Generalization of LSD-induced conditioned suppression*

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Thirsty rats were exposed to a conditioned suppression procedure in which a drug, LSD, was the US and a 6,000-Hz tone was the CS. All animals demonstrated conditioning in that responding to obtain water on a VI schedule was suppressed during CS presentation. It was then demonstrated that stimulus generalization occurred when tones between 2,000 and 10,000 Hz were presented during subsequent extinction.

Estes & Skinner (1941) described a conditioning procedure in which an originally neutral stimulus is paired with a US in a respondent conditioning paradigm (i.e., independent of the animal's response) and is superimposed on some instrumental behavior usually maintained by an appetitive schedule. The measure of conditioning is the extent to which the disruption of the instrumental behavior, which originally occurred when the US was presented, begins to occur to the originally neutral stimulus. This procedure is now generally called either "conditioned suppression" or "the conditioned emotional response" (CER).

Goldberg & Schuster (1967, 1970) have demonstrated that conditioned suppression could also be produced by using a drug state as the US. This state resembled a "withdrawal syndrome" (which consisted of bradycardia, emesis, excessive salivation, and cessation of on-going appetitive behavior); it was induced by administration of nalorphine, a pharmacological antagonist of morphine, to morphine-dependent monkeys.

However, it was demonstrated that the "withdrawal syndrome" need not be involved in pharmacologically induced conditioned suppression. Injections of amphetamine (Whitney & Trost, 1970), scopolamine (Herrnstein, 1962), and large doses of LSD or chlorpromazine (CPZ) (Cameron & Appel, 1972) have been successfully employed as the USs in CER paradigms. In the LSD-conditioned animals, during the CS, the animals seemed to be "hyperactive" and not at all debilitated, while with CPZ, the animals appeared "poured out" (ataxic?) during the CS; but in neither case did a syndrome similar to that described by Goldberg and Schuster seem evident during visual observation.

In this experiment, we were interested in comparing some of the properties of drug- and shock-induced conditioned suppression. One way of doing this was to study the generalization of LSD-induced suppression and compare the results obtained with those of Hoffman and his coworkers (e.g., Hoffman, 1969a, b), who have studied stimulus generalization of the shock-induced CER extensively.

SUBJECTS

The Ss were eight naive male albino rats of the Sprague-Dawley strain, obtained from Charles River Breeding Laboratories, Wilmington, Mass. All Ss were approximately 120 days old at the beginning of the study, and weighed about 250 g. Food was always available in separate home cages in a room maintained at constant temperature (75°-78° F) and humidity (40%-50%). Ss were deprived of all water from Monday to Friday, except that which was obtained in the chamber (approximately 4 ml), and were given free access to water from Friday evening to Saturday afternoon; no water was then available until the Monday session. All Ss remained healthy under this deprivation procedure.

APPARATUS

A one-lever operant chamber was used. Reinforcement was 0.05 ml of tap water. The chamber contained a 28-V white houselight and a speaker. The tones used as stimuli were 40 dB re .002 dynes/cm^2 inside the chamber; they were produced by a Hewlett-Packard (Model 200AB) audio oscillator. The chamber was isolated in a sound- and light-attenuating box; all programming and recording was done automatically in an adjoining room.

BEHAVIORAL PROCEDURES

The Ss were shaped to barpress for water on a variable interval (VI) 30-sec schedule until rates were stable. Habituation procedures were then given to minimize (1) any possible disruption produced by the tone to be used as the training stimulus (6,000 Hz), (2) disruption produced by the injection [drug or saline was given by removing the S from the chamber for no more than 20 sec, and administering the fluid intraperitoneally (IP)], and (3) conditioning any aversive characteristics of the injection to the tone. Habituation involved (1) presenting the tone alone, (2) randomly presenting the tone and saline injection, and (3) pairing the tone with saline injection (injection was given half-way through the 2-min tone). Each of these procedures was continued until either no suppression of on-going behavior was observed or the data indicated that the S was not going to habituate.

After habituation was completed, conditioning was begun. For all Ss, the training stimulus was a tone of 40 dB at 6,000 Hz. The tone was 2 min long, and the US, 0.20 mg/kg of LSD, given IP, was injected at 1 min, making the onset of drug effect, about 1 min later, approximately coincide with tone offset. Conditioning continued for eight sessions, with one trial per session. Several "blank" days, on which the Ss ran for the full 1-h session with no interruption, were interspersed randomly with conditioning sessions. With this schedule, tolerance to the LSD US never appeared.

After conditioning was completed, testing was done during extinction in four consecutive sessions. For testing, each S was assigned one testing stimulus, 2,000, 3,000, 4,000, 5,000, 7,000, 8,000, 9,000, or 10,000 Hz. This range is in the "flat" region of the "threshold" gradient for rats (Cowles & Pennington, 1943; Gourevitch, 1965; Gourevitch & Hack, 1966). Four extinction test trials were given to each S with the appropriate tone being presented for 2 min, and a saline injection was given after the first minute.

DRUGS

The saline used for injections and drug dilutions was 0.9% sodium chloride and 0.9% benzyl alcohol in distilled water. LSD tartrate solution (0.20 mg/ml of LSD) was prepared from LSD-25 (Delysid) powder manufactured by Sandoz Pharmaceuticals, Hanover, N.J., and obtained from NIMH, Center for the Study of Narcotics and Drug Abuse.

RESULTS

Table 1 contains the number of responses for each S during the 2 min

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Table 1

	Ss															
	87		88		89		90		91		92		93		94	
	Pre	Tone	Pre	Tone	Pre	Tone	Pre	Tone	Pre	Tone	Pre	Tone	Pre	Tone	Pre	Tone
Habituation Days																
8	42	46	68	24	81	32	53	19	34	9	46	19	128	16	143	19
9	87	39	40	46	84	46	51	12	32	17	53	19	94	29	65	11
10	74	69	65	11	88	78	34	6	46	28	42	20	91	38	108	30
11	111	64	58	34	59	60	68	19	46	38	76	43	68	23	198	38
12	110	63	44	40	24	39	54	22	29	33	27	47	76	23	158	80
13	102	95	58	60	71	58	43	13	32	38	44	41	64	24	190	119
Conditioning Days																
1	102	91	60	62	65	76	81	18	54	43	44	43	88	6	211	93
2	107	97	62	47	122	105	43	22	77	34	72	49	47	7	171	87
3	80	61	52	36	127	64	48	10	48	18	44	2	157	39	107	103
4	130	79	70	52	255	107	58	12	75	21	41	35	77	14	209	53
5	120	68	56	42	148	98	42	18	79	32	49	36	82	5	173	43
6	144	39	32	23	145	41	44	5	56	15	43	17	77	3	172	18
7	77	24	38	10	159	30	22	0	38	7	41	9	39	0	59	3
8	122	42	58	16	100	15	38	2	29	10	41	27	59	3	111	6
Extinction Days																
1	122	45	34	44	73	8	22	2	46	11	27	8	34	1	144	3
2	114	76	33	47	115	74	49	22	51	27	26	18	64	0	43	2
3	185	125	29	37	95	57	33	19	39	43	38	21	53	12	95	10
4	102	79	46	37	71	67	31	22	67	45	39	46	64	30	143	71

of the last 6 of 13 tone-saline habituation pairings, 8 conditioning sessions, and 4 extinction test trials (tone); the number of responses during the 2 min immediately preceding each habituation, conditioning, and extinction trial is also presented (pre). As can be seen by comparing the number of responses during the pretone period to the number of responses during the tone period on Habituation Day 13, five of eight Ss had habituated (the pretone and tone values were approximately equal), but three Ss (Nos. 90, 93, and 94) had not. Even though there is no clear habituation in these, the conditioning and extinction data of S 90 was incorporated because it appeared to be consistent with the other five Ss that showed clear habituation. The data of the other Ss (93 and 94) were not incorporated in the presentation (Fig. 1).

Figure 1 contains the data of the four extinction trials for each S. The data are graphed as "inflection ratios." The formula for this ratio is: [(number of pretone responses) — (number of tone responses)]/(number of pretone responses). Using this ratio, a calculated value of 1.00 means total suppression, a value of 0.00 means no change, and a value less than 0.00 means facilitation. [Presenting the data in this way approximates both the method of data presentation of Hoffman (1969a, b) and the shape of the "normal generalizationgradient," e.g., Guttman & Kalish (1956).]

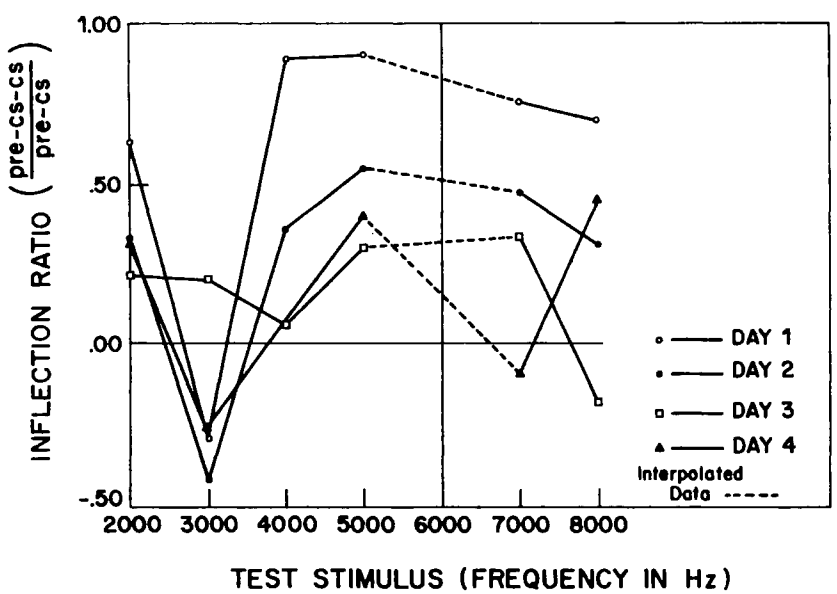

Fig. 1. Stimulus generalization gradient of LSD-induced conditioned suppression: Day 1, first extinction test trial; Day 2, second trial; Day 3, third trial; Day 4, fourth trial (one S tested at each frequency, except training stimulus—lines interpolated from 5,000 to 7,000 Hz—in four consecutive trials).

With the exception of the data of S 87 (at 2,000 Hz), the curve of Test Day 1 approximates a generalization gradient away from the training tone. (No S was tested at 6,000 Hz, the training stimulus. The lines connecting the data of S 90 at 5,000 Hz and 91 at 7,000 Hz were interpolated. The average ratio of the six Ss on the last training day was 0.71.)

Again, on Day 2, with the exception of S 87, the curve is similar to a generalization gradient. There is also a tendency toward extinction of conditioned suppression, in that the whole curve is displaced downward toward 0.00. The third test day shows even more extinction than the second, as well as a tendency toward flattening of the gradient. The 4th day indicates about the same overall level of extinction as the 3rd, but less stability between Ss. This loss of stability after 4-5 trials is consistent with previous findings (Cameron & Appel, 1972).

DISCUSSION

The data indicate that stimulus generalization to LSD-induced conditioned suppression can occur. While there were some difficulties with the data—the lack of habituation of Ss 90, 93, and 94; the inflection (change in direction of gradient) between Ss 88 and 87; and the instability on the 4th extinction day—the general appearance

of the curves reflect a clear gradient effect. While there certainly are procedural differences between the results of Hoffman (1969a, b) and those of the present study, the similarities are striking: (1) both studies demonstrate that stimulus generalization will occur in the conditioned suppression paradigm—a finding which indicates at least some similarities in process or "mechanism" between drug-induced and shock-induced CERs—and (2) both support Hoffman's contention (see below) that the sharpening of the gradient in the shock-induced CER is a function of differential extinction of stimulus effects (presumably due to a difference in "strength" of initial conditioning) of stimuli at different "distances" from the training stimulus.

But there are differences between the data of Hoffman and his associates and those of the present study: (1) Hoffman observed gradients only after several extinction trials, while the gradients here appear on the first extinction trial; (2) Hoffman observed a tendency towards sharpening of the gradient, while here the tendency was toward flattening; and (3) Hoffman was still seeing clear conditioned suppression, at least to stimuli near the training stimulus, even after 25 extinction trials, while, in this study (as well as in the earlier demonstration of LSD-induced conditioned suppression), the suppression had either extinguished or become unstable by the fourth or fifth trial.

There does, however, seem to be a way to reconcile these data with those of Hoffman. He contends that the results which he obtained (the sharpening of the gradient) were a function of the faster appearance of extinction at tones which were farther from the training stimulus. If this is true, then the gradient obtained in this study could be likened to a continuation of extinction of conditioned suppression. It is as if the procedure used in this experiment, especially the drug-LSD US, produced a "weaker" conditioning, as if one had started testing Hoffman's Ss after the first 25 trials and continued until extinction had occurred with all testing stimuli. And, indeed, there is some justification for assuming that Hoffman's Ss were more "strongly" conditioned than the Ss in this study. Hoffman used 70 conditioning sessions with a 40-sec CS before initiating extinction testing, while in this study only 8 conditioning sessions (trials) and a longer CS (120 sec) were employed. While some other differences also existed—e.g., species of experimental Ss, intensity of the tone CS, and the obvious one (the variable of interest), the nature of the US (shock vs drug state)—many of the possible differences were controlled, e.g., modality of training stimulus (tone), gradient continuum (frequency), and baseline schedule (VI). [Work reviewed by Davis (1968) would indicate that more conditioning trials and a shorter CS would lead to "stronger" conditioning.] Admittedly, Hoffman gave many trials because suppression did not develop as fast in his study as in either this experiment or in another control group run in this laboratory (unpublished) in which Ss developed a "traditional" (shock-induced) CER in a similar number of trials (6-8) as with the LSD-induced CER group, with the same 2-min CS duration. In this control group, a high shock level (3.0 mA) was used; this could account for faster conditioning than Hoffman observed. But Hoffman used a longer shock (5-sec pulsing shock vs 1-sec), which might balance out the high level in the control group.

Despite the differences, these considerations seem to indicate that the LSD US is a "weaker" US for conditioned suppression than shock. And, while Whitney & Trost (1970), using amphetamine as the US, found fast extinction, similar to the LSD US results, Goldberg & Schuster (1970) found that many trials were required to extinguish "conditioned withdrawal," a pattern similar to that seen when shock is employed as the US. Therefore, the fast extinction is not a nonspecific effect observed when any drug state is used as a US for conditioned suppression. There appear tobe both similarities and differences in "mechanism," both between shock-induced vs LSD-induced conditioned suppression, and even between procedures in which different drug states are employed as the USs.

REFERENCES

CAMERON, O. G., & APPEL, J. B. Conditioned suppression of bar-pressing behavior by stimuli associated with drugs. Journal of the Experimental Analysis of Behavior, 1972, 17, 127-137.

COWLES, J. T., & PENNINGTON, L. A. An improved technique for determining auditory acuity in the rat. Journal of Psychology, 1943, 15, 41-47.

DAVIS, H. Conditioned suppression: A survey of the literature. Psychonomic Monograph Supplements, 1968, 2(14, Whole No. 30), 283-291.

ESTES, W. K., & SKINNER, B. F. Some quantitative properties of anxiety. Journal of Experimental Psychology, 1941, 29, 390-400.

GOLDBERG, S. R., & SCHUSTER, C. R. Conditioned suppression by a stimulus associated with nalorphine in morphine-addicted monkeys. Journal of the Experimental Analysis of Behavior, 1967, 10, 235-242.

GOLDBERG, S. R., & SCHUSTER, C. R. Conditioned nalorphine-induced abstinence changes; persistence in post-morphine dependent monkeys. Journal of the Experimental Analysis of Behavior, 1970, 14, 33-46.

GOUREVITCH, G. Auditory masking in the rat. Journal of the Acoustical Society of America, 1965, 37, 439-443.

GOUREVITCH, G., & HACK, M. H. Audibility in the rat. Journal of Comparative & Physiological Psychology, 1966, 62, 289-291.

GUTTMAN, N., & KALISH, H. I. Discriminability and stimulus generalization. Journal of Experimental Psychology, 1956, 51, 79-88.

HERRNSTEIN, R. J. Placebo effect in the rat. Science, 1962, 138, 677-678.

HOFFMAN, H. S. Stimulus factors in conditioned suppression. In B. A. Campbell and R. M. Church (Eds.), *Punishment and aversive behavior.* New York: Appleton-Century-Crofts, 1969. Pp. 185-234.

HOFFMAN, H. S. Stimulus generalization versus discrimination failure in conditioned suppression. In R. M. Gilbert and N. S. Sutherland (Eds.), *Animal discrimination learning.* London: Academic Press, 1969. Pp. 63-82.

WHITNEY, G. D., & TROST, J. G. Response disruption following amphetamine self- and programmed-administration. In T. Thompson, W. M. McIsaac, & C. R. Schuster (Eds.), *Drug dependence.* Austin: University of Texas Press, 1970. Pp. 198-213.