# CONDITIONED RESPONSES TO CORTICAL STIMULATION

by

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# INTRODUCTION

The recent development of convenient stimulating and recording techniques for use with essentially intact animals, unanesthetized and normally active, has made possible new experiments dealing with the neural basis of behavior. One problem which seems especially appropriate for investigation with such methods concerns the neural mechanisms of conditioning. The present study approaches this problem by the use of intra-cranial stimulation as a conditioned stimulus.

Since historical accounts of conditioning have appeared in many textbooks, including a comprehensive treatment by Hilgard and Marquis (1940), a review of the entire literature is unnecessary. Instead, consideration will principally be given to studies of the neural mechanisms using methods of brain stimulation and electrographic recording. The studies involving brain extirpation, a method used since the experiments of Pavlov to determine the relation of conditioned responses to anatomical structures, will not be included.

The stimulation experiments which are most directly relevant to the present study are those utilizing intracranial stimulation as conditioned (CS) or unconditioned stimulus (UCS); but there are other experiments, in which stimulation was found to interfere with the acquisition and performance of learned responses, which are important in understanding the mechanisms involved. The recording studies with which we shall be concerned are those involving EEG conditioning.

## Intra-cranial stimulation as UCS

Pavlov's theory proposed that conditioning involves irradiation from sensory centers to motor centers of the cortex, and that conditioning will be established if afferent and efferent processes occur together. The experiments of Leucks and co-workers, in which a response was made to occur in the presence of a stimulus, were a test of this proposition. The results of the experiments appear to indicate that the mere concurrence of these processes is not a sufficient condition for behavioral conditioning.

Intra-cranial stimulation was used to produce the undonditioned response (UCR) in several experiments done at the Pavlovian laboratory in Baltimore. This was, in fact, the first use of intra-cranial stimulation in learning experiments. (A method of stimulating alert, intact animals had been developed previously by Hess but he did not use it to study learning.) In the first experiment Loucks (1935) attempted to condition a movement of the hindleg of the dog, produced by faradic stimulation of the motor cortex, to the sound of a buzzer. The electrodes penetrating the brain were connected to a coil beneath the skin and stimulation occurred when a current was induced in it by a primary coil held over the dog's head. Loucks was unable to establish conditioning by this means in over 600 trials with any of three subjects.

The failure to obtain conditioning is not limited to the particular conditions of this experiment. Loucks and Gantt (1938) found that pairing a buzzer (CS) and direct stimulation to the dorsal roots and dorsal spinal cord (UCS) which produced reflexive leg movements, did not lead to conditioning. Masserman (1941) also failed to condition more complex motor responses similar to those associated with fear, rage and other strong emotions, which were produced by stimulation in the region of the hypothalamus in cats. The CS elicited neither the emotional motor responses nor conditioned instrumental responses in an avoidance conditioning situation.

These results indicate that contiguity of afferent and efferent activity is not enough, by itself, to produce conditioning, when the efferent activity is aroused by direct stimulation. Since the evoked motor movements appeared passive and devoid of any true emotional or motivational involvement, Masserman's own conclusion was that the action of the UCS in other, more "normal", circumstances, in which the CR does get established, is not merely to arouse efferent activity; it must set up a motivational state as well (Loucks, 1935 expresses the same view, although in somewhat different terms; also see Culler, 1938). We shall return to this question of motivation later.

In the meantime, we may consider other possible reasons for the failure of conditioning to occur in experiments in which the response is produced by direct stimulation of efferent systems. The first possibility is that a conjunction of afferent and efferent activity is enough to produce conditioning, provided that the efferent activity is normally aroused; in other words, the failure to establish conditioning in the Loucks and Masserman experiments may have resulted because direct electrical excitation of motor pathways deviates sufficiently from excitation by other neurons to prevent the occurence of synaptic changes necessary for the CR.

This can be tested experimentally by procedures involving the less direct activation of motor pathways by electrical stimulation (i.e., stimulation of a system that leads to the motor area, not the motor area itself). An experiment apparently showing that conditioning can be obtained in this way was done by Brogden and Gantt (1942), who conditioned leg movements produced by stimulation of the cerebellar lobes. The cerebellum is known to have afferent connections with the cerebral cortex, so it might be concluded that conditioning was successful because the efferent activity was produced by afferent systems, and not directly. However, this is not the whole story, because motor movements produced by stimulation of the dorsal roots and dorsal columns of the spinal cord (Loucks and Gantt, 1938) were not conditioned. Furthermore, there is some indication that the cerebellar stimulation produced a motivational state: the animals attempted to resist the forced movements and frequently the conditioned responses were antagonistic to the responses produced by electrical stimulation.

A second possible explanation of the failure to obtain conditioning in the experiments of Loucks and Masserman is that there was interference resulting from these anticipatory movements, resisting the forced movements produced by the stimulation. The first observation of the phenomenon was made by Loucks and Gantt (1938) when intense stimulation of the spinal cord was the UCS. The CR and UCR differed considerably: the stimulation produced a rough jerking of the leg away from the body, but the CS (a tone) produced an anticipitory movement of the leg toward the body (e.g. Dog 97, Sally), which in the words of Loucks and Gantt tended to "break the force of the unconditioned movement"

(p. 423). A similar observation was made by Lilly, Austin, and Chambers (1952), while determining the threshold stimulation of motor cortex for evoked movements. They found that a tone presented 5 seconds before stimulation, in order to alert the observers, was soon utilized by the monkey, which responded by setting its muscles to resist the induced movements. In the conditioning experiments, therefore, it might be that the tendency to resist the forced movements was suppressing the occurrence of CRs.

There is, however, some difficulty for this hypothesis, and it seems that we must return to the suggestion the conditioning did not occur because motivation was lacking. There is no indication that opposition movements were made by the animals in the experiments in which Loucks and Masserman failed to get conditioning. This could mean (1) that there was a precise balance between the tendency to make a CR and the tendency to make opposition movements, resulting in no movement at all - a somewhat unlikely proposition; or (2) much more likely, that the animal lacked the motivation to respond.

It should be emphasized, however, that no general statement can be made about the necessity of motivation for all forms of learning: the latent learning experiments (Tolman, 1948), but more particularly the sensory preconditioning experiments (Brogden, 1939), and the EEG conditioning experiments to be considered later, all show that learning can take place without the animal's being specially motivated by hunger or pain. The point that is being made is that motivation may be necessary for certain aspects of learning; namely, for the occurrence of the conditioned behavioral response.

## Motivation and the performance of conditioned responses

The conditioning experiments discussed in the previous section suggest that if behavioral conditioning is to occur the afferent-efferent processes (behaviorally, the stimulus-response sequence) must enter into an ongoing goal-directed activity. When Loucks (1935), after failing to condition the forced leg movement with three dogs, made two other dogs hungry and presented food after each trial, the association of buzzer with leg flexion was readily demonstrated. The procedure was then similar to operant conditioning except that at first the correct response by the animal was a forced movement produced by cortical stimulation.

Conditioning was also established by Loucks and Gantt (1938) when they made the stimulation to the spinal cord quite intense. They conclude from this result that stimulation of afferent neurons can serve as an adequate UCS providing it activates nociceptive neural systems.

Even the experiment of Brogden and Gantt (1942) suggests the importance of motivation for behavioral conditioning. Although they believed that the stimulation of the cerebellar lobes was not painful to the animal, the fact that the conditioned movements were antagonistic to the induced movements indicates that the animal was attempting to prevent the induced movements and thus that it was motivated.

More complex motor movements of emotional expression, which Masserman (1941) was unable to condition, also can be conditioned if motivation is aroused in producing them. For instance, Delgado (1955), stimulating central structures that are known to be involved in the transmission of noxious peripheral stimuli, observed that cats and monkeys became conditioned to the apparatus in which they were stimulated and soon began to exhibit anxiety-like responses when placed in it. Delgado, Roberts, and Miller (1954) earlier had shown that such intra-cranial stimulation produced the same wheel-turning responses that the animals had learned to make in escaping a peripheral shock, and that these escape responses to intra-cranial stimulation could be conditioned to a flickering light or to a 2000-cycle tone.

It appears that Masserman failed to condition complex, emotional responses because his electrodes were not located in the same areas as those of other workers (Delgado, Roberts, and Miller, 1954; Delgado, 1955; Cohen Brown, and Brown, 1957) and no motivational state was produced. Masserman found, for instance, that in his cats intra-cranial stimulation only interfered with eating while they were being stimulated, because of the forced motor movements, and that the animals resumed eating immediately afterwards; whereas Delgado, Roberts, and Miller (1954) report that intra-cranial stimulation delivered to their cats while eating caused them to avoid the food. Furthermore, Masserman recorded no electrical changes from the region of his electrodes when noxious stimuli were applied peripherally, while points stimulated by the Yale group were among those structures found to be involved in the transmission and elaboration of noxious stimuli (Delgado, 1955). So it seems clear that Masserman's failure to get conditioning was because the structures stimulated as UCS induced movements only, and did not initiate a motivational state (as he himself concluded).

Other experiments in which intra-cranial stimulation was used to induce a drive state further demonstrate the role of motivational processes in performance. In these experiments the animal first learns to make conditioned responses in the presence of a drive state (i.e. hunger or electric shock) so that the associative connections are formed. Intra-cranial stimulation is then used to induce the drive state (in the situation in which the animal had responded while the "normal drive" was present) and the same responses are then made. Although the relevant situational cues are present from the time the animal is placed in the apparatus, the learned responses are not made until the drive state is induced by the stimulation.

One experiment of this kind is that of Delgado, Rosvold, and Looney (1956) which involved the production of a fear drive by stimulation of sub-cortical structures. When fear was elicited by stimulation the monkey made the same responses as it had made earlier to a CS which had been paired with peripheral shock. Andersson and Wyrwicka (1957) also found that the conditioned responses which had been acquired to obtain water could be elicited by stimulation of the hypothalamic "drinking area". The goat while thirsty was conditioned to ascend the steps of a platform where it was presented with water. The critical test was done while the goat was sated for water. In this state it did not make the conditioned responses. However, when the sated goat received brain stimulation to the "drinking area" or "thirst area" the learned responses were made. (For a description of other studies in which instrumental responses were made when a drive state was produced by electrical stimulation of the brain, see Miller, 1958).

A series of experiments which are of great interest, although not as directly relevant to our discussion, are the self-stimulation studies which began with the experiment of Olds and Milner (1954). It appears that intra-cranial stimulation, in these experiments, has the paradoxical effect of both producing a drive and of satisfying it. Each intra-cranial burst maintains the drive which is satisfied by the animal's making conditioned instrumental responses for further stimulation. These experiments provide another demonstration of the occurrence of learned responses when a drive state is initiated artificially by electrical stimulation.

## EEG conditioning

It was pointed out earlier that no general statement can be made about the necessity of motivation in learning. Although it is clear from the previous section that the animal must be specially motivated to perform conditioned behavioral responses, it does not follow that no learning can be established without the manipulation of motivational processes. Here we shall consider the EEG conditioning experiments as providing evidence that neural processes produced by contiguous sensory stimuli become associated, apart from any special motivational state.

The EEG conditioning experiments began when several investigators (Durup and Fessard, 1936, cited by Morrell and Jasper, 1956; Loomis, Harvey, and Hobart, 1936; Jasper and Cruikshank, 1937) were studying the alpha-blocking response, to light in human subjects (i.e. the disappearance of the 10-per-second alpha rhythm). They observed that the blocking response soon began to occur to a tone which, originally, was presented only to prepare the subject for the presentation of the light. Some association was formed between the neural processes initiated by the contiguously occurring stimuli, so that the electrical response originally produced only by the light was now produced by the tone. Other experiments showed that the alpha blocking response can be conditioned and extinguished just as a peripheral response can (Travis and Egan, 1938; Jasper and Shagass, 1941; Knott and Henry 1941). (A review of these experiments has recently been made by Ellingson, 1956).

Alpha production may also be used as a UCR. In a study by Bentachili and Vorobiev (cited by Gastaut,

1957) the subject was in a lighted room and the UCS was the production of temporary darkness, which resulted in re-appearance of the alpha waves. The response was readily conditioned to an auditory stimulus.

It is generally assumed (and has been assumed in this review) that EEG conditioning experiments provide direct information about the neural processes of behavioral conditioning, and that by eliminating Start (the behavioral CR a simplified approach is provided for the study of learning. Chow, Dement, and John (1957) have questioned this assumption and on the basis of their data, which show that EEG conditioning can be established without behavioral concomitants, express doubt that "the neural mechanism of ... the conditioned EGG process is similar to that involved in behavioral conditioning" (p. 492). They also suggest that "The former [EEG conditioning] may not be a prototype enabling more direct neurological study of the latter [behavioral conditioning]" (p. 492). Alternatively, however, this experiment may mean only that the connections are involved in but are not sufficient to mediate behavioral CRs.

This appears to be a more reasonable view when other data are considered. Two forms of evidence will be presented to justify the positinn that conditioned electrical changes and conditioned behavioral changes are related. First, several authors (Livanov, Korolkova, and Frenkel, 1951, cited by Gastaut, 1957; Beck, Doty, and Kooi, 1956; Galambos, Sheatz, and Vernier, 1956; Jouvet and Hernández-Peón, 1957; and Yoshii, 1957) have shown a temporal relationship between conditioned electrical and conditioned behavioral responses. The fact that electrical changes precede conditioned behavioral responses (Beck, Doty, and Kooi, 1956, 1958; Jouvet and Hernandez-Peon, 1957) and outlast them during extinction (Galambos, Sheatz, and Vernier, 1956) seems to show that the conditioned electrical potentials are an index of neural processes involved in mediating behavioral responses. From such data most authors agree that the "neural alterations thus precede and probably are prerequisite to behavioral manifestations" (Beck, Doty, and Kooi, 1956, p. 433).

The second form of evidence is that modification of the behavioral response has been found to be accompanied by modification of the neural response (Artemiev and Besladnova, 1952, cited by Liberson, 1957; Morrell and Jasper, 1956; Yoshii, 1957). The alteration of the neural response during the establishment of behavioral CRs is usually from generalized activity to more restricted and specific activity.

Such evidence seems adequate to show that the neural changes recorded during EEG conditioning are related to learned behavioral responses. The EEG conditioning experiments, then, may be regarded as demonstrating the formation of associative connections without the manipulation of motivational processes. Another contribution of these experiments is the information they provide about the course of development in the neural changes that occur during conditioning.

Analysis of the neural events involved in conditioning has been the emphasis in a series of experiments involving EEG conditioning by Morrell and co-workers. Significant changes in the EEG response have been shown to occur as conditioned responses are established (Morrell and Jasper, 1956; Morrell, Naquet, and Gastaut, 1957), which are regarded as evidence of the functioning of different neural systems at different stages of conditioning. Factors which might modify these neural events, such as discharging lesions (Morrell, Roberts, and Jasper, 1956) and drugs (Morrell, Naquet, and Gastaut, 1957), have also been investigated.

An important development, begun during the past three or four years, is the recording of electrical changes from several cortical and sub-cortical regions at the time that behavioral CRs are being established and extinguished.

Most of the studies, some of which were referred to above, are only in the preliminary stages; however, it appears that a promising new line of research has been initiated for dealing with the neural basis of conditioning and learning.

A word might be said about one of these studies (Jasper, Ricci, and Doane, 1957) which is unique since both surface and unit activity of the cortex was recorded, the latter by means of micro-electrodes, while monkeys made conditioned avoidance responses (shock to the fore-limb was the UCS). During the presentation of the CS and during the CR it was found that units might increase in activity, decrease in activity or show no change. While recording from motor cortex the most common unit response to the CS was a decrease in activity; whereas during the CR the activity usually increased. Records were also taken from parietal cortex; here, unlike motor cortex, units were not active during the CR but during the CS the units often responded at the frequency of the photic stimulus (CS). When the unreinforced stimulus was presented during differential conditioning parietal units were usually inhibited. Although it is too early to understand the real implications of these results it is clear from work of this sort that the neural correlates of the conditioned response are very complex, and in identifying the critical neural circuits "Our research should be directed to non-sensory-motor cortex and probably to centrally situated neuronal systems of the brain stem ... " (Jasper, Ricci, and Doane, 1957).

## Intra-cranial stimulation as the CS

We can turn now to conditioning experiments in which intra-cranial stimulation is used as the CS. When the procedure involves the stimulation of afferent processes (Loucks, 1938; Doty, Rutledge, and Larsen, 1956) it is not surprising that conditioning occurs, since a portion of the neural structures normally involved in transmission of the CS is activated. Loucks was mainly interested in seeing what neural components were indispensable for conditioning and did not deal with the neural changes that occur; and Doty, Rutledge, and Larsen also did not consider the neural mechanisms involved. The value of these studies is their contribution to methodology. In other recent uses of intra-cranial stimulation as the CS (Loucks, 1955; Rutledge and Doty, 1955) the emphasis has been primarily on the study of brain functions.

Loucks performed the first experiment in which intra-cranial stimulation was the CS. When the motor cortex was stimulated as the UCS in an experiment referred to earlier (Loucks, 1935), it was found with one dog that stimulation of an area that produced movement of the hindleg could be used as a CS. Shock to the skin of the fore-limb provided the UCS. (This procedure does not involve simply the association of contiguous sensory events; the animal received shock and hence was also motivated to respond.)

In following up this observation, Loucks (1938) stimulated the occipital cortex of four dogs with electrodes in areas 17 and 19. Conditioned salivation was produced in two dogs when the UCS was acid placed in the mouth, and conditioned leg flexion was produced in the other two with shock to the skin of the fore-limb as the UCS. Loucks ran elaborate controls and it seems certain that the animals were responding to activation from the stimulation unit (however, as we shall see in a moment, the experiment is inconclusive since it is likely that there were mechanical vibrations produced by the unit; both the vibration and the electrical stimulation may have served as CS). The controls included: (a) passing the primary coil anterior and posterior to the imbedded coil as it was brought over the animal's head, (b) inserting a rubber sponge beneath the primary coil, and (c) placing a magnetic shield between primary and secondary coil. In each case the conditioned responses ceased.

These precautions, however, did not control another factor. Using a technique similar to that employed in Louck's experiments, Clark and Ward (1937) found that when a secondary coil placed subcutaneously was activated by the primary coil brought near to the animal's head it sometimes vibrated and "produced a sensory stimulation that at times caused a ducking of the head and flattening of the ears even though the electrode touching the cortex had been disconnected from the coil" (p. 941). It is very likely that such vibrations of the coil served as a signal, as well as the cortical stimulation; hence, the results are not conclusive.

However, controls seem adequate in a recent experiment by Doty, Rutledge, and Larsen (1956). With electrical stimulation of marginal (visual), suprasylvian (second sensory or association) and ectosylvian (auditory) gyri as the CS they conditioned leg flexion in a large number of cats with shock to the fore-limb as the UCS. The possibility that stimulation of non-cortical elements was responsible was ruled out by a number of controls. The most important control was the use of measurements of galvanic skin response to detect stimulation of non-cortical elements and ipsilateral trigeminal neurotomy to eliminate this effect. Sectioning the trigeminal nerve was considered to denervate the region about the electrode effectively and this eliminated the activation of peripheral nerves of skin and blood vessels which might serve as a CS. It appears that this experiment has conclusively established that conditioning can occur when the CS is cortical stimulation.

Both Loucks and Doty have modified the techniques used in the experiments just described in order to investigate special aspects of brain function during conditioning. In recent experiments with hens, Loucks (1955) has attempted to determine the relative efficiency of electrodes at various depths in the brain and the effects of placing shields around the stimulating electrodes so as to isolate the cells that were being stimulated directly. He found no relationship between depth of electrode and rate of conditioning. This agrees with the results of Doty, Rutledge, and Larsen (1956) who concluded that there was no relation between either electrode penetration, or position, and ease of conditioning.

In attempts to isolate the cortical neurons being stimulated, Loucks found that collar-shaped barriers placed around the electrodes had no effect on conditioning, but hoe-shaped tangentially-directed barriers which went along-side and beneath the electrode, temporarily disrupted conditioning. This result suggests that connections formed during conditioning involve vertical rather than horizontal routes, but since the cortex is absent or very thin in birds the basal ganglia rather than the cortex was probably being stimulated; hence these results may not be applicable to mammalian cortex.

The technique used by Rutledge and Doty (1955) involved the administration of chlorpromazine after the animals had first learned to make CRs to both cortical stimulation and peripheral stimuli. They found that the drug had differential effects on the CRs produced by these two types of conditioned stimuli; the animal ceased to respond to the tone and light but continued to respond to the cortical stimulation. The interpretation given by Rutledge and Doty is that "... chlorpromazine acts somewhere in the afferent mechanism and ... direct cortical stimulation to a large degree circumvents this system" (p. 126).

A complicating factor in the use of intracranial stimulation as CS (and probably as UCS) in conditioning experiments is the possible interference effects of electrical stimulation on learning processes, which has been reported in a number of recent experiments. Although the mechanism of the interference effects is in most cases not clear, and no consistent picture appears as yet, it has generally been assumed that the effects were either on associative (Rosvold and Delgado, 1956; Glickman, 1957; Mahut,

1957) or motivational (Milner, 1954; Correll, 1957) processes. (Of course, it is difficult to make this distinction precisely in some cases.) Since both processes must be functioning simultaneously for behavioral conditioning (according to the analysis given earlier in this review), interference with one of these processes might very well have some effect on conditioning.

Part of the difficulty in understanding some of the effects of electrical stimulation on learning (as well as in understanding learning in general) lies no doubt in the concept of motivation. The term is used in this review in a general sense to refer to processes which produce persistence and direction in behavior. Motivation is assumed to be represented neurally by a central state which, it was pointed out earlier, must be present if the contiguous occurrence of afferent and efferent processes is to lead to behavioral responses. But the nature of motivational processes is not understood very well neurologically. In fact, at present it is difficult to find any neural basis for the distinction just made between motivational and associative functions.

The interference experiments are one of a number of recent approaches initiated in attempts to understand the motivational and associative functions neurologically. Especially relevant to the results to be reported later in which intra-cranial stimulation served as the CS, is the observation that cortical stimulation can interfere with learning. Burns and Mogenson (1958a) found that cortical stimulation, delivered while rats pressed a bar for food, interfered with the acquisition of the bar-pressing response. In other studies Burns (1958) has reported that cortical stimulation produced a decrement in the performance of the same response after it had been learned. A detailed consideration of the nature and mechanisms of interference effects is not necessary here; however, it is of practical interest to recognize that such interference effects might be a complicating factor in experiments where cortical stimulation is used as the CS since the stimulation might not only act as a signal but also as a disrupter of learning.

## THE PRESENT INVESTIGATION: PURPOSE AND GENERAL PLAN

The purpose of the present investigation was to learn more about the way in which cortical stimulation functions as a CS, following the recent experiments of Loucks and Doty.

Some preliminary investigation was necessary to find a suitable procedure for such conditioning with the rat as subject. Leg flexion was found to be an inappropriate technique because of difficulties that were encountered in confining rats in a harness. The use of cortical stimulation as a signal that a pellet of food could be obtained by pressing a bar was also found to be unsuitable.

In a preliminary study of conditioning with this method, cortical stimulation was delivered simultaneously with each bar press, with the idea that an association would be established between delivery of cortical stimulation and the obtaining of food. However, most of the rats did not learn to press for pellets in such a situation and there is reason to conclude that the stimulation, though it might function as a CS, was also interfering with habit acquisition. This observation led to a series of experiments, concerning the nonspecific effects of cortical stimulation on learned behavior, which are described elsewhere (Burns and Mogenson, 1958a; Burns 1958).

The first satisfactory results were obtained with the shuttlebox, using cortical stimulation as the CS for an avoidance response. Only a small number (about 15 per cent) of the animals were conditioned to criterion with this procedure. However, all the animals showed evidence that the cortical stimulation was being utilized as a signal of the shock that followed it; when the CS was presented various emotional or "anxiety" responses were made.

It was clear therefore that the stimulation was serving as a signal, and it appeared that if a different response was required a higher proportion of the animals could be conditioned. For this purpose the conditioned emotional response (CER) procedure (Estes and Skinner, 1941) was considered suitable; conditioned anxiety responses similar to those displayed by the animals tested in the shuttlebox would interfere with the performance base line in the Skinner box and be recorded as a CR. The second experiment was done to see if cortical stimulation could serve as a CS in the CER procedure.

The results of Experiment II showed that it could. In the next experiment (Experiment III) the CER procedure was refined somewhat so as to provide a more sensitive measure of the rate of conditioning and strength of the CR when various cortical loci were stimulated as the CS.

## General procedures

Certain aspects of procedure which are common to all experiments may be mentioned now before reporting each experiment separately. The subjects were male hooded rats obtained from the Royal Victoria Hospital colony and weighing 190 to 210 grams. After being handled for a few days and after receiving preliminary treatments, such as becoming accustomed to a feeding schedule, the animals had electrodes implanted following the method described by Olds and Milner (1954). After a recovery period of 3 to 5 days, experimental procedures were begun. At the completion of testing the rats were killed with ether and perfused with physiological saline and 10 percent formalin. The brains were then removed from the skull, fixed in solutions of 10 percent formalin for a few days, followed by 20 per cent alcohol, and histological sections prepared in order to determine the locus of electrodes.

The stimulation was 60-cycle sine wave controlled manually by means of mercury switches. The voltage used for stimulation was selected before the experimental procedures began, in each case at an intensity well below the threshold for motor movements, ranging from 1.25 to 6 volts. The duration of stimulation varied somewhat from experiment to experiment.

When a UCS was employed it was a 1 to 1.5 mA current delivered through the grid floor of the apparatus and also controlled manually by means of mercury switches. Upon the occurrence of a CR the CS and UCS were terminated.

## EXPERIMENT I

The animals were tested in a shuttlebox, which was large (20" x 16" x 24") and oval-shaped in order to minimize the chances of the animals' loosening their electrodes by banging them against the walls of the apparatus while escaping the shock. There was a window 4" x 6" in one side. After preliminary handling the animals were given up to twenty trials in the shuttlebox with electric shock (UCS) alone; any that did not learn to escape the shock by running promptly to the other side of the box were eliminated. Electrodes were then implanted and after a few days for recovery the testing began. Eight to ten trials were given daily, spaced three to five minutes apart. The CS consisted of three 2-second trains of stimulation separated by 3 seconds.

The data are reported for 17 animals; electrode placements are shown on a dorsal view of the brain in fig. 1. Although more animals were tested, several were excluded because testing was possible for only a short time or infections were found in the electrode track at autopsy.

Three of the 17 animals were conditioned to a criterion of 25 CRs in 30 trials and reached criterion after 46, 73 and 83 trials. The electrode placements of these three animals may be seen in fig. 1. There did not appear to be any relation between occurrence of conditioning and cortical locus, since some of the animals in which conditioning was not successful had electrodes in the same areas. However, there was a relation between the depth of penetration into the cortex and the occurrence of conditioning. The electrodes of the three conditioned animals (in lower layer V and layer VI) were deeper than the electrodes of other animals.

The 14 animals that did not reach criterion, however, did show some signs of conditioning; a conditioned response was obtained on 1 to 20 percent of the trials. Furthermore, when barrier crossing did not occur the animals often showed diffuse "anxiety responses" (mean frequency, 58 percent of the trials). These consisted of alerting during and following the CS, moving back and forth, approaching the barrier and returning to the end of the box, sometimes crouching and defecating.

When the histological sections of the brains of these 14 animals were examined, there also appeared to be a relationship between electrode depth and number of CRs. The largest percentage of CRs was made by rats with shallow electrodes (layers I and II) and deep electrodes (layers V and VI). (Also, as mentioned above, the 3 animals in which conditioning was successful had electrodes in layers V and VI). Animals with electrode tips in or near layer IV seemed to make the smallest percentage of CRs. When a rank order correlation was done for the 14 non-conditioned rats between number of CRs and deviation of electrode tips from layer IV a correlation of $+.62$ was obtained, which is significant ($p < .01$).

## EXPERIMENT II

This experiment was done to see if the emotional responses observed in the first experiment could be conditioned to cortical stimulation.

The procedure was adapted from the method of Estes and Skinner (1941). Nine animals (7 experimentals, 2 controls) were trained to press a bar for pellets in a conventional Skinner box (5" x 12", with a bar and food cup at one end) on a variable ratio reinforcement schedule. (This training was given after the animals had learned to operate the lever on continuous reinforcement.) Electrodes were then implanted in all and, after a few days to permit recovery, the animals were again given an opportunity to press for pellets in the Skinner box. After a stable rate of responding had been obtained, a CS (cortical stimulation, or tone) was presented for 30 seconds. The CS had been paired previously with shock in a grill box. Cortical stimulation was the CS for 7 of the animals and tone was used for the 2 controls. The stimulation consisted of 1-second bursts of 60-cycle sine wave spaced 5 seconds apart. The conditioned emotional response was indicated by a depressed rate of responding in the Skinner box during the presentation of the CS. The rate of responding was determined by means of counters.

The pairings of CS-UCS in the grid box were made in the evening; 10 pairings were given each day. The next morning the animals were tested in the Skinner box for 15 minutes and the CS was presented during the first half of the 4th and 10th minutes. The number of responses during these two 30-second periods was compared with the number of responses during each minute prior to the presentation of the CS. Criterion of conditioning was considered as 3 out of 4 consecutive trials in which the response rate during the 30-second CS interval was less than one-third of the rate of the previous minute.

The 2 control animals were readily conditioned to make responses to tone (Table I, nos. 8 and 9) and 6 of the 7 experimental animals were conditioned to cortical stimulation after 1 to 13 trials. The electrode placements of the experimental animals are shown in fig. 2 by the triangular markings. Although it was several days before most of the animals reached criterion, frequently the response rate was depressed on the first or second day.

The data of rat no. 2 are somewhat misleading, making it appear that conditioning had not occurred.

The animal was clearly responding to the CS as a signal for the shock but instead of displaying a depressed response rate it often pressed more when the CS was presented by crowding into the end of the box where the bar was located. The behavior of this animal prompted modification of the apparatus so that for the next experiment, the UCS, presented in the Skinner box, was delivered only at the end of the box where the bar was located so that the animal would respond to the CS by backing away from the bar rather than by crowding into it.

The results of this experiment clearly show that cortical stimulation can be utilized as a CS for a conditioned emotional response. Since the electrode placements and depth of penetration were similar to those of animals in the first experiment, which did not reach criterion in avoidance conditioning in the shuttlebox, a comparison can be made between the results of the two experiments. It appears therefore that the same cortical stimulation is an unsatisfactory CS for avoidance conditioning (only 3 out of 17 animals being conditioned in Experiment I) whereas it serves effectively as a CS for a conditioned emotional response. The reason for this difference will be considered later.

The CER procedure was quite satisfactory to demonstrate that a conditioned emotional response can be made to cortical stimulation, but the particular method used for this experiment was not adequate for studying other problems such as possible differences when various areas are stimulated as the CS. Since a block of 10 CS-UCS presentations was given several hours before each conditioning test in the Skinner box, only a very gross indication was obtained of the number of trials necessary for conditioning to be established. In the next experiment the procedure was modified to provide a more sensitive measure of the rate of conditioning.

## EXPERIMENT III

The third experiment was done to investigate possible differences between various cortical areas being stimulated as the CS. The procedure of the previous experiment was modified so that the presentations of CS-UCS were made while the animal was performing in the Skinner box. A cumulative recorder was used so that a CR was registered as a deflection from the smooth slope recorded as the animal operated the bar for partial reinforcement (cf. fig. 3). After the CR was established the CS was presented alone until extinction had occurred.

The data for this experiment are presented in Table II. The distribution of scores for both acquisition and extinction was bimodal; there were two distinct groups with no over-lap. Group A consisted of animals in which the CR was readily established and was resistant to extinction. Group B, on the other hand, consisted of animals in which it was difficult to establish conditioning and whose performance was also quite unstable and extinguished rapidly. A comparison of these two groups shows a significant difference in number of reinforcements to learn ($t = 2.8$, $p < .01$) and in number of trials to extinction ( $t = 2.5$, $p < .05$).

The histological data were examined to see if there was some difference in electrode placement between animals of the two groups. The electrodes of the animals in Group A were found to be in sensory and motor cortex, whereas the electrodes of Group B were in association cortex. The importance of this finding will be considered in the Discussion.

The records of some of the rats are presented in figs. 3 to 7; they were selected as representative of animals of the two groups. Fig. 3 shows some of the conditioning and extinction records for rat no. 4-3 (the first number represents the cortical area according to Krieg (1946) in which the electrode was placed). The first CR was made after 3 reinforcements. Record 2 shows the response of this animal to cortical stimulation after 6 reinforcements. Some of the responses during extinction are also presented (fig. 3: records 3 to 6) and indicate that extinction was complete after ten trials. When the CS was again paired with shock the conditioned response reappeared. (The absence of any response to the CS prior to its pairing with the UCS, plus the extinction and re-conditioning of the CR, are considered as evidence that the cortical stimulation was not noxious and had no affective quality until associated with shock.)

The records of another animal with the electrode in motor cortex are shown in fig. 4. This animal took longer to acquire the CR, 7 reinforcements were required as compared to 3 in the rat previously discussed. The reason for this is possibly that the electrodes were very shallow in the cortex (see brain section, fig. 4); the data of other animals provide further support for this view.

Fig. 5 presents data for an animal with the electrode in occipital cortex (the border of areas 17 and 18). The CR was readily established; the response after 5 reinforcements is shown in record 2. An even stronger response was made after 7 reinforcements (fig. 5, record 3). The CR, as in the case of the other two rats discussed above, was quite resistant to extinction; 10 extinction trials were given (fig. 5: 4-7) before the response was extinguished.

As mentioned earlier, the data presented in figs. 3 to 5 were of animals in Group A, representing sensory and motor electrode placements. The next two figures are from animals in Group B; responses were difficult to establish and readily extinguished.

Some of the data for rat no. 29b-1 are shown in fig. 6. Twelve reinforcements were given before this animal made a CR (fig. 6: record 3). The response was not only slow to be established but also unstable; no response was made on the third extinction trial (fig. 6: record 5). A similar result was obtained with rat no. 10-3. CRs were not made until 19 reinforcements had been given; the responses were readily extinguished as well (fig. 7: 3-4). More detailed consideration of this difference between animals of Groups A and B, which has been illustrated by these figures and by Table II, will be given in the Discussion.

# DISCUSSION

This investigation has been concerned with studying conditioned responses to cortical stimulation. The main finding was that cortical stimulation can serve as a CS but that its effectiveness varies with the nature of the response which is being conditioned and with the position of the electrodes.

The first experiment showed that motor responses could not be successfully conditioned to cortical stimulation although there were indications that emotional responses could be. Experiment II demonstrated that emotional reponses were in fact readily conditioned. In Experiment III it was shown that even for establishing conditioned emotional responses stimulation was a less effective CS in some areas of the cortex than in others.

Let us first consider the difference in results between Experiments I and II, the difficulty in conditioning an avoidance response to cortical stimulation and the ease of conditioning an emotional reaction. It is clear that what the animal has to learn in the two cases is not the same. The required response in the shuttlebox consists of a well-integrated series of motor movements which result in crossing the barrier; whereas in the CER procedure a recordable response need only involve cessation of pressing for food, which usually occurs because the animal displays anxiety behavior. When a peripheral CS was used, it was found (in agreement with other workers) that 10 to 15 times as many trials were required in the shuttlebox as in the CER procedure. This indicates that even with a peripheral CS it is much more difficult to learn to make the adequate response in the former situation than in the latter.

Actually the learning that takes place in the CER procedure is only one phase of the learning that occurs in the shuttlebox. An association of the CS with shock, so that the CS is able to elicit an anxiety reaction, is a correct response in the CER procedure; but this is only the initial stage in the shuttlebox, since the animal must then learn to make motor movements which enable it to avoid the shock. Many more trials must be given before the second phase is complete,and it is not until the correct avoidance response has been learned that CRs are recorded in the shuttlebox.

The greater difficulty of conditioning motor responses is not the only reason for the differing results in Experiments I and II. If that were so, then conditioning to cortical stimulation would take longer in the shuttlebox, but the animals should eventually learn. Most of the animals tested in the shuttlebox, however, did not learn.

Another possibility is that there was destruction or permanent damage of cortical tissue by the electrical stimulation. It is not inconceivable that such damage might affect conditioning of the more difficult response without affecting the easier one. This suggestion seems unlikely, however, in view of preliminary results of an experiment in which rats were stimulated for a number of days prior to being tested in the Lashley III maze (Burns and Mogenson, 1958b) Stimulation of the cortex interfered with the retention of the maze, but once the animals had reached criterion in the retention test there was no effect on a retest given 2 weeks later. Also there was no affect of stimulation on the acquisition of the maze. Since the stimulation must be given during acquisition testing in order to produce any interference (Burns and Mogenson, 1958a) it seems that it is activity produced by the stimulation, and not any destruction or damage it might cause, that is responsible.

This brings us to a third explanation for the difficulty of conditioning motor responses to cortical stimulation; the possibility that stimulation interferes with learning. Cortical stimulation has been shown to interfere with learning to press a bar for pellets( Burns and Mogenson, 1958a) so it is quite conceivable that avoidance conditioning might also be disturbed. That motor responses might be more vulnarable to disturbance than autonomic responses is suggested from an experiment of MacLean, Flanigan, Flynn, Kim and Stevenson (1956). They found that abnormal neural activity originating in the hippocampus had differential effects on autonomic and motor responses. Using a trace conditioning technique, which tended to exaggerate the differences, it was shown that animals could make conditioned autonomic responses although they were unable to make conditioned motor responses.

The interference effects of the cortical stimulation are probably on central integrative and associative mechanisms; although, there is also the possibility that interference with learning occurs because of motor consequences of the stimulation. Stimulation of the motor cortex has been shown to disturb motor responses in both humans and animals. In humans Penfield and Jasper (1954) reported that arrest of voluntary movements was often produced by electrical stimulation of the motor cortex. The arrest of on-going behavior has also been observed in cats on stimulation of the motor cortex (Delgado, 1952). Stimulation of other cortical areas may also have some effect on motor movements; Rossi and Brodal (1956) have found a projection of fibers from all parts of the cerebral cortex to the pontine and medullary reticular formation and point out that this could provide the anatomical substrate for cortical influences on somato-motor activity.

That such motor effects of cortical stimulation can interfere with learning has never been demonstrated. However, the motor consequences of stimulating other neural structures have been considered responsible for the disturbance of learned responses. For instance, the interference with delayed-alternation performance by stimulation of the caudate nucleus (Rosvold and Delgado, 1953) is regarded by Teuber (1955) as due to the disturbance of postural components of the behavior. And Chiles (1954) attributes the interference of diencephalic stimulation with bar pressing responses to motor consequences of the stimulation. In these experiments stimulation was not given during the acquisition of learned responses, but it is unlikely that an animal would learn if it could not perform the correct response.

Although the influence of motor effects of the stimulation may sometimes be an important factor it is probably not the answer in every case. There are reasons for doubting that it was an important factor in the difficulty of conditioning avoidance responses to cortical stimulation. In Experiment I the stimulation had no motor consequences such as were reported by Chiles (1954), for example. Also the animals made prompt escape responses to the shock (UCS) showing that the stimulation was not having any significant effect on the relevant motor pattern. Finally, with the intensity and small number of presentations of stimulation used in these experiments there was no effect of the stimulation on response rate in the Skinner box in Experiment III prior to its being paired with shock. For these reasons we may rule out motor disturbances as an important factor in the failure to condition avoidance responses, and turn to consider in more detail the ways in which stimulation might interfere with the integrative and associative functions of the cortex.

One explanation for such a disturbance is that direct stimulation of the brain may excite components simultaneously that normally respond sequentially to sensory input. A suggestion of this sort was originally made by Hebb (1950) and is considered by Bishop and Clare (1953) as one of the crucial differences between direct and indirect activation of the cortex. The effect of telescoping neural events in this way would be to disturb the patterning and timing of neural firing, which are considered to be very important in mediating complex behavior.

The fact that stimulating association cortex was found in Experiment III to be a less effective CS than stimulating sensory cortex might be related to the more complex timing involved in the functioning of association cortex. Hebb (1950) distinguishes two types of transmission systems in the brain, parallel conduction and divergent conduction, the former being characteristic of afferent systems and to some extent of sensory cortex, and the latter of association cortex. "Stimulating a point in the first type of system will have effects similar to its normal physiological action; but stimulation of contiguous cells in the second type of system may simply fire, all at once, cells which for their normal function must fire separately" (Hebb, 1950, p. 182). The greater difficulty of conditioning with stimulation of association cortex as the CS may be because there the timing and patterning of activity are much more vulnerable to disruption by the stimulation; we shall return to this point later. Another aspect of the interference phenomenon related to the results of Experiments I and II should first be considered.

There is some indication from Experiment I that the degree of interference varies with the depth of the stimulating point in the cortex. It was found that stimulation at the depth of layer IV produced the smallest percentage of CRs, and that it was only animals with deep placements that were conditioned to criterion. Also, it was found in the maze experiment (Burns and Mogenson, (1958b), referred to earlier, that stimulating in the region of the white matter of the corpus callosum did not interfere with the retention of the maze. From these results it appears that cortical disruption is greatest from stimulating in the region of layer IV and least or non-existant in the region of the white matter.

It is somewhat surprising that stimulation at the depth of layer IV was a less effective CS. There are several reasons that might lead one to predict that at this depth stimulation would most closely duplicate normal cortical function. For one thing it is the region of the termination of sensory afferents. Also the reverberating mechanism (Chang, 1950), which produces secondary responses (Adrian, 1936; Forbes and Morison, 1939) is maximally active there. The secondary response is considered to facilitate learning (Chang, 1950) by making activity persist long after cessation of the stimulus that produced it, thus providing greater opportunity for the formation of associations with other neural activity. Finally, Golgi type II cells, believed by Chang (1950) to have an "amplifying" function, are found predominantly in layer IV.

Recent evidence that there are inhibitory cells in the cortex (Phillips, 1956, cited by Purpura and Grundfest,

1957) is easier to reconcile with our results. If it is Golgi type II cells which have the inhibitory function, and it seems that they do (see the discussion of this given by Milner, 1957), then stimulating in the region where they are most densely concentrated (layer IV) may produce the greatest deviation from normal cortical function.

In contrast to the interference effects from stimulating in other portions of the cortex, there was no apparent effect when layer VI or the corpus callosum were stimulated; only animals with deep placements were conditioned in Experiment I; furthermore, as mentioned above, retention of the maze was not affected by stimulation of the corpus callosum (Burns and Mogenson, 1958b). The structure, and probably the function, of the internal layers of the cortex differ from those of the more superficial regions. Chang (1953), from a study of Golgi and Golgi-Cox preparations in mouse and rat, found that layer VI is where most callosal fibers originate. These fibers then pass through the corpus callosum and terminate throughout the cortical layers of the other side, especially in layers I, II and III. Lack of interference from stimulating layer VI or corpus callosum may be because such stimulation leads to essentially normal firing patterns in the neurons of the opposite hemisphere, whereas firing these neurons directly produces abnormal activity.

The evidence reviewed by Bremer (1958) of his experiments and those of Chang demonstrating callosal facilitation in acute preparations makes it quite conceivable that callosal stimulation may even facilitate learning. Although there is as yet only suggestive evidence for such effects, this is an interesting possibility that deserves further study.

The evidence for a facilitation of learning by callosal stimulation was provided in the experiment in which cortical stimulation was found to interfere with the acquisition of the bar pressing response (Burns and Mogenson, 1958a). While re-examining this data, Mr. Burns has found that the animals that did learn, in spite of the stimulation, had electrodes in the corpus callosum and that their rate of acquisition was somewhat higher than that of the controls. Since the difference is not statistically significant, it must remain for the present an open question as to whether stimulating the corpus callosum facilitates learning. It is quite clear, however, that callosal stimulation at least does not cause interference.

If callosal stimulation is found to facilitate learning it may be due to a diffuse arousal effect on the cortex, in the same way that facilitation via the reticular system (Fuster, 1958) is believed to operate. In considering possible mechanisms for callosal facilitation in acute preparations, Bremer (1958) says that a conditioning stimulus applied to the corpus callosum "could exert a special sensitizing effect on the dendritic component" (p. 432) of the cortical reponse to direct stimulation very similar to the effect of stimulating the non-specific thalamic system with a conditioning shock (Jasper and Ajmone-Marsan, 1952).

Finally we will return to consider the question of why stimulation of sensory areas is a more effective CS than stimulation of association areas. The possibility that stimulation of association areas might produce a more severe interference with the conditioning process has already been mentioned. Perhaps the most important factor, however, is that the sensory areas are part of the normal pathway for peripheral stimuli; stimulation there should give rise to modes of cortical firing more closely resembling that set up by sensory events. Moreover, all the animal's previous learning has served to strengthen the connections between sensory and other areas of the brain and these connections may be of help in associating the cortical stimulation with the appropriate response.

In order to test this possibility an experiment has been done using stimulation of the visual cortex as a CS in rats peripherally blinded either at an early age or later in life. Preliminary results with two animals in each group indicate that the late blind animals are conditioned just about as readily as controls whereas the early blind are conditioned with great difficulty or not at all; the results with the latter being very similar to those with stimulation of association cortex. These tentative results suggest that the acquired connections may be an important factor in the difference in effectiveness as a CS of stimulating sensory and association cortex.

# SUMMARY

Rats received electrical stimulation to the cortex through permanently implanted electrodes. The effectiveness of this stimulation as a CS was studied using the shuttlebox and the conditioned emotional response (CER) procedures. Avoidance responses in the shuttlebox were conditioned successfully in only a few of the animals, whereas, cessation of bar pressing which constituted the response in the CER procedure was readily conditioned in most of the animals. The interference effects that electrical stimulation is known to have on learning were considered to be important in producing this difference, the avoidance responses being much more vulnerable to disturbance than the cessation of bar pressing. Using the CER procedure it was found that conditioning was more readily established when the CS was stimulation of sensory cortex as compared to stimulation of association cortex. This result was attributed to structural differences between the two types of cortex and to differences in the degree to which acquired connections are formed with other areas of the brain.

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Table I. CONDITIONED EMOTIONAL RESPONSES TO CORTICAL STIMULATION

| Rat No. | C. S. (1) | Criterion Trial (2) |
|---|---|---|
| 1 | cortical stimulation | 5 |
| 2 | " | - |
| 3 | " | 13 |
| 4 | " | 5 |
| 5 | " | 6 |
| 6 | " | 9 |
| 7 | " | 1 |
| 8 | Tone | 1 |
| 9 | " | 3 |

---

(1) Stimulation voltage ranged from 1.25 to 2.25 V

(2) Criterion was 3 out of 4 consecutive trials on which pressing rate during presentation of the CS was less than one-third of the control rate. The first of 3 such trials has been called the criterion trial.

Table II . CONDITIONED EMOTIONAL RESPONSES TO CORTICAL STIMULATION AS THE CS

| | | | Mean Number of Trials | |
|---|---|---|---|---|
| Group | N | Electrode Locus | To Learn | To Extinction |
| A | 12 | sensory and motor | 4.2 | 6.9 |
| B | 8 | association* | 17.2 | 1.8 |
| C | 2 | tone as CS | 2.0 | ____ |

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*Three of these animals were not conditioned so the means of this group are based on an N of 5.

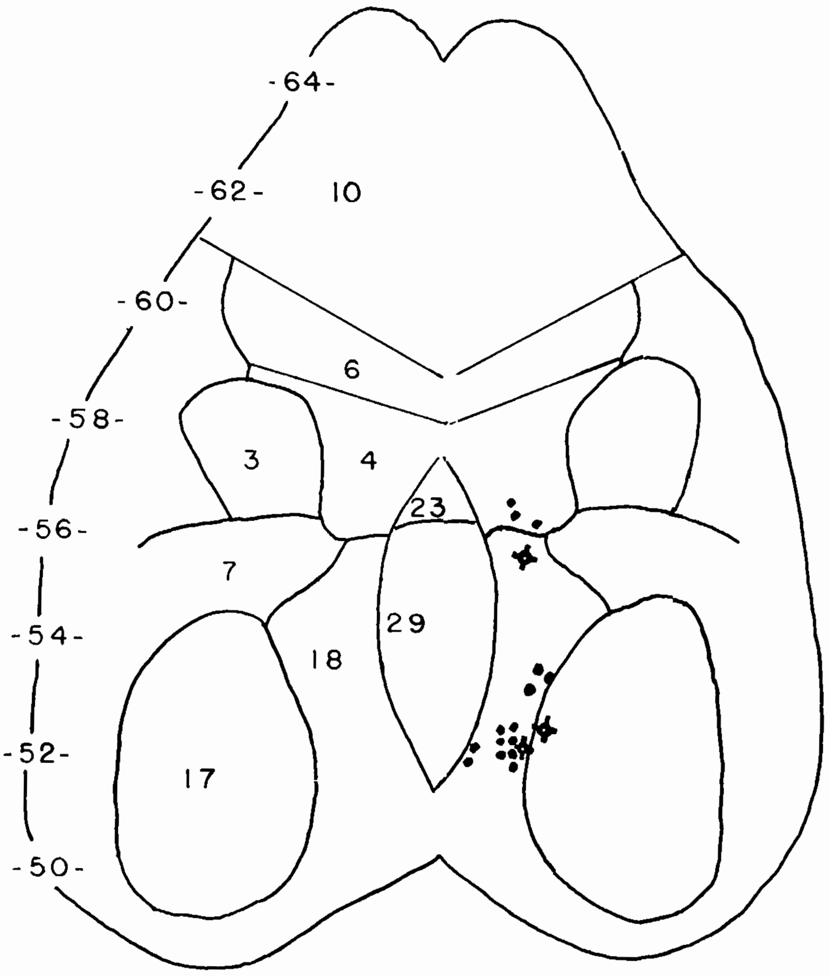

Fig. 1. Electrode placements of animals tested in the shuttlebox. + - animals conditioned to criterion

● - animals not conditioned

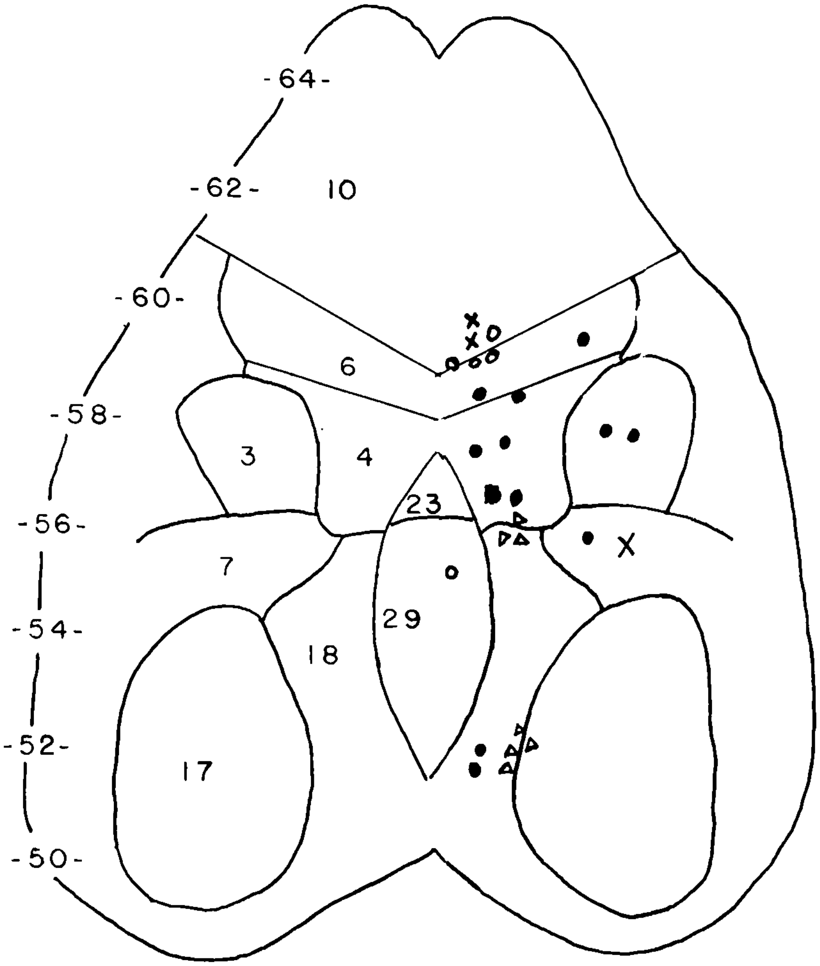

Fig. 2. Electrode placements of animals tested in CER procedure.

Experiment 2 : ▲ - animals conditioned

Experiment 3 : ● - conditioned readily

○ - conditioned with difficulty

✕ - not conditioned

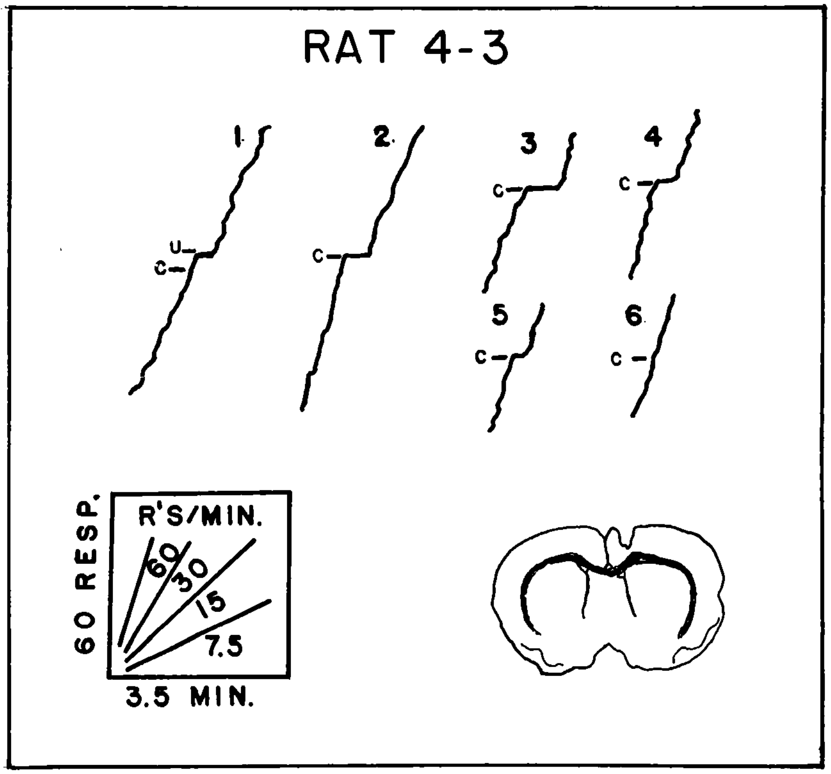

Fig. 3. Conditioning records for animal with electrode in area 4 at depth of layer 5. 1. second reinforced trial, 2. test trial after 6 reinforcements, 3. second extinction trial, 4. fourth extinction trial, 5. seventh extinction trial, 6. tenth extinction trial.

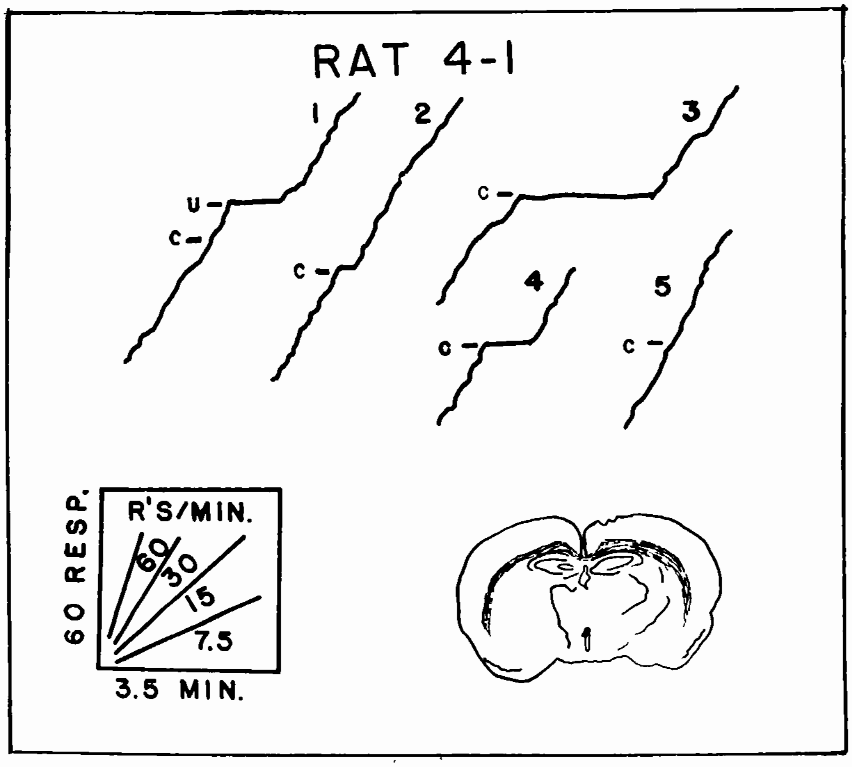

Fig. 4. Conditioning records for an animal with electrode in area 4, layer I.

1. fifth reinforced trial, 2. test trial after 7 reinforcements, 3. second extinction trial, 4. fourth extinction trial, 5. seventh extinction trial.

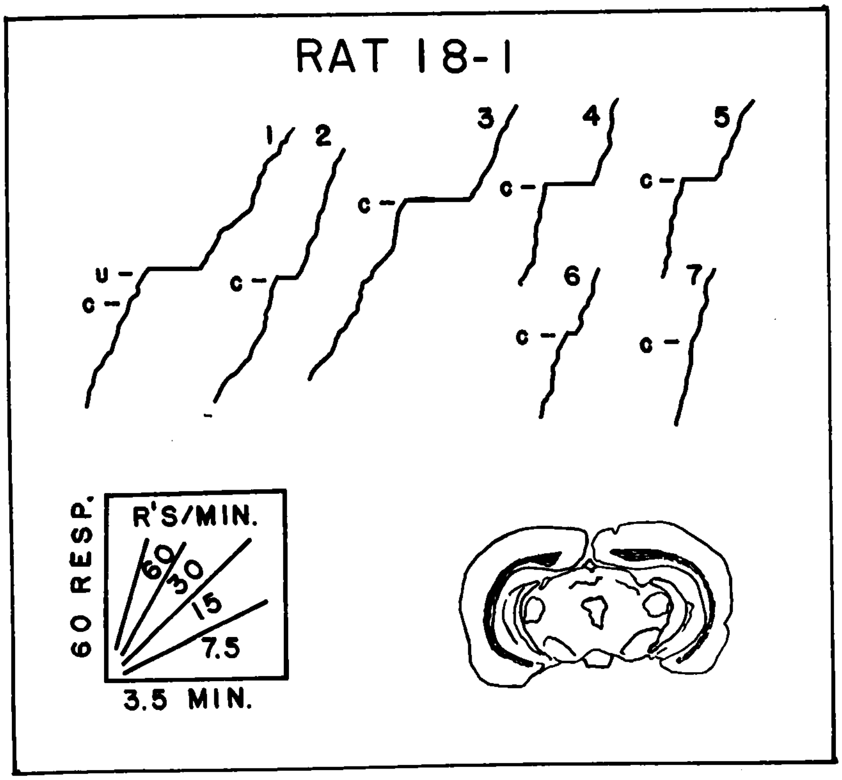

Fig. 5 Conditioning records for an animal with electrode on border of areas 17 and 18, layer 2.
1. second reinforced trial, 2. test trial after 5 reinforcements, 3. test trial after 7 reinforcements, 4. second extinction trial, 5. sixth extinction trial, 6. ninth extinction trial, 7. tenth extinction trial.

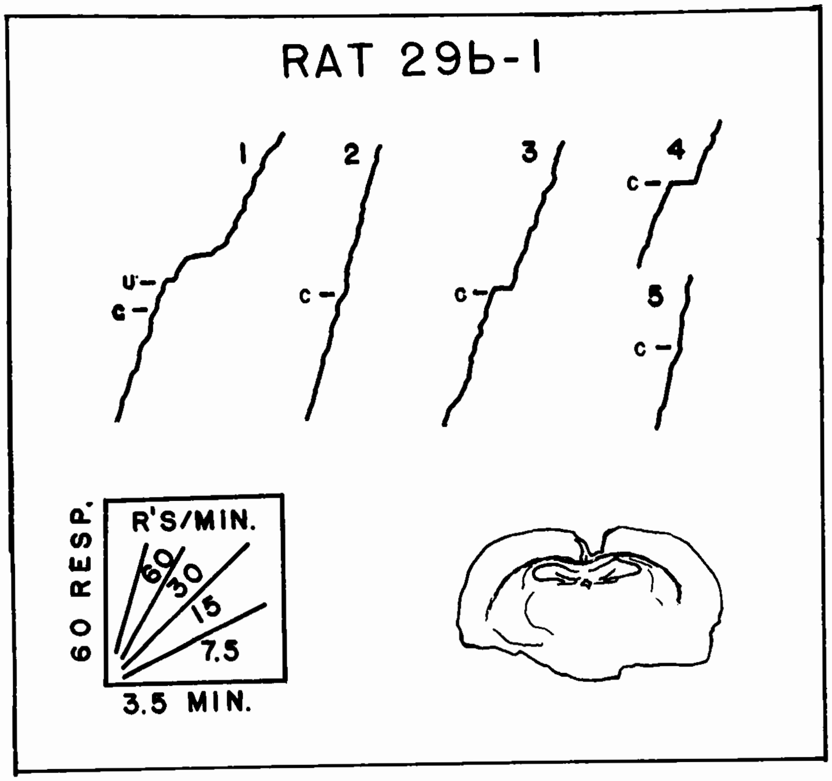

Fig. 6. Conditioning records for an animal with electrode in area 29b, layer 6.
1. sixth reinforced trial, 2. test trial after 8 reinforcements, 3. test trial after 12 reinforcements, 4. first extinction trial, 5. third extinction trial.

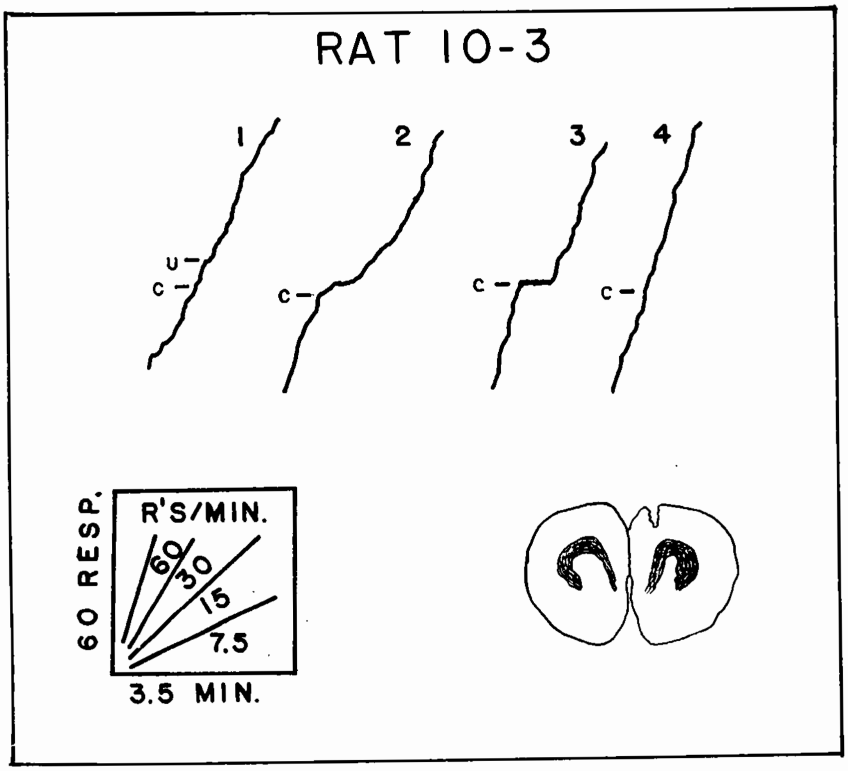

Fig. 7 Conditioning records for an animal with electrode in area 10, layer 4.

1. twelfth reinforced trial, 2. test trial after 19 reinforcements, 3. first extinction trial, 4. third extinction trial.