	2.23	2.12
			2.22	2.13
	4	1.91	2.11	2.22
			2.16	2.33
Pellets delivered	8	2.18	2.19	2.20
		0.32	0.56	1.0
			1.8	3.2
Dose (mg/kg)	2	2.08	2.06	1.99
			1.69	1.36
	4	2.00	1.98	1.99
			1.58	1.04
Pellets delivered	8	2.03	1.95	1.99
			1.58	1.12
Rats		1.8	3.2	5.6
				10.0
	2	2.03	1.66	1.72
			1.84	
Dose (mg/kg)	10	1.79	1.59	1.76
			1.82	
Pellets delivered		0.32	1.0	
	2	2.05	1.64	
	10	2.03	1.49	

Bold – Intercept for 2-s (or 2-pellet) condition significantly different than 4-s or 8-s (or 10-pellet) condition