Are "no-drug" cues discriminated during drug-discrimination training?

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Rats were trained in a two-lever operant chamber to discriminate the presence versus the absence of a drug. During drug sessions, the training procedure involved reinforcing presses on lever 1 with saccharin-sweetened water but not reinforcing presses on lever 2. During no-drug sessions, only presses on lever 2 were reinforced. After this discrimination was learned, each rat was trained to discriminate presence versus absence of a second drug. All rats learned this second discrimination. Finally, the rats were tested to determine whether they could still discriminate the first drug, as well as other pharmacologically related compounds; most rats could. Training drugs were phenobarbital 30-35, nicotine 0.4, amphetamine 0.4, cyproheptadine 7, phencyclidine 4, cyclazocine 1.5, fentanyl 0.04, and scopolamine 0.2 mg/kg. The results indicate that drug versus no-drug discrimination training does not disrupt discriminative control previously established with a different drug. When considered in combination with the results obtained during substitution tests conducted after drug-versus-no-drug training, the data suggest that, instead of discriminating drug cues versus no-drug cues, rats discriminate presence versus absence of particular drug cues.

Drug discriminations (DDs) can be established in a training compartment that allows either of two different instrumental responses by reinforcing one response during sessions conducted in one drug condition and the second response during sessions in a second drug condition. When animals are trained to discriminate between two different drugs (D1 vs. D2), there is general agreement that the "stimulus effects" of D1 act as discriminative stimuli for the first response, and that D2 provides discriminative stimuli for the second response. However, when animals are trained to discriminate a drug (D) versus no drug (N), there is some disagreement concerning the nature of the stimuli (cues) that underlie DDs and the type of learning that takes place during DD training.

One formulation asserts that animals discriminate between cues present during D sessions (drug cues) and those present during N sessions (no-drug or saline-induced cues), that is, that the D response becomes contingent on cues produced by the training drug and that the N response becomes contingent on specific cues that occur only in the N state. For example, Brown, Feldman, and Moore (1968) state that

injection of drug "produces cues which are discriminable from the cues produced by injection . . . of saline" (also see Browne & Ho, 1975; Jones, Grant, & Vospalek, 1976; Schechter, 1973). Several investigators apparently accept this theory, and most studies on state-dependent learning are explained in this fashion (e.g., Belleville, 1964; Heistad, 1957).

According to the second formulation of the consequences of D vs. N training, the N state is not considered to have significant interoceptive cuing properties. Animals are believed to discriminate the specific collection of cues associated with the D state and to learn to make the D response only when those cues are present. N-state response selection is believed to occur when the D cues are *absent*, rather than in response to the presence of N-state cues. Animals are presumed not to attend to N-state cues, even if they exist. This formulation, like the preceding one, can be found in previously published reports. Colpaert (1978) has stated clearly that animals discriminate between the presence and absence of the specific collection of cues produced by the training drug, and such a "no-cue" interpretation of the N state is at least implicit in many other reports in which animals are described as discriminating presence versus absence of the training drug (e.g., Appel, White, & Kuhn, 1978; Rosecrans, Kallman, & Glennon, 1978; Shannon & Holtzman, 1977).

Although these two rather different interpretations of the nature of D versus N discriminations have coexisted in the literature for several years, there are no published discussions of the differences between these models, and there have been no explicit at-

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tempts to distinguish between them experimentally. The distinction is not trivial, because quite different predictions derive from the two formulations in some cases. In general, there is a discernible trend in the DD literature towards adoption of the second formulation in most recent reports, but reports on state-dependent learning still commonly refer to no-drug cues.

Data from substitution tests are relevant to these models. After D vs. N training with a particular drug in a two-lever operant task, animals can be tested with a variety of other drugs, and during such tests the animals usually make the N response unless the test drug is closely related pharmacologically to the training drug. Random alternation between the two responses is not observed; the N response is the default choice. Many investigators have reported data of this type (e.g., Barry, 1974; Bueno, Carlini, Finkelfarb, & Suzuki, 1976; Cameron & Appel, 1973; Overton, 1971).

Let us consider the theoretical consequences of these data. The first formulation (Figure 1A), which we shall call the "N-cue" (or "small N-cue") model, predicts that novel test drugs (A, B, C) will not all be expected to consistently produce either N or D responses, since they do not produce either set of discriminative stimuli established by prior training; random response selection (or no responding) is expected during tests with at least some of these drugs. Hence, the data from substitution tests suggest rejection of this N-cue model. According to the second formulation, called the "no-cue" model, D vs. N training will create the situation shown in Figure 1E.

Figure 1. Theoretical diagrams showing the results of drug-discrimination training predicted by each of three theoretical models. The rectangular boxes are the entire set of interoceptive cues. Each enclosed area shows the set of cues that will lead to the indicated response.

N choices will occur during tests with novel drugs (A, B, C) because the training drug cues are absent. Apparently, this no-cue formulation is compatible with the data from substitution tests. In addition, there is a third formulation, shown in Figure 1C, one that is also compatible with the test data and that we will call the "large-N-cue" model. Presumably, during a series of training sessions, a considerable variety of N cues are associated with the N response, reflecting variations in the degree of hunger, thirst, fatigue, etc., that occur during N training sessions. Possibly the N state, at one time or another, includes many of the sensory cues that can be produced by most test drugs. This would result in Figure 1C. Even though such a "large-N-cue" description of the outcome of D versus N training is not entirely in accord with most theories of discrimination learning, it is directly suggested by the substitution test data.

To review, the traditional N-cue vs. D-cue model (Figure 1A) is rejected by the substitution test data. Both Figures 1C and 1E are compatible with these data. Hence, we attempted to develop an experimental paradigm that would explicitly distinguish between the interpretations of response selection shown in Figures 1C and 1E.

In the present experiments, rats were first trained to discriminate one drug (D1) versus no drug, and then subsequently trained to discriminate a second drug (D2) versus no drug. Finally, they were tested to determine whether discrimination of D1 had been disrupted by D2 vs. N training. We reasoned that, if animals actively learned to make N choices in response to all cues other than the training drug cues during D1 vs. N training (Figure 1C), then D2 vs. N training similarly should cause the animals to make N choices when subsequently tested with drugs dissimilar to D2, including D1, as shown in Figure 1D. Alternately, if animals discriminated presence versus absence of training drug D1 (Figure 1E), then the D1 state should maintain its ability to produce drug-lever choices even after the animal was "retrained" to discriminate D2 vs. N (Figure 1F). To anticipate our results, after D2 vs. N training, rats made drug-lever responses when tested with D1—a result most easily reconciled with a "no-cue" interpretation of N-state effects (Figure 1E). Note that the results of this particular experiment are also compatible with a "small-N-cue" model (Figure 1B), but this interpretation is rejected by the results of substitution tests.

EXPERIMENT 1

In this experiment, rats were trained to discriminate D1 versus N, then trained to discriminate D2 versus N, and then retrained to discriminate D1 versus N. The first D1 retraining session was taken as a test of whether D1 could still be discriminated after D2 vs. N training. A variety of specific drugs

were used as D1 and D2. Our original intention was to select drugs sufficiently dissimilar so that D2 would not produce D1 choices after D1 vs. N training.

Method

Subjects. Twelve experimentally naive male hooded rats of the Long-Evans strain were obtained from Blue Spruce Farms and housed individually throughout the experiment with dry food available at all times in their home cages. Two weeks before the beginning of training, a 23.75-h water-deprivation schedule was imposed, allowing the rats access to water for 15 min each day. At the beginning of training, the rats weighed 200-300 g.

Apparatus. Pretraining compartments, constructed of aluminum and Lucite, were 30 cm wide $\times$ 18 cm deep $\times$ 21 cm high. These boxes had a steel rod floor and were equipped with one lever. A solenoid valve, which dispensed 0.1 ml of water, was mounted next to the lever.

Discrimination training compartments were 30 cm wide $\times$ 32 cm deep $\times$ 31 cm high (Gerbrands Converta-cage Model G7105). The ceiling and walls were aluminum; the door was Plexiglas; the floor was composed of steel rods. Two levers were mounted 20 cm apart and 5 cm above the floor on the wall opposite the door, along with a solenoid valve capable of delivering 0.1 ml of 0.3% saccharin solution to a spout located on the wall, midway between the two levers. Illumination was provided by two 3-W light bulbs mounted on the ceiling. The entire training compartment was located inside a larger lightproof, sound-attenuating compartment equipped with a ventilating fan.

Reinforcement contingencies and data recording were implemented by a SKED software system (Snapper & Kadden, 1970) operated by a DEC PDP-12 computer, which was subsequently used for data reduction.

Procedure. All drugs were administered by intraperitoneal (ip) injection. A 20-min interval separated the injection from the beginning of the training session. No injection was given prior to "no-drug" sessions. The six training drugs and dosages are indicated in Table 1. Whenever possible, drugs were dissolved in water or saline in concentrations such that a 1.0-ml/kg injection was required; cyclazocine was dissolved in weak tartaric acid.

Pretraining was conducted in compartments containing one lever. Starting 1 week after implementation of the water-deprivation schedule, rats were accustomed to drinking from the solenoid delivery spout, shaped to press in the single-lever boxes using 0.1 ml water as a reinforcer, and accustomed to fixed-ratio (FR) schedules with increasing response requirements (FR 2, FR 4, . . . FR 32) during a series of 12-h sessions, which terminated when more than 100 reinforcers were earned during two sessions under an FR 32 schedule.

Discrimination training took place in two-lever compartments. Each discrimination training session consisted of a "test ratio," during which responses were not reinforced, followed by a 15-min "training period," during which responses were reinforced. The test ratio lasted until the rat had completed 10 responses on either lever 1 or lever 2. Thereafter, during the training period, responses on the correct lever were reinforced on an interlocking FR 10-/FI 90-sec schedule of reinforcement. Under this schedule, if the rat started to respond immediately after reinforcement, the 10th response produced saccharin solution; if responding did not occur immediately, the ratio requirement was decreased by one response every 10 sec until an FR 1 requirement was reached. Throughout the session, responses on the incorrect lever were recorded but had no programmed consequence. Drug was injected before Sessions 2, 4, 6, . . . , during which responses on lever 1 were reinforced. No injection occurred prior to Sessions 1, 3, 5, . . . , during which presses on lever 2 were reinforced.

The first 10 discrimination training sessions lasted longer and employed lower ratio schedules than subsequent sessions to facilitate transfer of responding into the two-lever compartments (e.g., Sessions 1 and 2 used FR 2 for 300 min, Sessions 5 and 6 used FR 10 for 60 min, etc.).

During Sessions 1-49, the rats were trained to discriminate D1 versus no drug (see Table 1). During Sessions 50-109, the rats were trained to discriminate D2 versus no drug. Prior to Session 110, D1 was injected, and performance during the test ratio of this session was recorded to indicate the extent to which the rats still discriminated drug 1.

Leverpressing during the test ratio at the beginning of each session was used to indicate whether the rat was discriminating between the D and N training conditions. For each session, percentage of presses on the correct lever during the test ratio was computed. Two indices were used to reflect the speed with which discriminations were learned: (1) number of training sessions prior to the beginning of criterion performance (STC), where criterion was defined as 8 of 10 consecutive sessions with more than 66% correct responses during the test ratio; and (2) average test ratio accuracy during acquisition (i.e., Days 1-30 of training), including both D and N sessions (this index corresponds to the area under the learning curve). To indicate the final, or asymptotic, degree of discriminative control achieved in each rat, we computed average test ratio accuracy across Sessions 30-49 and 80-109, including both D and N sessions in the computation.

Results and Discussion

All rats discriminated the first training drug, and subsequently discriminated the second training drug. The plots showing percent correct test-ratio presses, latency before the beginning of pressing, and total presses per session on each lever were "typical." In Session 110, before which drug 1 was injected, 11 of 12 rats made more than 50% of their test-ratio presses on lever 1, indicating that they still discriminated the initial training drug.

Table 1 shows that, for most rats, 3-14 training sessions were required before the beginning of criterion performance with both the first and the second training drugs. Discrimination of the first drug was learned neither faster nor slower than discrimination of the second drug, suggesting that training with D1 vs. N neither impaired nor facilitated the subsequent acquisition of the D2 vs. N discrimination. The values for average test-epoch accuracy during early training sessions (Days 1-30 during D1 vs. N training, Days 50-79 during D2 vs. N training) correlated highly with STC ($r = -0.82$, $p \leq .01$), suggesting that this index also reflects the speed of acquisition of drug discriminations.

The table also shows that most rats achieved average test ratio accuracies of 80% to 90% after the 30th session of both Phase 1 and Phase 2 training. This shows that both the D1 vs. N and D2 vs. N discriminations were learned to a moderately high level of accuracy.

Two exceptions to this general pattern can be noted. First, amphetamine was discriminated more slowly than the other drugs. Rats trained with this drug required more sessions before the beginning of criterion (geometric mean = 22.1) and had lower average accuracies on Sessions 1-30 (mean = 59.8) and lower asymptotic accuracies after Session 30 (mean = 79.5) than did rats trained to discriminate other drugs. Second, in Rats 9-12, discriminative control generalized from the first training drug to the

Table 1
Indices Reflecting Acquisition and Asymptotic Accuracy of Performance as 12 Rats Learned to Discriminate One Drug Versus No Drug, Then Learned to Discriminate a Second Drug Versus No Drug, and Finally Were Retested With the Original Drug.

First Training Drug (D1, Days 1-49)					Second Training Drug (D2, Days 50-109)				PDC with Drug 1 on Day 110
Rat	Drug and Dose	Sessions to Begin Criterion	Average Percent Correct		Drug and Dose	Sessions to Begin Criterion	Average Percent Correct		
			Days 1-30	Days 30-49			Days 50-79	Days 80-109	
1	Phenobarbital 30	11	60.3	92.7	Nicotine 0.4	11	69.3	94.9	100
2	Phenobarbital 30	7	83.1	90.0	Nicotine 0.4	12	62.9	91.8	100
3	Nicotine 0.4	12	72.7	73.2	Phenobarbital 30	4	88.4	96.7	91
4	Nicotine 0.4	6	76.1	95.7	Phenobarbital 30	13	73.7	81.9	0
5	Amphetamine 0.4	16	61.6	75.5	Cyproheptadine 6	12	71.5	89.5	100
6	Amphetamine 0.4	22	54.6	92.5	Cyproheptadine 6	0	81.4	96.1	56
7	Cyproheptadine 7	2	84.2	87.5	Amphetamine 0.4	40	57.3	66.8	91
8	Cyproheptadine 7	8	68.5	89.6	Amphetamine 0.4	17	66.0	83.5	100
9	Phencyclidine 4	10	75.3	92.8	Cyclazocine 1.0	0	89.4	80.3	100
10	Phencyclidine 4	14	69.9	89.3	Cyclazocine 1.5	0	86.2	76.1	100
11	Cyclazocine 1.5	14	74.5	86.7	Phencyclidine 4	0	93.3	86.0	100
12	Cyclazocine 1.5	4	82.3	87.7	Phencyclidine 4	0	92.0	91.4	100
Average in Rats 1-8		8.6*	70.1	87.1		9.3*	71.3	87.7	

Note—Columns 3 and 7 show the number of training sessions prior to criterion performance of each discrimination, with criterion taken as 8 out of 10 consecutive sessions with test ratio accuracy greater than 66%. Columns 4 and 8 show average accuracy during the first 30 sessions of training with each drug. This reflects the area under the learning curve. Columns 5 and 9 show the average accuracy of each discrimination subsequent to the first 30 days of training. Column 10 shows whether the first training drug was still discriminated after training with the second drug was completed. PDC = percent drug choices. *Geometric mean. Doses in mg/kg.

second training drug. During training with the second drug, the number of sessions prior to criterion performance was zero in these rats, and average accuracy on Sessions 1-30 of training with drug 2 (Days 50-79) was comparable to that achieved during Days 30-50 of training with the first drug. In previous studies, pigeons trained to discriminate cyclazocine versus no drug subsequently made drug choices when tested with phencyclidine (Herling, Coale, Hein, Winger, & Woods, 1981). Conversely, cyclazocine substituted for phencyclidine after discrimination training with phencyclidine versus no drug (Holtzman, 1980). These reports suggest that the cues provided by cyclazocine and phencyclidine are similar—a conclusion also supported by the present results. In effect, Rats 9-12 trained with cyclazocine and phencyclidine can be regarded as a control group illustrating the results obtained when drugs D1 and D2 produce overlapping discriminable effects.

In Rats 1-8, training with drug 1 did not facilitate retraining with drug 2. This indicates that drugs 1 and 2 produced dissimilar discriminable effects. Nonetheless, training with drug 2 did not disrupt discrimination of the original training drug (except in Rat 4) as shown by the test ratio data on Day 110.

EXPERIMENT 2

In this experiment, as in Experiment 1, rats first discriminated D1 versus N and then D2 versus N. A

series of substitution tests with various other drugs was conducted after D1 vs. N training, and again after D2 vs. N training. We expected that after D1 vs. N training, D choices would generalize only to drugs that produced discriminable effects similar to those of D1. A priori, it appeared that three outcomes were possible after Phase 2 of training: (1) D choices only during tests with drugs similar to the Phase 2 training drug, indicating that Phase 2 training had disrupted the originally learned D1 vs. N discrimination; (2) D choices during tests with drugs similar to the Phase 2 and Phase 1 training drugs; and (3) D choices with all test drugs, indicating that the rats had learned a generalized "any-drug" vs. no-drug discrimination.

Method

Subjects. Four male hooded rats, comparable to those in Experiment 1, were employed.

Apparatus. The pretraining and training compartments were the same as those used in Experiment 1.

Procedures. The nine drugs used in this experiment were selected from three pharmacological groups: depressant, antimuscarinic, and opiate. The depressant drugs employed were sodium phenobarbital, flurazepam diHCl, and chlordiazepoxide. The antimuscarinics were scopolamine HBr, atropine sulfate, and Ditrin. The narcotics were fentanyl citrate, morphine sulfate, and heroin. Drug preparation and injection procedures were the same as in Experiment 1, except that fentanyl was injected subcutaneously, since this drug is relatively ineffective when administered intraperitoneally.

Pretraining was the same as in Experiment 1, except that ratio size was increased in larger steps (FR1, FR5, FR10, FR30).

Shaping in the two-lever boxes started with a series of six sessions, before which drug was injected and during which only presses on lever 1 were reinforced. These were followed by four no-drug shaping sessions with lever 2 responses reinforced. The first shaping session on each lever lasted 12 h and utilized an FR 2 schedule. Subsequent shaping sessions were of increasingly shorter duration (60, 30, 15 min) and utilized gradually increasing ratios (FR 2, FR5, FR10).

Discrimination training procedures were the same as in Experiment 1, except that the ratio requirement was incremented by one after every 10th reinforcer up to a maximum of FR 20.

After the rats had discriminated the training drug, they received "substitution tests," prior to which various drugs were injected. The substitution test sessions lasted 2.5 min. Presses on either lever were reinforced on the FR 10-/FI 90-sec schedule. Substitution tests (ST) were interspersed between continuing D and N training sessions following the sequence TrD TrN ST ST TrD TrN ST ST, etc.

The experiment included six stages: (1) pretraining, (2) two-lever shaping, (3) Phase 1 D1 vs. N discrimination training, (4) Phase 1 substitution tests, (5) Phase 2 D2 vs. N discrimination training, and (6) Phase 2 substitution tests.

During Phase 1 discrimination training, the rats were trained to discriminate fentanyl or phenobarbital, as shown in Table 2. Training continued for 80 sessions so that the D1 vs. N discriminations would be well learned.

Phase 1 substitution tests included two or more tests with each of the nine test drugs listed above, as well as with other drugs tested as part of another experiment.

During Phase 2 discrimination training, each rat was trained for 60 sessions to discriminate the second drug shown in Table 2 from no drug.

Phase 2 substitution tests were the same as those conducted in Phase 1.

For training sessions, leverpresses during the test ratio were used to indicate the degree of discriminative control by the training drug conditions. An index reflecting the speed of acquisition of discriminative control was computed from the "number of reversals in training state" (RTC) prior to the beginning of criterion performance; criterion was defined as 8 of 10 consecutive sessions with test ratio accuracy greater than 66%. This RTC index is similar to the STC index used in Experiment 1, except that when two or more consecutive sessions employed the same drug condition,

only the first was evaluated for criterion performance (e.g., the sequence NNNNNNDDDDND contains three state reversals and four sessions in which performance was evaluated). To indicate the degree of discriminative control ultimately achieved in each rat, average percentage of test-ratio presses on the drug lever was computed for the D and N training sessions interspersed between substitution tests.

For substitution-test sessions, all responses during the entire 2.5-min session were included in the computation of percentage of presses on the "drug" lever. Because of the small number of test sessions per test drug, percentage of drug-lever presses during substitution tests was averaged across the three drugs in each pharmacological group.

Results and Discussion

All rats learned to discriminate drug 1, and subsequently to discriminate drug 2. Learning curves were "typical." Table 2 shows that more reversals of training state were required prior to criterion discrimination of drug 1 than prior to discrimination of drug 2; this differs from the results obtained in Experiment 1. A procedural error occurred early in Phase 1 training in Experiment 2, which may account for this result (presses on the incorrect lever were reinforced during one session). The table also shows that the rats achieved test ratio accuracies under the training conditions ranging from 61% to 100% (mean = 90.1%), showing that both the D1 vs. N and the D2 vs. N discriminations were learned by most rats.

Table 2 shows that, during substitution tests conducted after Phase 1 training, each rat predominantly responded on the D lever when tested with the training drug or with drugs that produced similar effects and on the N lever when tested with other drugs. Hence, the rats showed a "normal" degree of specificity, that is, they made D choices only during tests

Table 2
Results of Experiment 2

Rat	Training Drug	Dose mg/kg	PDP on Training Days			PDP during Substitution Tests		
			RTC*	D-Days	N-Days	Depres- sant	Antimus- carinic	Nar- cotic
Results During Phase One								
1	Phenobarbital	35	9	88.3	0.0	81	9	1
2	Phenobarbital	35	6	93.5	0.0	67	1	0
3	Fentanyl	0.04	11	80.4	6.4	2	0	98
4	Fentanyl	0.04	11	93.4	0.0	17	24	76
Results During Phase Two								
1	Scopolamine	0.2	3	96.2	11.7	94	97	31
2	Fentanyl	0.02	0	71.9	8.3	100	2	99
3	Phenobarbital	35	5	61.6	3.1	98	0	32
4	Scopolamine	0.2	1	94.8	8.1	34	100	99

Note—Rats discriminated the Phase 1 drug, were tested with other drugs, discriminated the Phase 2 drug, and were tested again with other drugs. Reversals to criterion (RTC) indicates the amount of training required before the discriminations were learned. Percent presses on the drug lever during training sessions were computed from responses during the test ratios of Sessions 84-134 in Phase 1 and Sessions 59-105 in Phase 2 (averages include training sessions only). Percent presses on the drug lever during substitution tests were computed from all presses during the 2.5-min test sessions. Depressant test drugs were phenobarbital 35, chlordiazepoxide 10 or 14, and flurazepam 20 or 30 mg/kg. Antimuscarinic test drugs were atropine 5, 6, 8, or 10, scopolamine 0.2, and Ditrane 2 mg/kg. Narcotic test drugs were fentanyl 0.02, 0.03, or 0.04, morphine 7 or 10, and heroin 10 or 15 mg/kg. PDP = percent drug presses.

*RTC = number of reversals of reinforced lever before the beginning of criterion discrimination.

with drugs pharmacologically similar to the Phase 1 training drug.

After Phase 2 training, the rats predominantly responded on the D lever when tested with pharmacological relatives of either the Phase 1 or the Phase 2 training drugs, and on the N lever with the remaining test drugs. The only exception to this pattern was Rat 3, which showed a strong "preference" for the N lever at various points during training; this accounts for the low average accuracy during D training sessions in Phase 2, and may have caused the low percentage of D choices during tests with narcotic drugs after Phase 2 training (32%).

Consistent differences between the test results obtained with the various drugs in each pharmacological group were not observed during either phase of testing.

The results of this experiment essentially replicate those of Experiment 1, even though several procedural details differed in the two experiments. After Phase 2 training, N responses still occurred during tests with drugs dissimilar to both the Phase 1 and Phase 2 training drugs. This suggests that the N response may still have been the default choice except when drugs similar to D1 or D2 were tested.

GENERAL DISCUSSION

The results of both experiments showed that retraining with a second drug (D2) did not disrupt a previously learned D1 vs. N discrimination. It appears that D1 vs. N training defines a set of cues (D1 cues) in the presence of which the D response will occur. Further training involving D2 vs. N does not disrupt the D1 vs. N discrimination, but instead adds another set of cues (D2 cues) in the presence of which the D response also will occur. These results, in combination with the results of substitution tests, are poorly described by stating that the animal discriminates drug cues versus no-drug cues. They can be described better by stating that the animal discriminates presence versus absence of the training drug, that is, that it discriminates drug cues versus no cues, or drug cues versus the absence of drug cues.

Theoretical interpretations of state-dependent learning have recently been revised in such a fashion as to be congruent with our present conclusions. In most early studies of state-dependent learning (SDL), impairment of retrieval was expected after either D→N or N→D state changes (symmetrical SDL), because the N response was thought to be contingent on N cues and the D response contingent on D cues (e.g., Belleville, 1964; Heistad, 1957; Otis, 1964). Additionally, when a drug was administered, D cues were assumed to displace N cues so that the animal could not experience N and D cues simultaneously. Once these assumptions were made, asymmetrical state dependency (with generalization of responding

from N to D but amnesia after a D-to-N state change) was inexplicable, and had to be regarded as an artifact or as a different phenomenon (Deutsch & Roll, 1973; Overton, 1968). However, a "no-cue" interpretation of the N state has been suggested in several recent reports on SDL (Barry, 1978; Boyd & Caul, 1979; Overton, in press). Such a "no-cue" interpretation of the N state radically alters our expectations regarding the outcome of 2×2 SDL experiments, and makes asymmetrical SDL an expected finding. According to this formulation, drug stimuli do become retrieval cues required for performance of responses learned in the D state, resulting in retrieval deficits after a D→N state change. However, performance of N-state responses is contingent only on apparatus cues and on interoceptive cues such as fear or hunger that are present during both D and N test sessions; hence, responses learned in the N state generalize into the drug state. Such asymmetrical SDL has, in fact, been reported in a substantial proportion of the 2×2 SDL studies in the literature, and these results support the revised theoretical formulations which minimize the importance of no-drug cues.

It should be clear that we are not arguing against the existence of no-drug cues, or even disputing the fact that learned responses are strongly conditional on such cues in both SDL and DD paradigms. Instead, we are simply suggesting that they do not acquire discriminative control, because most "no-drug" interoceptive cues are also present in the D state. Also, it should be obvious that there are several other interpretations in addition to those diagrammed in Figure 1, and that our data do not select between all of these alternatives. For example, it is possible that a few N cues are changed when drug is administered, and that D responses become somewhat conditional on the absence of this subset of N cues as well as on the presence of D cues. Our experiments lack the power to distinguish this alternative from the simplistic hypothesis that the presence versus absence of N cues exerts no response control.

In addition to our concern with the theoretical issue of the degree of discriminative control acquired by N-state cues, we also had a more practical reason for wanting to test the degree to which D2 vs. N training would interfere with an already established D1 vs. N discrimination. We recently reported that the degree of specificity produced by DD training could be increased by concurrent training with several drugs, that is, we found that training of the form D vs. (N or X or Y or Z) in a two-lever compartment allowed fewer drugs to substitute for D than substituted for it after D vs. N training (Overton, 1982). As an extension of this approach, we reasoned that training of the form D vs. (R or S or T . . .) vs. N in a three-lever compartment might allow animals to sort novel drugs into three categories: (1) D-like drugs; (2) drugs with discriminable actions unrelated to

those of D; and (3) drugs lacking discriminable effects. However, this scheme could be used only if animals were capable of simultaneously discriminating several dissimilar drugs (R, S, T) versus no drug. In this context, the present study served as an initial test of feasibility. Since discrimination of D1 was not disrupted by subsequent D2 vs. N training, it appears that the two discriminations only minimally interfered with one another, that is, our results indicate that two drugs can be concurrently discriminated from no drug. Next, one might reasonably try to establish concurrent discriminations of several unrelated drugs (i.e., D1 or D2 or D3 vs. N) to determine how many drugs can be concurrently discriminated from no drug. If several drugs can be concurrently discriminated, paradigms involving such collections of training drugs might be used in DD studies designed to investigate pharmacological questions.

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