ures on two factors (*10*). The analysis of the CNV latency data revealed no significant effects or interactions. The CNV amplitude data and analysis are presented in Tables 1 and 2.

The effect on CNV amplitude of the sex category of stimulus proved to be highly significant ($P \leqq .001$). The Newman-Keuls test procedure (*10*) applied to the data revealed that males and females both responded with greater CNV amplitude to stimuli of opposite sex than to either same sex or "neutral" stimuli ($P \leqq .01$). Only female subjects, however, demonstrated a significantly greater response to same sex than to "neutral" stimuli ($P \leqq .05$). When the pattern of amplitude scores of the 24 individual subjects was examined, 18 of the 24 were found to exhibit greater CNV response to opposite than to same sex stimuli [$P = .001$, sign test (*11*)]. This level of discrimination was true for both the first and second 25 trials of exposure to the stimulus classes. A somewhat higher proportion of male subjects responded in the predicted direction. These data are particularly impressive in view of the fact that possibly deviant subjects were not screened out of the sample population.

A significant interaction was observed between subject sex and stimulus trials ($P \leqq .01$). Female subjects exhibited overall higher CNV amplitudes in response to the first 25 trials of the stimulus classes. Male subjects considerably increased their CNV amplitude response to the "neutral" category from the first to second 25 trials of exposure, while female subjects exhibited precisely the opposite pattern. The pattern suggests that as the experiment progressed both male and female subjects came accurately to perceive the subject of the "neutral" slide category as female. This interpretation is supported by data from the questionnaires in which only 4 of the 24 subjects responded to the "neutral" stimulus as "masculine" on the "masculine-feminine" dimension.

Whether the observed amplitude differences are to be interpreted as CNV enhancement with opportunities to view preferred object stimuli, or CNV inhibition in conjunction with nonpreferred object stimuli, cannot be answered conclusively. However, the response pattern noted above with the "neutral" category lends support to an interpretation of CNV enhancement.

The data indicate a clear relation between the level of averaged CNV amplitude and the expected degree of sexual interest in the stimulus categories. These findings support the potential utility of the method as a research and clinical tool for objectively determining sexual interest and object preference patterns in both males and females. Application of the method to subjects with known deviant sexual preferences should more clearly establish its reliability and validity.

RONALD M. COSTELL
*Adult Psychiatry Branch,*
*National Institute of Mental Health,*
*Bethesda, Maryland 20014*
DONALD T. LUNDE, BERT S. KOPELL
WILLIAM K. WITTNER
*Department of Psychiatry,*
*Stanford University School of Medicine,*
*Stanford, California 94305*

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8. Details of this procedure are in J. Corby and B. Kopell, *Psychophysiology*, in press.
9. Figure 1 reveals a long latency positive potential arising at S1 off and merging with the CNV. This potential was observed in most subjects and is fully described in a longer research report in preparation. This potential is similar to phenomena described by H. Vaughan in *Averaged Evoked Potentials*, E. Donchin and D. Lindsley, Eds. (NASA, Washington, D.C., 1969). Its amplitude was related to stimulus categories at a marginal level of significance, but in a pattern unrelated to that described with CNV. The two measures do not appear to confound, but the presence of the positive potential required a CNV amplitude measurement technique similar to that reported in D. McAdam and E. Rubin, *Electroencephalogr. Clin. Neurophysiol.* **30**, 511 (1971).
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13. Leonard Macpherson designed the experimental apparatus, Carol Dickerson Smith ran the experiment, and Judie Ford and Helena Kramer analyzed the data. This work was supported by the Veterans Administration and was conducted at its Palo Alto Hospital.

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## Lysergic Acid Diethylamide and Stimulus Generalization: Rate-Dependent Effects

Abstract. *A stimulus generalization procedure was used to investigate the effects of LSD on sensitivity to auditory stimuli in rats. The shape of the generalization gradient was changed after administration of the drug only with a dose which produced decreases in relatively high rates of responding.*

Several kinds of perceptual disorders have been reported among users of lysergic acid diethylamide (LSD) (*1*). Attempts have been made to study these effects in animals, but the results obtained to date have been confounded by the numerous procedures, experimental subjects, and doses of the drug employed by different investigators. One of the procedures used to demonstrate the effects of drugs such as LSD on perceptual behavior is that of stimulus generalization. It is thought that this procedure may serve as a useful tool for analyzing the sensitivity of normal and drugged animals to changes in their external environment (*2*).

In studies involving stimulus generalization, an animal is trained to respond in the presence of one stimulus or to respond differentially in the presence of two or more stimuli. A generalization test is then given during extinction; several stimuli along the same dimension as the training stimulus are presented, and the animal's tendency to respond in the presence of each test stimulus is recorded. The extent to which the animal's behavior is controlled by the original training stimulus is related to the slope of the gradient obtained. A flat gradient, showing equal amounts of responding in the presence of all test stimuli, indicates little discrimination, whereas a steep gradient, showing maximal responding at the training stimulus, indicates that the animal is under good stimulus control (*3*). By measuring the amount of generalization during both drugged and nondrugged states, information about a drug's effect on stimulus control is obtained.

When generalization is measured in terms of the relative probability of responding to each of several test stimuli, LSD does not appear to alter the obtained generalization gradient (*4*). In view of the fact that (i) this compound has been found to have a large variety of "perceptual" effects (*5*) and (ii) other drugs which similarly alter perception also alter stimulus generalization (*2, 6*), we decided to reexamine the effects of LSD on a more traditional

(that is, rate) measure of generalization (*7*).

Eleven male albino rats of Sprague-Dawley strain were trained to discriminate between two auditory stimuli in the manner described by Jenkins and Harrison (*8*). During daily training sessions, one of two tones (600 or 1000 hertz) was presented during each of 42, 30-second stimulus-on periods, separated by 7-second blackouts (no tones or reinforcement). In the presence of one of the tones ($S^D$), animals were reinforced with sweetened milk for responding on a variable-interval, 30-second schedule. In the presence of the other tone ($S^\Delta$), responding was not reinforced. Training sessions were continued until the average rate of response during $S^D$ periods was at least four times greater than during $S^\Delta$ periods.

Each animal then received two generalization tests consisting of the repeated presentation of seven stimuli ranging in frequency from 500 to 1100 hertz under extinction conditions. Each stimulus was presented six times for 30 seconds by a random schedule. On the first generalization test day, five of the rats received 0.50 ml of saline immediately before testing. The other six rats received one of two LSD regimens. In one regimen—0.16 mg/kg given ½ hour before testing—LSD has been shown to depress ongoing behavior (*5*). In the other regimen—0.08 mg/kg given in three hourly doses—acute tolerance occurs to the usual LSD-induced decreases in rate of responding, but not to other measures of drug effect (*9*). After at least 7 days of retraining, a second generalization test was given. In this test the animals that had originally received saline received one of the drug regimens. The animals that had originally received drug received saline; one animal was given saline on both test days.

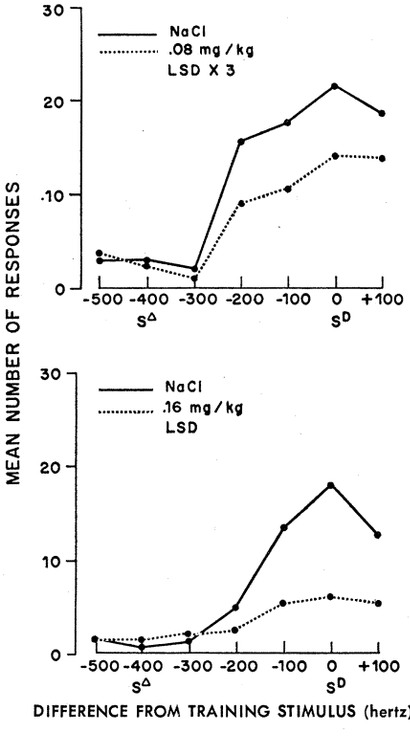


Fig. 1. Generalization gradients under drug and control conditions for five animals. Average number of responses during each of seven stimuli is shown as a function of stimulus frequency.

In Fig. 1 the mean number of responses emitted in the presence of each testing stimulus is plotted as a function of the distance from $S^D$. During control days (solid lines) responding is greatest at $S^D$, the stimulus which had been reinforced during training, and generally decreases as the distance from $S^D$ increases. The overall shape of the gradients did not change significantly either (i) when percentage of total responding during each test stimulus was recorded (Fig. 2) or (ii) as a function of repeated testing; that is, there was no difference in the shape of the two gradients in the animal which received saline during both generalization tests.

The effects of three doses of 0.08 mg/kg and of a single dose of 0.16 mg/kg of LSD are shown in Figs. 1 and 2. Neither dosage regimen altered the shape of the gradients (maximal responding at $S^D$, decreasing responding as the distance from $S^D$ increases), regardless of whether rate or percentage of responding was plotted. A two-way analysis of variance was performed on the data obtained during the two generalization tests. The variables were stimuli (seven frequencies including $S^D$ and $S^\Delta$) and drug or control regimens. The effect of stimuli was significant at the .001 level for all measures [$F$ (rate: 0.08 × 3 versus saline) = 8.7; $F$ (rate: 0.16 versus saline) = 20.4; $F$ (percent: 0.08 × 3 versus saline) = 36.6; $F$ (percent: 0.16 versus saline = 35.4; d.f. = 6/56].

Both drug regimens reduced the rate of response (Fig. 1) and 0.16 mg/kg lowers the rate more than three hourly doses of 0.08 mg/kg. This effect of the drug was significant only when the mean rate of responding was measured [$F$ $(0.08 \times 3) = 4.7$, $P < .05$; $F$ $(0.16) = 30.3$, $P < .001$; d.f. = 1/56].

While the decrease in response rate following three doses of 0.08 mg/kg of LSD was independent of the test stimulus (that is, the slope of the gradients following saline and three doses of 0.08 mg/kg were essentially the same), 0.16 mg/kg of LSD produced a disproportionate decrease in responding at those stimuli in the presence of which control rates were high—that is, at the stimuli closest to the training stimulus ($S^D$). This effect was confirmed statistically by the significant interaction between 0.16 mg/kg of LSD and the test stimuli ($F = 6.4$, $P < .001$; d.f. = 6/56). This interaction was not present with three doses of 0.08 mg/kg of LSD.

In Fig. 2 generalization is measured in terms of the percentage of total responding. Here 0.16 mg/kg also *appears* to flatten the slope of the generalization gradient (the slopes of the 0.16 mg/kg of LSD and control curves were significantly different from each other; $F = 6.13$; $P < .05$; d.f. = 1/6). This apparent flattening, however, is probably an artifact of the drug's effect on rate and should not be taken as an indication that the drug affected the animal's ability to discriminate (that is, its sensitivity). This can be shown in several ways. First of all, when a

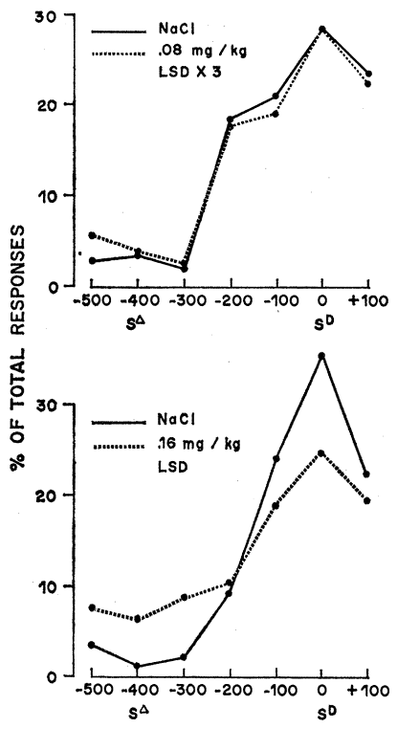


Fig. 2. Generalization gradients under drug and control conditions for five animals. Relative percentage of responding occuring during each of seven stimuli is shown as a function of stimulus frequency.

large overall volume of the drug was given in a regimen that abolished the usual decreases in rate following large doses of LSD (three doses of 0.08 mg/kg), the apparent attenuation of discrimination was not present (Fig. 1, top). This is, though the rate decreased somewhat, this decrease did not alter the shape of the generalization gradient. Furthermore, when a percentage measure was used, the effect of three doses of 0.08 mg/kg of LSD was completely obliterated (Fig. 2, top). The differences between 0.16 mg/kg and control (Fig. 2, bottom) probably can be accounted for by the fact that the animal emits only very few responses after 0.16 mg/kg of LSD. In that case, a difference of only one or two responses between stimuli represents a dramatic change in the percentage measure. Therefore, in spite of apparent alterations in the animal's ability to discriminate after 0.16 mg/kg of LSD, these effects can be attributed to drug-induced changes in the animal's rate of responding; thus, the drug is not affecting sensitivity but is, rather, affecting the animal's response output.

These results are consistent with our own work with LSD on discrete trial generalization (*4*) as well as with the results of a signal detection analysis in which the effects of LSD on sensitivity are measured separately from its effects on response bias. The results are also consistent with numerous reports that the rate of occurrence of a behavior is an important determinant of drug effects (*10*). They also point out the importance of eliminating the confounding effect of changes in response output from measures of sensitivity (*11*).

LINDA A. DYKSTRA*
JAMES B. APPEL†
*Department of Psychiatry, University of Chicago, Chicago, Illinois 60637*

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* Present address: Department of Pharmacology, University of North Carolina, Chapel Hill 27514.
† Present address: Department of Psychology, University of South Carolina, Columbia 29208.

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## Facilitation of the Long-Term Store of Memory with Strychnine

Abstract. *Female mice (C57BL/6 strain), repeatedly administered strychnine sulfate for 10 days after exposure to a six-unit maze, showed significantly improved learning when trained again. This facilitation effect was not due to overall enhancement of learning ability and could not be attributed to retrograde facilitation of consolidation processes.*

Low dosages of analeptic compounds, such as strychnine, can facilitate memory processes (*1*). The evidence accumulated thus far indicates that facilitation of memory occurs only when the drug is injected within several hours after the daily training session (*1, 2*). It is generally accepted that such drug treatments operate on the labile phase of memory and that as the memory trace stabilizes it becomes more resistant to facilitating or impairing agents (*1, 3*). Although the period of susceptibility to enhancing treatments appears to be less than 1 hour after training, the susceptibility interval for interference has been shown to be several hours or even longer (*3*), depending on the treatment used. The facilitation and interference studies provide the strongest evidence for a time-dependent or consolidation notion of memory. Even though time-dependent aspects of memory have not been quantified, it is generally agreed that within 24 hours a memory trace has consolidated to the extent that it is part of the long-term store (*1–3*). To test whether a trace in the long-term memory store could be facilitated, we administered strychnine long after the period of susceptibility to enhancement effects.

Adult female mice (158; 60 to 95 days of age) of the C57BL/6 strain, housed six to ten to a cage and deprived of water for 48 hours, were exposed, on a single trial, to six successive brightness discriminations (*4*). The maze contained six units, in addition to a starting box and a goal box, linearly arranged (*5*). The starting box and the entryways into each discrimination unit and the goal box were painted flat gray. The goal box was painted flat white. Each of the six discrimination units was divided into two alleys, one painted flat black and the other flat white. The white side of the unit was unobstructed and considered correct. The black alley was obstructed by a transparent vinyl barrier that could not be detected by the animals at the choice point. The six units were arranged such that white appeared LRRLLR (L, left; R, right), eliminating solution of the problem with either a position or alternation preference. On entering the goal box, the subjects were allowed access to a 0.3 percent solution of saccharin in tap water for 20 seconds and were not able to reenter the maze. Initial errors (first entry into the incorrect alley of each discrimination unit) and total errors (initial and all reentries into incorrect alleys) were scored. A subject, therefore, could make no more than six initial errors on a single trial, whereas the range of total errors was not constrained. Latency to enter the goal box after introduction into the starting box was also measured. Approximately 30 minutes after the last animal finished running the maze, all animals were given access to water for 1 hour. Twenty-four hours later, each animal was given a second trial in the maze, with the above procedure. One hour after the last animal completed its training session, all animals were given free access to water.

We balanced for initial errors on the two trials and formed six nearly equivalent groups. Although there was a small, unsystematic overall reduction in error scores on the second day, analyses of variance on this trial showed no significant differences among the groups for initial errors ($F = .65$; d.f. = 5,100) or for total errors ($F = .34$; d.f. = 5,100). Beginning 24 hours after the last maze trial, each animal in the six groups received the first of a series