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A QUANTITATIVE INTERRESPONSE-TIME ANALYSIS OF DRL PERFORMANCE DIFFERENTIATES SIMILAR EFFECTS OF THE ANTIDEPRESSANT DESIPRAMINE AND THE NOVEL ANXIOLYTIC GEPIRONE

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We describe an interresponse-time analysis of performance on a differential-reinforcement-of-low-rate 72-s schedule. This analysis compares the obtained interresponse-time distribution of individual rats to a corresponding random interresponse-time distribution. The random interresponse-time distribution is a negative exponential probability function; it predicts the relative distribution of interresponse times if the rat emitted the same number of responses randomly (i.e., with a constant probability) with respect to time. The analysis provides quantitative measures of peak location and dispersion of the interresponse times toward random performance. In Experiment 1, an unexpected outcome of this analysis was that the rats would have obtained more reinforcers had they responded at the same rate but randomly. Based on the interresponse-time analysis in Experiment 1, it was shown that rats trained on the differential-reinforcement-of-low-rate 72-s schedule could increase the number of reinforcers obtained in two ways: first, by a coherent shift of the interresponse-time distribution toward longer durations and, second, by dispersal of the interresponse times toward a random interresponse-time distribution. Experiment 2 applied the analysis described in Experiment 1 to the effects of desipramine and gepirone. Both drugs decreased response rate and increased reinforcement rate, but their effects on the distribution of interresponse times were different. The increase in reinforcement rate observed with desipramine was accompanied by a coherent shift of the peak of the interresponse-time distribution to the right. The increase in reinforcement rate observed with gepirone was accompanied by dispersal of the interresponse-time distribution toward the random negative exponential prediction.

Key words: interresponse time, differential reinforcement of low rate, desipramine, gepirone, antidepressant, anxiolytic, lever press, rats

The contingency of reinforcement implemented by the differential-reinforcement-of-low-rate (DRL) schedule specifies that only responses that result in interresponse times (IRTs) greater than a specified criterion duration are reinforced. The DRL schedule results in steady low rates of responding (Ferster & Skinner, 1957). When IRT distributions generated by subjects responding on DRL schedules are examined, they usually reveal that the IRT distributions have peaks in close temporal proximity to the criterion IRT duration. This fascinating result indicates that the subjects are in some manner timing their response output. Changes in the peak location and shape of the IRT distribution may be particularly sensitive for investigating behavioral effects of drugs. The DRL schedule has a long history of use as a tool for studying the behavioral effects of drugs, beginning with Sidman (1955) and Kelleher, Fry, Deegan, and Cook (1961). Moreover, antidepressant drugs have unique effects on DRL schedule performance (Seiden & O'Donnell, 1985).

Over the past decade, studies from this laboratory have found that antidepressant drugs decrease response rate and increase the reinforcement rate of rats performing on a DRL 72-s schedule of reinforcement. Drugs from other therapeutic classes do not have this effect (Marek, Li, & Seiden, 1989; Marek & Seiden, 1988a, 1988b; McGuire & Seiden, 1980a, 1980b; O'Donnell & Seiden, 1982, 1983, 1985). Based on these observations, we have proposed that performance on the DRL 72-s schedule may serve as a screen for identifying potential antidepressant drugs. In many of these studies, examination of IRT histograms has indicated that antidepressant drugs increase the number of IRTs > 72 s without changing the basic profiles of the IRT distributions (Marek & Seiden, 1988a, 1988b; McGuire & Seiden, 1980a, 1980b; O'Donnell & Seiden, 1982, 1983). The effect of antidepressant drugs on DRL 72-s IRT distributions has been var-

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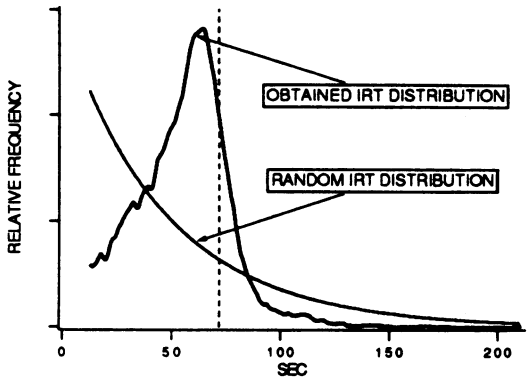


Fig. 1. Obtained and corresponding random IRT distributions of a hypothetical rat trained on a DRL 72-s schedule. The random negative exponential curve indicates what an IRT distribution of random responding would look like given an equal number of responses. The dashed line indicates the 72-s criterion IRT duration.

iously characterized as a shift to the right of the IRT histograms (O'Donnell & Seiden, 1983) or as an enhancement of temporal discrimination (Marek & Seiden, 1988a). Perhaps the most straightforward interpretation of these observations is that antidepressant drugs increase reinforcement rate at doses that do not disrupt the profile of the IRT histogram (Seiden & O'Donnell, 1985).

However, recently we have collected data that demonstrate that a decrease in response rate and an increase in reinforcement rate can be accompanied by two different IRT distributions. We have reported that the serotonin 1A agonists (5-HT1A) buspirone and gepirone decreased response rate and increased reinforcement rate of rats performing on DRL 72 s (Hand, Marek, Jolly, & Seiden, 1989), indicating that these drugs are potential antidepressants. Subsequent analysis of the profile of the IRT distribution from these studies indicated that these drugs dramatically altered the profile of the IRT distribution at the same doses that significantly increased reinforcement rate (Richards, Sabol, Jolly, & Seiden, 1990), a very different result from what has been previously reported for compounds that have tested positive on the DRL 72-s antidepressant screen. These observations have pointed out that further analysis of DRL 72-s IRT distributions is needed in order to characterize the effects of clinical classes of drugs on the DRL 72-s schedule.

The analysis of IRT histograms is problematic because the terms used above to describe effects of drugs on IRT distributions, such as "disrupted" and "profile of the IRT distribution," reflect qualitative judgments. Demonstration of the validity of these interpretations is provided in the form of representative IRT histograms of single subjects even though the reinforcement and response rate measures involve groups. Our goal here is to provide a quantitative analysis of DRL 72-s IRT distributions that avoids subjective interpretation of individual IRT histograms.

We shall use an approach to analyzing IRT distributions that compares each subject's obtained IRT distribution to a corresponding random IRT distribution. This random IRT distribution is a negative exponential curve that describes the IRT distribution obtained if a rat responds randomly with respect to time (by *random* we mean that the probability of a response occurring does not change as a function of the time since the last response). This constant-probability random IRT distribution is described by a negative exponential function. A negative exponential function has been used by a number of investigators in operant conditioning (Blough, 1963, 1966; Mueller, 1950; Sidman, 1954) and behavioral ethology (Duncan, Horne, Hughes, & Wood-Gush, 1970; Slater, 1975) to analyze interevent data (for an informative discussion of the use of negative exponential curves see Fagen & Young, 1978).

Rats trained on a DRL 72-s schedule of reinforcement produce IRT distributions that look like the relative frequency IRT distribution in Figure 1. The negative exponential curve in Figure 1 shows the appearance of the IRT distribution if the hypothetical rat in Figure 1 responded randomly with respect to time.

For any given number of responses distributed over time, a corresponding negative exponential random IRT distribution can be constructed. The corresponding random IRT distribution takes into account the total number of IRTs and the length of time it took to make them. The random curve in Figure 1 shows that by chance shorter IRTs will occur more frequently than longer IRTs, thus decreasing the opportunity for the occurrence of longer IRTs. This observation also served as the basis of the per opportunity analysis developed by Anger (1956). The per opportunity analysis and the present approach are similar in that both rely on a constant-probability neg-

ative exponential function for interpretation (Anger, 1963; Blough, 1966). In this way the present analysis is an extension of the per opportunity analysis. However, the present approach is more similar to the IRT analysis used by Sidman (1954), who compared obtained IRT distributions directly to corresponding negative exponential IRT distributions. Further comparison with the approaches of Anger and Sidman will be made in the discussion section.

In the analysis described below, we focus on two aspects of the IRT distribution: the location of the distribution's peak and how much the obtained IRT distribution differs from random. The peak location and the difference between the obtained and random IRT distributions form the basis of a quantifiable IRT analysis. For example, treatments that have disruptive effects on DRL 72-s performance may cause dispersal of the obtained IRT distribution toward a random distribution. Disruptive effects would then decrease the difference between the obtained distribution and the corresponding random distribution. In contrast, other treatments may cause coherent changes in the shape of the IRT distribution. Examples of coherent effects would be shifts of the peak to the left or right and/or increases in the magnitude of the peak.

In this paper we will concentrate on the analysis of IRT distributions obtained from rats performing on a DRL 72-s schedule of reinforcement. However, the same analysis is applicable to IRT distributions generated by different DRL values as well as other kinds of reinforcement schedules. Below we present two experiments. Experiment 1 provides a detailed description and explanation of the method of analysis. In this experiment we describe the DRL 72-s performance of 8 rats and come to the conclusion that on this schedule of reinforcement, the rats would have obtained more reinforcers had they responded at the same rate but randomly. In Experiment 2 we use the IRT analysis presented in Experiment 1 to compare the effects of the antidepressant drug desipramine with the effects of the novel anxiolytic gepirone. As was previously noted, we have made preliminary observations (Hand et al., 1989; Richards et al., 1990) showing that although both desipramine and gepirone increased reinforcement rate on the DRL 72-s schedule, the effects of these two drugs on the IRT distribution were markedly different using a qualitative analysis of the IRTs. For this reason we chose to investigate the effects of these drugs on the IRT distribution using the quantitative analysis described below.

EXPERIMENT 1

METHOD

Subjects

Eight male Sprague-Dawley rats, weighing between 390 and 480 g at the time of the experiment, were used. The rats were housed 2 per cage in hanging stainless-steel wire cages. Lights were on in the colony room from 6:00 a.m. to 8:00 p.m. Food (4% Teklab rat chow) was available ad lib. Access to water was restricted to 20 min per day. On training days the rats received 20-min access to water at the end of their training session. On nontraining days (weekends), the rats were given 20-min access to water between 10:00 a.m. and 2:00 p.m.

Apparatus

Eight operant chambers were used. Each operant chamber was 20.5 cm wide, 20.5 cm deep, and 23.5 cm long. The operant chambers had grid floors, aluminum front and back walls, and Plexiglas sides. A lever was mounted 3 cm above the grid floor, 4.5 cm from the nearest side. A downward force of 0.15 N was required for a lever press to be registered. A solenoid-operated dipper (Gerbrands Model G5600) was mounted 10 cm to the left of the lever. Access to the dipper was through a round hole (4.5 cm diameter) in the front panel. A lever press that resulted in reinforcement caused the dipper mechanism to lift the dipper (0.025 mL) from a water trough to within reach of the rat's tongue for a duration of 4 s. A stimulus light mounted 15 cm above the floor on the back wall of the chamber served as the houselight and was turned on when a session began and off when the session ended. The operant chambers were enclosed in 80-quart Coleman ice chests to attenuate external stimuli. Fans mounted on the ice chests provided ventilation and masking noise. The operant chambers were connected to a PDP-11/73® microcomputer via a Coulbourn Lablinc interface. The schedule contingencies were programmed and sequential IRTs were recorded

in centiseconds using the SKED-11® software system (Snapper, Stephens, Cobez, & Van Haaren, 1976).

Training

Upon arrival in the colony, the rats were adapted to the 20-min-per-day access to water regimen for 1 week. The rats were then trained on the DRL 72-s schedule using a regimen that involved three phases: (a) initial bar-press response training, (b) DRL 18-s training, and (c) DRL 72-s training. In all three phases the rats were placed in the chambers overnight from approximately 6:00 p.m. to 8:00 a.m. Overnight training was conducted two or three times per week.

Initial bar-press training consisted of exposing the rats overnight to four 30-min training sessions during which an alternative fixed-ratio (FR) 1, fixed-time (FT) 1-min schedule of reinforcement was in effect. These 30-min sessions were separated by 2 hr. The duration of each session was signaled by turning on and off the houselight. If the rats did not begin responding after four overnight sessions, the bar-press response was shaped by the experimenter.

The rats were then shifted to the DRL 18-s training regimen for 5 or 6 nights. DRL 18 overnight training consisted of 6 1-hr sessions. A 30-min timeout (houselight off) separated the sessions. Overnight training on DRL 72 s was then implemented for an additional five or six overnight training sessions. The DRL 72-s overnight training was the same as the DRL 18-s training except that the schedule parameter changed from 18 to 72 s.

At the end of the overnight training regimen, the rats were trained during daily (5 days a week) 1-hr sessions under the DRL 72-s schedule for 5 weeks before the data reported here were collected.

Procedure and Results

Removing Bursts from the IRT Distribution

Figure 2 shows IRT frequency distributions for the 8 rats trained on the DRL 72-s schedule. The data shown are from the 25th daily session. The histograms depict the frequency of IRTs that fell within successive 12-s bins. Examination of the IRT absolute frequency histograms in Figure 2 reveals that some (i.e., 253, 256, 257, 258), but not all, of the rats had a mode in the first 12-s bin. In contrast, other rats (i.e., 251 and 252) had no or very few IRTs in the first bin. Ignoring the first 12-s bin, all 8 rats in Figure 2 had a modal point (or peak) in their IRT distributions close to the 72-s criteria. Similar observations in many different groups of rats clearly suggest that DRL 72-s IRT distributions consist of two separate and independent distributions: a highly variable (between rats) burst distribution, and a less variable pause distribution.

The histograms in Figure 3 show the same data as Figure 2; however, the Figure 3 IRT distributions have been plotted as relative frequencies and "debursted" by removing all IRTs < 6 s. The 12-s bins in Figure 3 run from 6 to 18, 18 to 30, and so on. The justification for removing the burst distribution is that the overall IRT distribution is in fact made up of two distributions, a burst distribution (IRT $<$ 6 s) and a pause distribution (IRT $\geq$ 6 s) reflecting different behavioral categories. This approach is the suggested technique for analyzing data that occur in bouts (or bursts) separated by relatively long periods of nonoccurrence (Fagen & Young, 1978) and allows the pause and burst distributions to be considered separately.

The 6-s cutoff used here greatly reduced the number of IRTs falling within the first 12-s IRT bin (Figure 3). A shorter cutoff (e.g., 2 s) would have increased the number of IRTs in the first bin only slightly. The longer cutoff was chosen to assure separation of the burst and pause distribution (Slater & Lester, 1980). It should also be noted that some rats (i.e., 251 and 252) did not produce bursts. However, their IRT distributions were also "debursted" in the same way (with little effect, because these rats had few IRTs < 6 s). The validity of a particular cutoff value depends on the orderliness of the resulting data.

Further evidence that bursting (IRTs < 6 s) and pausing (IRTs ≥ 6 s) represent fundamentally different processes comes from correlating the number of burst and pause IRTs with the number of reinforcers obtained. Because the DRL 72-s schedule reinforces only those responses that occur >72 s since the last response, one might predict that rats with a high frequency of burst responding would obtain fewer reinforcers. Table 1 shows the rate of burst and pause responses (responses per hour) as well as the rate of obtained reinforcers

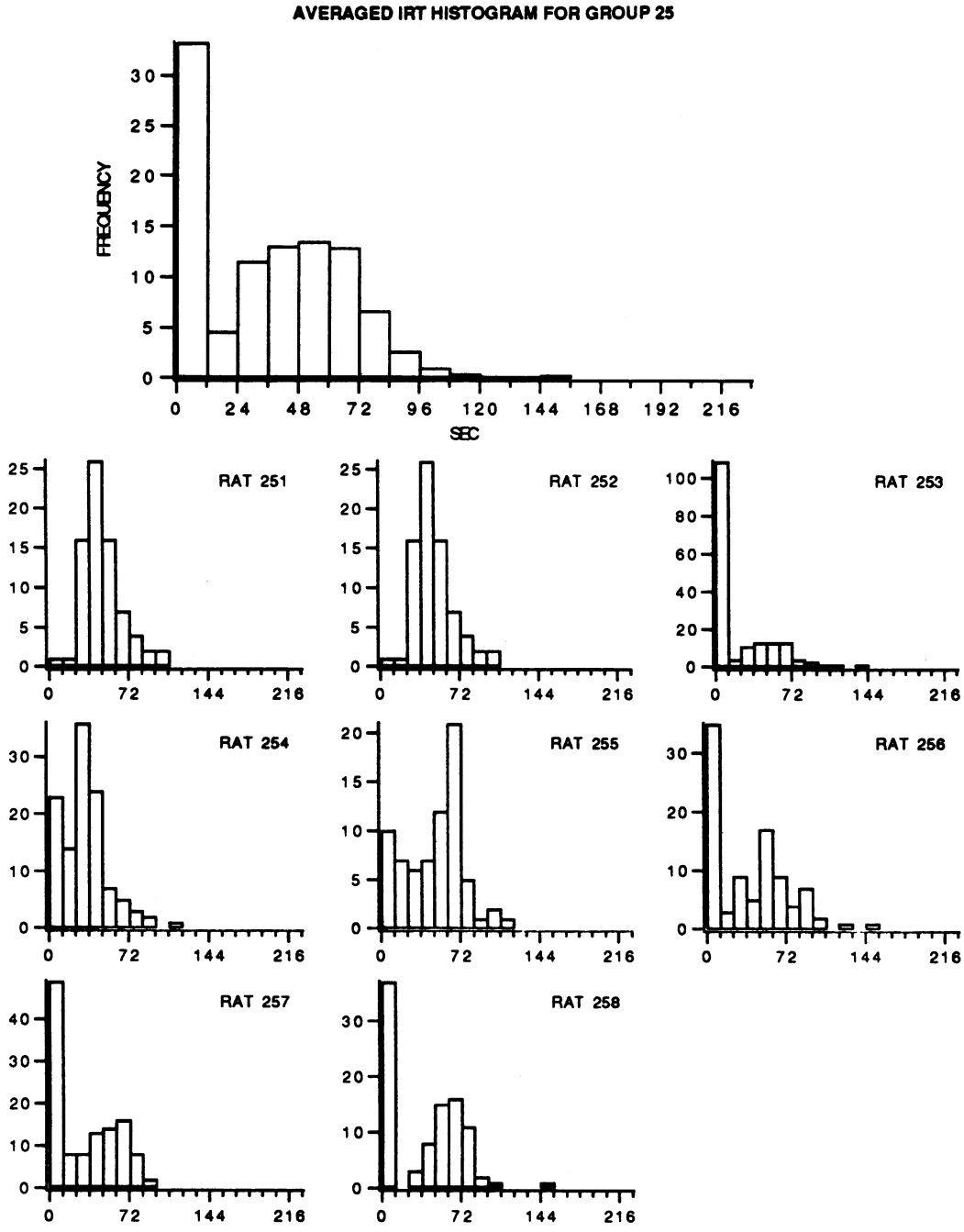


Fig. 2. IRT distributions of a group of 8 rats trained on DRL 72 s. The large histogram on top shows the averaged IRT distribution for the 8 rats. The smaller histograms below it show the IRT distributions for the individual rats. Each IRT bin is 12 s wide.

(reinforcers per hour) for each of the 8 rats under consideration here. The correlation coefficient for bursting versus reinforcements was $R = -0.037$ ($p > .05$), indicating that rats with higher rates of burst responding did not earn significantly fewer reinforcers. In contrast, the correlation coefficient for pausing versus reinforcements was $R = -0.864$ ($p <$

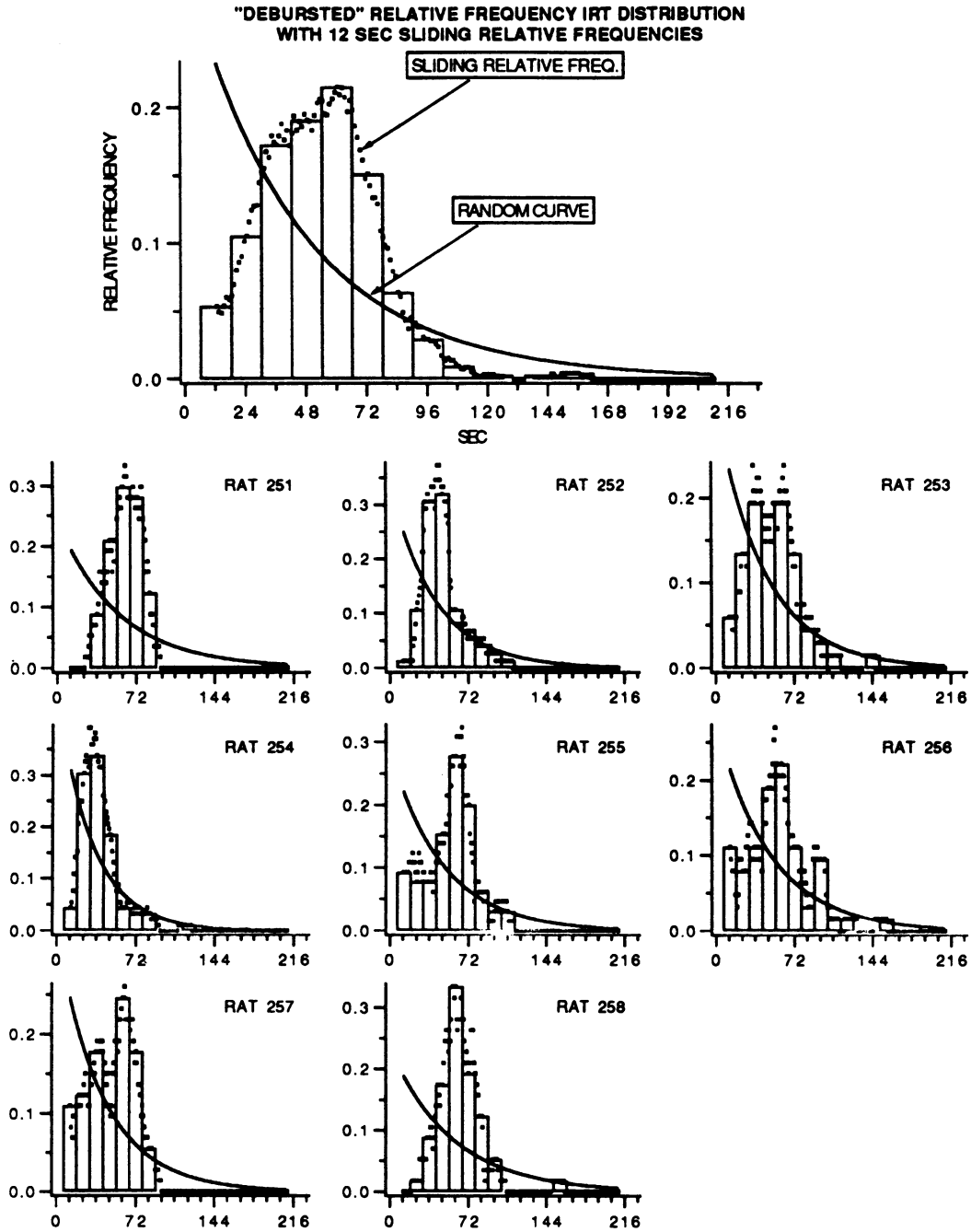


Fig. 3. Deburstered relative IRT frequencies with sliding relative frequencies. The bar histogram shows the relative frequencies of IRTs in successive 12-s bins. The dots show sliding 12-s relative frequencies. Each successive dot shows the relative frequency of a 12-s bin that has been "slid" to the right by 1 s. The solid line indicates the corresponding negative exponential random distribution. This curve indicates what the IRT distribution would have looked like had the rats randomly emitted the same number of responses. The large graph is averaged across 8 rats. The smaller graphs below it show the same data for the individual rats. The data from which these graphs are constructed are the same as presented in Figure 2, except that IRTs < 6 s (bursts) have been eliminated.

Table 1

Experiment 1: summary of interresponse-time analysis of DRL 72-s behavior.

Rat	Responses/hr		Peak	KSD score	p value	IRT > 72 s (Reinforcers/hr)	
	Burst	Pause				Obtained	Predicted
251	2	57	66.3	.403	.0000	16	17.4
252	0	75	44.0	.361	.0000	8	15.4
253	106	67	58.5	.246	.0006	10	15.5
254	23	92	34.8	.283	.0000	6	12.1
255	7	65	63.4	.287	.0000	9	16.5
256	30	63	57.9	.237	.0016	15	16.7
257	45	73	63.5	.244	.0003	10	15.5
258	37	57	64.4	.373	.0000	15	18.0

Note: Burst responses are responses that resulted in IRTs < 6 s. Pause responses are responses that result in IRTs ≥ 6 s. The peak is the IRT duration at which there was the greatest difference between the obtained IRT distribution and the corresponding random IRT distribution. KSD is the Kolmogorov-Smirnov (goodness-of-fit test) difference score. The larger the KSD score, the larger the difference between the obtained IRT distribution and the corresponding random IRT distribution. p value is the significance level of each rat's KSD score. "Obtained" indicates the number of responses emitted by the rat that resulted in reinforcement. "Predicted" indicates the number of reinforcers the rat would have obtained had it responded randomly (see text for details).

.01), indicating that rats with higher rates of pause responding earned significantly fewer reinforcers. This result and inspection of the individual data in Table 1 indicate that bursting (at least at the frequencies observed here) does not affect the rate of obtained reinforcement. These correlations are consistent with the idea that pause responses but not burst responses reflect the temporal contingency enforced by the DRL 72-s schedule.

Sliding Relative Frequencies

In addition to removal of all IRTs < 6 s, the y axis in Figure 3 has been changed from absolute frequency to relative frequency. To compute the relative frequency, the total number of IRTs in each 12-s bin is divided by the total number of IRTs. This assures equal weighting when comparing IRT distributions between rats, because each rat's relative frequency histogram sums to 1. This equal weighting is particularly important for the averaged graph at the top of Figure 3, because all rats contribute equally. If the absolute frequencies are averaged, rats with larger numbers of IRTs would contribute disproportionately to the averaged distribution.

One goal of the present analysis was to localize the peak of the IRT distribution. However, given a bin width of 12 s, it is difficult to localize the peak with any degree of specificity. To better localize the peak of the IRT distribution, we smoothed the distribution using a 12-s sliding window. To do this we first accumulated the IRTs of each rat into 210 bins, each 1-s wide. Only IRTs > 6 s were used to eliminate bursting. The number of IRTs in the 12-s intervals following each second were then counted. This resulted in 198 sums (210 − 12) for successive 12-s intervals shifted to the right by 1 s. The 12-s sums were then divided by the total number of pause responses. The resulting 12-s sliding relative frequencies are indicated by the dots in Figure 3. Each successive point represents the relative frequency of a 12-s bin displaced to the right by 1 s. For example, the left three dots in Figure 3 represent relative frequencies for three bins with the following upper and lower bounds: 6 to 18, 7 to 19, and 8 to 20 s. These points are plotted at the median location of each 12-s bin so that the points are plotted at locations 12.5 s, 13.5 s, 14.5 s, and so on. As can be seen in Figure 3, these sliding relative frequencies allow a clearer visualization of the IRT distribution peak. In addition (as will be discussed below), the sliding relative frequencies permit a more precise quantitative determination of the peak of the IRT distribution.

Computation of Random Distribution

Computation of the random negative exponential distribution for a given obtained IRT distribution requires the mean IRT length or its reciprocal, response rate (r):

$$f(t) = re^{-rt}, \quad (1)$$

where t is the time elapsed since the last response.

In practice we need to be able to determine the probability of an IRT falling between two time points (for example, the upper and lower limits of the 12-s time bins in Figure 3). If the IRTs are exponentially (randomly) distributed, the probability that an IRT will be greater than t is:

$$p(\text{IRT} > t) = e^{-rt}, \quad (2)$$

where r is responses per second.

From Equation 2 it is then possible to compute the probability that an IRT will fall between two time points $t1$ s and $t2$ s according to the random negative exponential distribution:

$$p(t1 < \text{IRT} < t2) = e^{-rt1} - e^{-rt2}. \quad (3)$$

The random curve for the pause distribution is computed taking into account that IRTs < 6 s have been removed. The mean of the debursted IRTs is computed. Six seconds are subtracted from the debursted mean and the upper ($t2$) and lower ($t1$) bounds of each 12-s bin. The response rate (r) is then determined by taking the reciprocal of the mean. For other examples of this approach see Fagen and Young (1978) and Duncan et al. (1970). For each sliding relative frequency bin (dots in Figure 3), a corresponding random distribution is computed using Equation 3. The negative exponential curves in Figure 3 were constructed in this way.

Difference Curves

As discussed earlier, the approach we have taken to analyzing DRL 72-s responding is to compare obtained IRT (pause) distributions with corresponding random negative exponential IRT distributions for each rat. Figure 4 presents the data shown in Figure 3 in the form of difference curves. The difference curves presented in Figure 4 were calculated by subtracting the random negative exponential curve from the obtained 12-s sliding relative frequencies (see Figure 3). The horizontal line at zero now represents the corresponding random negative exponential. The points below zero represent IRTs that occur at lower frequencies than predicted by the negative exponential model. The points above zero represent IRTs that occur at higher frequencies than predicted by the negative exponential model. As can be seen in Figure 4, the difference curves for the individual rats all have the same characteristic form. The typical difference curve begins below zero, intercepts zero at Point A (the positive intercept), reaches a peak (usually well before the 72-s criterion), and then falls below zero at Point B (negative intercept). Figure 4 shows that rats performing on the DRL 72-s schedule have IRT distributions different from the constant-probability random distribution (different from the horizontal zero). It also shows that the difference curve transformation provides clearly defined peaks that usually occur well before 72 s. For example, the IRT distribution of Rat 253 has a broad, badly defined peak when viewed as a relative frequency distribution in Figure 3. In contrast, the difference curve transformation shown in Figure 4 provides a relatively well-defined peak for Rat 253.

Quantitative Analysis

Up to this point we have presented a qualitative graphical analysis of DRL 72-s responding, but now we will present a quantitative way to characterize this IRT analysis. As previously discussed and elaborated below, two aspects of the IRT distributions are important: (a) peak location and (b) the difference between the obtained relative frequency IRT distribution and the constant-probability random distribution (Figure 4).

Peak location. Peak location designates the IRT length at which there is the greatest difference between the obtained relative frequency distribution and the corresponding random distribution (i.e., the peak of the difference curves presented in Figure 4). Importantly, peak location, as defined here, is not necessarily the IRT duration at which there is the greatest deviation from absolute zero (Figure 3). One approach to finding this peak would be simply to find the location with the largest positive deviation from zero in Figure 4 and designate it the peak location. Experience has shown us that this approach is subject to fluctuations in the data and sometimes results in variable or spurious peak values. Instead, we find the zero intercepts A and B shown in the top graph in Figure 4 and then compute the median of the deviations from zero between these two points. This is done by a computer program that computes the difference curves shown in Figure 4. The program

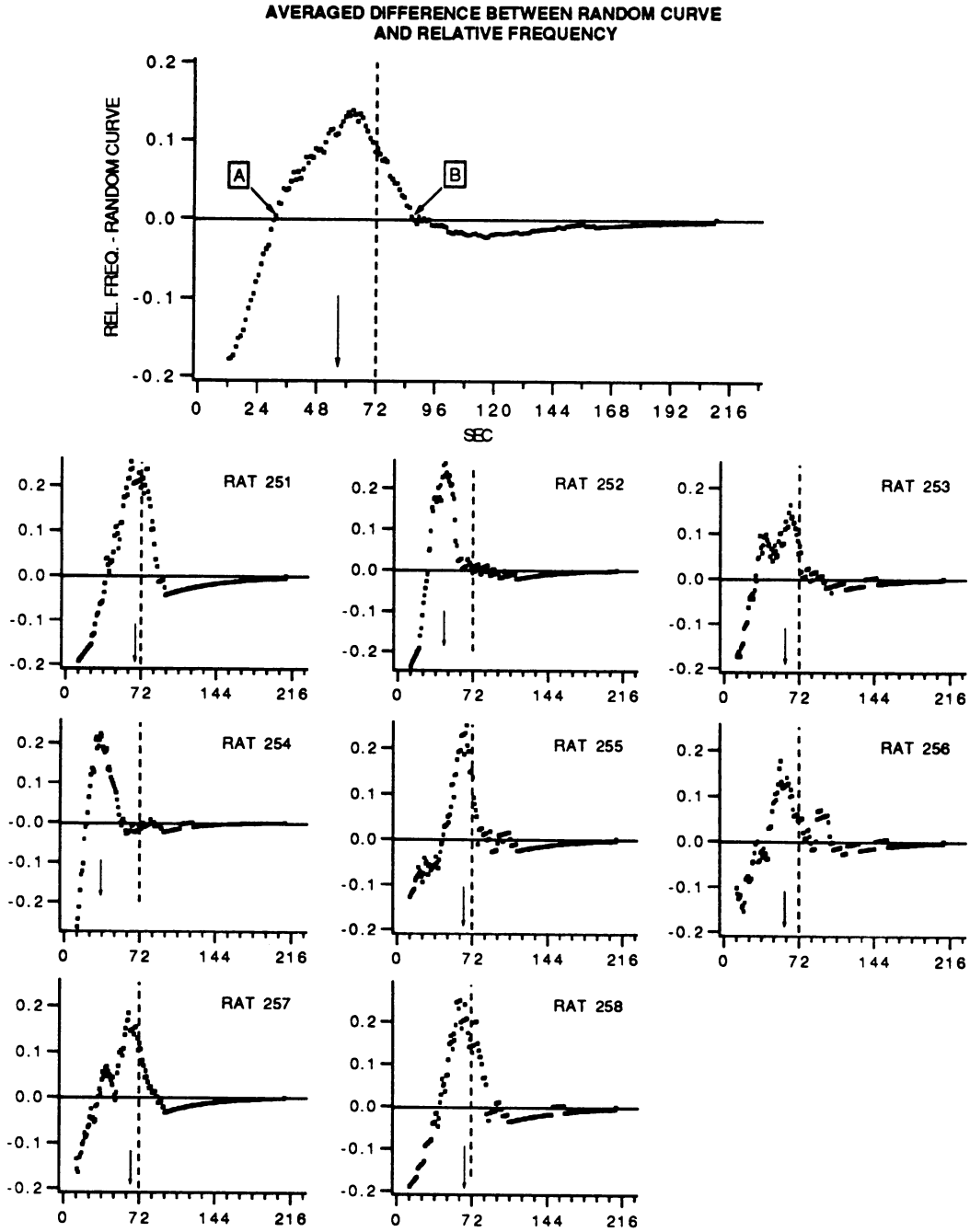


Fig. 4. Difference curves. The dots indicate difference curves that show the results of subtracting the negative exponential random IRT distribution from the obtained 12-s sliding frequency curves shown in Figure 3. The arrows indicate the peak location of the difference curve. Intercepts A and B are used to calculate the peak location of the difference curve (see text). The dashed line indicates the DRL 72-s criterion duration. The large graph on top is averaged across 8 rats. The smaller graphs below it show the same data for individual rats.

first finds the point in each difference curve with the largest positive deviation from zero (modal point). Ties are broken by taking the median of the tied points. Intercept A is found by searching in the direction of zero (on the x axis) from the modal point for the last y value ≥ 0. If a y value ≥ 0 is not encountered before the 18-s IRT bin, 12.5 is taken as Point A. Intercept B is found by searching (again starting from the modal point) in the direction away from zero for the last point on the difference curve $\geq$ zero. The median of the deviations of the difference curve from zero (on the y axis) between Points A and B is then taken as the measure of peak location. The values of the peak location for the 8 rats are given in Table 1.

The peak-finding algorithm described above is carried out on the data of individual rats. In Figure 4 the peak locations are indicated by the arrows above the x axis. The peak location indicated in the averaged graph at the top of Figure 4 is an average of the peak locations for the 8 rats.

Difference between the obtained and negative exponential random IRT distributions. The difference curves in Figure 4 are highly processed representations of the data. Although these are suitable for finding peak location, they are problematic to interpret in terms of absolute deviations from zero. For this reason we use another approach, the Kolmogorov-Smirnov difference score (KSD), a nonparametric measure of goodness of fit that does not rely (directly) on the data representations in Figure 4. The KSD statistic provides a difference score indicating how different two distributions are from one another (Gibbons, 1985; Press, Flannery, Teukolsky, & Vetterling, 1989; Siegel, 1956). In our case the difference between the obtained IRT distribution and the corresponding negative exponential random distribution is indicated. The KSD score is obtained from the unbinned IRTs and so eliminates inaccuracies due to binning. The KSD score is defined as the absolute maximum difference between two cumulative relative frequency distribution functions. In our application the two cumulative relative frequency distributions are (a) the obtained IRTs of individual rats and (b) the corresponding random negative exponential curves. An important aspect of the KSD statistic is that it allows statistical judgments to be made about the IRT distributions of individual rats. This means that a rat's KSD score can be evaluated to determine whether its obtained IRT distribution is significantly different from its corresponding random negative exponential curve.

To retain the graphical form of the negative exponential curve, we chose to display the cumulative relative frequency distribution as a survivor function. A survivor function is the inverse of a cumulative relative frequency distribution. This means that we plot the fraction of IRTs $> t$ on the y axis instead of the fraction of IRTs $< t$ (as shown in Press et al., 1989). To construct the survivor function of the debursted IRT distribution, the obtained pause IRTs are first sorted into ascending order. After this is accomplished, a y value on the survivor curve for each IRT $= t$ is computed by determining the fraction of all the IRTs $> t$. Figure 5 shows the survivor plots for the same rats as Figures 2 through 4. The abscissa corresponds to time t and the ordinate displays the fraction of IRT durations greater than t.

The survivor function predicted for each IRT duration by the negative exponential curve is calculated using Equation 2. Six seconds are subtracted from the debursted mean IRT duration. The response rate (r) is then determined by taking the reciprocal of the debursted IRT mean. The negative exponential survivor curves are shown in Figure 5. The KSD score is then found by locating the IRT duration at which there is the largest absolute difference between the survivor function of the obtained relative frequency distribution and the survivor function of the random negative exponential curve. The difference at this location is the KSD score (see Figure 5). Because the KSD score is taken from a cumulative curve, it reflects an overall difference between the two distributions and not just the difference at a single point. The level of significance for the difference between the obtained distribution and the corresponding random negative exponential distribution is determined by the KSD score and the number of observations in the sample (Gibbons, 1985; Siegel, 1956).

Table 1 shows the actual KSD scores obtained for the 8 rats in Figure 5. The larger the KSD score, the greater the difference between the obtained IRTs and the random negative exponential curve. It is interesting to compare the KSD scores with the difference curves in Figure 4 to observe the correspon-

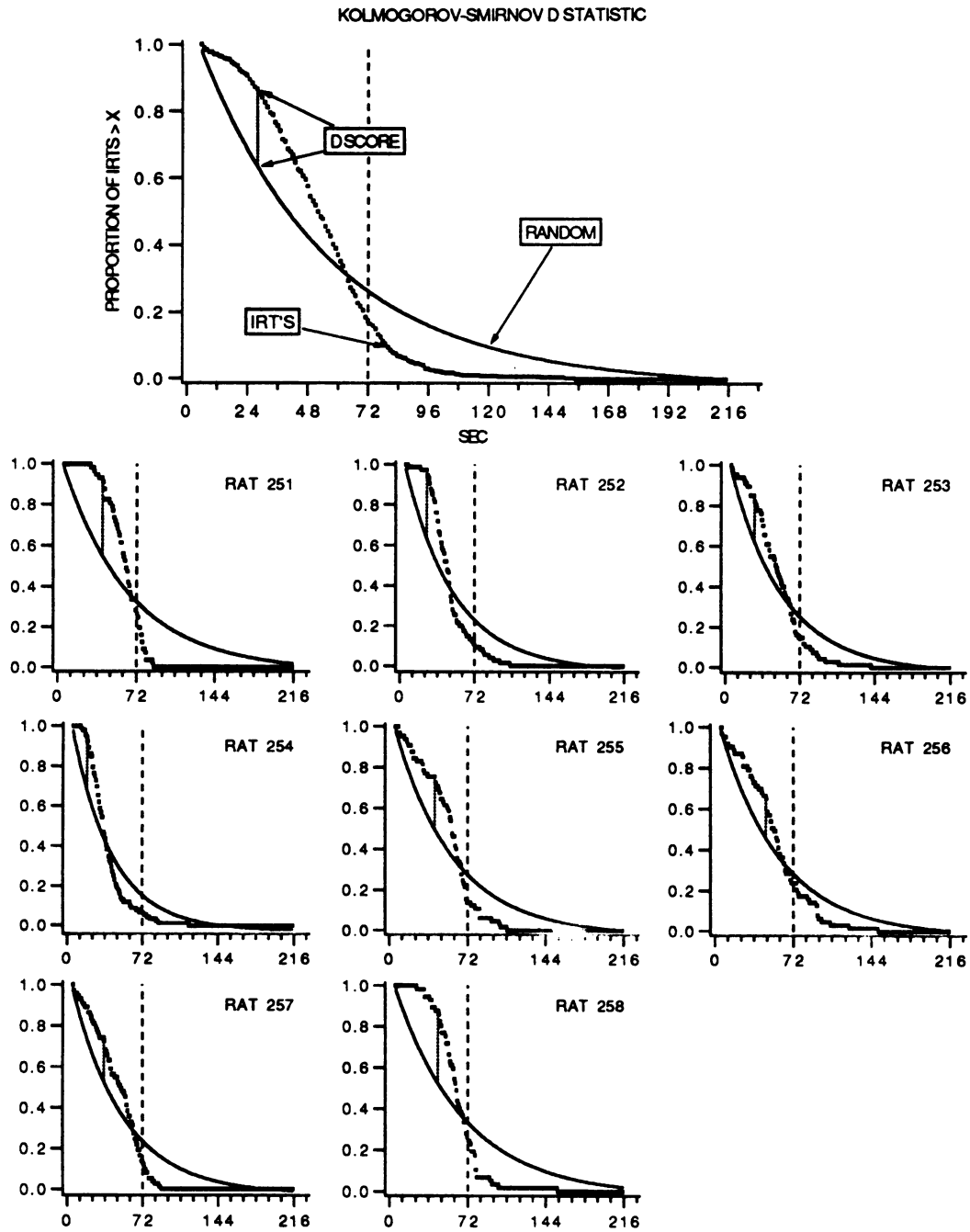


Fig. 5. Survivor curves. The dots show the survivor function for the obtained IRT distributions shown in Figure 3. The solid line shows the survivor function for the corresponding negative exponential random distribution. In these plots, y values indicate the fraction of IRTs to the right of the corresponding x value. The vertical dotted lines between the obtained survivor function and the corresponding random negative exponential survivor function indicate the location at which there is the greatest difference between the two curves. The difference at this location is the Kolmogorov-Smirnov difference score. The large graph on top is averaged across 8 rats. The smaller graphs below it show the same data for individual rats. The dashed line indicates the DRL 72-s criterion duration.

dence between the qualitative graphical presentation and the quantitative KSD score measure. For example, compare Rat 251 (KSD score = .403) and Rat 253 (KSD score = .246). The difference curve of Rat 251 has a greater amplitude than the difference curve of Rat 253.

As discussed above, the KSD statistic evaluates KSD scores for individual rats. A significant KSD score indicates that the null hypothesis (that the two distributions are the same) should be rejected. The significance levels of the KSD scores for each of the 8 rats are indicated in Table 1. In this group, all 8 rats had $p < .01$, indicating that all of these rats had IRT distributions significantly different from their corresponding random IRT distributions.

Predictions of the Random Model

An important aspect of DRL 72-s performance is the number of IRTs > 72 s (reinforced responses). Figure 3 and Table 1 show that rats performing under the DRL 72-s contingency generally produce IRT distributions that are significantly different from the random negative exponential prediction. Presumably these peaked distributions result from the rats adjusting their behavioral output in accordance with the temporal contingency of reinforcement provided by the 72-s criteria. However, Figure 4 and Table 1 show that the rats have peaks in their IRT distributions that occur before 72 s. It is informative to compare the number of obtained IRTs > 72 s with the number of IRTs > 72 s predicted by the negative exponential model. This can be done by using Equation 2 presented above, setting $t = 72 - 6$ s, and multiplying the resulting probability by the total number of pause IRTs (N):

$$\text{Frequency of IRTs} > 72 = Ne^{(-rt)}. \quad (4)$$

The number of obtained IRTs > 72 s and the number predicted by the negative exponential model are shown in Table 1. Surprisingly, the rats would have obtained more reinforcers had they responded randomly. In other words, had the rats responded at the same overall rate but dispersed their responses randomly in time, they would have obtained more reinforcers.

Discussion

An important aspect of the IRT analysis presented here is that burst responding and pause responding are fundamentally different. The distinction between burst responding and pause responding has been made previously by a number of different investigators. The tendency for a large number of IRTs to fall within the first bin of DRL IRT distributions (for some rats) was first noted by Sidman (1956), who described these short IRTs as bursts. Since then many other investigators have also noted bursting on DRL schedules of reinforcement (for a review see Kramer & Rilling, 1970). Blough (1963, 1966) presented data indicating that bursting reflects the response topography of individual subjects. Blough showed that the occurrence of bursting is highly variable among subjects (as we noted above) and that the IRTs that make up bursting are insensitive to reinforcement.

The result indicating that burst responding was not negatively correlated with the number of reinforcers obtained is consistent with a recent report by Wearden (1990). Using computer modeling, Wearden showed that short IRT responses have no consequential effect on the overall obtained reinforcement rate. Because of this, Wearden proceeded to model responding on DRL schedules taking into account only longer IRTs or what he termed "timing responding."

Experiments using DRL schedules to study the effects of benzodiazepine anxiolytics and psychomotor stimulants provide additional evidence indicating that burst responding is inherently different from pause responding. Both anxiolytics and psychomotor stimulants increase the rate of responding on DRL schedules of reinforcement; however, they do this in two different ways. Anxiolytics specifically increase burst responding, whereas the psychomotor stimulant amphetamine does not (Sanger & Blackman, 1989).

It should be emphasized that when we discuss "debursted" IRT distributions we do not mean to say that we have eliminated burst responding. Rather, we view "debursting" as separating a heterogeneous IRT distribution into two more homogeneous IRT distributions. Furthermore, we do not intend to ignore burst responding because (as pointed out above) it can play an important role in determining drug effects.

Whatever the explanation is for the short IRTs that make up bursting, it seems likely that burst IRTs are categorically different from the longer IRTs that make up DRL pause

IRT distributions. We have come to view DRL IRT distributions as reflecting brief periods of interaction with the lever (bursting) separated by longer intervals of noninteraction with the lever (pausing).

As was noted in the introduction, the present approach to IRT analysis was developed from previous analyses described by Sidman (1954) and Anger (1956). Anger's IRT per opportunity (IRTs/op) analysis takes into account the fact that compared to long IRTs, there are a greater number of opportunities for short IRTs to occur. Anger adjusted for this difference by differentially weighting the longer IRTs to make IRTs of different durations equivalent. The IRTs/op measure is calculated by dividing the number of responses in each IRT time bin by the number the opportunities for those responses to occur, where the number of opportunities equals the number of responses in that bin plus the number of responses in the remaining longer IRT bins. This approach is similar to the present approach in that if an IRT distribution that exactly followed a negative exponential curve were plotted using the IRTs/op measure, the result would be a flat horizontal line (see Blough, 1966, p. 583, Figure 1). Perhaps the most important contribution of Anger's (1956) IRTs/op measure is conceptual. The IRTs/op measure makes explicit the concept that for an IRT of a given duration to occur, IRTs of shorter duration cannot have occurred. Consequently, by chance there is a higher probability of short IRTs occurring than long IRTs. This is the relationship described by the negative exponential function.

Sidman's (1954) analysis was very similar to the analysis described in this paper. Sidman directly compared negative exponential curves to obtained IRT distributions in the form of survivor curves as in Figure 5 of the present paper. The present approach further develops Sidman's technique by providing ways to better visualize and quantitatively evaluate the difference between the obtained and corresponding negative exponential (e.g., difference curves, peak location, and KSD score).

As Anger (1956) pointed out, two difficulties exist with the IRTs/op measure. First, the IRTs/op measure becomes less reliable as the number of remaining IRTs decreases. Second, the IRTs/op measure at any given IRT duration is dependent upon the occurrence of IRTs at shorter or longer durations. This second difficulty makes it problematic to determine the overall shape of the obtained distribution. For example, with the IRTs/op measure it is difficult to localize a peak location. In contrast, the approach taken in this paper of direct comparison of obtained IRT distributions to corresponding negative exponential distributions permits comparison of the overall shapes of the distributions and can be readily used to determine peak location. Anger (1963) argued that the approach used by Sidman (1954) (i.e., directly contrasting the obtained IRT distribution with the corresponding negative exponential) was less sensitive then the IRTs/op measure. However, the evidence presented by Anger in support of this argument was graphical and not quantitative. The present IRT analysis, using the basic technique of Sidman, provides specific quantitative tools (i.e., peak location and KSD score) for characterizing the difference between the obtained and corresponding negative exponential IRT distributions.

A further advantage of the present approach to IRT analysis is that the corresponding negative exponential allows predictions about random performance to be made. For example, the present results showed that rats can obtain more reinforcers on the DRL 72-s schedule in two very different ways: first, as would be expected, by shifting the peak of the IRT distribution to the right and, second, by dispersal of the IRTs toward the corresponding random negative exponential distribution.

In the IRT analysis described above, an increase in IRTs > 72 s caused by a peak shift would be detected as a significant shift in the peak with no significant decrease in the KSD score. An increase in IRTs > 72 s caused by random dispersal of IRTs should be indicated by a significant decrease in the KSD score and the absence of a peak shift to the right.

Experiment 2 demonstrates that desipramine (DMI) and gepirone have similar effects on reinforcement rate (increases) while having two very different effects on the obtained IRT distributions.

EXPERIMENT 2

METHOD

Subjects, Apparatus, and Training

Fifteen rats were used. The rats were maintained as described in Experiment 1. The ap-

paratus and training regimen were the same as Experiment 1.

Procedure

Drug administration. Both gepirone hydrochloride (Bristol-Myers) and desipramine hydrochloride (DMI) (SIGMA) were dissolved in saline to form an injectable solution of 1 mL/kg. DMI was administered intraperitoneally an hour before the session. Gepirone was administered subcutaneously 10 min before the session. All doses were given in ascending order, with the exception of 6.0 mg/kg gepirone, which was given after the 10.0 mg/kg dose. Eight rats received DMI, and 7 rats received gepirone. The drugs were given on Tuesdays and Fridays.

Data analysis. The effects of DMI and gepirone on response rate and reinforcement rate were determined. Response rate was broken down into two components: burst responses per hour (responses that resulted in IRTs < 6 s) and pause responses per hour (IRTs ≥ 6 s). The effects of DMI and gepirone on DRL 72-s IRT distributions were evaluated using the analysis described in Experiment 1.

In addition to presenting the data of individual rats at each drug dose, we also evaluated the group data for statistical significance across doses. This was done for burst and pause response rate, reinforcement rate, and peak location using a single-factor repeated-measures analysis of variance. If the overall F score was significant, subsequent multiple comparisons were done using Duncan tests (Keppel, 1973). The KSD score was evaluated in two ways, first on a single-subject basis to determine if each rat's obtained IRT distribution was significantly different from the corresponding random negative exponential distribution and, second, across drug-dose groups using the nonparametric Friedman test (Gibbons, 1985; Press et al., 1989; Siegel, 1956). Control data, for graphical purposes only, were collected on Thursdays.

Results

DMI

DMI significantly decreased both burst responses per hour, $F(7, 24) = 4.34$, $p < .05$, and pause responses per hour, $F(7, 24) = 6.8$, $p < .01$. DMI increased reinforcers per hour (IRT > 72), $F(7, 24) = 5.155$, $p < .01$. Burst, pause, and reinforcement rates for individual rats at each dose of DMI are given in Figure 6.

The peak of each rat's IRT distribution was shifted to the right (toward longer IRTs) in a dose-dependent fashion by DMI. The shift in the peak of the IRT distribution is shown in graphical and tabular forms for each dose of DMI in Figure 6. The shift in the peak of the IRT distribution is significant, $F(7, 24) = 4.161$, $p < .05$. Estimates of peak location were not computed when the total number of pause responses was less than 25. For this reason the peak was not computed for Rat 353 at the 20.0 mg/kg dose of DMI. The mean of the remaining 7 rats was used for the peak value of this rat when computing statistics.

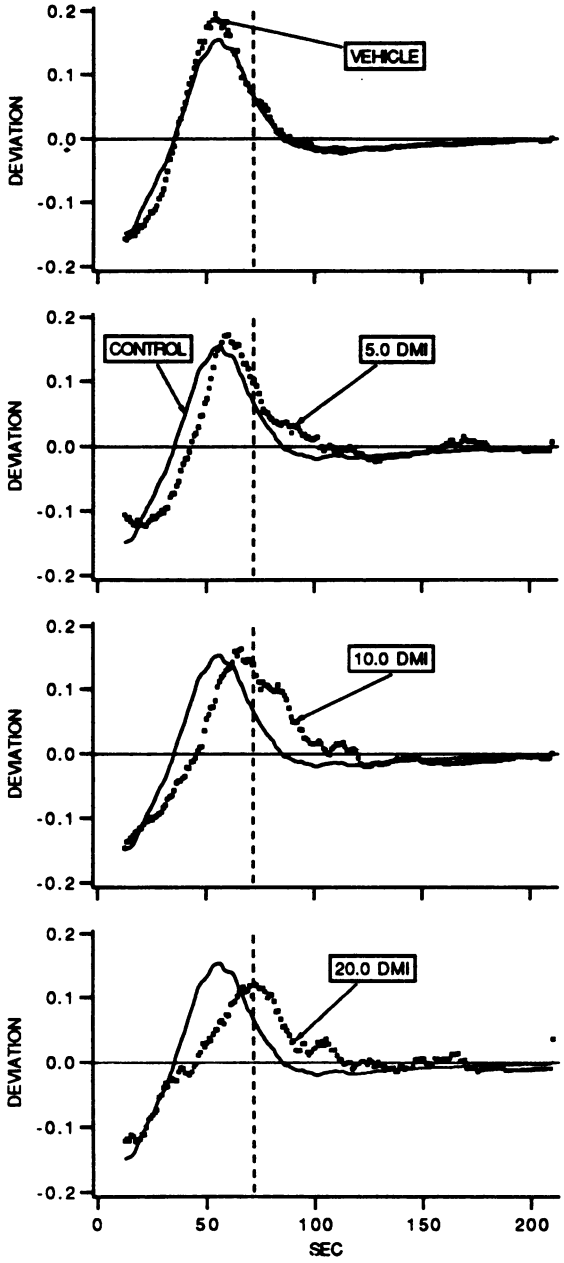
The KSD statistic was affected at only the highest dose of DMI. At this dose, Rats 253 and 254 had nonsignificant KSD scores, indicating that their IRT distributions were not significantly different from their corresponding random IRT distributions. This result indicates that the 20.0 mg/kg dose of DMI had disruptive effects. At lower doses of DMI, no similar effects on the KSD score were observed. Application of a Friedman test to the KSD scores across doses of the drug indicated no significant effect of the drug on this measure, $\chi(3) = 1.2$, $p > .05$.

The pattern of results shown in Figure 6 is consistent with the notion that DMI causes a coherent shift to the right of the IRT distribution. This shift accounts for the observed increase in reinforcement rate.

Gepirone

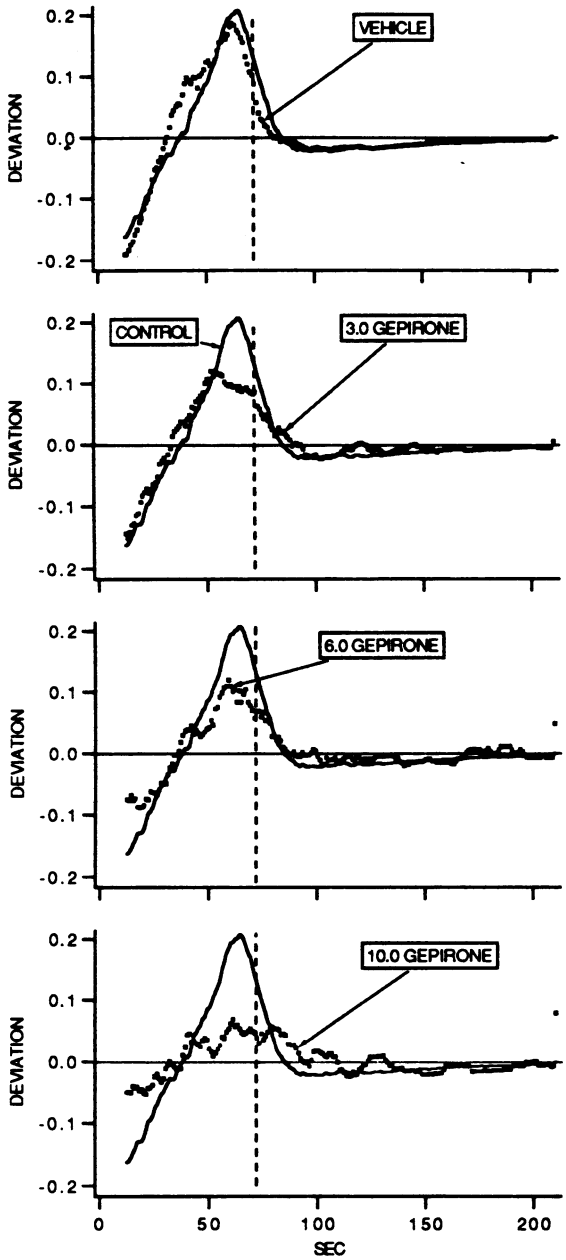
Gepirone caused a significant decrease in pause responses per hour, $F(6, 21) = 6.468$, $p < .01$, but not burst responses per hour, $F(6, 21) = 2.67$, $p > .05$. Gepirone significantly increased reinforcers per hour, $F(6, 21) = 6.671$, $p < .01$. These results are shown in tabular form in Figure 7 for individual rats.

The peak of the IRT distribution was not significantly affected by gepirone, $F(6, 21) = 0.699$, $p > .05$. The peak was not estimated for Rat 265 at the 10.0 mg/kg dose because the number of pause responses fell below 25. For statistical purposes the mean of the remaining 6 rats was used. Examination of the difference curve in Figure 7 shows that the amplitude of the difference curve is decreased by gepirone. This indicates that gepirone decreases the difference between the obtained



RAT	BURST	PAUSE	REINF	PEAK	KSD
351	35	76	7	47.2	.301
352	13	65	8	60.4	.372
353	36	81	7	51.6	.222
354	0	61	16	60.2	.335
355	21	62	14	57.8	.314
356	13	71	7	53.0	.310
357	20	59	14	59.1	.384
358	17	67	15	50.5	.329
MEAN	19.3	67.8	11.0	55.2	.321
351	6	56	15	64.3	.355
352	16	71	7	55.3	.343
353	21	76	9	58.0	.284
354	3	49	22	70.7	.322
355	3	29	25	97.0	.356
356	5	66	11	61.0	.322
357	37	62	19	76.0	.273
358	13	59	12	60.5	.357
MEAN	13.0	58.5	15.0	67.8	.326
				*	
351	0	48	23	74.1	.310
352	11	52	17	62.7	.393
353	7	49	29	80.1	.392
354	1	39	27	98.5	.332
355	4	51	23	70.1	.421
356	3	71	8	56.3	.257
357	23	58	21	73.5	.300
358	23	58	11	63.6	.338
MEAN	9.0	53.3	19.9	72.4	.344
	*	*	*	*	
351	2	50	23	69.1	.326
352	7	55	20	64.8	.273
353	1	20	15	- - . -	.189 N.S.
354	0	35	22	49.4	.209 N.S.
355	1	37	28	80.9	.433
356	5	68	8	58.4	.317
357	2	51	21	71.5	.468
358	16	62	17	66.5	.215
MEAN	4.3	47.3	19.3	65.8	.304
	*	*	*	*	

Fig. 6. Effects of desipramine on DRL 72-s performance. The four graphs on the left show difference curves obtained from rats injected with four doses of DMI. These difference curves are averaged across 8 rats and indicate the deviation of the obtained IRT distributions from the corresponding random distributions. The solid line represents a difference curve from 3 nondrug control days. The dots indicate performance on drug days. The tabular data to the right of each difference curve present corresponding data for individual rats. The burst, pause, and reinforcer columns indicate hourly rates. The asterisks indicate that the group means are significantly different from vehicle ($p < .05$). N.S. indicates that the Kolmogorov-Smirnov (KSD) statistic is not significant ($p > .01$).



RAT	BURST	PAUSE	REINF	PEAK	KSD
261	23	69	5	59.1	.284
262	7	71	14	63.4	.251
263	10	63	7	59.9	.342
264	1	64	9	59.1	.329
265	17	78	12	39.7	.257
266	18	88	1	47.1	.274
257	7	57	11	63.4	.453
MEAN	11.9	70	8.4	55.9	.313

261	43	69	9	54.9	.281
262	4	46	19	64.8	.353
263	19	67	11	54.2	.300
264	6	53	19	60.7	.252
265	11	77	10	51.7	.187
266	16	80	8	61.9	.161 N.S.
267	15	65	13	60.6	.215
MEAN	16.3	65.3	12.7 *	58.4	.250

261	42	74	12	56.4	.261
262	7	48	18	83.9	.085 N.S.
263	12	64	11	54.1	.312
264	7	37	20	69.6	.215 N.S.
265	10	31	14	15.0	.130 N.S.
266	3	25	13	40.8	.219 N.S.
267	13	59	12	66.5	.394
MEAN	13.4	48.3 *	14.3 *	55.2	.231

261	4	54	17	74.4	.209 N.S.
262	13	59	19	69.8	.270
263	4	35	12	46.9	.254 N.S.
264	5	48	17	61.9	.196 N.S.
265	4	11	8	- - -	.219 N.S.
266	0	25	17	30.28	.120 N.S.
267	4	27	18	106.0	.108 N.S.
MEAN	4.9	37.0 *	15.5 *	64.9	.193

Fig. 7. Effects of gepirone on DRL 72-s performance. The four graphs on the left show difference curves obtained from rats injected with four doses of gepirone. These difference curves are averaged across 8 rats and indicate the deviation of the obtained IRT distributions from the corresponding random distributions. The solid line represents a difference curve from 3 nondrug control days. The dots indicate performance on drug days. The tabular data to the right of each difference curve present corresponding data for individual rats. The burst, pause, and reinforcer columns indicate hourly rates. The asterisks indicate that the group means are significantly different from vehicle ($p < .05$). N.S. indicates that the Kolmogorov-Smirnov (KSD) statistic is not significant ($p > .01$).

IRT distribution and the random negative exponential IRT distribution. These qualitative graphical observations are supported by the increasing number of nonsignificant KSD scores as the dose of gepirone increases (see Figure 7). In addition, a Friedman test indicated that the decrease in KSD scores across doses was significant, $\chi(3) = 10.371$, $p < .05$.

These results indicate that gepirone disrupts the IRT distributions of rats performing on the DRL 72-s schedule. Given the absence of a peak shift and the decrease in KSD scores, the observed increase in reinforcement rate is probably due to the dispersal of the IRTs toward the random negative exponential IRT distribution.

Discussion

In Experiment 1 we described an IRT analysis that separates the IRT distribution into burst and pause distributions. The burst distribution was made up of responses that terminated in IRTs < 6 s, and the pause distribution was made up of responses that resulted in IRTs ≥ 6 s. The pause distribution was then further analyzed for each rat by computing a corresponding negative exponential distribution. This random IRT distribution was based on the actual number of responses emitted and the assumption that the rat had a constant probability of responding. The obtained and corresponding random IRT distributions were then compared to determine the peak of the obtained IRT distribution and to determine how different the obtained distribution was from the corresponding random IRT distribution. The results of Experiment 1 showed that the DRL 72-s performance of well-trained rats was different from the corresponding random distribution.

An outcome of our analysis of DRL 72-s IRT distributions is that the rats would have obtained more reinforcers had they responded at the the same rate but randomly. Our analysis of IRTs showed that after the exclusion of burst responding, the probability of a response occurring at short IRTs started out lower than the constant-probability random model and increased as IRT duration increased, reaching a peak above the corresponding random distribution (see Figure 4). However, the peak of the IRT distribution generally occurred well before the 72-s criterion for reinforcement, ensuring that a large proportion of the IRTs were not reinforced.

The implication of this analysis is that there are two identifiable ways for rats to obtain more reinforcers on the DRL 72-s schedule of reinforcement: a systematic shift in the IRT distribution to the right (a peak shift) and dispersal of the IRTs toward the random negative exponential distribution. The results from Experiment 2 showed that DMI and gepirone increased reinforcement frequency in these two very different ways.

DRL and Antidepressants

Consistent with previous reports from this laboratory, we found that the antidepressant DMI increased the number of reinforcers obtained and decreased the number of responses emitted. Quantitative analysis of the IRT distribution showed that this increase in the frequency of reinforcement was accompanied by a coherent shift to the right of the IRT distribution. Generally, DMI did not cause dispersal of the IRT distribution. These results confirm earlier qualitative descriptions of the effects of DMI on DRL 72-s IRT distributions (McGuire & Seiden, 1980b; O'Donnell & Seiden, 1983).

Similar to DMI, the 5HT1A agonist gepirone also increased reinforcement frequency and decreased response rate. However, analysis of the IRT distribution revealed that the effects of gepirone on the IRT distribution were very different from the effects of DMI. In contrast to DMI, gepirone caused a dispersal of the IRTs toward the random negative exponential curve.

The similarity of DMI and gepirone in terms of their effects on response and reinforcement rate and their dramatically different effects on the IRT distribution serve to highlight the utility of the analysis of IRT distributions for characterizing drug effects. Perhaps the above result is a peculiarity of the DRL 72-s schedule. It could well be that rats performing on DRL schedules with shorter, more commonly used criterion values (e.g., DRL 18 s) would not obtain more reinforcers if the IRTs were dispersed toward random. To reiterate, rats trained on the DRL 72-s schedule typically obtained fewer reinforcers than predicted by the corresponding negative exponential. Thus, dispersal of the IRTs toward the corresponding negative exponential causes an increase in the number of reinforcers obtained (provided that response rate stays the same). In contrast, if rats trained on shorter criterion DRL schedules (e.g., DRL 18 s) typically obtain more reinforcers than predicted by the corresponding negative exponential, then dispersal of the IRT distribution should not increase the number of reinforcers obtained.

We are currently investigating this question in our laboratory. For example, rats on a DRL

18-s schedule may obtain the same or a greater number of reinforcers than predicted by the corresponding negative exponential. In this case, drugs such as gepirone should not increase the frequency of reinforcement. On the other hand, drugs such as DMI, which cause a coherent shift of the IRT distribution toward longer durations, could still increase reinforcement frequency on the DRL 18-s schedule. In support of this latter statement, we have reported that DMI increases the frequency of reinforcement on a DRL 18-s schedule of reinforcement (McGuire & Seiden, 1980b).

As was noted in the introduction, previous work from this laboratory has shown that increased reinforcement frequency on the DRL 72-s schedule is a reliable indicator of antidepressant drugs. According to this criterion gepirone is an antidepressant drug. In fact, preliminary clinical trials (Rausch, Ruegg, & Moeller, 1990; Robinson, Alms, Shrotriya, Messina, & Wickramaratne, 1989) have indicated that gepirone is an antidepressant. On the other hand, the effects of gepirone on DRL 72-s IRT distributions are different from the effects of antidepressants previously reported from this laboratory (Marek & Seiden, 1988a, 1988b; McGuire & Seiden, 1980a, 1980b; O'Donnell & Seiden 1982, 1983). It should be pointed out, however, that these previous reports were qualitative descriptions of IRT histograms.

DRL and Anxiolytics

Perhaps the different effects on IRT distributions can be explained by the fact that although the 5HT1A receptor agonist gepirone may be an antidepressant, it is generally acknowledged to be a novel nonbenzodiazepine anxiolytic similar to buspirone (Broekkamp, Berendsen, Jenck, & Van Delft, 1989; Feighner & Boyer, 1989). It is possible that the dispersal of the IRT distribution toward random reported here is caused by gepirone's anxiolytic effects. As previously mentioned, preliminary data (Richards et al., 1990) have shown that two other novel nonbenzodiazepine anxiolytics, buspirone and ipsapirone, also increased reinforcement frequency on DRL 72-s schedules by dispersal of the IRT distribution toward random. Other DRL 72-s data from this laboratory (O'Donnell & Seiden, 1982) have shown that the benzodiazepine anxiolytic drug chlordiazepoxide does not increase reinforcement frequency. However, in contrast to gepirone, chlordiazepoxide also significantly increased response rate. This difference in response rate could have negated the reinforcement rate-increasing effects of IRT dispersion on the DRL 72-s schedule. The IRT distributions for this experiment were not described, so the effects of chlordiazepoxide on IRT dispersal are not known.

Using shorter criterion DRL schedules, other researchers (Sanger, 1980; Sanger & Blackman, 1975; Sanger, Key, & Blackman, 1974) have also found that chlordiazepoxide increases response output on DRL schedules of reinforcement. Interestingly, similar to gepirone, chlordiazepoxide may have caused dispersal of the IRT distribution. Evidence for this comes from examining the individual rat IRT histograms from Sanger et al. (1974). This figure shows the effects of increasing doses of the benzodiazepine anxiolytic chlordiazepoxide, and indicates to us that chlordiazepoxide tends to disperse the IRTs toward a negative exponential curve. Confirmation of this judgment by a quantitative IRT analysis, such as the one presented here, is needed (see Sanger et al., 1974, p. 165, Figure 5).

In addition, Sanger et al. (1974) noted that a distinguishing characteristic of the response rate-increasing effects of chlordiazepoxide on DRL schedules in comparison to the response rate-increasing effects of stimulants such as amphetamine is that chlordiazepoxide differentially increases burst responding whereas amphetamine does not. In contrast to these results, gepirone does not increase overall response output, nor does it increase bursting. However, burst responding was not significantly reduced, but pause responding was.

In the preceding discussion of DRL and anxiolytics, it appears that for the therapeutic class in general, neither reinforcement frequency, pause response rate, nor burst response rate is changed predictably. Dispersal of the IRTs however is a potential common denominator for both the benzodiazepine anxiolytics and the novel nonbenzodiazepine anxiolytics. In support of this conclusion, we have demonstrated that in the case of the novel anxiolytic gepirone, the IRTs are dispersed toward the random negative exponential function.

In summary, it is possible that DRL 72-s IRT distributions are, in general, affected in

two different ways by antidepressants and anxiolytics. Antidepressants cause a coherent shift in the IRT distribution to the right, and anxiolytics cause dispersal of the IRTs toward the random negative exponential distribution. The present results indicate that both of these effects on the IRT distribution can result in increases in reinforcement frequency. In terms of using the DRL 72-s schedule as a screen for antidepressant drugs, the present results raise the following question: Is an increase in reinforcement frequency a sufficient indicator of antidepressant activity regardless of effects on the IRT distribution? Up to now, increases in reinforcement frequency reported for antidepressant drugs typically have been accompanied by a coherent shift to the right of the IRT distribution (when IRTs were examined). As was shown in Experiment 2, increases in reinforcement caused by anxiolytic drugs such as gepirone are accompanied by dispersal of the IRTs towards the random negative exponential distribution. It is possible that this pattern of results indicates a drug that is both an anxiolytic and a antidepressant, whereas drugs that cause a coherent shift to the right are exclusively antidepressants. Clearly, further research is required in order to answer the question posed above.

The IRT analysis described and used in this paper allows a quantifiable analysis of the temporal structure of operant performance. As was demonstrated above, separate measures of bursting, peak location, and IRT dispersal in conjunction with more commonly used response and reinforcement rate measures provide a foundation for making discriminations between classes of psychoactive drugs. In this laboratory we have used the DRL 72-s schedule to identify potential antidepressant drugs. With the IRT analysis described here, it may be possible to make further determinations about classes of psychoactive drugs using DRL schedules of reinforcement.

REFERENCES

Anger, D. (1956). The dependence of interresponse times upon the relative reinforcement of different interresponse times: *Journal of Experimental Psychology*, **52**, 145–161.

Anger, D. (1963). The role of temporal discriminations in the reinforcement of Sidman avoidance behavior. *Journal of the Experimental Analysis of Behavior*, **6**, 477–506.

Blough, D. S. (1963). Interresponse time as a function of continuous variables: A new method and some data. *Journal of the Experimental Analysis of Behavior*, **6**, 237–246.

Blough, D. S. (1966). The reinforcement of least-frequent interresponse times. *Journal of the Experimental Analysis of Behavior*, **9**, 581–591.

Broekkamp, G. L. E., Berendsen, H. H. G., Jenck, F., & Van Delft, A. M. L. (1989). Animal models for anxiety and response to serotonergic drugs. *Psychopathology*, **22**(Suppl. 1), 2–12.

Duncan, I. J. H., Horne, A. R., Hughes, B. O., & Wood-Gush, D. G. M. (1970). The pattern of food intake in female brown leghorn fowls as recorded in a Skinner box. *Animal Behaviour*, **18**, 245–255.

Fagen, R. M., & Young, D. Y. (1978). Temporal patterns of behaviors: Durations, intervals, latencies, and sequences. In P. W. Colgan (Ed.), *Quantitative ethology* (pp. 79–114). New York: Wiley.

Feighner, J. P., & Boyer, W. F. (1989). Serotonin-1A anxiolytics: An overview. *Psychopathology*, **22**(Suppl. 1), 21–26.

Ferster, C. B., & Skinner, B. F. (1957). *Schedules of reinforcement*. New York: Appleton-Century-Crofts.

Gibbons, J. D. (1985). *Nonparametric methods for quantitative analysis* (2nd ed.). Columbus, OH: American Sciences Press.

Hand, T. H., Marek, G. J., Jolly, D. C., & Seiden, L. S. (1989). Antidepressant-like effects of the 5HT1A agonists buspirone, gepirone, 8OHDPAT, and 5MEODMT in rats on the DRL 72 sec schedule: Differential blockade by methysergide and purported 5HT1A antagonists. *Society for Neuroscience Abstracts*, **15**, 1282.

Kelleher, R. T., Fry W., Deegan, J., & Cook, L. (1961). Effects of meprobamate on operant behavior in rats. *Journal of Pharmacology and Experimental Therapeutics*, **133**, 271–280.

Keppel, G. (1973). *Design and analysis: A researcher's handbook*. Englewood Cliffs, NJ: Prentice-Hall.

Kramer, T. J., & Rilling, M. (1970). Differential reinforcement of low rates: A selective critique. *Psychological Bulletin*, **74**, 225–254.

Marek, G. J., Li, A. A., & Seiden, L. S. (1989). Selective 5-hydroxytryptamine-2 antagonists have antidepressant-like effects on differential-reinforcement-of-low-rate 72-second schedule. *Journal of Pharmacology and Experimental Therapeutics*, **250**, 52–59.

Marek, G. J., & Seiden, L. S. (1988a). Effects of selective 5-hydroxtryptamine-2 and nonselective 5-hydroxytryptamine antagonists on the differential-reinforcement-of-low-rate 72-second schedule. *Journal of Pharmacology and Experimental Therapeutics*, **244**, 650–658.

Marek, G. J., & Seiden, L. S. (1988b). Selective inhibition of MAO-A, not MAO-B, results in antidepressant-like effects on DRL 72-s behavior. *Psychopharmacology*, **96**, 153–160.

McGuire, P. S., & Seiden, L. S. (1980a). Differential effects of imipramine in rats as a function of DRL schedule value. *Pharmacology Biochemistry and Behavior*, **13**, 691–694.

McGuire, P. S., & Seiden, L. S. (1980b). The effects of tricyclic antidepressants on performance under a differential-reinforcement-of-low-rates schedule in rats.

Journal of Pharmacology and Experimental Therapeutics, **214,** 635–641.

Mueller, C. G. (1950). Theoretical relationships among some measures of conditioning. *Proceedings of the National Academy of Sciences,* **36,** 123–130.

O'Donnell, J. M., & Seiden, L. S. (1982). Effects of monoamine oxidase inhibitors on performance during differential reinforcement of low response rate. *Psychopharmacology,* **78,** 214–218.

O'Donnell, J. M., & Seiden, L. S. (1983). Differential-reinforcement-of-low-rate 72-second schedule: Selective effects of antidepressant drugs. *Journal of Pharmacology and Experimental Therapeutics,* **224,** 80–88.

O'Donnell, J. M., & Seiden, L. S. (1985). Effect of the experimental antidepressant AHR-9377 on performance during differential reinforcement of low response rate. *Psychopharmacology,* **87,** 283–285.

Press, W. H., Flannery, B. P., Teukolsky, S. A., & Vetterling, W. T. (1989). *Numerical recipes in Fortran.* Cambridge: Cambridge University Press.

Rausch, J. L., Ruegg, R., & Moeller, F. G. (1990). Gepirone as a 5-HT1A agonist in the treatment of major depression. *Psychopharmacology Bulletin,* **26,** 169–171.

Richards, J. B., Sabol, K. S., Jolly, D. C., & Seiden, L. S. (1990). Differential effects of 5HT1A agonists 8OHDPAT, buspirone, gepirone, ipsapirone and 5MEODMT on a DRL 72 sec schedule of reinforcement. *Society for Neuroscience Abstracts,* **16,** 752.

Robinson, D. S., Alms, D. R., Shrotriya, R. C., Messina, M., & Wickramaratne, P. (1989). Serotonergic anxiolytics and treatment of depression. *Psychopathology,* **22**(Suppl. 1), 27–36.

Sanger, D. J. (1980). The effects of caffeine on timing behaviour in rodents: Comparisons with chlordiazepoxide. *Psychopharmacology,* **68,** 305–309.

Sanger, D. J., & Blackman, D. E. (1975). The effects of tranquilizing drugs on timing behaviour in rats. *Psychopharmacologia,* **44,** 153–156.

Sanger, D. J., & Blackman, D. E. (1989). Operant behavior and the effects of centrally acting drugs. In A. A. Boulton, G. B. Baker, & A. J. Greenshaw (Eds.), *Neuromethods: Vol. 13. Psychopharmacology* (pp. 299–348). Clifton, NJ: Humana Press.

Sanger, D. J., Key, M., & Blackman, D. E. (1974). Differential effects of chlordiazepoxide and *d*-amphetamine on responding maintained by a DRL schedule of reinforcement. *Psycopharmacologia,* **38,** 159–171.

Seiden, L. S., & O'Donnell, J. M. (1985). Effects of antidepressant drugs on DRL behavior. In L. S. Seiden & R. L. Balster (Eds.), *Neurology and neurobiology: Vol. 13. Behavioral pharmacology: The current status* (pp. 323–338). New York: Liss.

Sidman, M. (1954). The temporal distribution of avoidance responses. *Journal of Comparative and Physiological Psychology,* **47,** 399–402.

Sidman, M. (1955). Technique for assessing the effects of drugs on timing behavior. *Science,* **122,** 925.

Sidman, M. (1956). Time discrimination and behavioral interaction in a free operant situation. *Journal of Comparative and Physiological Psychology,* **49,** 469–473.

Siegel, S. (1956). *Nonparametric statistics for the behavioral sciences.* New York: McGraw-Hill.

Slater, P. J. B. (1975). Temporal patterning and the causation of bird behaviour. In P. Wright, P. G. Caryl, & D. M. Vowles (Eds.), *Neural and endocrine aspects of behaviour in birds* (pp. 11–33). Amsterdam: Elsevier.

Slater, P. J. B., & Lester, N. P. (1980). Minimising errors in splitting behaviour into bouts. *Behaviour,* **79,** 153–161.

Snapper, A. G., Stephens, K. R., Cobez, R. I., & Van Haaren, F. (1976). *The SKED software system: OS8 and time share SKED.* Kalamazoo, MI: State Systems.

Wearden, J. H. (1990). Maximizing reinforcement rate on spaced-responding schedules under conditions of temporal uncertainty. *Behavioural Processes,* **22,** 47–59.

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