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# Reward Summation and the Effects of Pimozide, Clonidine, and Amphetamine on Fixed-Interval Responding for Brain Stimulation

GLENN E. HUNT*†[1] AND DALE M. ATRENS‡

*Departments of *Psychiatry, †Pharmacology, and ‡Psychology, University of Sydney, Sydney, New South Wales, Australia*

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HUNT, G. E. AND D. M. ATRENS. *Reward summation and the effects of pimozide, clonidine, and amphetamine on fixed-interval responding for brain stimulation.* PHARMACOL BIOCHEM BEHAV 42(4) 563-577, 1992.—Two models of reward summation were examined in 16 rats lever pressing for intracranial stimulation under fixed-interval (FI) reinforcement. The first model examined rate-frequency functions and the second model traded off frequency and train duration. The second model was selected to assess the effects of three drugs on reward summation. Both clonidine and pimozide inhibited FI self-stimulation, but pimozide's effect could not be distinguished from a performance deficit. Two amphetamine isomers facilitated self-stimulation in a manner suggesting enhanced reinforcement. The dextro isomer was four times more effective than the levo isomer to facilitate self-stimulation. This study shows that the combination of the FI schedule with a reward-summation model is well suited for evaluating the effects of drugs on self-stimulation. The advantages of this model are that interreinforcement intervals are separated, which minimizes priming and stimulation aftereffects, and more responding does not increase stimulation availability, thus eliminating rate-dependency effects.

Self-stimulation Fixed-interval Reward summation Pimozide Clonidine Amphetamine Lateral hypothalamus

SOON after the discovery of self-stimulation (56), the first reports appeared using self-stimulation as a model for screening tranquilizer drugs (55, 57). Over the next two decades, a multitude of studies led to the development of the catecholamine hypothesis of reward (33). Briefly, drugs that increased the availability of catecholamines facilitated self-stimulation, whereas drugs that decreased the availability of catecholamines attenuated self-stimulation (19,33,70). Although these drugs alter self-stimulation, there is still disagreement whether these effects are due to changes in the rewarding properties of brain stimulation or other factors such as altering performance (3,19,46,70,74). One of the reasons for this uncertainty is that most of the studies used rate of lever pressing under continuous reinforcement (CRF) and this schedule does not discriminate between reward and performance effects (46,66).

The effect of a drug can be evaluated over a range of responding using brain stimulation because the experimenter can control the stimulation parameters (current, frequency, and train duration) that formulate the reinforcement (16,20, 24,26,31). Plotting the behavioral output for a given level of stimulus input results in a reward-summation function (65). It is claimed this procedure can dissociate changes in the rewarding value of the stimulus from other effects that can alter performance (15,21). However, this paradigm still relies on an uncontaminated response measure to quantify changes in reinforcement magnitude (46,66).

It is well documented that the behavior sustained by brain stimulation relies on other factors beside the rewarding value of the stimulation (16,24-26,31,47,51). These factors include the reinforcement schedule, recency of the previous reinforcement (priming effect), and amount of the stimulation (24). In addition, if the reinforcement effect persists it would obviate the need to respond for a finite period (stimulation aftereffects) (66). Using a reward-summation paradigm under CRF does not solve the intrinsic problems with CRF because higher rates increase the number of reinforcements per unit of time. This means that there is a greater contribution in responding from priming and stimulation aftereffects at the

[1] Requests for reprints should be addressed to Glenn Hunt, University of Sydney Clinical Sciences Block, Department of Psychiatry, Concord Hospital, Concord, New South Wales 2139, Australia.

upper end of the curve, where the interreinforcement interval is short, compared to the lower end, where the interreinforcement interval is long.

Many of difficulties associated with using rate measures under CRF are due to the reinforcements being delivered in close temporal proximity (66). One obvious way to avoid this problem is to separate the interreinforcement intervals and ensure that more responding does not increase stimulation density. The fixed-interval (FI) schedule used in the present experiments is well suited for testing the effects of drugs because, unlike CRF, more vigorous responding does not increase stimulation availability. In addition, operant responding under an FI schedule concurrently provides a number of performance measures that can be used to assess changes in reinforcement (12,40,44). By themselves, partial reinforcement schedules may improve the detection of drug effects because intermittently presented reinforcement may provide a lower level of motivation by requiring greater effort for each stimulus (44). Thus, under these schedules subtle drug effects may become more prominent because lower doses may have a more pronounced effect (12).

The first experiment in this study investigated reward-summation functions under FI reinforcement to develop a model for studying the effects of drugs on self-stimulation. The second experiment investigated the effects of a number of drugs on reward summation that have been implicated in modulating self-stimulation. Clonidine and pimozide were chosen to investigate the ability of the model to measure response inhibition after disruption of adrenergic and dopaminergic neurotransmission, respectively. Amphetamine was chosen to test the ability of the model to measure response facilitation. Moreover, *d*- and *l*-amphetamine were given separately to evaluate potency differences between the two isomers. This study demonstrates the sensitivity of combining a reward-summation model with an FI reinforcement schedule to detect drug effects on self-stimulation.

## EXPERIMENT 1

The temporal summation characteristics of brain stimulation have been examined in a runway paradigm using trade-off functions between current, frequency, and train duration (15,16,24-26,30,31). This model was an advance over previous reward-summation studies because the effects of priming and reward could be independently studied. In one of these studies (15), a number of performance-inhibiting factors decreased the maximal running speed, but did not affect the locus of the sharp rise thought to reflect changes in reward magnitude. Thus, it was concluded that performance variables affected maximal running speed, but did not affect the locus of the sharp rise. This conclusion has not been supported in a lever-press task where performance variables affected maximal performance, as well as producing moderate lateral shifts in the reward-summation function (51). However, this study had serious limitations because priming effects were not controlled in the operant task under CRF (51). The present study examines reward-summation functions in an operant chamber using FI reinforcement. The advantages of using this combination are that priming effects and stimulation aftereffects are controlled because increased responding does not increase stimulation availability. In addition, this procedure has an advantage over the runway paradigm because most self-stimulation studies use an operant chamber, thus allowing a more direct comparison between studies.

Experiment 1 examined temporal summation of positive reinforcement under FI reinforcement using two models. The first part investigated the effect of frequency manipulations when train duration remained constant. The second part investigated the effect of train duration under various stimulation frequencies. The second part was designed to test two hypotheses of reward summation: the constant-charge hypothesis (68) and the leaky integrator hypothesis (25). The constant-charge hypothesis would predict that delivery of fixed numbers of pulses would produce equivalent effects on responding regardless of their frequency. In contrast, the leaky integrator hypothesis would predict that behavioral output is dependent upon relative charge and train duration. Two groups of rats were used to test both of the models. One group received 60 reinforcements (trials) per condition and the other group 25 reinforcements. The importance of the number of trials was examined so that the length of the experimental session could be kept to a minimum in subsequent drug studies.

### METHOD

#### *Subjects*

Subjects were 16 male Wistar rats implanted with monopolar electrodes aimed at the lateral hypothalamic component of the medial forebrain bundle. Rats were screened in the shuttle-box and trained to lever press for FI 20-s brain stimulation as described previously (40). Most of these rats were also used in Experiment 2 prior to histology. At the conclusion of all testing, rats were sacrificed and electrode placements were verified as previously described (40).

#### *Procedure*

*Part A.* Five frequencies (0, 33, 50, 66, and 100 Hz) were tested under an FI 20-s schedule. The 0 pulse condition was tested with the stimulator turned off to examine extinction. Each reinforcement consisted of 1-s trains of monophasic (cathodal) brain stimulation. Pulse width (200 $\mu$s) and currents (individually determined, range 150-300 $\mu$A) were held constant during the experiment. All rats received all five frequencies on the same day in randomized order. Eight rats received 60 trials (10 warm-up) for each frequency condition and the other rats received 25 trials (5 warm-up) per condition. The data from the warm-up trials were not used in the analysis. The apparatus was programmed so that in the event of a rat not pressing the lever within 60 s the stimulation was automatically delivered. If the rat did not complete 25 reinforcements for a condition within 20 min, the experiment was stopped, the data were saved for subsequent analysis, and the next block of trials using different stimulation parameters was commenced.

*Part B.* Train duration was varied so that rats received 20, 50, or 100 pulses per reinforcement at 50, 100, and 200 Hz. The three train durations that produced 20, 50, and 100 pulses for 50 Hz were 0.4, 1.0, and 2.0 sec; for 100 Hz the train durations were 0.2, 0.5, and 1.0 s; and for 200 Hz the train durations were 0.1, 0.25, and 0.5 s. An additional condition of 0.1-s stimulation at 100 Hz was also given for graphing the reward-summation curve using 100-Hz frequency. All other conditions were the same as in Part A except that the nine randomized tests were conducted over 2-3 days.

#### *Analysis*

In Part A, the data were subject to a one-way analysis of variance (ANOVA) with repeated measures on frequency. In Part B, the data were subject to a two-way ANOVA with

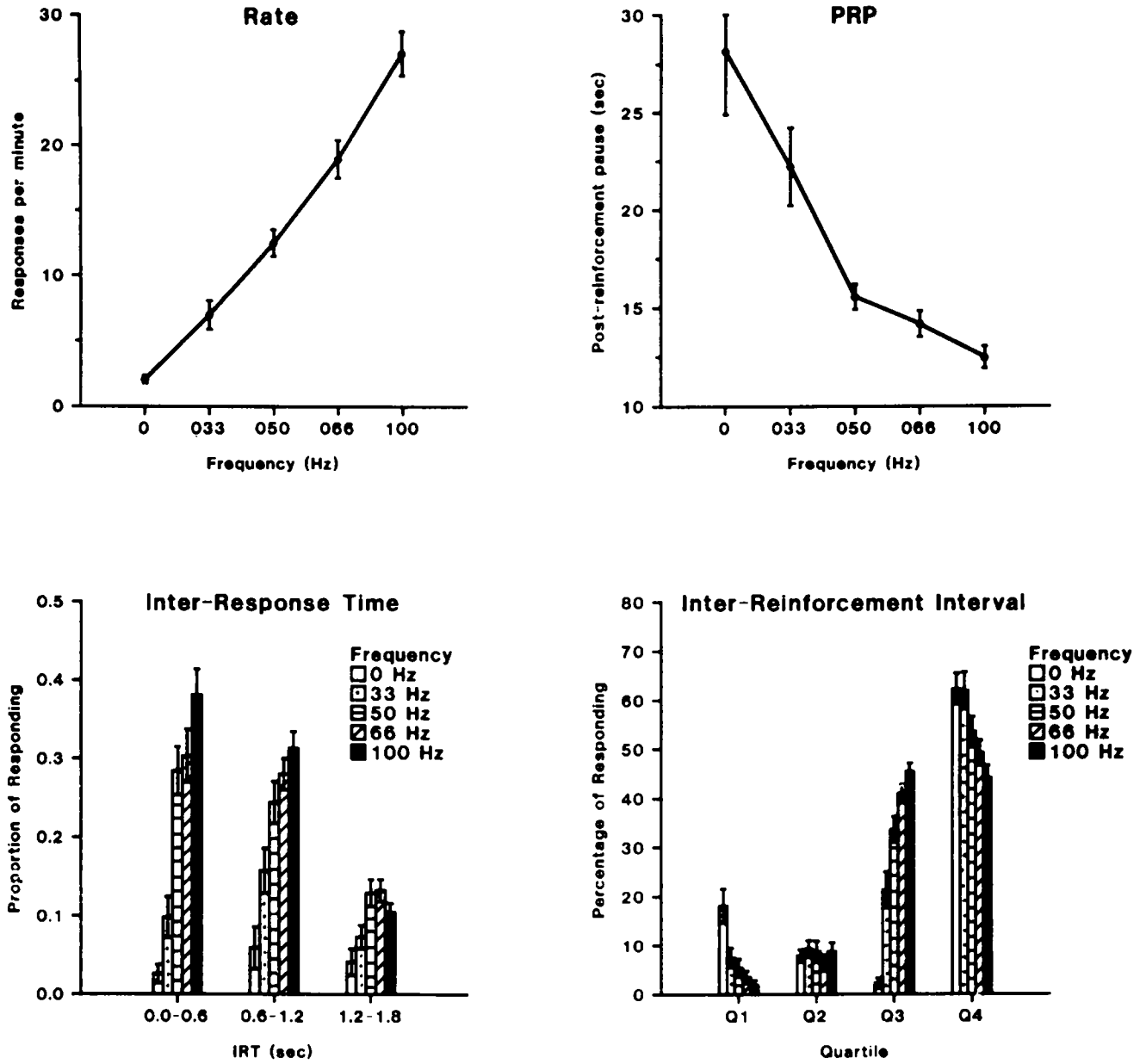


FIG. 1. Effect of increasing stimulation frequency on operant responding for 1-s trains of brain stimulation under a FI 20-s reinforcement schedule. The four panels represent different aspects of FI performance: response rate (top left panel), the postreinforcement pause (top right panel), interresponse times between successive lever presses (lower left panel), and the proportion of responding in each quartile of the interreinforcement interval (lower right panel). Vertical bars indicate 1 SEM ($n$ = 16).

repeated measures on both factors. The two factors were frequency (50, 100, and 200 Hz) and pulses per reinforcement (20, 50, and 100 pulses). Posthoc comparisons using the Newman-Keuls procedure were made only after significant differences were indicated by ANOVA. The FI measures used for analysis were: lever-press rate (responses per minute), postreinforcement pause (expressed in s), the proportion of interresponse times (IRTs) between 0 and 1.8 s, and percentage of responding in each quartile of the interreinforcement interval. The IRTs between 0 and 1.8 s were subdivided into three 0.6-s bins to determine the proportion of responding between successive lever presses. Each FI measure was analyzed separately. In Part A, a factor analysis with principal components extraction and Varimax rotation was performed using stimulation frequency and the FI measures as dependent variables (54). In Part B, the data from the 100-Hz stimulation conditions using three train durations (0.2, 0.5, and 1.0 s) and the extinction data (0 pulses) were subject to a factor analysis.

## RESULTS

### *Part A*

Since there was no indication that numbers of experimental trials (50 vs. 20) affected the reward-summation curves, the data were pooled for the two groups. The results presented in

Fig. 1 (upper left panel) illustrate the effect of frequency on rate of FI 20-s responding when train duration was fixed (1 s). There was a significant difference in response rates between stimulation frequencies, $F(4,60) = 91.39$, $p < 0.001$. Posthoc contrasts revealed each frequency step produced a significant ($p < 0.05$) increment in mean response rate. The reward-summation function was linear between 33 and 100 pulses per reinforcement and the point at which 50% of maximal response rate occurred was between 50 and 66 Hz (Fig. 1, upper left panel).

The other panels in Fig. 1 show that as stimulation frequency was increased the temporal patterning of FI responding also changed. Three response measures increased with higher-frequency stimulation: the percentage of responding in the third quartile of the interreinforcement interval, $F = 62.27$, $p < 0.001$ (lower right panel) and the proportion of responding in the first, $F = 39.00$, $p < 0.001$, and second IRT bins, $F = 24.68$, $p < 0.001$ (lower left panel). Conversely, three response measures decreased with increasing levels of frequency: the postreinforcement pause, $F = 16.91$, $p < 0.001$ (upper right panel) and the proportion of responding in the first, $F = 11.48$, $p < 0.001$, and fourth quartiles, $F = 7.12$, $p < 0.001$, of the interreinforcement interval.

A factor analysis was performed using stimulation frequency and the FI response measures as dependent variables. The correlation matrix prior to rotation indicated high correlations between stimulation frequency and a number of performance variables. The first factor explained 58.1% of the variance and the second factor explained 16% of the variance. The territorial map of Factors 1 and 2 after rotation is presented in Fig. 2. The cluster of variables on the right side of the $X$ axis indicates IRT bin 1; response rate and responding in the third quartile are positively correlated to stimulation frequency. Responding in the first quartile was negatively correlated to these variables and appears on the left side of the $X$ axis. The second factor had the highest loading from bin 3, which appears on top of the $Y$ axis, and a negative loading from the postreinforcement pause, which appears toward the bottom of the $Y$ axis.

*Part B*

The data presented in Fig. 3 illustrate the effects of train duration and frequency on FI self-stimulation. The conditions were selected to deliver three blocks of pulses (20, 50, and 100) at three frequencies (50, 100, and 200 Hz). There was no indication that numbers of experimental trials (50 vs. 20) affected the reward-summation curves so the data were pooled prior to analysis. The two-way ANOVA with repeated measures indicated significant differences between response rates and levels of frequency, $F(2,30) = 37.92$, $p < 0.001$, and the number of pulses, $F = 66.72$, $p < 0.001$. Posthoc tests revealed response rates for 50-Hz stimulation were less than that for 100- or 200-Hz stimulation even though train durations were adjusted to deliver the same numbers of pulses per reinforcement (upper left panel, Fig. 3). The interaction term between frequency and number of pulses per reinforcement was not significantly different, indicating the three lines have similar slopes.

Other panels in Fig. 3 show the changes in temporal patterning of FI responding. The most vigorous responding represented by the proportion in IRT bin 1 (0.0–0.6 s) increased as a function of stimulation frequency, $F = 15.53$, $p < 0.001$, and pulses per reinforcement, $F = 37.00$, $p < 0.001$ (lower left panel). Similar increases were observed in the proportion of responding in the third quartile of the interreinforcement interval (lower right panel). In contrast, the postreinforcement pause was inversely related to these measures and it was higher for 50-Hz stimulation than for 100- or 200-Hz stimulation (upper right panel). The factor analysis of all the

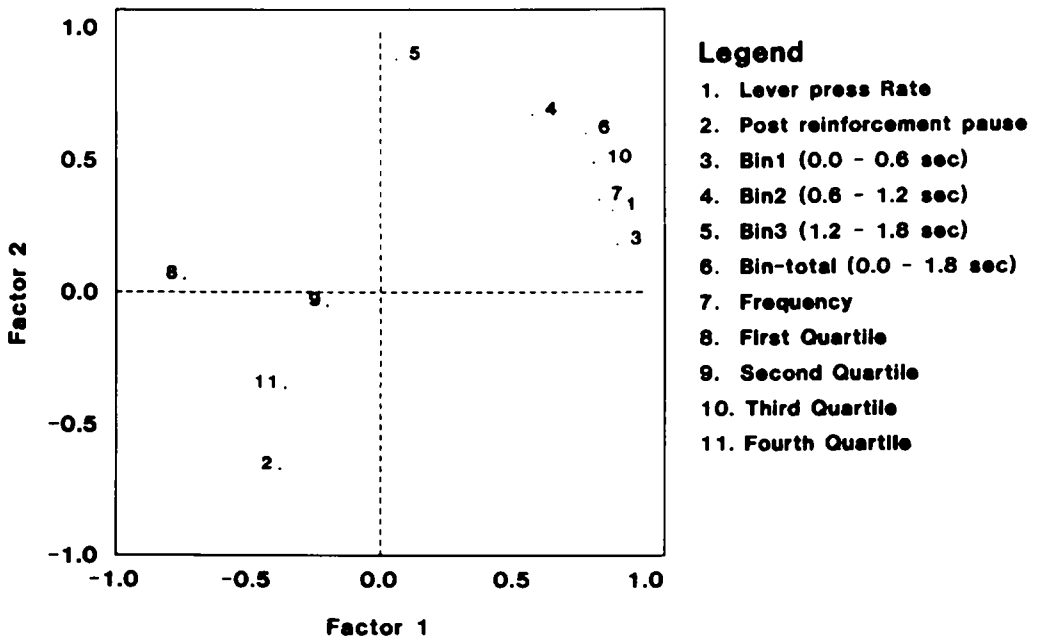


FIG. 2. Results from the factor analysis of FI responding for different stimulation frequencies (0, 33, 50, 66, and 100 Hz). The coordinates of the territorial map correspond to the factor loadings for the Varimax-rotated solution. Variable names are represented by numerals indicated in the legend (see the text for definition of these variables).

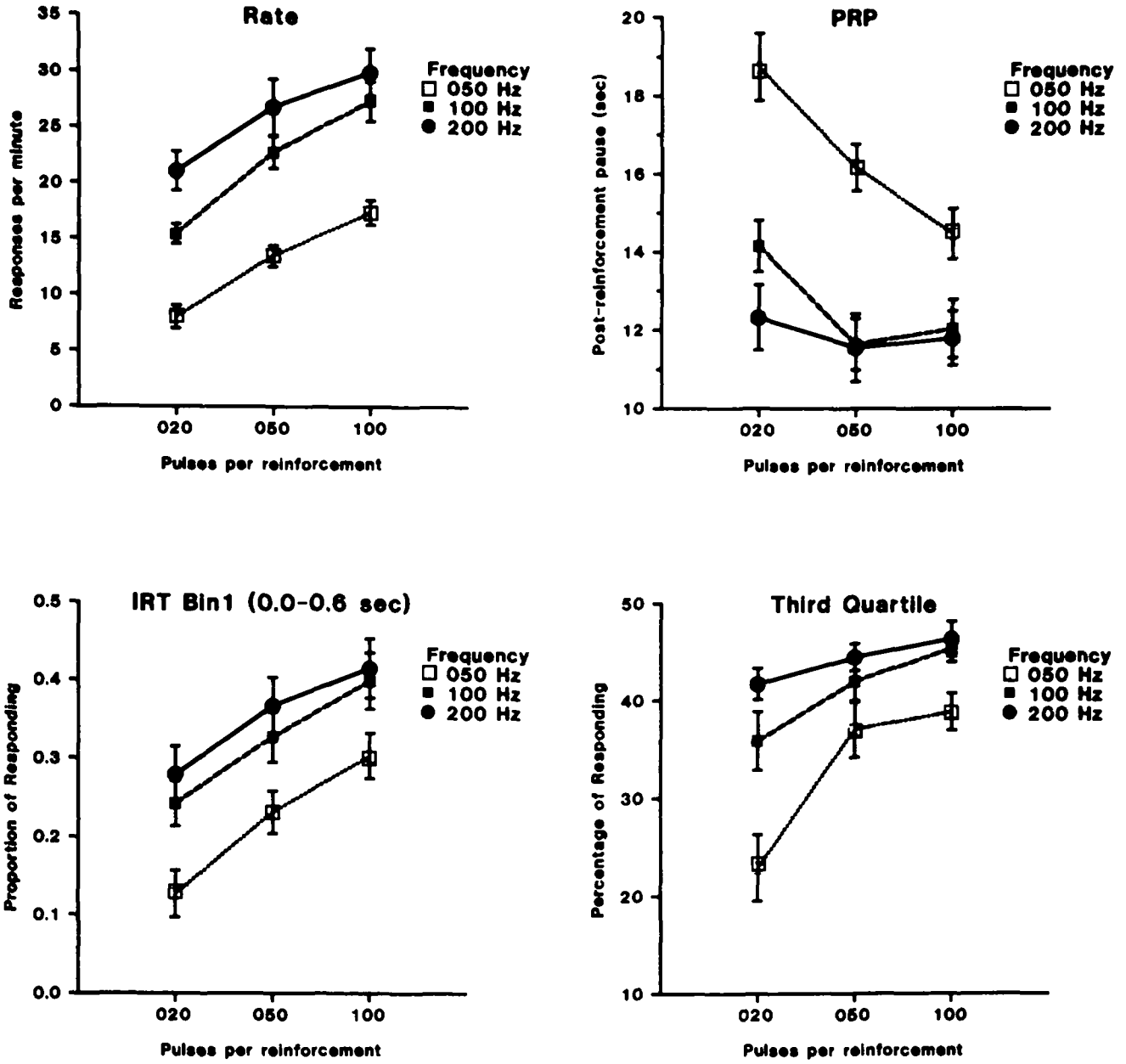


FIG. 3. Effect of trading off train duration and frequency on operant responding for brain stimulation under Fl 20-s reinforcement. Train durations were chosen to deliver 20, 50, and 100 pulses at 50, 100, and 200 Hz. Each panel represents a different aspect of Fl performance. Vertical bars indicate 1 SEM ($n$ = 16).

performance indices using various train durations (0, 0.2, 0.5, and 1.0 s) at 100 Hz was practically identical as that in the first part and so the data are not shown.

*Comparing Reward-Summation Functions*

Two reward-summation functions are plotted in Fig. 4. One curve was derived from Part A using a fixed-train duration (1 s, line A) and varying frequency and the other curve was derived from Part B using a fixed-frequency (100 Hz, line B) and varying-train duration. The number of pulses required to produce 50% of maximal responding was lower for line B (1.3 log pulses) than for line A (1.75 log pulses). The slope of line A between 33 and 100 pulses was steeper ($\beta$ = 0.30, constant = −2.42) than the slope of line B between 10 and 100 pulses ($\beta$ = 0.20, constant = 9.36).

*Histology*

All 16 electrode tips were located in the medial forebrain bundle except for one rat, whose electrode was placed near the dorsomedial hypothalamus.

## DISCUSSION

The results from Part A indicate that as stimulation frequency was increased this produced higher response rates. Not only did the overall response rate increase over the reward-

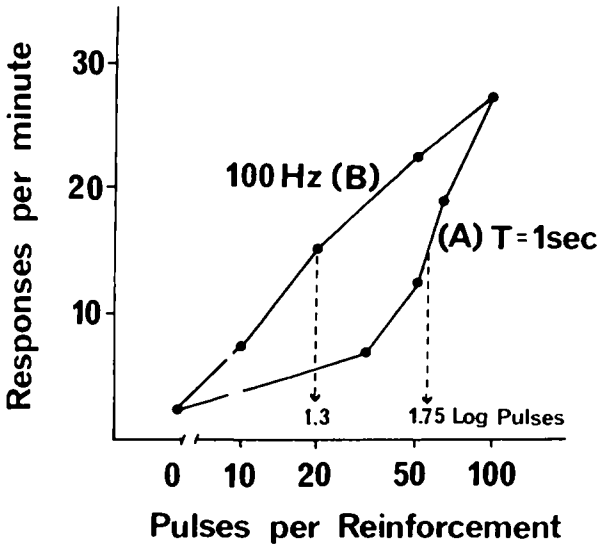


FIG. 4. Reward-summation functions using (A) fixed train duration (1 s) and varying frequency and (B) using fixed frequency (100 Hz) and varying train duration. The broken lines indicate the number of (log) pulses required to maintain half-maximal response rates.

summation curve, but other FI measures mirrored this effect. Two performance indices were highly correlated with rate: the responding in the first IRT bin (0.0–0.6 s) and responding in the third quartile of the interreinforcement interval. The factor analysis shows that certain performance indices can be used interchangeably with lever-press rate to measure changes in reinforcement magnitude. The advantage of using more than one variable to measure changes in the reward-summation function becomes more important when testing the effects of drugs because these variables may be more sensitive to drug effects.

The second part of this experiment traded off frequency with train duration and showed that reductions in performance produced by halving stimulation frequency from 200 to 100 Hz can be compensated by doubling the train duration. However, with greater shifts in frequency from 200 to 50 Hz responding for 50-Hz stimulation never reached the levels obtained with 200 Hz in the range of values tested. Thus, even though equivalent numbers of pulses were delivered per reinforcement, self-stimulation was dependent upon stimulus frequency and not on the overall pulse number. These results argue against the summation hypothesis, which ignores relative charge of the stimulation (68), and are consistent with the leaky integrator hypothesis (25).

According to the hypothesis proposed by Gallistel (25), the neural substrate for the rewarding effect of brain stimulation involves a synaptic network that behaves as a leaky integrator (25). The longer it takes to fill the integrator, the less rewarding the stimulation. Therefore, low-frequency stimulation, no matter how long it is delivered, will not be as rewarding as high-frequency stimulation because the integrator never fills due to exponential decay. A good example of this decay is shown in Fig. 4 comparing two reward-summation models. The slope is steeper when frequency was varied and train duration was fixed (Fig. 4, line A) compared to responding when train duration was varied and frequency (100 Hz) was fixed (Fig. 4, line B). The summation characteristics suggest a more accurate summing over time with short bursts of high-frequency (100 Hz) stimulation compared to longer bursts of low-frequency (33–50 Hz) stimulation.

Both the reward-summation models investigated in the present study are superior to testing the effects of a drug on only one point of the input-output curve. Drugs that increase or decrease positive reinforcement should produce lateral shifts in the reward-summation curve with either of these models (47,65,67).

However, trading off a number of frequencies against train durations appears to be a better way to test the effects of drugs than univariant models (27–30). There are four main advantages of the trade-off model. The same stimulation frequencies are used in both baseline and drug conditions. The experimental sessions are of the same duration and each block of trials can be presented in the same order under all conditions. The change in reward summation is not dependent upon maximal performance since it is the relationship between the slopes over a range of pulses or frequencies that measure changes in the reinforcing value of the stimulus. Standard reward-summation curves can be derived over a range of train durations (e.g., 0.2, 0.5, and 1.0 s) instead of a single arbitrarily selected duration.

One of the problems of testing the effects of drugs on reward summation is that the test session may be longer than the duration of the drug effect. In the present study, there were no significant differences between the reward-summation curves for rats that received 25 or 60 trials per condition. Accordingly, the length of the experimental sessions in Experiment 2 was kept to minimum by testing each stimulation condition for 30 trials under the FI 20-s reinforcement schedule.

## EXPERIMENT 2

The reward-summation paradigm described in Part B of Experiment 1 was used in this experiment to test drugs consistently reported to increase (amphetamine) and decrease (pimozide and clonidine) lateral hypothalamic self-stimulation. Amphetamine was chosen to test the ability of the model to measure response facilitation because it is one of the few drugs consistently shown to facilitate self-stimulation after low doses (4,13,17,33,41,62). However, high doses of amphetamine decrease self-stimulation (5,73), possibly due to stereotyped behavior interfering with responding (20), the occurrence of hyperthermia (7), or activation of the receptors and rendering the operant behavior superfluous (3,74). The mechanism of amphetamine's facilitation of self-stimulation is unknown because it has a complex mode of action (52). Early reports using *d*- and *l*-amphetamine showed that *d*-amphetamine was several times more potent than *l*-amphetamine in facilitating self-stimulation of the lateral hypothalamus (5, 23,34,59). However, many of the procedures used to test the effects of amphetamine did not control for the rate-dependency effects of amphetamine (61). As previously mentioned, the FI schedule that controls reinforcement availability is ideal to test the effects of amphetamine because more vigorous responding does not increase the interreinforcement interval.

While the effects of amphetamine on FI responding reinforced by food and water are well documented (1,14,38,49), very few studies have investigated the effects of amphetamine on FI self-stimulation. Two studies reported that *d*-amphetamine (1 mg/kg) increased response rates under FI reinforcement, but they did not analyze other performance indices such as interresponse times or the effects on the characteristic FI scallop (36,63). Without such a microanalysis, it is not clear whether the drug enhancement represents an increase in rein-

forcement or a compulsive motor pattern. One early study reported amphetamine (1 mg/kg) increased overall self-stimulation, as well as responding within each 15-s portion of a FI 60-s schedule (8). However, no studies have investigated the effects of amphetamine in a reward-summation model under FI reinforcement.

A wide variety of dopamine antagonists decrease self-stimulation. These range from relatively nonspecific antagonists such as chlorpromazine (57) to more specific dopamine antagonists such as pimozide (27,29,35,43,64,72), haloperidol (72), and spiroperidol (70,71). However, it has been difficult to dissociate the effects of dopamine blockade on the reinforcing properties of self-stimulation from the motor dysfunctions commonly produced by altered dopamine transmission (3,19, 46,75).

Low doses of pimozide (0.1–0.3 mg/kg) have a greater impact on shifting the reward-summation function than on depressing maximum running speed in a runway model (21, 27,29). In addition, pimozide blocks reward without altering the priming effect from lateral hypothalamic stimulation in the runway (69). These studies using the runway paradigm suggest that the inhibition of self-stimulation produced by pimozide is primarily due to reductions in the rewarding value of the stimulation. In the operant chamber, low doses of pimozide (0.1–0.3 mg/kg) produced large shifts in the reward-summation function, suggesting it reduces the rewarding value of the stimulation while only marginally decreasing asymptotic CRF rates (28,51). The use of CRF rate to determine reward-summation functions contain serious limitations that include the inability to separate reward from priming effects and the development of fatigue due to the high rates emitted over the session (28,51). Using FI reinforcement with a reward-summation paradigm does not contain these limitations because stimulation availability is controlled and the lower response rates (and prolonged pauses) avoid the development of fatigue. A previous study that used FI 60-s reinforcement showed that pimozide decreased self-stimulation but the disruption of behavior was not identical to an extinction-like pattern (35). However, this study did not investigate the effects of pimozide on reward summation (35).

Clonidine, an $\alpha_2$-adrenoceptor agonist, has consistently been shown to decrease self-stimulation using a number of tasks and procedures (22,32,39,41,42,48,71). Previous studies showed that clonidine, like pimozide, shifts the reward-summation curve to the right (21,28). That is, higher frequencies or longer durations are required to attain the same level of performance after clonidine. However, like the dopamine antagonists, clonidine produces a wide variety of behavioral effects that may interfere with responding (45). In the present study, the same rats were given pimozide and clonidine so that their effects on self-stimulation could be more easily compared.

## METHOD

### *Subjects*

Twelve of the rats from Experiment 1 and 2 naive rats were implanted with monopolar electrodes, screened in a shuttlebox, and trained to lever press for FI 20-s brain stimulation.

### *Procedure*

Rats were tested twice weekly using the reward-summation model described in Part B of Experiment 1. The first test session for each week was used to check for baseline stability and the second test session for drug effects. Each session consisted of blocks of trials (reinforcements) in which the duration of the stimulation was adjusted to deliver 20, 50, or 100 pulses per reinforcement at frequencies of 100 and 200 Hz (pimozide and clonidine) or 50 and 100 Hz (*d*- and *l*-amphetamine). An extra block of trials was added to the amphetamine testing (100 Hz at 0.1 s), as well as a block of extinction trials in which the stimulators were turned off. The first 10 trials of each 30-trial block were considered warm-up trials and not included in the analysis. The blocks of trials were arranged so that rats received either frequency in ascending or descending order of pulse number followed immediately by ascending or descending pulses of the other frequency. Every 3 weeks, the order of presentation was changed for each rat and counterbalanced for drug effects. If the rat did not complete 30 reinforcements for a condition within 20 min, the experiment was stopped, the data were saved for subsequent analysis, and the next block of trials using different stimulation parameters was commenced.

### *Drugs*

All drugs were injected IP at volume of 1 ml/kg body weight and spaced 1 week apart. All doses refer to the salt.

Five rats received pimozide (0.125 and 0.250 mg/kg), clonidine (0.025, 0.050, and 0.100 mg/kg), and their respective vehicle controls (1 mg/kg tartaric acid and saline). The doses were selected from previous studies using pimozide (64) and clonidine (41,42). The doses were presented in a random order. Pimozide (Janssen Pharmaceutica, Beerse, Belgium) was dissolved in 1 mg/ml tartaric acid. The doses were injected 3.5 h prior to testing (peak effects 3–8 h) (2,43). Clonidine HCl (Boehringer Ingelheim, Sydney, Australia) was dissolved in saline and injected 15 min prior to testing (peak effects 15 min–3 h) (58).

Nine rats were given three doses of *d*-amphetamine (0.25, 0.50, and 1.0 mg/kg) and three doses of *l*-amphetamine (1.0, 2.0, and 4.0 mg/kg). The doses were selected from previous studies using *d*- and *l*-amphetamine (4,23,41). The treatments were presented in a random order. Saline was used as a vehicle control. *d*-Amphetamine sulfate (Faulding, Adelaide, Australia) and *l*-amphetamine sulfate (Smith Kline & French, Sydney, Australia) were dissolved in saline and injected 20 min prior to testing. This interval was selected on the basis of demonstrations that the peak effects of *d*-amphetamine occur 15 min–2 h postinjection (11).

### *Analysis*

The data were analyzed using a three-factor ANOVA with repeated measures on all factors. The three factors were treatment (vehicle and dose level), frequency (two levels), and number of pulses per reinforcement (20, 50, and 100). The data for each drug were analyzed separately. During amphetamine testing, the blocks of extinction trials were not included in the ANOVA and were used for graphing reward-summation functions.

FI response measures were the same as in Experiment 1. The dose required to reduce lever-press responding by 50% from vehicle was calculated by averaging the rates over all conditions of frequency and number of pulses per reinforcement.

## RESULTS

### *Pimozide and Clonidine*

The first part of the results focuses on the overall treatment effects of pimozide and clonidine and the second part on re-

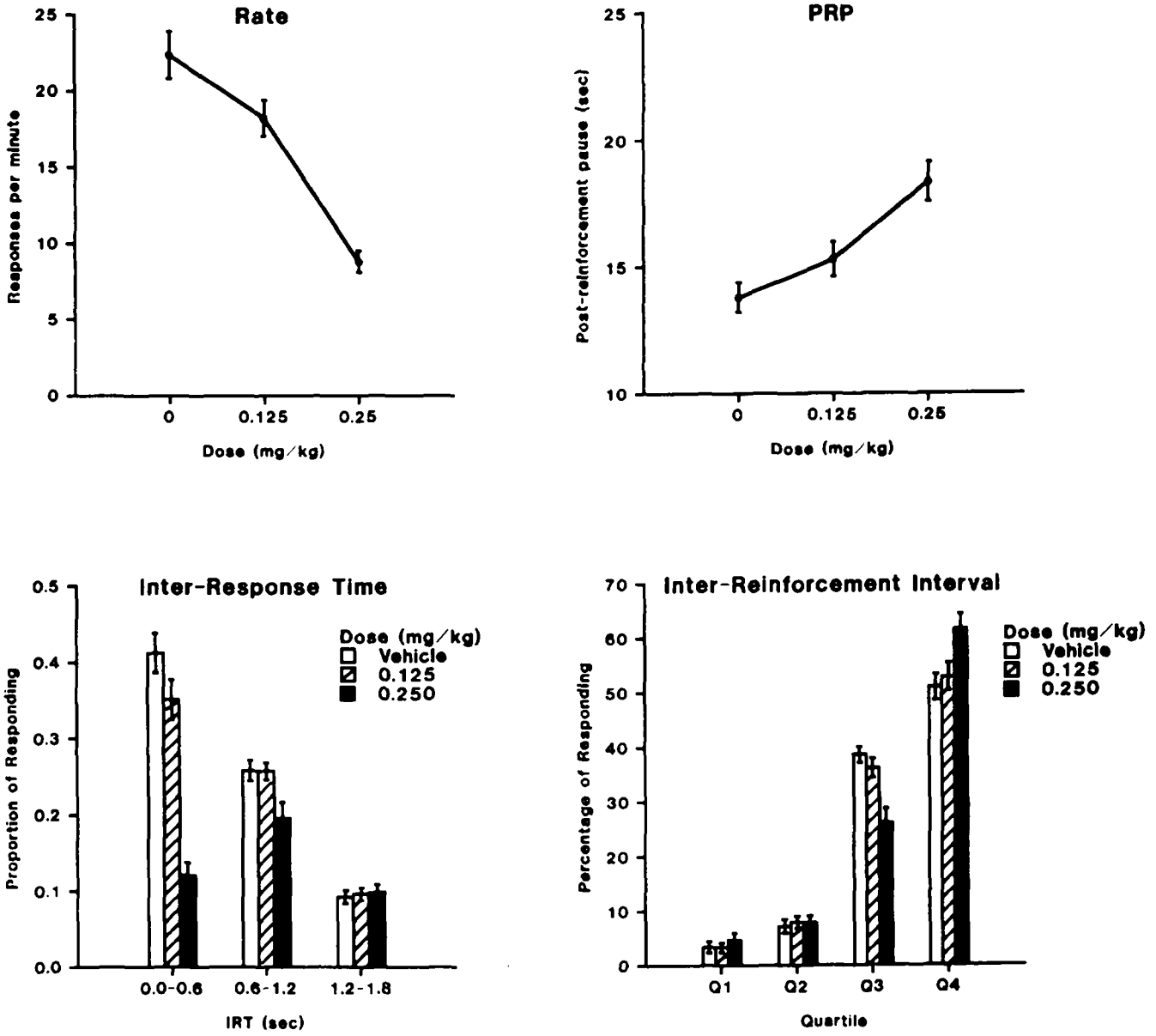


FIG. 5. Effect of pimozide on FI 20-s self-stimulation. Tartaric acid was used as vehicle control (0 dose). The four panels illustrate different aspects of FI performance as described in Fig. 1. Values for each treatment are averaged over the reward-summation curve (see Fig.7) to illustrate dose-response functions on the various performance indices. Vertical bars represent 1 SEM ($n$ = 5).

ward summation. The effects of pimozide and clonidine on all performance indices are shown in Figs. 5 and 6. Values were averaged over six blocks of trials in which train duration was adjusted to deliver 20, 50, or 100 pulses per reinforcement at 100 and 200 Hz. Both pimozide and clonidine decreased response rates under FI reinforcement ($p < 0.001$), but the dose-response curves differed between the two drugs. The dose-response curve for pimozide was very steep (between 0.125-0.250 mg/kg) (Fig. 5, upper left panel). In contrast, the dose-response curve for clonidine was gradual over all three doses (Fig. 6, upper left panel). The effective dose to reduce baseline responding by 50% was 0.050 mg/kg for clonidine and 0.200 mg/kg pimozide.

The postreinforcement pause was dose dependently increased by both drugs ($p < 0.05$) (Figs. 5 and 6, upper right panels).

The change in IRTs at the shorter intervals (0.0-0.6 s) mirrored the changes in rate of responding (Figs. 5 and 6, lower left panels). As observed with rate of responding, the decreased IRTs in bin 1 reflected a steep dose-response curve after pimozide compared to clonidine. Neither clonidine nor pimozide affected responding in the third IRT bin (1.2-1.8

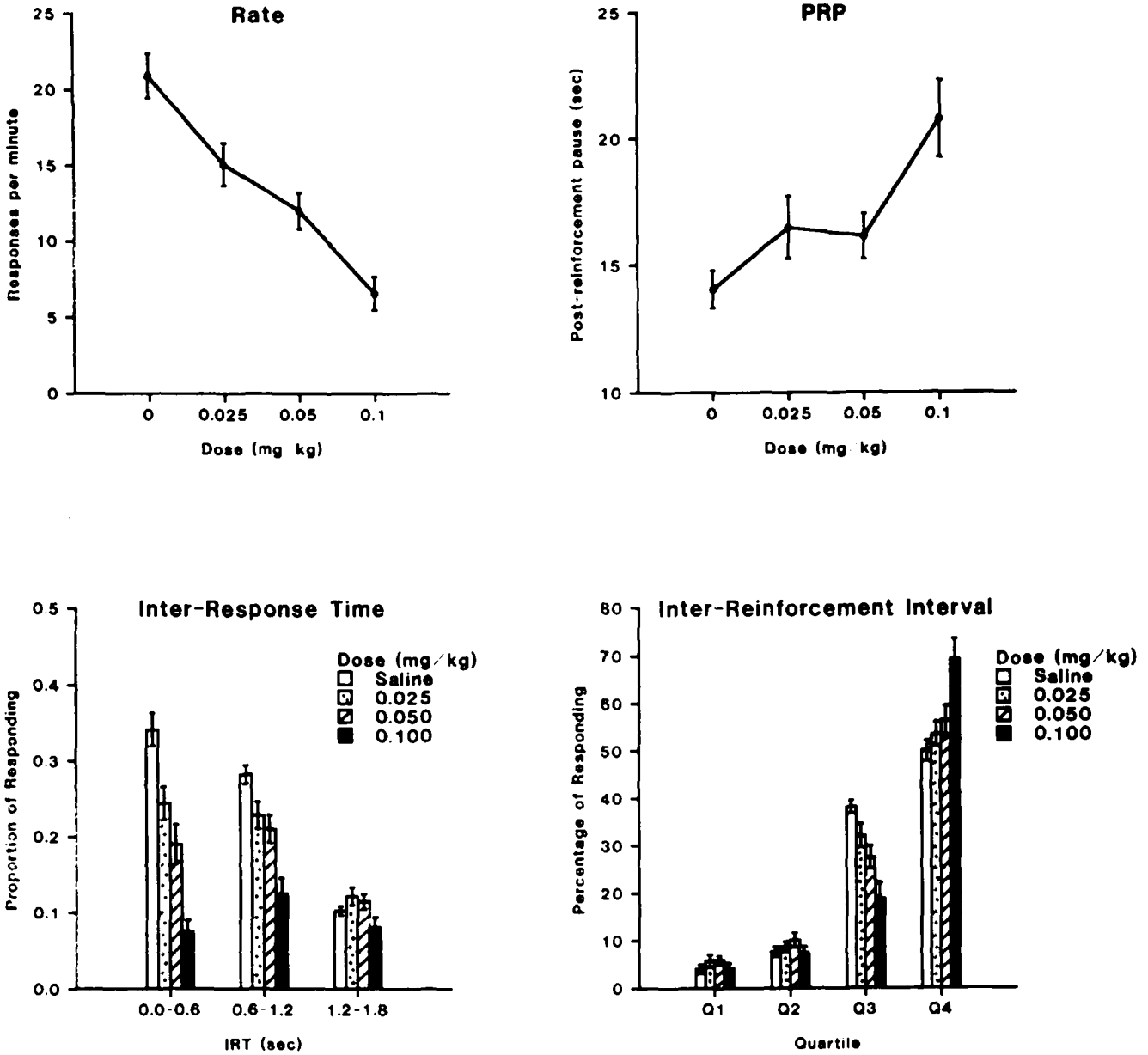


FIG. 6. Effect of clonidine on FI 20-s self-stimulation. Saline was used as control (0 dose). The four panels illustrate different aspects of FI performance as described in Fig. 1 Values for each treatment are averaged over the reward-summation curve (see Fig. 7) to illustrate dose-response functions on the various performance indices. Vertical bars represent 1 SEM ($n$ = 5).

s). Therefore, both drugs reduced the vigorous responding normally associated with FI 20-s responding.

The percentage of responding in each interreinforcement quartile indicated that neither drug altered responding in the first or second quartile, but both drugs decreased responding in the third quartile (Figs. 5 and 6, lower right panels). These data show the typical FI scallop, which indicates that the reduced responding was still under schedule control.

The data are graphed in Fig. 7 to visualize the effects of clonidine and pimozide on reward summation using response rate as the dependent variable. The lower panels of Fig. 7 show that after saline response rates increase with longer trains at both frequencies. All three doses of clonidine (0.025, 0.050, and 0.1 mg/kg) decreased responding, but rates increased with longer trains or higher frequencies. The slopes of all three lines at 200 Hz were not significantly different from saline, indicating they were parallel. These data suggest that the suppressive effects of clonidine can be reversed by increasing the frequency or increasing the number of pulses per reinforcement.

The upper panels of Fig. 7 show that 0.125 mg/kg pimozide produced inconsistent effects on reward summation compared to vehicle. Following 0.250 mg/kg pimozide, the response rates did not increase with higher frequency and only

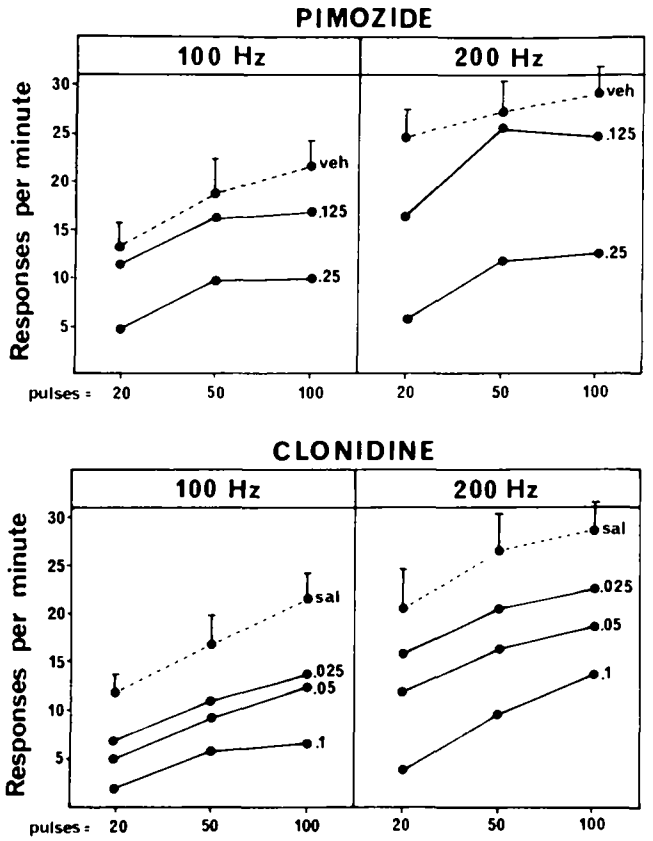


FIG. 7. Effect of pimozide (upper panels) and clonidine (lower panels) on reward summation at 100- (left panels) and 200-Hz stimulation (right panels). The control for pimozide was tartaric acid vehicle (veh) and for clonidine it was saline (sal). Each point represents the mean value from five rats.

marginally rose with longer train durations. Thus, no reward summation was apparent following the higher dose of pimozide, indicating that the decreased responding was insurmountable with the frequencies tested.

### d- *and* l-*Amphetamine*

The effects of *d*- and *l*-amphetamine on self-stimulation are shown in Figs. 8 and 9. Values were averaged over six blocks of trials in which train duration was adjusted to deliver 20, 50, or 100 pulses per reinforcement at 50 and 100 Hz. Both amphetamine isomers dose dependently increased response rates under FI reinforcement ($p < 0.001$) (upper left panels). However, *d*-amphetamine was approximately four times more effective than *l*-amphetamine. Response rates almost doubled when the dose of *d*-amphetamine was increased from 0.5 to 1.0 mg/kg. This effect was not observed when the dose of *l*-amphetamine was increased from 2.0 to 4.0 mg/kg. This suggests that potency differences are greatest with high doses of *d*-amphetamine.

Both amphetamine isomers dose dependently decreased the postreinforcement pause (Figs. 8 and 9, upper right panels) and increased the proportion of responding in the first two IRT bins (0.0–1.2 s) (lower left panels). Moreover, both isomers increased the percentage of responding in the second and third quartile of the interreinforcement interval (lower right panels).

The effects of *d*- and *l*-amphetamine on reward summation are illustrated in Fig. 10. Compared to saline, fewer pulses were required for a given level of performance after amphetamine. The highest dose for both amphetamine isomers also increased responding during extinction. This effect was more pronounced for *d*-amphetamine (18 responses per min) than *l*-amphetamine (10 responses per min). This contrasts with less than three responses per minute after saline. The microanalysis showed that high levels of responding during extinction were no longer under schedule control because responding was evenly distributed over the trials.

## GENERAL DISCUSSION

The present study demonstrates that FI self-stimulation is inhibited by clonidine and pimozide and facilitated by amphetamine. Although clonidine and pimozide both inhibited self-stimulation, there were several differences between the effects of the drugs. The most obvious difference was the shape of the dose-response curves. Pimozide produced a very steep dose-response curve whereas clonidine reduced responding in a more progressive manner.

Both drugs depressed several performance indices previously shown to be sensitive to changes in reinforcement magnitude (Experiment 1). Clonidine and pimozide reduced lever-press rates and also changed the following measures: the proportion of responding in IRT bin 1 (0.0–0.6 s), the postreinforcement pause, and the percentage of responding in the third quartile of the interreinforcement interval. Neither clonidine nor pimozide increased the proportion of responding in the first two quartiles, which suggests that the reduced responding was still under schedule control.

Clonidine decreased the overall response rates after 0.025 and 0.050 mg/kg, but the slopes of the reward-summation curves were parallel to the slopes after saline. This suggests that clonidine produced a specific effect on reward magnitude. There were no obvious changes in the behavior or appearance of rats following 0.025 or 0.050 mg/kg clonidine, whereas the highest clonidine dose (0.100 mg/kg) produced mild ataxia and increased diuresis (10). Thus, the highest dose of clonidine could have disrupted responding by interfering with lever pressing. However, the reduced responding observed at the two lower doses suggests that the inhibition of self-stimulation represented an inhibition of reinforcement.

These data confirm and extend previous findings in our laboratory using clonidine in the free-operant shuttle-box (41,42), as well as in a discrete trials paradigm (64). They are also in agreement with previous studies using reward-summation paradigms (21,28). These studies showed that a low dose of clonidine (0.03 mg/kg) produced a lateral shift in the reward-summation function. Higher doses (>0.1 mg/kg) were accompanied by changes in performance effects (21,28). The narrow dose range of clonidine that produces a selective shift in the reward-summation curve does not contradict the involvement of noradrenaline in self-stimulation (28). The shallow dose-response curve could be due to the fact that clonidine can stimulate both pre- and postsynaptic $\alpha_2$-adrenoceptors or that clonidine is a relative weak agonist (10).

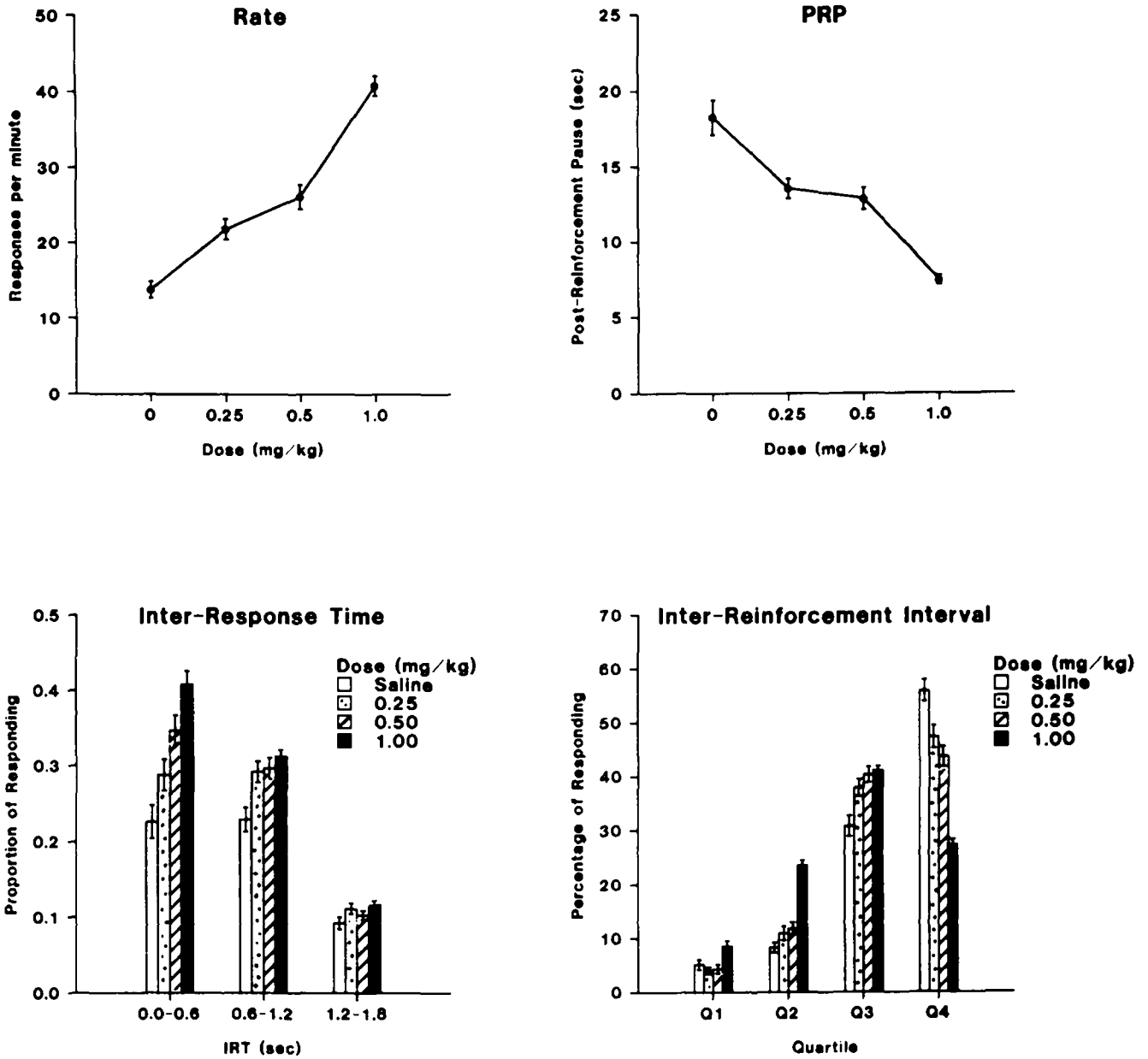


FIG. 8. Effect of *d*-amphetamine on FI 20-s self-stimulation. The panels illustrate different aspects of FI performance. Values for each treatment are averaged over the reward-summation curve (see Fig. 10) to illustrate dose-response functions of the dextro isomer on the various performance indices. Vertical bars represent 1 SEM ($n$ = 9).

The involvement of noradrenaline in self-stimulation needs further investigation with more selective and potent adrenoceptor agonists and antagonists. The use of a FI schedule combined with a reward-summation model should facilitate this investigation.

No obvious behavioral changes were observed after the lower dose of pimozide (0.125 mg/kg), nor did this dose significantly inhibit self-stimulation. The higher dose of pimozide (0.250 mg/kg) inhibited self-stimulation but also reduced muscle tone (rats were limp on handling) and produced mild catalepsy (resting on the response lever). Although rats appeared to be sluggish, the higher dose of pimozide did not seem to disrupt normal stimulus-bound movements such as running away from the lever. However, higher rates were not emitted over the reward-summation curve within the range of stimulus inputs tested, suggesting the inhibition was insurmountable. This is consistent with findings that dopamine antagonists inhibit numerous other operant, exploratory, and appetitive behaviors, likely inhibiting response initiation (74,75).

Previous results have shown that doses of pimozide between 0.1 and 0.3 mg/kg inhibit free-operant self-stimulation in a shuttle-box (64) and inhibit FI 60-s self-stimulation (35). Using even higher doses (0.5-2.0 mg/kg) of pimozide sup-

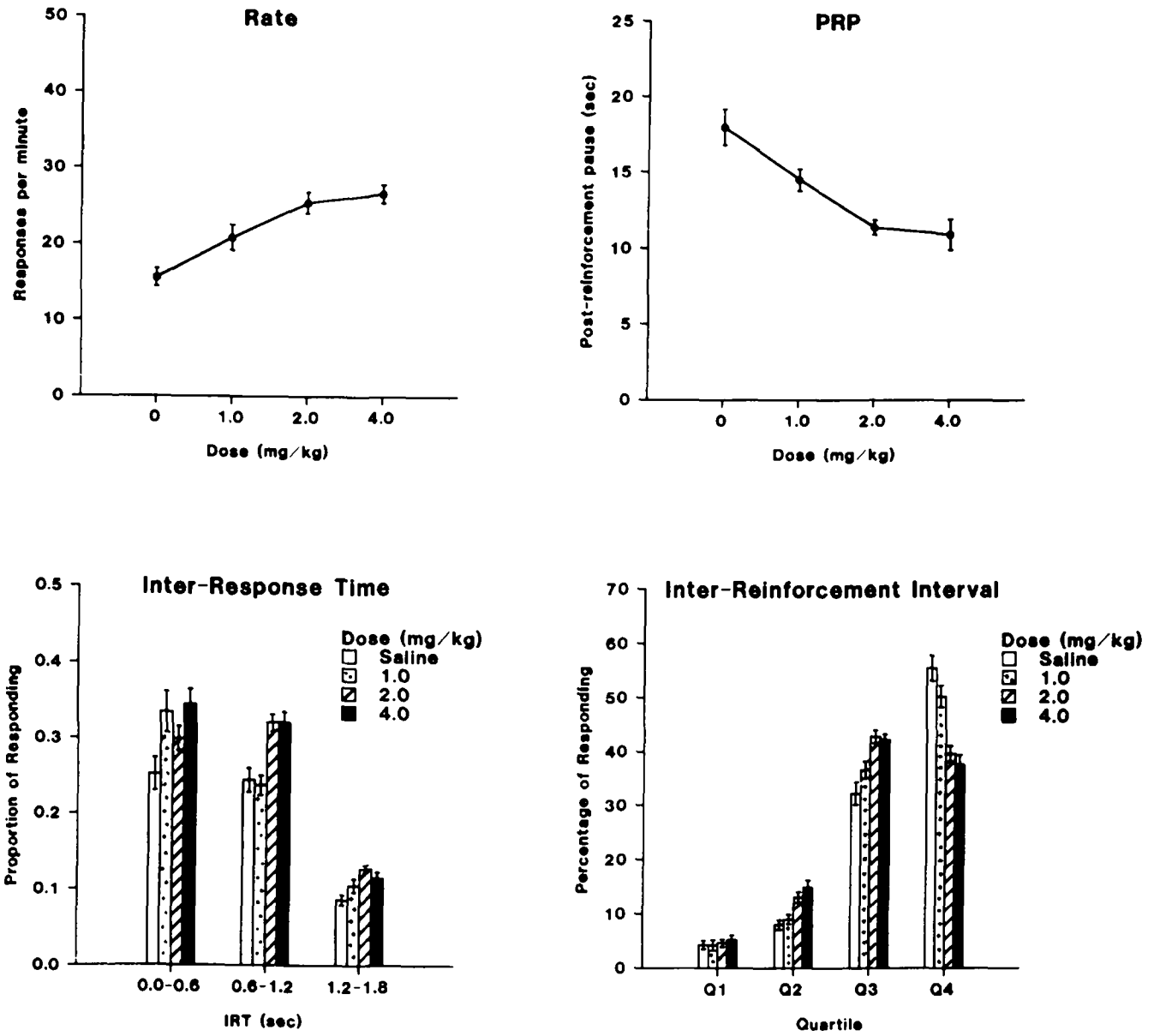


FIG. 9. Effect of *l*-amphetamine on FI 20-s self-stimulation in the same rats given the dextro isomer. The panels represent different aspects of FI performance. Values for each treatment are averaged over the reward-summation curve (see Fig. 10) to illustrate dose-response functions of the levo isomer on the various performance indices. Vertical bars represent 1 SEM.

presses all responding except for the first few trials of the session (27,35,64,69). Thus, the nonspecific inhibitory effects of pimozide observed in the present study are consistent with previous reports that pimozide produces both reinforcement and motor impairments (3,18,19,37,50,72,74,75). Experiments with food reinforcement have led to similar conclusions (53,60). While the present study varied frequency and train durations over a limited range, further studies seem justified using this type of paradigm over a wide range of inputs or utilizing other stimulus combinations (current and frequency) (20,28). The effect of dopamine $D_1$ and $D_2$ antagonists on FI self-stimulation will be explored in a subsequent article.

Both *d*- and *l*-amphetamine enhanced self-stimulation in a dose-dependent manner. Both isomers decreased the number of pulses required to maintain FI responding and increased maximal response rates. The higher doses of both amphetamine isomers shortened the postreinforcement pause. The shortened pauses after amphetamine have also been reported under FR schedules (9) and using water reinforcement (6). Moreover, once at the lever the response pattern was vigorous as indicated by the high proportion of responding at IRTs between 0 and 1.2 s. The greater potency of *d*-amphetamine than *l*-amphetamine confirms the observations of several other investigators (5,23,34,59). The *d*-isomer has also been reported to produce a greater enhancement of locomotor ac-

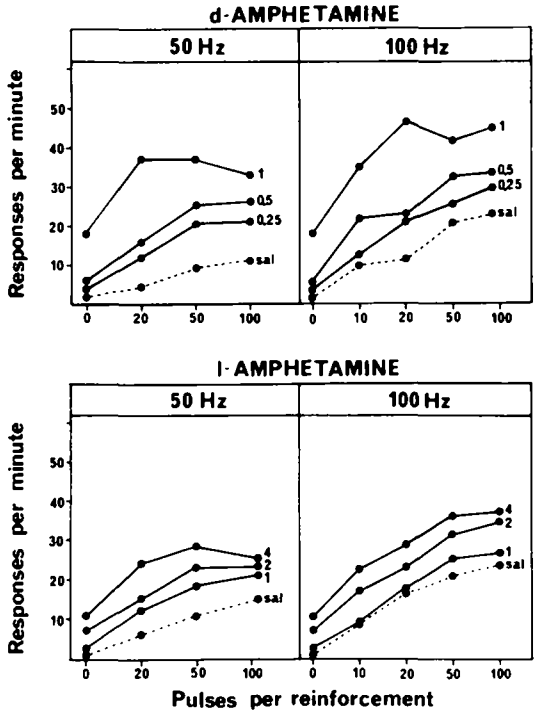


FIG. 10. Effect of *d*- and *l*-amphetamine on reward summation at 50 Hz (left panels) and 100 Hz (right panels). Saline (sal) was used for comparison. Numerals on the right of each curve indicate dose (mg/kg). Zero pulses indicate responding under extinction, in which the stimulators were turned off. Each value represents the mean of nine rats.

tivity, stereotyped behaviors, and self-administration compared to the *l*-isomer (52).

At the highest dose, both isomers of amphetamine increased performance during extinction. This responding during extinction differed from performance for brain stimulation. The responding during extinction was evenly distributed over the trials, indicating a loss of schedule control. This loss suggests that the enhancement of self-stimulation produced by high doses of amphetamine partly reflects potentiated motor behavior such as is seen in stereotypy (52).

In conclusion, the present study demonstrated the sensitivity of a new self-stimulation paradigm in detecting drug effects on self-stimulation. Low doses of clonidine and pimozide that inhibit self-stimulation using a wide variety of procedures were shown in this study to inhibit FI self-stimulation. However, unlike clonidine, the effect of pimozide on reward summation suggests a performance deficit. Both isomers and amphetamine enhanced FI self-stimulation in a dose-dependent manner. The dextro isomer was four times more effective than the levo isomer. Moreover, the microanalysis of the FI behavior and reward-summation curves for brain stimulation are consistent with the concept that amphetamine produces an enhancement of reinforcement. Since the increased responding under the FI schedule did not result in more frequent stimulation availability, these data indicate that the response facilitation produced by amphetamine was rate independent.

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