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Rate-Dependent Effects of Amphetamine on Responding Under Random-Interval Schedules of Reinforcement in the Rat

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LUCKI, I. *Rate-dependent effects of amphetamine on responding under random-interval schedules of reinforcement in the rat.* PHARMACOL BIOCHEM BEHAV **18**(2) 195–201, 1983.—The parameters of 12 random-interval schedules (cycle length and interreinforcement interval) were varied systematically in order to examine the ability of these schedules to separate the usual relationship between response rate and reinforcement frequency using rats. Response rates varied over a two-fold range for the same frequency of reinforcement under random-interval 30-sec schedules. However, cycle length did not alter response rates significantly at other interreinforcement intervals. Subsequently, the effects of amphetamine on random-interval responding were examined in order to evaluate the roles of control rates of responding and reinforcement in amphetamine's actions. Amphetamine's effects were significantly correlated with both control response rate and control rate of reinforcement. However, by comparison, control response rate was the better predictor of amphetamine behavioral effects. The results support the rate dependency hypothesis that control rate of responding is closely associated with amphetamine's effects on operant behavior.

Amphetamine Rate dependency hypothesis Operant behavior Random-interval schedules Path analysis

THE rate dependency hypothesis or principle describes how variations in the control rate of responding alter the direction and magnitude of amphetamine's effects on operant behavior [7, 8, 20]. Amphetamine usually increases response rate under schedules that maintain low control response rates (e.g., DRL and FI schedules; [3, 5, 14, 26, 29]). In contrast, amphetamine usually does not affect or decreases response rate under schedules that maintain high control response rates (e.g., FR and VI schedules [1, 13, 22]). Moreover, when the control response rates of DRL, FR, or VI schedules are altered by changing the parameter values of these schedules, amphetamine's effects also change as predicted by the rate dependency hypothesis [1, 6, 9, 13, 21, 29]. The effect of amphetamine administration, expressed as an output ratio, is often plotted as a function of the control response rate [9,15]. Such rate-dependency functions generally show a significant linear relationship with a negative slope indicating that amphetamine increases low rates and decreases high rates of control responding [9]. Rate-dependent effects of amphetamine have been shown in a number of species, under a variety of reinforcement schedules, using several types of reinforcers, and for a range of responses with only a few exceptional circumstances (for reviews see [9, 16, 26].

One criticism of the rate dependency hypothesis is that other schedule variables may be exerting influences on amphetamine's behavioral effects besides the control response rate. For example, reinforcement frequency is highly correlated with response rate under conventional ratio, interval and DRL schedules (see [28]). This correlation between control response rate and reinforcement frequency confounds many prior demonstrations of amphetamine's rate-dependent behavioral effects (cf., [1, 21, 29]). Functions could conceivably be constructed that would show a similar relationship between amphetamine's effects and control reinforcement frequency as the functions used to support the rate dependency hypothesis. However, comparisons of amphetamine's effects between two schedules that differ in response rate at a single rate of reinforcement have shown that amphetamine's effects still vary in accord with the rate dependency hypothesis [18, 19, 23]. Unfortunately, these studies only examined schedules that were equated to a single reinforcement rate value.

Random-interval (RI) schedules of reinforcement provide a number of useful features not found with conventional reinforcement schedules [25]. Among them, altering the parameter values of RI schedules can vary response rate and reinforcement frequency independently in pigeons [10], although no parametric studies have been reported for rats. This property of RI schedules could be used to determine whether control response rate or reinforcement frequency is a better predictor of amphetamine's behavioral actions across a range of schedule values. The present study employed 12 RI schedules to systematically explore the effects of variations of two RI parameters on response rates in separate groups of rats. The effect of amphetamine on responding under these schedules was subsequently examined. The results showed that the control rate of responding was the best predictor of

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TABLE 1

MEAN CONTROL RATES OF RESPONDING AND REINFORCEMENT UNDER RANDOM-INTERVAL SCHEDULES*

	Cycle Length (T)								
	3.75 sec			7.50 sec			15.0 sec		
Mean Interreinforcement Interval (T/p)	Resp Rate	Rf Rate	N	Resp Rate	Rf Rate	N	Resp Rate	Rf Rate	N
30 sec	75.5 ±8.6	1.70 ±0.06	5	100.0 ±15.0	1.97 ±0.03	5	50.6 ±4.5	1.99 ±0.03	6
60 sec	64.2 ±9.1	0.79 ±0.06	6	70.9 ±15.5	0.92 ±0.04	5	51.6 ±16.5	0.99 ±0.03	5
120 sec	45.1 ±11.5	0.35 ±0.04	6	29.5 ±5.9	0.40 ±0.02	6	40.5 ±4.5	0.46 ±0.02	6
240 sec	16.2 ±10.7	0.07 ±0.02	6	20.5 ±6.3	0.16 ±0.03	6	19.8 ±6.8	0.19 ±0.03	5

*All values represent the mean of six determinations of control performance, expressed as responses/min or reinforcers ± 1 SE. Control performance determinations were the average obtained during the three sessions prior to each weekly administration of amphetamine or saline.

amphetamine's effects on RI responding, although amphetamine's effects were also correlated with the control rate of reinforcement.

METHOD

Animals

Male albino rats from the Holtzman Company (Madison, WI), 70 days of age upon arrival in the laboratory, served as subjects. They were housed singly with Purina Rat Chow and water freely available for eight days. The weight of each rat was recorded and averaged over 76–78 days of age. Thereafter, each rat was held at approximately 80% of its predicted body weight by restricting the amount of water given during a brief daily period between 30 and 60 minutes following the experimental session. Predicted body weight was readjusted upward daily, with growth estimated from the daily mean weight obtained from a randomly chosen group of six rats that were allowed continued free access to food and water for the duration of the experiment. The animal colony was maintained on a 12-hour light-dark cycle, with lights on at 0800. Red lights were used when it was necessary to enter the animal colony during the dark hours.

Apparatus

Six 30×23×24-cm operant conditioning chambers were used. Each chamber had two sidewalls and a hinged top made of clear Plexiglas and end panels made of sheet aluminum. A 0.6-cm diameter stainless steel lever projected 2.2 cm into the chamber at the midline of one of the end panels. The associated microswitch was activated by a 0.1-cm depression of the lever with a 6-g weight. Centered 6.2-cm above the lever was a 3.6-cm diameter aperture which provided access to a recessed water cup. The reinforcer was 0.1 ml of distilled water delivered to this cup by means of a constant-pressure water system and solenoid-operated valves. The conditioning chambers were enclosed within sound-attenuating chests, each of which was illuminated by a 6W 24V DC houselight located behind the end panel on which the lever was mounted. An exhaust fan ventillated each chest, and a 10.2-cm speaker provided 80-dB white masking noise. Experimental control and data collection were provided from a separate room by a PDP-8/F computer (Digital Equipment Corporation, Maynard, MA) using the SKED software system (27) to control a solid-state interface (12).

Procedure

Rats were randomly assigned to 12 squads of six rats each and trained to press a lever for water reward. Subsequently, each squad of rats was placed under one of 12 different random-interval (RI) schedules of reinforcement. RI schedules were defined by the selection of two parameters: T was the length of a temporal interval that remained free-running or cycling; and p was the probability of reinforcement for the first response that occurred in a given cycle [10,25]. Restrictions governing reinforcement were that only the first response during a given cycle could produce delivery of the reinforcer, according to the parameter p, and that the first response in a cycle was reinforced no matter when it occurred during that cycle. Additional responses during the same cycle could not produce reinforcer delivery. Opportunities to receive a reinforcer were missed when an animal failed to emit at least one response during each cycle. Accordingly, the T/p ratio predicted the mean interval expected to elapse between consecutive reinforcer availabilities. A factorial design of three T values and four T/p values (interreinforcement intervals) was employed. T values were 3.75, 7.5, and 15 sec. T/p values were 30, 60, 120, and 240 sec.

Five rats eventually died during the experiment due to illness leaving five or six rats in each squad that completed the experiment. Experimental sessions were scheduled daily during the dark hours, between 2230 and 0630. Rats were trained in 30-min sessions under the above RI schedules until stable performance developed, as determined from visual inspection of the data. In addition, all groups met a stability criterion: The difference between the means of two consecutive three-session blocks did not exceed 5% of the overall six-session mean [4]. A total of 84 sessions were required

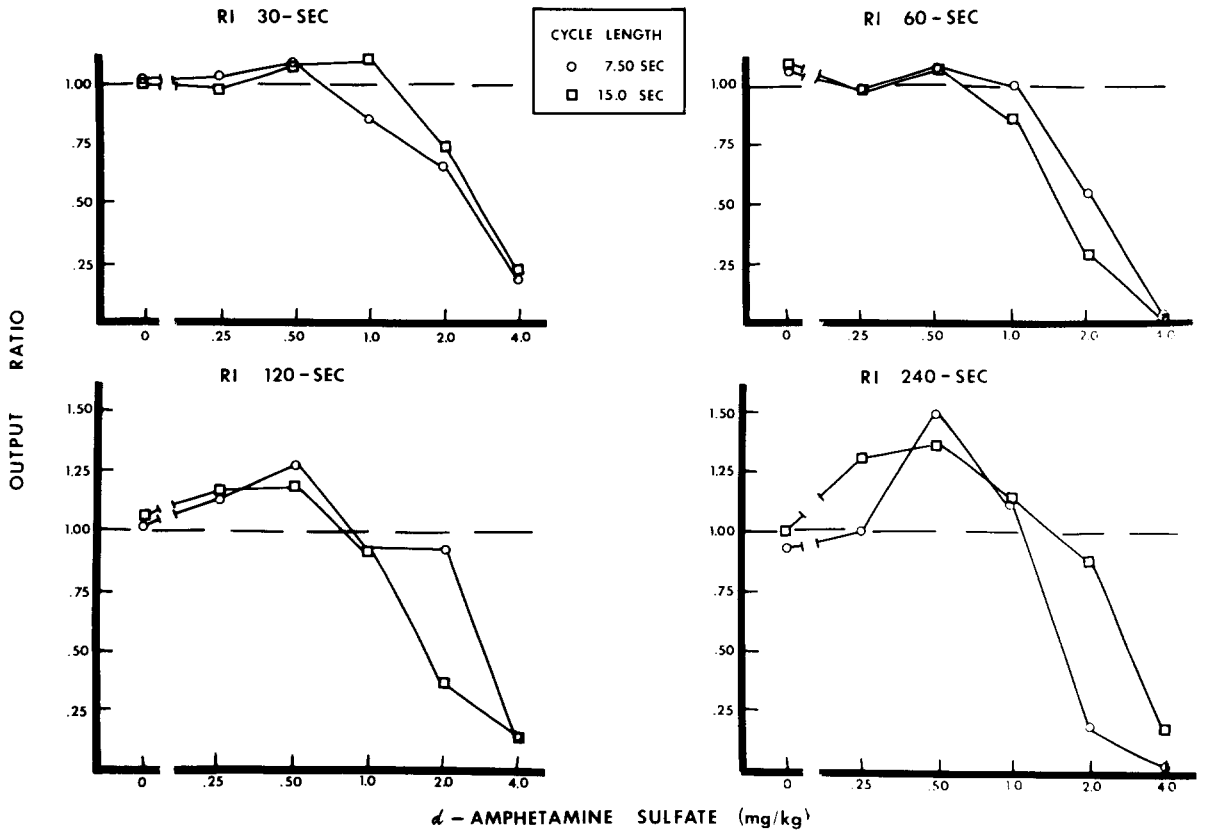

FIG. 1. Mean output ratios for random-interval schedules using a 7.50- or 15.0-sec cycle length as a function of dose of amphetamine. The broken line when output ratio=1.0 indicates when amphetamine produced no change in responding relative to control response rates. Critical allowances calculated for each schedule using Dunnett's test were (T=7.50 sec, 15.0 sec): RI 30-sec, 0.41, 0.31; RI 60-sec, 0.28, 0.37; RI 120-sec, 0.56, 0.36; RI 240-sec, 1.15, 0.83. See Method for an explanation of Dunnett's allowances.

before all groups met this criterion, and then drug testing began.

Drug Testing

All solutions were freshly prepared on the day they were used. *d*-Amphetamine sulfate (Sigma Chemical Company; St. Louis, MO) was dissolved in sterile physiological saline and injected intraperitoneally in a volume that was adjusted to 1 ml/kg. All doses were calculated as the salt. Each rat was injected with *d*-amphetamine (0.25, 0.50, 1.0, 2.0 and 4.0 mg/kg) and saline, administered in an ascending series. Injections occurred 30 minutes prior to the 30-min experimental session for that day. Consecutive drug injections were separated by one week.

Calculation of Drug Effects

The control performance, expressed as rate of responding or reinforcement, was averaged over the three days prior to injection of each dose of amphetamine. Differences in control performance between RI schedules were examined by analysis of variance.

Drug effects were expressed as an output ratio, calculated by dividing response rate at a particular drug dose by the control response rate over the three days prior to testing of that dose of amphetamine. An output ratio of 1.0, then, indicated that amphetamine had no effect on responding. An output ratio greater than 1.0 indicated that amphetamine increased response rate, and an output ratio less than 1.0 indicated that amphetamine decreased response rate relative to the control rate. Analysis of variance including T, T/*p*, and repeated measures on Dose were performed on output ratios under drug (0 to 4.0 mg/kg). A critical allowance was calculated for follow-up individual comparisons of means between saline administration and each dose of amphetamine using Dunnett's test, $\alpha=0.05$, two-tailed. The critical allowance represents the difference in output ratio necessary for responding under amphetamine to differ significantly from saline values, $p<0.05$.

RESULTS

Control Responding.

The average control rates of reinforcer delivery under each of the 12 RI schedules are presented in Table 1. As expected, fewer reinforcers (per min) were obtained at T/*p* values increased, $F(3,55)=1293.5$, $p<0.001$. However, reinforcer delivery rates also varied significantly according to the cycle length (T value) employed, $F(2,55)=25.3$, $p<0.001$. Specifically, follow-up analyses indicated that the 3.75-sec cycle length produced a lower rate of reinforcer delivery than either the 7.50-sec cycle length ($p<0.05$, Tukey's HSD test), or the 15.0-sec cycle length ($p<0.01$). Reinforcer delivery did not differ significantly between the 7.50- and 15.0-sec cycle lengths ($p<0.05$). Because the 3.75-sec cycle length produced lower overall rates of reinforcement than the other

TABLE 2

CORRELATION OF AMPHETAMINE'S EFFECTS WITH CONTROL RATES OF RESPONDING AND CONTROL RATES OF REINFORCEMENT*

Dose *d*-Amphetamine Sulfate	Correlation of Output Ratio with Control Response Rate	Partial Correlation Subtracting the Relationship with Control Reinforcement Rate	Correlation of Output Ratio with Control Reinforcement Rate	Partial Correlation Subtracting the Relationship with Control Response Rate
0.25 mg/kg	−.21		−.28	
0.50 mg/kg	−.89†	−.53‡	−.84†	−.10
1.0 mg/kg	−.75†	−.52‡	−.65†	+.14
2.0 mg/kg	−.60		−.13	
4.0 mg/kg	−.34		−.30	

Correlations are Pearson product-moment correlation coefficients between logarithmic (base 10) transformations of mean output ratio with mean control response rate and mean output ratio with mean control reinforcement rate under 12 random-interval reinforcement schedules, df=10. Control performance consists of the average of three days prior to administration of the dose of *d*-amphetamine. Output ratio is defined as response rate under amphetamine divided by the control response rate.

†$p<0.01$, Student's *t*-test.

‡$p<0.05$, Student's *t*-test.

cycle lengths, subsequent analyses treated the four 3.75-sec groups separately from the remaining eight groups. Thus, confounding from different rates of reinforcement was avoided when analyzing the effects of cycle length on RI rates of responding.

Mean control response rates for the RI schedules that employed 7.50- and 15.0-sec cycle lengths are also presented in Table 1. Rates of responding under the RI schedules were a function of both cycle length and interreinforcement interval, as revealed by a significant interaction between T and T/*p* values, $F(3,36)=3.43$, $p<0.05$. Analysis of the simple main effects revealed that response rate decreased as the interreinforcement interval was lengthened from 30- to 240-sec for both cycle lengths ($p<0.05$). Furthermore, the two cycle lengths under the RI 30-sec schedule produced significantly different rates of responding: responding was nearly twice as frequent when T=7.50 sec than when T=15.0 sec ($p<0.01$). As predicted, then, different response rates can be produced by RI schedules that arrange the same mean interreinforcement interval. Response rates did not differ significantly between cycle lengths at other interreinforcement intervals. There were no significant differences in response rate between weeks, nor a significant interaction involving weeks, indicating that control response rates were stable over the duration of the drug-testing period. Mean control response rates under the RI schedules that employed the 3.75 sec cycle length (Table 1) showed lower response rates at longer interreinforcement intervals in a manner similar to the other cycle lengths, $F(3,19)=6.4$, $p<0.01$.

Effects of Amphetamine

In order to examine possible rate-dependent effects of amphetamine on RI responding, drug effects were calculated as output ratios and are presented in Fig. 1 for the RI groups with 7.50- and 15.0-sec cycle lengths. The main effect for Dose was significant, $F(5,180)=49.3$, $p<0.001$. Low doses of amphetamine appeared to produce greater effects on RI schedules with long interreinforcement intervals. This was most evident at 0.50 mg/kg amphetamine, where the largest output ratios were produced under the RI 120- and 240-sec schedules. Despite these apparent graphic differences in output ratio, analysis of variance did not reveal a significant interaction between either cycle length or interreinforcement interval and Dose of amphetamine ($p>0.05$). At higher doses, amphetamine decreased responding under all RI schedules.

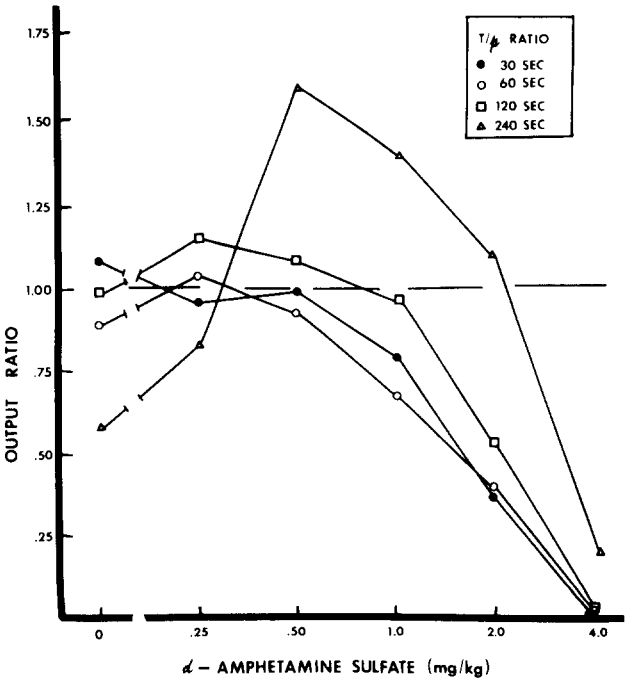

FIG. 2. Mean output ratios for the random-interval schedules using a 3.75-sec cycle length as a function of dose of amphetamine. Critical allowances calculated for each schedule using Dunnett's test were: RI 30-sec, 0.36; RI 60-sec, 0.46; RI 120-sec, 0.56; and RI 240-sec, 1.30. The four dose-effect curves did not differ significantly according to analysis of variance ($p>0.05$).

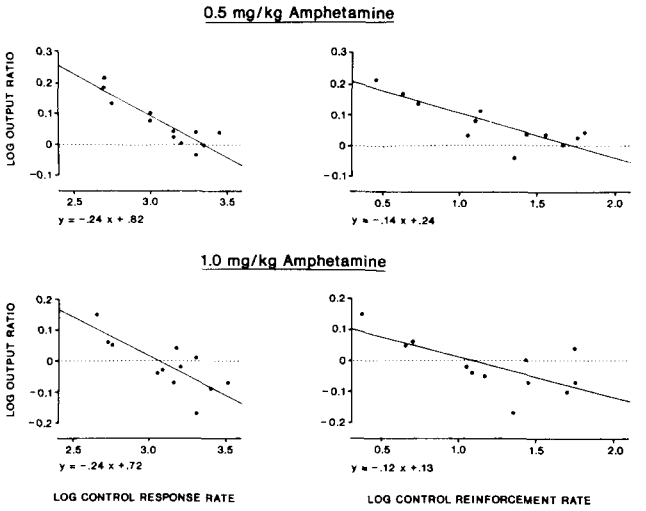

FIG. 3. Response rate-dependency and reinforcement rate-dependency functions for amphetamine's effects on the 12 random-interval schedules at 0.5 and 1.0 mg/kg amphetamine. Abcissa: log transformation of group mean control response rate (responses/session) or control reinforcement rate (reinforcers/session). Control performance was the average on three days prior to administration of the particular dose of amphetamine. Ordinate: log transformation of the group mean output ratio, defined as response rate under drug divided by the control response rate. Best-fitting regression lines and equations were determined by the method of least-squares.

The dose-effect curves for RI schedules using a 3.75 sec cycle length (Fig. 2) reveal a similar pattern of drug effects as a function of Dose, $F(5,95)=14.1$, $p<0.001$. Although the largest increases in output ratio appeared with RI schedules at long interreinforcement intervals, a significant interaction between interreinforcement interval and Dose of amphetamine was not obtained, $F(15,95)=1.38$, $p>0.05$.

Comparison of Control Response Rate and Reinforcement Rate with Amphetamine's Effects

Since RI schedules with long interreinforcement intervals produced the lowest control response rates, the larger amphetamine effects obtained under these schedules would be consistent with the rate dependency hypothesis. However, this pattern of drug effects could also indicate that amphetamine's effects are related to the control reinforcement rate. The 12 RI schedules provided an opportunity to examine and compare amphetamine's effects with both variables.

Conventional response rate-dependent effects of amphetamine were examined by plotting the log mean output ratio versus the log mean control response rate for each of the 12 RI schedules at each dose of amphetamine tested. Pearson correlation coefficients for the rate-dependency functions are given in the left panel of Table 2. Control response rate was significantly and negatively correlated with amphetamine's effects at 0.50 and 1.0 mg/kg (see Fig. 3). At 1.0 mg/kg amphetamine, drug effects were different in both direction and magnitude as a function of control response rate, indicating that the significant correlations were not caused simply by a ceiling effect. A ceiling effect cannot explain why high control response rates would be reduced by the same dose of amphetamine that increased low control response rates [9]. These results are in agreement with expectations based on the rate dependency hypothesis.

The relationship between amphetamine's effects on RI responding and control rate of reinforcement was examined in the same manner as the relationship with control response rate. That is, reinforcement rate-dependency functions were constructed by plotting the log mean output ratio versus the log mean control reinforcement rate obtained during the control sessions prior to administration of each dose of amphetamine. Pearson correlation coefficients for the reinforcement rate-dependency functions are given in the right panel of Table 2. The reinforcement rate-dependency functions are similar to the response rate-dependency functions (see Fig. 3). Control reinforcement rate was significantly correlated with amphetamine's effects at 0.50 and 1.0 mg/kg.

In order to determine which of the two variables, control response rate or control rate of reinforcement, better predicted response changes under amphetamine, partial correlation coefficients were calculated between output ratio and each variable with the effects of the other variable statistically deleted. These data are presented in Table 2 at 0.50 and 1.0 mg/kg amphetamine, the doses where both control response rate and reinforcement rate were significantly correlated with output ratio under amphetamine. The correlation coefficients between control response rate and output ratio were reduced, but still statistically significant, when the effect of rate of reinforcement was partialled out of the relationship, respectively, $r(9)=-.53$ and $-.52$, $p<0.05$. In contrast, the correlation coefficients between control rate of reinforcement and output ratio were reduced to near-zero and nonsignificant levels when the effects of control response rate were partialled out, respectively $r(9)=-.10$ and $+.14$, $p>0.05$. These results indicate that control response rate, not control rate of reinforcement, was the better predictor of drug effects at 0.50 and 1.0 mg/kg amphetamine.

DISCUSSION

The random-interval schedules reduced the strong correlation between rates of responding and reinforcement usually found with conventional reinforcement schedules. Response rates increased nearly two-fold by reducing the cycle length from 15.0 to 7.5 sec under the RI 30-sec schedules, but did not differ significantly between cycle lengths at longer interreinforcement intervals. In comparison to other VI schedules where between 87% to 98% of the variance in response rate could be accounted for by the rate of reinforcement [1,5], only 48% of the variance in response rate for the 12 RI schedules could be accounted for by the rate of reinforcement, although this relationship was still statistically significant, $r(10)=+.69$, $p<0.05$. The effects of varying RI schedule parameters on operant responding have not been examined previously in rats, although they were reported to vary response rates similarly in pigeons [10]. Further characteristics of RI responding in the rat have been described elsewhere [17].

The 12 RI schedules were used to examine and compare amphetamine's effects across a nearly eight-fold range of control response rates and a 28-fold range of control reinforcement rates. It appeared that amphetamine produced larger increases in responding under RI schedules with low control rates of responding and reinforcement, although these effects were not statistically significant. However, when amphetamine's effects were combined across all RI schedules to construct response rate-dependency functions

[9], amphetamine's effects on RI responding were significantly correlated with control rates of responding as predicted by the rate dependency hypothesis. Thus, a similar relationship was found for RI schedules as reported by other prior demonstrations of amphetamine's rate-dependent effects [1, 13, 15]. Recently, Byrd has criticized the use of rate dependency functions to support the rate dependency hypothesis because replotting them shows that response rate under amphetamine is independent of control response rate [2,11]. However, others have argued that Byrd's observations are not contradictory to the rate dependency hypothesis and that Byrd's suggestions do not reflect the most useful method for measuring changes in behavior produced by drugs [20].

On the basis of the usual association between rates of responding and reinforcement under most operant behavior schedules [28], the presence of a similar relationship between amphetamine's effects and control reinforcement rates could also be expected. Although the correlation between response rate and reinforcement rate was reduced by the RI schedules, the reinforcement rate-dependency functions indicated that amphetamine's effects on RI responding could also be predicted from the reinforcement frequencies during control sessions.

Partial correlation coefficients were used to assess the relative value of each variable, control response rate and reinforcement rate, in predicting amphetamine's effects with the effect of the other variable statistically deleted from the relationship. Control rate of responding remained significantly correlated with amphetamine's effects when the correlation between reinforcement rate and amphetamine's effects was removed. In marked contrast, removing the correlation between response rate and amphetamine's effects reduced the correlation between control reinforcement rate and amphetamine's effects to near-zero and nonsignificant levels. Thus, correlational methods revealed that control rates of responding were decisively favored in predicting amphetamine's effects, in agreement with the rate dependency hypothesis.

The support for the rate dependency hypothesis provided by the present study agrees with other comparisons of response rate and reinforcement rate as possible determinants of amphetamine's effects on operant behavior that used other methods to equate rates of responding and reinforcement. MacPhail and Gollub [19] and Sanger and Blackman [24] compared amphetamine's effects between VI schedules that employed different pacing requirements (a tandem VI DRL schedule) to equate reinforcement frequencies in rats and pigeons. Also, multiple schedules have been used to vary rates of responding at a similar reinforcement frequency in the same subject by using a yoked reinforcement procedure [18]. In all three studies, amphetamine differentially altered responding between schedules in precisely the manner predicted by the rate dependency hypothesis [18, 20, 24]. By comparison, amphetamine did not alter responding differentially between components of a multiple random-ratio schedule with similar control rates of responding but at different rates of reinforcement [18].

In summary, the effects of varying RI schedule parameters were shown to reduce the usual strong association between rates of responding and reinforcement in rats. Subsequently, RI schedules were used to examine whether control rates of responding or reinforcement better predicted the behavioral effects of amphetamine. Control rate of responding proved to be the better predictor of amphetamine's effects, corroborating the special relationship between the effects of amphetamine and control rates of responding emphasized by the rate dependency hypothesis. Even though variations in reinforcement rate appear to be related to amphetamine's effects, reinforcement rate may only influence amphetamine's actions indirectly by altering the control rate of responding.

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