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# RELATION BETWEEN THE SIZE AND FORM OF POTENTIALS EVOKED BY SENSORY STIMULATION AND THE BACKGROUND ELECTRICAL ACTIVITY IN THE CEREBRAL CORTEX OF THE RAT

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When a peripheral nerve is stimulated with a brief electrical shock, a complex potential change is evoked in the primary sensory receiving area of the cerebral cortex. Unless the animal is deeply anaesthetized, both the size and the shape of this evoked potential are extremely variable from one shock to another, even when the parameters of the stimulus are kept constant and there are no obvious physiological changes occurring in the general condition of the experimental animal.

There are a number of relay stations in the centripetal course of a sensory pathway and it is possible that part of the variability may be introduced at each relay, for it is known that control of transmission is exerted at these points (Hagbarth & Kerr, 1954; Dawson, 1958*a*, *b*; Malcolm & Darian Smith, 1958; Angel & Dawson, 1961, 1963; Iwama & Yamamoto, 1961).

However, in the experiments reported in this paper it was found that the major part of the variability of the evoked potential occurring in the undisturbed, anaesthetized animal, was cortical in origin. An anatomical basis for a system which could modify the cortical response is provided by the presence in the cortex of association fibres and 'non-specific' thalamocortical afferents (Lorente de Nó, 1922, 1938). The term 'non-specific' was introduced by Lorente de Nó to include those afferents of thalamic origin which did not degenerate when the direct sensory tract, or 'specific' afferent system, was interrupted at the thalamic synapse. Scheibel & Scheibel (1958) describe the 'non-specific' thalamic system as having profuse intracortical branching which is widely distributed throughout the volume of the cortex, and has a very large number of synapses on cortical neurones and their basal and apical dendrites. Dempsey & Morison (1942) first showed that the stimulation with repetitive electrical pulses of this 'non-specific' system gave rise to the 'recruiting response', and Jasper & Ajmone-Marsan (1951) showed that when this

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response was present in the optic cortex a change in the amplitude of sensory evoked potentials occurred. Li (1956) extended this observation to include the effects of 'non-specific' thalamic stimulation upon the spike activity of individual neurones. He showed that although there was no synaptic connexion between the 'non-specific' fibres and the 'specific' cortical neurones which would make the latter discharge, there was, nevertheless, a mechanism which enabled 'non-specific' thalamic volleys to facilitate the discharge of cortical sensory neurones.

We have investigated the relation between the spontaneous variations in the potential level of the cortex, which we have found is affected by the degree of activity in the 'non-specific' thalamic system, and the size and shape of the evoked potential. When the cortical surface becomes relatively positive, the evoked potential has a large negative wave, while a relatively negative cortical surface is associated with a smaller and mainly positive-going evoked potential.

## METHODS

### *Surgical procedure*

125 rats weighing approximately 250 g each were anaesthetized with an intraperitoneal injection of either tribromethanol (2·5 % solution, 1 ml./100 g body weight; light anaesthesia was maintained by additional injections), or urethane (36 % ethyl carbamate, 0·56 ml./100 g body weight). There were certain differences both in the evoked potential and in the general electrical activity associated with depth of anaesthesia and the nature of the anaesthetic used; these were not relevant to the results reported in this paper.

The surface of the skull was exposed and a trephine hole, 4 mm in diameter, was made over the somato-sensory cortex on one side. The dura mater was left intact in some experiments, but in others approximately 2 $mm^2$ was removed. In order to reduce interelectrode shunting along the surface of the skull a polyethylene collar (5 mm internal diameter, 3 mm in depth) was cemented to the surface of the bone around the trephine hole with Horsley's wax so as to form a cup. This was filled with either Krebs's solution (mM: NaCl 115, $NaHCO_3$ 24·1, KCl 4·6, $KH_2PO_4$ 1·15, $MgSO_4$ 1·15, $CaCl_2$ 2·46, glucose 8·85; aerated with 5% $CO_2$ and 95 % $O_2$) or saline (NaCl 0·9 g/100 ml.). The skull was immobilized with a clamp on the incisor teeth and a Perspex cone fixed into each external auditory meatus. For the experiments involving thalamic recording a similar trephine hole was made over the thalamus, or in some experiments drill holes of approximately 500 $\mu$ diameter were made in the skull for both thalamic and cortical electrodes.

### *Electrical recording and stimulation*

Electrical activity from the sensory cortex was recorded with glass micro-electrodes filled with a solution of either 12 % KCl or 10 % NaCl. The tip diameter was between 1 and 5 $\mu$. Recordings were made between two such electrodes or in other cases between one and a non-polarizable indifferent electrode, which was usually placed under the skin of the back of the neck. The two electrodes were connected, in series with a calibrator, to a cathode follower. A direct-coupled amplifier (Palmer & Read, 1962) having a flat characteristic up to 50 kc/s was used, and the output taken to an oscilloscope. Resistance-capacity coupling was not used because of the distortion produced, particularly in the slow waves, except for recording unitary action potentials, when a time constant of 2 msec or

400 μsec was inserted into the appropriate channel of amplification. A positive potential change of the active micro-electrode tip is indicated by an upward deflexion in all the records.

To evoke potential changes in the sensory cortex, electrical stimuli were applied to the contralateral forepaw. The stimulating electrodes were fine needles inserted under the skin and the stimulus strength and pulse width were adjusted to produce a just perceptible twitch. The pulse duration was usually 100 μsec and the frequency was 0·5 c/s.

The thalamus or cortex was directly stimulated with positive pulses via either a saline-filled, non-polarizable micro-electrode, a steel micro-electrode varnished except at its tip, or two fine enamelled copper wires 60 μ in diameter bared at their tips, carried inside a stainless-steel tube, 250 μ in diameter and sharpened at its tip.

In most experiments the deep body temperature of the animal and the temperature of the cortical surface were maintained at 35° C, by means of a modification of the transistor-controlled heating device described by Deite-Spiff, Ikeson & Read (1962). A fall in temperature gave rise to larger evoked potentials which showed less spontaneous variability (see Lippold & Redfearn, 1960). Measurements of records were made by enlargement with a projector, and areas were measured with a planimeter.

### *Localization of electrodes*

In experiments involving thalamic recording the position of the electrodes was determined as follows:

*By means of stereotaxic positioning.* The atlas of the rat brain published by Gurdjian (1927) was used. A micromanipulator calibrated in three planes enabled the electrodes to be inserted at measured distances from bony landmarks.

*By histological control.* The brain was removed whole at the end of each experiment, and a coronal slab 4 mm thick was preserved in a mixture of 40 % formalin and 2·5 % potassium ferricyanide. After 24 hr, serial sections 50 μ thick were cut on the thermo-electric freezing microtome described by Brown & Dilly (1962), and stained with cresyl violet. Shrinkage was measured by inserting fine marker wires at measured distances apart in three planes and remeasuring the distances after fixation.

Brief polarization of the electrode tip at the end of the experiment enabled sufficient ferrous iron to be deposited in the tissue to give a localized Prussian-blue reaction. In the experiments with glass micro-electrodes the same reaction was obtained by filling them with potassium ferricyanide made up in 10 % saline and staining the cut sections with ferrous sulphate.

*By the effect of stimulation.* A short train of stimuli given via the thalamic micro-electrode resulted in a potential shift measured at the cortical surface when the electrode tip was within the mid-line thalamic nuclei. This effect was localized to less than 500 μ of travel in the vertical plane (e.g. at 5·5 mm below the cortical surface no effect could be obtained with a given stimulus strength; at 6·0 mm the potential response to the same stimulus was obtained). A single strong stimulus produced no effect on the cortical surface potential, except in the thalamic regions from which a recruiting response could be obtained, hence there was no stimulus spread to the specific thalamic nucleus or to the cortex.

## RESULTS

### *Spontaneous variability of the evoked potential*

In the lightly anaesthetized animal the normal evoked potential was small and variable.

The potential complex consists of, first, an initial small positive potential (1), up to 100 μV in amplitude, 1–2 msec in duration, occurring about 5 msec after the stimulus is

given to the forelimb (Fig. 1). This wave represents the specific thalamocortical volley and is always present over the primary receiving area (Chang & Kaada, 1950; Perl & Whitlock, 1955). Angel & Dawson (1963) have shown that this wave is in certain circumstances diphasic and its size can be related to changes recorded in the thalamus. Then there is a second, larger, positive potential (2), up to 2 mV in amplitude and from 2 to 15 msec in duration. Occasionally the evoked potential consists only of these two waves, (1) and (2), for example, when the stimulus strength is very low, when the anaesthesia is deep or when $\gamma$-aminobutyric acid is topically applied. However, wave (2) is usually cut short, or indented by a negative-going potential (3) of variable magnitude, duration and latency. The latency of wave (3) is seldom so short that wave (2) is completely obscured.

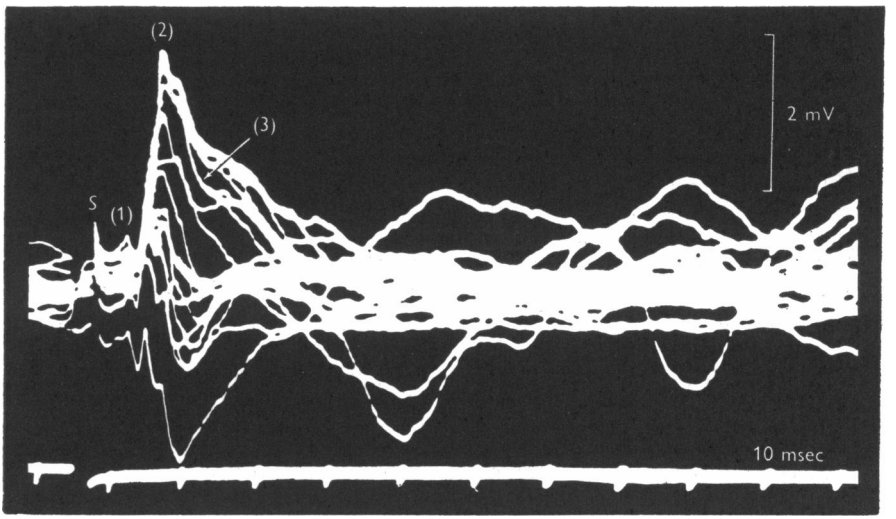


Fig. 1. Rat, light urethane anaesthesia. Recording of 20 consecutive potentials, evoked by just supra-threshold electrical pulses to the skin of the forepaw. Each pulse 100 $\mu$sec in duration and pulse interval 2 sec. The stimulus artifact ($S$) is followed by the first positive wave (1), second positive wave (2) and a negative wave (3) cutting into wave (2) by a varying amount. 4 sec time constant inserted to reduce base-line shifts; time marker, 10 msec; calibration bar = 2mV. In these and subsequent figures a positive potential change at the recording electrode is shown as an upward deflexion.

The waves (2) and (3) are commonly considered to be post-synaptic in origin; depolarization limited to the primary receiving zone 400 $\mu$ or more below the cortical surface gives rise to the positive wave (2) because the surface acts as an electrical source. If the depolarization spreads to involve surface neural elements (or if they are excited in any other way) the negative wave (3) is present. The size of wave (3) depends partly on the magnitude of the spread to the surface and its time course (Eccles, 1951; Cragg, 1954; Cragg & Hamlyn, 1955; Chang, 1959).

When the stimulus strength was kept constant, variations occurred in the over-all amplitude of the normal evoked potential and in the degree to which the negative wave (3) interrupted positive wave (2). Figure 2 shows how the amplitudes of the various waves may vary during the

course of 6 min, when successive stimuli are of constant strength. It can be seen that the negative wave (3) is the most variable, whereas the positive wave (1) is the most stable in size.

The greater part of the variability of the evoked potential is not due to variation in the size of the specific thalamic discharge, because there is, in fact, very little correlation between the thalamic discharge and waves

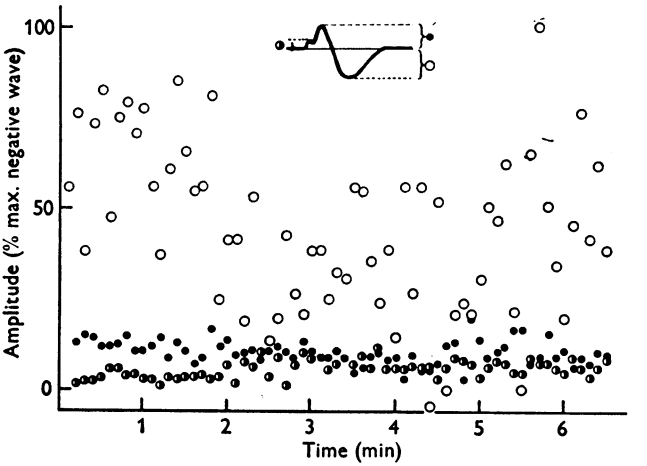


Fig. 2. Variability of evoked potential. Graph showing the amplitudes measured from base line at the start of each trace, of waves (1), (2) and (3) plotted during the course of approximately 6 min while the stimulus strength was kept constant. Conditions and symbols as in Fig. 1. ◑ = positive wave (1), ● = positive wave (2) and ○ = negative wave (3).

(2) and (3) of the cortical evoked potential. The variability was diminished by several experimental procedures. The topical application of $\gamma$-amino-butyric acid, slight damage to the surface layer of the cerebral cortex or deep anaesthesia gave rise to entirely positive potential complexes when the forelimb was stimulated. On the other hand, lowering the temperature of the cerebral cortex (Lippold & Redfearn, 1960) the topical application of various drugs such as D-tubocurarine (Cairnie & Malcolm, 1960) or penicillin, the early stages of asphyxia, and prolonged exposure of the cortical surface, were associated with relatively uniform complexes having a large negative wave (3). The greatest variability was obtained when the animal was in good condition, under light anaesthesia, and the stimulus strength was inadequate to produce a maximum response.

The major part of the variability in shape of the evoked potential is due to the lability of the negative wave (3) at the surface. Attempts to measure the true amplitudes of wave (2) and wave (3) are vitiated by the fact that the two waves overlap in their time course and partially cancel each other out. Furthermore, the larger the negative wave (3) the smaller is the apparent amplitude of wave (2), which is cut off earlier (Fig. 1). The relation

between the apparent latency of wave (3) and its size is not simple. That the positive wave (2) is in fact the source for the deeper-lying depolarization has been shown by the good correlation between the surface-positive wave (2) and the negative potential simultaneously recorded at the depth of minimum latency (Bindman, Lippold & Redfearn, 1962).

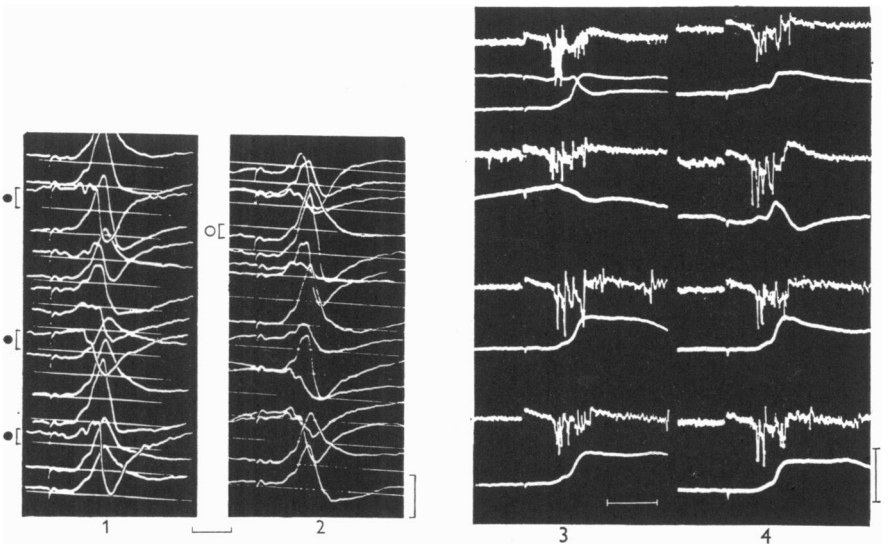


Fig. 3. Influence of pre-existing potential level at cortical surface upon the form of the evoked potential. Rat, 250 g, lightly anaesthetized intraperitoneal (urethane). Records from sensory cortex of potentials evoked at 2 sec intervals by shocks to skin of contralateral forepaw. In ladders (1) and (2) the two traces consist of the evoked potential and a base line (representing an arbitrary zero potential). When the cortical potential level is relatively positive, i.e. the evoked potential begins above the base line, there is a resultant large negative wave (see traces marked ● in left column). When the potential at the time of the stimulus artifact is relatively negative and below the base line, the evoked potential is mainly positive-going (○ in column 2). In ladders (3) and (4), from another preparation, the pairs of traces consist of: (upper trace) unitary discharge associated with the evoked potential recorded from a depth of 500 $\mu$ and (lower trace) the evoked potential recorded from the cortical surface. The surface potential level is indicated by the distance of the lower trace from the beginning of the upper trace (top left-hand record shows two consecutive pairs of responses superimposed). Time bar 10 msec, voltage calibration 1mV.

*The influence of cortical potential level on the evoked potential*

The potential level of the cortical surface varied continuously with fast and slow rhythms (see Caton, 1877). When recording with the DC amplifier it was observed that the size and form of evoked potentials were related to the potential level of the cortex at the time of arrival of the sensory volley (Fig. 3).

When the cortical surface showed a relative positivity the evoked

potential at that time was mainly negative, i.e. the positive wave (2) was small, whereas the negative wave (3) was large and had a shorter latency. Conversely, a negative swing of the potential level of the cortical surface was followed by a positive evoked potential, i.e. one having a large and long-lasting positive wave (2) and a small or absent negative wave (3). The extent of this correlation is shown in Table 1. A preliminary account has already been published (Lippold, Redfearn & Winton, 1961).

TABLE 1

| | | Evoked response | |
|---|---|---|---|
| | | positive | negative |
| Potential level | positive | 19 | 103 |
| | negative | 119 | 10 |

Correlation between relative cortical potential level at time of stimulus artifact and subsequent form of evoked potential. Results from three experiments (2 under urethane; 1 avertin) $\chi^2 = 148$; $P < 0{\cdot}001$. The procedure adopted was to measure the amplitudes of the positive and negative waves from the base line. If the positive exceeded that of the negative, the potential was classified as positive-going.

### *Spontaneous variability of cortical potential level*

The potential level under urethane anaesthesia usually fluctuated between maximum positivity and negativity in a series of plateaux occurring approximately once every second. At the positive level faster activity was present in the form of superimposed irregular waves at a frequency of 10/sec or higher, whereas there was very little electrical activity while the potential level was relatively negative. The amplitude of the fast activity was small compared with that of the plateaux. The periods of quiescence when the potential level was negative were lengthened by increased depth of anaesthesia (Fig. 5). Under tribromethanol anaesthesia the precise form of these fluctuations was different, but there was a similar relation between pre-existing potential level and the evoked potential. Occasionally negative-going and diphasic plateaux were observed at the cortical surface. These may have represented regions of depolarization at some distance from the recording site.

### *The influence of cortical potential level on the response to intracortical stimulation*

If the major part of the variability of the evoked potential occurs as a result of changes in cortical excitability, it should be possible to demonstrate a similar relation between potential level and the response to intracortical stimulation. The cortex was excited directly by stimulating through a glass micropipette. This was inserted at an angle into the grey matter to a depth of 0·5–1·0 mm. Threshold pulses applied between this

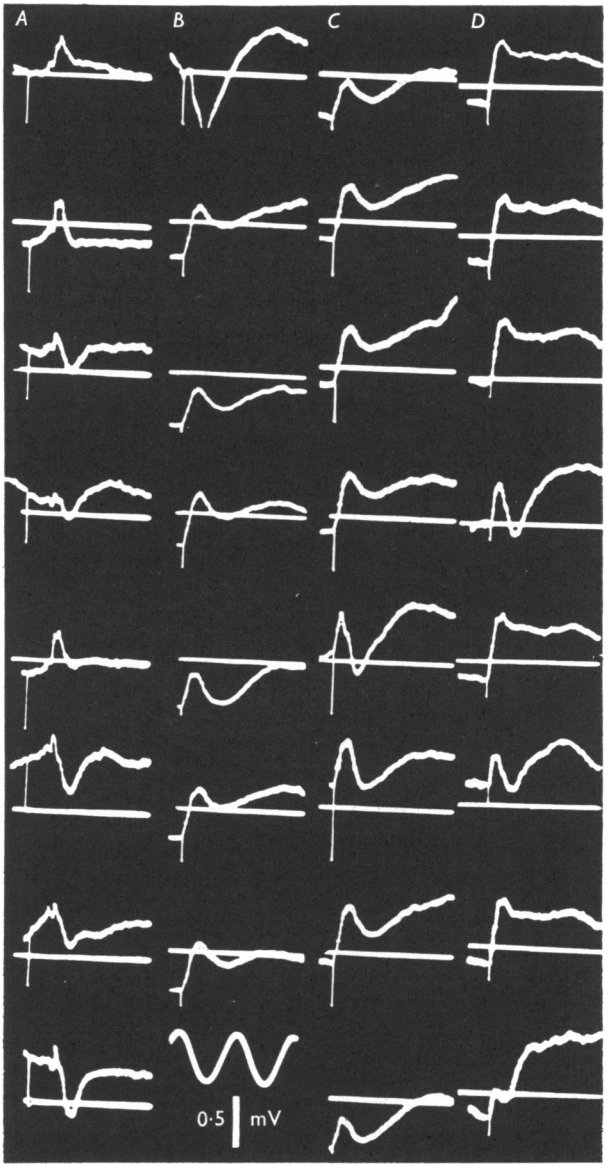


Fig. 4 (*a*). Potentials evoked at 2 sec intervals recorded from the cortical surface to show the relation between variations in shape and pre-existing potential level. Each pair of traces in ladders shows the evoked potential and a base line indicating an arbitrary zero potential level. Column *A*: potentials evoked by stimulation of the skin of contralateral forepaw. Columns *B*, *C*: potentials evoked by stimulation at depth of 800 $\mu$ in cortex; same animal and electrode position as in *A*. Column *D*: same as in *B*, *C*, but different animal and slightly weaker stimulus strength. At foot of column *B*, voltage calibration and 50 c/s trace.

deep electrode and an indifferent electrode produced a wave which was negative at a depth in the cortex and positive when recorded from the cortical surface above the stimulating electrode (see Adrian, 1936). If the stimulus voltage was increased, a surface-negative wave of latency

TABLE 2

| | | Response to intracortical stimulation | |
|---|---|---|---|
| | | positive | negative |
| Potential level | positive | 13 | 65 |
| | negative | 110 | 9 |

Measurement of potential level and classification of response as in Table 1. Results from 3 experiments under urethane. $\chi^2 = 115{\cdot}4$; $P < 0{\cdot}001$.

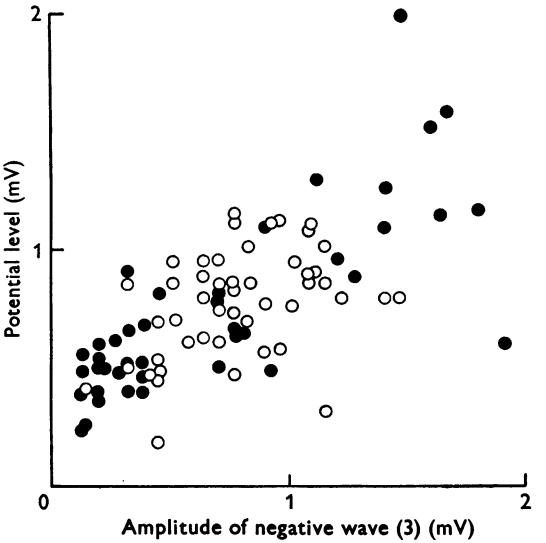


Fig. 4(*b*). Graph showing relation between the potential level of the cortex and the amplitude of the surface-negative wave of the response to intracortical stimulation (●) and of the negative wave (3) of the potential evoked by peripheral stimulation (○). Abscissa, amplitude of negative waves measured from beginning of negativity to peak of negative wave: ordinate, potential level of cortex with respect to an arbitrary base line, measured at stimulus artifact of response to intracortical stimulation for ● and at beginning of positive wave (1) of potential evoked by peripheral stimulation for ○. The two types of potential were recorded from the same animal. For 41 consecutive responses to cortical stimulation $r = +0{\cdot}82$; and for 48 consecutive responses to peripheral stimulation $r = +0{\cdot}54$.

2–6 msec cut into the positive wave (Goldring, O'Leary, Holmes & Jerva, 1961). With a stimulus of intermediate strength the amplitude of the negative wave varied. The shape and size of this complex varied with the pre-existing potential level of the cortical surface in a similar way to the

potential evoked by peripheral stimulation. Figure 4*a*, *b* shows the relation between the cortical potential level and the complex evoked by stimulation of the forepaw (column *A*) and the relation between the cortical potential level and the complex evoked by stimulating the grey matter (columns *B*, *C*) in the same animal, and in a different animal (column *D*).

Figure 4*b* shows the correlation between the negative wave (3) of the cortical response to peripheral stimulation and the potential level of the

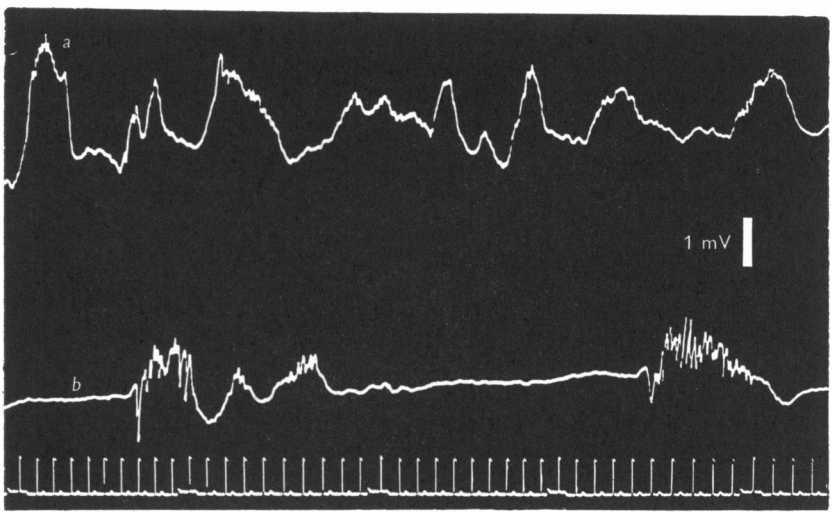


Fig. 5. Fluctuations in potential level of the sensory cortex. *a*: rat lightly anaesthetized with urethane. *b*, deeper anaesthesia, same experiment as *a* but 30 min later, showing long quiescent periods between positive plateaux. Records from surface of sensory cortex. No external stimulation; room quiet. Time trace, large signals at 100 msec intervals; voltage = 1 mV.

cortex; also the correlation between the negative wave of the response to intracortical stimulation and potential level. In this graph the magnitudes of the waves and the corresponding potential levels are plotted. The product moment correlation coefficients are $r = +0{\cdot}82$ in the case of intracortically-induced negative waves and $r = +0{\cdot}54$ in the case of peripherally-evoked negative waves.

Thus a spontaneously occurring positive swing of the potential level of the cortical surface indicates a lowered threshold of cells in the depth of the cortex, and results in an increased probability that depolarization will spread from the depth of the cortex to involve the surface layers.

In view of the fact that the fast irregular activity occurred during the positive plateaux it seemed likely that a positive potential swing at the

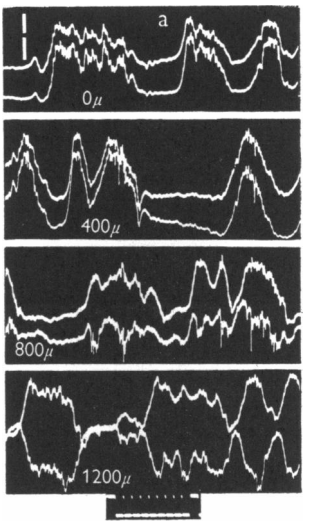


**Fig. 6 (*a*). Recordings of cortical potential level at different depths below the pial surface (conditions as Fig. 5*b*). From above downwards: surface, 400, 800, 1200 μ; records taken at 2 min intervals at each depth. The upper trace of each pair is recorded between a micro-electrode on the pia mater and an indifferent electrode on the neck. The lower trace is recorded between a micro-electrode at the stated depth and an indifferent electrode.**

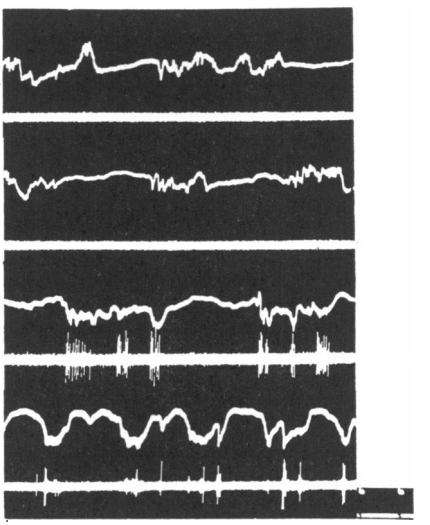

**Fig. 6 (*b*). Different experimental animal. Potential level at different depths (upper trace of each pair), and record from same micro-electrode at greater amplification through a time constant of 2 msec (lower trace of each pair). Note that in this animal the plateaux are reversed at 650μ. From above downwards depths are, surface, 300, 650 and 1000 μ.**

cortical surface was associated with increased neuronal activity. Recording at different depths below the surface showed that at about 400–600 $\mu$ the plateaux were absent, although the periods of intermittent fast activity still occurred; below 500–800 $\mu$ the plateaux were reversed in polarity and the fast activity then occurred on negative-going peaks. Therefore the major part of the neuronal activity responsible for the

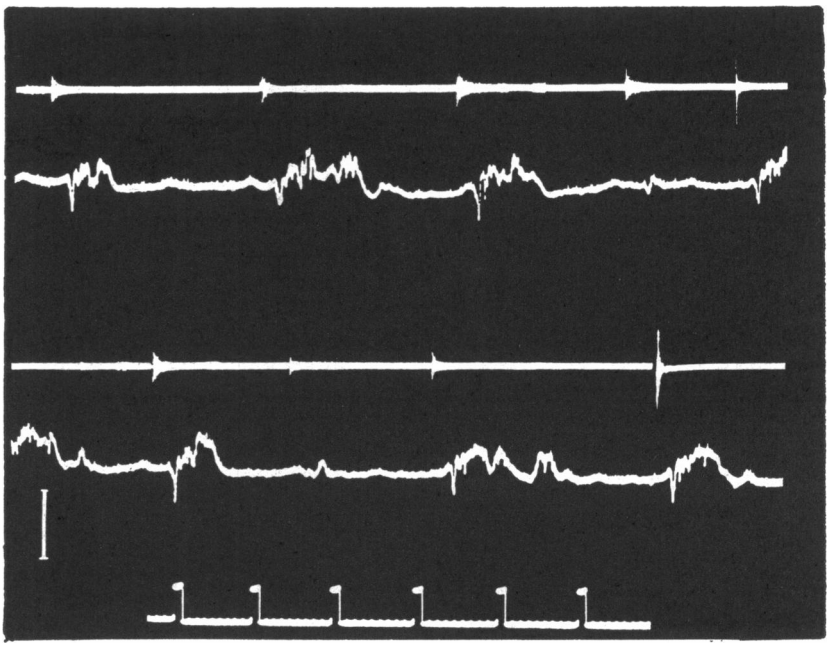

Fig. 7. The effect of sounds upon the electrocortical activity of the somatosensory area of the rat. Note plateaux commencing with a large negative wave about 40 msec in duration. Top trace from microphone near animal; the sounds were produced by claps, bangs, hisses, etc. Second trace shows record from cortical surface over primary receiving zone for the right forepaw. Bottom two traces follow the top two. Time signal = small signals 100 msec and large signals 1 sec; voltage calibration = 1 mV. Anaesthetic level deep (to give long periods between spontaneous plateaux: see text).

plateaux is likely to be depolarization occurring at 500–800 $\mu$ and below (Fig. 6*a*). This conclusion was substantiated by recordings of deep cortical unit discharges which occurred during the plateaux when the surface was relatively positive and which were absent during the quiescent periods between plateaux (Fig. 6*b*).

*Evoked variations in cortical potential level.* We found that it was also possible to produce cortical plateaux, similar in appearance to those occurring spontaneously, by various stimuli which would presumably

alert the unanaesthetized animal, such as loud sounds (Fig. 7) and tactile stimulation. Figure 8 shows the increase in size of the negative wave of the evoked potential at a depth and at the surface, together with a surface-positive potential shift, which occurred during continuous pinching of the tail. The effect of pinching the tail on the size of the negative wave of the response to intracortical stimulation was less marked than it was

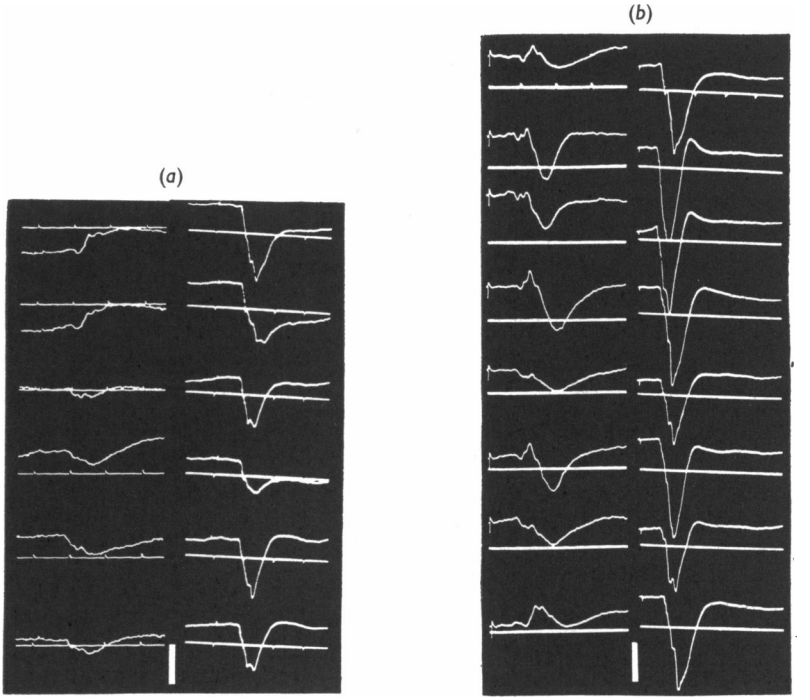


Fig. 8. The effect of pinching the tail. Block *a* shows, left-hand column, recordings of successive evoked potentials from the sensory cortex; the right-hand column shows the same evoked potential simultaneously recorded at a depth of 500 $\mu$ (indifferent electrode, in this case, on surface). The potential level is shown in each case by the distance between the trace and the base line. Block *b*, the same but immediately after pinching the tail. Note the positive change in potential level at the surface (particularly in the first four traces) and the larger negative waves of the evoked potential. Stimuli every 2 sec; time marker = 10 msec; voltage = 2 mV.

in the case of the evoked potential. This probably indicates that part of the augmentation of the latter response occurred at the thalamic relay (see Angel & Dawson, 1963).

*Potential gradients in cortical neurones.* The facts that the surface-positive plateaux reverse at about 600 $\mu$, and that the neuronal action potentials associated with plateaux are only found at this depth and

below, indicate that the plateau is produced by depolarization of structures having inactive processes which extend up to the surface, and act as electrical sources. When we recorded between an electrode at the surface

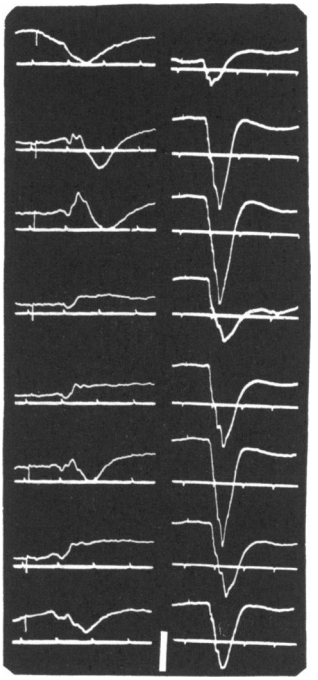

Fig. 9. The same experiment as in Fig. 8 but in the absence of any non-specific stimulation. The records show the normal variability associated with light depth of anaesthesia (right-hand columns recorded between surface and 300 $\mu$ depth). Time marker = 10 msec; voltage calibration = 2 mV.

TABLE 3

| | | Evoked response | |
|---|---|---|---|
| | | positive | negative |
| Potential level at 300$\mu$ | positive | 31 | 16 |
| | negative | 11 | 48 |

Correlation between sign of the evoked potential (measured as in Table 1) recorded at the surface, and the potential level at 300 $\mu$ beneath the pia mater. The potential level was measured with the DC amplifier between one electrode on the cortical surface and the other at a depth of 300 $\mu$ below it. $\chi^2 = 25{\cdot}5$; $P < 0{\cdot}001$.

and one at a depth of 300 $\mu$, we found that pre-existing negativity at 300 $\mu$ was associated with a negative-going evoked potential at the surface (recorded between the surface and an indifferent electrode). The changes

in potential level which are recorded between the surface and an indifferent electrode are produced by a vertical potential gradient in the cortex, i.e. one that is orientated in the same direction as the apical dendrites of the pyramidal cells (Figs. 8, 9 and Table 3).

The anatomical distribution of the non-specific projections makes it likely that the control of cortical afferent activity is exerted at all depths in the grey matter. The relation we have described between the potential level and the evoked potential is only apparent in normal cortex near its surface. If however, these surface layers are inactivated (e.g. by the use of $\gamma$-aminobutyric acid), it is possible to demonstrate the relation at any depth in the grey matter.

$\gamma$-aminobutyric acid applied to the cortical surface slowly diffuses down into the grey matter and blocks depolarization, the passive properties of membranes being unaffected (Bindman, Lippold & Redfearn, 1962). Under these circumstances the evoked potential is positive under the surface in the affected layer. The positive wave (2) of the evoked potential (which is normally not present below 200–300 $\mu$) was occasionally followed by a negative wave (3); the form of the evoked potential was as variable at a depth under these conditions as it was at the surface of the normal cortex. The same relation between the potential level and the form of the evoked wave obtains in these circumstances as in the normal cortex.

*Thalamic origin of cortical plateaux*

It is well known that the mid-line thalamic nuclei are non-specific in nature, i.e. their neurones can be activated by a wide variety of sensory stimuli (Starzl, Taylor & Magoun, 1951). The relation between the cortical plateaux and thalamic firing was investigated and it was found that a positive plateau at the surface of the cortex was associated with unitary spike activity and a potential change in the non-specific nuclei of the thalamus (Fig. 10). If the intralaminar nuclei of the thalamus were stimulated through the same electrode used to record this non-specific activity, a positive potential change at the cortical surface (or a negative change at about 800 $\mu$) with increased cortical activity was produced (Fig. 11).

The effects described in the last paragraph could be obtained from certain regions in the medial thalamus as follows:

*Thalamic plateaux.* By recording simultaneously from the somatosensory cortex and the thalamus with direct-coupled amplifiers, it was possible to demonstrate that there were plateaux which began and ended at approximately the same time in both channels. In the nucleus centralis, for example, a plateau began earlier than did the corresponding plateau in the somatosensory cortex. Although plateaux could also be recorded

from other mid-line nuclei, such as the dorsomedial nucleus, they invariably began later than the corresponding ones in the cortex.

*Thalamic unit activity.* Thalamic units, which fired at approximately the same time as the positive plateaux appeared at the cortical surface, could be recorded from micro-electrodes in the dorsomedial nucleus and the posterior paraventral nucleus. In these sites it was usual to find, in

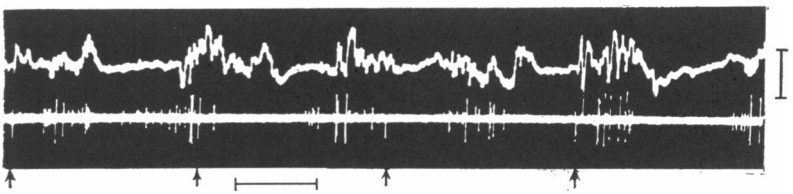

Fig. 10. Upper trace, recording made at cortical surface; lower trace, recording made in thalamus at position shown in Fig. 13 (No. 14 *L*). Shocks given to contralateral forepaw at arrows. When the potential level is relatively negative the evoked potentials have large positive waves (1st and 4th responses); when the potential level is positive the evoked potentials have small positive waves (2nd and 3rd responses). Voltage calibration, 0·5 mV; time bar, 1 sec.

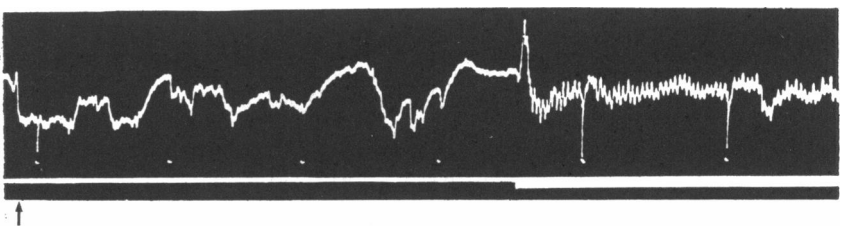

Fig. 11. Recording made from micro-electrode inserted to a depth of about 800 $\mu$ in the cortex. Upper trace: background activity in cortex together with evoked potentials, before and during thalamic stimulation. Note the similarity between positive wave at arrow occurring before a spontaneous negative plateau, and the positive wave elicited by thalamic stimulation. During the negative potential shift induced by the thalamic stimulation the evoked potentials are large and negative-going. Bottom trace: dots above base line indicate when shock was given to contralateral forepaw. Where bottom trace is thick electrical shocks were delivered through a stimulating electrode in mid-line thalamus (drawing 360 in Fig. 13) at 16/sec.

addition, spike discharges which occurred in the absence of any cortical positivity and also positive plateaux at the surface which were not accompanied by any spike discharges. In most experiments spike discharges from these regions occurred slightly later than the onset of positivity in the somatosensory cortex.

Thalamic units, however, could be recorded from the nucleus centralis, which invariably began firing before the onset of a spontaneous cortical plateau and were always related to the production of a plateau. Figure 10

shows the relation of thalamic unitary firing, potential level of the somatosensory cortex and the size of the evoked potential. When the units in the nucleus centralis fired, the cortical surface, 2–3 msec later, become positive and an evoked response at the cortex was large and was predominantly negative. During the intervening quiescent period, when the non-specific thalamus was not firing and the cortical surface was relatively negative, the evoked potential was small and had a larger positive-going component.

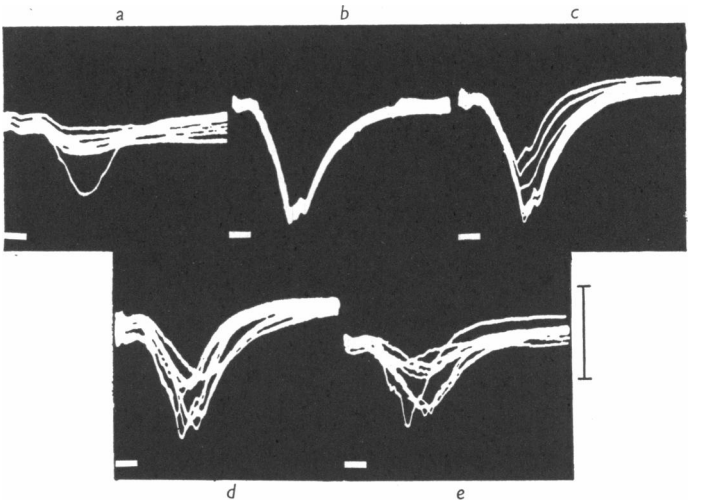


Fig. 12. Evoked potentials recorded from a depth of about 400 $\mu$ in cortex; ten superimposed traces. *a*. Control; *b*. During thalamic stimulation (Fig. 13; in region of upper black dot in expt. 375); *c*. Immediately after thalamic stimulation; *d*. 30 min after *b*; *e*. 1 hr 5 min after *b*. Voltage calibration 0·5 mV. The white marks indicate level of base line.

*Stimulation of thalamus.* The two methods which were employed to stimulate the thalamus gave the same result. Only from circumscribed regions in the mid line, as can be seen from Fig. 13, was it possible to produce a potential shift at the cortical surface on electrical stimulation. As the micro-electrode tip or the wire electrodes were advanced into the brain a point was reached, for example, about 5·5 mm below the surface, where maximum stimuli at about 30/sec would just give a positivity on the surface of the cortex. At 6·0 mm a maintained cortical positivity could be produced with a stimulus voltage reduced by a factor of 20. During this positivity, evoked potentials were large and had large negative waves (3).

Figure 12 shows superimposed tracings of evoked potentials recorded (*a*) during a control period, and (*b*) during thalamic stimulation. There is a positive shift of the base line (= cortical potential level) in record *b* and the evoked potential has a large negative wave.

It was interesting to note that this effect on the evoked potential usually took about 30 sec to reach its maximum level; the evoked potentials remained large for 1–30 min after the stimulation had ceased (Fig. 12*c* and *d*). After three or four repetitions of the train of stimuli it was usually found that the response declined and often vanished. Under these

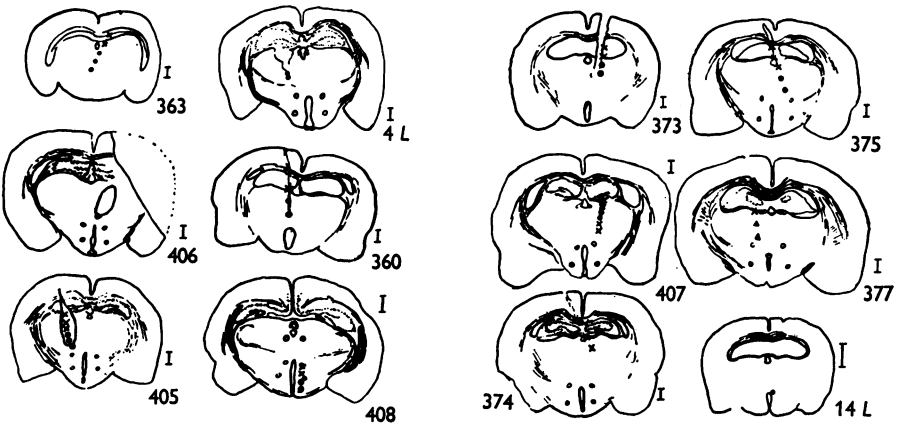


Fig. 13. Each drawing (except 363 and 14 *L*) was made by tracing the projected image of a section of the rat brain in which the deepest electrode position was marked by Prussian blue stain. Other tip positions, in each track, were calculated by taking into account the shrinkage. 1 mm bar refers to unfixed preparation. In all tracings except 360, 373, 363 and 14 *L* the nuclei were stained with cresyl violet. In 360 and 373 the sections were left unstained. 363 and 14 *L* are freehand drawings made from the sectioned frozen block of the brain, the sections of which were not preserved. Drawings 363, 4 *L*, and 360 show points (filled circles) from which recruiting waves were elicited. At high rates of stimulation a potential shift was obtained in experiments 363 and 360, but not in experiment 4 *L*. In five experiments (363, 406, 360, 405 and 408) stimulation of the thalamic or hypothalamic points, marked with filled circles, elicited a potential shift in the cortex which was positive when recorded from the surface (405, 406 and 408) or negative when recorded from a depth greater than 600 $\mu$ (363, 360), together with an associated increase in the size of the negative wave (3) of the evoked potential. Drawings 373, 375, 407 show thalamic points (filled circles) which when stimulated produced an increase in the negative wave (3) of the cortical evoked potential. The potential level was not recorded in these three experiments. Drawing 377 shows two points (filled triangles) which when stimulated elicited a potential shift in the cortex but no consistent change in the size of the evoked potential.

In all drawings points marked X indicate regions which when stimulated produced no effect on the cortical potential level or on the evoked potential. Drawing 14 *L* shows the electrode position from which the records shown in Fig. 10 were taken. Bar indicates 2 mm in unfixed slab.

circumstances the potential level at the surface was no longer varying in plateaux but appeared to be relatively flat. Presumably the non-specific nucleus had been damaged by the passage of current.

Figure 13 shows the anatomical location of the tips of micro-electrodes in the thalamus in twelve experiments.

Often cortical plateaux commenced with a large negative wave of about 40 msec duration (Figs. 5, 7). Neural elements responsible for this initial potential were near the pial surface because the polarity reversed within the top 600–800 $\mu$ of the grey matter as the recording micro-electrode was lowered into the cortex. This wave increased in amplitude as the anaesthetic depth was increased (Fig. 5).

We found that a similar surface-negative wave, equivalent to the 'recruiting' wave first described by Dempsey & Morison (1942), could be evoked in the cortex by stimulation of parts of the mid-line thalamus (Fig. 14). The surface-negative component was of about 40 msec duration, and at a depth in the cortex of 600–800 $\mu$ it reversed in sign. Hanbery & Jasper (1953) noted that the recruiting response in the cat became more easy to detect as anaesthesia deepened. An evoked 'recruiting' wave was often followed by a plateau; it may well be that the surface-negative wave preceding a plateau is the spontaneous equivalent of a recruiting response, since the characteristics of the two waves are similar.

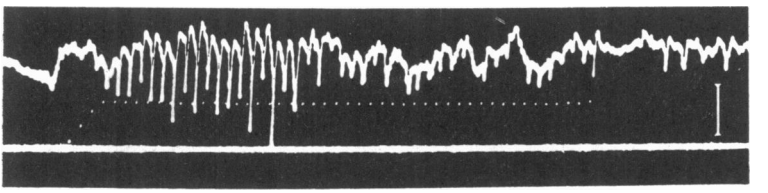

Fig. 14. Top trace, surface-negative 'recruiting' waves elicited by stimulation of mid-line thalamus (Fig. 13, drawing 4*L*). Recording made with electrode on cortical surface. Lower trace, shocks given via electrode in thalamus, at 10/sec. Voltage calibration, 1 mV.

The surface-negative wave and the plateau are the results of activity in different systems, for the following reasons:

(1) The wave and plateau were of opposite polarity both at the surface and at a depth in the cortex (Figs. 6*a*, 14 and 15).

(2) The neurones producing the spontaneously occurring surface-negative wave were more resistant to anaesthesia than those responsible for a plateau; it was possible to abolish the latter with deep anaesthesia and yet still to record this large wave. The surface-negative recruiting waves also followed faster rates of stimulation than did the plateaux (Fig. 15).

(3) When a train of recruiting waves was elicited with no concomitant potential shift, the negative component of the sensory evoked potential was depressed, as was previously shown by Hanbery & Jasper (1953). During surface-positive plateaux the negative wave of the evoked potential was enhanced.

(4) Stimulation of regions of the mid-line thalamus shown in experiments 360 and 363 produced a recruiting wave followed by a plateau; stimulation of other regions produced one independently of the other.

## DISCUSSION

In spite of the large volume of experimental work that has been published in recent years, the way in which the cerebral cortex functions is still, to a large extent, unknown. It is possible, at the present time, to track nerve impulses from the receptor organs via their various relay stations to the relevant regions of the cortex, where they generate complex potential changes. The outflow from the motor areas and other parts of

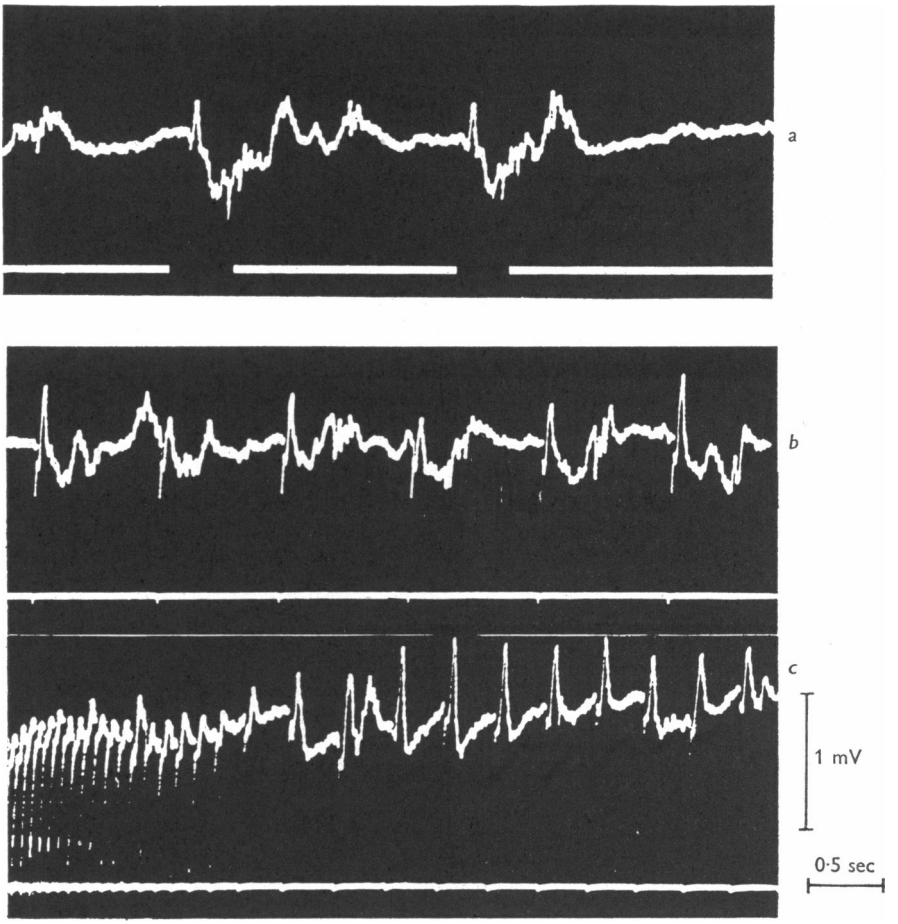


Fig. 15. Recording made from electrode at depth of 800 $\mu$ in the cortex. *a*: upper trace shows positive-going recruiting waves elicited by stimulating shocks given via electrode in mid-line thalamus (Fig. 13, drawing 363) and following negative plateaux. Lower trace, break indicates train of shocks delivered via thalamic electrode. *b*: upper trace, recruiting waves elicited about twice as frequently as in *a*. Note that a plateau follows each recruiting wave. Lower trace; single shocks delivered via thalamic electrode. *c*: the frequency of the stimulus eliciting the recruiting waves is altered. At frequencies of stimulation greater than in *b*, a plateau does not follow each recruiting wave. Time bar, 0·5 sec; voltage calibration 1 mV.

the cortex can also be traced, including 'feed-back' which has been shown to regulate the amount of sensory information which is allowed to penetrate to the cortical level.

The interdependence of the sensory inflow to the cortex and the motor outflow was first pointed out by Adrian (1941). He took advantage of the

fact that there is a certain degree of overlap between the somatosensory and the corresponding motor areas; there are large pyramidal cells present in the sensory areas. He found that a motor discharge in the pyramidal tract occurred whenever the evoked potential (resulting from skin stimulation) in the appropriate cortical area displayed a large negative wave. When the evoked potential was small, or consisted of a positive wave only in response to sensory stimulation of the skin, there was no motor discharge. It was clear, therefore, from Adrian's work that the cortex itself was exerting a controlling influence on the input-output characteristics of the system.

The discovery of the 'non-specific' thalamic afferents in the rat by Lorente de Nó (1922) indicated a possible mechanism whereby such a control system at the cortical level could operate. Surprisingly, there is little speculation in the literature about such a possibility, apart from a short paragraph written by Jasper (1949). There is now good evidence (Burns & Smith, 1962) that incoming information is routed to many cortical regions; possibly this occurs in a selective manner. Lilly & Cherry (1955) have recorded travelling waves of electrical activity which can be elicited by sensory stimulation or which originate spontaneously in the cortex. The waves spread out from a point of origin in all directions; they by no means follow predetermined paths but tend to vary in their distribution from one instant to the next. The peak amplitude of such a wave is about 500 $\mu$V positive relative to the surrounding regions. It is suggested that the travelling figures recorded at the surface are due to activity in a system of deep cortical cells and their processes, with rich interconnexions parallel to the surface.

Buerle (1956) has discussed, theoretically, cortical function in terms of co-operative activity of cell masses which give rise to various kinds of stationary and moving patterns of excitation. This type of co-operative activity in cell masses might be responsible for the electrical changes described by Lilly & Cherry (1955), where spontaneous activity, which is thought to occur at a depth, spreads out parallel to the cortical surface.

Our experiments show that the precise form and size of a sensory evoked potential are closely related to the standing potential level of the cortex at the time of arrival of the sensory nerve volley at the primary receiving area. Moreover, it appears likely that the potential level can be controlled *inter alia* by the activity of the intralaminar thalamic nuclei. On the basis of results obtained by recording at various depths in the cortex simultaneously, it is generally agreed that negativity (wave 3) recorded at the pial surface during an evoked potential probably represents spread of excitation to involve surface neural elements. (It could of course also represent direct activation of these surface elements by thalamocortical paths of

longer latency than is exhibited by the direct connexions.) This spread to the surface may, at the same time, involve lateral travel of the zone of excitation but we have no evidence for this at present.

In our experiments a relatively positive (by +2 mV or so) standing potential of the cortical surface was associated with large, mainly negative-going potentials. Further, this positive potential level of the cortex could be produced by thalamic intralaminar discharges. In the absence of thalamic firing the surface potential became relatively more negative again and the evoked potential reverted to a mainly positive form. Thus it is possible for the mid-line thalamus to control the excitability of the cortex in such a way that the spread of activity to the surface (and possibly laterally also) is regulated.

It should be emphasized that a mechanism such as this does not necessarily play the major role in cortical integration. We have used the anaesthetized animal in a steady state and have taken care to exclude as many extracortical variable factors as possible. For instance, there is little doubt that other modes of cortical stimulation can initiate positive cortical potential shifts similar to the plateaux that we have described, which do not necessarily depend on simultaneous intralaminar firing (e.g. as shown in isolated cortical slabs, Burns, 1954). These may also influence the properties of an evoked potential.

The size and form of the evoked potential seem to depend on the pre-existing state of excitability of cortical neurones, which under the conditions of our experiments is shown by a change in the cortical potential level at the surface. This potential gradient arises as the result of differential depolarization of neurones having processes directed towards the surface. Examples of such cells would be the type $P_1$ and $P_2$ cells of Sholl (1955) which have apical dendrites. When the cell bodies and basal dendritic systems of such cells are depolarized relative to their apical branches, they have a lower threshold for excitation. Under these circumstances the wave of activity induced by an incoming volley would tend to spread more widely within the cortex, since more cells would be activated. At the same time the difference in the membrane potential between the deep and superficial parts of a group of such cells would be recorded, by an electrode on the pia, as a relative potential shift of positive sign.

It can be confirmed that such a gradient can in fact have the effect of increasing or decreasing the magnitude of these later components of the evoked potential (waves 2 and 3), by artificially imposing a potential field across the cortex when a small current source is used. When the surface is made relatively positive, the effects we have described in this paper as occurring spontaneously during a positive plateau are produced and vice

versa. The changes which take place spontaneously and when the cortex is artificially polarized in this way are similar (Lippold, Redfearn & Winton, 1961). Possibly the imposed potential gradient is acting in the same way as do the naturally occurring plateaux, by differentially depolarizing apical and basal regions of the $P_1$ and $P_2$ type neurones.

Recent work has shown that different regions of the mid-line thalamus, when stimulated, give rise to differing types of electrical activity within the cortical grey matter. Schlag & Chaillet (1963) showed that, although both desynchronization of the e.e.g. and recruiting responses could be produced by stimulation of one thalamic locus, if the stimulating electrodes were moved a very small distance (0·5 mm) it was possible to demonstrate that either response could be produced independently of the other.

It is clear that the mechanisms concerned with cortical integration are extremely complex and that new techniques, such as multiplex recording, will be necessary before a fuller account of the interaction of the thalamus and the cortex can be given.

## SUMMARY

1. Simultaneous recordings have been made of the spontaneously fluctuating potential level of the cerebral cortex and the sensory evoked potential in the rat.

2. A positive swing of the potential level at the cortical surface is associated with a large evoked potential which is predominantly negative in sign. Conversely, a negative potential swing is associated with a small positive-going evoked potential.

3. The spontaneous slow fluctuations ('plateaux') in potential level of the cortical surface are preceded by discharges in the non-specific thalamic nuclei. Stimulation of these nuclei produces similar cortical potential changes.

4. The relation between the potential level of the cortex and the evoked potential arises as the result of the interaction of specific and non-specific afferent systems within the cortex.

5. Thus the changes in excitability of cortical neurones brought about by activity in the non-specific activating systems may account for the major part of the variability in the size and intracortical spread of the evoked potential.

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