EFFECTS OF CHLORPROMAZINE ON APPETITIVE AND AVERSIVE COMPONENTS OF A MULTIPLE SCHEDULE¹

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A multiple schedule having both an appetitive and an avoidance component was maintained in two dogs to create a complex behavioral base line for observing the effects of chlorpromazine. Both soluble and "Spansule" chlorpromazine generated similar functions relating drug dose to measures of behavioral output. Although the dose ranges and the drugging procedures differed markedly for the different preparations of CPZ, the functions generated were comparable. There was no evidence that chlorpromazine had a differential depressing effect as a function of type of reinforcement. At low doses, rates of responding on the food-reinforced components increased slightly, whereas rates on the avoidance components remained relatively unchanged. At higher doses, both components showed an approximately equal depression of responding. These results are discussed with reference to some of the logical and experimental difficulties inherent in making comparisons across components of a multiple schedule and across schedules in general.

Many investigators have been particularly interested in comparing the effects of drugs on behavior maintained by positive reinforcement with their effects on behavior maintained by negative reinforcement. Much of this interest has resulted from the clinical use of drugs and the interpretations of their clinically observed effects. The purpose of the present experiment was to investigate the effects of chlorpromazine (CPZ) on a multiple schedule having both appetitive and avoidance components.

Research comparing drug effects on schedules of positive and negative reinforcement has yielded ambiguous results. Weissman (1959), using a multiple-schedule procedure with rats, found that CPZ had a more depressing effect on avoidance than on food-maintained behavior. On the other hand, Olds (1959), using rats and a brain-stimulation technique,

found that CPZ inhibited responding to positive stimulation (approach), but failed to do so to negative stimulation (escape).

A similar state of affairs exists over the behavioral effects of reserpine. For example, Wenzel (1959) has reported that reserpine tends to increase response latencies to a greater extent and for a longer period of time on an avoidance schedule than on a food-reinforced schedule. Other reports fail to support Wenzel's result (Miller, 1956; Weiskrantz & Wilson, 1955). Furthermore, Dews and Morse (1960) have questioned Wenzel's results on methodological grounds. More data would seem desirable because of these ambiguous results.

The method used by Weissman (1959) and Wenzel (1959) offers several advantages over other methods. Because it is a special case of a multiple schedule having both appetitive and avoidance components (Herrnstein & Brady, 1958; Herrnstein, 1958; Brady, 1959), drug effects can be observed on both positively and negatively reinforced behavior in the same subject almost simultaneously. The food-reinforced component in Weissman's schedule has several limitations, however. For example, the CRF schedule used placed a very low upper limit on response-output measures, *i.e.*, number and rate. A less constrained schedule would seem more appropriate.

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METHOD

Subjects

The subjects were two male beagle dogs approximately 2 years old at the start of the experiment. They were maintained throughout the experiment on 300 g of Big Red dog chow⁴ per day plus a vitamin-mineral supplement once a week. This regime kept the animals at approximately 80% of their free-feeding weights.

Apparatus

The apparatus consisted of a cubical with a specially constructed grid floor and a nose manipulandum (Waller, 1960). Discriminative stimuli were presented by a 100-watt bulb in a flush-mounted ceiling fixture which directed the light on the manipulandum. Food was presented through a tube connected with a Gerbrands⁵ universal feeder. Each reinforcer consisted of two pellets of Big Red dog chow having a combined weight of approximately 5 g. The electric shock, administered through the grid floor and programmed through a grid scrambler,⁶ had an intensity of 2.5 ma and a duration of 1 sec.

Procedure

Subjects were deprived of food and shaped via CRF to a VI 1 min schedule for food reinforcement. The program was then altered to a mult VI 1 min S^A 25 min. Continuous light was the stimulus condition correlated with the VI 1-min component, and the no-light condition was correlated with the S^A 25 min. After a stable performance developed, the schedule was altered to mult VI 1 min S^A 25 min avoid RS 20 sec SS 20 sec S^A 25 min. A flashing light (on 0.5 sec, off 0.5 sec) was correlated with the avoidance component. Both Ss were then shaped to the avoidance component in a single 9-hr session in which the avoidance component was introduced as a single 6-hr block. In the following sessions, components were of variable duration, *i.e.*, either 10, 20, 30, or 40 min. Under these conditions, Ss were run daily in 5-hr sessions until performance on all components was

stable (approximately 400 hr), at which point the first drug procedure was carried out.

The initial drug procedure consisted of administering either 30, 75, 105, 180, or 225 mg of CPZ in "Spansule" form (sustained release capsules) 2 hr before a session. Subjects were run 7 days a week, with drug administered on alternate days. Four observations were taken for each drug dosage. The order of dosage was counterbalanced within these limitations. After approximately 10 months, during which time various changes had been made in the schedule, the schedule was returned to mult VI 1 min S^A 25 min avoid SS 20 sec RS 20 sec S^A 25 min for a second drug analysis.

In the second drug experiment, CPZ was used in soluble form ("thorazine" pills) at four dose levels: 25, 50, 100, and 150 mg. Subjects were run 5 days each week, and the drug was administered on Friday 2 hr before the session began. These sessions were 4 hr long. Each dose of the drug was administered twice for each S.

RESULTS

The data reported in all figures are based upon performance during the fifth and sixth hours after drug administration, which were the third and fourth hours after the session began. This particular selection was based on the repeated observation that drug effects were maximal and stable during this period. The numbers reported in Fig. 1 were obtained by measuring the cumulative records.

Figure 1A shows the results of the first drug analysis, in which "Spansule" CPZ and a somewhat chronic drugging procedure were used. This procedure restricts the interpretation of these data, since the data cannot be interpreted as a dose-response function. No systematic change indicating drug tolerance was observed. The Ss are presented separately.

By plotting output ratio, *i.e.*,

$$\frac{\text{mean drug rate of response}}{\text{mean control rate of response}}$$

on the ordinate, relative changes in response output for both the variable-interval and the avoidance components can be compared directly. Each point represents the mean of four drug observations. Thus, the change with increasing amounts of drug is comparable in most respects for the two components. For

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Fig. 1. Output ratios based upon responses/minute under drug and control conditions. Figure 1A shows means of four replications with "Spansule" CPZ. Figure 1B shows means of two replications with soluble CPZ in oral doses.

both subjects, however, the rate on the food-reinforced component tended to increase at the lowest dose, whereas a small decrease was observed on the avoidance component. Both components show decreases after greater doses which are progressive to the maximum dose given. Performance in the S^A components is not shown because response output was minimal under all conditions.

Figure 1B shows the results of the later drug experiment. In this figure, each point represents the mean of two drug observations. Only a single valid observation was obtained for Dog D at the 150-mg dose. A second observation of this dose was grossly deviant: Both components showed virtually no drug effect, indicating that the animal vomited following the oral administration. Evidence of nausea following large oral doses of CPZ was not uncommon. The similarity of the drug effects on the two components is striking for Dog D. Dog C showed an increase in rate on the

VI 1-min component at low doses of chlorpromazine. Further, for Dog C, CPZ may have a greater depressing effect on avoidance responding. The first obvious depression of responding in both subjects followed the 100-mg dose.

Figure 2 shows segments of the cumulative records for both subjects. Because neither time nor the response count is directly comparable from segment to segment, records must be compared as to slope. Figure 2A shows segments of the cumulative records for Dog C taken from the "Spansule" procedure. These segments were from the records approximately 4-6 hr after drug administration. Note the comparability of the drug effect on the variable-interval component and on the avoidance component. Figure 2B shows comparable segments of the cumulative records for Dog D taken from the records for the later drug analysis in which soluble CPZ was used in oral doses. Again, a similar effect is observed on

Fig. 2. Portions of the cumulative records obtained during the 5th and 6th hours after the drug administrations indicated. Figure 2A shows the performance of Dog C following "Spansule" CPZ administration, and Fig. 2B shows Dog D after oral dosage with soluble CPZ.

both the food and shock-avoidance components. The S^A components are not shown because virtually no responding was evident in S^A under any condition.

DISCUSSION

The results of these experiments suggest that over a considerable dose range, chlorpromazine has a similar effect on both food- and

avoidance-maintained behavior. At very low doses the rate of food-reinforced responding tended to increase when compared with control performance, whereas a slight decrease in rate occurred in avoidance-maintained responding. At higher dose levels, both food and avoidance responding were generally depressed to a comparable degree. If by sensitivity we mean any deviation from con-

trol performance, the results suggest that food-maintained behavior is more sensitive to the effects of CPZ than is avoidance responding. Although low doses of CPZ tended to increase response output in the food-reinforced component, the same doses had little or no effect on the avoidance component.

A second observation is of some interest. The drugging operation was somewhat different in the two drug procedures. In the first series, chlorpromazine was administered every other day and in "Spansule" form—a relatively chronic procedure; but in the second procedure, the regular oral form of chlorpromazine was administered once a week. The similarity of the two dose-response functions indicates that for gross approximations the chronic procedure is probably an adequate method for establishing the shape of the dose-response function for chlorpromazine.

The failure to find a gross difference in the effects of CPZ on food-reinforced and avoidance-maintained responding raises several questions which should be discussed at length. The first concerns the logic underlying cross-schedule comparisons, in general, and positively versus negatively reinforced schedules, in particular. The second question deals with cross-schedule versus cross-drug interaction, *i.e.*, when several drugs are compared on the basis of their cross-schedule effects. Although drugs will be used as a variable to develop both arguments, the analysis is more general and is applicable to other variables as well.

Schedule of reinforcement is not a unitary variable. A logical analysis will reveal that "schedule" encompasses a number of variables, two of which are rather obvious. Schedule specifies "contingency of reinforcement," *i.e.*, fixed ratio, fixed interval, DRL, or variable ratio. Furthermore, within broad limits, contingency of reinforcement can be manipulated independently of parameter value or "density of reinforcement." Experimental evidence supports this logical analysis. In a series of recent experiments, Dews (1958, 1960) has demonstrated unequivocally that parameter value or "density of reinforcement" is a variable of importance in the analysis of drug effects where contingency of reinforcement is held constant. There is no unequivocal evidence that contingency of reinforcement is a variable determining drug effects, but there is considerable evidence that contingency of

reinforcement has an effect on behavior (Ferster & Skinner, 1957; Hearst, 1958)

If both density of reinforcement and contingency of reinforcement are variables determining drug effect, cross-schedule comparisons that do not consider both variables are obviously confounded. In fact, because schedule is not a unitary variable, comparisons across schedules are necessarily second-order comparisons, *i.e.*, comparisons of the interactive function of two variables. Although such comparisons are legitimate both logically and empirically, the interactive function must be specified.

Comparison of positively and negatively reinforced behavior, particularly where schedules are involved, is somewhat more complex. Parameter value or density of reinforcement and contingency of reinforcement seem rather inappropriate as variables specifying schedules of negative reinforcement. Even if shock-shock intervals and response-shock intervals could be translated into variables having scale properties similar to density and contingency of reinforcement (and this may well be experimentally feasible), other variables present equally difficult problems of experimental analysis. One of these is equivalence of magnitude of reinforcement. Obviously, shock, the avoidance of shock, the reduction of anxiety, or whatever serves as the negative reinforcer, is scaled on a different continuum than is food or water. Logically, a quantitative comparison of positive versus negative reinforcement requires that the magnitudes of reinforcement can be equated. Empirically, a quantitative comparison of positive and negative reinforcement demands that the magnitudes of reinforcement be scalable and that these scales be known.

The comparability of dependent variables should also be considered. There is reason to believe that an avoidance response is not directly comparable with a food-reinforced response (Sidman, 1958). However, there is little reason to believe that other indices of responding are any better. Certainly, the practice (Herrnstein, 1958; Weissman, 1959) of comparing number of shocks taken on the avoidance schedule with rate of response on the food schedule only complicates matters further.

There is no easy way out of the problems of cross-schedule comparisons. The problem is

not unlike that of comparisons across species in comparative psychology. Only a careful experimental analysis will yield the functional relations which are necessary for such comparisons. Although the "double dissociation" experimental design described by Weiskrantz (1959, pp. 53-56) represents a logical improvement over simpler designs, it does not and, as currently used, cannot generate the basic functional relations required for cross-schedule comparisons. In fact, the addition of a cross-drug dimension to cross-schedule experiments leads to further difficulties in experimental analysis in that the new dimension generates other requirements.

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