THE EFFECT OF CERTAIN CONDITIONING PROCEDURES ON AFTER-DISCHARGE THRESHOLD OF THE CAT CEREBRAL CORTEX

by

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CHAPTER I

INTRODUCTION

Although the disease of epilepsy is probably as old as civilization, and indeed we find reference to it as early as 2080 B.C. in the Code of Hammurabi, the treatment of this disorder has been largely unsuccessful until the last 50 years and perhaps completely unsuccessful before Samuel Wilks introduced the use of bromide of potassium in 1859[39]. Still, epilepsy is far from uncommon, although the public has not been made aware of it as it has of polio, tuberculosis, cancer, or heart disease. About one in every 200 people, or a total of approximately one million people in the United States, are afflicted with epilepsy[47]. As many people suffer from this disease as from diabetes or active tuberculosis, and the incidence of epilepsy is many times that of polio.

The socio-economic importance of epilepsy is great not only because this disease incapacitates the sufferer during the ictal or convulsive phase, but he is also directly handicapped in that he does not know when he will have a seizure. This fact physically restricts him from many activities in which he would be predisposed to injury if a seizure were to take place. Perhaps more than any other disease this is a socially disabling disease of major proportions. Although we have come a long way since the day when epileptics were thought to be possessed by the devil and cast out or destroyed, the epileptic is still ostracized from society to a degree. Although personality disorders are seen as a common occurrence in epileptics, the cases which have

an organic basis for the personality disorder represent probably only a very small percentage. The majority of personality disorders are probably secondary to the distortion of the environment produced by social ostracism, constant fear of having an attack, etc. It is then readily apparent what great socio-economic value the control of this condition is, not only in enabling epileptics to obtain gainful employment, but also to allow them to develop psychologically to practice good mental health, particularly when (as in 75% of the cases) it is a child who is involved. It has been estimated that the cost to the nation, not counting lost manpower, amounts to at least $60,000,000 a year(47). The monetary cost is of little importance compared to the personal and social bereavement suffered by those afflicted and their families. The encouraging point is that, given adequate medical care, 80% of these people can live relatively normal productive lives.

Although some hereditary influences have been noted in specific types of epilepsy (i.e., pyknolepsy), a much greater proportion (95%) of these have now been shown to be caused by a specific insult to the brain, the more prominent of these causes being trauma to the head, vascular insults, neoplastic growths, and infectious processes(15). Merritt and Putnam led the way in the treatment of these disorders with the development of the first truly specific anticonvulsant drug, diphenylhydantoin(33). These specific anticonvulsant drugs not only may alleviate or decrease the frequency of occurrence of the seizures, but in some cases offer complete control. Although considerable excellent research has been done in the last twenty years to discern the mechanism of action of these drugs and the pathological alterations of the nervous system which are associated with the disease, much re-

mains to be resolved. Of particular importance is a more complete understanding of the manner in which behaviour in neuronal aggregates like the cerebral cortex is different from that characterizing the normal.

ELECTROCORTICAL CHARACTERISTICS

The Spike

The seizure state has long been known to be associated with a specific type of electrocortical activity which is characterized by a potential wave pattern of high voltage and relatively short duration called the "spike" (18, 22). These spikes may occur singly, in paroxysmal bursts sometimes called polyspike activity, or in continuous runs of activity of varying frequencies. The generation of these abnormally high potential waves is thought to be due to hypersynchronous firing of the neuronal units of the epileptogenic focus[18]. The rhythmicity with which these high voltage potentials recur during a seizure may then be attributed to an oscillation in and out of a state of hypersynchrony.

Rhythmicity

The mechanism underlying the ability of the central nervous system to generate oscillatory electrocortical activity lies either intrinsic in the nerve cells themselves [6] or is a function of the manner in which they are interconnected[15]. Rhythmic activity is not a phenomenon restricted to the mammalian cerebral cortex but has been observed in many much less well differentiated nervous system components[1, 11] and muscular elements[46, 38]. Lorente de Nó[31] and Lehmann[27] have shown that a spontaneous, rhythmic succession of compound spikes may be set up in a vertebrate nerve trunk

following a single brief, adequate stimulus. Brink, Bronk, and Larrabee[8] noted that depolarization, whether produced electrically or by drugs, may itself enhance spontaneous activity. Since 1938, when Lorente de Nó developed the concept of reverberating circuits from his study of the activity of the chains of internuncial neurons in the spinal cord[30], this hypothesis has been used as an explanation for the mechanism of different types of spontaneous rhythmic cortical activity such as spindling and the alpha rhythm.

Rhythmic Activity in the Thalamo-cortical System

There has been much evidence that the alpha rhythm and spindling are produced in the cerebral cortex by activity in the mid-line and intralaminar or non-specific projecting nuclei of the thalamus. Bursts of potential waves having the alpha frequency and modulation characteristics can be recorded from these nuclei in man and in the cat[21] even after complete decortication, thus obviating the possibility of activity in thalamo-cortical reverberating circuits. That this alpha activity is modified by the cortex has, however, also been demonstrated[36, 34]. Stimulation of the non-specific projecting nuclei by single shocks results in the appearance of bursts of alpha frequency activity in all neo-cortical areas and in the striatum complex (the so-called tripped spindles)[34, 23, 35]. When the diffuse projecting nuclei are stimulated by repetitive shocks at the frequency of alpha activity, electrocortical waves of gradually increasing amplitude are evoked[35, 23, 34]. The frequency of the alpha activity in the cat is not modified by fluctuation of the temperature of the cortex alone but is influenced by fluctuations in the general body temperatures which affect the temperature of the subcortical structures as well as that of the cortex[7].

Ralston and Ajmone-Marsan[40] have shown that certain drugs which affect the frequency of rhythmic cortical activity when applied to the diffuse projecting nuclei of the thalamus do not produce an effect when applied to the cortex directly. And finally, the undercutting of a cortical area results in a diminution of the potential of the rhythmic cortical activity and an increase in the spacing between spindle bursts[26, 44].

Spontaneous alpha waves in continuous sequences or in evoked bursts and the waves of spontaneous spindles all show similar time course and the same predominant surface negativity. Li, Cullen, and Jasper[29] noted that when these waves were recorded from the depths of the cortex using microelectrodes they exhibited similar potential distribution within the cortex. Spencer[43], in studying electrocortical augmenting, recruiting, and spindle waves recorded at different depths in the sensori-motor cortex of cats, was able to differentiate two basic depth-time-potential patterns. The first pattern was noted predominantly in augmenting responses, while the second pattern predominates in the recruiting response. In spindle waves a mixture of the two patterns was noted with neither pattern predominant in a majority of the spindle waves. It has also been noted that slight hypoxia or anesthesia readily suppresses the discharge of cortical cells, recorded as unitary spikes, without affecting the rhythmic slow waves. From this significant finding and confirming, with the microelectrode technique, Adrian and Moruzzi's early observations[2], Li, McLennan, and Jasper[28] concluded that there is no support for the supposition that the slow waves result from envelopes of spike discharge.

Cyclic Excitability of the Cortex

A mode of production of rhythmic electrocortical activity may be in the cyclic excitability of the nerve cells. This was alluded to by the observations of Bishop in 1933[4] and of Clare and Bishop in 1952[12] of a phase of cortical depression following the responses to stimulation of specific sensory afferents in the cat and in the rabbit. This depression was then followed by a return to at least normal excitability after an interval close to the interval between alpha waves. Clare and Bishop[13] in a later study of potential wave mechanisms in the cat cortex were able to show that both thalamic nuclear stimulation and stimulation of the thalamic radiation fibers were capable of inducing rhythmic excitability changes in the cells of the cortex. This cycle of excitability consisted of a phase of depression following the first recruiting wave or spontaneous spindle wave, which lasted for one-tenth to one-sixth of a second, and then passed over into a phase of supernormal excitability. This phase of cortical depression is noted to be temporally similar to the interlude between waves of naturally occurring alpha activity, spontaneous spindles, and also the waves of the recruiting and augmenting responses. It was noted by Clare and Bishop in this latter study that either spontaneously occurring 10/second spindles or evoked recruiting waves occlude other spontaneous activity and also tend to occlude each other. This tendency of these patterns to occlude each other would suggest that they all may occupy the same structures.

It has thus been demonstrated that a high voltage low frequency type of electrocortical activity may occur spontaneously over the cortex and may also be either "tripped" or produced artificially by diencephalic electrical stimulation. An increase in cortical excitability which occurs in a cyclic

fashion has been noted to occur with, and to be in close temporal relationship to, several varieties of this high voltage low frequency type of electrocortical activity.

ACTIVATING PROCEDURES

In the EEG laboratory, procedures which bring out intrinsically abnormal electrocortical activity have been found to be of great value to the clinical neurologist studying epilepsy and to the neurophysiologist studying the mechanisms underlying the disease of epilepsy. By activation of an epileptogenic focus is meant a procedure by which the enviromment of the group of abnormal neurons which make up the focus may be changed in such a way as to cause or allow them to produce the electrocortical activity (i.e., spikes) characteristic of abnormal function. These activation procedures, which (as is the case of many other diagnostic tools) are accepted on an empirical basis, appear to be of greater value in certain specific types of epilepsy. The most commonly used activation procedures in clinical EEG studies are those of hyperventilation, photic stimulation, sleep activation, and metrazol activation(42). Besides visual activation, other types of sensory stimulation such as acoustic, olfactory, and tactile stimulation have also been found to be of value in selected cases(22).

Hyperventilation

The most common method of activation used is that of hyperventilation, which is almost a routine part of the diagnostic electroencephalographic procedure on any patient suspected of having a convulsive disorder(42). It would appear that hypocarbia with resultant moderate alkalosis and electrolyte shifts predispose the nerve cells to epileptic activity either by

direct effect on the nerve cells themselves or perhaps by vasoconstriction of the cerebral capillaries, with a resultant slight drop in the oxygen supplied to the cells[42]. The electrocortical response which is noted in man (other than spike activity) is that of moderately high voltage (approximately 100 mv. or above) and moderately low frequency (in the alpha frequency band). In the normal patient this high voltage low activity usually is replaced by normal activity within ten to twenty seconds, but in the epileptic patient it may persist.

Photic Stimulation

The second most commonly used method of activation used in the clinical electroencephalography laboratory is that of photic activation[42, 18]. In this procedure a fairly bright light is flashed in the patient's eyes, which may be either opened or closed. The photic stimulus may be presented either singly or in trains or repetitive bursts. A frequency of 8.5 to 24 cps. has been found to be most effective in EEG activation[25]. Although a specific response to photic stimulation is noted over the occipital cortex[22], there is no direct evidence available at this time supporting a diffuse cortical influence by involvement of the non-specific thalamocortical system. Wall, Remond, and Dobson[45], however, have demonstrated an increase in the height of all components of a pyramidal volley evoked by cortical stimulation when preceded by a light flash. These authors also found that a similar effect could be produced by other types of sensory stimulation and that stimulation of the femoral cutaneous nerve appeared to have greater effect on the pyramidal volley than did the visual stimulation. In ablation experiments it was also found that the occipital cortex and the superior colliculus were not

necessary for the facilitation of the pyramidal response by photic stimulation. Thus, a generalized diffuse excitatory influence may be exerted on the cerebral cortex over an undetermined pathway following sensory stimulation.

Sleep

It is common clinical knowledge that many epileptic patients have their seizures only during sleep. It is, therefore, natural to expect that some of these individuals would present specific electrocortical abnormalities only during this functional state. This has been found to be the case in a great number of epileptic patients, particularly those with psychomotor epilepsy. Gibbs et al.(17) found in a study of 300 cases diagnosed as psychomotor epilepsy that only 30% of this group showed seizure discharges during sleeping EEGs. Merlis et al.(32) in 210 cases of various manifestations of epilepsy found an increase from 37% to 47% in sleeping EEGs over waking. They also found in 102 normal or borderline patients that 14.7% demonstrated seizure discharge during sleep. These sleep recordings were found to contribute most in that group of patients with psychomotor seizures, and Merlis found sleep studies of especial value in demonstrating anterior temporal spike foci in these patients.

Glaser and Golub(19), however, found in 110 children (of ages one and one-half to sixteen years) with psychomotor seizures that EEG recordings during sleep contributed little more in the way of abnormal EEG activity. This would seem to indicate that the activating factor present in the adult is lacking at least to some degree in the adolescent. While many differences in the infant and adolescent as contrasted to the adult EEG are known,

none have been shown to produce an effect which might explain this phenomenon[22].

As to the level of sleep which seems to produce the best degree of activation of the EEG, Gibbs [17] found seizure activity to be maximal during light sleep. This level of light sleep and drowsiness is seen to correspond with an EEG waveform of low frequency and high potential known as spindling. Natural sleep and sleep induced by drugs were found to be similarly effective; however, it is preferable to obtain natural sleep whenever possible, as sedative agents modify the sleep pattern and may limit the true evaluation of the sleep record in some epileptic patients.

It should be noted at this point that hyperventilation and light sleep are associated with the production of a generalized type of high voltage low frequency activity. A similar type of high voltage activity localized to the occipital cortex may be produced by photic stimulation of a frequency in the alpha range or slightly above.

Before turning to the consideration of the mechanisms whereby these activation procedures precipitate abnormal focal discharge, it seems pertinent to call attention to the fact that high voltage low frequency activity can also be induced in the electrocorticograms of experimental animals by several techniques. In many respects the experimentally induced waves resemble those produced by activation procedures in man. Spindle bursts, comparable to those seen in light sleep, may be induced by large mesencephalic lesions which render the animal comatose[5]. Direct electrical stimulation of thalamic relay nuclei at low frequencies induces augmenting waves which may be comparable to the occipital waves induced by photic

stimulation. Electrical stimulation of the midline thalamic nuclei at low frequencies induces a cortical electrical phenomenon called recruitment, which in many respects resembles bursts of sleep spindles. Although, in terms of time course and direction of surface potential change, all of these experimentally induced phenomena have certain characteristics in common with each other and with the results of activation procedures, it is impossible at this time to be certain that identical underlying mechanisms are responsible. At least two major patterns of intracortical electrical changes have been defined, one pattern predominant in the augmenting response, the other predominant in recruitment, and a mixture of these patterns with neither predominant in experimentally induced spindles[48].

ORIGIN OF ABNORMAL FOCAL ELECTRICAL ACTIVITY

Since the time of Hughlings Jackson, it has been assumed that the functional pathological site responsible for the disease of epilepsy lies in abnormal neuronal hyperactivity. There has been little actual evidence of this until the past several years, when microelectrode techniques have made the recording of unitary electrical activity feasible. One of the first studies of unitary activity in an epileptic focus was that of Schmidt, Thomas, and Ward[41], in which chronic cortical epileptogenic foci were produced by the injection of alumina cream into the cerebral cortex of monkeys. They were able to record frequencies of cellular discharge in neurons in these foci that were considerably above those seen in normal cortical neurons. The cells which produced this autonomous high frequency burst activity appear to be of small or intermediate size. Spike activity was not correlated

with any specific event at the cellular level, and it was proposed that the characteristic EEG of focal epileptic discharge was due to a summation of massive dendritic potentials which may occur synchronously. The authors concluded that the fundamental property of the epileptic neuron is the capacity for sustained autonomous discharge.

Thalamocortical Influences on Cortical Excitability

Brookhart and Zanchetti in 1955[9] were able to demonstrate increase in the responsiveness of the cortico-spinal system during evoked augmenting waves and spontaneous spindle waves. A similar alteration in responsiveness of the efferent neuron system was not, however, noted during recruitment. Wall, Remond, and Dobson[45], as previously noted, found an increase in cortical excitability of the sensorimotor cortex as measured by an increase in all components of an evoked pyramidal response, during optic stimulation, and also during peripheral sensory stimulation. The findings of Clare and Bishop[13] of a phase of hyperexcitability following waves of recruitment and spindle activity, when considered with these other experimental observations, indicate that the thalamocortical circuit may at times have an excitatory effect on the cortex which might affect the susceptibility of the cortex to either the initiation or the spread of abnormal electrical activity.

Andy, Chinn, Allen, and Shawver[3], investigating any influence that mesencephalic and diencephalic stimulation might have on limbic system seizures, noted no specific changes in the after-discharge characteristics produced after preactivation stimulation of the diencephalon at points which produced recruiting responses, or after stimulation of the brain stem. The effect of the preactivating procedures on the susceptibility of the regions

of the limbic system tested to respond to the electrical stimulation by after discharge, however, was not noted.

It is readily apparent that there are many difficulties in the evaluation of the susceptibility of any neuronal aggregate to the development of abnormal electrical activity, the first of which is a criterion measuring susceptibility capable of quantitative analysis. As different regions of the cortex are known to have different susceptibilities(16) to the amount of current necessary to produce abnormal electrical activity, this factor must be taken into account in any attempt to measure changes in cortical seizure threshold. As in the case of most biological systems, there will be many variables which cannot all be eliminated but whose effect may best be minimized by the use of paired observations of the control and conditioned threshold.

STATEMENT OF PROBLEM

The following series of experiments represent an attempt to ascertain any effect on the excitability or susceptibility of the sensorimotor cortex which has been preconditioned by the induction of high voltage low frequency waves resembling those which are produced by many of the activation procedures.

In the conduct of these experiments it was necessary to develop a method for testing the excitability of the cortex in a quantitative fashion. Given an adequate test and criterion, any changes occurring in excitability of the cortex during periods of high voltage low frequency electrocortical activity should be discernible in the form of an alteration in the measure

of excitability. The threshold for the production of after-discharge by electrical excitation of the cortex has been compared to the threshold for the production of after-discharge in the same fashion during augmenting activity, recruiting activity, and spontaneous spindling.

CHAPTER II

METHOD

The surgical preparation of the animals was carried out under ether anesthesia. The trachea was routinely cannulated and a polyethylene catheter was inserted in the right saphenous vein for intravenous administration of fluids throughout the surgical and experimental periods. The animal's head was then secured in a steriotaxic instrument. The cranial vault was exposed by means of a cruciate incision in the scalp and retraction of the scalp and muscular layers. A trephine hole was made through the frontal sinus on the left side in order to expose the left sensory-motor cortex for cortical stimulation. A similar trephine hole was then made in the parietal region for insertion of the thalamic electrodes. Small burr holes were made in the frontal, temporal, and occipital regions bilaterally with a dental burr to provide a seat for the surface recording electrodes. Two similar, but larger, burr holes were made over the cerebellum to admit the trigeminal coagulation electrodes, which entered the skull at a 30° angle in order to bypass the large venous channels in this region. In the experiments in which spindling was investigated, similar burr holes were placed for the mesencephalic tegmental coagulation.

In order to produce local anesthesia over the scalp, a method of procaine infiltration of the edges of the scalp was first attempted. Because of a rather large increase in threshold following the injection of procaine, this method was discarded in favor of DC coagulation of the trigeminal nuclei[10]. The latter method had no apparent effect on the threshold, and

the anesthesia was permanent. As the method of procaine infiltration of the scalp is commonly used in electrophysiological studies of the cortex, this finding, if valid, would be of considerable importance. Coagulation of the mesencephalic tegmentum in the spindling cats was accomplished by means of an electrosurgical unit. The electrodes used for coagulation of the trigeminal nuclei of the mesencephalic tegmentum were stainless steel rods which were insulated except for the distal 4 mm. The cats used in the study of the effects of augmentation and recruitment were then placed on artificial respiration after the administration of 2 mg. of decamethonium bromide and were maintained immobile by 1 mg. dosages of this drug every 45 to 60 minutes after ether anesthesia to the termination of the experiment.

Thalamic and hypothalamic stimulating electrodes were bipolar concentric electrodes with a tip separation of approximately 0.5 mm. and were placed sterotaxically. The surface recording electrodes were 3/8" x 2" brass wood screws which were seated in the burr holes over the frontal, temporal, and occipital regions. A spring-mounted, ball-tipped, silver wire bipolar electrode with a tip separation of approximately 6 mm. was used for cortical stimulation and was placed visually on the left anterior sigmoid gyrus through the trephined hole in this region.

All stimuli used in this group of experiments were rectangular pulses which were slightly distorted by isolation transformers. In the stimulation of the cortex, a ten second train of impulses with a pulse width of one m sec. and frequency of 100/sec. was used. This stimulus was delivered through a calibration circuit by means of which the current delivered to the cortex was monitored oscillographically. The cortical impedence was also measured during the period of stimulation by a bridge circuit. The stimulus electrode

was then adjusted to the region of the anterior sigmoid gyrus which apparently had the lowest threshold to electrical stimulation. This electrode was not moved again until the termination of the experiment in most cases.

Conditioning of the cortex was accomplished by stimulation of the left ventrolateral nucleus of the thalamus in the case of the augmenting response, and by stimulation of the centramedian nucleus and Nucleus Reuniens in the case of the recruiting response. Before the experiment the optimum position for thalamic stimulation was determined by monitoring the responses on the EEG, and the electrodes were then not moved until the termination of the experiment. The thalamic stimuli consisted of a 3.2 second train of one m sec. wide rectangular pulses delivered at frequencies from about 8 to 12 per second. The intensity of the stimuli were usually in the range of one to five volts. In order to precondition the cortex, the train of thalamic stimuli was initiated approximately one-half second before the onset of the cortical stimulation (Figure 1D, page 18). In the case of the spindling animal with the mesencephalic lesions, arousal was produced by hypothalamic stimulation approximately ten seconds before cortical stimulation. The stimulus delivered to the hypothalamus was a one second train of one m sec. wide rectangular waves at a repetition rate of 100 per second. Voltages of one to four were usually of sufficient intensity to produce a satisfactory state of EEG arousal (Figure 1C, page 18).

Cortical recordings were achieved by means of a Grass Model III electroencephalograph. A standard method of recording was used throughout all of the experiments. This consisted of unipolar leads from the frontal, temporal, and occipital regions on both sides and a bipolar frontal-occipital

FIGURE 1

PROCEDURES FOR CONDITIONING ELECTROCORTICAL ACTIVITY

Representative records from four preparations, illustrating the manner in which electrocortical activity was altered in preparation for threshold measurements during high voltage, alpha frequency rhythmic discharge.

A: Augmenting waves confined to ipsilateral frontal cortex during stimulation of nucleus ventralis lateralis at 8-12 cps.

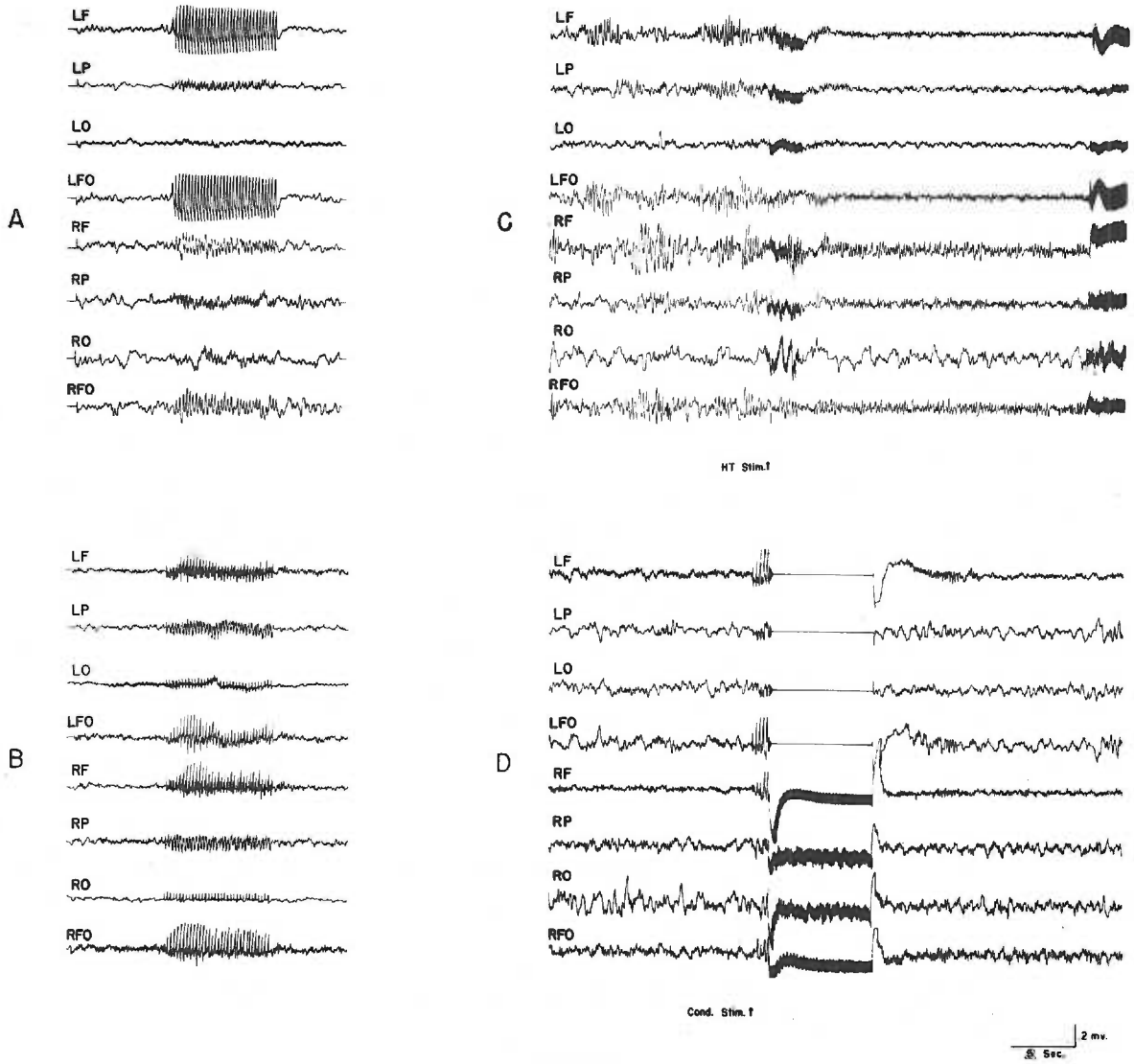
B: Recruiting waves generally distributed during stimulation of Nucleus Reuniens and nucleus centremedian, 8-12 cps.

C: Spontaneous spindles in animal with central mesencephalic destruction. The conditioned thresholds were determined during spindling. Control thresholds were determined during temporary abolition of spindles following one second of hypothalamic (HT) stimulation at 100 cps. with one m/sec. pulse width. This record terminates with the onset of a burst of testing stimulation.

D: Conditioning and testing stimulation combined. Thalamic stimulation was initiated for 1/2 second before and continued for 2-7/10 seconds after the start of direct cortical stimulation at 100 cps. and 1 m sec. pulse width. In this example the test stimulus initiated a threshold afterdischarge.

Lower right: time and sensitivity calibrations for all records.

Monopolar leads designated with two letters referring to right (R) and left (L), and to position: frontal (F), parietal (P), and occipital (O). Bipolar leads designated with three letters.


A
LF
LP
LO
LFO
RF
RP
RO
RFO
C
LF
LP
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LFO
RF
RP
RO
RFO
HT Stim.↑
B
LF
LP
LO
LFO
RF
RP
RO
RFO
D
LF
LP
LO
LFO
RF
RP
RO
RFO
Cond. Stim.↑
2 mv.
5 Sec.

lead from both hemispheres. On the unipolar recordings a phonograph needle was inserted in the region of the left mastoid for use as a reference lead.

The times recorded in the data are from a zero time at the completion of the surgical procedure. This zero time, therefore, also coincides with the time the animal began to come out of ether anesthesia.

Coordinates used for stereotaxic placement of the thalamic and hypothalamic bipolar concentric electrodes were derived from the atlas of Ajuone-Marsan and Jasper[24]. Upon termination of the experiment, the left carotid was isolated and injected with approximately 40 cc. of 10% formalin solution. The brain was then removed and deposited in 10% formalin. After an interval of at least three days, blocks of nervous tissue containing the electrode tracks and the trigeminal and mesencephalic lesions were frozen, sectioned, and photographically printed without staining, as described by Guzman, Alcaraz, and Fernendez[20] for histological follow-up. The criterion for threshold stimulus intensity was the presence of a typical change in the electroencephalographic pattern called an after-discharge. In order to qualify as an after-discharge, a potential of greater than 0.1 mv. occurring within ten seconds following the cortical stimulus and clearly distinguishable from the activity in the prestimulus record was deemed necessary.

In order to ascertain the threshold current a method of "tromboning" was used, in which the interval between a subthreshold and a threshold value was gradually decreased until an interval of about 0.03 ma. between the threshold and a subthreshold stimulus was achieved. The stimuli were presented at intervals not less than five minutes apart in order to minimize any effects of the preceding stimulation. When the afterdischarge became generalized or prolonged over more than 20 seconds, an additional period of re-

covery was allowed, depending upon the severity of the response.

In the experimental procedure control threshold values were obtained intermittantly among the conditioned threshold values in all of the experiments. Because of the variability of the control threshold during a single experiment, control values were taken either alternately or in a ratio of one to every two conditioned threshold values. In order to minimize the effects of other variables which may act on the after-discharge threshold and which cannot be brought under rigid control, a method of statistical analysis using paired observations was selected. To obtain paired control and conditioned threshold values it was necessary to derive mathematically a control threshold value by interpolation from the control threshold values obtained before and after the conditioned threshold on the basis of time, assuming the variation in control threshold to be linear. The hypothesis that there is no significant difference between the means of the two populations was then tested statistically by the use of Student's t test at the 5% and 1% levels of significance[14]. The probability of the acceptance of a false hypothesis was also mathematically evaluated for these sample sizes.

CHAPTER III

RESULTS

After-Discharge Patterns

The criterion used for after-discharge was the appearance of one or more EEG spikes of a potential greater than 0.1 mv. occurring within ten seconds following the test stimulation and clearly distinguishable from the normal pre-stimulus activity (Figure 2, page 22). During the experiment the after-discharge patterns noted were many and diverse. The most commonly seen pattern (Figure 2B, page 22) was that of a rhythmic, moderately high voltage type of poly-spike activity which occurred in frequencies of from 12 to 48 per second. The duration of this activity was seen to range from one minute to only a fraction of a second (being confined to one or two spikes). The after-discharge terminated by either becoming lower in frequency or decreased in amplitude, or both. A period of latency up to nine seconds from the termination of the testing stimulus until onset of the after-discharge was occasionally noticed (Figure 2C, page 22), although the after-discharge usually followed the testing stimulus by less than one second. A third type of after-discharge pattern was one which was characterized by the lack of rhythmicity, consisting of completely irregular poly-spike activity (Figure 2D, page 22). This pattern frequently terminated in a spike and dome complex reminiscent of that associated with petit mal epilepsy.

These varieties of after-discharge were not constant from trial to trial in the same animal. The pattern of after-discharge in a single animal was unpredictable and not related to the duration of the experiment. On the few

FIGURE 2

CRITERIA FOR THRESHOLD INTENSITY OF STIMULATION

Representative tracings from four different preparations showing post-stimulation activity which has been defined as "after-discharge".

A: Subthreshold intensity of stimulation failed to evoke any response in 10 seconds of recording following period of stimulation. Stimulation: at 100 cps., 1 msec. pulse width.

B: Threshold intensity of stimulation evoked rhythmic polyspike activity beginning promptly and lasting approximately 20 seconds. After-discharge like that shown in the initial phases of this pattern was most frequent in occurrence. Later phases varied within and between preparations depending on whether the after-discharge terminated as a reduction in amplitude or a frequency or both. Stimulation: 100 cps., 1 msec.

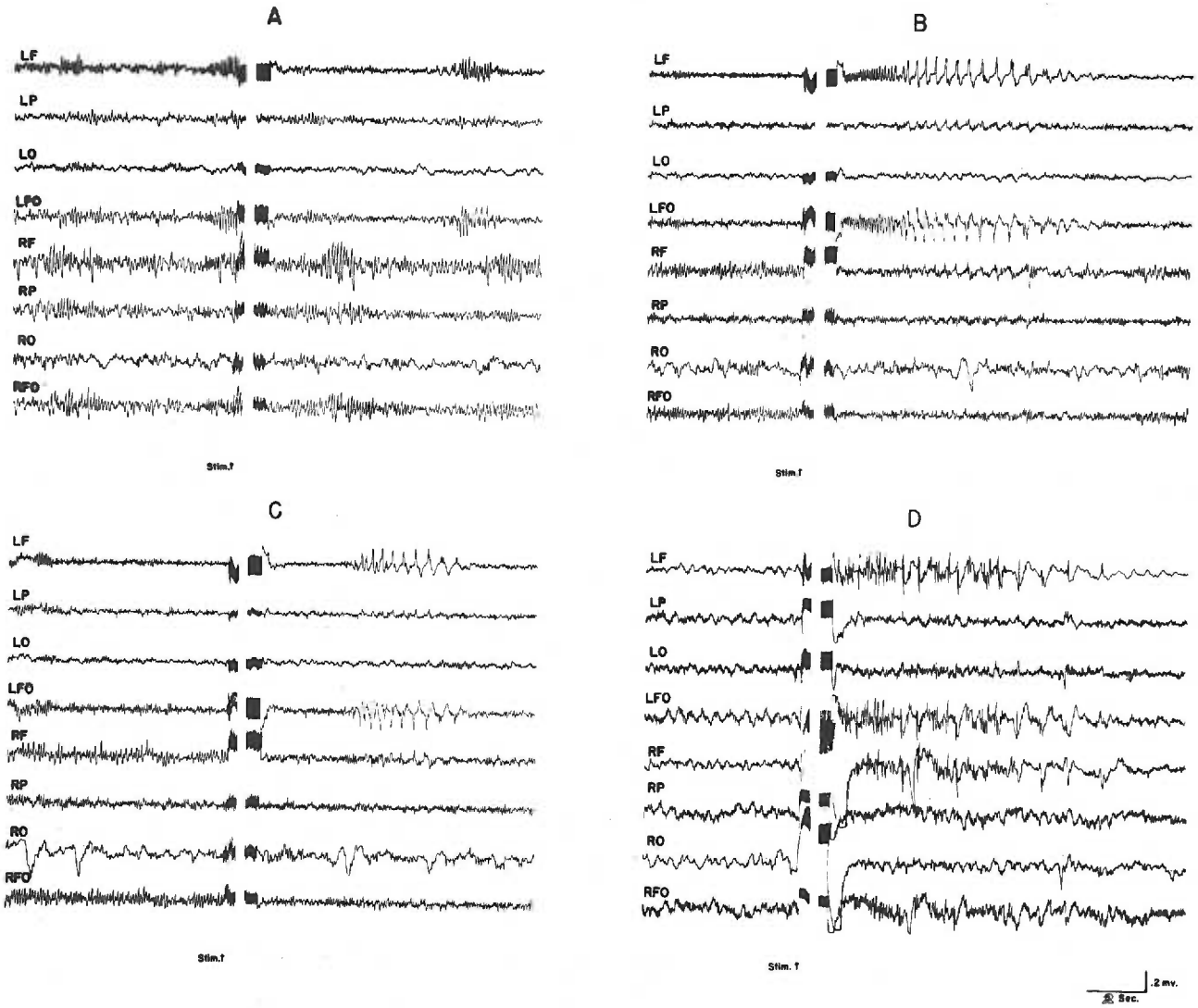
C: After-discharge appeared after brief latency. This period varied from one to nine seconds and was inconstant for any one preparation. Stimulation: 100 cps., 1 msec.

D: Arrhythmic polyspike activity terminating in spike and dome pattern. Stimulation: 100 cps., 1 msec.

Lower right: timing and sensitivity calibrations applicable to all records.

Monopolar leads designated with two letters referring to right (R) and left (L), and to position: frontal (F), parietal (P), and occipital (O). Bipolar leads designated with three letters.

Note spread to contra-lateral frontal lead in B, C, and D.


A
LF
LP
LO
LFO
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B
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RO
RFO
Stim.↑
D
LF
LP
LO
LFO
RF
RP
RO
RFO
Stim. ↑
.2 mv.
1 Sec.

occasions when supra-threshold stimuli gave rise to a generalized, self-sustained electrocortical seizure, the initial phases of the after-discharge were not uniformly of one pattern. The three conditioning procedures utilized to alter cortical activity had no discernible effect on the pattern of threshold after-discharge.

The distribution of after-discharge was constant, both from trial to trial in a single animal, and between different animals, for threshold stimulation. The after-discharge was most prominent in the stimulated left frontal region with minimal spread, in approximately 75% of the cases, to the right frontal regions. After-discharge activity was not noted in the other monopolar leads until stimuli approximately twice threshold were applied. If the after-discharge became generalized, the voltage of the electrocortical activity was higher over the frontal and occipital regions. The distribution of the after-discharge was not influenced by the three conditioning procedures.

Variations in Control Threshold

The control threshold drifted in several of the experiments. No relationship between rectal temperatures and the threshold variations could be found. In several experiments the threshold was seen to drop during the first 60 minutes following the cessation of ether anesthesia, but this was not consistent. The most important factor in stabilization of the control threshold was the prevention of any disturbance of the preparation or of the electrode placements. In the experiments involving conditioning by augmentation and recruitment, several animals showed a tendency to develop electrocorticographic activity suggestive of light sleep. In order to prevent an

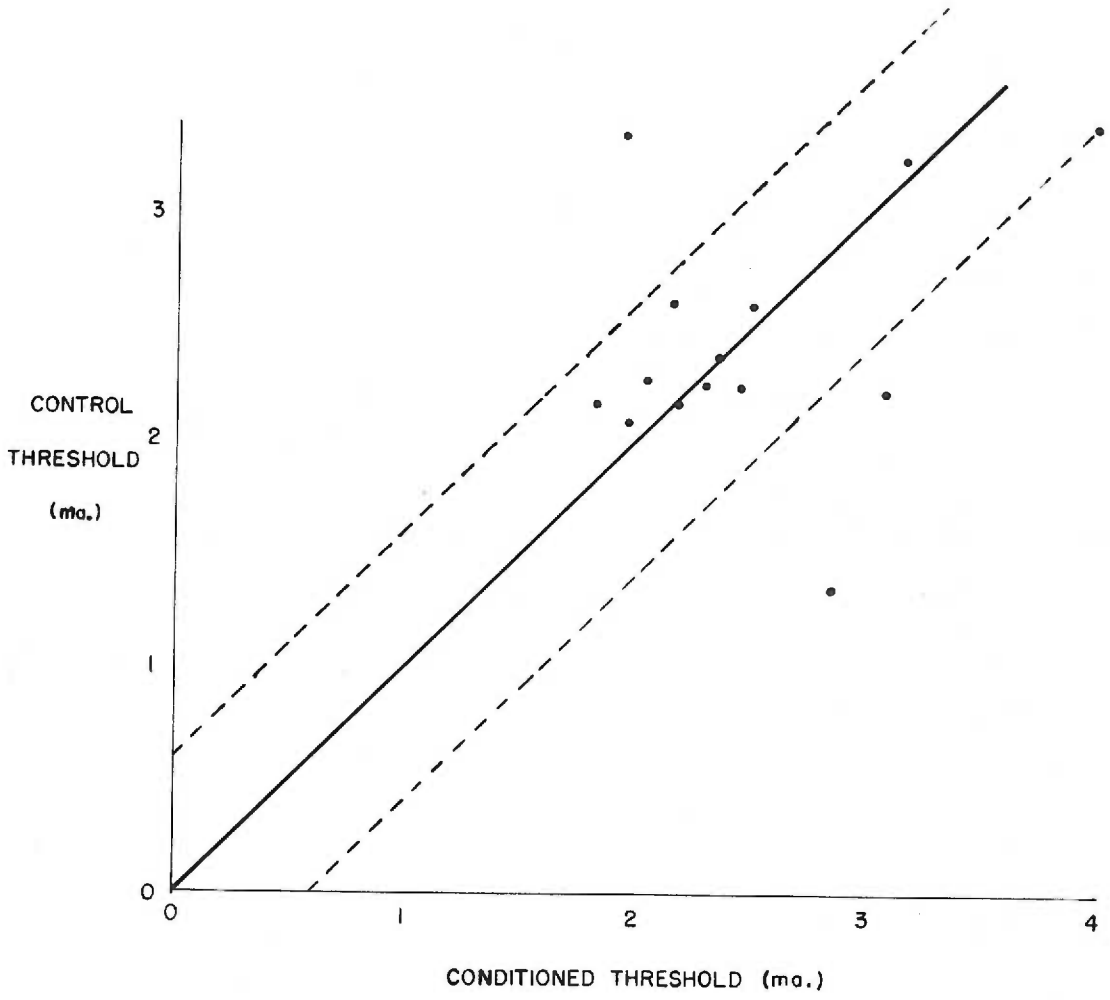
interaction between drowsiness and evoked activity, the animal was kept in a state of arousal by auditory stimuli (clapping, whistling, etc.). Even in those animals whose thresholds remained stable throughout the experimental period, differences in threshold were noted between animals. This may partially reflect variation in the site of stimulation on the anterior sigmoid gyrus, variations of threshold within cats, and physiological responses to the surgery and experimental procedure.

The variations in the control and conditioned threshold values are evident on inspection of Figures III (page 25), IV (page 26), and V (page 27). It may be readily noted that the spread of control thresholds was greatest in the experiments concerned with the effect of recruitment, although the lowest threshold values were found in the spindling experiments. These variations in control threshold, of course, have no relation to the type of conditioning under test.

The progressive changes in control threshold introduced a complication in the analysis of the results. Since it was obviously impossible to measure both control and conditioned thresholds at the same time, it was necessary to estimate the degree of change of control threshold which could be presumed to have occurred between two measurements. In order to obtain the paired values required for the analysis, it was assumed that the change in control threshold occurred in a linear fashion between two measurements. The estimated control value to be paired with an experimental value was obtained by simple interpolation to the time of measurement of the conditioned threshold.

FIGURE 3

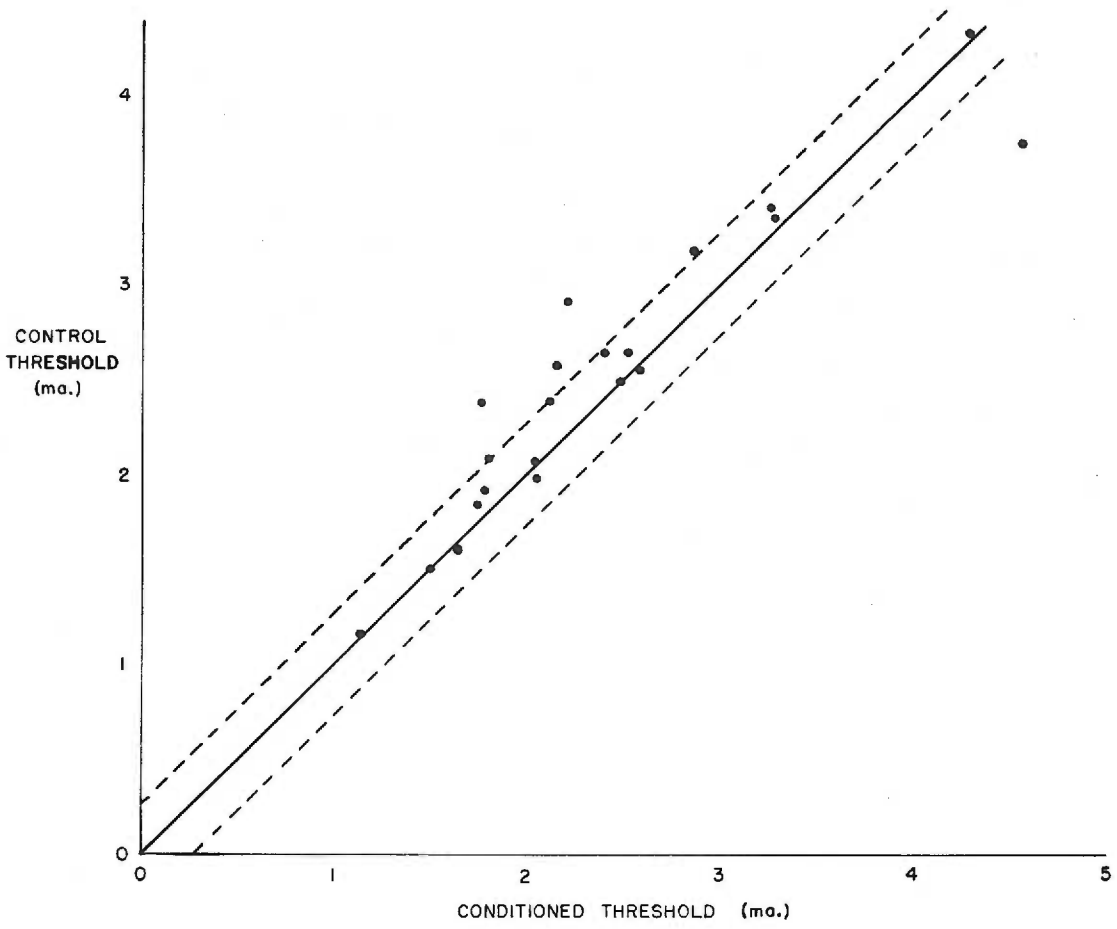
The points plotted represent paired threshold values. The solid line represents the hypothetical mean, testing the assumption that conditioning the cortex with the augmenting response produces no alteration in the after-discharge threshold. The dotted lines indicate 2.58 standard deviations on either side of this mean.



AUGMENTING RESPONSE

FIGURE 4

The points plotted represent paired threshold values. The solid line represents the hypothetical mean, testing the assumption that conditioning the cortex with the recruiting response produces no alterations in the after-discharge threshold. The dotted lines indicate 2.58 standard deviations on either side of this mean.

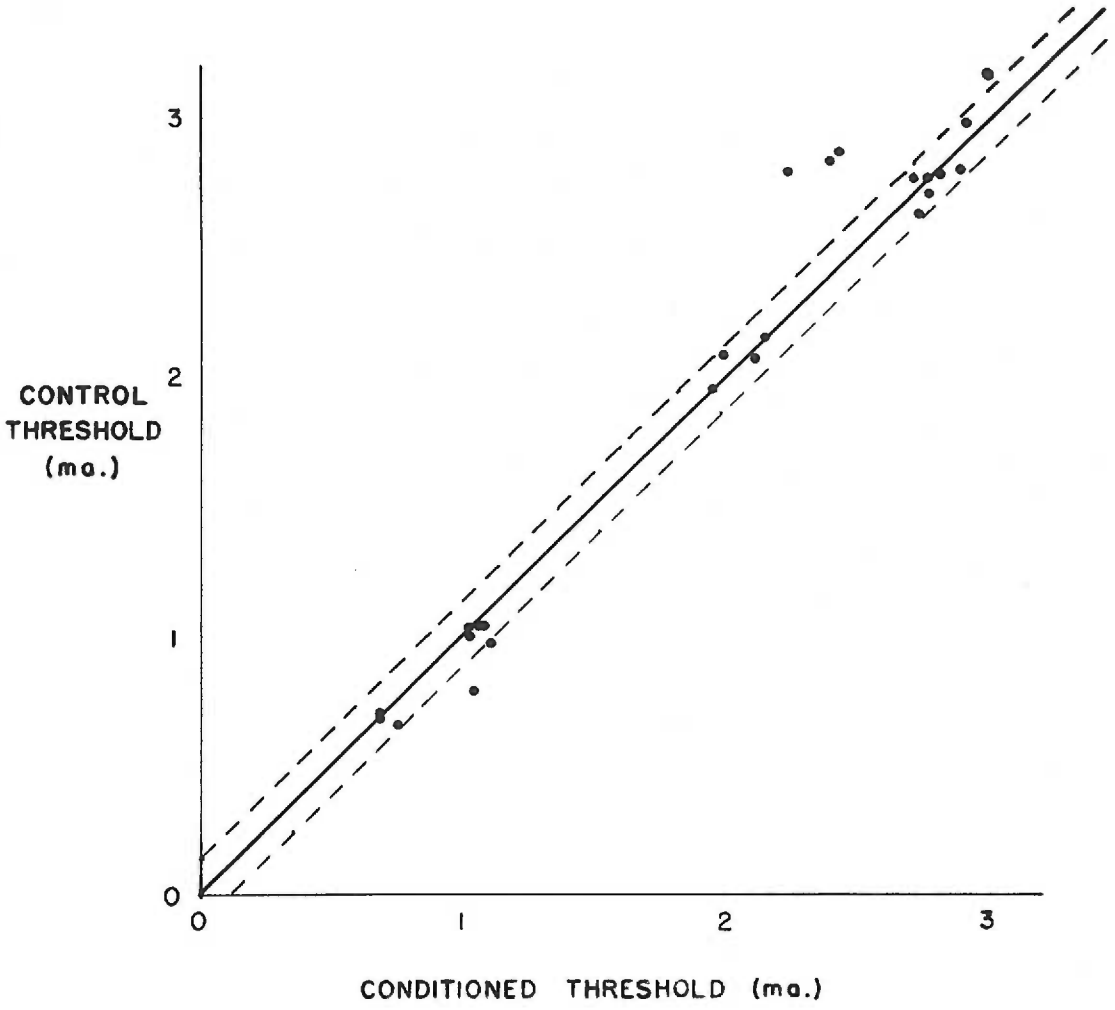


RECRUITING RESPONSE

FIGURE 5

The points plotted represent paired threshold values. The solid line indicates the hypothetical mean, testing the assumption that conditioning the cortex with spindling produces no alteration in the after-discharge threshold.

The dotted lines indicate 2.58 standard deviations on either side of this mean.



SPINDLING

After-Discharge Threshold during Conditioning

To determine if conditioning the cortex had an effect on the after-discharge threshold, a means of comparison of the paired threshold values was needed. In order to depict clearly the relationship between the control and conditioned thresholds, the paired values have been plotted on separate graphs for each of the types of conditioning (Figure 3, page 25; Figure 4, page 26; Figure 5, page 27). The control threshold values have been plotted on the ordinate and the conditioned threshold values on the abscissa. A heavy black line is drawn to represent the locus of points designating control and conditioned thresholds of equal value. If the hypothesis is accepted that there is no significant difference between the mean of the control threshold and the mean of the conditioned threshold, then the paired observations would be expected to fall in a normal distribution about this line. The dotted lines in these illustrations represent the boundaries of 2.58 standard deviations of the differences on either side of the hypothetical mean. The area between the dotted lines would include 99% of the observations if these observations follow a normal distribution.

After-Discharge Threshold during Augmenting Responses

The influence of augmenting waves on after-discharge threshold was determined by fourteen observations in eight animals. Augmenting waves were produced by stimulation of the left nucleus ventralis lateralis at the frequency of 8 to 12 per second, using a train duration of 3.2 seconds. Approximately one-half second after the onset of thalamic stimulus, the testing stimulus was delivered to the sensori-motor cortex.

In order to demonstrate the variations on threshold obtained, the paired observations were plotted graphically (Figure 3, page 25). It is evident upon inspection of the graph that the variation among the conditioned threshold values is approximately the same as that among control values. The plotted values are distributed fairly symmetrically about the heavy black hypothetical mean line. The difference between the paired observations, as judged by the displacement of the plotted point from the mean line, varies considerably. Ninety-nine percent of the paired observations may be expected to fall in the region between 0.23 mv. on either side of the hypothetical mean line, assuming normal distribution. In Table I (page 30) it may be seen that the differences in the paired observations were positive in eight of the fourteen observations and that large positive and negative differences both occurred. The mean of all differences was found to be plus 0.04 ma., signifying that the control threshold values were slightly higher, on an average, than conditioned thresholds. The standard deviation of the differences was calculated to be 0.09. With 13 degrees of freedom and a 5% significance level, the hypothesis that there is no significant change in threshold upon preactivating the cortex with the recruiting response would be acceptable with a t greater than minus 2.16 or less than plus 2.16. As the t value obtained was 0.44, it may be concluded that evoked augmenting waves have no effect on after-discharge threshold under the stated criteria. The probability of accepting a false hypothesis was then statistically tested and it was found that this probability was less than 5% at this sample size.

After-Discharge Threshold during Recruiting Responses

In evaluation of the effect of the recruiting response on seizure

TABLE I

AUGMENTING RESPONSE

Experiment Number	Control Threshold (ma.)	Conditioned Threshold (ma.)	Difference
30	3.25	3.15	+.10
31	2.22	3.08	-.86
32	1.35	1.85	-.50
33	3.35	1.94	+1.41
34	2.17	2.18	-.01
35	2.08	1.96	+.12
38	3.39	3.98	-.59
	2.60	2.50	+.10
39	2.61	2.15	+.46
	2.37	2.35	+.02
	2.27	2.04	+.23
	2.17	1.82	+.35
	2.24	2.45	-.21
	2.25	2.30	-.05

Mean of the differences = +0.041

Standard deviation of the differences (s) = 0.09

$t = 0.44$

The difference is significant if t is less than -2.16 or greater than +2.16 (5% level). No significant difference is found in the threshold current necessary to produce an after-discharge when the cortex is preconditioned with an augmenting response at the 5% level of significance.

If we assume a significant difference in the threshold to be 0.10 ma., then it may be seen statistically that there is a greater than 95% probability that a false hypothesis has not been accepted.

threshold, 22 observations were made in 10 cats. The recruiting response was elicited by repetitive stimulation of the centre median nucleus and Nucleus Reuniens of the thalamus. This conditioning stimulus was, as in the case of augmenting responses, initiated 0.5 second preceding, and persisted for 2.7 seconds after, the application of the cortical stimulus to the anterior sigmoid gyrus.

Upon inspection of the plotted relationships of the paired observations (Figure 4, page 26), it may be seen that the variation in differences among paired observations is less than that in the preceding group of experiments. A "best fit" straight line of these points would appear to lie slightly above the middle range of the plotted line and to have a little less slope. It is, however, very close to the plotted mean line and certainly visually compatible with acceptance of the hypothesis that evoked recruitment produces no effect on cortical seizure threshold. The smallness of the variations was particularly evident in Experiment 42 (Appendix I, page 52), wherein the threshold values for both control and conditioned responses varied only 0.52 ma. over a period of five hours (300 minutes). The area containing 99% of the observations in this study was confined to 0.16 ma. on either side of the hypothetical mean line (the area represented by dotted lines on the graph).

In Table II (page 32) it is noted that the differences range from minus 0.81 to plus 0.72 with positive values occurring in 16 of the 22 trials. The mean of the differences is found to be 0.12 ma. with a standard deviation of 0.06. With 21 degrees of freedom and a significance level of 5%, the t value obtained must be less than plus 2.08 and greater than minus 2.08 to permit acceptance of the hypothesis that the mean of control threshold is

TABLE II

RECRUITING RESPONSE

Experiment Number	Control Threshold (ma.)	Conditioned Threshold (ma.)	Difference
29	1.60	1.64	-.04
30	2.07	2.04	+.03
32	1.16	1.14	+.02
33	2.58	2.15	+.43
34	2.92	2.20	+.72
35	1.98	2.05	-.07
38	1.61	1.64	-.03
	1.50	1.50	.00
40	4.33	4.28	+.05
	3.74	4.55	-.81
	3.41	3.26	+.15
	3.35	3.28	+.07
	3.18	2.86	+.31
41	2.38	1.76	+.62
	1.84	1.74	+.10
	2.08	1.80	+.28
	1.92	1.78	+.14
42	2.39	2.12	+.27
	2.49	2.48	+.01
	2.55	2.58	-.03
	2.64	2.40	+.24
	2.64	2.52	+.12

Mean of the differences = 40.12 s = 0.063 t = 1.91

The difference is significant if t is less than -2.08 or greater than +2.08. No significant difference is found in the threshold current necessary to produce an after-discharge when the cortex is preconditioned with a recruiting response at the 5% level of significance.

If we assume a significant difference in the threshold current to be 0.10 ma., then it may be seen statistically that there is a greater than 95% probability that a false hypothesis has not been accepted.

equal to the mean of the conditioned thresholds. Since a t value of plus 1.91 was obtained, the hypothesis that preconditioning the cortex with the recruiting waves produces no significant change in the threshold to electrical stimulation of the anterior sigmoid gyrus is acceptable. The mathematical probability of acceptance of a false hypothesis at this sample size is found to be less than 5%.

After-Discharge Threshold during Spontaneous Spindling

In the analysis of the role of spindling as a factor affecting the excitability of the sensorimotor cortex to electrical stimulation, 24 paired observations were made on four animals which were subjected to electrolytic destruction of the mesencephalic reticular formation. This induced a state of coma which was characterized electroencephalographically by the frequent appearance of spontaneous spindle bursts in frequencies of 8 to 12 cycles per second and up to 0.5-0.6 mv. in intensity. In order to obtain a state of EEG arousal for determination of the control threshold, a one second train of stimuli was delivered to the hypothalamus (Figure 1C, page 18). This resulted in a disappearance of the spontaneous spindle activity and its replacement by the faster low voltage activity characteristic of the waking electroencephalograms of cats. Although it is stated that the animal is electroencephalographically aroused, it must be emphasized that this animal was not behaviorally aroused, as no motor responses were noted either during the periods of stimulation or between these periods. When a painful stimulus was applied to an extremity of the cat, it was noted to respond by weak withdrawal. In recording the conditioned thresholds an interval between the onset of the spindle burst and the cortical stimulus was manually

provided. The spontaneous spindle activity was seldom interrupted for any length of time by the cortical stimulus itself. The duration of electroencephalographic arousal after hypothalamic stimulation was usually greater than 45 seconds. The cortical test stimulation did not appreciably prolong the period of electrocortical arousal.

The paired values for control and conditioned thresholds varied less from the hypothetical mean in the spindling experiments than in the other two groups of experiments. In this series the maximum deviation was 0.57 ma. and the mean deviation was only 0.05 ma. (Figure 5, page 27). From visual examination of the plotted values, the closeness of fit of the paired threshold to the hypothetical mean line is readily apparent and indicative of the lack of effect of spontaneous spindles on cortical excitability as measured by after-discharge threshold. Three points which vary considerably from the mean line are found to lie in the direction that would indicate lowering of the threshold following the spindle burst. On further analysis of the data, however, factors which would enable differentiation of these paired observations from the others were not found, and it must be concluded without further evidence that these merely represent random variations from the mean.

The area in which 99% of the paired observations fall is within 0.10 ma. on either side of the hypothetical mean line. The fact that the numbers of positive and negative signs are almost equal in Table III (page 35) is evidence of the symmetry with which the observations fell about the hypothetical mean line in Figure 5 (page 27). This symmetry is also evidenced by the small mean of the differences value of 0.04 ma. The standard deviation of

TABLE III

SPINDLING

Experiment Number	Control Threshold (ma.)	Conditioned Threshold (ma.)	Difference
43	2.79	2.22	+.57
	1.95	1.94	+.01
44	1.03	1.02	+.01
	1.04	1.06	-.02
	1.04	1.08	-.04
	1.00	1.02	-.02
	.97	1.10	-.13
	.79	1.04	-.25
	.70	.68	+.02
	.66	.75	-.09
	.68	.68	.00
46	2.07	2.10	-.03
	2.08	1.98	+.10
	2.15	2.14	+.01
	2.87	2.42	+.45
	2.83	2.38	+.45
47	3.17	2.98	+.19
	2.98	2.90	+.08
	2.80	2.88	-.08
	2.78	2.80	-.02
	2.77	2.76	+.01
	2.77	2.70	+.07
	2.71	2.76	-.05
	2.63	2.72	-.09

Mean of the differences = +0.048 s = 0.039 t = 1.28

The difference is significant if t is less than -2.07 or greater than +2.07. No significant difference is found in the threshold current necessary to produce an after-discharge between the spindling and the aroused cat, at the 5% level of significance.

If we assume a significant difference in the threshold current to be 0.10 ma., then it may be seen statistically that there is a greater than 99% probability that a false hypothesis has not been accepted.

the differences is found to be 0.039. With 23 degrees of freedom and at the 5% level of significance, the hypothesis that there is no significant difference between the control and conditioned thresholds must be rejected if the t value is less than minus 2.07 or greater than plus 2.07. Since a t value of plus 1 was obtained, the hypothesis that spontaneous spindle activity produces no significant change in the after-discharge threshold is acceptable. The probability of the acceptance of a false hypothesis was found to be less than 5% at this sample size.

CHAPTER IV

DISCUSSION

The experiments reported here have been concerned with an attempt to determine if high voltage, alpha frequency electrocortical activity as seen in certain electroencephalographic activation procedures produces any effect on after-discharge threshold. In unanesthetized animals, preconditioning the cortex by the augmenting and recruiting responses was found to have no effect on the after-discharge threshold. Spindle activity, when presented during the test period, was similarly ineffective with respect to after-discharge threshold. Different patterns of after-discharge were noted from time to time in the same animal. The different types of after-discharge were not correlated with either the presence or the absence of conditioning or with the type of conditioning used. Upon threshold stimulation of the cortex, the after-discharge in the left frontal cortex was accompanied by a minimal after-discharge in the right frontal cortex in about 75% of the cases. This degree of spread was not altered by conditioning.

In focal epilepsy the region of the cortex containing the epileptogenic focus has been shown to be hyperexcitable to electric stimuli in that excitation of these specific regions, with stimuli which are ineffective when applied to normal cortex, may produce a seizure similar to those that the epileptic has under normal conditions[39]. The neurons in experimentally produced epileptogenic lesions have been shown to have the properties of increased rate of discharge and susceptibility to hypersynchronous discharge during the interictal period as compared with similar neurons in normal

cortex[41]. It has been suggested that these properties of the epileptogenic focus may be brought about by several different mechanisms. Relative anoxia has been proposed as an inciting factor[39]. This may be brought about by vascular anomalies, scar tissue formation (gliosis) following a traumatic insult, infiltration of neoplastic cells, infection with reactive changes, or by a vascular insult. Penfield and Jasper have indeed concluded that, "the various types of lesions, expanding or atrophic, ... produce continuing or recurring ganglionic ischemia" and "propose the hypothesis that this mild or recurrent chronic ischemia is irritating to nerve cells and that it is the cause of epileptic discharge"[39].

In the human afflicted with a focal type of epilepsy, or in the cat in which an epileptogenic lesion has been created, we may imagine that the normal cortex has uniform excitability over all its parts, and that a state of hyperexcitability exists only in the epileptogenic focus. In the analysis of factors thought to affect the production of abnormal electrocortical activity over the region of the cortex containing the focus, two mechanisms of action may be considered. The effect of the high voltage, alpha frequency activity may act on the entire cortex to produce a generalized increase in excitability. The hyperactivity of the epileptogenic cortex in this case would be proportionally increased. The epileptogenic focus would fire before normal areas of cortex because of the summation of its own state of hyperexcitability with the additional excitatory influence exerted upon it by the activating procedure. Another means by which activation may take place is through a specific effect on the abnormal aggregate of neurons within the focus. These neurons, with their propensity to increased rate of

discharge and increased susceptibility to hypersynchronous discharge, may well be much more susceptible to the activating influences of high voltage, alpha frequency electrocortical activity than is the normal cortex. Although there is little evidence available that evoked cortical slow wave activity may produce a specific effect on abnormal epileptogenic neurons, there is definite evidence that many of the neuronal components of the cortex are excited during this type of activity. Brookhart and Zanchetti[9] have demonstrated an augmentation of responsiveness in the cortico-spinal system during the high voltage, alpha frequency electrocortical activity of the augmenting response and of spontaneous spindling.

Starting from the point of view that high voltage, alpha frequency activity has an excitatory influence on some cortical cells, we have proposed that this effect is accompanied by a decreased threshold of normal cortex to the production of epileptiform activity. We have tested the hypothesis stated above that the effect of activation procedures is generalized over all regions of normal cortex. Since the emphasis has been on the behavior of normal cortex, there has been no need to use epileptic animals in this series of experiments. Because augmentation, recruitment, and spontaneous spindling have been found not to affect the after-discharge threshold in this study, we may then tentatively accept by exclusion the counter-hypothesis that the activating influence of high voltage, alpha frequency electrocortical activity is exerted primarily on the abnormal epileptogenic neurons. This is consistent with the observation that these activating procedures, as used clinically, are not capable of producing an abnormal electrocortical discharge in the normal cortex. The lack of evidence of a generalized effect

on the cortex from initiation of a high amplitude electrocortical activity is consistent with the clinical observation that the abnormal electrical activity which is elicited by these activating procedures is usually limited to the region of the focus.

Li, McLennan, and Jasper[28], using microelectrode recording techniques, have shown brief spikes representing action potentials resulting from the discharge of cortical cells. These spikes were shown to be related to the evoked slow waves of approximately 10 m sec. duration and the spontaneous brain waves of the cortex. Li, Cullen, and Jasper[29], studying cortical potentials evoked by repetition of stimulation of the ventral posterior nucleus of the thalamus and of a peripheral afferent nerve, demonstrated that the surface-negative phase of the evoked potential complex decreases in amplitude until the microelectrode reaches layers IV and V of the cortex. At this point the electrical activity became reversed in sign. This evoked potential complex is proposed as a wave of electrotonic depolarization propagated over ascending apical dendrites following transynaptic activation of large nerve cells in the depths of the cortex. It was also noted in this latter work that intracellular spikes may not be preceded by any detectable prepotential or "generator potential".

Spencer[43], studying depth records of the electrical activity in the cerebral cortex associated with spontaneous and evoked rhythmic waves, noted a similar reversal of the cortical potential evoked by stimulation of the posterior lateral nucleus of the thalamus. It was concluded in this study that the reversal in the third and fourth layers which develops in augmenting and spindle waves represents the synaptic activation of the neurons in these

layers at the level of their basal dendrites and cell bodies. In recording unitary activity associated with recruiting and Type II spindles, Spencer found that the waveforms involved a less powerful, less synchronized, and therefore presumably more indirect activation of the neurons whose cell bodies lie within the third, fourth, and fifth layers of the cortex.

The thalamocortical projection pathways may be differentiated into two major classes[31]. Fibers from the specific projecting thalamic nuclei have been shown to have the greatest number of synapses with cells in the fourth layer of the cortex and to a lesser extent with cells in the third layer. These afferent fibers branch widely in these layers, forming a dense dendritic plexus, and have synapses with cells such as the long pyramids, the long spindles in their shafts, the medium pyramids, and the medium spindles. This anatomical knowledge lends credibility to the observation that pericorpuscular connections appear to be designed for the reliable transfer of sensory information. Li, Cullen, and Jasper[29] concluded that the primary response appeared to involve the specific cortical afferents which presumably activate Golgi type II cells. These cells in turn probably exert their effects through their pericorpuscular synapses with the pyramidal cells[31].

While the non-specific projection fibers from the midline nuclei of the thalamus give collaterals ending chiefly in layer IV, many of these fibers extend as far as layer I. It has been suggested [43] that these neurons facilitate or inhibit transmission over pericorpuscular synapses. This suggestion is consistent with the idea that the fibers terminate in paradendritic endings, which seem more appropriate for modulation of the excitability of the cell body[43]. The response to repetitive stimulation of the

non-specific projecting nuclei (recruiting response) and some spontaneous spindle waves seem to be mediated by unspecific cortical afferents which terminate in synapses on the apical dendrites[43]. Evidence that synaptic connections on the apical dendrites produce a modulatory effect on the excitability of the nerve cell is found in the work of Bishop and Clare[12]. In an attempt to analyze the unitary activity associated with 8 to 12 second electrocortical activity, similarities between augmentation, recruitment, and spindling were illustrated. These authors imply that these similar types of slow cortical waves are essentially dendritic potentials. The basic frequency of this activity is explained on the basis of a recovery cycle of certain synaptic regions on the apical dendrites of cortical pyramidal cells.

The finding of a minimal spread to the contralateral cortex in 75% of the threshold records is indicative of activation of callosal fibers. These fibers have been shown to arise mainly in the fifth and sixth layers of the cortex and to terminate in layers I to IV, but mostly in layers II and III. As the spread of after-discharge was not affected by the presence of different types of slow wave activity, it may be concluded that the excitability of the cells of origin of callosal fibers was not altered. Furthermore, the uniformity of the spread may also be taken as evidence that the cortical elements in the contralateral areas in which callosal fibers terminate were not altered by the conditioning procedures.

The modulation effects of the non-specific cortical afferents, the excitatory effects of the specifically projecting cortical afferents, and the electrotonic involvement of the apical dendrites associated with spontaneous spindles certainly involve a diffuse influence on all layers of the cortex.

Consequently, this influence would also be exerted upon the neurons which are responsible for the after-discharge. The lack of any effect on the after-discharge noted in this study would indicate the absence of a factor, present in the epileptogenic focus, which predisposes to a specific reduction in the threshold for this region of the cortex during high voltage, alpha frequency conditioning.

In the chronic animal with an epileptogenic lesion we would be able to test directly the hypothesis that the activation procedures in question produce their effect on an abnormal aggregate of neurons contained in the focus rather than to accept this by exclusion. This could be tested both by measuring the effect of conditioning the cortex with high voltage, alpha frequency activity upon the after-discharge threshold and by use of unitary recording techniques to measure the effects of this activity on the already hyperactive, hypersynchronous abnormal focal neurons.

CHAPTER V

SUMMARY

1. In this study the effect of induced and spontaneous high voltage, alpha frequency cortical activity was determined by measuring the susceptibility of the sensory motor cortex of the cat to the production of an after-discharge by electrical stimulation. This study represents an attempt to determine whether clinical electroencephalographic activation procedures which produce a similar electrocortical activity act by excitation of all of the cortical neurons, normal and abnormal, or whether the excitation affects only the abnormal constituents of the epileptogenic focus.

2. Different patterns of after-discharge were observed. No apparent relationship between the control and the conditioned threshold after-discharge patterns were noted, nor were differences noted between different types of conditioning.

3. The appearance of an after-discharge in the left frontal region associated with a threshold stimulation was usually accompanied by minimal after-discharge in the contralateral frontal cortex without spread to other regions of the cortex. This spread was not affected by conditioning the cortex with augmentation, recruitment, or spindling.

4. The duration of the after-discharge and the latency period before development of the after-discharge were not affected by conditioning the cortex.

5. Conditioning of the cortex with augmentation, recruitment, or spindling produced no significant difference in the threshold for production of abnormal electrocortical activity by electrical stimulation of the anterior sigmoid gyrus in the cat.

6. Implications of the results of this study to a mechanism responsible for the production of abnormal electrocortical activity associated with epilepsy are discussed.

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APPENDIX I

Experiment No.	Time	Threshold (ms.) Control	Paired Control	Conditioned*
28	40	5.8		
	75	3.88		
	100		3.39	3.98 (A)
	140		2.60	2.50 (A)
	145	2.50		
	230	1.64		
	240		1.61	1.64 (R)
	280	1.50		
	285		1.50	1.50 (R)
29	85	2.62		
	120	2.36		
	210	1.94		
	240	1.60		
	250		1.60	1.64 (R)
	260	1.60		
30	60	4.16		
	115	4.72		
	170	5.80		
	295	3.21		
	305		3.25	3.15 (A)
	330	3.35		
	395	2.07		
	410		2.07	2.04 (R)
	420	2.06		
31	25	1.40		
	90	2.20		
	185		2.22	3.08 (A)
	230	2.24		
32	125	1.66		
	185	1.95		
	250		1.35	1.85 (A)
	270	1.16		
	295		1.16	1.14 (R)
	300	1.16		

Experiment No.	Time	Threshold (ma.) Control	Paired Control	Conditioned*
33	45	4.35		
	115	3.67		
	150		3.35	1.94 (A)
	295	2.01		
	340		2.58	2.15 (R)
	380	3.08		
34	55	2.20		
	135	2.16		
	175		2.17	2.18 (A)
	200	2.18		
	230		2.92	2.20 (R)
	250	3.42		
	340	3.54		
35	75	2.10		
	110	2.14		
	120		2.08	1.96 (A)
	135	2.00		
	170	1.98		
	185		1.98	2.05 (R)
	200	1.98		
	230	1.70		
	270	1.76		
39	95	3.18		
	125		2.61	2.15 (A)
	135	2.42		
	165		2.37	2.35 (A)
	185	2.34		
	200		2.27	2.04 (A)
	225	2.15		
	235		2.17	1.82 (A)
	275		2.24	2.45 (A)
	280	2.25		
	295		2.25	2.30 (A)
	325	2.25		
40	125	4.85		
	165		4.33	4.28 (R)
	205		3.74	4.55 (R)
	225	3.46		
	250		3.41	3.26 (R)
	280		3.35	3.28 (R)
	295	3.32		
	315		3.18	2.86 (R)
	345	2.98		

Experiment No.	Time	Threshold (ma.) Control	Paired Control	Conditioned*
41	130	2.96		
	155		2.38	1.76 (R)
	180	1.80		
	185		1.84	1.74 (R)
	215		2.08	1.80 (R)
	230	2.20		
	260		1.92	1.78 (R)
	285	1.68		
42	85	2.24		
	130	2.48		
	215	2.54		
	250		2.39	2.12 (R)
	265	2.32		
	295		2.49	2.48 (R)
	305		2.55	2.58 (R)
	320	2.64		
	335		2.64	2.40 (R)
	355		2.64	2.52 (R)
	380	2.64		
43	155	4.50		
	185		2.79	2.22 (S)
	200	1.94		
	215		1.95	1.94 (S)
	240	1.96		
45	105	1.02		
	110		1.03	1.02 (S)
	120	1.04		
	130		1.04	1.06 (S)
	145		1.04	1.08 (S)
	150	1.04		
	165		1.00	1.02 (S)
	180		0.97	1.10 (S)
	210	0.90		
	240		0.79	1.04 (S)
	265		0.70	0.68 (S)
	275	0.66		
	300		0.66	0.75 (S)
	360		0.68	0.68 (S)
	380	0.68		

Experiment No.	Time	Threshold (ma.) Control	Paired Control	Conditioned*
46	270	2.06		
	295		2.07	2.10 (S)
	305		2.08	1.98 (S)
	315	2.08		
	325		2.15	2.14 (S)
	430	2.92		
	455		2.87	2.42 (S)
	475		2.83	2.38 (S)
	500	2.78		
47	150	3.36		
	175		3.17	2.98 (S)
	200		2.98	2.90 (S)
	220	2.84		
	245		2.80	2.88 (S)
	255		2.78	2.80 (S)
	270	2.76		
	290		2.77	2.76 (S)
	300		2.77	2.70 (S)
	315	2.78		
	330		2.71	2.76 (S)
	345		2.63	2.72 (S)
	360	2.56		

* Signifies preconditioned with:
(A) Augmentation
(R) Recruitment
(S) Spindling

APPENDIX II

The following graphs indicate the changes in both control and conditioned thresholds over a period of time in 16 experiments. The solid dots denote control threshold values, and the x's, conditioned thresholds. The control threshold values are connected by a solid line. The conditioned threshold values are connected by dotted lines, except where different types of conditioning are used.

Experiments 28, 29, and 30

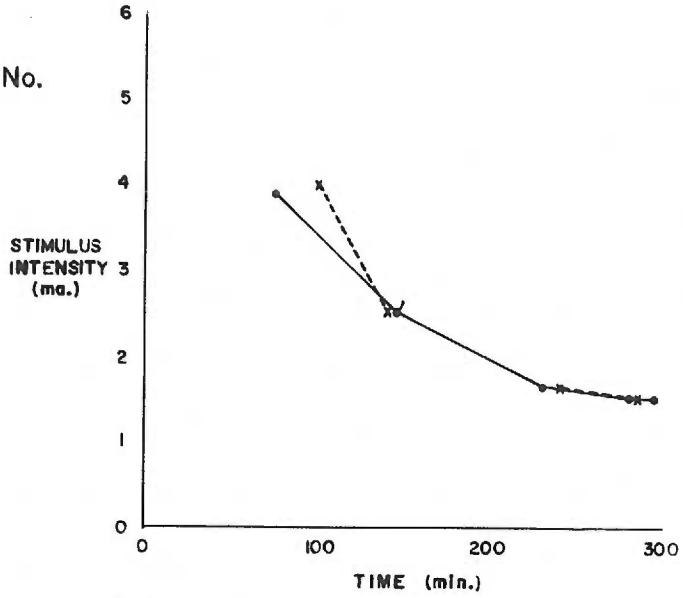
In experiment 28 the first two conditioned threshold values are for augmentation and the latter two for recruitment.

In experiment 29 only recruitment preconditioning was tested.

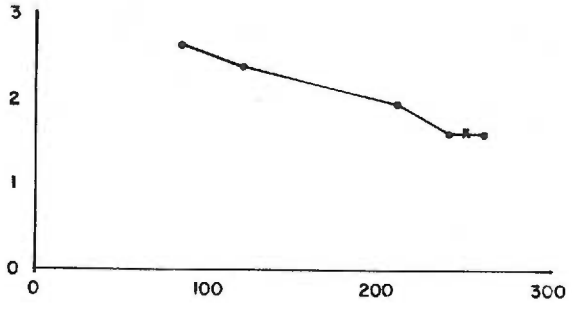
In experiment 30 the first conditioned value is an augmentation conditioned threshold, while the second is a recruitment conditioned threshold.

Experiment No.

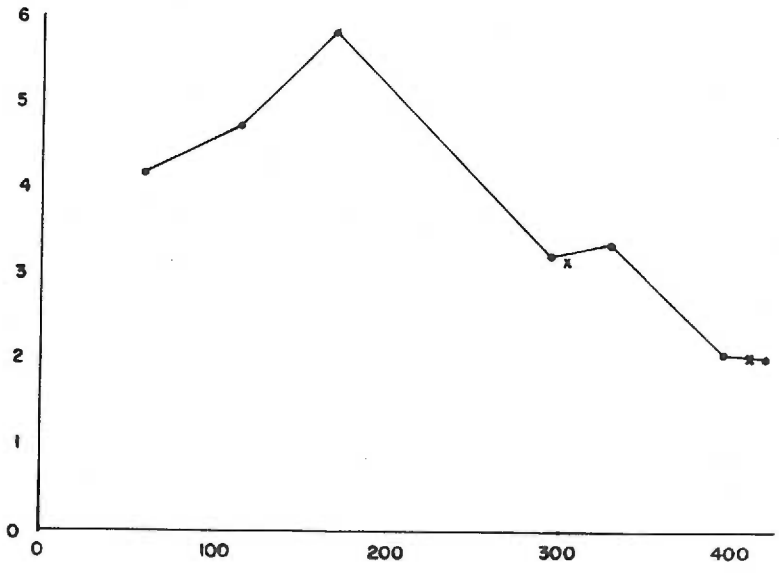
28



29



30



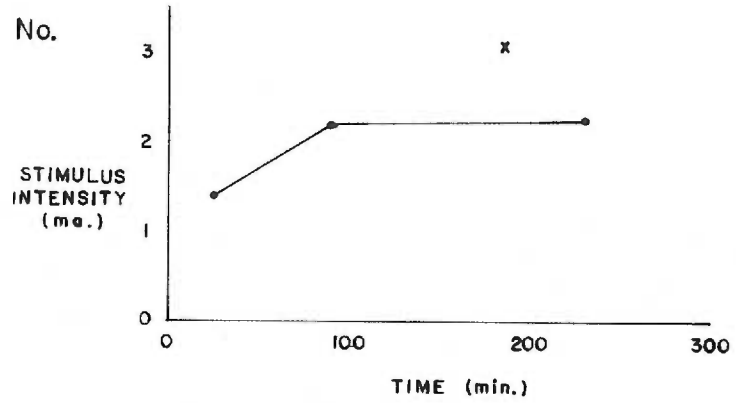
Experiments 31, 32, and 33

Experiment 31 deals only with conditioning by augmentation and experiment 32 only with conditioning by recruitment.

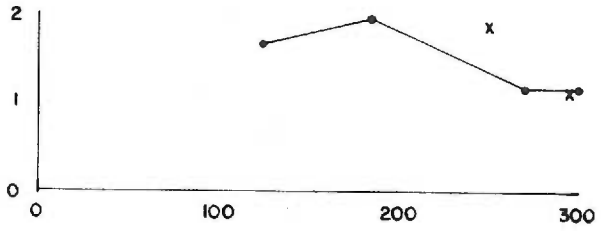
In experiment 33, the first conditioned threshold value is for augmentation, the second for recruitment.

Experiment No.

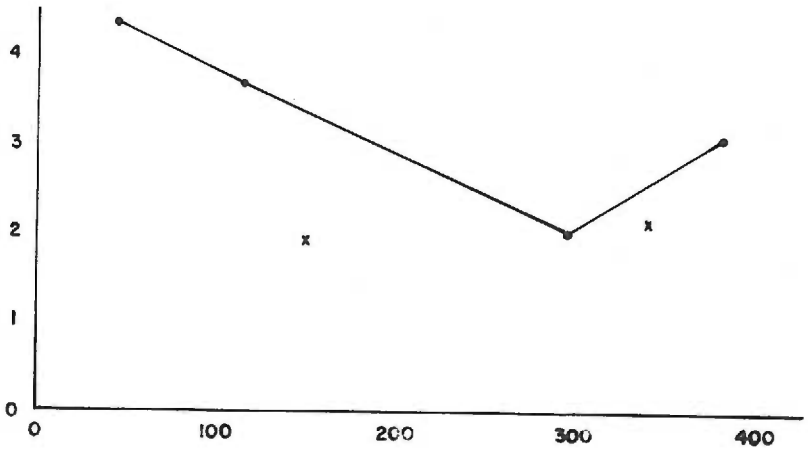
31



32



33



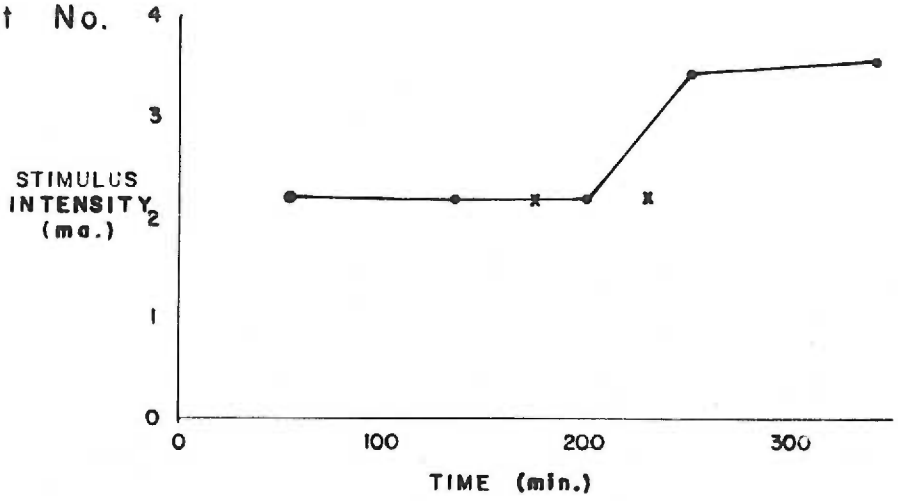
Experiments 34, 35, and 39

In experiments 34 and 35, the first conditioned threshold is for augmentation, while the second is for recruitment.

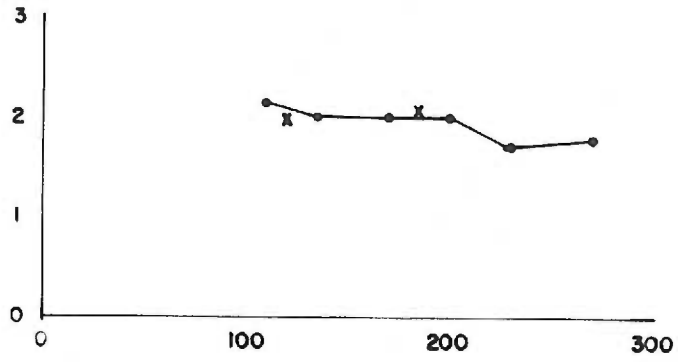
Only augmentation was used for conditioning in experiment 39.

Experiment No.

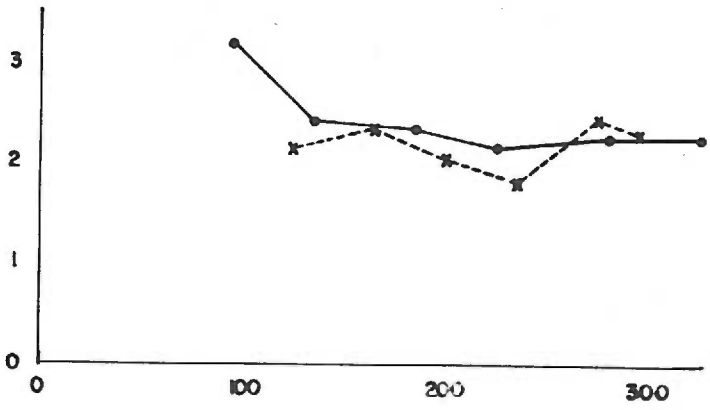
34



35



39



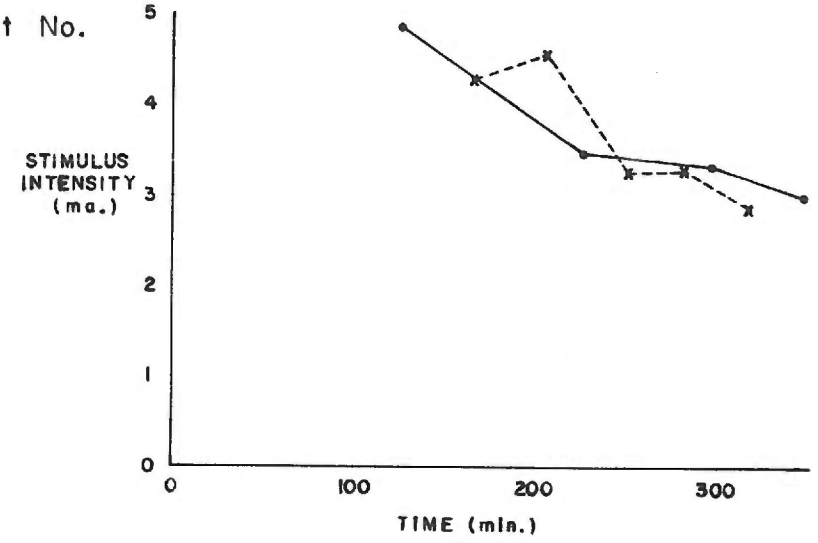
Experiments 40, 41, and 42

In experiment 40, only augmentation was used to condition the cortex.

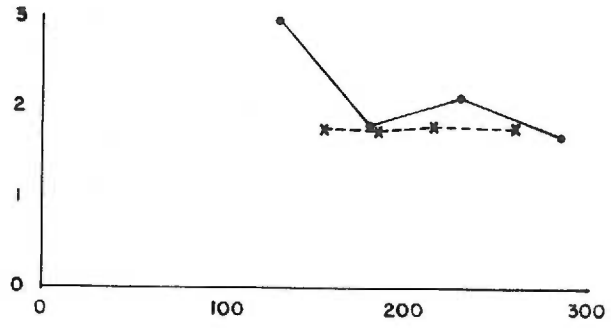
In experiments 41 and 42, only recruitment was used.

Experiment No.

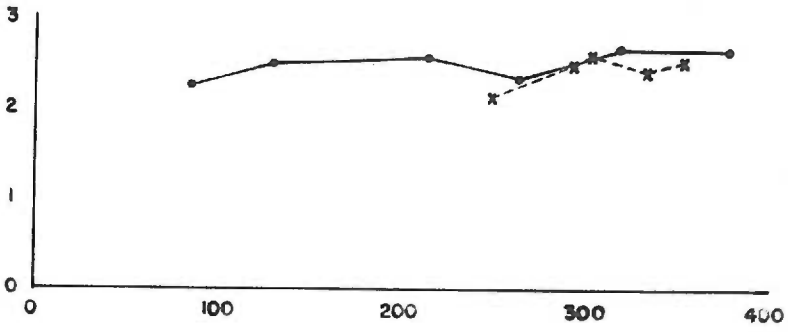
40



41



42

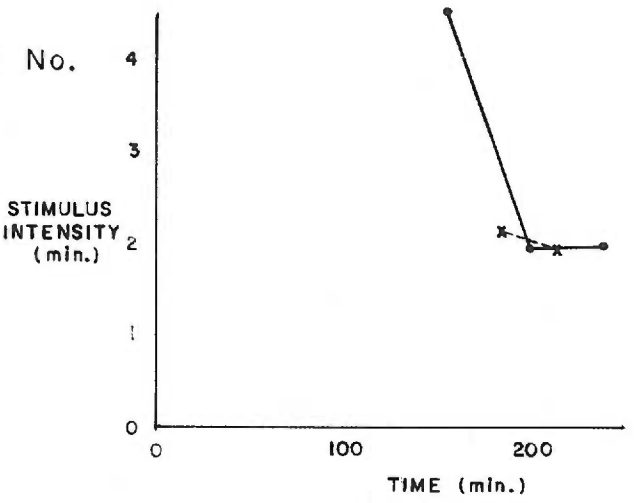


Experiments 43, 45, 46, and 47

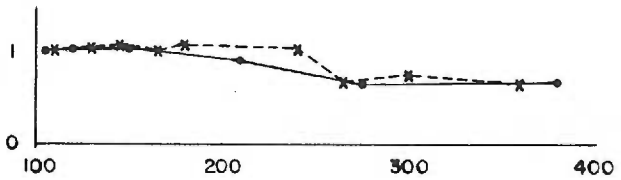
In experiments 43, 45, 46, and 47, spindling was the only conditioning activity used.

Experiment No.

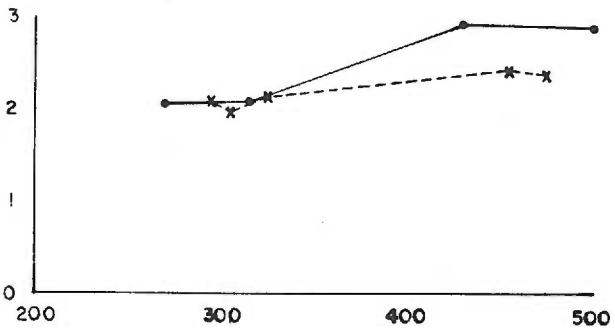
43



45



46



47