# ROLE OF THE RETICULAR FORMATION IN HABITUATION

by

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# INTRODUCTION

If a drop of water falls on the surface of the sea just over the flower-like disc of a sea anemone, the whole animal contracts vigorously. If, then, a second drop falls within a few minutes of the first, there is less contraction, and finally on the third or fourth drop, the response disappears altogether (Jennings, 1906). Here, in this marine polyp with the primitive nerve net is clearly exhibited one of the most pervasive phenomena of the animal kingdom--decrement of response with repeated stimulation. It is this phenomenon (but only in higher vertebrates) with which the present study is concerned.

The nervous system of the sea anemone is non-specific and diffuse. Activity initiated at one point spreads in all directions through the net exciting intermediate effectors en route, so that every stimulus to which the sea anemone is sensitive produces a non-specific excitatory effect. The nervous system of higher vertebrates, on the other hand, is characterized by long, discrete and relatively direct connections, which permit a rich variety of specific responses to be elicited either singly or in various combinations. For many years, psychophysiological thought has been dominated by the theory that the entire "integrative activity" of the vertebrate nervous system can be analyzed in terms of the action of stimuli on these specific neural pathways (Sherrington, 1906).

But in the last decade, a new concept of central nervous functioning has emerged. It has been shown that the specific pathways in the central nervous system coexist with--and, in a sense, are superimposed on--a diffuse neural network, the reticular activating system, which is not entirely dissimilar to the primitive nerve net of the sea anemone. Activity initiated at any point in this system spreads throughout the whole, producing a generalized activation of the central nervous system. Thus, even in the highest vertebrates, stimuli may have non-specific excitatory effects.

Moreover, and this is the central point of the present thesis, a repeated stimulus may lose its power to excite the non-specific reticular system, and yet continue to excite specific neural pathways. I shall use the term 'habituation' (in an unusually restricted sense; cf. Humphrey, 1933), to refer to the process by which a repeated stimulus loses its non-specific excitatory power. What we shall be concerned with is the physiological mechanisms subserving habituation, and with their psychological significance. In Part I we shall consider first the evidence from which the existence of the reticular system has been inferred; secondly, the evidence showing that this system ceases to respond to oft-repeated stimuli; thirdly, the relation between this loss of non-specific excitatory power and the extinction of specific conditioned and unconditioned reflexes; and finally, we shall consider the effects of habituation on the everyday behavior of animals. Part II will then report a series of experiments designed to elucidate the physiological

mechanisms responsible for habituation.

# PART I

## ANATOMY AND PHYSIOLOGY OF THE RETICULAR ACTIVATING SYSTEM

The reticular formation is an ill-defined structure in the medial brain stem forming a more or less continuous column from the lower part of the bulb through the midbrain tegmentum. In myelin-stained sections through the brain stem (Plate X), it is characterized by an interlacing network of small fiber bundles. These are interspersed with loosely organized groups of cells of varying size and structure (Olszewski, 1954). It is a primitive structure which follows the same basic plan throughout verterbrate phylogeny. The major cell groups present in cyclostome are also present in man (Kappers, Huber and Crosby, 1936).

The reticular formation, so described, is a morphological entity. In recent years, much research has been devoted to a functional entity, the reticular activating system, which is defined in terms of its capacity to exert a non-specific facilitatory effect on almost all neural processes. This activating mechanism is partly co-extensive with the reticular formation, and is therefore named after it, but the activating system also includes structures outside the reticular formation, in the hypothalamus, subthalamus and ventromedial thalamus. Similarly, the reticular formation includes specialized centers which are not, properly speaking, part of the activating mechanism. In this thesis, we shall be concerned with the reticular formation only insofar as it is coextensive with the activating system.

Perhaps the simplest approach to the reticular activating

system is to regard it as a kind of secondary, non-specific sensory pathway through which signals from all sensory modalities are conducted rostrally in the medial brain stem (French, Verzeano and Magoun, 1953a). All primary sensory systems send impulses into this medially situated pathway. Evoked potentials have been recorded from the reticular system following single shocks to the sciatic, splanchic and vagus nerves, and following auditory, visual, cutaneous and olfactory stimulation. These potentials are conducted slowly, as though over a multisynaptic pathway, to hypothalamic and subthalamic areas, and thence to the cortex (Starzl, Taylor and Magoun, 1951a, 1951b; Dell and Olson, 1951; Bremer and Terzuolo, 1952; French, Von Amerongen and Magoun, 1952; French, Verzeano and Magoun, 1953a).

Thus, every stimulus may initiate potentials which are conducted to the cortex simultaneously over two separate pathways: the rapidly-conducting primary sensory pathways situated in the lateral part of the brain stem, and the slowly conducting, medially-situated reticular system. Primary sensory potentials are conducted to discrete areas of the cortex, dependent on the nature of the stimulus. Reticular potentials, on the other hand, are conducted generally to all parts of the cortex, although perhaps predominantly to frontal and sensori-motor areas (Starzl, Taylor and Magoun, 1951a).

The pathways which reticular potentials follow to the cortex, when they have reached the level of basal diencephalon, are still obscure, although Starzl, Taylor and Magoun (1951a) have shown that both thalamic and extra-thalamic routes are available. So long as one

of these routes is intact, reticular potentials reach all areas of the cortex.

It is significant in this connection that the reticular system makes contact with the centers in the posterior hypothalamus which have been shown, by Murphy and Gellhorn (1945), Ingram, Knott and Wheatley (1949), and others, to exert profound effects on the electrical activity of the cortex. Also, in the thalamus, reticular potentials have been traced to the caudal and ventral borders of that area which comprises the thalamic recruiting system originally described by Morison and Dempsey (1942) and Dempsey and Morison (1942a, 1942b, 1943). Jasper and his associates (1946, 1948, 1949, 1952, 1954) have shown that this system in particular plays a fundamental role in regulating and integrating the activity of all areas of the cortex. It has been suggested that the recruiting system constitutes the thalamic relay station through which reticular effects are communicated to the cortex (Moruzzi and Magoun, 1949). Crucial evidence for this point is lacking, and in view of certain peculiar functional characteristics of the thalamic recruiting system (Jasper and Ajmone-Marsan, 1952), the current tendency to lump the two systems together conceptually as one massive, functionally homogeneous structure is perhaps unwise.

The nature of conduction through the ascending reticular system has been carefully analyzed by French, Verzeano and Magoun (1953a). They find that signals initiated by stimuli of entirely different modalities utilize the same reticular relays in their ascent

through the medial brain stem. In their experiments, responses to auditory, visual, sciatic or splanchic stimulation could be picked up from exactly the same electrode placement in the reticular system. This was not true in the lemniscal systems (i.e., the major sensory paths). Moreover, if rapidly paired stimuli of any two modalities were employed, the response to the second stimulus was occluded, which also indicates that different modalities utilize the same pathways in the reticular system. Amassian (1952) and Morruzi (1954), using microelectrode techniques, have observed single reticular units discharged equivalently by stimuli of different modalities.

Thus, the reticular system in the medial brain stem may be characterized as a diffusely connected, multisynaptic network through which sensory signals from all modalities merge and are conducted over common relays to hypothalamic, subthalamic and ventromedial thalamic areas, and thence to all parts of the cerebral cortex. The laterally situated primary sensory pathways, on the other hand, exhibit segregration of modalities and rapid conduction to discrete areas of the cortex (French, Verzeano and Magoun, 1953a).

Some light is cast on the function of this non-specific conduction system by stimulation studies: A single shock delivered directly to the reticular system of a sleeping or lightly-anesthetized animal may produce little more than a single, large evoked potential which is propagated rostrally through the medial brain stem (Starzl, Taylor and Magoun, 1951a). If, however, such shocks are presented in rapid succession, a striking change occurs in the electrical activity

of almost the entire cerebrum. The large, slow, rhythmic potential changes passing over the cortex during sleep or anesthesia are abruptly displaced by a rapid, low voltage discharge which may persist for many seconds after the termination of the stimulus (Moruzzi and Magoun, 1949; Starzl, Taylor and Magoun, 1951a; French, Von Amerongen and Magoun, 1952). This is the classic "activation pattern" of Rheinberger and Jasper (1937), so called because it is normally accompanied by arousal and behavioral activation. The head is raised, the muscles tense, the pupils dilate, there is an increase in reflex excitability, and the animal becomes more responsive generally. Microelectrode analysis indicates that during activation, the number of active units in the cortex, and the frequency with which they discharge, increases (Li and Jasper, 1953). All of these effects, normally associated with arousal from sleep, may be reproduced by direct, repetitive stimulation of the reticular system.

The results of experiments in which the brain stem is damaged indicate that the non-specific excitatory effect of peripheral stimuli is essential for the maintenance of alert wakefulness. Lesions in the hypothalamus or midbrain which interrupt the ascending reticular system but spare the primary sensory pathways produce chronic somnolence and hypokinesis (Ingram, Barris and Ranson, 1936; Ranson, 1939; Nauta, 1946; Lindsley, Bowden and Magoun, 1949; Lindsley, Schreiner, Knowles and Magoun, 1950; French and Magoun, 1952). On the other hand, large lesions in the lateral part of the brain stem, which interrupt auditory and somatic pathways but spare the reticular system, do not prevent the

animal from being aroused from sleep by auditory or somatic stimulation, nor from remaining awake and active for long periods of time (Lindsley et al, 1950).

Also, during barbiturate and ether narcosis, conduction through the reticular system is blocked, whereas the primary sensory pathways continue to function (French, Verzeano and Magoun, 1953b). Thus, the non-specific effects of peripheral stimuli, conducted through the reticular system, seem to provide the necessary background of diffuse excitation without which alert wakefulness and adaptive behavior are impossible.

It is necessary to emphasize the lack of specificity which characterizes the reticular action. During normal arousal, or following direct stimulation of the reticular system, gross changes occur in the electrical activity of the cerebrum, not only through the entire cortical mantle, but also through most of the diencephalon and mesencephalon (Starzl, Taylor and Magoun, 1951a). Gross changes also occur in the electrical activity of the rhinencephalon, although these differ somewhat in form from the changes recorded from the cortical surface (Green and Arduini, 1953). Up to this point, I have considered the reticular system as a kind of secondary sensory pathway which communicates its effects to the cerebrum and cortex, but the reticular system exerts its effects also on lower centers, in part, through reticulo-spinal relays ending both on motor neurons and on internuncial pools in the cord (Lloyd, 1941; Magoun, 1950). Here too, reticular activation is characterized by its lack of specificity: It results in

bilateral facilitation of spinal reflexes--both extensor and antagonistic flexor reflexes--and includes even the facilitation of reciprocal inhibition (Rhines and Magoun, 1946; Bach, 1950). (It should be recalled at this point that we are speaking of the functionally-defined reticular activating system, and of the brain stem reticular formation only insofar as it is co-extensive with this activating system.)

In some respects, the activating system is specific in its action. Thus, it produces dilatation of the pupil only, probably by inhibiting the oculomotor cells controlling the constrictor muscles of the iris (Moruzzi, 1954). There are other instances of this kind, but as a rule, such specific effects are adapted to a non-specific end--namely, to increase the organism's responsiveness to all peripheral stimuli.

The main source of the activity conducted through the reticular system seems to be the collateral sensory pathways in the brain stem (Starzl, Taylor and Magoun, 1951b). But the reticular system receives its "afferent" supply also from other sources, notably from the cortex itself. This has been shown by Niemer and Jimenez-Castellanos (1950), Jasper, Ajmone-Marsan and Stoll (1952), Livingston, French and Hernandez-Peon (1953) and others. Moreover, Bremer (1954) has shown that it is possible to produce generalized activation by stimulating the cortex directly, and that impulses delivered to the reticular system through corticofugal pathways excite the same relays

as do impulses delivered through brain stem collateral pathways. Thus, as Bremer has pointed out, the cortex may participate in arousal and the maintenance of wakefulness. It is in this manner, perhaps, that psychogenic insomnia and "wakefulness of choice" are to be explained (Kleitman, 1939, 1952; Bremer, 1954). It seems likely also that cortical intervention in arousal explains the powerful activating effect of stimuli which have acquired, through prior association, a strong affective tone (Jasper, Ajmone-Marsan and Stoll, 1952). However, it is quite clear that corticofugal influences on the reticular mechanism are normally incapable of maintaining wakefulness for more than a few seconds without the aid of activity delivered to the reticular system through brain stem collateral pathways. This is shown by the fact (i) that a medial mesencephalic lesion produces chronic sommolence even though primary sensory pathways to the cortex are intact (Lindsley et al, 1950), (ii) that high intensities of cortical stimulation are much less effective than weak peripheral stimuli in producing arousal (cortically induced arousal rarely lasts over 8 to 10 seconds; see below p.67), and finally (iii) that cortical stimulation does not produce activation in "cerveau isolé" preparations (see Grey Walter's comments on Bradley's work at C.I.O.M.S. symposium, 1954).

Finally, it is necessary to draw attention to the possibility that the activating mechanism is influenced by blood chemistry. We have seen that it is particularly susceptible to anesthetic agents

(French, Verzeano and Magoun, 1953b). There is also evidence that the activation produced by amphetamine is mediated by the reticular system (Bradley, 1953). Although evidence is lacking, it seems probable too that changes in blood chemistry, constituting homeostatic imbalance, influence the excitability of the reticular system. We know that thirst, hunger, bladder distension, excessive gonadal or other endocrine activity, deprivation of specific foods, and so on all may increase the level of general activity and promote wakefulness (Morgan and Stellar, 1950). It is possible that the increase in responsiveness produced by such states depends on reticular activation, either directly through the blood supply, through hypothalamo-reticular relays or through visceral afferents.

To sum up, then, influences are exerted on this system of diffusely-connected reticular relays from many sources--from collateral sensory pathways in the brain stem, both visceral and somatic; from the cortex and probably from other higher centers; and from the blood stream itself. The reticular system in turn exerts its non-specific effects on almost the entire central nervous system, increasing the responsiveness of the organism to peripheral stimuli, and supplying the background of diffuse excitation on which wakefulness and adaptive behavior depend. There are many gradations in wakefulness from deep sleep to extreme alertness (Davis, Davis, Loomis, Harvey and Hobart, 1935; Lindsley, 1952), and normally, we should expect continuous and subtle shifts in the degree of wakefulness as various external and internal influences play on the

reticular system.

These findings mean that another stimulus parameter must be introduced into psychophysiological thinking. We must consider not only the specific response elicited by the stimulus, but also its non-specific activating power. The idea is not a new one. It was frequently expressed in the old psychologies as the "theory of dynamogenesis": Every stimulus not only initiates special movements and mental processes dependent on the nature of the stimulus, but also exerts a facilitatory (or "dynamogenic") effect on nervous processes generally. William James discussed the concept at length in The Principles of Psychology, referring particularly to the work of Weir Mitchell and Lombard on the facilitation of the patellar-tendon reflex by irrelevant stimuli, and also to the work of Féré, who measured the dynamogenic effect of various stimuli on the strength of hand contraction in hysteric patients (Vol. II, pp. 379ff.). A dramatic demonstration of dynamogenesis may be obtained if a reflex is first extinguished, for then it may be restored (briefly) by introducing a completely irrelevant stimulus (Humphrey, 1933; see also Pavlov, 1927, on "disinhibition").

But the idea of dynamogenesis--of a truly non-specific excitatory effect--seems to have been mislaid in the history of recent psychophysiology. It has been supposed that a stimulus has no 'general excitatory power' apart from its power to excite certain particular neural elements dependent on the nature of the stimulus.

Our failure to realize that stimuli may have a truly non-specific excitatory effect may be attributed in part, perhaps, to the

remarkable success of the 'reflex arc doctrine'—the doctrine, so beautifully elaborated by Sherrington (1906), that the entire nervous system is a mosaic of specific reflex arcs, compounded with one another in such a way that one reflex interferes with another, reinforces a third, and so on, thus serving the "integrative activity" of the whole. The discovery of the reticular mechanism represents a new departure in psychophysiological thought. It means that, after all the cells serving specific reflexes have been parcelled out, there will remain in the reticular core of the brain stem (and perhaps the cord) a diffusely activing substratum, which serves no specific reflex but participates in all. To the principles of reflex action discovered by Sherrington and his successors, we shall have to add the principles of dynamogenic action, which we are just beginning to appreciate.

## HABITUATION AND EXTINCTION

One of the most important principles of dynamogenic action is the law of habituation: With repetition, the power of a stimulus to produce generalized activation is diminished. The clearest examples of habituation in this sense are supplied by studies of the electrical activity of the unanesthetized brain. Thus, Ectors (1936), Rheinberger and Jasper (1937), Clark and Ward (1945) and others, recording directly from the cortex of unanesthetized animals, have observed that a clap or whistle which is sufficiently intense to produce non-specific cortical activation loses this capacity when it has been repeated several times. Similarly, there is a decrement in the human alpha-blocking response to repeated stimuli (Knott and Henry, 1941), and Knott (1941) has described a case in which habituation of the alpha-blocking response persisted from one day to the next. This has been confirmed in a recent study by Popov (1953).

An experimental study of the general characteristics of habituation is reported in detail in Part II. Here, it is sufficient to say that an oft-repeated stimulus loses its capacity to excite the reticular system, although it may continue to elicit specific responses in the primary sensory areas of the cortex. This state of habituation is relatively specific to the repeated stimulus, and it may persist in part for several days, although it wears off eventually. Thus, the non-

specific activation system is especially sensitive to novelty in the sensory environment. This fact alone enables us to explain many perplexing psychological phenomena. Let us consider first some of the problems associated with extinction.

The extensive literature on the extinction of conditioned reflexes has been reviewed by Razran (1939) and Hilgard and Marquis (1940), and the extinction of unconditioned reflexes has been treated in detail by Humphrey (1933) and Harris (1943).

Extinction is often attributed to a change in the specific neural pathways mediating the stimulus-response arc. These pathways are supposed to become less responsive as a result of repeated activity. This hypothetical change in specific neural pathways is called (by Hilgard and Marquis, 1940), 'adaptation'. It must be understood that 'adaptation' does not refer to a momentary refractoriness, but to a long-lasting effect which may be established by relatively infrequent repetitions of the stimulus. Thus, it is similar in many respects to habituation, except that 'adaptation' refers to a decrement in the power to activate a specific stimulus-response arc, whereas 'habituation' refers to a decrement in the power to produce non-specific activation.

There are certain difficulties in assuming that specific stimulus-response connections are weakened by use. First, some poly-synaptic reflexes do not exhibit adaptation in this sense. The most obvious examples are the respiratory and pupillary reflexes (excepting pupillary dilatation during arousal or startle). Moreover, the opposite effect must occur at many neural junctions --namely, an

increased responsiveness, strengthening of the connection, post-tetanic potentiation (Lloyd, 1949; Eccles, 1953).

In any case, it is possible to account for most of the phenomena associated with extinction without assuming that it depends on adaptation of the specific pathways mediating the response. The response to be extinguished depends for its occurrence on (i) the specific signal from the conditioned stimulus and (ii) the background of diffuse background excitation provided by the reticular system. Moreover, in an otherwise constant and unchanging environment, the conditioned stimulus itself may help to supply the necessary background of diffuse excitation through its action on the reticular system. If, then, habituation occurs, so that the non-specific activating power of the stimulus is diminished, the response may fail to occur even though its specific connections are unchanged. This is the hypothesis. Now, let us see how it accounts for the facts.

First, it explains the intimate connection between extinction and sleep that was so frequently observed by Pavlov and his collaborators. For Pavlov, of course, extinction was a kind of "internal inhibition" and sleep was the "irradiation of inhibition". Pavlov's interpretation of extinction has long been passé, but he presents a tremendous wealth of data on the connection between extinction and sleep that have not yet been satisfactorily explained by other writers:

> The fundamental condition of the appearance and development of internal inhibition and sleep is exactly the same....In the

> case of extinction of a conditioned reflex some animals even at the first extinction showed not only a disappearance of the conditioned secretory and corresponding motor reaction but also a great dullness as compared with the normal state of the animal before extinction. Repetition of extinctions, in the course of a number of days, even if all the conditioned stimuli were reinforced in between, led in every case to an obvious drowsiness and even sleep of the animal in its stand, though no such symptoms had ever previously been observed....
>
> All our experiments abound with observations showing that internal inhibition invariably passes into sleep unless special precautions are taken. (Pavlov, 1927, pp. 252f.)

According to the hypothesis proposed here, both wakefulness and the occurrence of the conditioned response depend on the background of diffuse excitement provided by the reticular system. If the conditioned stimulus is frequently repeated without reinforcement, its dynamogenic value will be diminished, and in an otherwise constant environment this may lead to a fall in the level of diffuse background excitation below that required for the occurrence of the response. This will mean extinction first, and, if the same process is continued, sleep.

The hypothesis also accounts for what Pavlov termed "disinhibition": If an irrelevant novel stimulus is suddenly introduced into the conditioning situation, the extinguished response may be restored temporarily (Pavlov, 1927; Razran, 1939). All that is needed to restore an extinguished response is a sufficient level of diffuse background activity,

and this can be supplied by any stimulus that excites the reticular system. Thus, any exciting stimulus can produce disinhibition (provided only that it does not also have specific effects definitely incompatible with the extinguished response).

A similar effect may be obtained by administering benzedrine which, as we have seen, acts primarily on the reticular system. Thus, Skinner and Heron (1937) have shown that benzedrine slows extinction. Depressants, on the other hand, speed extinction (Razran, 1939; Hilgard and Marquis, 1940). Gellhorn (1946) has shown that insulin shock results in the recovery of extinguished reflexes, and he attributes this effect to an increased discharge in the hypothalamic portion of the non-specific activating system.

The speed of extinction seems to depend on the amount of effort or work output involved in the response. Mowrer and Jones (1943) and Solomon (1948) found that effortful responses (depressing a heavy bar, jumping a long distance) extinguished more rapidly than did a response requiring less effort. This point has been emphasized by Hull (1943) in his systematic theory of behavior. It seems likely that effortful responses require a higher level of background facilitation; hence, they should disappear first as the dynamogenic value of the conditioned stimulus diminishes. In general, responses that require a high degree of alertness extinguish more rapidly.

Thus, the theory that extinction depends on habituation of the reticular activating system explains many of the phenomena normally associated with extinction: The intimate connection between extinction

and sleep, disinhibition, the differential effects of drugs, the speed with which effortful responses are extinguished, and also, of course, spontaneous recovery and the relative efficiency of massed over distributed trials. On the other hand, the theory is not adequate to account for all extinction phenomena. As Razran (1939) and Hilgard and Marquis (1940) have clearly shown, other factors must be involved in many instances of extinction, such as the development of antagonistic conditioned responses, possibly a lasting degeneration of specific connections with disuse, and so on.

Moreover, the theory must be qualified in virtue of the findings of Prosser and Hunter (1936), who obtained extinction of spinal reflexes in rats after the cord had been transected. They observed both disinhibition and spontaneous recovery. In such cases, extinction cannot depend on habituation of the brain stem reticular system. However, it seems likely that the cord contains a diffuse network similar in nature and function to the reticular system. Magoun (1950), in fact, has suggested that the reticular system is simply a rostral extension and enlargement of collections of interneurons present throughout the intermediate grey of the cord. Normally, this diffuse network in the cord must be dominated by higher centers. This is indicated by the transient depression of spinal reflexes which follows spinal transection--"spinal shock". All reflexes are temporarily abolished, in the frog for only a few seconds, in higher animals for many hours or days (Fulton, 1949).

Sherrington (1906) suggested that spinal shock depends on the sudden withdrawal of facilitation from higher centers, and this view is now generally accepted. Moreover, spinal shock depends on transection of the ventral quadrant of the cord, that part containing the reticulo-spinal and vestibulo-spinal tracts (Fulton, Liddell, and Rioch, 1930). This is consistent with the view that the diffuse propriospinal network is dominated by the activating centers in the brain stem. Released from this domination, it may gradually take over the non-specific activating functions of the higher centers.

## THE RESPONSE TO NOVELTY

It is a matter of everyday experience that novelty in our sensory environment is exciting. In recent years, Hebb (1949) has drawn attention to the fact that the excitatory effect of novelty raises a difficult neurophysiological problem. He suggests that the specific neural processes ("phase sequences") initiated by a novel stimulus persist for a longer time than do those produced by familiar stimuli, and that, therefore, novel stimuli dominate in the control of behavior. This treatment of the problem has not seemed altogether satisfactory, however, and now an alternative hypothesis is possible—namely, that the impact of a novel stimulus depends on its dynamogenic or arousal value rather than on any specific effect which it may have. We know that when a stimulus becomes familiar its capacity to excite the reticular system is diminished. The only question is whether this is sufficient to explain the peculiar effects of novelty on the behavior of organisms.

In the first place, of course, novel stimuli—stimuli to which we have not yet become habituated—tend to keep us alert, awake and active. An unfamiliar murmur may arouse us from the deepest sleep, while a strident but familiar voice leaves us undisturbed. Almost everyone has experienced difficulty in sleeping or relaxing in a new environment, however comfortable, and even a slight rearrangement of the furniture of an otherwise familiar room may produce insomnia.

Similarly, a monotonous, unchanging environment may produce boredom, apathy, sommolence, work-decrement, motivational and intellectual deterioration (Barmack, 1937; Bartlett, 1943; Bartley and Chute, 1947; Davis, 1948; Mackworth, 1950; Broadbent, 1953; Bexton, Heron and Scott, 1954; Scott, 1954).

Novelty has the peculiar property, not only of producing generalized excitement and maintaining vigilance, but of attracting animals. When a sophisticated laboratory rat is first placed in an unfamiliar maze, it is moved to a high level of activity which gradually declines as the situation becomes more and more familiar. But this activity shows a kind of orderliness. When one part of the maze becomes familiar, the animal moves to another, as if it were positively attracted by the least familiar part of its environment (Montgomery, 1951, 1952). Similarly, if the rat is placed in a familiar field containing one novel object, it will almost invariably approach that object (Berlyne, 1950). Thus, there exists a kind of "novelty tropism"—the animal is attracted to the unfamiliar part of an otherwise familiar environment.

It is easy enough to explain the general excitatory power of novelty in terms of its dynamogenic or non-specific activating power. But is it possible in these terms to account for an actual attraction of the animal? Let us analyze a special instance: Tolman (1925) noticed that if rats are run in a T-maze, which has food in both arms, they tend to alternate systematically, running to opposite arms on successive trials. Recently, Glanzer (1953) has shown that this depends on the relative familiarity of the two arms, the rat running each time to the

most unfamiliar side. In such circumstances, the rat commonly exhibits "vicarious trial and error" behavior at the choice point (Muenzinger, 1938)—that is, it hesitates at the choice point, looking first in one direction and then in the other, as if it were in some sense sampling the alternatives before choosing. The stimuli which it experiences when it turns towards the relatively novel side should, according to our principle, produce an increment in diffuse background excitation, so that any response towards which it happens to be disposed at the time will receive additional facilitation. Thus, the animal will tend to choose the most exciting alternative—the most unfamiliar side.

This concept can be elevated into a general principle of motivation: We scan the alternatives available to us in a given stiuation. When we come to an exciting alternative, there is a generalized activation of the nervous system, and consequently, the alternative which we are then considering is apt to go over into overt behavior.

But there must not be too much activation. Excessive non-specific activation may be inconsistent with on-going cerebral processes, resulting in emotional disturbance (Hebb, 1949; Lindsley, 1951). The point is nicely illustrated by an observation of Whiting and Mowrer (1943), quoted by Berlyne (1950):

> Preliminary observations showed that if animals were placed in a maze without prior habituation, they showed considerable anxiety. This was first indicated by great cautiousness of movement and excessive urination and defecation. Later there was a great period of feverish exploration, during which animals ignored

food even though they had not eaten for 24 - 36 hours. These observations suggest that 'curiosity' is perhaps more closely related to anxiety than is ordinarily supposed.

A certain level of diffuse excitation is consistent with, and indeed, necessary for organized, adaptive behavior (Hebb, 1949). Extreme activation, however, may produce hypertension, freezing, trembling, and a powerful autonomic discharge, or perhaps, violent movements, startle, running, jumping and vocalization. These are the manifestations of fear and anxiety, and Lindsley (1951) has presented persuasive arguments that emotional responses of this type depend on excessive reticular activation.

It would be unwise, however, to oversimplify the matter. Thus, we cannot suppose simply that the more unfamiliar a stimulus is, the more likely it is to produce emotional disturbance. Hebb (1949) has shown very clearly that an unfamiliar object may have more emotional impact if it is composed of familiar elements than if it is entirely unfamiliar in every respect. He suggests that this effect depends on a disruption of habitual patterns of cortical activity. In Part II, we shall see how an unusual pattern of cortical activity may produce generalized activation through its action downwards on the reticular system.

# PART II

# METHOD

A series of twenty-four adult cats was used in these experiments. In the first four experiments, attempts were made to obtain data from acute preparations fixed in a stereotaxic instrument and anesthetized by various agents including pentobarbital sodium, diallylbarbituric acid and dibucaine hydrochloride plus D-tubocurarine chloride. The advantages of this method were that it permitted surgery and manipulation of electrodes during the course of the experiment. The disadvantages were the difficulties in maintaining just the right degree of anesthesia over a sufficiently long period of time to observe changes in the animal's responses to successive stimuli, and the possibility that even light anesthesia might alter the phenomena which were being studied. In practice, the disadvantages appeared to outweigh the advantages, and after four cats had been expended in this manner, attempts to work with acute preparations were abandoned in favor of the chronic preparations with implanted electrodes.

## Electrodes

The electrodes used for chronic implantation were similar to those devised by Delgado (1952). They were of two types (Plate I): (i) a "needle electrode" for recording from subcortical structures, and (ii) a "plate electrode" for recording from the surface of the

cortex. The needle electrodes were made of five commercially enameled stainless steel wires, 0.127 mm. in diameter, cemented together to form a needle less than 0.5 mm. in diameter. The tips of the wires were bared of insulation for 1 mm. and separated by distances of 2 - 3 mm. along the shaft of the needle. That part of the needle which extended outside of the skull was protected by polyethylene tubing and terminated in a miniature five-pin socket to which leads could be attached during the recording sessions (Milner, 1954).

The cortical electrodes consisted of polyethylene plates in which were embedded five stainless steel discs less than 0.5 mm. in diameter separated by distances of 4 - 5 mm. In all other respects, the cortical electrodes were similar to the subcortical needle electrodes.

Operative technique

Electrodes were implanted under pentobarbital sodium anasthesia with full aseptic precautions. A midline scalp incision was made which extended to a point just posterior to the occipital protruberance. Plate electrodes were introduced through a small trephined hole over the posterior suprasylvian gyrus. The dura was slit with a fine knife, and the polyethylene plate was slid into position under the dura. The electrode was then fixed to the skull by stainless steel sutures at the edge of the orifice of trephining and at the occipital protruberance (see X-ray, Plate I). Plate

electrodes were usually placed over frontal and sensori-motor areas of both hemispheres, and occasionally over the auditory areas. The usual distribution of the electrodes on the surface of the cortex is shown in the diagram of Plate I.

Needle electrodes were oriented by means of a stereotaxic instrument. They were passed through a small hole in the skull produced by a dental burr and fixed in position by a small quantity of dental cement. After the cement had become quite firm, the needle was bent so that it lay flat against the skull and was sutured to the occipital protruberance by stainless steel wire. In some experiments, this wire was brought out through the skin with the electrodes to serve as an indifferent or ground lead.

After the electrodes were fixed in place, the muscle, subcutaneous tissue and skin were sutured, leaving a small incision just posterior to the occipital protruberance through which the electrodes passed. There were rarely any signs of infection, but antibiotics were routinely administered. The animals appeared to suffer no discomfort from the electrodes, and indeed, appeared to be unaware of their presence.

In some experiments, lesions were produced in cortical and subcortical structures. The methods used in the production of such lesions depended on the nature of the experiment, and are described in the appropriate context below.

Histological technique

The cats were usually sacrificed within three weeks after the implantation of electrodes. The position of cortical electrodes was determined by inspection at autopsy. The subcortical recording points were marked by electrolytic deposit of iron and stained for iron. When the brain was normal, the involved part was sectioned on a freezing microtome and stained with cresyl violet. When surgical sectioning or removal had been done, the involved part was fixed in paraffin, sectioned, and stained for both cells and fibers. Cortical lesions were mapped grossly at autopsy, and this map was checked and corrected during the examination of serial sections. Both in the histological studies and in the stereotaxic placement of electrodes, constant reference was made to the atlas of the cat diencephalon prepared by Jasper and Ajmone-Marsan (to be published).

Recording technique

The animal was allowed at least two days to recover from the operation before recording was begun. Recording sessions took place on successive nights, usually for a period of a week or more, and each session lasted from four to ten hours.

All data were obtained by bipolar recording, the potentials being led into the usual condenser coupled (Offner Type A) amplifiers and recorded by means of a six-channel (Offner Dynograph) ink-writing apparatus. In addition, the responses were frequently monitored on a five-beam cathode-ray oscilloscope, and occasionally the oscilloscope

tracings were recorded photographically. The cat was shielded in a Faraday cage, and in some experiments it was grounded directly through the steel wire fixed to the occipital protruberance.

Activation produced in a waking animal would probably appear only as a slight increase in the frequency of the already rapid background activity. In order to observe and compare the activation patterns produced by successive stimuli, therefore, it was necessary to establish a relatively persistent and stable synchrony in the electrical activity of the brain. This proved to be the greatest single technical problem confronted during the series of experiments. It was possible, of course, to induce synchrony by anesthesia, and this method was tried with the first four (acute) preparations. The right degree of anesthesia would permit the animal to be aroused, briefly, by an afferent stimulus, but it would prevent the animal from remaining awake for long periods of time. While it was possible to obtain this degree of anesthesia momentarily, it was extremely difficult to maintain the same degree of anesthesia over a sufficiently long period of time to compare the effects of successive stimuli. In addition, of course, it was possible that anesthesia itself disrupted the delicate mechanisms being studied.

All the data reported here, consequently, were obtained during natural sleep without the aid of anesthesia or sedation. The experimenter simply waited until an appropriate degree of sleep was indicated by the electrocorticogram (Hess, Koella and Akert, 1953) before stimulating. This proved to be a workable procedure, although

it was time-consuming, tedious and inflexible. In an ideal recording session, the cat would go to sleep within an hour after having been placed in the Faraday cage, and return to sleep rapidly each time it was awakened by peripheral stimulus. Frequently, however, it happened that the cat would wake spontaneously at a critical point in the testing procedure and remain alert and active for hours. Some animals also displayed a tendency to "catnap" in the experimental situation—to alternate spontaneously between sleep and wakefulness. These difficulties could be met only by patience, by repeating the tests with more cooperative animals, or with the same animals during subsequent recording sessions.

In order to encourage sleep, the cat was fed immediately before each recording session. Its cage was draped so that it would not be disturbed by the experimenter's movements, and slight noises were masked by the constant background noise produced by the ink-writing apparatus. In some experiments, particularly when responses of auditory cortex were to be recorded, the animal was placed in a specially constructed chamber insulated on all sides by a thick layer of fiber glass, and ventilated by air forced through a fiber glass baffle. This chamber reduced the usual level of background noise by an estimated 75 per cent. It was not used generally, however, because it seemed to have no particular advantage in promoting sleep, and because the animals could not be observed while they were in the chamber.

Auditory signals were commonly used as arousal stimuli. These were delivered by means of a four inch speaker placed one to three feet

from the animal and driven through a transformer by the output of a Grass Model S4 Stimulator. The output voltage of the stimulator provided a rough measure of the intensity of the signal, and is given in decibels above one volt. Using this measure, a 500 c/sec. tone of 17 db was almost as loud as the sound produced by an average alarm clock or doorbell. Usually, low tones (100-1000 c/sec.) were used, since the response of the speaker fell off rapidly with higher frequencies. Efforts were made to take account of possible differences in the intensity or subjective loudness of different tones in the design of experiments.

In the few cases where direct intracranial stimulation was employed, the signals were generated by a Grass Model S4 Stimulator and delivered to the animal through an RF coupling output circuit.

## NORMAL EEG PATTERNS IN THE CAT

The normal EEG patterns recorded during these experiments resemble closely those reported by previous investigators for the unanesthetized cat (Rempel and Gibbs, 1936; Derbyshire, Rempel, Forbes and Lambert, 1936; Rheinberger and Jasper, 1937; Clark and Ward, 1945; Lindsley, Schreiner, Knowles and Magoun, 1950; Hess, Koella and Akert, 1953). As in man, there is a very close relation between frequency and amplitude of cortical activity and degrees of alertness. In the alert animal, all areas of the cortex exhibit rapid (20 - 40 c/sec.) waves of low voltage (50 $\mu$V). During sleep, an irregular but distinctive pattern appears which is present to some degree in all parts of the cortex but especially evident in frontal and sensori-motor areas. This consists of slow (1 - 3 c/sec.) waves of very high voltage (up to 500 $\mu$V) interspersed with some rapid activity and an occasional spindle-like burst of regular 11 - 16 c/sec., 200 - 400 $\mu$V waves.

These patterns are similar to those recorded in man during alertness and during the D-stage of sleep (Davis, Davis, Loomis, Harvey and Hobart, 1938). According to Hess, Koella and Akert (1953), patterns comparable to the deeper stages of human sleep are not seen in cats, but on a few occasions, especially on the fourth or fifth day of recording when the animal had become thoroughly accustomed to the experimental situation, we have seen patterns typical of the

E-stage of human sleep---continuous slow waves uninterrupted by spindles.

The EEG patterns of the normal cat differ most from those of the human in the intermediate stages between sleep and alertness. In the human adult, cortical activity during rest is usually characterized by a sustained regular 10 c/sec. rhythm--the Berger or alpha rhythm. In the cat, the most likely candidate for the alpha rhythm is the 5 - 7 c/sec. rhythm which, according to Clark and Ward (1945), arises in the occipital region just before the onset of sleep. Hess, Koella and Akert (1953) observed that this rhythm was unstable, however, and compared it rather with the similarly unstable 4 - 5 c/sec. pattern supposed to be characteristic of relaxation in the human infant. In the present experiments, electrodes were not placed on occipital cortex (posterior suprasylvian and marginal gyri) and long trains of 5 - 7 c/sec. waves were seldom observed.

During the transition from alertness to drowsiness, the frequency of activity gradually decreases and its amplitude increases as if the underlying neural processes were coming into phase. During this period, the frequency ranges from perhaps 8 - 15 c/sec. and the amplitude ranges from 50 to 200 $\mu$V. Such rhythms, from frontal and sensori-motor cortex at least, may be regarded as characteristic of the resting state in the cat. However, in the present experiments, sustained regular rhythms characteristic of rest but distinct from both sleep and waking activity were rare. Rather, in the stages

intermediate between sleep and wakefulness, patterns of cortical activity were inconstant and changeable.

The behavioral signs of sleep and wakefulness were most clearly associated with the activity of frontal and sensori-motor areas. The slow waves and spindle bursts characteristic of sleep appeared first in this region during the onset of sleep and were generally most marked here, in agreement with the findings of Clark and Ward (1945). The auditory areas, on the other hand, displayed a peculiar resistance to the appearance of sleep activity. These areas always displayed a relatively rapid activity, and even when slow waves and spindle bursts appeared in auditory cortex, they were more irregular and of less amplitude than those recorded from frontal and sensorimotor cortex.

It seems likely that this peculiarity in the activity of the auditory areas was due to the constant presence of background noise. Bremer (1943) has shown that afferent volleys may selectively activate auditory cortex in his encéphale isolé preparation. Thus, auditory signals may initiate short runs of high frequency, low amplitude activity which are more or less restricted to the auditory regions. In the present experiments, however, the relative "busy-ness" of the auditory areas was not reflected in a similar busy-ness of the somatic sensory areas, nor was it appreciably diminished when the animal was placed in a sound-insulated chamber which reduced background noise by approximately 75 per cent.

It is interesting, in this connection, that Dempsey and Morison (1942), Starzl and Magoun (1951) and Hanbery and Jasper (1953) have all reported that it is difficult to obtain slow wave responses from auditory cortex during stimulation of the thalamic recruiting system, although, according to Jasper (personal communication), recruiting responses may be picked up occasionally from auditory cortex if the laboratory is very quiet. Somatic sensory regions, on the other hand, commonly give good recruiting responses (Hanbery and Jasper, 1953). These findings suggest that the neural organization chiefly responsible for synchrony in cortical activity may be poorly represented in the auditory cortex of the cat.

Activation patterns

Activation patterns appeared most distinctive in frontal and sensori-motor cortex where the contrast between typical waking and sleep patterns was most marked, although activation patterns in this region were always accompanied by high-frequency, low-voltage activity in other regions from which records were taken. Activation patterns were usually associated with the behavioral signs of arousal--pupil dilatation, increase in muscle tonus and the rate of respiration, changes in posture (the animal may lift its head), and so on. The electrical activity of the cortex was assumed to provide more reliable indices of arousal than overt behavior, however, since frequently activation patterns appeared in the electrocorticogram unaccompanied

by readily visible behavioral changes.

The latency, degree and duration of activation varied greatly depending upon the nature of the stimulus, the depth of sleep and the previous experience of the animal. The more intense a stimulus, the more efficient it was in arousing the animal. Oddly enough, however, intensity was not the most important parameter in determining the arousal value of a stimulus. The arousal mechanism tended to be more sensitive to the noise content, irregularity or degree of change involved in a stimulus than to its intensity. Thus, in all preparations, a modulated tone (a sound which changed in pitch) was more effective in producing arousal than a pure tone of the same or greater intensity. The importance of variation in the afferent signal was frequently demonstrated, too, when the animal was aroused from a deep sleep by slight irregular noises superimposed on the constant background noise—the sound of a dropping pencil, the crinkle of a cellophane cigarette wrapper, the jingle of the watchman's keys in the corridor (see also Clark and Ward, 1945).

Precise measurements of the latency and duration of activation patterns could not be obtained, since it was impossible to determine the exact points at which activation began and ended. Usually, activation patterns began within 0.5 seconds after the onset of the stimulus, the minimum latency being about 0.1 seconds. However, the latency varied greatly, and in some cases, activation patterns might appear on the cortex as long as ten seconds after the termination of a brief arousal stimulus. Such remarkably long

latencies were difficult to interpret. That they were not dependent upon a coincidental association between spontaneous arousal patterns and stimuli was indicated by two facts: (i) they usually occurred only after the animal had become thoroughly habituated to the stimulus, and (ii) they frequently occurred when the electrocorticogram exhibited consistent sleep patterns for many minutes preceding the presentation of the stimulus.

In three cats, records were taken simultaneously from cortical and subcortical structures. In general, potentials led from diencephalic electrodes were not strikingly different from those recorded on the surface of the cortex. In the alert waking state, both mesial thalamus and posterior hypothalamus exhibited rapid, low-voltage activity, and during sleep, the same regions displayed trains of slow, large amplitude waves. Spindle bursts were rarely recorded from the posterior hypothalamus. They were occasionally picked up from thalamic leads, and then tended to occur synchronously with cortical spindles, but there was by no means a one-to-one correspondence (Spiegel, 1936, 1949; Morison and Dempsey, 1942; Jasper, 1949; Lindsley, Bowden and Magoun, 1949; Hess, Koella and Akert, 1953).

Considerable interest attaches to the activity of mesial thalamus and posterior hypothalamus during arousal, since these regions are supposed to be involved in the non-specific activating mechanism. Starzl, Taylor and Magoun (1951a, 1951b), Gellhorn and Ballin (1946) and others have observed desynchronization in the electrical activity

of these regions following peripheral or direct stimulation of the brain stem activating system. In the present experiment, too, diencephalic activation patterns occurred during arousal which resembled those simultaneously picked up from surface electrodes.

In one cat, needle electrodes were placed bilaterally in the mesencephalon at the level of the IIId nerve nucleus (see diagram, Plate II). Here also, slow waves could be recorded during sleep, and there was some flattening during arousal. However, the contrast between sleep and waking patterns was not as marked as in the diencephalon and cortex. In some placements (e.g., R2 and R5, Plate 2), slow waves tended to persist through waking periods. In others (L2 and L4, L3 and L5), the record was dominated by regular, relatively high-frequency rhythms even during sleep. Because of the circumstances of recording, it was not possible to determine the exact anatomical origin of these patterns.

## HABITUATION

The findings of Ectors (1936), Rheinberger and Jasper (1937), Knott and Henry (1941), Clark and Ward (1945), Popov (1953) and others that stimuli lose their power to elicit cortical activation on repetition was confirmed many times during the present experiments. Moreover, this was true not only of cortical activation but also of activation in the medial brain stem. Wherever arousal was accompanied by flattening in the electrical activity of the brain, whether in cortex, diencephalon or mesencephalon, this flattening ceased to occur when the animal had become accustomed to the stimulus.

In this section, we present data on habituation of the activation reaction in normal animals. Most of the data were obtained from cats in which only cortical electrodes had been implanted, but in the three cats in which subcortical electrodes were also implanted, cortical activation and activation of the medial brain stem were closely associated and seemed to depend on the same factors. Before describing the general characteristics of the phenomenon, it may be useful to present in some detail the results of a typical recording session. Plate III shows sample tracings from a recording session during which a normal cat became completely habituated to a 500 c/sec. tone. The conventions used in displaying tracings in this and subsequent illustrations and some of the details of the experimental method will be clarified in the following abbreviated protocol:

Cat P54-80

Operation: 2-25-54. Pentobarbital sodium (i.v.) anesthesia. Cortical electrodes placed over frontal (g. proreus), motor (presigmoid g.), sensory (postsigmoid g.) and association (ant. suprasylvian g.) cortex of both hemispheres. Animal recovers rapidly without ill effects.

1st Recording Session (Plate III): 2-27-54. After being fed warm milk, cat with leads attached is placed in draped cage. Electrodes are tested and recording begins about 8 P.M. During first hour, cat is restless, moves frequently, washes, etc., and during this period, all channels show very rapid activity with many movement artifacts. By 9:30 the cat has settled down, and occasional slow waves and spindles appear in electrocorticogram. A consistent sleep pattern lasting for many minutes does not appear until about 10:30.

The first stimulus, an intense (16 db) 500 c/sec. tone of about 3 second duration, is presented at 10:45. This arouses the animal, producing runs of activation in all channels which last slightly over 3 minutes (1st tracing). Atypically, the first stimulus fails to produce overt movements.

As soon as sleep patterns have returned to the electrocorticogram, the 500 c/sec. tone is repeated, and so on for many trials. The duration of activation patterns progressively decreases, rapidly during the first ten trials and slowly and irregularly thereafter. Table I gives the estimated duration and latency of the activation

TABLE 1

Effects of successive presentations of a 500 c/sec. tone. Time in seconds.

| Duration of Activation | Latency of Activation | Time since Last Stimulus |
|---|---|---|
| 192 | 0.2 | 0 |
| 100 | 0.2 | 220 |
| 210 | 0.2 | 337 |
| 30 | 0.2 | 262 |
| 15 | 0.5 | 112 |
| 19 | 0.5 | 90 |
| 5 | 0.5 | 69 |
| 75 | 0.7 | 115 |
| 12 | 0.7 | 182 |
| 7 | 2.0 | 32 |

TABLE 2

Speed of habituation

| | |
|---|---|
| Relay click . . . . . | 6 trials |
| Hand clap . . . . . | 10 trials |
| 100 c/sec. tone (2.5 sec., 17 db) . . . . . | 12 trials |
| 500 c/sec. tone (3 sec., 16 db) . . . . . | 30 trials |
| Sharp tug on fur of hind leg . . . . . | 40 trials |
| Modulated tone (500 - 1000c/sec., 12 db) .. | 60 trials |

patterns produced by the first ten stimuli, together with the time elapsing between successive stimuli.

During the period from 10:45 to 12:00, the stimulus is repeated 35 times. By the 30th trial, the animal has become more or less completely habituated to the 500 c/sec. tone, and subsequent presentations of this tone produce little or no alteration in the electrocorticogram (2nd tracing). After several repetitions of the 500 c/sec. tone fail to produce activation, a new tone (100 c/sec.) is presented. The animal is immediately aroused and remains awake for over a minute (3rd tracing). When sleep patterns have returned to the electrocorticogram, the familiar 500 c/sec. tone is repeated several times and consistently fails to produce arousal (4th tracing). On the 43rd trial, another novel stimulus--a 1000 c/sec. tone--is presented. This too arouses the animal, producing a run of activation which lasts well over 30 seconds (5th tracing). Several subsequent presentations of the familiar 500 c/sec. stimulus fail to produce activation, and the recording session ends.

General characteristics of habituation

During the habituatory process, three changes occurred in the activation patterns elicited by successive stimuli: (i) The most reliable change was a progressive decrease in the duration of activation. In all preparations, the period of activation decreased rapidly at first and then more slowly. The change did not occur with perfect regularity, of course, and occasionally after an animal had become almost completely

habituated to a stimulus, the next repetition of the stimulus for no apparent reason produced an activation pattern which lasted several minutes. (ii) As the stimulus was repeated, the time elapsing between the onset of the stimulus and the beginning of the activation pattern increased. Unlike the change in duration of activation, this increase in latency tended to occur slowly at first and then more rapidly. It seldom occurred in a very regular fashion, however, and sometimes when habituation had been partially established, alternate stimuli produced brief activation responses which differed in latency by several seconds. (iii) With the development of habituation, slow, large-amplitude waves tended to encroach on the activation pattern, so that the apparent flattening of the electrocorticogram became less marked with successive stimuli. Of these three changes, the decrease in duration of activation seemed to be most reliable and was commonly used as an index of habituation.

The number of trials required to establish complete habituation--i.e., a state such that the stimulus fails completely to produce cortical activation--varied greatly and depended upon many factors: the intensity, duration and nature of the stimulus, the rate of stimulation, the depth of sleep and previous experience of the animal, and so on. It was impossible to control all of these factors in any one experiment, so that reliable data on the speed of habituation could not be obtained, but some idea of the range of magnitudes encountered during these experiments may be acquired from Table 2 which shows the number of trials required in

various experiments to establish more or less complete habituation. The values given in this table were obtained from different experiments, usually with different cats, different average intertrial intervals, and different and varying depths of sleep, so that they are hardly comparable and cannot be regarded as norms.

It seemed quite clear that habituation required fewer trials during deep sleep. The depth of sleep was beyond the experimenter's control and frequently varied during a single recording session. When a stimulus lost its effectiveness in producing arousal, therefore, it was necessary to make sure that this was not due simply to the animal falling more deeply asleep. This difficulty was met by three controls: (i) The electrocorticogram provided some indication of sleep. (ii) Stimuli were commonly used which were sufficiently intense to arouse the animal on their first occurrence regardless of the depth of sleep. This use of intense stimuli retarded habituation considerably, but if such a stimulus ceased entirely to produce arousal, one could be sure that the loss of responsiveness was due to repetition of the stimulus. (iii) Finally, if a novel stimulus of equal or less intensity aroused the animal after it had ceased to respond to a familiar stimulus, the effect could not be ascribed to an increased depth of sleep.

One of the most remarkable properties of the habituatory process was its specificity. There was, of course, some generalization of habituation along the pitch continuum. Thus, if habituation to a 500 c/sec. tone had been established, a 600 c/sec. tone would not be very effective in producing arousal, but invariably in these experi-

ments, when an animal had become completely habituated to a 500 c/sec. tone, it could still be aroused by a 100 or 1000 c/sec. tone and vice versa. This specificity of habituation must be taken into account in consideration of the physiological mechanisms underlying the process. Thus, it clearly rules out the possibility that habituation depends on a generalized fatiguing of the activating system.

Duration of habituation

In the protocol given above, after the cat had been more or less completely habituated to a 500 c/sec. tone, it was awakened for a brief period by a novel stimulus (100 c/sec. tone), and yet when it returned to sleep, the 500 c/sec. tone still failed to elicit activation. This capacity of habituation to persist through a brief waking period was observed in most experiments, and suggested that the state of habituation was not a dynamic affair dependent upon the maintenance of some delicate pattern of reverberatory activity but rather a relatively stable state which was not easily disrupted by gross changes in neural activity.

Whatever the nature of the state of unresponsiveness established by our procedure, it dissipated rapidly in time. Thus, if a quarter of an hour or so were allowed to elapse without stimulation, the next repetition of the familiar stimulus usually elicited an activation pattern. But then complete habituation could usually be reestablished in a few trials, indicating that it had not been dissipated entirely. It was not possible to obtain precise quantitative data on the rate of

decay of habituation, but it seems likely that, in common with other biological processes involving loss of responsiveness with repeated stimulation, habituation decays exponentially in time (Harris, 1943).

Knott (1941) and Popov (1953) in studying habituation of the alpha-blocking response in humans observed some persistence of the effect from one day to the next. In the present series of experiments too, the animal frequently seemed to be less responsive and habituated more rapidly to tones which it had experienced many times in previous recording sessions. It was not always possible to tell, however, whether this indicated a genuine day-to-day persistence of the habituation to a specific tone established in previous recording sessions, or whether it indicated merely a general loss of responsiveness as the animal became accustomed to the experimental situation. In order to get a clean demonstration of the day-to-day persistence of habituation to a specific tone, therefore, the following experiment was performed:

A speaker was attached to the home cage of a normal, unoperated cat. By means of a programming device, a 500 c/sec. tone (about 2sec., 17 db) was sounded every quarter of an hour for about ten days (probably much longer than was needed). Then electrodes were implanted and, before testing, <u>two days were allowed to elapse during which the cat was not exposed to the stimulus</u>. The results are shown in Plate IV: The first occurrence of the familiar 500 c/sec. tone after the two-day rest period produced a rather poorly differentiated activation pattern lasting not

over 15 seconds (1st tracing). The first occurrence of a novel 100 c/sec. tone, on the other hand, awakened the animal completely, producing a run of activation which lasted over 15 minutes (2nd tracing). Normally, a 500 c/sec. tone is slightly more effective in producing arousal than a 100 c/sec. tone--certainly not less so.

During the remainder of the recording session, these two tones were presented more or less in alternation until the animal had become completely habituated to both. During the first eight trials, the 100 c/sec. tone was clearly more effective in producing arousal than the familiar 500 c/sec. tone (the duration of the activation patterns produced by the first eight stimuli is shown graphically in Plate IV). But with repetition, the 100 c/sec. tone rapidly lost its initial advantage, and this advantage was never recovered either in this or subsequent recording sessions. The habituation, having once been generalized to include the 100 c/sec. tone, remained general throughout the experiment. It was clearly demonstrated, however, that habituation to a specific tone could persist at least in part through a two-day rest period.

## ROLE OF THE PRIMARY SENSORY SYSTEM IN HABITUATION

Thus, we see that after being repeated many times, a loud tone may lose its power to produce non-specific activation both in the cortex and brain stem, that the state of habituation so established is relatively specific to the repeated tone, and that it persists in part for several days. Our next task is to investigate the physiological mechanisms subserving the phenomenon. In this section, we consider the possibility that habituation depends on special properties of the primary sensory system.

It is possible that habituation depends on the establishment of a block in the primary sensory pathways. It may be that signals entering the sensory pathways of the brain stem are edited somehow, so that familiar signals are damped or inhibited before they reach either the arousal mechanism or higher auditory centers. If this were so, we should expect that a stimulus to which the animal had become habituated would fail to produce evoked potentials in the primary sensory areas of the cortex.

The hypothesis seems <u>a priori</u> unlikely, since it is possible to record evoked potentials from primary sensory cortex even under deep anesthesia. Nevertheless, as Adrian has suggested, anesthesia may disrupt the functioning of the damping or inhibiting mechanism responsible for the sensory block, supposing that it exists. Thus,

> We know that in very deep anaesthesia sensory signals can

> still enter the cortical receiving areas. Marshall and Bard's localising studies depend on this, and the block, as Bremer has pointed out, comes somewhere beyond the afferent endings in the cortex. Yet it is conceivable that the deep anaesthesia has suppressed an inhibitory activity which would check some or all of the signals at a lower level if it were operative (Adrian, 1954).

In order to test this hypothesis, therefore, an attempt was made to record the primary responses of the auditory cortex in unanesthetized animals.

In no case was it possible to record a distinctive primary response of auditory cortex to tones. The primary response may have been obscured by the normal background activity of the auditory regions, or electrodes may never have been placed in maximally responsive zones. Short latency responses to clicks could be picked up from auditory cortex, but it was not always possible to distinguish the primary response to an isolated click from normal background activity. In order to overcome these difficulties, a series of clicks (5/sec., for about 2.5 seconds) was used as the arousal stimulus, and the responses were both recorded by an ink-writer and visualized on an oscilloscope whose sweep was triggered synchronously with each click. The results are shown in Plate V. Not only did the stimulus continue to produce evoked potentials in auditory cortex after it had lost its power to produce generalized arousal, but these potentials tended to be even larger when they occurred against a background of slow waves. Clearly, if these results are generally valid, habituation of the activation reaction does not depend on the establishment of a block in the primary sensory pathways.

Destruction of auditory cortex

The auditory cortex continues to respond to stimuli to which the animal has become completely habituated. This does not rule out the possibility, however, that auditory cortex or other higher auditory centers play an essential role in habituation to sound.

Niemer and Jimenez-Castellanos (1950), Jasper, Ajmone-Marsan, Stoll (1952), Livingston, French and Hernandez-Peon (1953) and others have demonstrated rich corticofugal projections to the reticular activating system, so that cortical activity may exert a profound influence on the reticular mechanism. Moreover, the speed of conduction in the reticular system is so slow that a specific afferent stimulus may send an impulse to the rostral portions of the reticular system indirectly through corticofugal fibers in less time than it takes for the signal to ascend the multisynaptic pathways of the medial brain stem. According to French, Verzeano and Magoun (1953a), in monkey there may be a difference of as much as 3 to 6 msec. between the arrival of a specific potential at the auditory cortex and the arrival of a non-specific potential at the midline thalamic nuclei (see also Ingvar and Hunter on evoked visual potentials, 1953).

The possibility must be considered that the corticofugal impulses are chiefly inhibitory--that the auditory cortex functions as a negative feed-back mechanism, blocking the response of the reticular system to frequently repeated sounds.

In order to test this hypothesis and study the role of primary cortical receiving areas in habituation generally, auditory areas I and II were destroyed bilaterally in two cats. In a single operation,

auditory cortex on both sides was aspirated through a glass pipette. The extent of the lesions is shown in Plate VI. They included all of the areas previously shown to be electrically excitable by auditory stimulation (Bremer and Dow, 1939; Ades, 1941, 1942; Woolsey and Walzl, 1942; Mickle and Ades, 1952, 1953). In one cat (P53-297), the lesions included also most of the suprasylvian gyrus. To allow time for thalamic degeneration, electrodes were not implanted until at least a month after the operation. Subsequent histological studies showed that the medial geniculate bodies of both cats had almost completely degenerated.

During testing, both cats showed habituation to specific tones. The results for cat P53-297 are particularly interesting, since this animal was also tested for the day-to-day persistence of habituation. The procedure was essentially the same as that described in the preceding section: the animal was exposed to a 500 c/sec. tone (about 2 sec., 17 db.) every quarter of an hour for about ten days, electrodes were implanted, two days were allowed to elapse during which the cat was not exposed to the stimulus, and then testing was begun.

The results are shown in Plate VII. In the first few trials after the two-day rest period, a novel 100 c/sec. tone was clearly more effective in producing cortical activation than the familiar 500 c/sec. tone. As in the case of the normal cat, however, the 100 c/sec. tone lost its initial advantage in a few trials.

In the course of this and subsequent recording sessions, the habituation became generalized to include all tones from 100 to 900 c/sec.,

but then, as Plate VIII shows (1st tracing), a 5000 c/sec. tone presented for the first time produced an effective run of activation pattern. After about twenty repetitions, the 5000 c/sec. tone also ceased to elicit arousal (2nd tracing). Then, after the animal had become habituated to the 5000 c/sec. tone and also to all tones between 100 and 900 c/sec., a novel 2000 c/sec. tone produced arousal (3rd tracing).

Clearly, auditory cortex plays no essential role, as a negative feed-back mechanism or otherwise, in habituation to specific tones. Granting this, we may still ask whether damage to this structure does not alter the quantitative parameters of habituation. The experimenter's impression was that the two cats lacking auditory cortex were less activated by sound initially, that they became habituated to specific tones in fewer trials, and that the habituation generalized more rapidly. Thus, cat P53-296 became habituated to a 500 c/sec. tone for the first time in about 10 trials, whereas a normal cat (P54-80) required almost 30 trials to become habituated to the same stimulus. These observations of difference in degree cannot be regarded as reliable, however, because of the small number of subjects, lack of control of such factors as depth of sleep, and the large amount of individual variation. Nevertheless, it was clear that if there was any difference in degree, it was in the direction of less initial sensitivity to sounds and more rapid habituation for animals without auditory cortex.

Inferior colliculus and lateral lemniscus

The inferior colliculus is as important an auditory center, in

some species at least, as auditory cortex. It is enormously developed in the bat in which audition has evolved into a direction-finding sense (Kappers, Huber and Crosby, 1936). Moreover, the inferior colliculi may exert a powerful influence on the activity of the reticular mechanism through the superior colliculi and tectobulbar tracts. Thus, it may be that this structure plays an essential role in habituation to sounds--perhaps as a negative feed-back mechanism in the sense previously described.

One cat whose brain stem had been experimentally damaged over a year previous to the present experiment was studied. The inferior colliculi of both sides had been partially removed by suction after the occipital pole of the cortex had been retracted and the tentorium partly destroyed. The animal was otherwise intact and had received no experimental training either before or after the operation. After electrodes had been implanted, the animal was tested and proved to be no different from a normal cat in its capacity to become habituated to specific tones. Subsequent histological studies indicated, however, that the damage to the inferior colliculi was not very severe, so that the experiment could not be regarded as crucial.

However, it is possible by sectioning the lateral lemnisci just before they enter the inferior colliculi to functionally deafferent all higher auditory centers--inferior colliculi, medial geniculate bodies and auditory cortex. In this way, the possibility that any higher center plays an essential role in habituation to specific tones--as a negative feed-back mechanism or otherwise--may be tested.

An attempt was made to section the lateral lemnisci bilaterally in four cats. The lesions were produced by passing high-frequency current (500 kc.) through electrodes which had been introduced in the brain through the posterior fossa and oriented along the horizontal plane (H - 2) of the stereotaxic instrument (Plate IX). In order to produce sufficiently large lesions (up to 18 cubic mm.), 8 successive coagulating currents (12 - 15 mA. for 120 sec.) were passed at different sites throughout the region to be destroyed.

Cortical electrodes were implanted during the same operation, and the animal was tested after the usual two-day recovery period. Before each animal was sacrificed, a terminal experiment was run in an effort to determine whether the operation had actually succeeded in functionally deafferenting higher auditory centers. During this terminal experiment, the exposed cortex of the anesthetized animal was thoroughly searched for evoked potentials to clicks.

Three of the four preparations were failures, because of excessive damage to the brain stem resulting in somnolence or death, or incomplete severance of the lemnisci. The fourth was reasonably successful. In this cat (P53-434), the lateral lemniscus was entirely severed on the left side. On the right side, histological examination of the brain stem indicated that perhaps a few fibers passing directly into the brachium of the inferior collicus had been missed. A cross-section of this cat's brain is shown in Plate IX. In the terminal experiment, no evoked potentials could be picked up from the left hemisphere, and only a small focus of electrically excitable tissue

could be found on the right hemisphere. Here, the evoked potentials were weak and unstable, and were lost when the exploring electrodes were moved slightly from the critical zone. It seemed unlikely that the few fibers remaining intact could have been functionally significant.

The waking cat failed to flinch or exhibit any overt signs of having heard a loud clap presented just behind it. Nevertheless, it could be aroused from sleep by a loud sound. This confirms and extends the findings of Lindsley, Schreiner, Knowles and Magoun (1950) who were able to arouse animals by auditory stimulation after the brachium of the inferior colliculus had been sectioned bilaterally. In our experiment, not only the cortex and thalamus but also the tectum was deprived of specific auditory input, so that activation must have been mediated by collateral pathways entering the reticular substance from lower brain stem nuclei---the nucleus of the lateral lemniscus, the superior olive or dorsal cochlear nucleus (see Plate XV).

Moreover, the animal was capable of habituating to specific tones. This is shown in Plate X. A loud 100 c/sec. tone (20 db., 3 seconds) produced a short run of activation on its first occurrence (1st tracing), but within 5 trials the animal had ceased to respond to it (2nd tracing). Then, a novel 500 c/sec. tone could still produce flattening in the electrocorticogram (3rd tracing).

Because of the animal's initial lack of sensitivity to pure tones, this was not a very dramatic example of habituation. In order to get a more effective example, a modulated tone---a sound which

gradually changed in pitch from 600 to 1000 c/sec. during a 5 second period--was used in a subsequent recording session. As Plate XI shows, the first presentation of this stimulus produced a run of activation lasting over a minute and a half and accompanied by movements. The animal became completely habituated to this stimulus in about a dozen trials (2nd tracing), and then a different modulated tone (500 - 100 c/sec.) produced an activation pattern lasting over a minute (3rd tracing). After several repetitions of these stimuli (500 - 100 and 600 - 1000 c/sec.), the habituation generalized to include all sounds from 100 to 1000 c/sec. (4th tracing), but then another novel signal (10,000 - 4000 c/sec.) could still arouse the animal (5th tracing).

Thus, even after acoustic tectum, thalamus and cortex had been almost completely deprived of sensory input, the animal could still become habituated to specific stimuli. Evidently, higher auditory centers play no essential role in habituation to sound.

Taken in conjunction with other findings, our results mean that the entire forebrain, including thalamus, basal ganglia and cortex plays no essential role in habituation to sound. To see why this conclusion is justified, we must consider the nature of conduction in the reticular system, for in the absence of specific auditory pathways, any auditory signal reaching the forebrain must be transmitted through the reticular core of the brain stem. But, as we have seen, according to the work of French, Verzeano and Magoun (1953), French, Von Amerongen and Magoun (1952) and others, signals conducted forward

in the reticular system lose their identity. Conduction is non-specific in this system, and signals from different modalities utilize common relays. It follows that when the auditory receptor is excited in an animal lacking specific auditory pathways, no forebrain center is apprised of the nature of the stimulus. Hence, in such an animal, any discrimination between different tones (e.g., between a novel 500 and a familiar 100 c/sec. tone) must occur entirely in lower brain stem centers. Thus, neither higher auditory centers nor any forebrain center plays an essential role--as a negative feed-back mechanism or otherwise--in habituation to specific tones.

It remains possible that higher auditory centers <u>normally</u> function as negative feed-back mechanisms, inhibiting the response of the reticular system to familiar signals, but that there are alternative centers in the lower brain stem which take over the functions of the higher centers when the latter have been destroyed or deprived of sensory input. This is contra-indicated by the fact that the initial excitatory power of stimuli is reduced and habituation occurs more rapidly when higher auditory centers are damaged or deafferented. Thus, whereas a normal cat required 30 trials to become habituated to a 500 c/sec. tone, an animal whose auditory cortex had been destroyed required only 10 trials. A normal cat required 12 trials to become habituated to a 100 c/sec. tone, and the cat in which the lateral lemnisci had been severed required only 5 trials. For a modulated tone, almost 60 trials were required for a normal cat, against 12 for

the cat with lateral lemnisci sectioned. These are sample values, and cannot be regarded as norms. Still, the differences are very great and are probably significant. It appears that the main contribution of auditory cortex and tectum to the activating system must be excitatory rather than inhibitory.

Habituation and conditioned auditory reflexes

Our results on the role of higher centers in habituation must be considered and evaluated in connection with studies of conditioned auditory reflexes. No doubt, conditioning and habituation are closely related, but it does not follow that the two processes are identical. Indeed, habituation seems to be more closely related to the loss than to the acquisition of conditioned responses (see PartI). Since conditioning and habituation are not identical, it is conceivable that damage to some part of the brain might affect the two processes differently.

Bilateral destruction of auditory areas I and II in monkey (Evarts, 1952) and dog (Allen, 1945), and complete ablation of electrically excitable auditory cortex in cat (Diamond and Neff, 1953), does not prevent animals from acquiring conditioned differential responses to tones. Until the present study, there existed no comparable data on habituation to tones, and it seemed possible that auditory cortex might play an essential role in habituation--perhaps as a negative feedback mechanism--even though it was not necessary for the acquisition of specific conditioned responses. Our data show that this is not so, that

habituation to specific tones like the acquisition of differential conditioned responses to tones does not depend on the integrity of auditory cortex.

However, this conclusion must be qualified in the light of the findings of Meyer and Woolsey (1952). These authors report that if somatic area II is bilaterally destroyed in addition to auditory areas I and II in the cat, pitch discrimination is permanently lost (see also Allen, 1945). It is difficult to reconcile this study with that of Diamond and Neff. Unfortunately, in our experiments, somatic area II was not destroyed. At present, all we can say is that it seems hardly likely that the additional removal of somatic area II would prevent animals from becoming habituated to specific tones, since bilateral severance of the lateral lemnisci had no such effect.

At this point, we might ask how much reliance we should put on evidence from one cat. In the author's opinion, the results from one cat would be perfectly sufficient to establish the existence of habituation to specific tones below the level of the inferior colliculi if the lateral lemnisci had really been completely sectioned. Unfortunately, a remnant of the lateral lemniscus on one side was left intact, and although it is highly probable, we cannot be absolutely certain that the results would have been the same had the few remaining fibers also been interrupted.

Apparently, no data exist on conditioned pitch discrimination in animals in which brain stem auditory centers have been damaged. There have been a few studies of conditioned auditory reflexes after

brain stem damage in which the animals were not required to discriminate pitch but simply to respond to a tone by an avoidance reaction--running forward in a rotatable cage to avoid shock (Kryter and Ades, 1943; Raab and Ades, 1946). In these studies, if either inferior colliculi or auditory cortex remained functional, a normal conditioned response could be established. If the lateral lemnisci were sectioned so that the auditory system was intact only below the inferior colliculi, a conditioned response could still be established, but it was quite abnormal:

> The post-operative CR consisted in first raising or turning head and neck with onset of the tone and then, after a short delay, advancing the body in a kind of sliding movement. The whole behavior was hesitant, uncertain, imperfectly integrated as though the animal did not understand the significance of the tone (Kryter and Ades, 1943).

This suggests that the tone produced a kind of conditioned non-specific activation rather than a specific response. The movements are those which might easily accompany non-specific activation in a rotatable cage. It was as if the animal had been generally excited by something, without being capable of appreciating the nature of the exciting stimulus. This phenomenon appears to be the opposite of habituation: In virtue of being associated with a shock, the tone <u>acquires</u> non-specific activating power rather than losing it. Evidently both effects can occur even though higher auditory centers are deprived of sensory input.

## CORTICALLY INDUCED ACTIVATION

In this section, we shall see: (i) how excitatory cortico-fugal pathways to the activating mechanism may contribute to the specificity of habituation, particularly as regards the pattern or organization of the stimulus, and (ii) how an animal may become habituated to a stimulus applied directly to the cortex just as it becomes habituated to peripheral stimuli.

### Habituation to patterns

As we have seen, after many trials, a cat may become completely habituated to a modulated tone--e.g., a sound which gradually rises in pitch from 500 to 1000 c/sec. Now, holding the intensity and duration constant, it is possible to modify this stimulus in either of two ways: (i) We can change the frequency range which it covers, for example, from 500 - 1000 to 100 - 500 c/sec. Since habituation is tone-specific, the modified stimulus will arouse the animal. (ii) Without changing the tonal elements, we can alter the pattern of the stimulus, rearranging these elements in a different order. Thus, instead of using a sound which rises in pitch from 500 to 1000 c/sec., we can use one which falls in pitch from 1000 to 500 c/sec. This will not be as effective in arousing the animal as changing the frequency range, but it may produce a short run of activation. Plate XII shows the results of applying this procedure to a normal cat (1st and 2nd

tracings), and to the cat with lateral lemniscus sectioned (3rd and 4th tracings). In each experiment, the procedure was repeated several times with consistent results. The normal cat could be awakened by changing the pattern of the stimulus; the cat with lateral lemniscus sectioned could not. Evidently, pattern-specific habituation depends on the integrity of higher auditory centers. (It seems likely that the effect depends on the cortex; cf. Diamond and Neff (1953). Two additional cats with auditory cortex bilaterally destroyed were prepared especially to test this hypothesis, but the results were equivocal.)

These results do <u>not</u> mean that animals cannot become habituated to a patterned stimulus if higher auditory centers are deprived of sensory input. Indeed, such animals become habituated more rapidly than do normal animals. Rather, our results mean that habituation is less specific when higher centers are deprived of sensory input, and in particular, that it is not specific to the pattern or organization of the stimulus. There may also be some loss of specificity to tones, but if so, our experiments indicate that it is minor.

In the light of our previous findings, it is not difficult to see how this loss of specificity is to be explained: When the receptor organ of the intact animal is stimulated, excitatory impulses converge on the activating system from two sources: (i) Some are transmitted to the activating system directly through collateral pathways in the lower brain stem. (ii) Others are

transmitted to the cortex and tectum through primary sensory pathways, elaborated and modified in the complicated circuitry of these higher centers, and then relayed back to the activating mechanism.

Now, consider the effect of two sounds that differ only in pattern. The slight difference between the signals produced by these two sounds may be practically obliterated in the relatively crude brain stem collateral pathways. At the same time, this difference may be amplified and elaborated in cortical and collicular circuits. Thus, if higher centers have been deprived of sensory input, the signals sent to the activating system may be indistinguishable: habituation to one stimulus is pari passu habituation to the other. On the other hand, in the intact animal, some of the signals sent to the activating mechanism come from the cortex, and the differences between these may be magnified rather than obliterated. Thus, after the intact animal has become completely habituated to one sound, the other may still produce arousal through corticofugal pathways.

Habituation to cortical stimulation

Bremer (1954) has shown that brief "faradic" stimulation of the cortex may produce non-specific cortical activation in the encéphale isolé preparation. The effect cannot depend on proprioceptive feed-back from induced movements, since the spinal cord is sectioned in the encéphale isolé preparation. Nor can it depend on spread through cortico-cortical pathways, since, according to Bremer, stimulation of the cortex of one hemisphere may produce generalized activation of the

opposite hemisphere after section of the corpus callosum. Although crucial evidence is lacking, there is general agreement that the effect depends on pathways leading from cortex to brain stem activating system and thence back to the cortex.

Plate XIII (1st tracing) shows an activation pattern produced in a sleeping animal by direct stimulation of the cortex through implanted electrodes. The record was taken from sensori-motor cortex of the hemisphere opposite to the one stimulated. In this experiment, it was necessary to use a rather intense stimulus (7 volts), but no induced movements were observed. The activation patterns elicited by direct cortical stimulation were relatively brief compared with those produced by peripheral stimuli, but they usually outlasted the stimulus by 8 or 10 seconds—at least initially. With repetition of the stimulus, the activation patterns decreased in duration and increased in latency (2nd tracing), and after about 12 trials, the stimulus ceased to produce activation altogether (3rd tracing). A peripheral stimulus presented after the animal had ceased to respond to the cortical stimulus could still elicit arousal, and if the cortical stimulus were withheld for 20 minutes or so, it regained some of its potency. Thus, in all respects, habituation to a stimulus applied directly to the cortex resembled habituation to peripheral stimuli.

It is intriguing to consider the significance of habituation to stimuli applied directly to the cortex in connection with our everyday experience. It sometimes happens that during a state of drowsy reverie

or reminiscence, a new and intriguing idea occurs to us, or an old idea is cast in a new light. As a result, we may be immediately roused from our reverie, the nervous system is alerted, the muscles tense, and the mind spins with activity. Yet, the idea if it occurs to us subsequently, after we have considered its every aspect and explored all its ramifications, may have no more effect than any other fleeting and momentary thought. If thought can be reduced to activity reverberating in thalamo-cortical circuits, it may well be that such effects are explained by the sensitivity of the brain stem activating mechanism to novel patterns of cortical activity, and by its capacity to become habituated to oft-repeated patterns of cortical activity as it becomes habituated to oft-repeated signals from the external world.

## THE ULTIMATE NATURE OF HABITUATION

Usually, when nervous elements cease to respond to a stimulus, their lack of responsiveness can be attributed to (i) some form of adaptation or fatigue, or (ii) positive inhibition. The present data do not enable us to decide finally whether habituation depends on fatigue or inhibition of nervous elements, but they do enable us to restrict the form which either a "fatigue" or an "inhibition" theory may take.

### Adaptation and fatigue

Most of the studies of adaptation in nervous elements have been concerned with receptor organs (Adrian, 1928; Bronk, 1935). For sensory adaptation to occur, the stimulus must be nearly continuous, or at least repeated very frequently. If it is withdrawn, the adaptation decays within a few seconds. The parallel of sensory adaptation in nerve fibers is accommodation, and the time course of accommodation is even more rapid, usually being measured in milliseconds (Eccles, 1953). Thus, neither of these processes could account for habituation which, as we have seen, develops even when a brief tone is presented every quarter of an hour, and may persist for several days.

An adaptation-like process which lasts somewhat longer than either accommodation or sensory adaptation is fatigue. Fatigue can be

distinguished from accommodation by its temporal characteristics, and by the fact that it is necessarily an after-effect of activity (accommodation may occur even when the stimulus is too weak to elicit a nerve discharge). Fatigue is defined as decrement due to activity--to exhaustion of energy supplies which are gradually replenished in time, or to accumulation of the metabolic products of activity which are gradually dissipated. The longest known after-effect of activity in isolated nerve is a lengthening of the refractory period. Thus, after a short period of repetitive activity in frog nerve, the rate of recovery from a test impulse is slowed, and this slowed rate of recovery may persist for as long as an hour (Brink, 1951). It is conceivable that some fatigue-like process of this kind lasts for a much longer time in certain elements of the central nervous system.

If habituation is to be ascribed to some kind of long-lasting fatigue, our data enable us to restrict this fatigue to certain nervous elements. We know that the primary sensory pathways themselves do not become fatigued, since evoked potentials can still be recorded from auditory cortex after complete habituation. Nor does fatigue occur generally in the activating system during habituation, for, as we have seen, signals converge on common relays in this system. If these relays become fatigued, the animal would cease to respond not only to the repeated stimulus but also to all other stimuli. The block, therefore, has to occur between the primary sensory system and the final common pathway of the activation response.

Inhibition

Lloyd (1941, 1946), Eccles (1953) and others have clearly demonstrated the existence of direct inhibition in the central nervous system, and it now appears that direct, synaptic inhibition may be as fundamental a process in central nervous functioning as synaptic excitation.

Unlike fatigue, inhibition is an active process that decays within a few milliseconds. If habituation depends on inhibition, therefore, the inhibitory activity must be elicited by the familiar stimulus itself, or by some stimulus that immediately preceeds the familiar stimulus. With repetition, this inhibitory action would have to be increased or potentiated until it counteracted the excitatory effects of the stimulus. (The possibility that habituation depends on an increment in the inhibitory action of the stimulus, due to some process like the "post-tetanic potentiation" of Lloyd (1949) was suggested to me by Dr. Peter Milner.)

An inhibition theory of habituation would have to answer two questions: (i) Through what pathways is the inhibitory volley conducted? (ii) Precisely what elements are inhibited? With regard to the first question, we have already considered the possibility that auditory stimuli exert their excitatory effects on the reticular system through the brain stem collateral pathways, and their inhibitory effects through corticofugal and tectobulbar tracts. Such a neat division of function between brain stem collateral pathways and corticofugal and

tectobulbar pathways, however, has been ruled out by the experiments in which higher auditory centers were destroyed or deprived of sensory input. Nevertheless, it remains possible that inhibitory effects are conducted through pathways in the lower brain stem or cerebellum.

An inhibition theory of habituation would also have to say which elements are inhibited. Here, also, there are several possibilities: The inhibition may be exerted generally on the arousal mechanism or its final common pathway. Something like this is suggested indirectly by a much quoted experiment of Pavlov. In this experiment, the conditioned response to a tactual stimulus was thoroughly extinguished by repeating the stimulus many times without reinforcement. Then, when this stimulus was presented together with another ordinarily effective conditioned stimulus, it inhibited the response to the latter (Pavlov, 1927).

Plate XIV shows the results of an experiment designed to provide a more direct test of the hypothesis. After the animal had become thoroughly habituated to a 500 c/sec. tone, this tone was presented simultaneously with a puff of air delivered through a glass tube taped to the animal's back. If the familiar tone caused an inhibition to be exerted on the final common pathways of the reticular system, the activation reaction produced by the novel puff of air should have been suppressed. However, as Plate XIV shows, the activation reaction produced by a puff of air was not suppressed. If anything, it was facilitated. In another experiment in which two tactual stimuli were used, similar results were obtained. Clearly, habituation does not depend upon repeated stimuli acquiring inhibitory power over the entire

activating system, or over its final common pathway.

The possibility that inhibition is exerted through closed chains of neurons on the specific auditory pathways at a low level, so that auditory signals are blocked before they reach either the arousal mechanism or higher auditory centers, has been discussed above. It is precluded by the experiment showing that evoked potentials can still be recorded from auditory cortex after complete habituation of the arousal reaction.

Thus, if habituation depends ultimately upon the potentiation of inhibition, this inhibition must be exerted on collateral pathways between the specific auditory system and the final common pathway of the reticular activating system. Auditory signals must be inhibited before they have lost their identity in being transmitted forward in the reticular system, and after they have left the primary sensory system.

## SUMMARY

(i) Habituation to a repeated stimulus is indicated by the failure of the stimulus to initiate "activation patterns" both in cortex and medial brain stem.

(ii) The state of habituation is relatively specific to the repeated stimulus, and may persist in part for several days.

(iii) Auditory cortex continues to respond to auditory stimuli to which the animal has become completely habituated.

(iv) Neither higher auditory centers nor any forebrain center plays an essential role in habituation to specific tones.

(v) The main contribution of higher auditory centers to the brain stem activating mechanism is excitatory rather than inhibitory.

(vi) This excitatory contribution of higher centers increases the specificity of habituation. In particular, it enables habituation to be pattern-specific.

(vii) A stimulus applied directly to the cortex may produce non-specific activation, and the animal may become habituated to such a stimulus just as it becomes habituated to peripheral stimuli.

(viii) A stimulus to which the animal has become habituated does not acquire a generalized inhibitory power over the activating mechanism.

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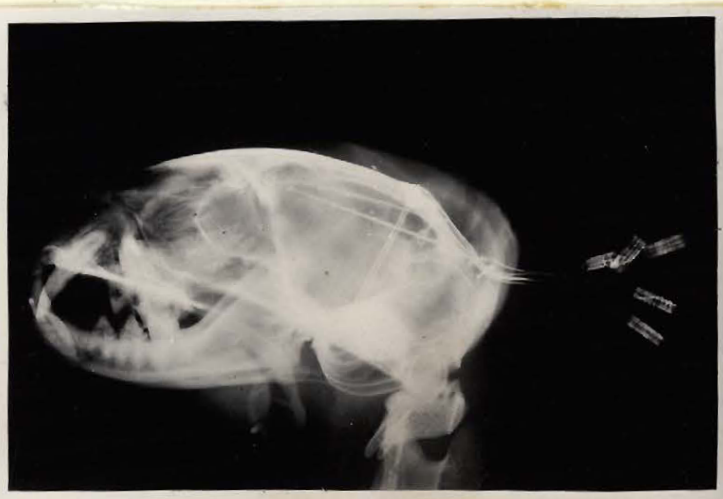
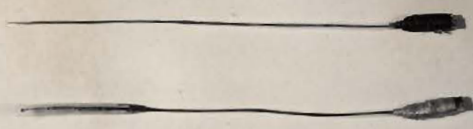
PLATE I

Top left: X-ray photograph of Cat P54-60. Electrodes implanted in cortex and mesencephalon. Top right: Usual distribution of cortical electrodes. Bottom: Cortical "plate" electrode and subcortical "needle" electrode.





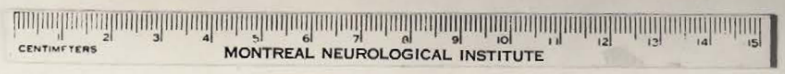

CENTIMETERS
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PLATE II

Cat P54-60. Position of electrodes in mesenscephalon.

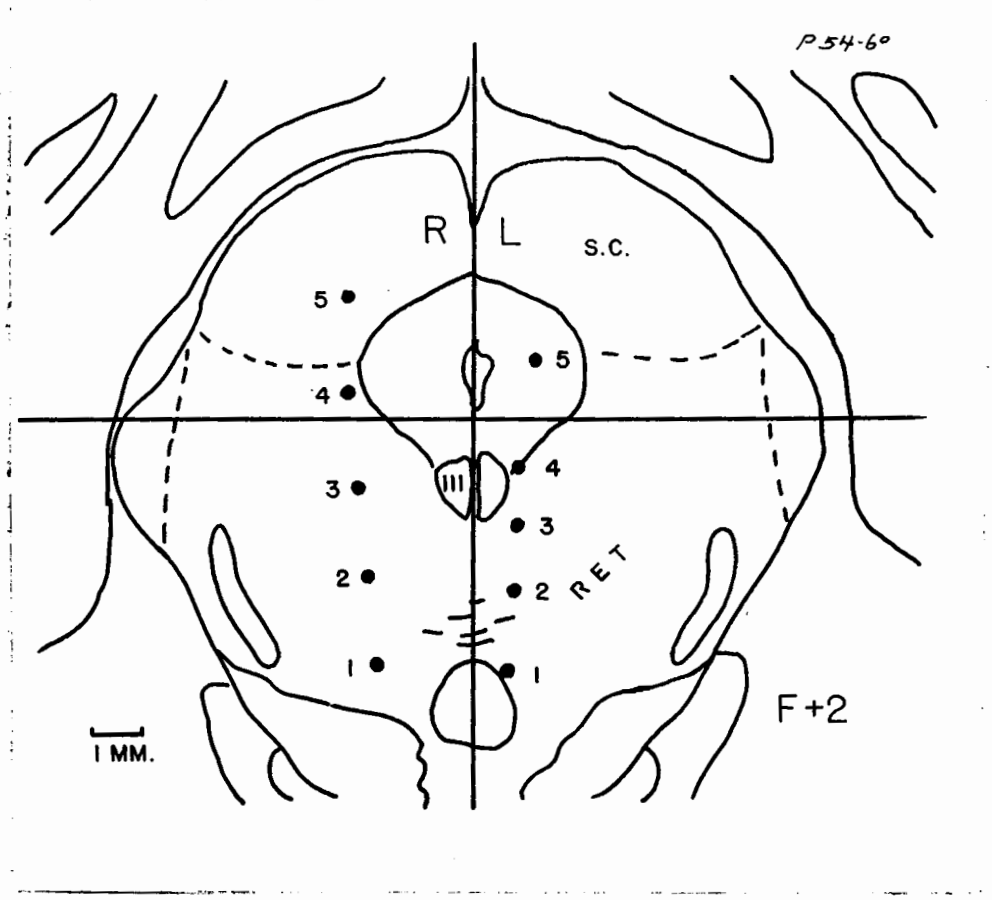
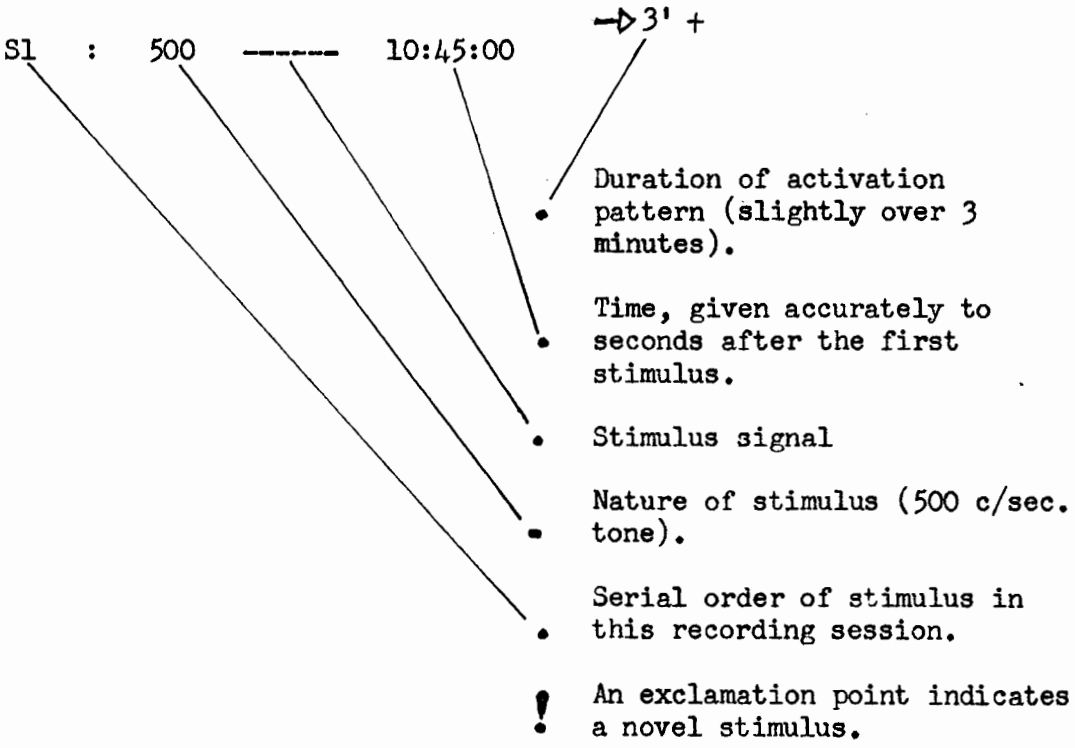

P54-60
R
L
S.C.
5
4
3
2
1
5
4
3
2
1
III
RET
1 MM.
F+2

PLATE III

Normal Habituation. Cat becomes completely habituated to a brief 500 c/sec. tone after about thirty trials. Then, a novel 100 or 1000 c/sec. tone produces activation.

Legend (see 1st tracing):



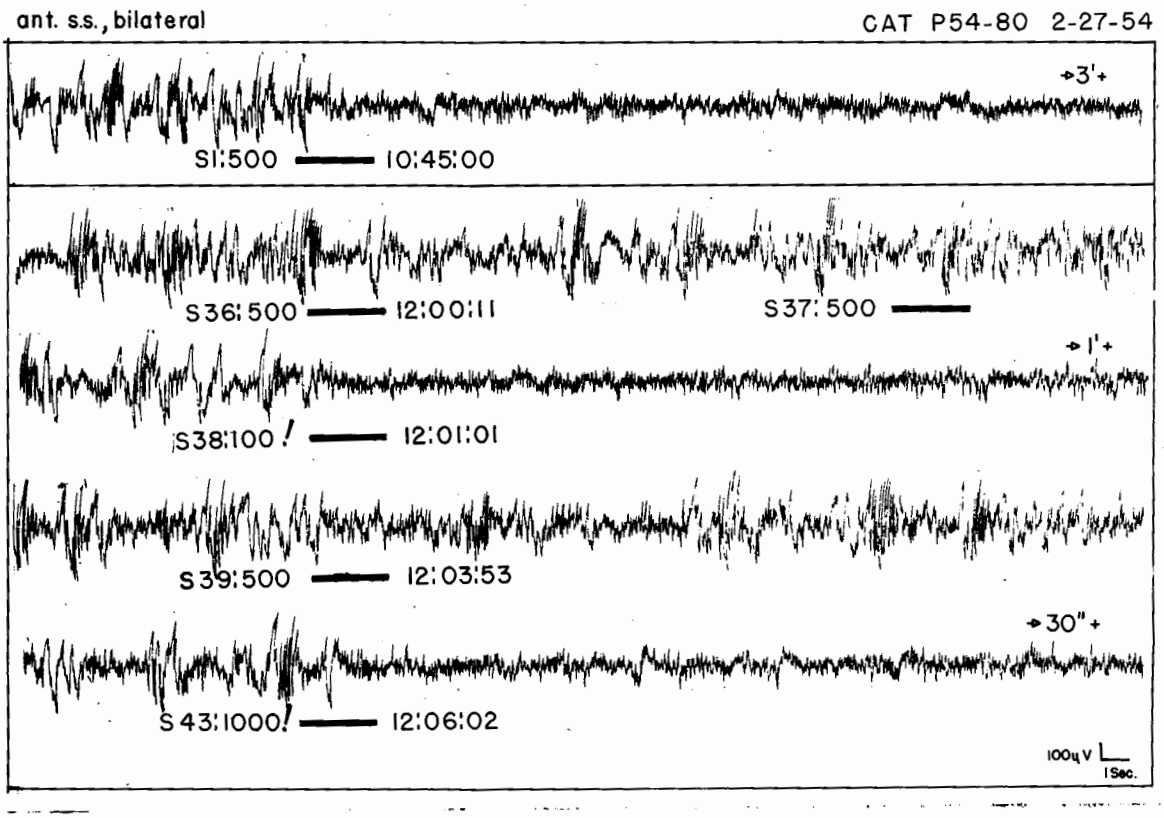

ant. s.s., bilateral
CAT P54-80 2-27-54
3'
S1:500
10:45:00
S36:500
12:00:11
S37:500
1'
S38:100!
12:01:01
S39:500
12:03:53
30"
S43:1000!
12:06:02
100μV
1Sec.

PLATE IV

Day-to-day persistence of habituation. Habituation to a 500 c/sec. tone persists in part through a two-day rest period. Bottom: Graphic representation of the duration of the activation patterns produced by the first eight stimuli following the two-day rest period. The familiar 500 c/sec. tone is less effective in producing arousal than an unfamiliar control stimulus.

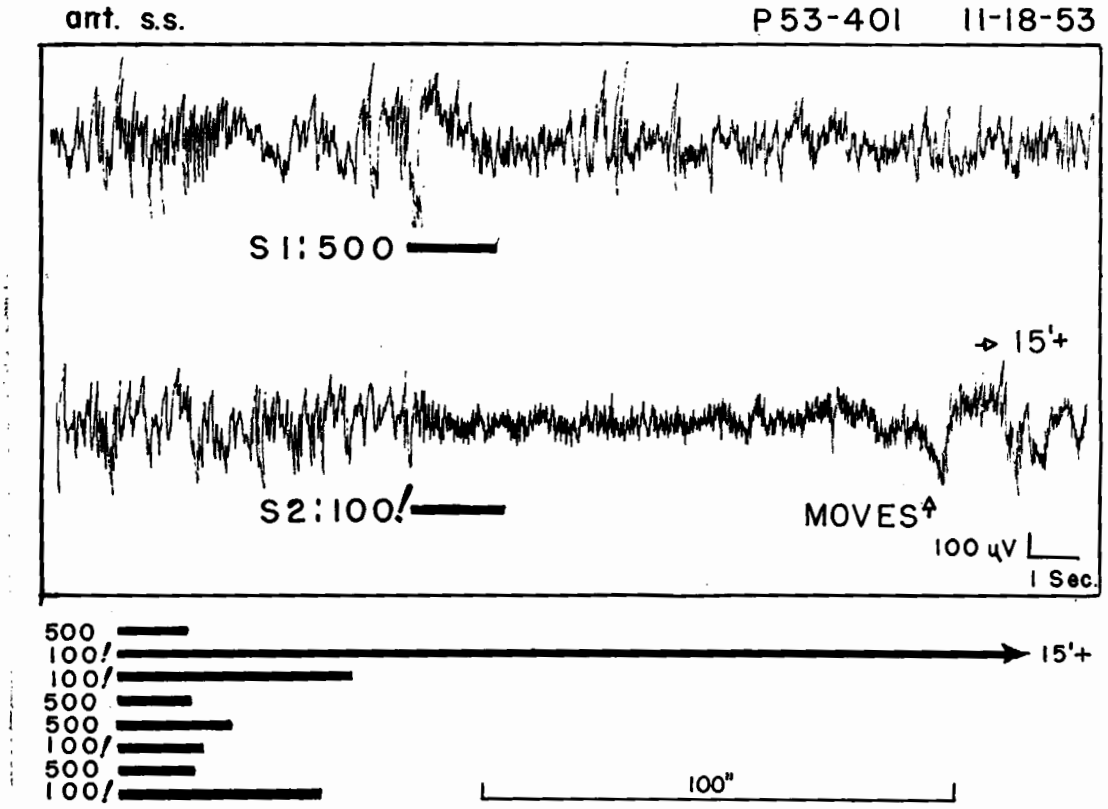

ant. s.s.
P53-401 11-18-53
S1:500
15'+
S2:100!
MOVES
100 μV
1 Sec.
500
100!
100/
500
500
100/
500
100/
15'+
100"

PLATE V

Evoked potentials (I) before habituation, (II) after habituation. Evoked potentials to a series of clicks may still be recorded from auditory cortex (and tend to be somewhat larger) after the ainmal has become completely habituated to this stimulus. (The disappearance of the large "on-response" in the reticular system was not a consistent finding.)

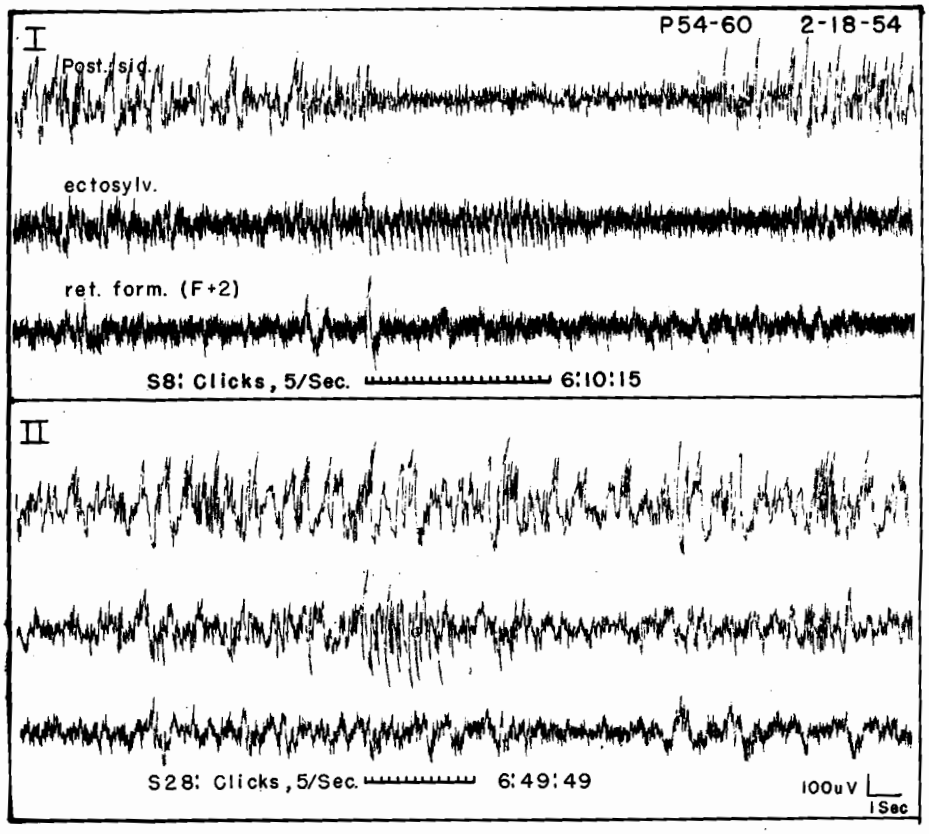
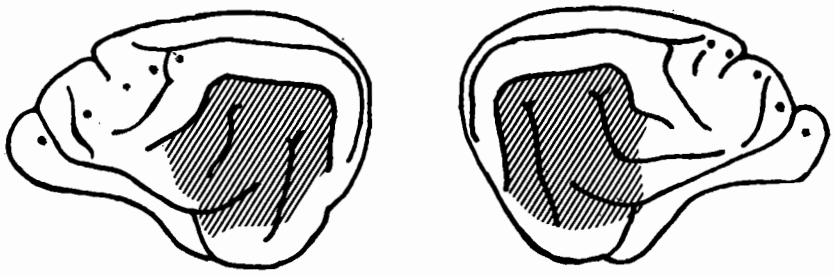

I
P54-60 2-18-54
Post. sig.
ectosylv.
ret. form. (F+2)
S8: Clicks, 5/Sec.
6:10:15
II
S28: Clicks, 5/Sec.
6:49:49
100uV
1Sec

PLATE VI

Site of cortical lesions

P53-296 OPERATED: 8-3-53
ELECTRODES IMPLANTED: 9-10-53
SACRIFICED: 9-19-53



P53-297 OPERATED: 8-3-53
ELECTRODES IMPLANTED: 11-11-53
SACRIFICED: 11-26-53

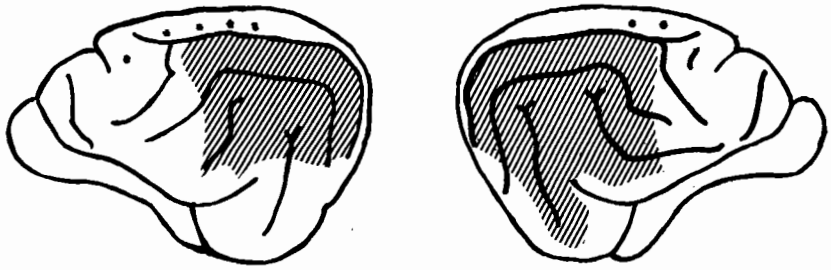
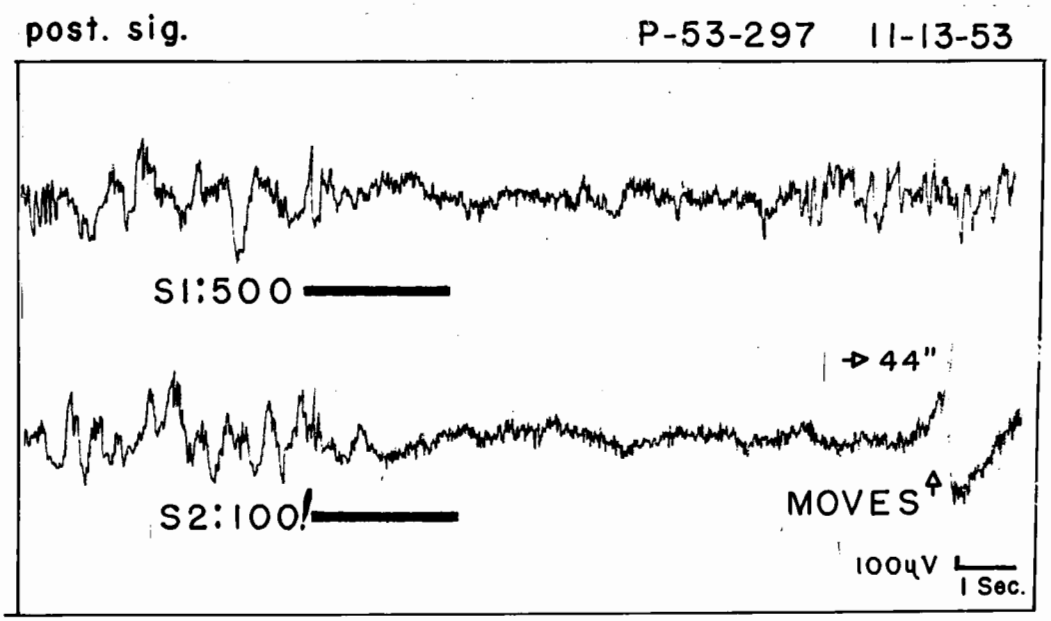


PLATE VII

Day-to-day persistence of habituation in animal with auditory cortex bilaterally ablated. Habituation to a 500 c/sec. tone persists in part through a two-day rest period. Bottom: Graphic representation of the duration of the activation patterns produced by the first four stimuli following the two-day rest period.




500
100!
500
100!

50"

PLATE VIII

Habituation to a 5000 c/sec. tone in a cat with auditory cortex bilaterally ablated.

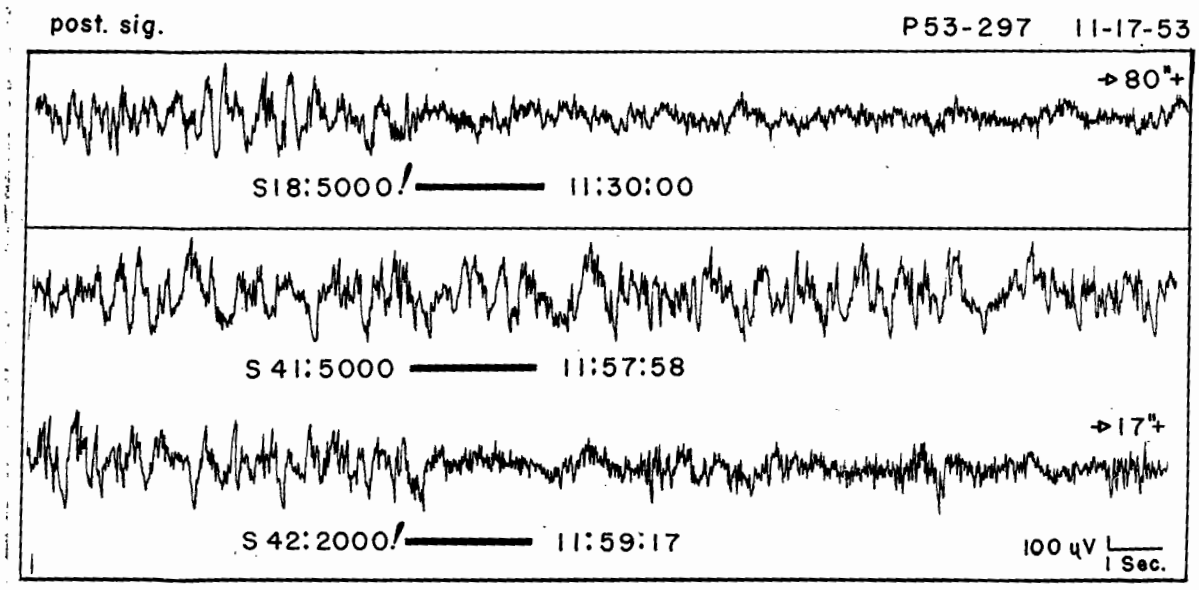
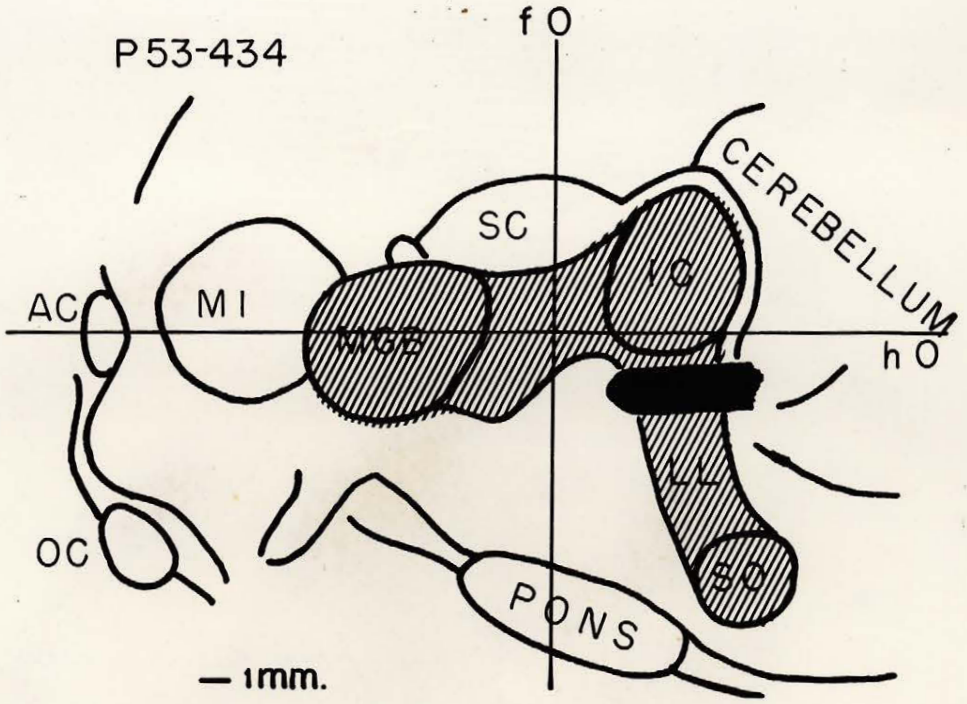

post. sig.
P53-297 11-17-53
→80"+
S18:5000
11:30:00
S 41:5000
11:57:58
→17"+
S 42:2000
11:59:17
100 μV
1 Sec.

PLATE IX

Sectioning of the lateral lemnisci. Top: Auditory pathways projected on midsagittal plane. The site of the lesion is shown in black.

(SO--superior olive, LL--lateral lemniscus, IC--inferior colliculus, SC--superior colliculus, MGB--medial geniculate body, MI--massa intermedia, AC--anterior commissure, OC--optic chiasma.) Bottom: Transverse section through inferior colliculi of Cat P53-434, showing lesions in lateral lemnisci.


P53-434
f O
CEREBELLUM
SC
AC
MI
MGB
IC
h O
LL
SO
OC
PONS
— 1mm.

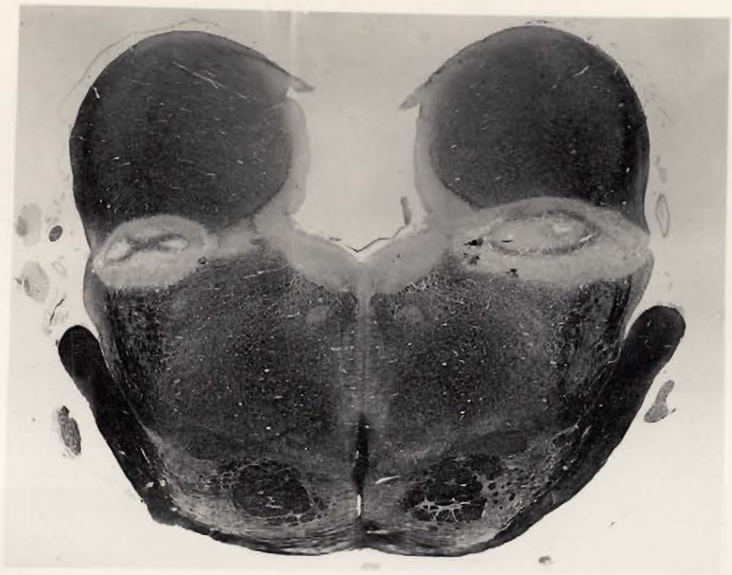


PLATE X

Rapid habituation to a 100 c/sec. tone in cat with lateral lemnisci sectioned.

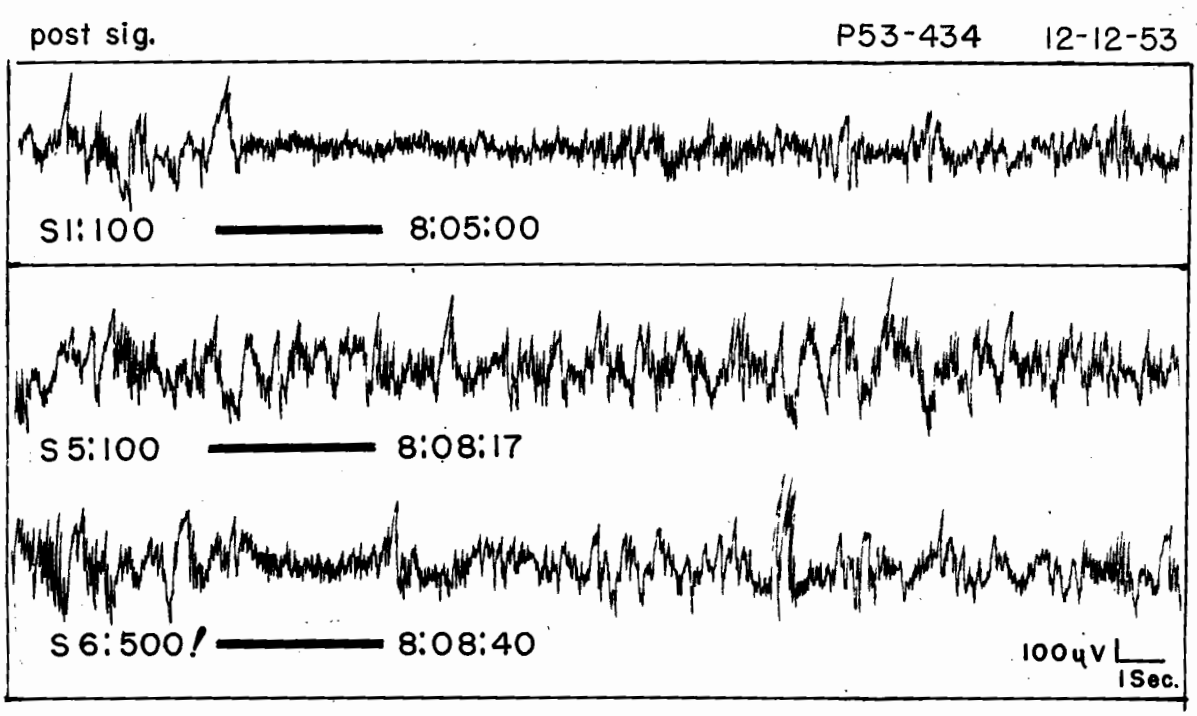

post sig.
P53-434 12-12-53
S1:100
8:05:00
S 5:100
8:08:17
S 6:500!
8:08:40
100μV
1Sec.

PLATE XI

Habituation to a modulated tone in cat with lateral lemnisci sectioned. The animal ceased to respond to a sound which gradually changed in pitch from 600 to 1000 c/sec. in about twelve trials. Then, a novel 500 to 100 c/sec. modulated tone produced arousal. After this had been repeated several times, the habituation generalized to include all tones between 100 and 1000 c/sec. Then, a modulated tone ranging over a higher band of frequencies (10,000 to 4000 c/sec.) produced arousal.

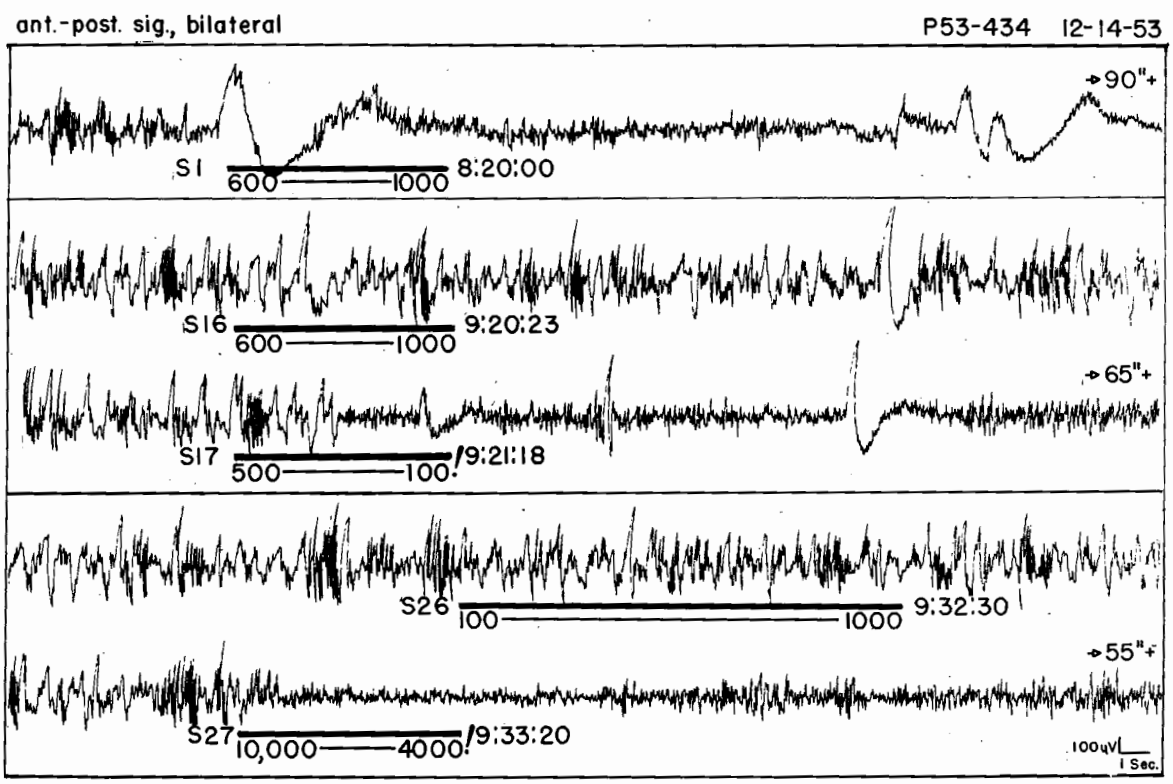

ant.-post. sig., bilateral
P53-434 12-14-53
90"+
S1
600
1000
8:20:00
S16
600
1000
9:20:23
65"+
S17
500
100
9:21:18
S26
100
1000
9:32:30
55"+
S27
10,000
4000
9:33:20
100μV
1 Sec.

PLATE XII

Pattern-specific habituation. Top: After a normal cat had become completely habituated to a modulated tone, it could be aroused briefly by changing the pattern of the stimulus (from one which rises in pitch to one which falls in pitch). Bottom: In the cat with lateral lemnisci sectioned, habituation was not pattern-specific.

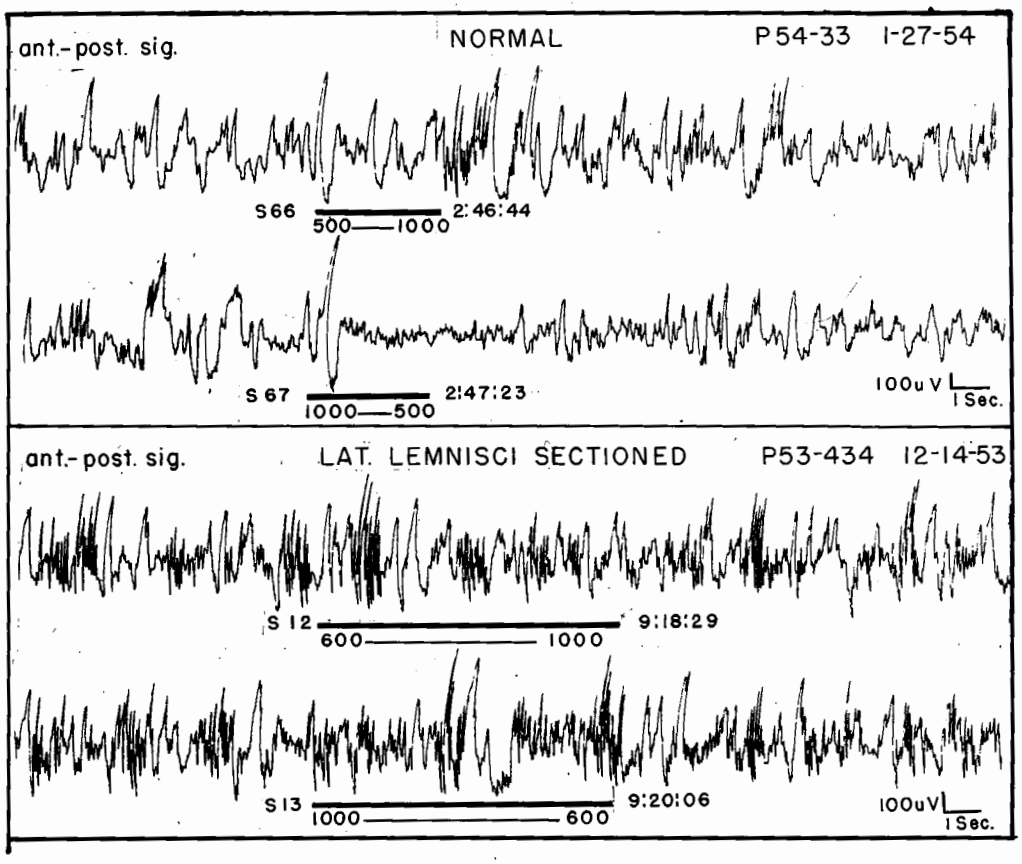

ant.-post. sig.
NORMAL
P54-33 1-27-54
S66
500—1000
2:46:44
S 67
1000—500
2:47:23
100uV
1 Sec.
ant.-post. sig.
LAT. LEMNISCI SECTIONED
P53-434 12-14-53
S 12
600—1000
9:18:29
S13
1000—600
9:20:06
100uV
1 Sec.

PLATE XIII

Habituation to a stimulus applied directly to the cortex. A series of brief shocks (7 volts, 5/sec.) to frontal cortex elicits arousal initially, but the animal becomes habituated to this stimulus in about twelve trials. Stimulus applied to right hemisphere; activation patterns recorded from left hemisphere.

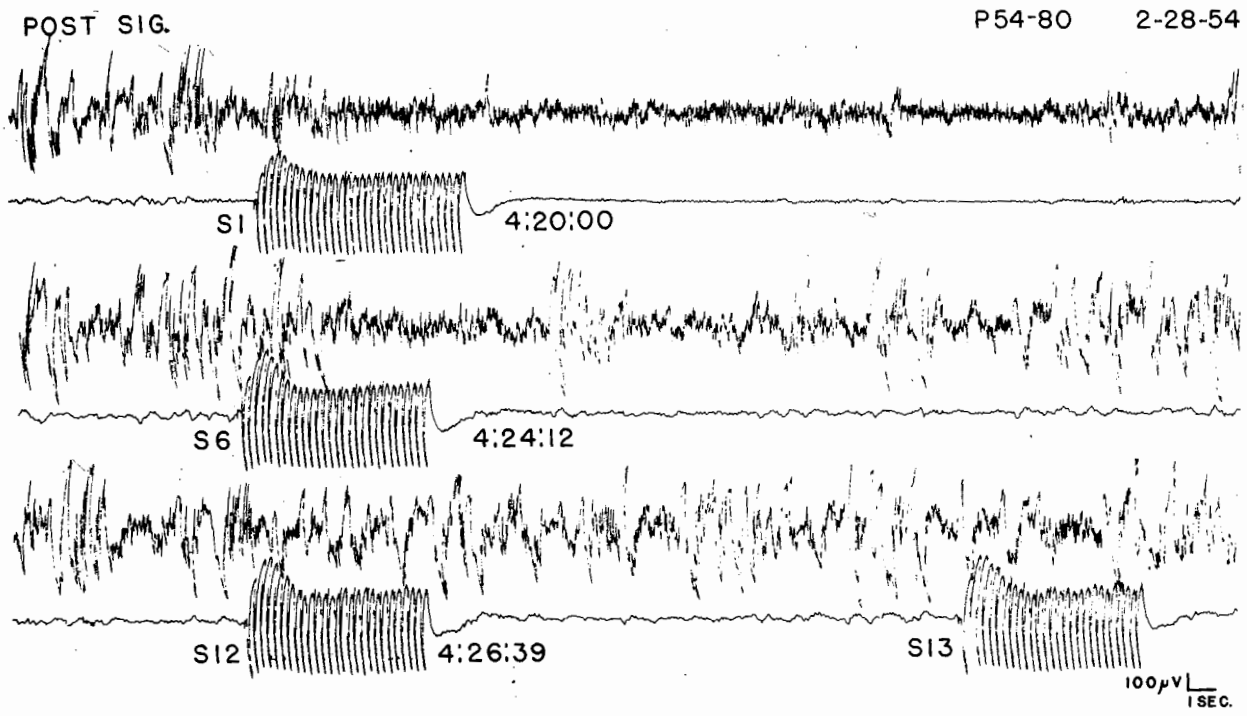

POST SIG.
P54-80
2-28-54
S1
4:20:00
S6
4:24:12
S12
4:26:39
S13
100μV
1 SEC.

PLATE XIV

Failure to obtain inhibition of the activation reaction. A stimulus to which the animal has become thoroughly habituated fails to suppress the activation elicited by a novel stimulus when it is presented simultaneously with the latter. Here the familiar stimulus is a loud 500 c/sec. tone, and the novel stimulus is a light puff of air directed against the animal's fur.

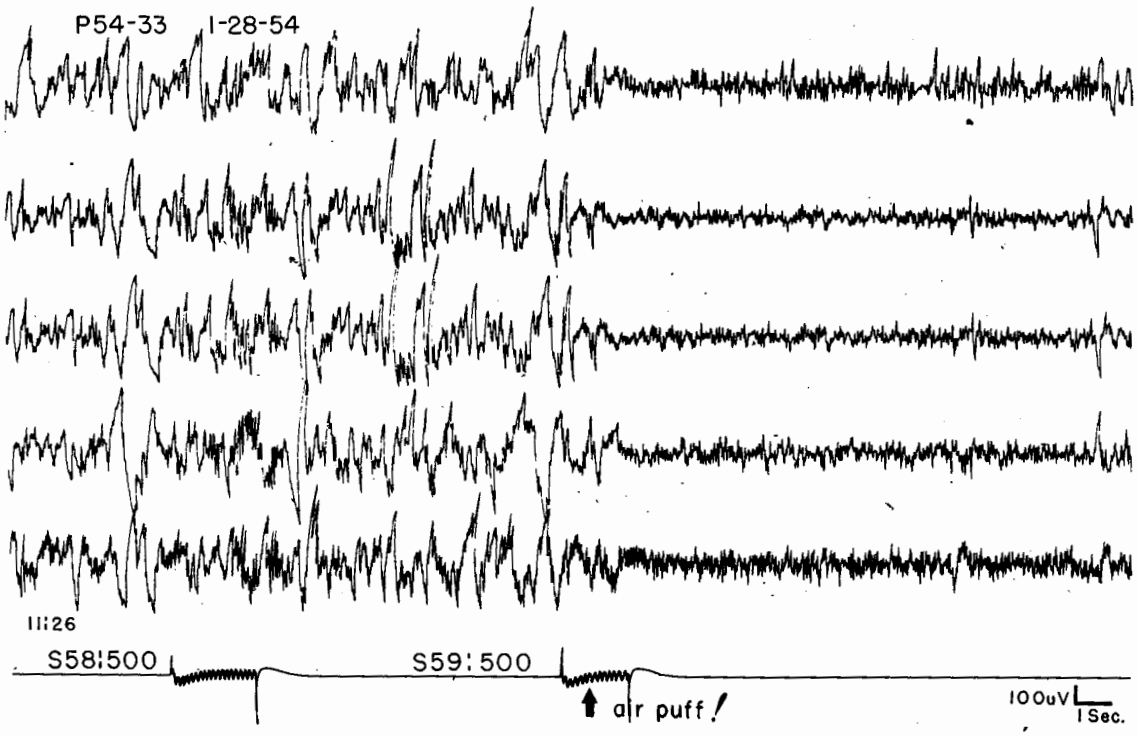

P54-33 1-28-54
11:26
S58:500
S59:500
air puff!
100uV
1 Sec.

PLATE XV

Schematic summary of collateral auditory pathways. The heavy lines represent crossed primary sensory pathways. Collateral pathways are represented by light lines. Fibers originating in the dorsal cochlear nucleus terminate in the reticular formation after passing through the acoustic striae (Barnes, Magoun and Ranson, 1943). According to Cajal (1909), the superior olive projects primarily to the reticular formation. The lateral lemniscus gives off fibers (including some from the superior olive) to the nucleus of the lateral lemniscus, and fibers from this nucleus are directed medially into the reticular formation (Cajal, 1909). The inferior colliculus sends fibers via the acoustico-optic tract to the superior colliculus, and many fibers originating in the superior colliculi pass to the reticular formation through the tectobulbar tracts (Ranson, 1947). Thus, fibers enter the reticular formation from the dorsal cochlear nucleus, superior olive, nucleus of the lateral lemniscus and tectum, and, of course, from auditory and association cortex. It has been generally assumed that collateral pathways in the lower brain stem mediate simple reflexes such as the contraction of tensor tympani and stapedius muscles, pinna twitching, and so on. But some of these pathways must be responsible for the non-specific activating effects of auditory stimuli.

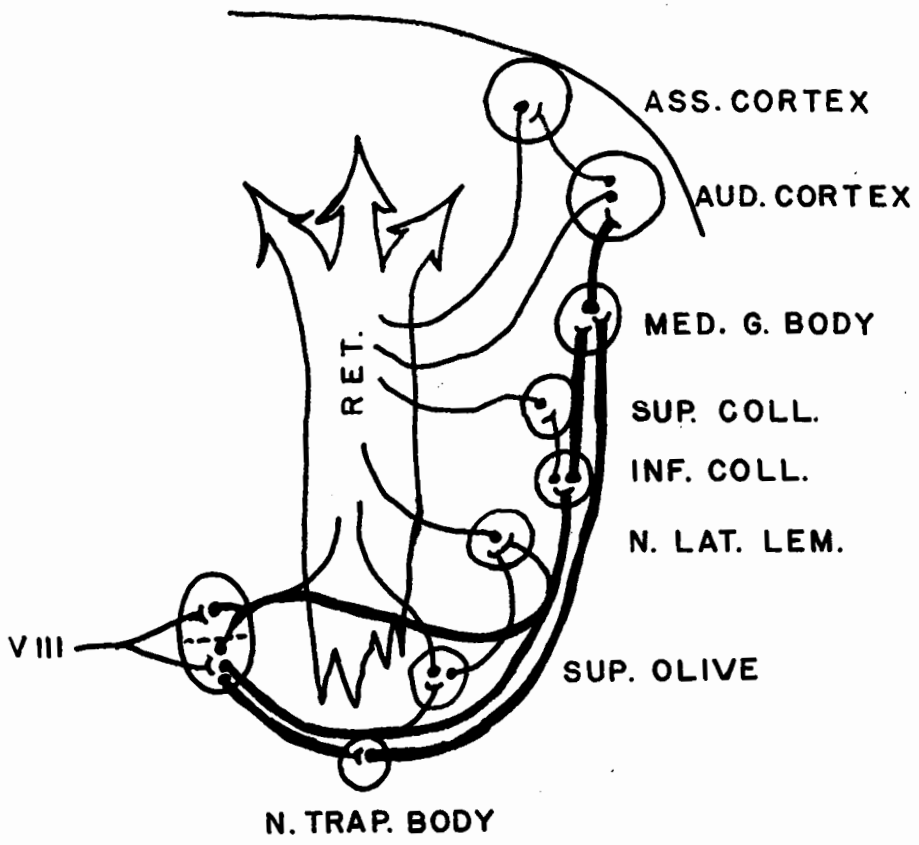
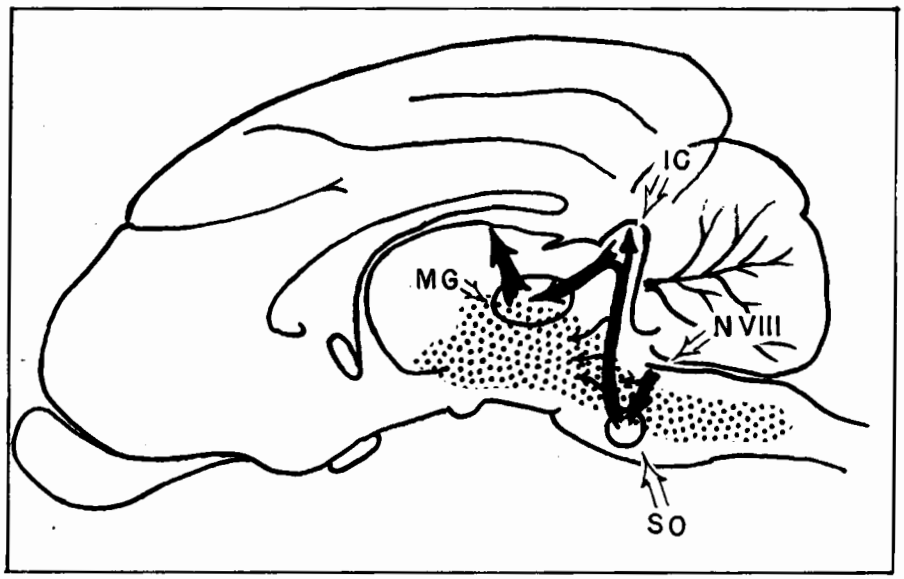

ASS. CORTEX
AUD. CORTEX
MED. G. BODY
RET.
SUP. COLL.
INF. COLL.
N. LAT. LEM.
VIII
SUP. OLIVE
N. TRAP. BODY

PLATE XVI

Drawing of the medial aspect of a cat's brain on which are projected (roughly) the primary auditory pathways and Magoun's reticular activating system.




RETICULAR ACTIVATING SYSTEM

AUDITORY PATHWAYS