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The Effect of Drugs on Discrimination and Sensory Generalisation of Auditory Stimuli in Cats

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With 3 Figures in the Text

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Introduction

It is a well known fact that indiscriminate arousal does not take place with every sensory stimulus. It is often the meaning of a stimulus, based on past experience, which determines its arousal or attentive value. For a specific tone the intensity of stimulation necessary to produce attentiveness or arousal from sleep is not the same in every animal and in any one animal may fluctuate depending upon the precise environmental conditions or the experimental procedures to which the animal has been subjected (KEY and BRADLEY 1960). By positive conditioning it is possible to increase the significance attached to a particular auditory stimulus and produce a lowering in the intensity of stimulation necessary to evoke arousal. Conversely, during the process of habituation there appears to be a loss of significance associated with a concomitant increase in the arousal threshold for the continually repeated stimulus.

In many ways *d*-lysergic acid diethylamide (LSD 25) appears to simulate the effects of conditioning for a wide range of sensory stimuli. Small doses of this drug produce a decrease in the thresholds for non-conditioned arousal responses, induced by auditory stimuli, both in terms of behaviour and the electrical activity of the cortex, but they do not alter the thresholds for conditioned arousal responses (KEY and BRADLEY 1960). Futhermore, a stimulus to which the animal has previously become habituated evokes a marked response following the systemic administration of LSD 25.

It is the purpose of this study to determine whether or not this apparent increase in responsiveness following the injection of LSD 25 and the differential effect on conditioned and non-conditioned arousal responses is due to the inability of the animal to distinguish between significant and insignificant sensory stimuli, or produced solely by a lack of discrimination between the physical parameters of auditory stimulation employed.

In order to test these possibilities use has been made of conditioned auditory discrimination techniques. In addition, since chlorpromazine is known to antagonise the effects of LSD 25 (BRADLEY and HANCE 1957) and in small doses to produce a progressive increase in all auditory induced arousal thresholds (KEY and BRADLEY 1960), the effect of this drug has also been studied on similar discriminatory problems.

Methods

Sensory Generalisation

Experiments were carried out in a double walled constant environment chamber fitted with a one-way observation window (BRADLEY and ELKES 1953). Eight adult cats were used and the training and testing of the animals were divided into two stages. Firstly, all animals were trained to cross the nine inch high barrier from one side of the constant environment chamber to the other on the presentation of a pure tone of 600 c/sec for five seconds. Failure to accomplish this 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. Training was carried out for periods of one to two hours on consecutive days until acquisition of the conditioned avoidance response was established. Each series of conditioning trials was always preceded by a period of acclimatisation to the conditioning environment and the rate at which the conditioning stimulus was presented was not kept constant but varied from one to five per ten minutes.

The animals usually reached the 100% correct response level after 200 to 300 trials and as soon as this level was attained either saline (as a control), chlorpromazine or LSD 25 was injected by the intraperitoneal route. The effects of the drugs were tested 30 minutes later on the extinction rate of the conditioned avoidance response and on the rate of extinction of barrier crossing responses evoked through sensory generalisation by different tones which had not been used during the conditioning trials. The conditioned stimulus was presented in random order with these tones, which were given in sets of eight with a period of one to two minutes between each tone. The intensity of the 600 c/sec conditioning stimulus was kept constant at 40 decibels above an arbitrarily chosen reference level of 1 millivolt into a 3 ohm impedence and the loudness of the neutral stimuli was equated to this level using the audiogram of the cat (DWORKIN, KATZMAN, HUTCHISON and MCCABE 1940). The tones were chosen within the range 200—2000 c/sec so that the effect of notes both higher and lower than the conditioned stimulus could be observed. During these trials no punishment was given for incorrect responses and the tones were presented until extinction of all barrier crossing responses.

The degree of sensory generalisation has been shown to be dependent upon the strength of conditioning (HOVLAND 1937a). Thus, in these experiments the rate of presentation of the stimuli, the parameters of stimulation and the environmental conditions were kept constant and the animals 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, and the conditioning was stopped as soon as this level was reached. Since the animals were used for more than one experiment it was expected that alterations in the rate of extinction of the responses might occur due to familiarisation with the experimental procedure. In order to obtain some assessment of these changes in relation to the effects of the drugs the experiments with each cat were carried out in a control, drug, drug, control sequence. Moreover, since chlorpromazine is known to produce alterations in the rate of extinction of a conditioned response (ADER and CLINK 1957), which may effect subsequent reconditioning rates the first drug to be given in the series was always LSD 25.

The results for each animal were expressed as the graph of generalisation of extinction by plotting the number of trials to extinction of each tone against its frequency. The degree of generalisation may be expressed as the gradient of the graph of generalisation of extinction when the auditory stimuli are scaled along a single psychophysical dimension, in this case pitch. The relationship between pitch and frequency, however, has not been worked out for the cat. Thus the data plotted for each animal was in the form of a composite graph of two components, the gradients of which differed, due to a Weber-Fechner effect, depending upon whether or not the tones were greater or lesser in frequency than that of the conditioned stimulus. For the purposes of analysis each component, i.e. frequencies between 200 to 600 c/sec and 600 to 2000 c/sec, were taken separately. Linear regression formulae, given by the term $y = a + b(x - \bar{x})$, were determined for each animal using suitable transformations ($\sqrt{y} = x$, and $y = 1/x$, respectively) and the differences produced by the drugs in the rate of extinction of the barrier crossing responses (given by a, the displacement of the graph) and the degree of sensory generalisation (given by b, the gradient of the graph) tested using the 'Student' t test for correlated data.

Auditory Discrimination

Method 1. The animals were also trained to discriminate between two tones of equal intensity and duration. For one tone (Tone A) they were required to jump the hurdle and for the other tone (Tone B) they had to remain where they were. There is a variety of techniques for training animals to distinguish between sensory stimuli of one modality but the one most widely used is that termed the 'Method of Contrasts'

(HILGARD and MARQUIS 1940). For this technique use is made of the phenomenon of sensory generalisation, since the responses evoked in this manner are more easily extinguished than the conditioned response. Thus discrimination can be produced by non-reinforcement of the generalised response while reinforcement of the conditioned response is continued. Eight cats were trained to discriminate between the two tones using this method, here termed Method 1, and the effects of chlorpromazine and LSD 25 were studied on the response.

Method 2. Subsequently, the animals were retrained using the same avoidance response situation as described above to discriminate between two other tones. This time the experimental procedure was modified and both auditory stimuli were reinforced, so that any incorrect response was punished by a mild electric shock delivered to the paws of the animal. When training was complete and a 90 to 95% correct response level had been attained the same procedure was adopted as in Method 1, namely, normal saline was injected as a control and 30 minutes later the animal tested over 20 non-reinforced trials. The stimuli, which were presented at the rate of one every two minutes, were given in random order so that during the control period there were 10 presentations of each tone. LSD 25 or chlorpromazine was then injected by the intraperitoneal route and the animal retested 30 minutes later, using the same procedure. One week was allowed to elapse for complete recovery from the effects of the drug and the animal again tested over a further 20 trials but this time without any injection.

Since each animal was taken as its own control, the effects of the drugs were assessed by employing a one-tailed sign test on the sign of the differences between the correct response scores before and after the administration of the drugs.

Results

The effect of drugs on generalised avoidance responses

The extinction of sensory generalised barrier crossing responses evoked by tones within the frequency range of 200 to 2000 c/sec was studied after the establishment of a conditioned avoidance response to a tone of 600 c/sec. The results are summarised graphically in Fig. 1, where data from all the animals has been pooled and the mean number of trials to extinction of each tone has been plotted against frequency in c/sec. The curves show that in the cat the number of non-reinforced trials needed to produce extinction of the generalised responses decreased with increasing difference in frequency from that of the conditioned stimulus. The greatest decrease in the gradient of generalisation of extinction occurred with only slight changes in frequency from 600 c/sec but even with gross differences there was still a significant amount of generalisation.

Comparison of the control graphs (Fig. 1) showed that although the differences which existed in the rates of extinction, before and after the drug treatments, were not significant ($P = 0.3$—0.2), there was a tendency in the second control for the rate of extinction to increase slightly. However, the expected modification produced by successive extinction of the same response appeared to have been eliminated by the interposition of the drug treatments. The degree of generalisation, given by the slope of the graphs, was also not significantly altered by familiarisation

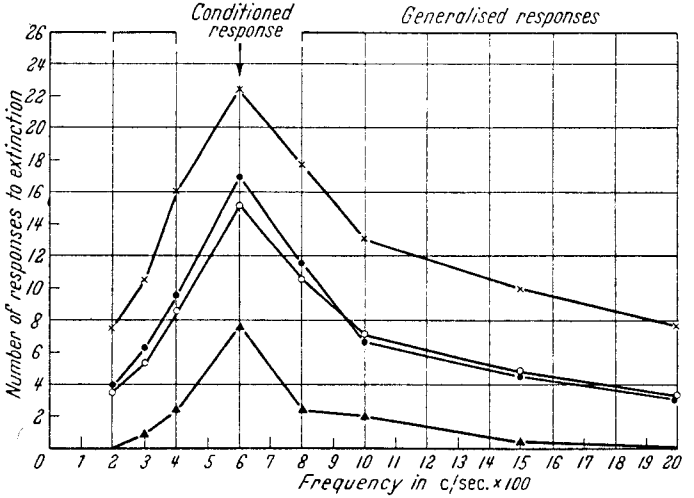

Fig. 1. The effect of drugs on the extinction of a conditioned avoidance response and qualitatively similar responses evoked through sensory generalisation. • First control. × 15 μg/kg of d-lysergic acid diethylamide i. p. ▲ 5 mg/kg of chlorpromazine i. p. ○ Second control

with the experimental procedure over the limited number of experiments carried out with each animal.

The effect of LSD 25 on the rate of extinction was marked (Fig. 1) and, following the intraperitoneal injection of 15 μg/kg., not only was there an increase in the number of trials required to extinguish the conditioned response but also a significant increase ($P = < 0{\cdot}001$) in the number of trials necessary to produce extinction of the sensory generalised responses in all animals. This decrease in the extinction rate, associated with the administration of LSD 25, was in complete contrast to the effect produced by chlorpromazine. After a dose of 5 mg/kg i.p. of this drug, all responses were extinguished more rapidly ($P = < 0.001$). For example, where previously 11 to 18 sets of tones were required for total extinction of all barrier crossing responses, following chlorpromazine only 6 to 9 were needed (Fig. 1). This effect was not accompanied by any signs of locomotor deficit or sedation, since the animal would still cross the barrier readily when the shock was presented alone.

Analysis of the regression coefficients of the graphs for each animal indicated that the gradients of generalisation were not significantly altered by either 15 μg/kg of LSD 25 or 5 mg/kg. chlorpromazine. Thus the degree to which the conditioned response was generalised to other auditory stimuli remained unchanged but, since the rate of extinction of the conditioned response was modified both by LSD 25 und chlorpromazine, the amount of generalisation, that is the number of tones capable of eliciting generalised responses, altered accordingly (Fig. 1). For example, after chlorpromazine the animals failed to respond to auditory stimuli of 200 and 2000 c/sec. although in the control these tones elicited barrier crossing responses for at least the first two to five trials.

The effect of drugs on auditory discrimination

A conditioned avoidance response involving discrimination between two auditory stimuli of equal intensity and duration was established using two different methods of training. Although the avoidance response was the same in each procedure the patterns of behaviour noted during the conditioning trials were not the same. This variation, which may have a bearing on the interpretation of the effects produced by LSD 25 may be illustrated graphically by considering the rates of learning for one of the animals under the two types of procedure (Fig. 2).

Method 1. The cat was conditioned to jump the barrier on the presentation of Tone A (600 c/sec). No other auditory stimulus was given at this stage until a 70 to 80% correct response level had been attained. Another tone of 400 c/sec, as Tone B, was then substituted in 50% of the trials. For some time the animal continued to cross the barrier to both tones, but by reinforcing the 600 c/sec note and not the 400 c/sec tone, the animal gradually learned to distinguish between the two and eventually would only carry out an avoidance response when the 600 c/sec tone was presented. This is shown by the steady rise to the 100% correct response level in the latter part of the graph in Fig. 2a.

At this stage in the conditioning a control injection of normal saline had no measurable action on the conditioned response but following 5 mg/kg of chlorpromazine the discrimination between tones A and B was apparently lost. All animals, without exception, rapidly failed to make the right response when tone A was presented and finally, after 5 to 10 trials, they stopped crossing the barrier altogether. Thus a lower mean correct response level of approximately 65% was recorded (Fig. 3a). On the other hand, after 15 μg/kg of LSD 25 the animals not only continued to respond to Tone A but also started to cross the barrier indiscriminately to Tone B. The incidence of barrier crossing responses therefore increased following the administration of this drug and resulted

in a correct response score of between 60 to 65%, which was again lower than the control levels (Fig. 3b). Upon recovery from the effects of the LSD 25 the conditioned discrimination response returned to control, or near control levels, whereas following the chlorpromazine experiments the correct response score was usually only just above the 50% chance level (Fig. 3a).

Method 2. Reinforced, random presentation of one or the other of the tones from the very beginning of the conditioning trials resulted in

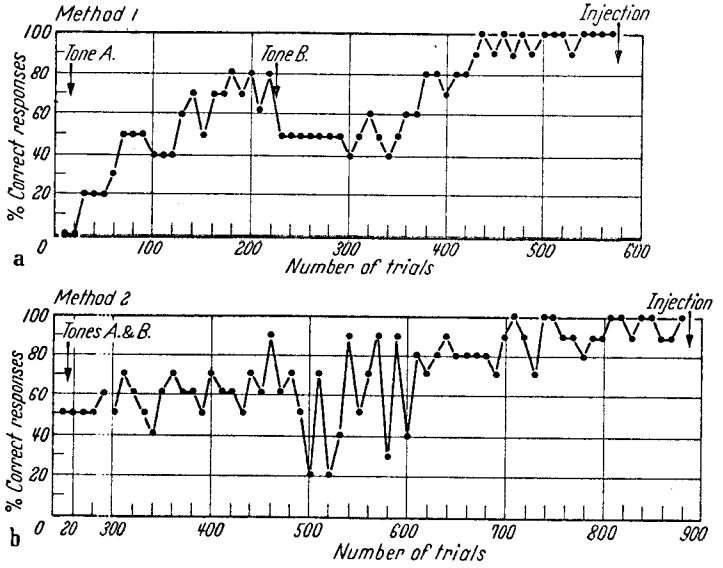

Fig. 2 a and b. Rate of learning of a conditioned auditory discrimination response. *Method 1* by reinforcing only one of the tones (*Tone A*), *Method 2* by reinforcing both tones

the development of a different behavioural pattern from that already described. Initially the animal did not cross the barrier until the punishing shock was administered, but as an association between the shock and the auditory stimulus was established, the animal began to carry out avoidance to both tones indiscriminately. As a result it received punishment in 50% of the trials when it arrived on the other side of the barrier. At this stage the animal became extremely excited, more so than during the training in Method 1, and presentation of either of the tones produced hissing, spitting and vocalisation, followed usually by the animal attacking the barrier. In three cases the behaviour of the animals became completely abnormal and conditioning had to be abandoned. These animals appeared perfectly normal in their home cages but immediately on returning to the conditioning environment the abnormal behaviour again developed.

Most animals however, appeared to notice some difference between the two stimuli after further trials, resulting in a period when they either responded correctly in 70 to 90% of the trials or failed to get more than 20 to 30% right. This stage is shown on the graph (Fig. 2b) by the large

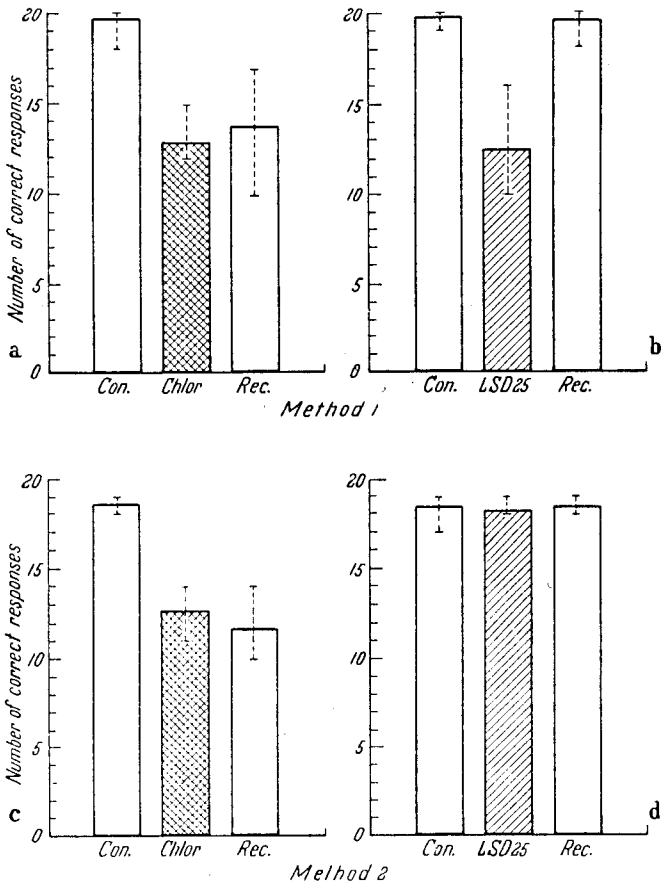

Fig. 3a—d. The effect of chlorpromazine and LSD 25 on a conditioned auditory discrimination response taught in *Method 1* by reinforcement of only one tone and in *Method 2* by reinforcement of both tones. *Con.* Control. *Rec.* Recovery. *Chlor* 5 mg/kg Chlorpromazine i.p. *LSD 25* 15 μg/kg d-lysergic acid diethylamide i.p. The number given is the mean correct response score in twenty consecutive trials for all the animals. Dotted lines indicate experimental variation

oscillations, a feature characteristic of the five animals which successfully underwent this type of training. Following this stage, acquisition of the conditioned avoidance response to the right stimulus was quickly attained although it was never possible to obtain more than a 90 to 95% correct response level and, compared with Method 1, the rate of learning was much slower.

The effects of LSD 25 and chlorpromazine on the conditioned discrimination response taught by Method 2 are shown in Fig. 3c and d. In the control and drug trials no reinforcement was given and after an injection of 15 μg/kg of LSD 25 there was no marked change in the level of response, but chlorpromazine, in a single dose of 5 mg/kg appeared, as before, to block discrimination in all animals. This drug, however, as shown in the experiments on sensory generalisation, produced an increase in the rate of extinction of conditioned avoidance responses, a fact which is verified further in these results for the animals responded correctly for the first 5 to 10 trials and then refused to move at all unless the shock was also presented. Moreover, in contrast to the results obtained following the administration of LSD 25, after recovery from the effect of chlorpromazine the conditioned response had in most cases disappeared or underwent rapid extinction, resulting in a response score lower than the original control levels (Fig. 3c).

Discussion

Cook and Weidley (1957) demonstrated that LSD 25, in doses from 100 to 500 μg/kg, had no measurable action on a conditioned avoidance response in the rat. From the results of the present study this observation would also appear to hold true for the cat, in that smaller doses of 15 μg/kg of this drug did not block a conditioned barrier crossing response. In addition, no change was produced in the degree to which a conditioned response was generalised to other, novel auditory stimuli. On the other hand, the amount of generalisation, that is the number of tones capable of eliciting the barrier crossing responses was markedly altered. Consideration of the graphs of generalisation of extinction in Fig. 1 shows that displacement of the curves along the 'y' ordinate will produce either an increase or a decrease in the range of tones evoking generalised responses. Thus the decreased rate of extinction of the responses produced by LSD 25 will effect an alteration in the amount of generalisation, since no change in the gradient of the graphs occurred. This observation could well provide an explanation for the increased responsiveness of animals to sensory stimuli after LSD 25 (Bradley and Elkes 1957) and the ability to awaken sleeping animals with stimuli which before the administration of the drug had failed to evoke an arousal response (Key and Bradley 1960).

Changes in responsiveness could, of course, be produced by alterations in auditory acuity, but the fact that LSD 25 does not produce any change in the threshold intensities of auditory stimulation necessary to evoke conditioned behavioural and electrocortical arousal responses (Key and Bradley 1960) would argue against this hypothesis. A possible explanation for the decreased rate of extinction may be that LSD 25 increases

the meaningfulness or significance level of the sensory stimuli. For example, the rate of extinction of a conditioned response is dependent, to a certain extent, upon the degree of conditioning. In conditioning trials as a tone/shock situation is repeated the psychological significance or meaning, in this case the fear of anxiety attached to the auditory stimulus, increases and there is a corresponding increase in the time taken to extinguish the response. The rate of extinction therefore, may be said to be related to the significance attached to the stimulus by the animal and any alteration in the level of significance is mirrored in the rate of extinction of the response. This hypothesis, although difficult to substantiate, could account for the differential effect of LSD 25 on the conditioned auditory discrimination responses. Obviously the blocking of the conditioned response established by reinforcing only one of the tones (Method 1) cannot be dependent upon the inability of the animal to distinguish between the physical parameters of stimulation, since a similar response taught by the reinforcement of both tones (Method 2) was not altered by the administration of LSD 25. In Method 2 both tones are paired with the electric shock, resulting in any incorrect response being punished. In this respect the tones may be said to have equal significance for the animal. In Method 1 only Tone A was reinforced and any response to the other tone in the initial stages of conditioning was due to generalisation. Owing to the differential extinction rates of a reinforced conditioned stimulus and a non-reinforced stimulus evoking a generalised response (HOVLAND 1937b) barrier crossing to Tone B was lost and with it the association of the punishing shock. Under the effect of LSD 25, however, since no change in the degree of sensory generalisation took place, significance was again added to Tone B as a result of the spread of generalisation of Tone A. Thus the animal started to cross the barrier to both tones indiscriminately. Upon recovery from the effects of LSD 25 the conditioned response returned to control or near control levels.

The effect of chlorpromazine on discrimination problems and sensory generalisation was in many ways opposite to that of LSD 25. In a single dose of 5 mg/kg, a dose which produced little sedation and no motor deficit, two effects were observed. Firstly, the rate at which the conditioned, as well as the generalised responses, were extinguished was significantly increased. Secondly, although the gradient of generalisation remained unaltered, the range of tones eliciting barrier crossing responses was markedly reduced. The ability of chlorpromazine to block conditioned avoidance behaviour has been demonstrated previously by numerous workers. ADER and CLINK (1957) established that this drug will affect the acquisition, or produce rapid extinction of a conditioned avoidance response in rats. MILLER, MURPHY and MIRSKY (1957a) also

found a more rapid extinction of avoidance responses following chlorpromazine, which by comparison with a phenobarbital control group was found to be independent of sedational effects or motor impairment. Similarly, chlorpromazine will produce rapid habituation of arousal response, both in terms of behaviour and the electrical activity of the cortex (KEY 1961).

The apparent rapid relearning which takes place under chlorpromazine offers an explanation of the blocking action of this drug on the conditioned auditory discrimination responses. The fact that changes in frequency discrimination are not involved is evidenced by the way the animals were able to distinguish between the two tones and respond at the 100% correct response level for the first 5 to 10 trials. Moreover, in agreement with the results of MILLER, MURPHY and MIRSKY (1957 b) in rats, spontaneous recovery of the conditioned response following the chlorpromazine experiments did not occur. Thus the eventual blocking of this response at a dose level of 5 mg/kg must be a consequence of the increased rate of extinction, an effect similar to that reported for conditioned and non-conditioned auditory-induced arousal responses (KEY and BRADLEY 1960).

In conclusion, it would appear that LSD 25 is able to alter the level of significance or meaningfulness of stimuli, thereby producing an increased amount of generalisation without modifying the discriminatory ability of the animal in terms of the physical parameters of stimulation. Chlorpromazine produces the opposite effect. The amount of generalisation is less and stimuli lose the significance attached to them by the animal, resulting in the indifference and lack of responsiveness to sensory stimuli characteristic of the central action of this drug.

These results may also have some bearing on the effects induced by chlorpromazine and LSD 25 in man. Generalisation and discrimination play important roles in perception. Generalisation is important in adaptive ability, since environmental situations never recur without some modification. The significance or meaning attached to one stimulus may be generalised to a wide range of sensory stimuli or in some cases restricted to quite a narrow range. If, by the administration of certain drugs such as LSD 25, the level of significance of the sensory information is altered, thus inducing changes in the balance of generalisation, then distortions of perception may occur, for the animal now responds, pays attention or arouses to stimuli which normally would not produce such an effect.

Summary

The effects of lysergic acid diethylamide and chlorpromazine have been studied on generalisation and discrimination of auditory stimuli. LSD 25 (15 μg/kg) produced a significant decrease in the rate of extinc-

tion of a conditioned avoidance response and, although not modifying the degree to which the conditioned response was generalised to other, novel auditory stimuli, elicited a marked effect on the number of tones capable of evoking barrier crossing responses. LSD 25 also appeared to block a conditioned auditory discrimination response which had been established by reinforcing only one of the tones, but failed to exert any significant effect on a similar response taught by reinforcing both tones.

Chlorpromazine (5 mg/kg) produced rapid extinction of conditioned and generalised responses without altering the gradient of generalisation. The number of tones capable of evoking avoidance responses, however, was significantly reduced. A possible explanation of these results has been discussed.

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