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Alterations in the Generalisation of Visual Stimuli Induced by Lysergic Acid Diethylamide in Cats

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With 4 Figures in the Text

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Introduction

The central action of small doses of lysergic acid diethylamide (LSD-25) is characterised by an alerting effect in cats (APTER 1957; BRADLEY and ELKES 1957). Unlike that of amphetamine the change produced is not due to a direct effect on the arousal mechanism but brought about indirectly by an increased responsiveness to environmental conditions (BRADLEY and KEY 1958). It has been suggested that this change in responsiveness is related to alterations in the level of significance or meaning attached to the sensory stimuli (KEY 1961; KEY and BRADLEY 1960). Tests involving auditory discrimination have demonstrated that the ability of an animal to distinguish between the physical parameters of different tones remains unimpaired following the administration of LSD-25, but the significance of one auditory stimulus is more readily generalised to other stimuli, which previously were without attentive or arousal value (KEY 1961).

This alteration in the amount of auditory generalisation could well account for the increased responsiveness and thus the alerting effect induced by LSD-25. It would be of interest to see if the change in responsiveness is specifically auditory in character or whether other sensory modalities play an equal role. The responsiveness of cats to visual stimulation, before and after the administration of LSD-25, has therefore been compared by assessing the degree to which a visually conditioned avoidance response was generalised to other non-conditioned visual stimuli differing only in intensity. Similar experiments have been conducted using small doses of amphetamine.

Methods

Twenty adult cats were used. They were trained to cross a nine inch high barrier from one side of a semi-sound proofed cubicle to the other at the end of the presentation of a visual stimulus. Failure to accomplish the

task within three seconds was punished by an electric shock of 0.5 mA delivered to the feet of the animal from a metal grid. The visual conditioning stimulus consisted of a series of five half-second light flashes delivered over a period of 4.5 seconds. They were presented in a non-directional way from concealed lights in the roof of the cubicle, so that the animal perceived a change in background illumination from 4 lumens per square metre to 42.6 lumens per square metre (Lm/m^2) rather than a flash from a discrete light source. Training was carried out at the rate of 40 trials per day on consecutive days until acquisition of the avoidance response was established. The parameters of stimulation and environmental conditions were kept as constant as possible and each animal trained irrespective of the number of trials to the 100% correct response level, i.e. the first ten correct responses out of ten consecutive trials. As soon as this level was reached, usually after 100—200 trials, the conditioning was stopped and 0.5 ml of normal saline injected intraperitoneally. Thirty minutes later its effects were assessed on the rate of extinction of the conditioned avoidance response and also on the rate of extinction of barrier crossings evoked through sensory generalisation by two other visual stimuli differing only in intensity and which had not been used previously in the conditioning trials. The conditioned stimulus was presented in random order with these two other visual stimuli, which were approximately one half (17.2 Lm/m^2), and one quarter (8.6 Lm/m^2) the intensity of the conditioning stimulus. No punishment was given for incorrect responses during these trials and the stimuli were presented until extinction of all barrier crossing responses.

Since each animal was to be given two drug trials with appropriate control runs, familiarisation with the experimental procedure was bound to occur. In order to make some assessment of the spontaneous changes taking place, the animals were divided into four groups of five. Group A was given only saline for each of the five test runs. The other three groups were given both LSD-25 and r-amphetamine at different dose levels. Amphetamine was always the last drug to be given so that any long term residual effects which might occur would not interfere with subsequent drug trials. Each animal therefore, was submitted after appropriate training and re-training, to five extinction procedures at approximately fortnightly intervals in the sequence: saline, LSD-25, saline, r-amphetamine, saline.

The results for each group of animals have been expressed as graphs of generalisation of extinction by plotting the number of trials to extinction of the avoidance response against the change in the intensity of background illumination which induced them. Analysis of the results was carried out to assess the change produced by the drugs, firstly in the rate of extinction of the responses evoked by each light intensity, i.e. the

displacement of the graph, and secondly, the gradient of generalisation of extinction within each group. Each animal was taken as its own control and significance of the difference in the number of responses before and after the administration of drugs determined for each light intensity using the Student 't' test for correlated data. Due to the limited number of points which could be plotted on each graph, changes in the gradient of the graphs were assessed by comparing the magnitude of the increases produced by the drugs at each light intensity, again using the Student 't' test for correlated data.

Results

The effect of repeated extinction trials on generalisation

The results are summarised graphically in Fig. 1, where the data from all animals in Group A has been pooled and the mean number of trials to extinction of the response plotted against the change in background illumination. The graphs show that in the cat the number of non-reinforced trials needed to produce extinction of generalised responses decreased with increasing difference from that of the conditioned stimulus. Moreover, the gradient was uniform, since with the limited number of points available the graph did not appear to differ from a straight line. Retraining the animal and extinguishing the response for a second time produced a change in the rate of extinction. There were marked decreases in the number of barrier crossing responses evoked by all three changes in the intensity of illumination yielding a significant displacement of the graph of generalisation along the 'y' ordinate ($P = .05-.02$). Subsequent extinction trails, carried out at fortnightly intervals after the appropriate retraining, brought about further decrements in the

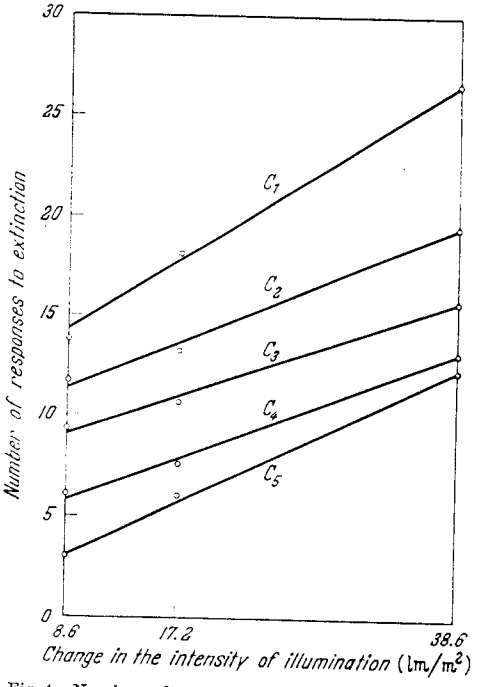

Fig. 1. Number of responses to extinction plotted against the change in the intensity of illumination, showing the effect of five repetitions (C 1—C 5) of the extinction procedure, after appropriate reconditioning, on the graphs of generalisation of extinction. Conditioned stimulus: 38.6 Lm/m². Generalised stimuli 8.6 and 17.2 Lm/m²

number of barrier crossing responses, again by all three intensities of illumination. The graphs of generalisation approximated to straight lines in each case, but the decrement in the response score for the conditioned stimulus (38.6 Lm/m^2) after each test situation was not uniform. There was a tendency for the difference between the scores to become gradually smaller. For example, between Control 1 and Control 2 the mean decrement was 7.2, between Control 3 and 4 it was 2.6, while Control 4 and 5 differed by only one response, the significance of which was doubtful ($P = .2—.1$). In contrast, the decrement in barrier crossing responses evoked through generalisation by a visual cue only one quarter the intensity of the conditioned stimulus (8.6 Lm/m^2) became gradually larger with each repetition of the extinction procedure (Fig. 1). This disparity between the rates of extinction of conditioned and generalised responses induced significant changes in the gradient of the generalisation graph. From Control 1 to Control 2, the graph was less steep ($P = .05$). After a third trial the gradient again differed from that of Control 1 ($P = .05—02$), but not significantly from Control 2 ($P = .2—.1$). A fourth and fifth repetition of the extinction procedure brought about a steepening of the gradient so that Control 5 was approaching parity with the initial control run (Fig. 1).

Familiarisation with the experimental procedure also brought about a reduction in total motor activity as indicated by the fall in the number of spontaneous avoidance responses. Spontaneous barrier crossing was common for all animals. In the initial control a mean number of 12.5 was recorded. In subsequent trials there was a progressive reduction: 12.0 for the second trial, 8.5 for the third and 2.8 for the fourth trial. Finally, in the fifth trial only two were observed.

The effect of d-lysergic acid and r-amphetamine on generalisation

LSD-25 was given intraperitoneally to Groups B, C and D in doses of 5, 10 and 20 $\mu g/kg$ respectively. After 5 $\mu g/kg$ there was no significant change in the rate of extinction of conditioned barrier crossing responses, but the number of generalised responses increased, producing a displacement of the graph of generalisation towards the horizontal position (Fig. 2A).

In Group C, 10 $\mu g/kg$ of LSD-25 produced an increase in the number of barrier crossing responses evoked by conditioned, as well as the generalised visual stimuli (Fig. 2B). The rise was similar for each light intensity, so that there was no appreciable alteration in the gradient of generalisation from control levels ($P = .7—.6$). A larger dose of 20 $\mu g/kg$, given to the animals of Group D, induced a similar effect but did not appear to increase the response level above that seen with 10 $\mu g/kg$. Such a result may indicate that within this dose range the effect on generalised re-

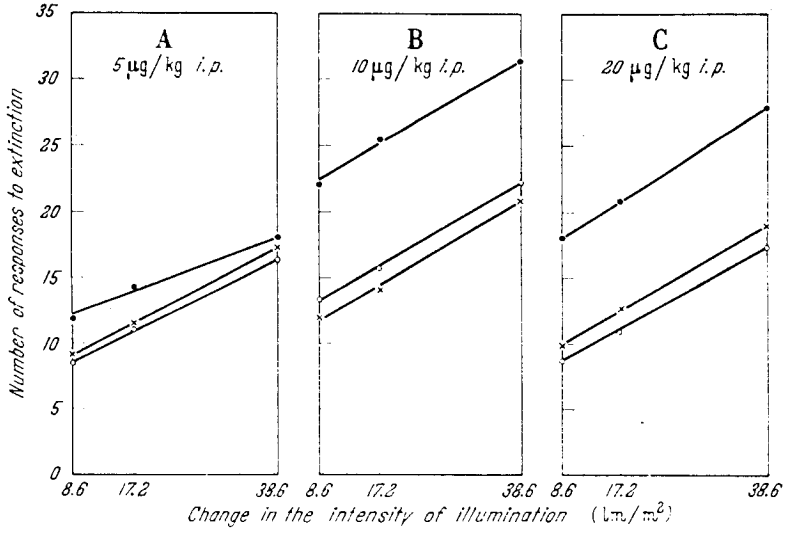

Fig. 2 A—C. The effect of different dose levels of lysergic acid diethylamide (LSD-25) on the graphs of generalisation of extinction of visual stimuli. Conditioned stimulus: 38.6 Lm/m². o——o first Control; •——• LSD-25; ×—— × recovery

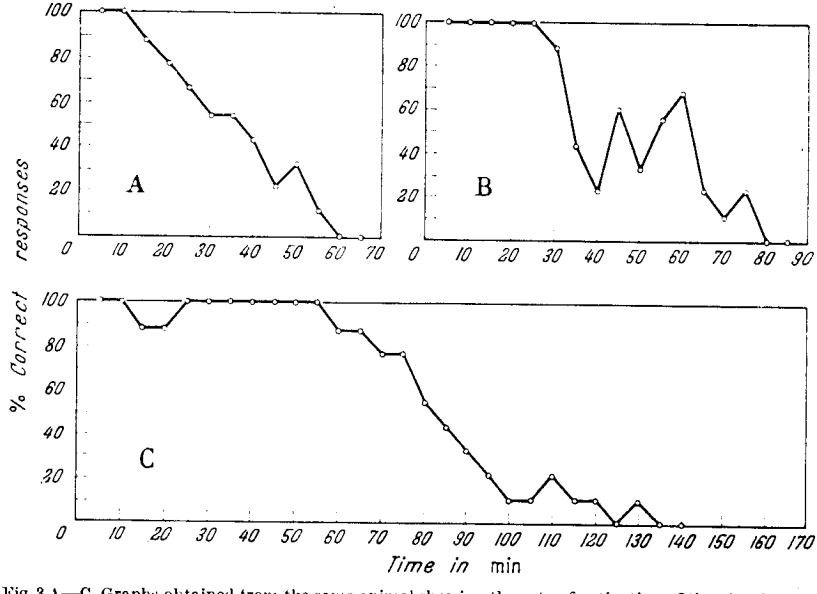

Fig. 3 A—C. Graphs obtained from the same animal showing the rate of extinction of the visual conditioned avoidance response and responses evoked through generalisation by two other visual stimuli differing only in intensity. A after saline i.p.; B after 20µg/kg LSD-25 i.p.; C after 0.25 mg/kg r-amphetamine i.p.

sponses, once obtained is not potentiated by larger quantities of the drug. Alternatively, a differential sensitivity of the two groups to LSD-25 may play some part. However, if the number of responses per unit of time is considered then a difference between the effect of 10 and 20 μg/kg of LSD-25 becomes apparent. Fig. 3 shows the number of barrier crossing responses per unit time of a typical series of experiments with the same animal in which saline, 20 μg/kg LSD-25 and 0.25 mg/kg r-amphetamine were given. Extinction after the saline injection was relatively smooth (Fig. 3A), whereas after 20 μg/kg i.p. of LSD-25 the response level showed considerable fluctuations (Fig. 3B). Sometimes

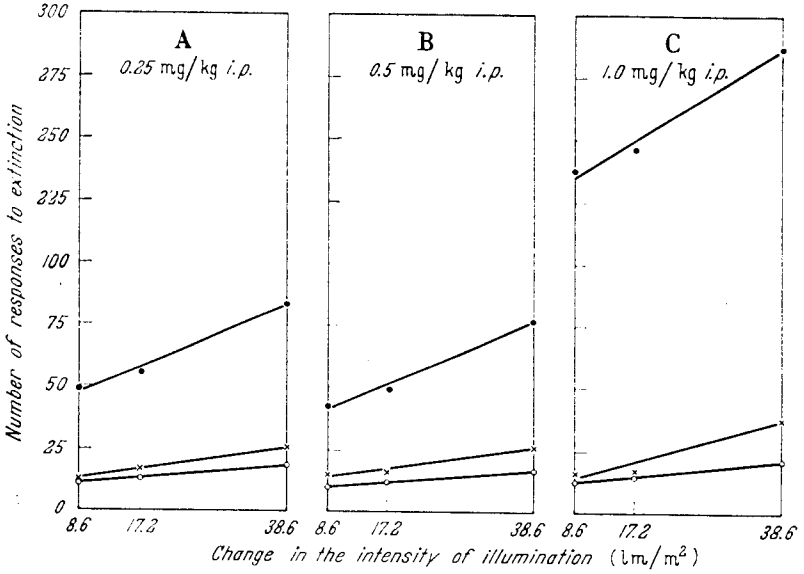

Fig. 4 A—C. The effect of different dose levels of r-amphetamine on the graphs of generalisation of extinction of visual stimuli. Conditioned stimulus: 38.6 Lm/m². o——o first Control; •——• r-amphetamine; ×——× recovery

the animal was very responsive, while at others it became indifferent for periods of 5—10 minutes to all visual cues and maintained a fixed stare at some object in the cubicle. Auditory stimuli tended to reverse this state and the animal would once more respond to visual stimulation. This periodicity in response was not so apparent with dose levels of 5 or 10 μg/kg. Thus the overall effect of 20 μg/kg of LSD-25 was to prolong the time taken to extinguish the avoidance response but the number of times the animal crossed the barrier did not differ from that obtained after 10 μg/kg i.p.

Small doses of amphetamine did not produce such a change (Fig. 3C). The animal, always alert, responded briskly and the extinction was a

smooth, if not prolonged procedure. The effect of r-amphetamine on the graph of generalisation of extinction was consistent for all groups of animals. There was a marked ($P = .01 - .001$) and progressive increase in the number of barrier crossing responses to all visual stimuli with doses of 0.25, 0.5 and 1.0 mg/kg i.p. of this drug (Fig. 4). The number of avoidance responses to the conditioned stimulus was far greater than produced by the generalised stimuli. So much so, that a significant change ($P = .01 - .001$) in the gradient of the graphs occurred in each group. Retraining and re-extinguishing the avoidance response two weeks later showed that there was still some residual effects of amphetamine. Even in Group C which had been given the smallest dose of 0.25 mg/kg i.p. the number of conditioned responses was still higher than the control levels and the gradient of the graphs slightly steeper (Fig. 4 A).

No significant differences from the initial control experiments were observed two weeks later after recovery from LSD-25 (Fig. 2). This is similar to the results previously obtained after LSD-25 for auditory generalisation curves (KEY 1961).

Discussion

The extinction of sensory generalised barrier crossing responses evoked by visual stimuli differing only in intensity was studied after the establishment of a conditioned avoidance response to another, more intense visual stimulus. With the limited number of points available the resultant graph of generalisation of extinction did not appear to differ from a straight line. GRANDINE and HARLOW (1953) using monkeys, MONTGOMERY (1953) and SCHLOSBERG and SOLOMAN (1943) working with rats also obtained graphs of generalisation which were essentially straight lines. In each group of studies the generalisation continuum was the intensity of reflected light. Every attempt was made in the present study to limit the directional aspect of the light source so that the animal responded to a change in background illumination, or the light reflected from the walls within the conditioning environment rather than a single localised source. Slight errors were inherent in this procedure, but nevertheless the similarity between the results obtained and those of workers using different techniques is apparent.

It is inevitable that familiarisation with experimental procedures will result in spontaneous changes in response scores and that such changes may interact or reduce the effect of drugs. Successive extinctions tend to produce a progressive decrease in the total number of conditioned responses (PAVLOV 1927), while due to the differential extinction rates of conditioned responses and responses evoked through generalisation by other stimuli, the decrement in the number of generalised responses is even greater (HOVLAND 1937). The control experiments in the present

study illustrate these changes. After five extinction trials the number of conditioned responses was 45% of the initial control level. The number of generalised responses, however, had fallen to below 22%.

Consideration of the graphs of generalisation of extinction showed that displacement of the curve down the 'y' ordinate produced a decrease in the range of visual stimuli evoking barrier crossing responses, but due to the decreasing decrement in the number of conditioned responses and the alterations in the slope of the graphs, the amount of generalisation did not change uniformly. In fact, a slight increase accompanied the first and second repetitions of the extinction proeedures. A slightly larger change, this time a decrease, was apparent between third and fourth trials, while Control 4 and 5 differed in the same direction but by a greater deficit. Thus the effect of familiarisation to the test procedure was one of reduction in the number of visual stimuli to which the animal will respond. This modification may be interpreted as an increase in discriminatory ability, or alternatively as a decrease in the overall responsiveness of the animal. Such changes may be of advantage in the present study for they tend to increase the significance of the effect produced by 10 and 20 μg/kg LSD-25, doses which prolonged the extinction time of both conditioned and generalised responses. The increase in the number of barrier crossing responses was similar for eaeh light intensity, producing a signifieant upward displaeement in the graph of generalisation without significantly affecting the gradient. Extending graphs to the 'x' abscissa demonstrates the ability of LSD-25 to widen the range of changes in light intensities capable of eliciting responses similar to that produced by the conditioned stimulus. Previous studies (KEY 1961) have shown that LSD-25 in doses of 15 μg/kg exerts a comparable effect on generalised responses initiated by auditory stimuli differing along a frequency continuum. Changes in auditory acuity or a lack of discrimination between the physieal parameters of auditory stimulation were excluded as causative factors. In the same way alterations in visual acuity are unlikely to explain the increased generalisation of visual stimuli observed in the present study, for paradoxically, increases in absolute visual thresholds have been reported for man (CARLESON 1954) and pigeons (BLOUGH 1958). The increase in the amount of generalisation does not appear to be entirely dependent upon the decreased rate of extinction of the conditioned response, for the primary effect of 5 μg/kg of LSD-25 was to increase the number of responses elicited by generalisation without inducing any significant alterations in the amount of conditioned avoidance behaviour.

It is interesting to compare the effect of 10 μg/kg of LSD-25 with that produced by 20 μg/kg. There appears to be little difference in the increase of barrier crossing responses at both dose levels, but at the higher dose

level fluctuations in the rate of responding occur which are not seen after 10 μg/kg. Such changes in response rate were not apparent in previous studies with auditory stimuli (KEY 1961). However, a periodicity in the activity of cats has been reported by URSIN (1962), in that long periods of sedation or inactivity with shorter episodes of spontaneous alerting and orientating behaviour occurred after the administration of 5 to 60 μg/kg i.v. of LSD-25. Sedative effects are known to occur with this drug in cats (KILLAM and KILLAM 1957; EVARTS 1957), but in these cases the dose was in excess of 80 to 100 μg/kg. It is difficult to provide an explanation for these ambivalent behavioural states, although according to observations of BRADLEY and KEY (1958) it would appear that environments providing a moderate level of ambient auditory stimulation tend to suppress or curtail the periods of 'sedation'.

No such fluctuations were noted in the response level after amphetamine had been given. Extinction of the conditioned response and responses evoked through generalisation by other visual stimuli was a smooth but prolonged procedure. After the smallest dose of amphetamine the number of conditioned responses was considerably in excess of that produced by 20 μg/kg of LSD-25, while following 1.0 mg/kg of amphetamine there was an approximate tenfold increase in the number of conditioned barrier crossing responses. However, even with the marked alteration in the rate of extinction of the conditioned responses, it was only at the 1.0 mg/kg dose level that amphetamine caused any change in the amount of generalisation, for this drug, unlike LSD-25, did not produce a uniform increase in the number of conditioned and generalised responses. If the graphs of generalisation are extended it will be seen that the number of visual stimuli capable of eliciting avoidance behaviour is not increased after 0.25 or 0.5 mg/kg of amphetamine. In fact there is a slight reduction from the initial control level in both cases. Two conclusions may be drawn from these results. Firstly, the increased responsiveness induced by LSD-25 is not due solely to a decreased rate of extinction of the conditioned avoidance response. Secondly, alterations in generalisation and the level of arousal or alertness are not dependent functions.

An interesting comparison between the effect of LSD-25 and amphetamine can be seen in the graphs of generalisation before and after the drug treatment. Two weeks following the administration of LSD-25 there was no significant difference between the recovery and control graphs, whereas the rate of extinction of the conditioned response tested a fortnight after even the smallest dose of amphetamine was still significantly different from the original control levels. The expected modifications produced by successive extinctions of the same response was eliminated by the interposition of the LSD-25 treatment. In the case

of amphetamine, however, a marked residual effect was apparent which lasted a further two or three weeks.

In conclusion, the alerting effect and the increased responsiveness of animals to sensory stimulation following the administration of LSD-25 could be accounted for by increased generalisation to visual stimuli. In the cat visual and auditory sensory modalities appear to play a similar role. Moreover, by comparison with the effects of amphetamine these changes in responsiveness are not dependent solely upon alterations in the level of arousal or alertness.

Summary

Cats were trained to carry out avoidance behaviour on the presentation of a visual stimulus. The effect of lysergic acid diethylamide and amphetamine were then tested on the rate of extincition of the conditioned response and responses evoked through generalisation by other visual stimuli which had not been used previously in the training procedure and which differed from the conditioned stimulus only in intensity. LSD-25 in doses of 10 and 20 μg/kg i.p. produced a significant increase in the number of generalised and conditioned responses without effecting the gradient of generalisation. A smaller dose of 5 μg/kg increased the number of generalised responses without modifying that of the conditioned response. At all three dose levels LSD-25 increased the amount of generalisation, that is the total number of visual stimuli capable of eliciting responses, either by producing upward displacement of the graph of generalisation of extinction or in the lower dose ranges by altering the gradient of the graph.

Amphetamine produced an increase in the number of conditioned responses and a relatively smaller rise in the number of responses evoked through generalisation. At each dose level there was a change in the gradient of generalisation but only after 1.0 mg/kg i.p. did the amount of generalisation alter significantly.

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