Chlorpromazine and pimozide alter reinforcement efficacy and motor performance

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Abstract. This study evaluated the effects of chlorpromazine and pimozide on reinforced responding. In each session, rats were exposed to a series of five variable-interval reinforcement schedules. The response requirement was a lever press, the reward was a small portion of water, and the reinforcement rate varied from about 20 to 660 reinforcers per hour. Response rate was a negatively accelerated function of reinforcement rate, and the relationship between the two variables was described by the equation for a rectangular hyperbola (the matching law). One parameter of the hyperbola is equivalent to the asymptotic response rate and the other parameter is equivalent to the rate of reinforcement that maintains a one-half asymptotic response rate. Chlorpromazine (0.75–3.0 mg/kg) and pimozide (0.1–0.4 mg/kg) dose-dependently decreased response rates. At low doses, the response rate decreases were, for the most part, restricted to the low reinforcement rate schedules. In contrast, the highest dose tested decreased response rates at both low and high reinforcement rates. The patterns of response rate decreases resulted in dose-dependent changes in the parameters of the matching law equation. The shifts in the matching law parameters were discussed in terms of the motoric and motivational interpretations of neuroleptic-induced response rate changes.

Key words: Chlorpromazine – Pimozide – Response rate – Reinforcement efficacy – Motor performance – Matching law – Variable-interval schedule – Lever press – Rat

In 1960 Olds and Travis reported that chlorpromazine decreased reinforced responding in rats. Their interpretation was that the drug may have reduced the subjects' "drives for positive reinforcements." In Olds and Travis' study, the reward was a brief electrical pulse to the hypothalamus and the response was a lever press. Since 1960, Olds and Travis' experimental result has been repeated numerous times. The results show that chlorpromazine and similar drugs, called neuroleptics, typically decrease behavior that is maintained by the presentation of a reward. For example, neuroleptics decrease rate of responding when the response has the effect of producing food (Wise et al. 1978), water (Gerber et al. 1981), or temperature change (Ettenberg and Carlisle 1985).

Although the empirical results are clear, Olds and Travis' motivational interpretation is questionable. In agreement, some research appears to show that neuroleptic-treated subjects had the motoric capacity to respond but nevertheless did not (e.g., Wise 1982). In contrast, other data seem to show that neuroleptic-induced response decreases were due to motor deficits (e.g., Ettenberg et al. 1981). Indeed, there is no shortage of evidence for either the motivational or motoric interpretation, and as a result a clear account of how neuroleptics change behavior is not available.

One source of difficulty is that the same set of results can often be interpreted from either the motivational or motoric point of view. For example, consider a study that is often cited as favoring the motivational interpretation. Wise and colleagues (Wise et al. 1978) found that pimozide produced an extinction-like pattern of response rate decline. In their study, the schedule contingency insured that reinforcement rate was proportional to response rate. Consequently, if pimozide had produced a motor deficit, not only would response rate go down, but reinforcement rate would decrease as well. The reinforcement rate decrease would, in turn, further decrease response rate, and because of this positive feedback loop, reinforcement rate and response rate would in lock-step drive each other ever lower. In support of this account, pimozide does not extinguish responding when the schedule contingency uncouples changes in reinforcement rate from changes in response rate, as in interval-schedule experiments (Fibiger et al. 1976). Consequently, the extinction-like pattern of decline, which is frequently cited as evidence for a motivational deficit (Gramling et al. 1984; Wise et al. 1978), may have been secondary to a motor deficit.

In this paper we use a method that provides quantitative criteria for deciding between competing interpretations of response rate changes. The method is based on a mathematical model of the relationship between response rate and reinforcement rate. The equation was introduced by Herrnstein (1970) as a quantitative version of the law of effect, and it is referred to in this paper as the matching law hyperbola. The customary notation is

$$B = \frac{kR}{R + R_e}, \qquad (1)$$

where B stands for response rate, R stands for reinforcement rate, and k and R_e are parameters, whose magnitudes are obtained by fitting Eq. (1) to the response rates. Recent

psychopharmacology experiments show that drugs systematically alter k and R_e, (Hamilton et al. 1985; Bradshaw et al. 1981; Heyman and Coons 1981; Heyman 1983; Heyman and Seiden 1985), and research on the matching law provides empirical (e.g., deVilliers and Herrnstein 1976) and theoretical (Heyman 1985) criteria for interpreting these changes.

The magnitude of the parameter R_e is by definition equal to the rate of reinforcement that maintains a one-half asymptotic response rate ($B = k/2$ when $R = R_e$). In studies in which R_e systematically changed but k did not, the experimenter manipulated deprivation conditions or aspects of the reinforcer, such as amount (Bradshaw et al. 1978; Bradshaw et al. 1983b; Conrad and Sidman 1956; Logan 1960; Guttman 1954; Kraeling 1961; Woods and Holland 1964; see deVilliers and Herrnstein 1976 for a summary of the experiments published before 1976). For example, increasing hours of deprivation decreased R_e in a study in which rats ran down a runway for food reward (Logan 1960; also see deVilliers and Herrnstein 1976). On the basis of these results, we propose that a change in R_e is a change in reinforcement efficacy. Note that R_e is inversely related to reinforcement efficacy: the less reinforcement needed for a one-half asymptotic response rate, the greater the efficacy of the reinforcer.

The magnitude of the parameter k is, by definition, equal to the response rate asymptote. In studies in which k systematically changed but R_e did not, the experimenters manipulated the response requirement (Bradshaw et al. 1983a; Hamilton et al. 1985; McSweeney 1978). For example, in studies with rats (Bradshaw et al. 1983a; Hamilton et al. 1985), adding weights to the response lever decreased k. On the basis of these results we propose that a change in k is a change in motor performance.

The experiments described in this paper extend the matching law analysis of the effects of chlorpromazine and pimozide on water-reinforced lever pressing in rats. Previously it was shown that pimozide decreased k and increased R_e for food-reinforced responding in rats (Heyman 1983), and, in a procedure that was identical to the one used in this study, low doses of amphetamine selectively decreased R_e and higher doses increased k and changed R_e bitonically (Heyman and Seiden 1985). Consequently, we expected that chlorpromazine and pimozide would reduce responding maintained by water reinforcement and that the decreases would be associated with an increase in R_e and a decrease in k. The predictions were borne out.

Materials and methods

Subjects. Fifteen, male, albino, Sprague Dawley rats (Holtzman Company, Madison, WI) served as subjects. The rats were approximately 2.5 months old at the start of the study, were housed two to a cage, and were kept on a water deprivation regimen in a colony room that was illuminated 16 h a day (lights on at 06:00 hours). There were eight subjects in the chlorpromazine experiment and seven in the pimozide experiment. During experimental sessions the rats earned approximately 3 ml water, and following the session they were given 25 ml water. In the home cage there was free access to laboratory chow (Teklad Mouse and Rat Diet).

Apparatus. The experiment was conducted in eight Lehigh Valley operant conditioning chambers (30.5 cm, 20.0 cm,

24.0 cm). A lever was located on the front wall of each chamber, 3.0 cm from the right side and 3.0 cm from a grid floor. To the right of the lever (4.5 cm) was a recessed opening that allowed the rat access to a 0.025-ml dipper of water. A downward force of more than 0.15 N operated the lever, and when the temporal component of the reinforcement contingency was fulfilled, a lever response raised the dipper into the recessed opening for 2.5 s. A Sonalert (dampened with resistors) and a light, located on the chamber back wall, signalled different phases of the session. The chambers were enclosed in sound-attenuating, ventilated boxes and connected to a PDP-8/e computer. The computer controlled experimental events and recorded responses and reinforcements.

Procedure. Experimental sessions consisted of a series of five variable-interval (VI) reinforcement schedules (a five-component multiple schedule). Each schedule was available for 420 s, and a 500-s time-out period separated consecutive schedules. The schedule order was random (without replacement) so that in each session the subject was exposed to five different reinforcement rates. The programmed rates were 24, 48, 120, 360, and 720/h, which corresponds to the series of schedules: VI 150 s, VI 75 s, VI 30 s, VI 10 s, and VI 5 s. The list of intervals for each schedule gave an approximately random temporal pattern of inter-reinforcement times. During reinforcement, 2.5 s, and the immediately following 1.5 s, the VI schedule timer did not operate and responses had no experimentally arranged consequences. The stimulus conditions were set by a houselight and Sonalert. The houselight was on when a reinforcement schedule was available, and it was off during the time-out period. The rate of the Sonalert tone indicated which reinforcement schedule was available, with low rates signaling low reinforcement rates and high rates signaling high rates. The lowest signal rate was 7.5/min, the highest was 40/min, and the on time was 1 s.

In addition to the five VI schedules, each session began with a brief warm-up period, during which the rats obtained six reinforcers according to the contingency that every fifth response or a 10-s interval without a response operated the dipper. The warm-up period was signalled by the houselight and was followed by a 120-s time-out period. During this time-out and the 500-s time-out periods between reinforcement schedules, the chamber light and Sonalert were off and responses had no experimentally arranged consequences, although they were recorded. The experiment was conducted five or six times a week at about the same time each day.

Drugs. Each rat received three doses of drug, and each dose was given on three different occasions. For chlorpromazine, measured as the salt, the doses were 0.75, 1.50 and 3.0 mg/kg, and the vehicle was saline. For pimozide the doses were 0.1, 0.2 and 0.4 mg/kg, and the vehicle was tartaric acid solution, buffered to a pH of about 4.0. In addition, there were five or six vehicle alone injections randomly interspersed between drug injections. Injections were delivered IP at a volume of 1 ml/kg and occurred on Tuesdays and Fridays. The chlorpromazine injections were given 1 h before the start of the session and the pimozide injections were given 4 h before the start of the session. Drug injections began once the response rates and parameters appeared stable. For most subjects, stability was achieved
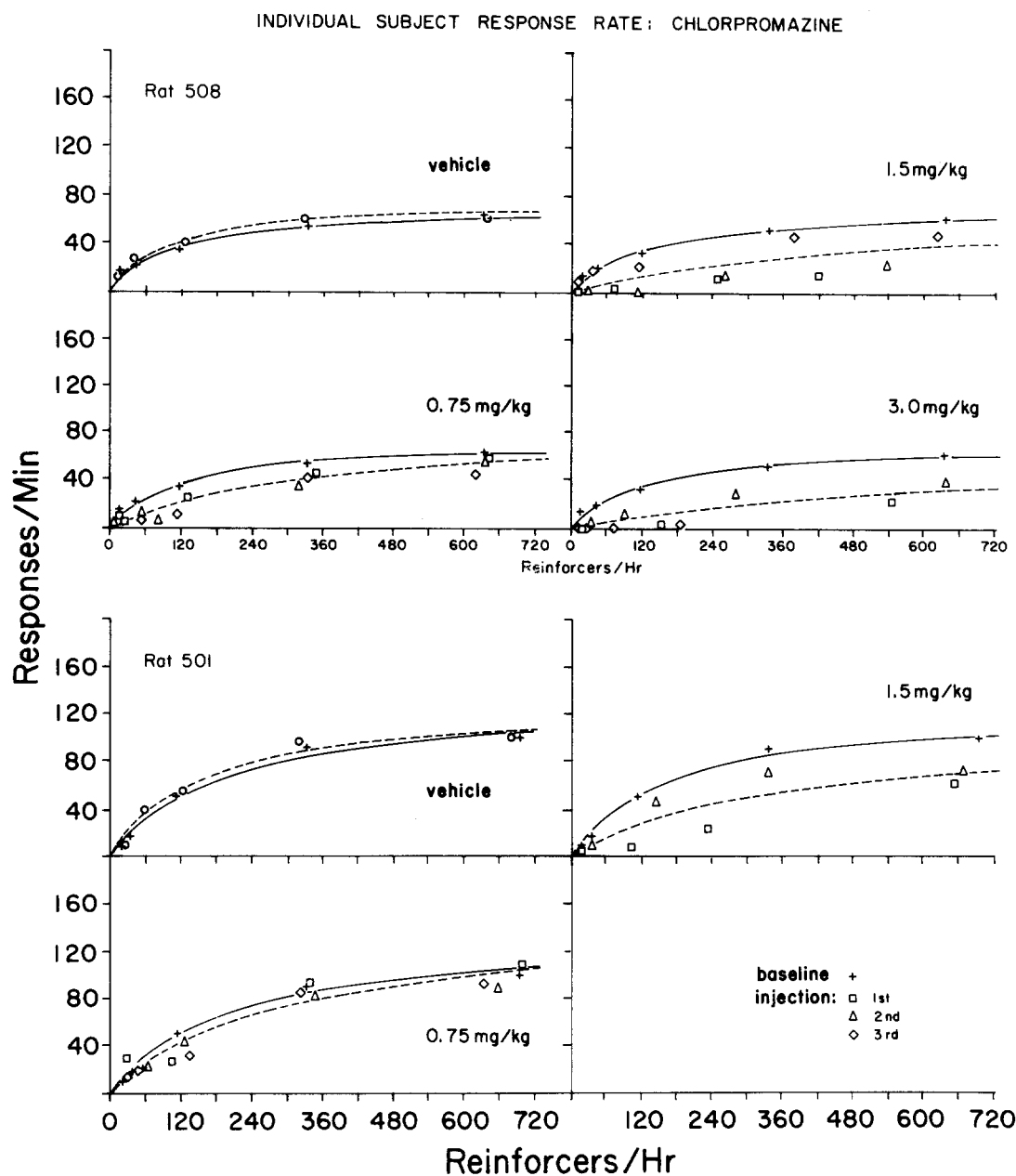
INDIVIDUAL SUBJECT RESPONSE RATE: CHLORPROMAZINE

Fig. 1. The effect of chlorpromazine on response rate for two representative subjects. In the panels showing drug effects, the different symbols distinguish the three sessions that each dose was given. The *squares* are for the first session; the *triangles* are for the second session; and the *diamonds* are for the third session. The *crosses* show the median response rates for the 18 baseline sessions, and the *open squares* in the vehicle panel show the median response rates for the vehicle injections (either five or six)

in 25–35 sessions. Once injections began, the standard for evaluating drug and vehicle effects was response rates in sessions that were not preceded by an injection. This sample was referred to as "baseline" responding; it was drawn from all sessions that occurred at least 2 days since the last drug injection.

Data analysis. Equation 1 was fitted to individual subject response and reinforcement rates. For baseline and vehicle sessions (18 and five or six sessions respectively), median response and reinforcement rates were used. For drug sessions, the three sessions at each dose were simply pooled. The parameter values were estimated on the basis of the least-squares criterion, minimization of the residuals. The solutions were obtained by an iterative method (Wether-

ington and Lucas 1980) since Eq. (1) is nonlinear. To determine the significance level of changes in the values of k and R_e, the scores were transformed into percentages relative to baseline, and then subjected to a paired t-test. In addition, group median response and reinforcement rates were calculated in order to provide overall summaries of the results.

Results

Figures 1 and 2 show representative individual subject results. The points for baseline and vehicle sessions indicate the median response and reinforcement rates for each of the five schedule components (18 and five or six sessions, respectively). The points for drug sessions are from each
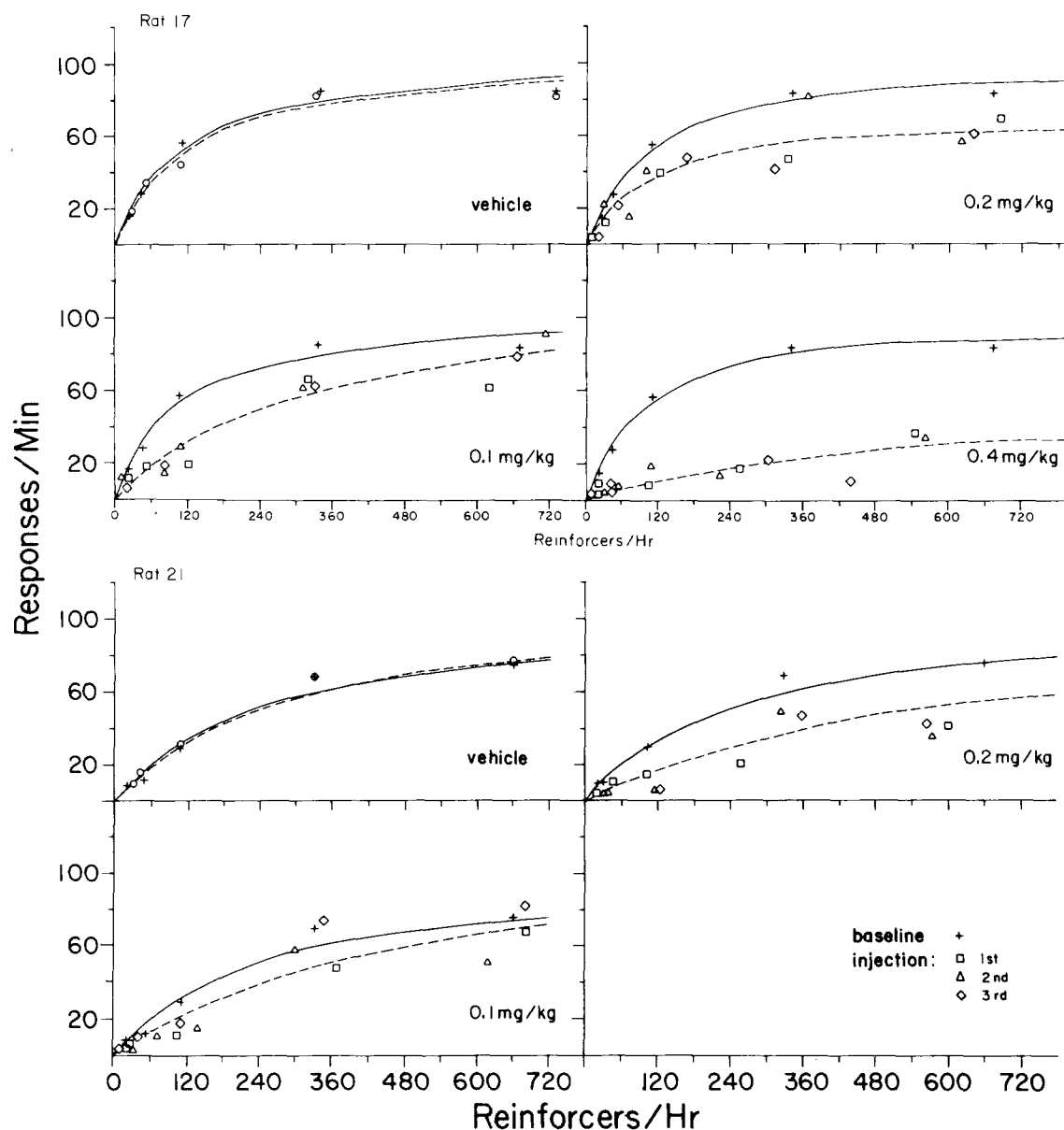
INDIVIDUAL SUBJECT RESPONSE RATE: PIMOZIDE

Fig. 2. The effect of pimozide on response rate for two representative subjects. The format is the same as in Fig. 1

component of each drug session (three sessions at each dose).

The pattern of response rate changes was similar for chlorpromazine and pimozide. At the lowest dose tested, both drugs decreased response rates at the leanest reinforcement rate schedules, but produced little or no decrease in response rate at the densest reinforcement rate schedule. In contrast, at the highest dose tested, chlorpromazine and pimozide decreased or eliminated responding in each of the five reinforcement schedules, and the percentage decreases tended to be somewhat larger in the leaner reinforcement rate schedules.

There were individual differences in the magnitude of the drug effects, but not in pattern. These are most easily seen at the lowest and highest drug doses. For example, at 0.75 mg/kg chlorpromazine consistently decreased response rate in Rat 508, but not in Rat 501. Similarly, at

0.4 mg/kg pimozide eliminated responding in Rat 17, but not in Rat 21.

Figure 3 shows the group median response and reinforcement rates. The medians reflect the individual subject results. For example, the relative magnitude of the response rate decreases was an inverse function of the level of reinforcement. There are no median data for the 0.4 mg/kg dose of pimozide, because six of seven subjects stopped responding at this dose. Similarly, the 3.0 mg/kg dose of chlorpromazine eliminated responding in four of eight subjects.

Changes in response rates can be summarized as follows: A 0.75 mg/kg dose of chlorpromazine and a 0.10 mg/ kg dose of pimozide typically decreased responding in the lower reinforcement rate components, while leaving intact responding in the highest reinforcement rate component. In contrast, the 1.50 and 3.0 mg/kg doses of chlorpromazine
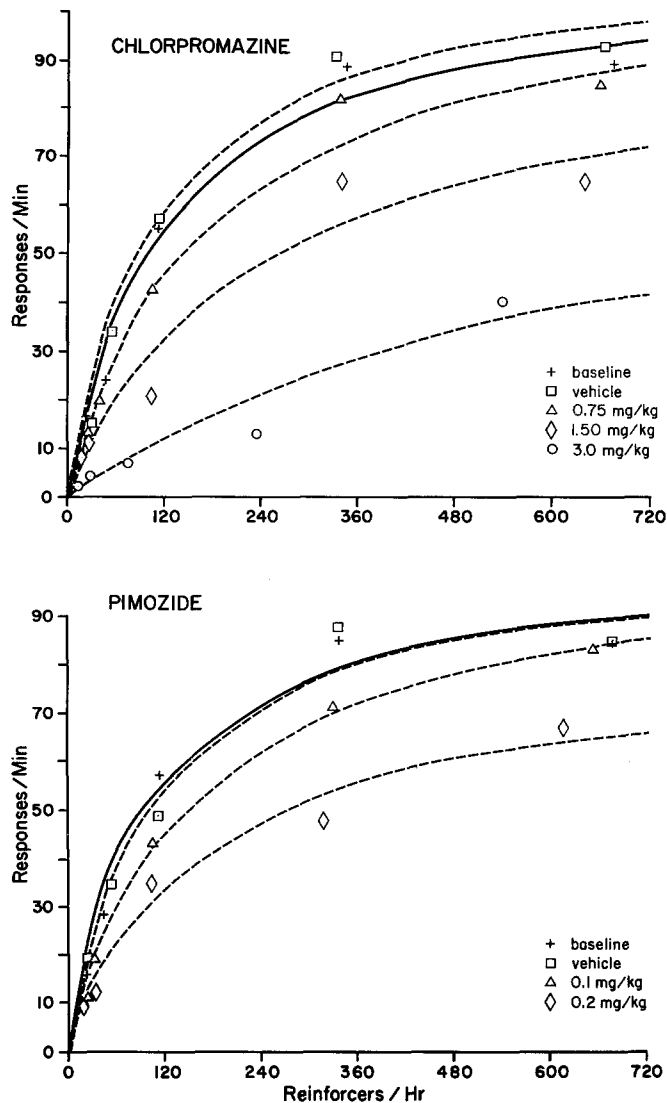
Fig. 3. The effect of chlorpromazine and pimozide on response rate, as shown by the group median results. For example, in the drug conditions, response rates are the medians from the sample provided by each subject in each of the three sessions of one of the dose levels. The *solid curve* is for baseline results

Fig. 4. The effect of chlorpromazine and pimozide on the parameters of the matching law hyperbola. For each subject the relative change in k and R_e was calculated, and the symbols show the average percentage change for the group. The *error bars* indicate one-standard error; the *asterisks* indicate the probability level for the null hypothesis according to a paired t-test: * for $P \leq 0.05$ and ** for $P \leq 0.01$

and the 0.20 mg/kg dose of pimozide decreased responding in each of the five components, including the one for the richest reinforcement schedule, and the decreases in response rate tended to be inversely related to reinforcement rate.

Figure 4 shows the effects of chlorpromazine and pimozide on the parameters of the matching law hyperbola (Eq. 1). Changes are displayed as percentage differences from baseline levels, and all statistics were calculated in terms of this measure. There was a dose-dependent increase in the rate of reinforcement necessary for a one-half asymptotic response rate, R_e, and a dose-dependent decrease in the asymptotic response rate, k. At the lowest doses tested, the drugs increased R_e without altering k. This pattern of parameter changes corresponds to decreases in response rates in the lower reinforcement rate components. (Since the response rate in the highest reinforcement rate component did not shift, there was no change in the estimated asymptotic response rate.) At higher drug doses there were
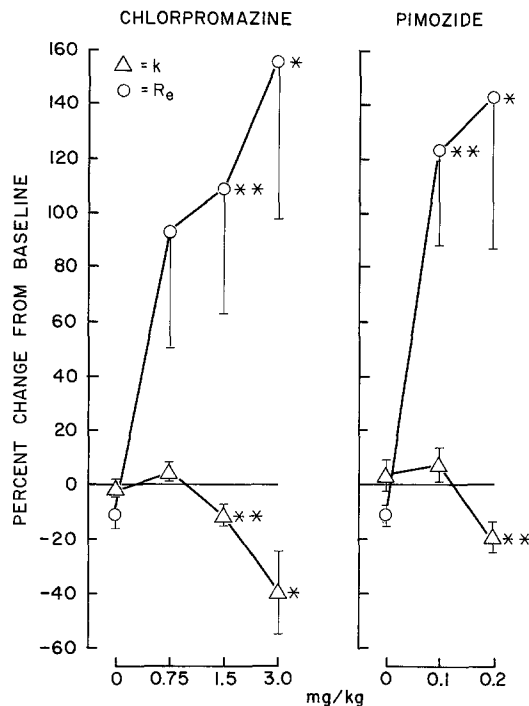
further increases in R_e and decreases in k. This means that here there was an increase in the rate of reinforcement required for a one-half asymptotic response rate even though the asymptotic response rate had decreased. The increases in R_e were large relative to the changes in k, and in all but one case were statistically significant ($P \leq 0.05$). At the 0.75 mg/kg dose of chlorpromazine, the percent change in R_e, 93%, had a probability, according to the null hypothesis of 0.056. If the one outlier from the sample of eight subjects is excluded, the change in R_e has a probability of less than 0.05 and the average change for the restricted group is an increase of 111%.

Tables 1 and 2 summarize the matching law equation results. The goodness of fit statistic, r^2, is for individual subjects, and the table lists the range and median values. Taking the chlorpromazine and pimozide results together, Eq. (1) typically accounted for more than 97% of the variance in response rates in baseline and vehicle sessions and for about 82% of the variance in drug sessions. The decrease in accuracy was due to several factors. The neuroleptics decreased response rates so that there was a decrease in the variance to be explained, and, thereby, a relative increase in the magnitude of the error term. In baseline sessions, Eq. (1) was fit to the median response and reinforcement rates and in drug sessions Eq. (1) was fit to pooled results so that there were more degrees of freedom for the drug results. Relatedly, since drug sessions were pooled, there was a between session error term that was not present in the baseline median and vehicle session response rates. The standard errors listed in the tables show within subject (between session) variability, whereas the

Table 1. Chlorpromazine-induced changes in k and R_e

	k (responses/ min)	SE (indiv.)[a]	Range[b]	R_e (reinforcers/h)	SE (indiv.)	Range	r^2 [c]	Range (indiv)
Baseline	126	4.5	78–217	142	16.9	18–259	0.99	0.87–0.99
Vehicle	125	8.2	77–213	136	22.0	12–297	0.98	0.83–0.98
0.75 mg/kg	130	9.4	73–208	222	31.6	48–451	0.93	0.50–0.98
1.50 mg/kg	113	21.0	67–197	317	81.0	30–604	0.86	0.56–0.92
3.0 mg/kg	75	17.8	27–142	352	96.5	71–603	0.71	0.57–0.81

[a] Average individual standard error (between session variation)
[b] Lowest and highest parameter values among group
[c] The r^2 from the subject that had the median value

Table 2. Pimozide-induced changes in k and R_e

	k (responses/ min)	SE (indiv.)[a]	Range[b]	R_e (reinforcers/h)	SE (indiv.)	Range (indiv.)	r^2 [c]	Range
Baseline	112	5.6	37–144	103	19.6	23–255	0.97	0.67–0.98
Vehicle	108	6.4	43–149	93	12.4	20–269	0.94	0.40–0.99
0.1 mg/kg	117	7.8	34–189	202	31.9	59–325	0.82	0.73–0.93
0.2 mg/kg	86	12.6	27–140	216	52.7	87–631	0.82	0.40–0.91

[a] Average individual standard error (between session variation)
[b] Lowest and highest parameter values among group
[c] The r^2 from the subject that had the median value

standard error bars in Fig. 4 show within-group variability. The effects of the drugs on the range of parameter values are also informative. For example, the 0.75 mg/kg dose of chlorpromazine increased the range of R_e from a low of 18 reinforcers per h and a high of 259 reinforcers per h (baseline values) to a low of 48 reinforcers per h and a high of 451 reinforcers per h. In contrast, this dose had no apparent effect on the range of k.

Figure 5 provides a combined summary of the response rate results and parameter changes. The coordinates were arranged so that the lines fit to the median response rates had a slope equal to $-R_e^{-1}$ and intersected the x-axis at k. This sort of presentation is widely used in receptor binding studies (Scatchard 1949), but heretofore has not been used in behavioral research. The method combines aspects of the previous figures. For example, the Scatchard analysis makes it clear that a response rate decrease in low reinforcement rate schedules corresponds to an increase in R_e.

Discussion

Neuroleptic drugs typically decrease reinforced responding. Since the factors influencing responding are not restricted to reinforcement rate, but include motor capacity, the reinforcement contingency, the response requirement, stimulus conditions, degree of deprivation and perhaps other factors, drug-induced changes in response rate have many possible interpretations. The matching law approach provides criteria for distinguishing between some of the interpretations. As noted in the introduction, previous studies show that changes in aspects of the reward or deprivation can selectively change R_e whereas changes in the response requirement can selectively change k. On the basis of these findings and theoretical developments (Herrnstein 1974; Heyman

1985), the results from the pimozide and chlorpromazine experiments have the following interpretations.

At the lowest doses tested, chlorpromazine and pimozide decreased the reinforcing efficacy of water. The evidence is an increase in the rate of reinforcement necessary for a one-half asymptotic response rate. At higher doses, the two drugs reduced motor performance and further decreased reinforcement efficacy. The evidence is a decrease in the asymptotic response rate and further increases in the rate of reinforcement necessary for a one-half asymptotic response rate. Wise (1982) and others (e.g., Gallistel and Karras 1984) concluded that neuroleptics reduced reinforcement efficacy, whereas Tombaugh et al. (1979) and others (e.g., Ettenberg et al. 1981) concluded that neuroleptics affect motor performance. The matching law approach provides a quantitative index for each interpretation, and according to these quantitative criteria both interpretations are to some extent correct.

Pimozide was behaviorally more potent than chlorpromazine. Using the amount of drug necessary to change R_e by 50%, interpolation shows that a 0.13 mg/kg dose of pimozide was equivalent to 1.70 mg/kg dose of chlorpromazine. Using the amount of drug necessary to change k by 25%, the functionally equivalent doses were 0.20 mg/kg pimozide and 2.25 mg/kg chlorpromazine. The dose ratios for the parameter changes are similar to one another and are also similar to (1) the dose ratios for dopamine antagonist binding (Creese et al. 1976) and (2) to the dose ratios for the average clinical daily dose (Creese et al. 1976).

Several investigators have used the matching law or similar methods to analyze the behavioral effects of neuroleptics. The results show that these drugs produce similar parameter changes in a variety of experimental settings. In a study in which rats were food deprived and reinforced
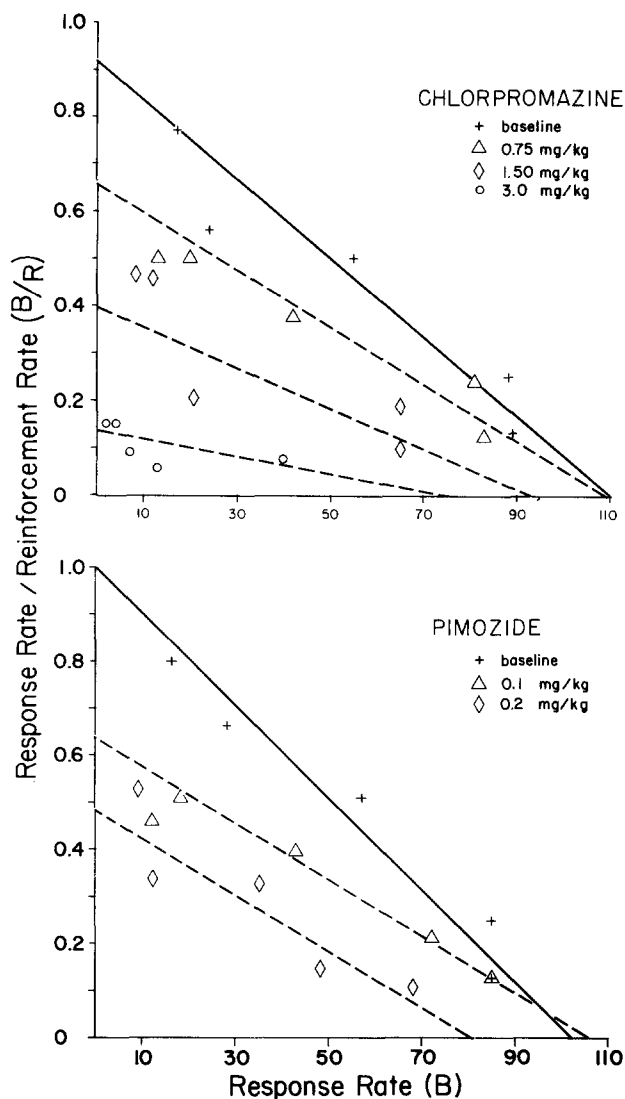
Fig. 5. A Scatchard plot analysis of the effects of chlorpromazine and pimozide on the relationship between response rate and reinforcement rate. The x-axis corresponds to response rate, and the x-axis coordinate of the fitted straight line at y=0.0 is equal to k (the response rate asymptote). The y-axis corresponds to the ratio of response rate to reinforcement rate, B/R, and the slope of the fitted straight line is equal to $-R_e^{-1}$, so that a change in slope is a change in the rate of reinforcement that produced a one-half asymptotic response rate. This method of plotting the response rates is obtained by a rearranging Eq. (1) so that $B/R = (k-B)/R_e$

with milk (Heyman 1983) pimozide decreased k and increased R_e, just as in the current study. Similarly, in studies in which the subjects were not deprived and brain stimulation was the reward (Franklin 1978; Gallistel and Karras 1984; Hamilton et al. 1985), several different neuroleptics have produced changes in response rate asymptotes and reward requirements that are similar to the ones observed in the current study. Moreover, the changes were the same when the response requirement was a lever press (Gallistel and Karras 1984; Hamilton et al. 1985) or traversing a runway (Franklin 1978). Together, these data suggest that neuroleptics decrease the efficacy of rewarding stimuli for a wide range of deprivation states and response requirements.

In contrast to the studies that show that pimozide and other neuroleptics increased R_e, Morley et al. (1984) describe results that they say indicate that pimozide did not increase R_e. In the study of Morley et al., rats responded on either a relatively rich reinforcement schedule, VI 10 s, or a relatively lean reinforcement schedule, VI 100 s. The authors point out that if pimozide increased R_e, responding should decrease relatively more in the VI 100 s schedule, whereas if it decreased k, responding should decrease proportionately in both schedules (see Heyman and Seiden 1985, and Morley et al. 1984 for a further discussion of these implications). The experimental results were unclear. At some doses, responding decreased more in the rich schedule, while at other doses, responding decreased more in the lean schedule. The inconsistencies may have been due to the order of the two conditions. Phase I of the study consisted of several weeks of training and drug injections on the rich schedule; Phase II consisted of several weeks of training and drug injections on the lean schedule. Consequently adaptation to drug treatment could have attenuated the drug effects in the lean schedule. For example, the 0.125 dose of pimozide consistently decreased responding in Phase I, whereas it had no effect or increased responding in Phase II. Since it is well established that pimozide does not increase responding for natural reinforcers, the effects of the 0.125 mg/kg dose in Phase II most likely reflect the subjects' experimental histories and not differences in reinforcement density. In any case, Morley et al. (1984) did not directly estimate the matching law parameters, and in every study in which experimenters used Eq. (1) or a similar form to evaluate the behavioral effects of neuroleptics, the rate of reinforcement necessary for a one-half asymptotic response rate increased.

The equation for a rectangular hyperbola, Eq. (1), has been used to described phenomena in physics, biology, and psychology (Heyman 1985). Consequently, it is possible to take advantage of the analytical techniques that have accompanied the application of this equation. For example, the Scatchard plot, developed for the analysis of binding of ligands to receptors, provides a convenient summary of response rate and parameter changes (Fig. 5) in the present study. Similar quantitative findings can be due to identical underlying mechanisms, analogous mechanisms, as with many normally distributed phenomena, (Mosteller et al. 1972), or dissimilar mechanisms, for example Fechner's just-noticeable-difference theory and Stevens' equal-ratio theory of sensory capacities (Geldard 1972). Elsewhere (Heyman 1985), it is suggested that the formal similarities between reinforced behavior and receptor binding studies are due to analogous mechanisms. However, whatever the underlying behavioral factors prove to be, the available data (Bradshaw et al. 1981; Hamilton et al. 1985; Heyman 1983; Heyman and Seiden 1985) suggest that Eq. (1) is a useful analytical tool for describing how drugs alter behavior.

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