Dissociation and Recovery of a Response Learned under the Influence of Chlorpromazine or Saline

Abstract. *Rats trained in an avoidance response while under the influence of chlorpromazine and then tested after receiving an injection of saline, or trained after receiving injections of saline and tested after an injection of chlorpromazine, showed greater dissociation and less recovery of the avoidance response than animals that received only injections of saline, or only injections of chlorpromazine during both training and testing sessions.*

Almost all of the behavioral drug research that has been published since 1954 has failed to take into account the consequences of any internal stimuli, such as physiological changes, which might result from drug administration. In this report, I will demonstrate that an internal state induced by a drug may function like a stimulus; that is, it may acquire habit loadings, or associative connections to responses.

Forty-eight rats were randomly assigned to one of two groups of equal size; group 1 was injected intraperitoneally with chlorpromazine, 1.25 mg/kg, and group 2 was injected with saline. The subjects were given five training sessions per day for 10 consecutive days on a conditioned avoidance pole-jumping response; the conditioning stimulus (CS) was a flashing light, and the unconditioning stimulus, a 1.0 ma shock to the floor; jumping onto the pole terminated the CS and disengaged the shock circuit. Failure to jump onto the pole during the 15-second CS period resulted in shocks to the floor for a total of 1 minute or until an escape response occurred. The interval between each trial varied between 60 and 180 seconds, randomly determined. All conditioning and testing trials were conducted approximately 1 hour after the animal received the injections.

After the 50 training sessions, the subjects were allowed to rest in the home cages for 22 days to permit complete detoxification of the drug (see *1*). The rats were then given five trials on each of three consecutive days in the avoidance apparatus. The schedule was as follows: day 1, no injections, CS but no shock; day 2, half of each group injected with chlorpromazine (groups 1C and 2C) and half with saline (groups 1S and 2S), CS but no shock; day 3, same as day 2 except that subjects were shocked for failure to jump onto the pole within 15 seconds after the CS onset.

Day 3 was followed by 40 days of rest, after which time all subjects were reconditioned by five training sessions per day on each of three consecutive days. During this time no injections were given in order to test whether the drug had any permanent effect on learning ability.

The animals in group 1 were inferior to those in group 2 in original learning. The median number of conditioned avoidance responses (CAR) during the 50 training trials for group 1 was 11.6, and for group 2 it was 19.3. This difference is significant at less than the .01 level of confidence ($\chi^2 = 8.33$). These results support previous findings that chlorpromazine retards learning (*2*).

During the five trials given on test day 1, 22 days after the last condtioning day, retention was measured in the absence of injection or shock. This condition represented the most dissimilar situation from the learning trials for both groups 1 and 2; if the internal stimulus hypothesis is correct, the conditions imposed on test day 1 were probably most dissimilar for the previously drugged group.

The results support the idea of greater dissimilarity for group 1. Out of 17 animals in group 1 that responded during the last conditioning trial, only seven responded on test day 1. In contrast, 19 of the 22 subjects that responded with one or more conditioned avoidance responses during the last day of the original training sessions also did so during test day 1. This difference is significant at the .01 level of confidence ($\chi^2 = 9.82$).

Defecation was also measured during the five trials without shock and without injections given during test day 1. Of great interest is the finding that groups 1 and 2 did not differ in the number of subjects defecating ($N = 17/24$; $\bar{\chi} = 5.5$ for drug group and $N = 20/24$, $\bar{\chi} = 6.0$ for the saline group); the combined groups, however, differed significantly ($\chi^2 = 7/16$) from a third group introduced for this analysis, that had never been in the test chambers before ($N = 5/12$; $\bar{\chi} = 2.3$). These results suggest that a conditioned emotional response (CER), which apparently is learned during training for the conditioned avoidance response, is retained as readily by group 1 as by group 2; the data also raise questions regarding the presumed "fear-reduc-

Table 1. Conditioning and testing of avoidance behavior under conditions similar and dissimilar to the conditions imposed during original learning. Data presented is for those animals that had met Grant's criterion of learning during the training sessions.

Similar					Dissimilar				
Subjects	CAR*	Responses on test days			Subjects	CAR*	Responses on test days		
		1	2	3			1	2	3
		Group 1C					*Group 1S*		
#1	22	4	2	2	#3	14	0	0	0
6	22	0	3	4	8	16	5	4	2
7	21	4	3	4	11	20	3	4	4
13	16	0	0	3	15	15	0	0	0
14	13	2	4	4	19	23	2	2	4
16	16	2	5	4	20	22	0	0	1
Mean	18.3	2.0	2.8	3.5		18.3	1.6	1.7	1.8
		Group 2S					*Group 2C*		
#26	24	3	5	4	#25	21	0	1	2
32	21	2	3	4	28	22	2	0	2
34	19	5	5	4	29	24	2	4	1
35	17	3	4	5	33	23	1	0	2
36	21	5	3	4	38	20	1	3	5
37	21	4	1	4	39	21	3	1	3
41	16	2	4	4	40	14	3	2	3
47	21	0	0	3	44	22	1	1	4
					45	21	1	0	3
					46	21	5	0	1
					48	17	5	3	3
Mean	20.0	3.0	3.1	4.0		20.5	2.2	1.4	2.6

* Number of conditioned avoidance responses made within 50 trials.

ing" properties of chlorpromazine as an explanation for the failure of learning during the conditioned avoidance response training.

Dissociation was further analyzed during test days 2 and 3 by considering the performance of animals that had sufficiently learned the conditioned avoidance response to satisfy Grant's criterion of learning during the original training trials. Grant (*3*) has published the probability of a sequence of correct responses during a series of learning trails when the probability of each correct response is known. Only 12 animals in group 1, and 19 in group 2, actually learned the conditioned avoidance response within the 50 training trials at the .05 level of significance (*3*). The criterion of learning was at least five consecutive conditioned avoidance responses, with a respond duration time of 10 seconds or less during the criterion trials; the probability of each correct response was 0.25.

Matched subgroups were formed and were run under changed and nonchanged internal conditions during test days 2 and 3. Only those animals that had met Grant's criterion for learning were considered, since non-learners obviously cannot show dissociation if little or nothing has been learned.

During test day 2, matched subgroups of animals in groups 1 and 2 were injected with saline or drug, such that 6 of the 12 animals in group 1 were tested after receiving injections of saline (group 1S), and 11 of the 19 in group 2 were tested after receiving injections of chlorpromazine (group 2C) (see *4*). The remaining animals of each group were tested under the same conditions as were imposed during original learning of the conditioned avoidance response (groups 1C and 2S). Neither groups 1S and 1C nor groups 2S and 2C differed from each other in the total number of conditioned avoidance responses during the 50 learning trials. Animals were not shocked during test day 2, but were shocked for failure to jump on to the pole within 15 seconds of the onset of the conditioning stimulus during test day 3; this procedure tested the adequacy of escape behavior.

During both test day 2 and test day 3, the combined subgroups (groups 1C and 2S) having the same injection conditions as during learning differed significantly from the combined subgroups (groups 1S and 2C) that were trained and tested under different injection conditions ($\chi^2 = 5.42$ and 9.31, respectively). These data are shown in Table 1.

Clearly, the changed internal conditions resulted in poorer retention—that is, more dissociation. Several weeks later the subgroups were reconditioned without injections during five trials on each of three consecutive days. Animals that had received drugs during any portion of the experiment learned as readily as those that had received only saline, indicating that no permanent loss of learning ability could be attributed to chlorpromazine.

These findings imply that some previous reports of changes in retention after drugs should be re-evaluated, if testing occurred under conditions that were dissimilar from the original baseline measurement period. If a portion of the learned response is tied, so to speak, to the internal stimuli resulting from drug administration, then responses learned while the subject is under the influence of a drug should be less in evidence—and under certain conditions, completely absent (that is, dissociated) —if the subject is tested when not under the influence of the drug. The same argument holds for subjects trained when not drugged but tested when drugged. Thus, if responses learned while the subject is drugged are tested when the effects of the drug have worn off, or if responses learned before the drug is administered are tested after it has been injected, are diminished in strength, this result may have little bearing on the central action of the drug in question. The diminution may be due, primarliy, to the altered conditions.

With few exceptions, almost all the behavioral research published thus far has failed to take this disquieting fact into consideration (for exceptions, see *5*). As a result, a re-evalution of the results of most behavioral studies in which changed drug conditions were in force between training and testing would seem to be in order.

These findings may also have implications at the human level. Therapeutic gains [which may be equated with new learning or the emergence of old, previously learned responses (*6*)] of hospitalized patients maintained on drugs may be so tied to the drugged condition that these gains may not survive when the patient is taken off drugs and returned to the community. This may be one reason for the high recidivist rate among patients receiving drug therapy. Dissociation would be expected to occur since therapeutic dosages are usually selected on a "ceiling basis"—that is, the highest dose tolerable with a minimum of side effects and a maximum of altered, more socially acceptable behavior.

Maintenance problems may be increased, but it would seem more appropriate to select doses of drugs which cause the least blocking of the patient's receptiveness to new learning, and which would cause the least deviation from the non-drugged condtion, especially if it is hoped that when the patient is cured (whatever that means) he can be taken off drugs permanently. The present method of keeping the patient on as high a dose regimen as he can tolerate probably works against permanent therapeutic gains; that is, not only will the patient be at a disadvantage insofar as new learning is concerned, but whatever is learned may be so tied to the drug state that it may not survive to the non-drug state, if the patient is taken off drugs.

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References and Notes

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7. Supported by contract Nonr-2993(00) between the Office of Naval Research and Stanford Research Institute. Ronald David assisted in the conduct of the research.

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