RESPONSE PROPERTIES OF NEURONS OF CAT'S SOMATIC SENSORY CORTEX TO PERIPHERAL STIMULI[1]

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INTRODUCTION

THE METHOD of single unit analysis has now been applied to three primary sensory receiving areas of the cerebral cortex (4, 14, 15, 16, 20, 21, 22, 23, 25). Among these studies, considerable attention has been given to the somatic sensory areas, for Li *et al.* in an extensive series of investigations (20, 21, 22, 23) have described the responses of neurons in this region to electrical stimulation of the specific relay nucleus of the thalamus, as well as to stimulation of those thalamic nuclei they designate as unspecific, or diffusely projecting. The discharge properties of neurons of the somatic sensory areas in response to peripheral nerve volleys have been detailed by Amassian (4), and he has also given the first description of the neuronal activity of a sensory association area (5). Preliminary reports of similar studies have appeared from the Paris laboratories of Albe-Fessard (2, 3, 11).

In the present investigation we wished to study the functional organization of the first somatic sensory cortex by the method of single unit analysis, and to determine as precisely as possible the firing patterns of cortical cells activated by stimuli delivered to the related sense organs. We wished also to determine which modality components of somatic sensibility project upon the somatic sensory cortex, as well as to gain some idea of the functional organization of that projection. Our purposes required that the activity of cortical cells be observed over considerable periods of time in a stable fashion. It appears from the published records that the technique of intracellular recording from cortical cells has not yet reached the stage of perfection required, for only Phillips (26, 27), dealing with the motor cortex, has been able to study cortical neurons for considerable periods of time after impalement without deterioration of resting or action potentials. His beautiful records, however, give examples of what may be hoped for with this technique. We have, therefore, persisted in the method of extracellular recording. A chamber has been developed by one of us (12) with which it is possible to obliterate cortical pulsations without the risk of direct pressure injury, yet allowing free lateral movement of the electrode carrier.

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In section I of the present paper the response patterns of cortical neurons of the first somatic sensory area of the cat are described, as well as the spontaneous activity encountered. The short term variability of and changes occurring in time of the spike amplitudes of single unit discharges are described, and a criterion is established by which a group of impulses can be identified as those of the same single neuron. The signs of onset and progression of injury are described. The spatial distribution of the action potential field about an active cortical cell is given, as well as the distribution in depth of all cells studied. Sections II, III, and IV deal, respectively, with the relation of response patterns to single peripheral stimuli to repetitive stimuli, and with the slow wave phenomena observed. In the paper which follows the modality and topographical attributes of neurons of the somatic cortical area are described, and an hypothesis concerning the functional organization of this cortical area is put forward which for the moment accords with the data obtained.

METHODS

Successful experiments have been carried out upon 59 cats, which were numbered consecutively, as were the cortical neurons studied in each animal. For example, in the text which follows, such a term as SC I-57-3 refers to the third neuron studied in the 57th experiment of this series. In all, 685 neurons have been isolated and some observations made upon each. Many of these were studied with only one purpose in mind, such as modality identification, or measurement of the peripheral receptive field, etc. More extensive studies, and photographic records of the responses, were made upon 113 of these neurons.

Animals weighing about 2.5 kg. were chosen when possible for the experiments; several heavier and a few lighter were used. Body temperature was maintained between 36 and 38 degrees C. In the first 18 cats anesthesia was induced by an initial intraperitoneal injection of 36 mg./kg. of sodium pentobarbital, and maintained by later injections of small amounts at a level at which spontaneous movements did not occur. At this and all deeper levels of anesthesia the number of active and drivable neurons encountered in the cortex is greatly limited. Much better conditions for the study of single cortical neurons were obtained in the remaining 41 animals in the following way. Anesthesia was induced with ether. After no more than one hour of ether, a regime of intravenous injections, alternating at about 30 minute intervals between 20 mg. of Pentothal and 1.0 mg. of d-tubocurarine chloride was begun; occasionally the amount of drug injected varied slightly. Respiration was maintained by a pump, when necessary. In this way the animals were carried under very light barbiturate narcosis, and spontaneous and reflexly induced movements were prevented by the neuromuscular blocking agent. Intermittent recovery from the block made it possible to be certain that the animal was unconscious at all times. Successful application of this regimen depends upon several things. First, if ether anesthesia is maintained for longer than about one hour there frequently occurs a prolonged period of depression of cortical cells, which persists long after the time when it is reasonable to suppose that all ether has been excreted in the expired air. Secondly, d-tubocurarine chloride has a central depressing action, and in our experience if given in large amounts or if continued for many hours will produce what appears to be a synaptic block at some level of the somatic afferent system. Decamethonium bromide, which we used in a few experiments, seems to have an even more marked central synaptic blocking action.

Method of recording. The microelectrodes were similar to those used earlier in a study of neurons of the thalamic tactile region (29). The electrode is a glass micropipette with a tip diameter of 2–4 μ. The pipette is filled to the tip with indium, and upon the indium surface first gold and then platinum are deposited electrolytically. The electrical properties of similar electrodes have been described by Svaetichin (32). We would like to emphasize that it is necessary for cortical recording to use electrodes of very gradual taper, in

order to avoid pressure damage. Our typical electrodes measured 10 μ in diameter at 1 mm. distance from the tip, and 35 μ at 2 mm. from the tip.

There are two major obstacles to stable recording from single cortical neurons. The first is the toughness of the arachnoid. Steady downward movement of a 3 μ microelectrode tip against the cortex results in an indentation of the cortex of remarkable extent, before penetration and plunge-through occur. This causes an undeterminable degree of damage to the cortex, and the actual first recording site may be as much as 1 mm. below the cortical surface. This was avoided by first removing a very small area of the arachnoid membrane, by dissection under a microscope, from the site of entry, previously chosen for topographic reasons by gross electrode recording of evoked potentials from the brain surface. With practice this dissection can be made without damage to vessels or cortex. The microelectrode can then be passed into the cortex under microscopic observation, without dimpling of the

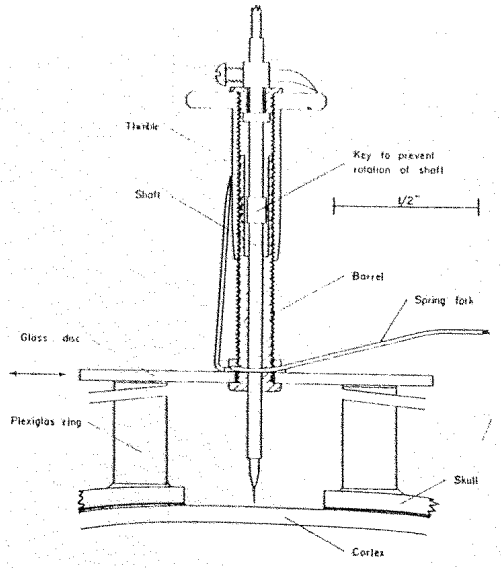

FIG. 1. Schematic drawing of closed chamber used for microelectrode recording from cerebral cortex. Glass cover, carrying electrode drive in its center, slides easily under pressure of spring fork. Inlet and outlet ports for displacement of air by saline solution shown but not labeled (after Davies, P. W. (12)).

cortex, and a reasonably accurate measurement can be made of the level of contact between the electrode tip and the denuded surface.

The second mechanical difficulty is the pulsatile and respiratory movement of the brain surface which occurs when the skull and dura are opened. We controlled these movements by recording through a rigid liquid filled chamber, which is shown in Fig. 1, and described in more detail elsewhere (12), attached to the skull over the bony and dural opening with dental impression compound. The microdrive is permanently mounted in the movable glass cover of the chamber, so that the electrode can be moved transversely at will, without opening the chamber. The electrode is mounted in the drive and the chamber filled with 0.9 per cent NaCl solution, which has been filtered. All the air is displaced by the solution and the ports tightly closed. The tip of the electrode can then be seen through the microscope, and oriented over the arachnoid opening. Accurate vertical movements of 4 μ can be made with the screw type drive. In this way the hydraulic relations existing in the intact head are to a considerable extent re-established, without the injury to the cortex which is likely to accompany the use of restraining devices pressed directly against its surface. Special effort was made to place the chamber on the skull so that the electrode approached the cortex as nearly perpendicularly as possible, for reasons that appear in the following paper.

Amplification and display of responses. The potential differences taking place between the microelectrode tip and a second lead clipped to scalp or headholder were amplified by a conventional four stage capacity coupled differential amplifier, designed by Dr. S. A. Talbot. This amplifier has a D.C. input impedance of about 0.5 megohm. It was operated

with one side of the input at ground potential, so that differential action was lost. In the first 30 experiments the amplifier was fed directly from the microelectrode. The overal frequency response curve of the recording system under these conditions was measured by inserting a test signal into a saline bath surrounding the microelectrode tip and observing the amplifier output at different frequencies. The results are shown in Fig. 2, curve A. In experiments 31 through 57 a cathode follower input circuit was used, which greatly improved the signal to noise ratio and the frequency response curve of the system, which is given as curve B of Fig. 2. In these later experiments the input signal was frequently delivered from the cathode follower to two amplifiers operated in parallel, one set with large and the other with small coupling capacitances. The frequency response of the latter

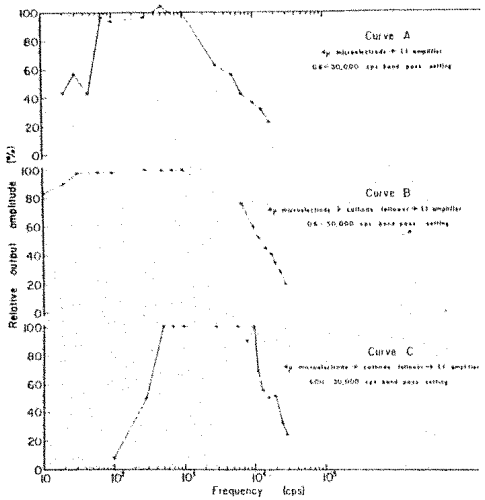

FIG. 2. Response curves of low input impedance (LI) amplifier used in these experiments. Curves A, B and C are for the various input conditions noted on graph. In each case a small signal of constant amplitude was applied at different frequencies to a saline medium surrounding microelectrode tip. Microelectrode was either connected directly to amplifier input (Curve A) or indirectly through a cathode-follower circuit (Curves B, C).

arrangement is given as curve C of Fig. 2. The recording conditions for each group records illustrating this and the following paper are given in the appropriate legends. It obvious that recording condition A leads to considerable distortion of such rapid transien as soma action potentials, while recording condition C will suppress brain wave activi Condition B yields good replicas of both slow waves and rapid impulse discharge. *We w to emphasize that none of the statements or conclusions in this paper are solely dependent up the form or time course of the potential changes observed.* The phenomena recorded were d played by a modified DuMont model 279 oscilloscope, and photographed with a Gr kymograph camera.

Methods of stimulation. Light mechanical stimulation of the body surface was used mapping the peripheral receptive fields related to particular cortical neurons. Such stir lation, with a small blunt instrument, served to differentiate those units driven by l movement from those activated by direct pressure upon the skin surface. For more curate timing of events electrical stimuli were delivered through a pair of sharp need mounted about 1 mm. apart and insulated to their tips, which were thrust into the sl The stimulating circuits provided a wide variety of pulse and train sequences, and varia pulse voltages and durations. Governing delay circuits allowed flexible sequences of stir lus intervals, sweep recurrence rates, etc. We assume that stimuli delivered in this v excite terminal branches of cutaneous afferent nerve fibres rather than sensory end orgs and that increases in strength of stimulus producing changes in cortical nerve cell dischs do so by recruitment of additional peripheral nerve fibers. In our experience this forn stimulation causes discharge patterns of single central neurons of the system which du cate in every way that we can measure those produced by brief mechanical displacem of hairs or of the skin surface. Joints were rotated by hand, and we have as yet no mea

of the extent or speed of the joint movements which drove the "position indicator" neurons described in the following paper.

A statistical treatment of certain groups of data has been made. The terms "highly significant," "significant," and "probably significant," when used to describe the differences between means, indicate a probability smaller than 0.001, 0.01, or 0.05, respectively, that such a difference could have arisen by chance (Welch's test for populations that cannot be assumed equal). The sizes of the samples for different groups of data vary, even though they may pertain to the same unit, for the number of records available for measurements of different values is different. Further, the number of units available for analysis of different observations differs. All records were measured or counted on the projected images of the original film records, enlarged 15 times. The records chosen for illustration have not been retouched. Large population counts of the numbers of spikes per response were made directly from the tube face.

The peripheral receptive fields the stimulation of which activated single cortical neurons were determined by weak mechanical stimuli, marked in india ink, and photographed. These photographs were later projected to natural size, traced, and the outline tracings measured with a polar planimeter to obtain the area of the receptive field.

Anatomical preparations. In 15 of the animals a block of cortex including the first somatic sensory area was fixed in formalin at the end of the experiment, embedded in paraffin, sectioned at 10 μ, stained with thionin, and every section mounted for anatomical study.

Results

I. Response Patterns of Cortical Neurons

Our observations of the cortical surface made with a dissecting microscope (16×) through the window of the closed recording chamber agree with the findings of others (17) that the hydraulic seal so imposed almost completely eliminates the movements of the cortex caused by the respiratory and vascular pulsations. Since this is so, an opportunity is presented to establish the range of variation of amplitude of the discharges of presumed single units in the absence of these disturbing factors, and to establish a definite criterion which might aid in establishing a population of spike-like discharges as those of a single neural source. Before presenting these data we wish first to describe the course of events as an electrode enters the cortex and the responses of cortical neurons to brief cutaneous stimuli, for it is this class of responses that is used most extensively for amplitude measurements.

I–1. *Course of events as microelectrode passes through cortex*

Once an electrode enters an active region of the cortex it is common to observe in the record several initially negative, spike-like potential variations. Each group of similar amplitude is presumably derived from the same single neuron. With electrodes larger than about 4 μ in diameter usually many such apparently unitary discharges are recorded at the same time, and only rarely can one isolate a group of discharges of one amplitude. Even using smaller electrodes this isolation is difficult to achieve, and it is rare to isolate initially negative discharges completely, for usually some electrical sign of the activity of distant units remains in the record. That this must be so follows from the fact that the potential field about an active cortical cell has a considerable spread, and the fields of adjacent cells overlap, which will be shown in section I–6.

I–2. *Early repetitive response and its modal value*

It will be clear from the charts and records of Fig. 3 that the usual response of a cortical neuron to a brief peripheral stimulus consists of a short repetitive train of impulses at high frequency. The number of spikes occurring most frequently in a population of such responses, *i.e.*, its *modal* value, is commonly from one to four, and uniquely in our material, five. It is also clear from Fig. 3 that the next most frequently occurring number of spikes

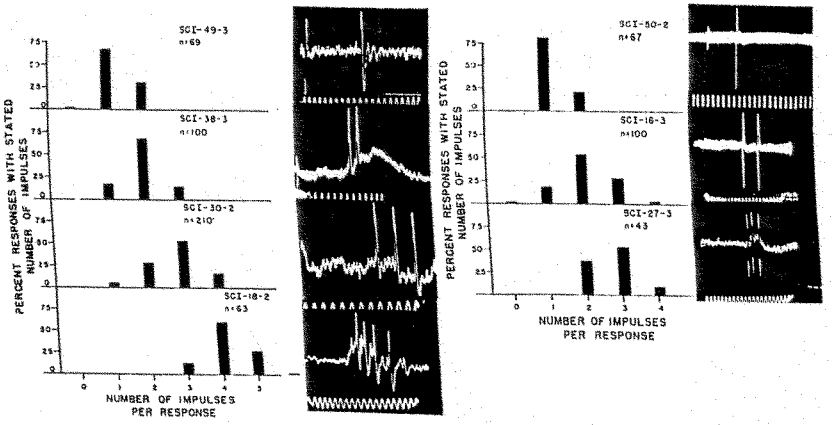

FIG. 3. Modal distributions for response populations of seven units, four discharging initially negative spikes to the left, and three with initially positive spikes to right. A representative response at modal value for each unit shown to right of each distribution graph. All are skin hair or skin pressure units, evoked by electrical stimulation of center of peripheral receptive field for each, at supramaximal strengths. Locations in depth below cortical surface, times the units were held under observation, and coefficient of variation of spike amplitudes where available are given as follows: unit 49-3, 980 μ, 45 min.; unit 38-3 1460 μ, 50 min.; unit 30-2, 1112 μ, 1 hr., 15 min., 6 per cent; unit 18-2, 1132 μ, 20 min.; unit 50–2, 1850 μ, 1 hr.; unit 16-3, 628 μ, 2 hrs., 25 min., 2.5 per cent; unit 27-3, 860 μ, 1 hr., 40 min., 3.5 per cent. Time lines, 1000 c./sec. for all except 50-2, where it is 500 c./sec.

per response (the paramodal value) may occur in a considerable percentage of the response population. Nevertheless, in each of the seven distributions illustrated more than 90 per cent of the responses fall within ±one spike of the modal value.

It is evident from our data that the responses of a cortical neuron to a series of slowly repeated peripheral stimuli of constant parameters have a certain and a stable distribution with relation to the number of impulses per response. It will be shown later that this modal distribution is sensitive to changes in the intensity, frequency, and position of the peripheral stimulus evoking these responses, as well as to the state of excitability of the cortical neuron itself. For the present we wish to use the first spikes of such trains, and those of one-spike responses, to determine what degree of variation in

amplitude is permissible in a population of responses deemed to be those of the same single unit.

I-3. *Short-term variability of spike amplitudes*

The histogram of Fig. 4, left, was constructed from measurements of each of the spikes shown in the record of Fig. 1 of the paper which follows (those of unit SC I-33-5). The unit responded steadily to a steady pressure upon its peripheral receptive field, a 1×2 cm.^{2} area of skin of the lower third of the contralateral foreleg. The histogram of Fig. 4, right, was constructed

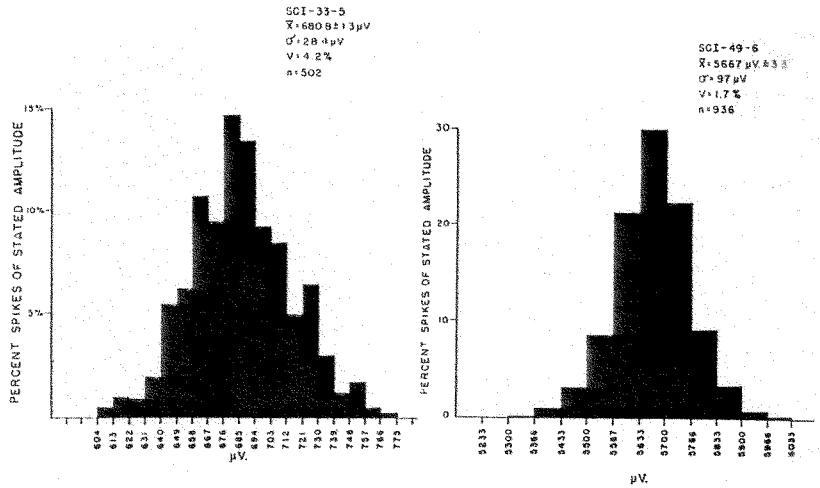

FIG. 4. Extent of short-term variability of spike amplitudes. SC I 33-5 isolated at depth of 645 μ beneath cortical surface, observed for 20 min., and first spikes of responses during frequency series measured; a skin pressure unit. SC I 49-6 isolated at depth of 430 μ, observed for more than 30 min., spike discharges occurring during adaptation study measured; a skin pressure unit.

in a similar way to indicate the distributions of the amplitudes of the initially positive discharges of unit SC I-49-6, which also responded steadily to steady pressure upon the skin. It is evident from these data that the amplitudes of spikes in the response population of a presumed single unit fall within a narrow and normal distribution about the mean, when the spikes of a population collected over any short period of time are measured. With one exception, all the units we have studied in this way and which have met all other criteria for single unit identification have shown coefficients of variation of 5 per cent or less. We have taken this figure as a further and more quantitative criterion. When available, this datum is given in the appropriate legend for each unit illustrating this and the following paper.

In the course of many of our microelectrode penetrations of the cortex units have been isolated and observations of one sort or another made, when the experimental plan did not allow collection of data of the type just described. Subjective criteria are then of great value in single-unit identification. Continuous observation of the spontaneous and evoked discharges from moment to moment, the all or none relation of spike to the peripheral stimulus evoking it, the pattern of variation of latencies and modal values of repetitive trains with changes in stimulus parameters – all these together lend strength to any particular identification of unitary action. However, when such an identification is crucial to the observation being made, such measurements are of considerable aid.

I-4. *Shifts in spike amplitude*

It is apparent from the small spreads shown in Fig. 4 that the responses of a unit may be exceedingly stable over any short period of time. Occasionally such stability persists over a long period of time, as illustrated in

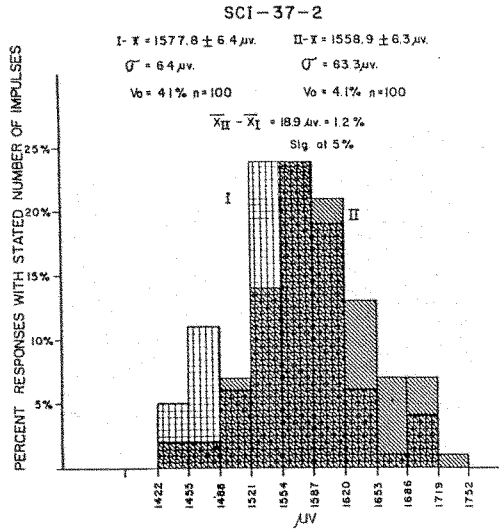

FIG. 5. Distribution of spike amplitude measurements of SC I 37-2, studied immediately after isolation during an intensity series, distribution I, and 55 min. later during a frequency series, distribution II. First spikes of responses measured in each case. Mean amplitude changed only 1.2 per cent; change was barely significant. Unit isolated at depth of 860 μ and observed for more than 1 hr.; modality, skin hair.

Fig. 5 for unit SC I-37-2. More commonly, changes in spike amplitude do occur during long periods of observations. These changes occur suddenly and are completed within a minute or so. The short-term variability at the new amplitude is never much greater, and is often much less than at the old. Rarely, such a change has occurred during a photographic recording of a unit's responses. Unit SC I-5-1 was isolated and studied for 3 hours and 34 minutes. Curve I of Fig. 6 indicates the amplitude measurements obtained during an intensity series, which was done immediately after isolation. More than 90 minutes later a recovery cycle was begun. During the interim the unit's discharges had increased in amplitude, as shown by curve II of Fig. 6. In the midst of this second series the animal had a paroxysm of coughing, which caused a sudden shift to a new amplitude, shown as curve III of Fig. 6, at which the unit was very stable ($V_{III} = 2.6$ per cent). While the second shift amounted to only 13 μV. (4.6 per cent), it is highly significant.

From observations such as these, it is evident that the conditions for recording are very stable, as measured by spike amplitudes, over any short period of time, and may continue to be so for very long periods. When changes occur they do so quickly, and a new and stable condition is reached. We attribute the sudden shifts in spike amplitude which occur to changes in the distance between recording tip and discharging cell.

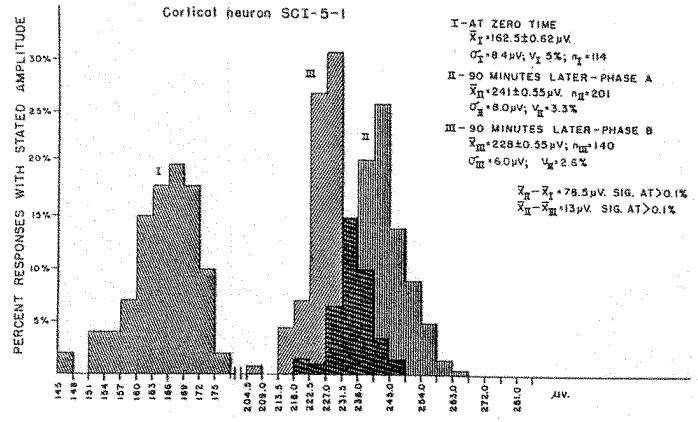

FIG. 6. Spike amplitude measurements of first spikes of responses of unit SC I 5-1, obtained initially during an intensity series, distribution I. Ninety min. later a large increase in amplitude to a new and steady level had occurred, distribution II. In midst of a recovery cycle study a sudden, slight, but highly significant downward shift occurred during a paroxysm of coughing by cat. Amplitude at the new level was steady, distribution III. Depth, 887 μ; observed for 3 hrs., 34 min.; modality, skin hair.

I–5. *Impulses of a repetitive train are those of same single unit*

Examination of the repetitive train responses displayed in Figs. 3, 9, and 13 reveals that frequently there is a marked reduction in the amplitude of the second spike of the high-frequency repetitive trains, with usually but not always a gradual recovery of third and fourth spikes, if they occur, towards the amplitude of spike one. This phenomenon has been observed by all who have recorded from single neurons of the central synaptic relay stations of the somatic sensory (4, 29), auditory (14), and visual (15, 16) systems and without exception authors have reached the conclusion that all the spikes of the train pertain to the same single unit. In a recent single-unit analysis of the activity of neurons of the thalamic tactile region (29), considerable attention was devoted to this problem, and the sensitive relation of the degree of amplitude reduction to the interval between the spikes, the frequency of firing, was established. It was found that the progressive recovery of spike amplitude paralleled the progressive lengthening of interspike intervals in the train. In that paper reasons for believing the repetitive trains to be discharged by the same single unit were summarized, and all of our experience

in cortical recording conforms with those arguments. Furthermore, intracellular recording (26, 27) from Betz cells has shown typical repetitive train discharges with amplitude reduction of second and subsequent spikes to occur under conditions in which the recording is almost beyond doubt confined to a single neural element. It seems reasonable to conclude that the repetitive train response is most unlikely to be due to the firing of a number of separate neurons, and that the spikes of the early repetitive train, though of different amplitude, are discharged by the same single cell.

I–6. *Spatial distribution of potential field surrounding an active neuron*

The spatial extent of the electrical field surrounding an active cortical neuron is indicated by the chart of Fig. 7, a graph in which the mean amplitudes of the first spike of the discharge of neuron SC I-48-2 are plotted against the depth of the electrode tip beneath the cortical surface. The near imposition of the two curves plotted upon penetration and withdrawal from the cortex is an indication of the stability of recording through a completely closed chamber. Sample records at each recording station are given to the right in Fig. 7. The extent of such a distribution will depend upon the distance of the electrode path from the center of the field. Since the cell was not contacted or destroyed during the traverse the electrode did not pass through the center of the field, and measured extent of distribution must be less than the full diameter of the field. The true extent of the field is un-

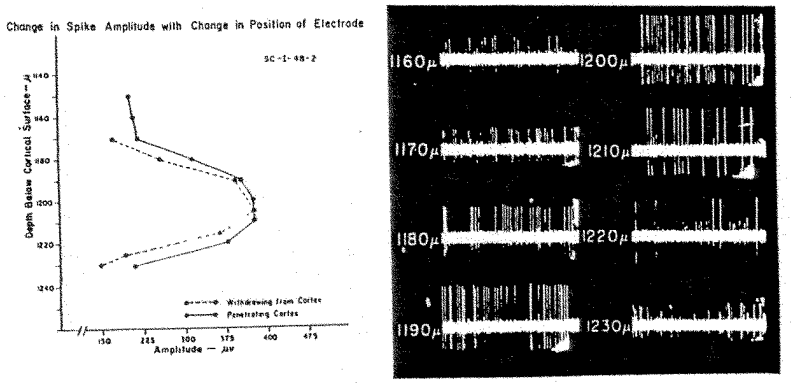

FIG. 7. *Left*, plot of spike amplitude measurements of unit SC I 48-2 at different depths of electrode tip below cortical surface, during penetration and withdrawal of electrode. Extent of action potential field measured equals about 70 μ. Unit observed for 20 min.; modality, skin hair. *Right*, short strips of records of this unit at depths indicated, during penetration bypass of electrode. Coefficients of variation of spike amplitudes are: 1160 μ—5.6 per cent; 1170 μ—5.8 per cent; 1180 μ—4.7 per cent; 1190 μ—3.3 per cent; 1200 μ—3.4 per cent; 1210 μ—1.7 per cent; 1220 μ—3.5 per cent; 1230 μ—5 per cent. Note overlapping potential field of a second unit appearing in record as a small spike at 1220 μ. At upper and lower extremes of field single-unit identification cannot be made with certainty, either by inspection of record or by quantitative criterion given in text.

known, but it is on the average certainly no less than 100 μ in its vertical direction; we have no information about its lateral extent. This figure, when compared with the diameter and close packing of cortical cells, indicates a wide overlap of the potential fields about adjacent cells, which we have in fact commonly observed. This accounts simply for the difficulty in isolating single elements of the cortex with extracellularly placed microelectrodes. Some theoretical implications of this overlap of fields will be described later.

I 7. *Isolation of initially positive spike discharges*

While the usual course of events as an electrode is lowered through the cortex is to traverse one after another the overlapping potential fields of

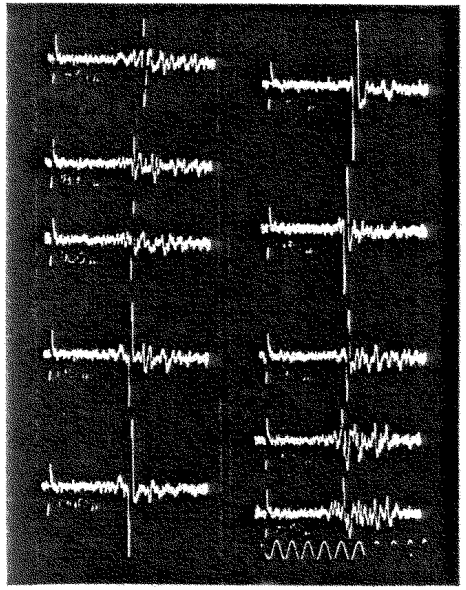

FIG. 8. Responses of unit SC I 50-2, showing sign inversion from initially negative to initially positive, during penetration of electrode, between 1890 μ and 1900 μ. During withdrawal, reverse change in initial sign occurs between 1910 μ and 1900 μ. Unit observed for 1 hr.; modality, skin hair.

units discharging initially negative spikes, one frequently observes such a unitary discharge to change its initial sign from negative to positive, while under continuous observation. This change occurs over a very short distance, and with slight further advance of the electrode the initially positive spike grows rapidly in amplitude. The appearance of such a discharge is always accompanied by an increased degree of isolation, *i.e.*, by a marked decrease in the background neural activity recorded. The records of Fig. 8 (see also Fig. 9-e) illustrate this change for unit SC I-50-2 as the electrode was advanced, and the reverse change as it was withdrawn. In all we have observed this reversal of initial sign 61 times. Two hundred and forty-one other initially positive units were studied, though the turnover process which we

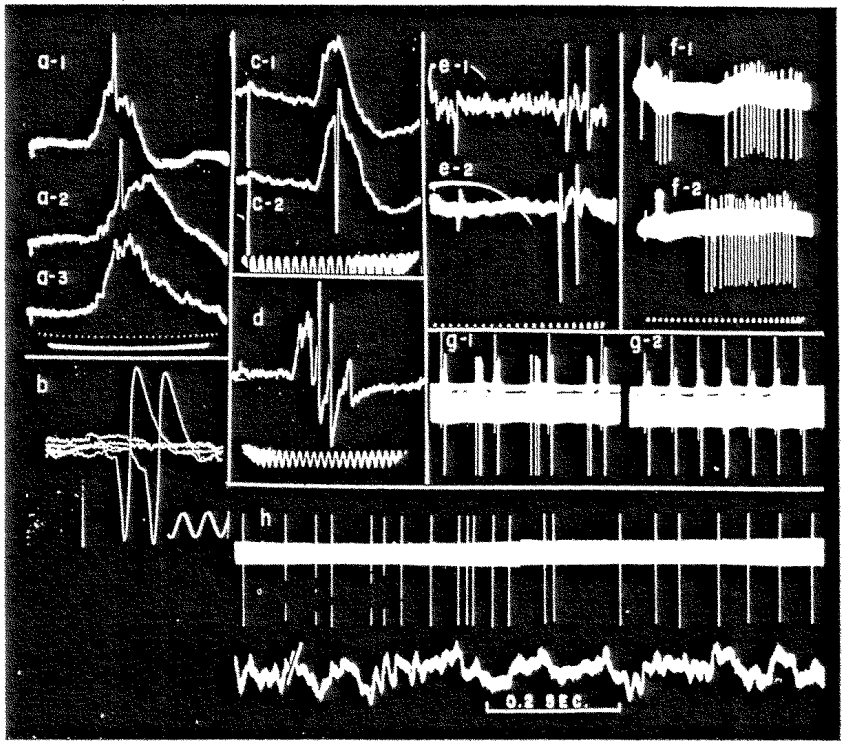

FIG. 9. Response of neurons of first somatic area of cat's cerebral cortex. a) Records illustrating slight variation in temporal relation of initially negative spike discharge to slow wave response, a-1 and a-2, and independence of slow wave of spike discharge, a-3, when latter fails. Unit SC I 57-2, depth 1050 μ; observed 20 min.; modality, skin hair; electrical stimulation of skin. Long time-constant recording, curve B of Fig. 2. b) Fast sweeps of initially positive spike discharges to show form. Slow initial deflection, spike take-off point, and inflection point visible. For discussion see (29). Unit SC I 49-6; depth 430 μ; observed for more than 20 min.; modality, skin pressure; electrical stimulation of skin; short time-constant recording, intermediate between curves A and C of Fig. 2. c) Records illustrating relation of initially positive discharge to slow wave response, c-2, and independence of slow wave of spike discharge, c-1, when latter fails. Unit SC I 49-1; depth 520 μ; observed 62 min.; modality, deep fascia; electrical stimulation of deep fascia. Long time-constant recording curve B of Fig. 2. V_0 of spike amplitudes = 1.7 per cent. d) Unusual response pattern; early repetitive response occurs nearly at end of evoked slow wave. Unit 18-3; depth 920 μ; observed transiently; modality, skin hair; short time-constant recording, curve A of Fig. 2. e) Records of responses of unit SC I 30-1 before, e-1, and after, e-2, sign inversion produced by advance of electrode. Slight latency shortening was not significant. Depth 1112 μ; observed for 1 hr.; modality, skin hair; electrical stimulation of skin. Short time-constant recording, curve C of Fig. 2. V_0 of spike amplitudes = 4.1 per cent, when negative. f) Early repetitive and late train responses, f-1, of unit SC I 33-3; f-2 shows late train response independent of earlier activation of neuron. Depth, 101 μ; observed 20 min.; modality, skin; electrical stimulation of skin. Long time-constant recording, curve B of Fig. 2. g) Responses of unit SC I 34-1 during frequency series, g-1, at 5 stimuli/sec. show sequences of stimulus artefact, one-spike early response, and multiple spike late response. g-2 at 10/sec. stimulation rate, shows only stimulus artefacts and early one-spike responses. Stimulus rate gives time line. Depth, 938 μ; observed for 1 hr., 10 min.; modality, skin pressure; electrical stimulation of skin. Long time-constant recording, curve B of Fig. 2. h) Comparison of single-unit spontaneous activity, upper tracing, with surface electrocorticogram, lower tracing; the latter recorded through gross electrode placed within 1 mm. of site of microelectrode entry. Unit SC I 25-3; depth 1474 μ; observed for 40 min.; modality, deep-claw unit. Upper trace, short time-constant, curve A of Fig. 2; lower trace, long time-constant, curve B of Fig. 2.

assume preceded their appearance was not directly observed. In every case except one the initially positive spikes have appeared during the advance of the electrode. While many of our records were purposely taken with short-time constant recording, which may produce an artificial second phase, we have frequently observed under long-time constant recording conditions that the second, the negative, phase of such spikes may be real (Fig. 9-c). The fact that such initially positive discharges are much more likely to be completely isolated than are those initially negative has resulted in their extensive use in single-unit analysis studies of the central nervous system. It is, therefore, necessary to consider the problem of the relation of the electrode tip to the discharging cell under these conditions, and to determine to what extent such positive discharges must be assumed to derive from neurons gravely injured by the electrode, and how that injury can be recognized.

(a) *Initially positive spike discharges may be recorded from an extracellular position.* At first glance one would assume *a priori* that any initially positive single-unit action potential must be recorded from an intracellular lead. There are several reasons, however, for believing that this is seldom the case, at least with electrodes of 3–4 μ diameter. (i) The initially positive spikes have been recorded from cortical cells when no steady D.C. potential existed between the electrode tip and the surround (4, 20). (ii) We have on 11 occasions observed two, and on two occasions three initially positive unitary discharges present at the same time. In each case these showed amplitude and response properties identifying them as the discharges of separate units. (iii) Such initially positive discharges can be observed in a very stable fashion for several hours. The large size of the electrode relative to cell size makes this very unlikely were the tip intracellular in position, for the cell membrane would almost certainly be severely rent by the initial penetration. (iv) We have been able to reproduce in other neurons the reversal phenomenon illustrated in Fig. 8 as many as five times without deterioration of the unit's response. It seems unlikely that the cell could for long sustain such multiple injuries, were the membrane punctured each time. (v) Once an initially negative spike has reversed to positive the electrode tip can still be advanced for considerable distances before the cell is destroyed.

It is, therefore, simplest to assume that such initially positive discharges are recorded from an extracellular position, and their initial sign accounted for by a direct impingement upon some part of the cell body. Perhaps the initial positivity is due always to cell damage, or, on the other hand, to capacitative linking across the membrane with the cell interior, assuming that the portion touched by the electrode is inactive.

(b) *To what degree are units discharging initially positive spikes to be considered damaged?* It has been shown by every way that they can be assessed that initially positive discharges may be recorded for long periods of time without signs of damage (14, 29). Nevertheless, signs of damage frequently do appear. The progress of this injury has two phases. The injury may first show as a reduction in modal value of the response, as shown in Fig. 10, left,

and as an elevation of threshold for the driving peripheral stimulus. This change may then be followed by a complete loss of drivability from the periphery. We have, for example, isolated a total of 383 initially negative spikes in the cat's somatic sensory cortex. Of these, 93.2 per cent responded to physiological stimulation of the skin or deep tissues of the body, and remained responsive while under study. By contrast, only 45.7 per cent of the 302 initially positive unitary discharges isolated could be driven in this way. Of the remaining positive discharges, many were observed to change from easy

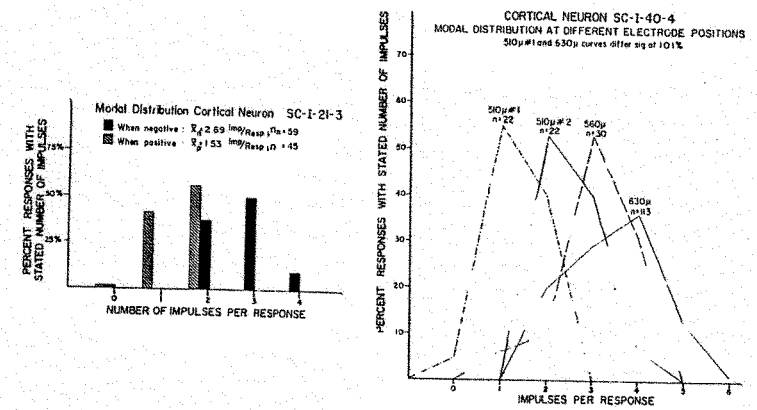

FIG. 10. *Left*, plot of modal distributions of response populations of unit SC I 21-3, obtained when discharging negative spikes (solid bar) and after inversion of initial sign to positive (lined bar). There has been a marked decrease in number of spikes per response with sign inversion. Depth, 1072 μ; observed for more than 1 hr.; modality, skin hair; both populations of responses obtained by strong stimulation of peripheral receptive field, which did not shift with sign inversion. *Right*, graphs of spikes-per-response distributions of populations of responses of unit SC I 40-4 at different recording electrode positions. Initial sign remained negative with advance of electrode, but unit was lost soon after data for 630 μ were obtained. Observed for 1 hr., 50 min.; modality, skin hair; all populations are of responses to identical supramaximal electrical stimuli of center of peripheral receptive field, which did not shift as electrode was advanced.

drivability to complete unresponsiveness upon sign reversal. It is important to say that the two groups were observed in randomly intermingled fashion, at a variety of anesthetic levels. The conclusion seems reasonable that the majority of neurons discharging initially positive spikes, under the conditions of these experiments, have sustained damage to cell body or synaptic scale which reduces their responsiveness.

With time or further advance of the electrode the classical signs of cell injury appear, with discharges of high-frequency bursts, and finally loss of the unit. These prolonged bursts which signal severe injury are clearly different from the early repetitive responses which we conclude are normal for cortical cells, for the former characteristically accelerate in the midst of the bursts. Evidence for this difference has been given in detail elsewhere (29).

Obviously data obtained from units in this state of injury can be accepted only with caution.

While it has been shown (14, 29) that initially negative spike train responses may continue to discharge in a very stable fashion as the electrode is advanced to and by the peak of the potential field, there is some evidence that this is not always so. In the case of two units we have observed an increase in modal value of response with advance of the electrode, such as Amassian (4) has described. The modal distribution charts for one of these units are given in Fig. 10, right. It must be concluded that under special circumstances initially negative discharges also display signs of injury. It is perhaps significant that in these two cases the units were both lost soon after the modal distribution data were obtained.

I-8. *Spontaneous activity*

During microelectrode penetrations of the cortex the presence of a unit is usually first discovered by the fact of its spontaneous discharges. The rate

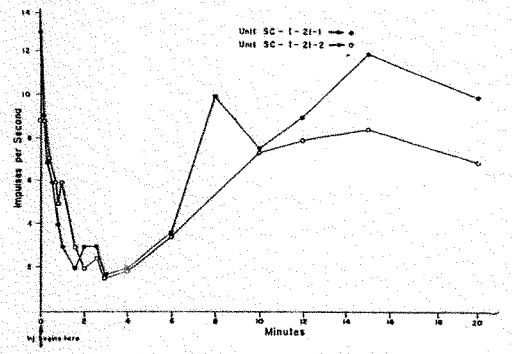

FIG. 11. Chart of changes in spontaneous impulse frequency following intravenous injection of 20 mg. Pentothal, in lightly anesthetized cat. Units SC I 21-1 and 21-2 observed simultaneously in record for 2 hrs., 5 min. Depth, 1150 μ; modality, deep joint.

of this discharge varies very greatly, particularly with the anesthetic state. The graphs of Fig. 11 illustrate the powerful action of an additional injection of a small amount of barbiturate upon the spontaneous discharge rate of two units which were observed simultaneously. Thus it seems likely that at very light anesthetic levels the great majority of cortical cells discharge in the absence of any overt stimulus. However, at least a small proportion of units may respond exquisitely to appropriate physiological stimuli when there is no spontaneous discharge at all. Such units are identified only by continuous stimulation of the periphery during microelectrode penetration.

While our observations of the simultaneous activity of cortical cells and the surface-recorded electrocorticogram have been very limited, we can confirm the observation of others (4, 23) that there is no evident correlation between the spontaneous activity of single cortical neurons and the surface-recorded electrocorticogram (Fig. 9-h).

I-9. *On the stability of recording*

Our aim of studying the cortex in terms of functional organization required that for each unit several types of data be obtained. This can be done only when units are held under observation for considerable lengths of time, and if their response patterns remain stable. Several lines of evidence suggest that this stability has been achieved by the technique of recording through an hydraulically tight chamber. For example, of the 113 units upon which photographic records were made, 50 were observed for 45 minutes or longer, often much longer. Of these 50, 39 were left intentionally after completion of the planned study, and 11 were lost. Of the remaining 63 units held less than 45 minutes, 45 were left intentionally and 18 were lost. In summary, of these 113 units 74 per cent were subjected to the planned study and then the electrode moved intentionally, substantiating the statement that under these recording conditions the duration of study of a given unit is usually under the control of the observer.

I-10. *Depth distribution of units observed*

The distribution chart of Fig. 12 indicates that only rarely has a unit been isolated above 200 μ—*i.e.*, in the region of the zonal lamina—or beneath about 2000 μ, the greatest thickness of the cellular layers of the somatic sensory region of the cat. The chart suggests a peaking of responsive units in the intermediate layers between 400 μ and 900 μ beneath the cortical surface. However, there are two reasons for believing that both the upper layers and the deepest layers have not been represented as fully as they should be.

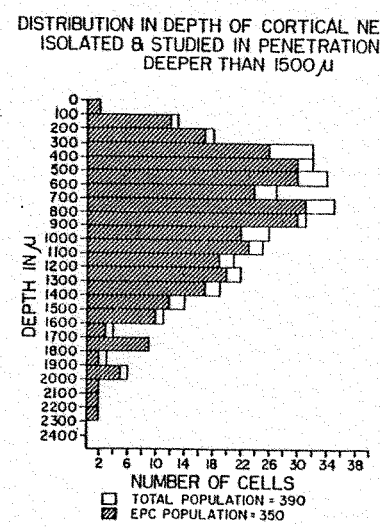

FIG. 12. Distribution in depth below cortical surface of locations of all units isolated in penetrations carried to or beyond 1500 μ. Lined portions of bars represent numbers of units observed under ether-Pentothal-*d*-tubocurarine anesthesia; additional clear portions of bars, units studied under deep sodium pentobarbital anesthesia. Number of cells is only 390, compared to total population of 685 studied, for many units were isolated in penetrations which did not reach depth of 1500 μ, and their inclusion would have produced a false skewing of the distribution.

In the first place, we have frequently observed that increased depth of anesthesia selectively depresses activity in both the superficial and the deepest layers; since 18 of the experiments from which the chart was compiled were done under moderately deep anesthesia, some distortion due to this effect would be expected. Secondly, the isolation of single units (compared with recording from multiple units) has always been easier in the middle layers of the cortex, in our experience; since the data in the chart are all from isolated single units, further distortion would result from this cause. Thus the peaking shown is probably not representative of the true distribution of responsive units through the cortex, and distribution may even be quite uniform for all layers except the first.

It should also be noted that very few "units" have been isolated at depths greater than those corresponding to the known thickness of the cortex, encouraging the belief that we have seldom, if ever, been recording action potentials from any of the fibers.

Our efforts to determine the depth at which recordings are made by the study of serial sections of the experimental brains have been unrewarding. Even after prolonged search of every section in the 15 series available, at both low and high magnification, we have been able to locate only 11 tracks of the 68 microelectrode penetrations known to have been made in these brains. In spite of this difficulty the absence of signs of injury to the brain is reassuring concerning the state of the cortex during the period of recording. Nevertheless, the exact location in depth from which records were obtained is an essential datum which we have only by measurements made from the cortical surface.

In summary, the neural elements studied were confined to the cellular layers of the cortex. Further, our data suggest the likelihood that in the absence of any drug the cells of the lower five cortical layers would all be active, and responsive to peripheral stimulation.

I-11. *Response patterns rarely encountered*

In addition to the typical response patterns described above, there are two patterns which we have seen very uncommonly.

(a) *Late spike responses.* Rarely the early repetitive response is followed by a second group of discharges of the same unit, after an interval which varies widely, from 40 to 150 msec. This late response has certain characteristics which differ from those of the early response. It frequently has a different modal value, and the number of spikes per late response is much less sensitive to changes in stimulus parameters than is that of the early response. The late response is not uniquely dependent upon the earlier activation of the neuron, for the stimulus frequently still evokes a late discharge when reduced below threshold for the early response. The late response is affected in some way by rhythmic stimulation, for it is frequently best seen at stimulus frequencies of about 5 per sec., and disappears completely at higher rates (Fig. 9-g). While these facts exhaust our knowledge of this response, and they are very limited in extent, they do suggest that it results from activation of the cell via a different afferent inflow and a different or numerically greater set of presynaptic terminals than those producing the early repetitive discharge. This late response has been described for neurons of the ventral thalamic nucleus (29) and earlier by Amassian (4) for the somatic cortex.

(b) *Late train response.* A second type of late train response is illustrated in Fig. 9-f. It differs from the late spike response, for it consists of a long train of spike discharges at low frequency. It too is independent of earlier cell activation, as illustrated in the figure, and is relatively insensitive to stimulus strength, once its threshold is reached. We have observed this complex and interesting response on only six occasions, and we believe it to be quite sensitive to the anesthetic agent employed.

II. Relation of Early Repetitive Response to Peripheral Stimulus

It will be shown below that the modal value of the early repetitive response is sensitive to changes in the parameters of the stimulus, and for that reason seems likely to serve the function of transmission of information concerning that stimulus. While latency changes *per se* seem less likely to serve in this manner, it will be shown that the latency also is sensitive to stimulus changes. These two properties of cortical cells, as well as of thalamic cells (29), have received so much attention for the reason that they give promise of serving as useful measures, not only in the study of information transmission, but of the effects of drugs and humoral agents upon the nervous system as well.

II-1. *Change in latency of response with change in intensity of stimulus*

The sensitive and reliable relation of the latency of the early repetitive response to the intensity of the peripheral stimulus is shown by the data and representative responses for one unit given in Fig. 13. Detailed information obtained for 40 units studied in this way is given in Table 1. It will be seen there that the latency shift which can be produced by increasing stimulus strength from threshold to three or more times threshold varies from a fraction of a msec. to more than 7.5 msec. In all of our material there are only two units, the data for which are shown at the foot of Table 1, for which such a latency shortening cannot be demonstrated. It seems reasonable to conclude that increasing stimulus strength causes a decrease in latency of cortical cells, and that this shortening is a normal event. We have no evidence that it ever takes place as a step function. We attribute it to recruitment of additional peripheral nerve fibers by the stronger stimuli, and to the increased synaptic excitation resulting from central convergence at each synaptic relay of the polysynaptic chain leading to the cortical cells. It has already been shown that at least a part of this shortening may occur at subcortical relays (29).

II-2. *Conditions which change modal value of early repetitive response*

(a) *Changes with intensity.* The data of Fig. 13 for a typical unit, and for all units studied, shown in Table 1, indicate that increasing intensity of

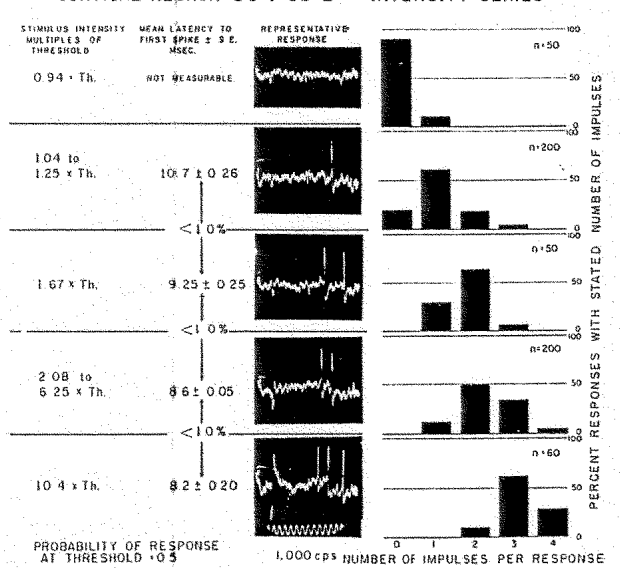

FIG. 13. Results of intensity series on unit SC I 30-2. Depth, 1112 μ; modality, skin hair; observed for 1 hr., 15 min. Electrical stimuli delivered to center of peripheral field; threshold arbitrarily that strength producing some impulse discharge on 50 per cent of applications. Data for each intensity range in rows to be read from left to right, then compared vertically. Representative responses at modal value and mean latency shown. Modal distribution charts for each population to right. Time, 1000 c./sec. V_0 of spike amplitudes, 6 per cent.

stimulation causes an increase in the number of spikes per response. That this is a gradual trend is suggested by the gradual shift of the distribution charts shown on the right of Fig. 13. While it is obvious that for any one response an increase in spikes per response can occur only stepwise, the probability of such an increase occurring seems to vary smoothly with increasing strength of stimulus. The sensitivity of this measure of stimulus strength is indicated by a comparison of any two adjacent distributions. Even when the modal values are identical, the distributions are highly significantly different. Only five of the 40 units for which data are given in Table 1 failed to show a significant increase in the number of spikes per response as the stimulus was made stronger, and in no case did strong stimuli cause a reduction in modal value.

(b) *Changes with frequency of stimulation.* Characteristically, the modal value of the response drops from its level in the unconditioned state if the stimuli are delivered so rapidly that time for full recovery of the system is not allowed. More complete treatment of the response of cortical cells to two stimuli at various intervals, and to repetitive stimuli at different frequencies, will be given in section III. Here we wish to point out that unresponsiveness

Table 1. Changes in responses of cortical neurons with changes in intensity of peripheral stimulus, given in multiples of threshold (xt)

Unit No.	Depth Source	n	Mean latencies to first impulse, in msec. 0.6–1.0 xt	1.01–1.4 xt	1.41–1.8 xt	1.81–2.2 xt	2.21–2.6 xt	2.61–3.0 xt	3.01–4.0 xt	4.01– & up	Diff. m–t	n	Mean number of impulses per response 0.6–1.0 xt	1.01–1.4 xt	1.41–1.8 xt	1.81–2.2 xt	2.21–2.6 xt	2.61–3.0 xt	3.01–4.0 xt	4.01– & up	Diff. m–t
3-1	705–P	68	11.01	10.38	10.2	10.16	10.67	10.63	—	10.37	0.64***	81	0.5	1.0	1.0	1.0	—	0.9	—	—	0.5**
5-1	887–P	142	—	14.76	—	14.60	—	—	15.50	11.98	2.78***	156	—	0.85	—	0.83	—	—	0.74	1.0	0.1**
5-1	590–P	86	—	20.96	—	17.2	—	15.6	13.8	13.43	7.53***	161	—	0.80	—	2.75	—	3.80	3.90	1.34	2.13***
6-1	242–P	93	—	8.23	7.82	7.7	—	—	7.6	7.43	0.80***	98	1.07	1.60	1.25	1.13	—	—	1.20	2.93	0.68***
9-2	655–U	137	9.3	9.3	9.3	—	9.1	—	8.8	8.6	3.70***	174	0.94	1.00	0.88	—	0.60	—	1.20	1.75	0.00
11-1	1060–P	43	18.5	16.8	16.6	—	15.5	14.2	—	—	3.00***	59	0.38	0.87	0.88	—	—	1.0	0.60	0.94	0.67*
14-2	1290–P	105	—	17.21	14.6	13.0	14.1	11.0	12.57	—	4.64***	105	—	0.81	0.86	0.81	1.20	0.93	1.07	—	0.26*
14-3	1828–P	134	—	13.02	12.97	12.1	—	—	—	11.71	1.31*	140	0.93	0.88	1.47	1.75	0.73	1.72	—	1.77	0.84***
16-1	972–U	120	12.57	—	12.24	—	—	12.23	—	11.30	1.27**	167	0.5	0.99	1.60	0.68	—	0.93	—	0.95	0.45***
16-3	926–F	103	14.8	14.15	12.1	—	—	—	12.1	12.1	2.7***	197	0.4	1.69	2.0	—	—	—	2.47	2.12	1.72***
18-1	754–F	127	14.83	12.48	11.78	—	11.78	—	11.13	11.00	3.83***	—	2.13	—	4.33	—	—	4.53	—	3.87	—
18-2	1132–P	118	14.96	10.8	10.15	10.81	—	9.5	—	9.26	5.7***	131	3.60	3.60	2.81	—	—	—	—	—	1.74***
21-3N	1072–P	87	13.56	12.83	11.34	—	—	—	—	—	2.75***	120	0.66	2.11	2.53	2.62	—	—	—	—	1.96***
25-1	1025–P	48	10.25	9.26	9.2	—	—	—	9.5	—	1.25***	95	1.05	1.53	1.60	2.00	—	—	—	—	0.95***
26-4	1330–U	126	10.2	9.7	9.5	—	10.1	—	9.26	7.9	2.3***	145	1.62	1.60	1.18	—	—	2.00	1.82	2.20	0.58000
27-3	860–P	64	—	10.23	—	—	9.31	—	8.72	8.21	2.03***	86	—	1.77	—	—	1.84	—	2.6	2.61	1.44***
29-1	340–F	96	10.01	9.61	8.66	—	—	—	—	—	1.73***	104	1.27	1.20	1.63	—	2.64	—	—	1.67	0.40*
30-1	775–P	82	11.5	11.25	11.0	—	9.9	—	—	9.77	1.29***	105	0.67	1.73	1.33	—	—	—	—	1.87	0.9**
30-2	1112–F	125	—	10.7	9.25	8.6	—	—	8.8	8.2	2.5***	660	0.60	0.99	1.76	2.42	1.87	—	2.33	2.91	2.41***
32-3	545–F	81	9.37	8.70	8.53	8.53	—	—	—	—	0.84***	91	0.67	1.53	2.17	2.75	—	—	—	—	1.42***
32-4	1388–F	67	—	10.0	9.26	—	—	—	—	—	1.76***	132	0.75	0.80	1.00	—	—	1.00	—	—	0.33*
33-1	572–P	81	15.23	—	14.2	—	13.8	9.16	13.2	13.5	5.63***	92	0.53	—	1.08	—	—	1.20	1.53	1.67	0.89***
33-2	655–P	65	12.82	7.7	7.55	—	7.0	7.19	—	7.40	1.21**	86	2.07	2.00	1.93	—	—	1.93	—	—	1.6***
33-3	945–F	78	8.61	—	—	—	—	9.12	—	—	0.63**	114	0.38	0.85	1.2	1.47	—	2.12	—	2.75	0.68**
34-1	938–P	34	—	9.46	9.06	8.83	—	—	—	8.96	1.30***	141	0.53	0.88	1.05	1.00	—	—	1.05	—	0.99***
37-2	880–F	115	10.34	10.0	9.5	9.16	—	—	9.04	—	3.1***	433	0.3	0.93	1.97	2.26	—	—	2.29	0.74	0.2100
37-4	1270–F	112	14.00	11.6	10.0	9.4	8.5	8.3	8.9	—	1.2***	175	0.73	0.87	1.63	2.00	—	2.13	1.47	1.93	1.20***
38-2	880–F	176	9.5	9.5	8.8	8.5	—	8.3	8.5	8.3	3.7***	630	0.64	1.24	1.63	1.67	1.63	1.87	2.21	—	1.57***
38-3	1460–F	30	10.7	9.4	9.1	9.1	—	8.3	7.6	7.0	1.4***	110	—	0.8	2.2	1.9	—	2.32	—	2.5	1.70**
40-1	510–U	105	8.1	7.7	7.7	—	—	7.1	—	6.7	1.20***	634	0.66	0.96	1.1	1.13	—	—	—	—	0.47***
46-2	730–T	134	9.03	9.08	12.19	12.01	—	—	—	7.86	5.37***	600	0.74	—	1.07	1.02	—	1.78	1.85	2.49	1.75***
46-3	610–T	118	13.23	—	11.4	9.59	7.77	—	8.53	—	2.33***	418	0.56	0.84	1.41	1.29	—	—	—	—	0.73***
48-3	890–F	106	12.02	11.4	7.57	9.04	—	9.42	—	—	1.18***	112	0.61	1.09	1.30	—	1.20	—	—	—	0.69***
50-2	1850–F	70	8.87	7.67	7.57	—	7.69	—	—	—	2.89***	484	0.66	1.64	2.33	—	—	2.36	—	—	1.70***
50-3	2150–F	118	12.09	10.04	9.24	—	—	—	—	8.48	1.53***	983	0.59	1.60	1.93	—	—	—	2.54	2.67	2.08***
52-1	796–F	175	10.01	9.74	9.44	—	—	—	—	9.33	5.08***	881	0.84	1.33	—	1.12	1.88	—	1.73	1.64	0.80***
52-5	1555–T	130	14.18	13.50	—	11.16	10.75	—	—	10.0	1.96***	426	0.44	1.1	1.35	1.36	1.99	—	1.85	—	1.40***
54-1	625–F	190	11.96	10.04	10.22	10.2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
27-2	735–P	33	14.5	—	14.8	—	14.6	14.6	—	—	0.1900	53	0.73	—	1.55	1.91	2.00	—	—	0.77	1.2700
16-2	1430–F	56	12.3	13.76	—	—	13.1	—	—	13.07	0.7700	110	0.53	0.76	—	—	0.81	—	—	—	0.2400

Detailed data on changes in mean latencies and mean numbers of spikes per response at different intensities of stimulation for the 40 units studied in this way. All units skin modality typed; electrical stimuli delivered to centers of peripheral receptive zones. Column 1 gives experiment and unit numbers. Column 2 gives depths below cortical surface at which units were isolated, in μ, and location of peripheral receptive field. P=forepaw, F=lower forelimb, U=upper forelimb, T=thorax. Columns 3 through 11 give mean latencies in msec. at indicated intensity ranges, in multiples of threshold as indicated. Arbitrary threshold is that strength of electrical stimulation of skin evoking spike discharges on 50 per cent of its applications. Column 12 gives shortening of mean latencies observed between threshold and highest strength tested. Reliability indicated by: 000=not significant, *=probably significant, **=significant, ***=highly significant, by Welch's test. Columns 14 through 25 give similar data on changes in mean numbers of spikes per response.

of the polysynaptic system results in a striking reduction in the modal value of the response; an example is given in Fig. 14.

(c) *Changes with position of stimulus within receptive field.* If, as we assume, the increasing excitation produced by stronger electrical stimulation of the skin is caused by the recruitment of additional peripheral afferent nerve fibers to the exciting volley, it follows that strong stimuli delivered to

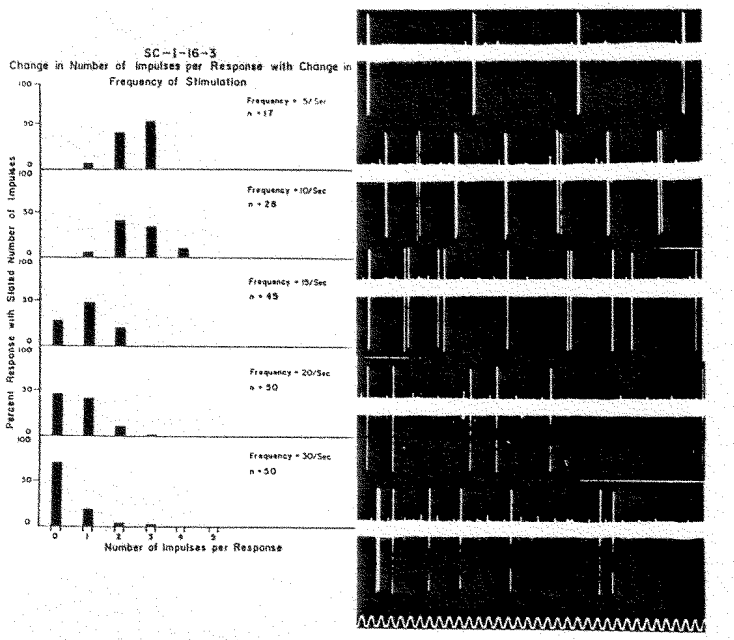

FIG. 14. Change in number of impulses per response with change in frequency of stimulus. Unit SC I 16-3. Supramaximal electrical stimulation of center of peripheral receptive field. Modal distributions for population of responses obtained at each stimulus frequency to left. Number of impulses per response counted at 15 times projection magnification. Representative strips of each record, beginning with onset of stimulation, to right; time line, 50 c./sec. Depth 628 μ; modality, skin pressure; observed for 2 hrs., 25 min. V_0 of spike amplitudes = 2.5 per cent.

different portions of its peripheral receptive field will produce different degrees of excitation of a cortical neuron. Such observations can be made best upon neurons whose receptive fields are large, which is to say those whose fields occupy the proximal portions of the limbs, or the trunk. An example is given in Fig. 15. It will be seen that a large portion of the field impinged maximally or nearly so upon the cortical neuron, but that this convergence and hence capacity for excitation shaded off gradually toward the anterior end of the field, and precipitously towards its posterior edge.

It follows from observations of this kind, taken together with those given

in the next paper, that a single spot upon the skin will occupy the peripheral receptive fields of many cortical neurons. It will lie near the center of some fields, and thus be capable of exciting maximally, and towards the periphery of those of others, and thus be able to provide for them only minimal excitation. Thus, the pattern of response of the cortical neurons occupying the discharge zone set up by a local stimulus to the skin can be reconstructed.

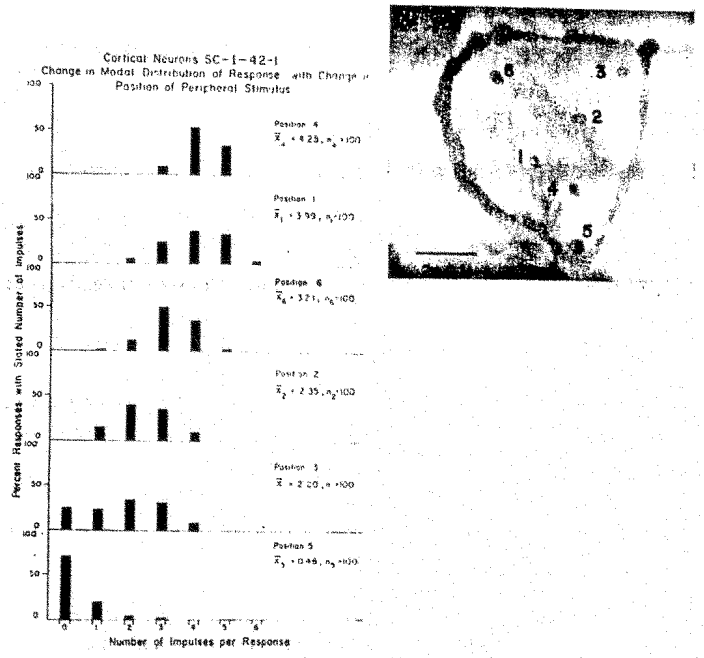

FIG. 15. Change in modal distribution of response with change in position of stimulus in peripheral receptive field. Unit had largest receptive field ever observed; black bar on inset = 2 cm. Receptive field (photograph in inset) marked on clipped skin with ink occupies shoulder and upper back-anterior to right, upper forelimb off picture below and to right. Spots marked in ink and numbered on photograph stimulated electrically at supramaximal strength, at rate of 0.5/sec. Distributions of spikes per response for populations for each point shown in charts to the left. Depth, 650 μ; observed for more than 1 hr.; modality, skin.

Those near and surrounding the center will discharge at a high modal value, and this value will shade off gradually towards the junction with cells which do not respond, those occupying the surrounding subliminal fringe. A form of afferent inhibition so disposed as to sharpen the discharge zone is described in the following paper.

(d) *Are changes in latency and modal value of early repetitive response interdependent?* The data of Table 1 which concern latency shortening and modal

change have been treated to determine their relation to each other. The coefficient of correlation is only 0.3, from which fact we conclude that these two changes are not necessarily due to a single variable.

III. Responses of Cortical Neurons to Repetitive Peripheral Stimuli

We have made an attempt to determine the capacity of the cortical cells to respond to repetitive volleys. Two facts were evident almost at once: firstly, the unresponsive period of the polysynaptic system is much prolonged, when compared to the refractory period of the cell itself. Secondly, recovery of responsiveness is a property sensitive to the level of anesthesia. There are two ways (see III-1 and III-2) in which recovery can be measured, which give results that can be correlated.

III-1. *Responses to two stimuli at various intervals: recovery cycle of the system*

Experiments of this type have been carried out with a total of 17 units. The resulting curves fall into two classes. Four of the first class are shown in Fig. 16, left. Each point represents the mean number of spikes per response (n = 10–30 for each point) to the second of two strong stimuli delivered at the interval indicated, as percentage of the mean number evoked by the first stimuli. Here the mean gives a better estimate of the central tendency at each interval than does either the mode or the median. The curves suggest that under moderately deep sodium pentobarbital anesthesia the system is unresponsive for 20–30 msec. and gradually recovers to full responsiveness at about 100 msec.

We have found quite different results in animals under the combined Pentothal-d-tubocurarine regime, and four curves of this second type are

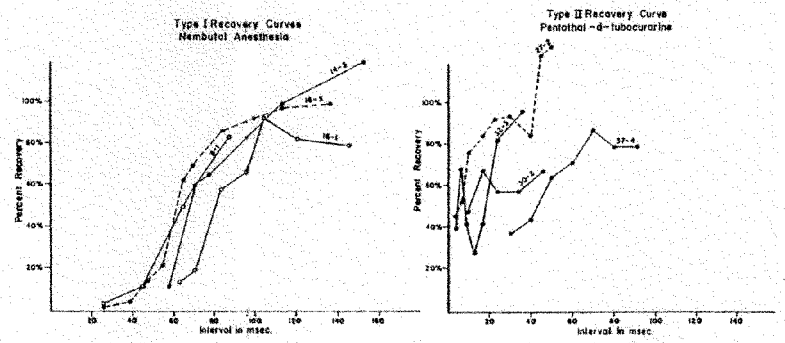

Fig. 16. Recovery curves for eight units, those to left obtained under deep sodium pentobarbital anesthesia, those to right under ether-Pentothal-*d*-tubocurarine regime. Each point on curves represents mean number of spikes per response (10–30 responses) to second of two equal supramaximal stimuli, as per cent of mean response to first. All units were of skin modality types. See text and Table 2.

shown in Fig. 16, right. While these curves are highly irregular—even though the responses to unconditioned stimuli were stable (see Figs. 3, 13)—it is clear that the responsiveness is regained very rapidly, after a few msec. Obviously, we have not been able to measure it accurately.

III-2. *Responses to stimuli delivered repetitively at various frequencies*

Studies of this type have been made upon 18 units. When supramaximal stimuli driving a cortical neuron are repeated slowly, at rates up to 20–30 per sec., the unit's responses usually will follow the stimulus beat for beat. When trains of stimuli are delivered at higher rates one common event is for the response to *equilibrate*, to come to an overall average response rate. Such an equilibrating unit responds to some stimuli of the train, and not others; while the stimuli which elicit responses are randomly intermingled with those which do not, study of all of our records indicates that the relation between a given adequate stimulus and the response to it is rarely if ever random. Records of such an equilibrating unit are shown in Fig. 14, and response curves (for the first second only of each stimulation) for five such units are shown in Fig. 17. Unit 27-3 is unique in our material, for it achieved a discharge rate of 135/sec., at which overall rate it responded when trains up to 500/sec. were delivered.

A second type of response curve commonly encountered is indicated by the curve for unit 9-1, shown also in Fig. 17. Such units follow beat for beat trains up to 20 or so per sec. When trains of higher frequency are delivered such units respond to the first few stimuli, and then *cease to respond at all* during the remainder of the train. Such "cut-off" units can be held in this unresponsive state for as long as the train of stimuli is continued.

Table 2 shows the degree of correlation between recovery and frequency

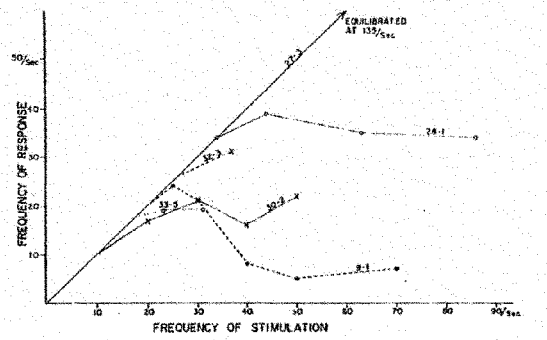

Fig. 17. Plots of frequency of spike discharge responses at different frequencies of stimulation. Supramaximal electrical stimuli delivered to center of peripheral receptive fields; all units of skin modality types. Unit 27-3 was highest level equilibrator observed; 26-1, 32-3, 33-5 and 30-2 represent common forms of equilibration. Unit 9-1 is representative of a group of units studied under deep sodium pentobarbital anesthesia, which display "cutoff" frequency characteristics. See text and Table 2.

TABLE 2

Types of recovery and frequency response curves for cortical neurons upon which both studies were done

Unit no.	Recovery curve	Frequency curve
SC I 9-1	Type I	Cut-off
14-2	I	Low level equilibrator—10/sec.
14-3	I	Low level equilibrator—18/sec.
16-3	I	Cut-off
21-3	I	Cut-off
27-3	II	Equilibration
30-2	II	Equilibration
32-3	II	Equilibration
32-4	I	Cut-off
37-2	(Mixed) I–II	Cut-off tendency
40-4	II	Equilibration

Correlation between types of recovery and frequency response curves. All units having combinations of Type II recovery curves and equilibrating frequency response curves were studied under regime of ether-Pentothal-*d*-tubocurarine anesthesia.

studies for 11 units upon which both were done. It is clear that units with Type I recovery curves commonly have either "cut-off"-type frequency curves, or equilibrate at very low levels, while units having Type II recovery curves always have equilibrating-type frequency response curves. We believe that this state of unresponsiveness, revealed by the association of Type I recovery and "cut-off"-type frequency curves for the same unit, is produced by the depth of the anesthesia.

IV. Slow Phenomena Recorded Within Cortex

A peripheral stimulus which evokes the discharge of a cortical cell evokes also an initially negative slow wave response. This wave is identical in latency, duration and form, but opposite in sign, to the evoked potential recorded on the surface of the cortex. The evoked single-unit spike discharges are invariably of longer latency than the wave, and commonly appear on its ascending phase, or near its summit. The exact temporal relation of the two oscillates within a narrow range in a population of responses of a single neuron evoked by a repeated stimulus of the same strength. Examples of this relation are shown in Fig. 9-a and 9-c for both initially negative and initially positive spike responses. Very rarely, in our sample only twice, the unitary discharges may appear after the summit or even after the completion of the slow wave (see Fig. 9-d). This particular temporal relation has, however, been shown to occur quite frequently in the auditory cortex (14). We have never, with long time-constant recording, seen unit responses to occur before onset of the slow wave. The evoked slow wave falls in amplitude in parallel with reduction in the strength of the peripheral stimulus, but a significant wave always remains when stimulus strength is below threshold for evocation of any associated unitary discharges. In many response populations an occasional stimulus fails to discharge the cortical cell even with strong stimuli (Fig. 9-a, c) without marked change in the slow wave. From these two observations, we conclude that the evoked slow wave is not uniquely dependent upon firing of the cell, that it is a population response recorded from many elements. All observations suggest a causal relation between some preliminary event, of which the slow wave is the electrical sign, and activation of the cortical cells, perhaps similar to the local postsynaptic potential recorded in other synaptic regions (10).

IV-1. *Evoked slow wave during penetration of cortex*

Our studies of the changes in the evoked slow-wave response during microelectrode penetration of the cortex have, by comparison with those of others (4, 21, 25), been very limited. Nevertheless, our observations are so different from those reported as to warrant description. As a microelectrode is lowered through the saline-filled chamber and nears the cortical surface, an initially positive slow wave is recorded through it, evoked by a brief stimulus at the topographically appropriate region of the body surface. Upon contact and penetration the wave becomes initially negative at that depth during cortical penetration when spontaneously active or drivable single unit discharges appear in the record. This most commonly occurs between 200 μ and 250 μ beneath the pia-arachnoid surface (see Fig. 18), and is not

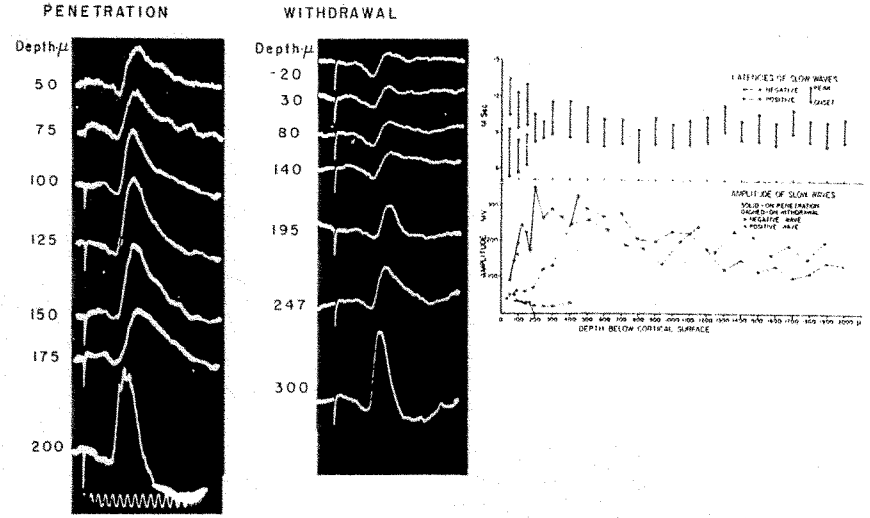

Fig. 18. Study of primary evoked potential during microelectrode penetration of cortex. Experiment 49, penetration 2. Responses to electrical stimulation of skin at center of peripheral receptive field, on lower forelimb. Time, 500 c./sec. Column of records to left obtained on penetration; center, those obtained on withdrawal at depths indicated. Plots of amplitudes on penetration and withdrawal, and of onset and peak latencies on penetration, to right. Each point on these charts mean of 20 responses. Full description in text.

so much a direct reversal of sign as a dwindling of the positive wave and a shortening of the onset latency of the negative wave.

We have regularly observed that any damage to the cortical surface at the site of entry is likely to cause the upper layers of the cortex to be silent and completely devoid of active neurons, a condition which also occurs at deep levels of anesthesia. Under these circumstances the evoked slow wave remains initially positive in these silent layers, to turn initially negative only when an active cellular region is entered. This course of events is most likely to follow pressure damage and dimpling of the cortex at the time of penetration. Amassian (4, 6) has reported this same experience, indicating also that the less severe the pressure damage the higher in the cortex is the level of sign inversion of the slow wave.

The observations reported fit simply with what is known of the potential field distributed about an active dipole in volume conductor, with the assumption that the nearly instantaneous sink of the dipole is created by the negative local postsynaptic responses of the cell bodies activated almcst synchronously by the thalamocortical inflow, a column of cells extending from layer II downwards throughout the cellular thickness of the cortex. This interpretation fits with all observations made, and demands no commitment as to the nature of the slow wave itself, although it fits best with the hypothesis that the slow-wave evoked potential is the electrical sign of the nearly synchronous local postsynaptic responses of cortical cells, and is not generated by the discharge of conducted impulses by those cells. This idea is also supported by the fact that the surface-recorded initially positive evoked wave is seen best at very deep levels of barbiturate anesthesia, under which conditions it is a rarity to find on microelectrode penetration neurons which discharge impulses in response to peripheral stimuli. The alternative hypothesis, that the evoked slow wave is produced by synchronous depolarization of large numbers of presynaptic terminals of thalamo-cortical fibers, cannot be disproven, and there is only indirect evidence favoring the first of these possibilities.

IV-2. *A local spontaneous intracortical slow-wave event*

There is one other species of slow-wave phenomena which we wish to describe. This is a relatively slow spontaneous potential oscillation of limited spatial extent. An example is given in Fig. 19. These records show that as the electrode is slowly advanced in 4 μ steps it approaches, passes the peak of, and leaves a local source of slowly oscillating potential change. The microelectrode recorded these oscillations at a gain that showed scarcely any brain waves when the electrode was at the surface of the cortex. We have studied this event on 16 occasions, and observed it many other times. The spatial extent has varied from 20 μ to 70 μ, with a mean of 32 μ. The peak of the source has been found in all layers of the cortex. The rhythmic potential oscillations vary from 15 to 25 per sec., and some preliminary observations

with gross electrode recording on the surface indicate that they are not synchronized with the waves of the electrocorticogram.

The local slow-wave event is unrelated to impulse discharge, and we have not seen the two present at the same time. It differs also in that it seems to be unaffected by peripheral stimulation. It is exceedingly stable both in amplitude and spatial distribution, though short runs of isopotential are occasionally interpolated in the midst of the oscillations, and such a run is shown in one of the records of Fig. 19. There is some evidence that this slow-wave activity does not result from damage *per se*, for that shown in Fig. 19 survived 12 passages of the electrode through its field.

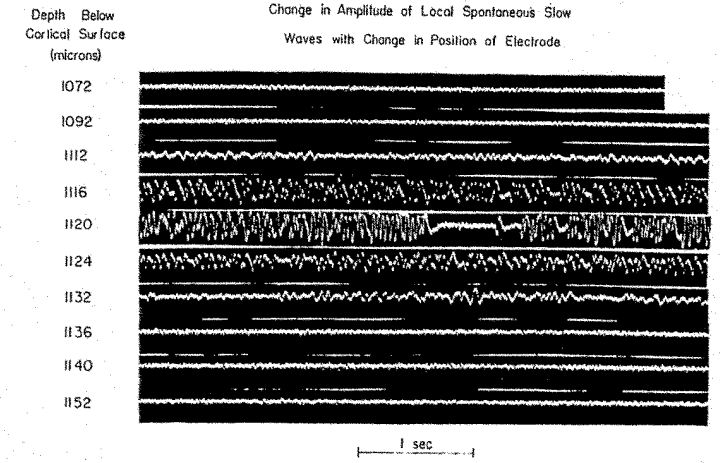

FIG. 19. Local spontaneous slow wave event of limited spatial extent, recorded at depths below cortical surface indicated in μ for each record. Experiment 31, penetration 1. Cat under ether-decamethonium bromide-Pentothal anesthesia. Long time-constant recording, curve B of Fig. 2. Full description in text.

All of these observations suggest that this event is the sign of local non-conducted oscillations in the membrane potential of the soma or dendrites of cortical cells, but we have no direct evidence that this is so, and the chance that glial cells may be responsible for it must be considered. It should be noted that this local change, or something similar to it, was encountered during microelectrode studies of the hippocampus (28).

DISCUSSION

I. METHOD OF SINGLE-UNIT ANALYSIS IN STUDIES OF CORTICAL FUNCTION

One of the major aims of this study has been to develop the possibilities and to emphasize the limitations of the method of single-unit analysis in studies of the functional organization of the cerebral cortex. It is clear that

there are three major requirements for successful use of this method. Firstly, the activity of single units must be recorded for considerable periods of time, in a stable fashion. That this requirement for stability has been met by a further development of the closed chamber recording technique is attested, we believe, by the spike amplitude measurements given in Section I. These conditions permit the setting up of a definite quantitative criterion by which the spike discharges of a given population can be identified with reasonable certainty as those of a single neural element, that is, that the amplitude measurements show a coefficient of variation no greater than 5 per cent. The stability of recording is indicated also by the persistence of response patterns unchanged over long periods of time. The duration of observation proved in 74 per cent of the units subjected to detailed study to be under the control of the observer.

The second requirement is that the activity of single neurons be observed without damage to the cell under study. Our data suggest that the initially negative discharges recorded extracellularly at some distance from the cell may be considered to derive from elements the least damaged. As the electrode approaches the cell, perhaps contacting some part of the cell membrane, inversion of the initial sign of the recorded action potential occurs, an event observed by several authors (4, 14, 21, 23, 29). This inversion takes place without the appearance of a resting membrane potential (4, 20). While there is evidence available (14, 29) that neurons in this spatial relation to the electrode may continue to respond to appropriate stimuli in a stable and predictable fashion for long periods of time, this is unusual. Signs of damage usually appear. The commonly observed increase in discharge, the rippling explosion of long trains of action potentials, must be considered only the terminal or lethal phase of that damage. There is an earlier and more subtle form of damage, seen as a decrease in responsiveness of the neuron. We conclude that such extracellularly recorded initially positive discharges can be considered those of an undamaged element only if the unit is studied in some detail both before and after sign inversion. This is seldom possible. It is clear then that initially negative discharges are more suitable for study, but even with them the requirement of avoiding damage has not been completely satisfied.

Thirdly, successful use of the method requires that the recording instrument sample randomly the population under study, and not reject any particular segment—for example, because of neuron size. It seems likely that the requirement of isolation does reject small neurons from the sample studied. The presence of an anesthetic agent also causes the rejection, to a varying and undeterminable degree, of elements of the cortical population. In this regard, we would like to emphasize that the use of unanesthetized animals held motionless by neuromuscular blocking agents offers no solution to this problem, for those agents themselves appear to have powerful effects upon central synaptic transmission. It is, therefore, necessary to say that all the observations of this and the following paper are confined to those cortical

elements which can be isolated, and which remain active at light anesthetic levels. It is a highly selected population. Such a limitation applies even more stringently with the method of intracellular recording.

II. The Neural Elements Studied are Cortical Cells

The assumption that the unitary discharges recorded are derived from cortical neurons is basic to all of our conclusions. That it is reasonable appears from the following statements. Firstly, the depth distribution of both the units isolated (Fig. 12) and of all observed unitary activity fits reasonably well the actual limits of the cellular region of the cortex. Secondly, our electrode records little sign of single-unit activity from active regions of white matter. Thirdly, the distribution patterns of receptive fields and modality types, described in the following paper, would be highly improbable if the recordings were made from an intermingled sample of cells and fibers. Fourthly, the elements recorded from are extremely susceptible to local injury, while cut thalamo-cortical axons continue for some time to conduct up to the site of transection (4, 25). Admittedly, all those reasons are circumstantial, and there is no direct proof that this basic assumption is a correct one. Such proof awaits a method of directly tagging the element recorded from in such a way that it can be identified in serial sections.

III. Response of Cortical Neurons to Peripheral Stimuli

1. *Drivability.* It is our belief that in the normal unanesthetized state all the neurons of the first somatic sensory area are open to direct driving by stimulation of the appropriate peripheral sense organs. It is well known (14) that the presence of an anesthetic may prevent such direct activation. Our experience suggests that damage to cell membrane or synaptic scale by the recording electrode is another potent factor in producing an apparent independence of a cortical neuron of a sensory receiving area from its afferent input. Thus, 54.3 per cent of the initially positive unitary discharges observed by us were undrivable, and we have on numerous occasions observed transition of a unit from a state of easy and direct driving to a complete unresponsiveness, simultaneously with inversion of the initial sign. Corollary support is given by the fact that 93.2 per cent of the initially negative units were drivable from the periphery, though observed randomly intermingled with the population of initially positive units, and at a variety of anesthetic levels. We conclude, therefore, that no direct evidence exists which would define a class of neurons of this somatic receiving area which are independent of its afferent input, such as Jung has observed in the visual cortex (15, 16).

2. *Early repetitive response.* Evidence has accumulated from these studies and those of several authors (4, 14, 29) that the early repetitive response of a cortical neuron to a brief peripheral stimulus is a normal event. The reasons for assuming this multiple discharge to derive from the same single neural source have been summarized (1, 29). Such repetition is characteristic of the

discharges of neurons of the thalamic relay nucleus of the system. It seems likely that this repetitive input is imposed upon the postsynaptic cell of the cortex as a smoothly graded transynaptic excitation, to which it responds in a smoothly graded way, for no step functions in the relation of response to strength of stimulus appear in our data (Fig. 13, Table 1). That this postsynaptic response occurs in some part of the cortical cell not invaded by the conducted action potentials it evokes seems likely, for it is not destroyed by the discharge of spikes. Such a maintained depolarization during repetitive firing appears also in the intracellular records of Phillips (26, 27), derived from cells of the motor cortex during direct electrical stimulation. The alternative hypothesis, that repetition is caused by a maintained or rapidly intermittent presynaptic excitation to which the postsynaptic cell responds repeatedly, with full recovery cycles and repeated local responses intervening, seems somewhat less likely.

3. *Modal distribution of a population of responses as a measure of stimulus intensity.* While from one stimulus to another some variability of the number of impulses per response of a cortical neuron does exist, study of a sufficiently large population of such responses reveals a normal distribution about a modal value, when the stimulus is supramaximal. Our data indicate that this modal distribution is a most sensitive index of the intensity and frequency of the stimulus. The modal value drops gradually as a supramaximal stimulus is moved from the center to the edge of a peripheral receptive field. However, it should be emphasized that a change in the latency or number of spikes in the response of a cortical unit does not necessarily signify a shift in the position of the peripheral stimulus (4, 5, 6). Indeed variations in the strength of stimuli delivered to the center of the receptive field can cause the response of a cortical cell to traverse the entire range of latencies, numbers of impulses per response, and frequency of firing of which the cell is capable.

IV. Spatial Distribution of Action Potential Field about Cortical Cells

Our measurements of the spatial extent of the current field developed about an active cortical cell (Fig. 7) suggest that the diameter of the field is at least 100 μ, and is likely to be much larger. Such a wide distribution has important physiological implications. Using the quantitative data of Sholl (30, 31) one can estimate that a shell 100 μ in diameter with the cell center as its center must transect on the order of a few hundred perikarya of other cells. Though Sholl's data obtain for cells of the visual cortex of the cat the figure given certainly represents the correct order of magnitude. It seems possible that an active cortical neuron will influence its neighbors by ephaptic action and the geometrical relations which exist make it likely that both excitatory and inhibitory effects occur.

V. Relation of Action Potentials to Slow Waves in Cerebral Cortex (8, 9, 13)

Our observations confirm the earlier ones of others (4, 23) that there is no evident correlation between the spontaneous surface-recorded electrical activity and the spontaneous discharge of cortical cells. All observers agree upon the close correlation between evoked single-unit responses and the evoked deep-negative slow wave. Our observations are consonant with the interpretation that this deep-negative slow wave is the integrated sign of the local postsynaptic responses of many cortical neurons.

Several authors have studied the changes in sign, amplitude and latency of the evoked slow wave which takes place as an electrode passes from the surface down through the cortex. Li *et al.* (22) have described an inversion of initial sign occurring 0.8–1.2 mm. beneath the cortical surface, and on this as well as other evidence have ascribed this response to a prolonged activity of the presynaptic terminals of thalamo-cortical fibers. Our own observations, which conform more closely with the later ones of Amassian (6), indicate that with an active cortex and minimal penetration damage the initial sign of the slow wave has regularly inverted at that level at which cellular discharges are first encountered. It is clear that inactivation of the upper layers of the cortex by pressure injury or anesthetic agent produces lower inversions of the initial sign of the evoked slow wave, for then only the intermediate and lower layers of the cortex are active. Deep inversions can be produced at will in this manner. Obviously data obtained on withdrawal of the electrode will falsely suggest a deep inversion point, the upper layers having accommodated the thicker portions of the electrode shaft during the tip's penetration to 2 mm. or more. That the latency of the isopotential point between positive and negative waves is longer close to the surface of the cortex than it is in deeper layers (see Fig. 18) has suggested to Amassian (4, 6) a serial synaptic activation of cells of the more superficial layers following on the initial responses of cells of the middle layers to the thalamo-cortical volley. None of our observations upon the evoked slow wave are in contradiction to this interpretation, but our data on average latencies of cells at different depths, given in the following paper, suggest that this serial activation, if it occurs, must involve a minimal number of synapses.

Summary

1. A description is given of a method of recording from single neurons of the first somatic sensory cortical area in the cat; by it the circulatory and respiratory movements of the brain are eliminated. A quantitative criterion of considerable aid in identifying a population of action potentials as those discharged by the same single unit is evolved from measurements of spike amplitudes.

2. Initially negative and initially positive single unit discharges, both recorded extracellularly, are examined from the standpoint of reliability and degree of cell injury. It is concluded that the former are recorded from cells the less likely to be damaged by the recording electrode, and are more suitable for studies of the functional organization of the cortex.

3. The typical discharge patterns of a neuron of the first somatic cortical area in response to a brief stimulus to its peripheral receptive field is a short

train of impulses at high frequency. This repetitive train is a normal event. Its latency, frequency and number of impulses are sensitively dependent upon the properties of the peripheral stimulus. Some complex response patterns, rarely seen under anesthesia, are described.

4. The distribution in depth of the neurons studied corresponds to layers II through VI of the somatic cortex. It is concluded from various lines of evidence that in the normal waking animal cells of all these layers are mediately open to activation by sensory stimuli.

5. The spatial distribution of the potential field developed about an active cortical cell was measured. Its extent, when compared with the degree of interlocking of the dendritic fields of cortical cells, makes ephaptic interaction between those cells possible.

6. A study of the surface-positive, deep-negative primary evoked potential of the cortex was made, as well as of its relation to the evoked discharges of single cortical cells. It is suggested that this wave is the integrated sign of the local postsynaptic responses of large numbers of cortical neurons.

7. The properties of a local spontaneous slow wave event of limited spatial extent within the cortex are described.

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