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ELECTRICAL STIMULATION OF THE UNEXPOSED CEREBRAL CORTEX

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The present work has been undertaken in order to investigate the effects of stimulation of the brain through electrodes applied to the surface of the head; the main purpose was to find out how large would be the area directly excited; and also to see whether it was possible to record through external leads action and slow potentials from the zone involved and any further physiological spread of electrical activity.

METHOD

The experiments have been performed on baboons under ether and N_2O anaesthesia; when necessary, the anaesthetic was discontinued.

The unidirectional electrical stimuli were either saw-tooth pulses or square waves: their strength, frequency and duration could be varied independently.

The body of the animal was insulated and the anode earthed.

The electrodes were Ag/AgCl disks, 23 mm or 8 mm across, fixed to the skin of the head in the required places by rubber bands. The ohmic resistance of the contact was kept at 800–900 Ω. In routine experiments the cathode was placed over the upper end of the motor area and the anode either at its lower end or in the middle of it.

In some experiments bi-temporal electrodes were also used.

The electrical activity of the cortex during or immediately after stimulation was recorded through differential amplifiers with independent a.c. and d.c. gain control (Matthews, 1953), and a double-beam cathode-ray tube. The recording leads were similar to the stimulating ones, and the shock artifacts were small. Records were made from various regions, two being taken at a time. Movements due to electrical stimulation were analysed with standard and slow motion films.

The same stimulation and recording technique has also been used sometimes on men.

RESULTS

Stimulation of the motor cortex

Muscular contractions

During stimulation through electrodes placed over the two ends of the motor area, there was contraction of the ipsilateral muscles of the face and

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neck when the current had reached 2–4 mA (frequency 20/sec). On increasing the strength, the upper part of the arm also became involved, but never the forearm. None of this took place if the anode was moved to the middle of the motor area. With the anode in either position, discrete contralateral movements appeared when the strength was further increased: the muscles involved were different according to the frequency of stimulation, and the threshold varied between 70 mA at 20/sec and 40 mA at 150/sec. All the movements developed progressively up to a maximum. At just threshold or slightly above, the muscles relaxed slowly as stimulation continued. With stimuli at less than 10/sec the movements followed the frequency of stimulation, but this did not happen at higher frequencies. Stimuli at over 50/sec induced first a maximal contraction of the particular muscles, then a period of relaxation; finally slow pendular movements began, increased in amplitude, and after 40–50 sec spread to other muscles also, if the stimulation was continued.

There was always a delay between the beginning of stimulation and the onset of peripheral effects, and also between the first contraction and the spread to other muscles. With threshold stimulation at 20/sec the maximum delay was 24 sec. This decreased rapidly as either the strength, or frequency, or both were increased.

In consecutive periods of stimulation no deviation of response was ever observed provided that there were intervals of at least 2–3 min between them. After shorter intervals extension instead of flexion, or contraction of different muscles could occur during stimulation of the same site.

A detailed analysis of the movements showed that at first they involved one muscle only or one group of muscles, producing a movement in only one direction. Other contractions only appeared, if at all, after delays of some seconds.

Examples

(i) Stimulation at 30/sec just above threshold, with the cathode over the foot area: delay between the beginning of stimulation and the first peripheral effect, 22 sec. Flexion of the ankle without any movement of toes or leg, fully developed in 3·5 sec; stimulation kept on for 30 sec without any further effect; the foot regained its original position about 0·25 sec after the end of stimulation (Fig. 1*a*).

(ii) Stimulation at 30/sec, with a strength 1·3 times threshold, in the same place as above: delay from the beginning of stimulation 12 sec. Same movement as above, developing in 3 sec; interval before a second movement 1 sec. Second movement: eversion of the foot of about 60° developing in 3 sec. Stimulation kept on for further 20 sec without any new effect. Complete return to the original position in 0·25 sec after the end of stimulation. The remainder of the leg was completely still, as were the other foot and leg.

(iii) Stimulation with a strength 1·6 times threshold, same frequency and position as above: delay 3·5 sec. First movement: flexion of the ankle, much bigger than the previous one, developing in 0·5 sec. Second delay 0·25 sec. Second movement: forearm of the same side, rotation outwards of about 40° in 0·66 sec, followed almost immediately by the third movement, general extension;

contralateral foot maximally flexed, contralateral arm completely extended, ipsilateral foot extended, ipsilateral arm nearly completely flexed (see also Fig. 2).

(iv) Stimulation with electrodes placed on the two foot areas, strength 1·3 times threshold, frequency 30/sec. First movement: flexion of the foot contralateral to the cathode. Development of the movement in 2 sec. Second delay: 5 sec. Second movement: flexion of the other foot and slight rotation upwards of both arms by about 25°; both these movements occurred simultaneously and were fully developed in 3·5 sec. When stimulation was stopped the second movement disappeared and the limbs returned to their original position, but the contralateral foot remained flexed (first movement).

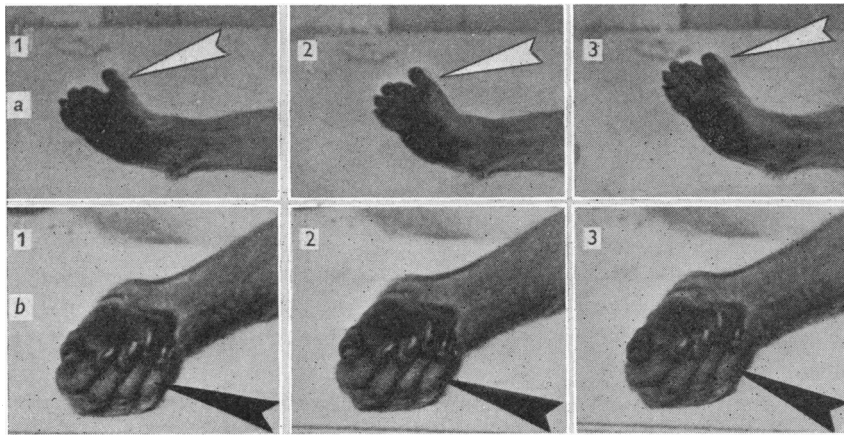

Fig. 1. Three photographs of the foot (*a*) and hand (*b*) taken before (1) and during (2–3) stimulation in baboon. (*a*) progressive movement of the foot at a frequency of 30/sec, and (*b*) of the hand (3rd, 4th and 5th finger) at a frequency of 60/sec through electrodes kept over the same site. For particulars see text.

(v) Stimulation with cathode over the foot area and anode over the hand area (small electrodes); frequency 60/sec, strength 1·3 times threshold. Delay 1·25 sec. Flexion of the fifth and slight flexion of the fourth finger of the contralateral hand (Fig. 1*b*). Second delay 0·7 sec. Flexion of the thumb and the other fingers till the whole hand was clenched.

(vi) Stimulation in man: cathode over the right motor area in the arm region, anode over the corresponding area on the left side. Frequency of stimulation 30/sec, strength 1·7 times threshold. Delay 1 sec. First movement: adduction of the left hand towards the radial side developing in 0·5 sec. Second delay 1·5 sec. Second movement: external rotation of about 20° of the left forearm in 0·66 sec. No further movement appeared during the remaining period of stimulation which was continued for 40 sec. No other muscles (not even of the face or of the opposite arm) were involved. Return to the original position at the end of stimulation (Fig. 3).

Electrical changes in the cortex

The electrical activity of the cortex was recorded by using two pairs of recording electrodes simultaneously; one electrode of each pair was on one of the following areas: the motor area, 2 mm from the cathode, 2 mm from the anode, and midway between them; the sensory area; the ipsilateral pre-

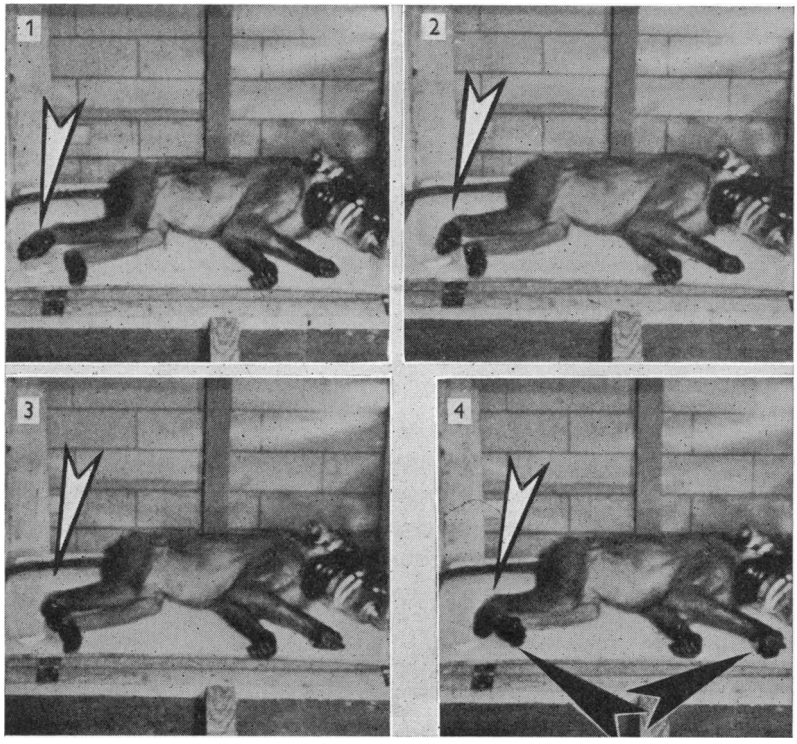

Fig. 2. Stimulation of the left motor area with saw-tooth pulses; frequency 30/sec; strength 1·6 times threshold. Cathode in the standard position; anode, earthed, in the middle of the motor area. Four photographs showing: (1) the baboon before stimulation; (2) beginning of the first movement after 3·5 sec latency: flexion of the right ankle (white arrow); (3) the movement is completed 0·5 sec later; (4) spread of the movement: the right foot relaxes, the left foot (black arrow) is flexed, the right hand (black arrow) extends.

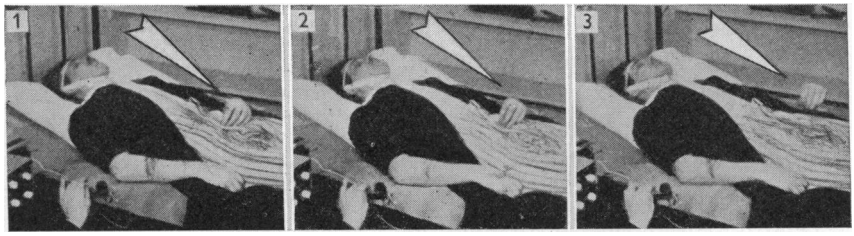

Fig. 3. Three photographs taken before (1) and during (2–3) stimulation of the right motor area in man. Movement in two stages of the left hand (arrowed). For particulars see text.

motor area; and the contralateral motor area. The other recording electrode was roughly 2 cm away.

The time constant of the amplifiers was such as to cut out the slow spontaneous rhythms and leave only the potentials of up to 10 msec duration. Sometimes the gain of the d.c. amplifiers was set independently to record slow potentials of 1 mV or more in amplitude. Except in the region very near the cathode the number of action potentials and the duration of discharge slowly increased to a maximum; the longest time this took to occur was 27 sec: in this case the frequency of stimulation was 4/sec and the strength about 1·3 times threshold. With higher frequencies the build-up was similar in form, but more rapid.

When simultaneous records were taken from regions both active at the same time, some action potentials appeared synchronized in the two records, but most of them did not. No slow variation was ever recorded in association with this fast activity (Fig. 4).

A different picture was observed near the cathode (Fig. 4): the discharges built up to a maximum, showing increasing recruitment, but no increase in duration; the result was a progressive synchronization until the volley of spikes fused into a single wave of constant duration and increasing amplitude. This discharge appeared on top of a negative wave which might last as long as 1 sec. During repetitive stimulation temporal summation was recorded (Fig. 5): the fast discharge started when the wave had reached a certain height, usually between 1 and 1·5 mV; thereafter a further increase in negativity accompanied the increasing discharge, but the two phenomena were not strictly correlated, as the discharge went on increasing after the slow wave had reached its maximum. The maximal negativity recorded was 4·8 mV.

It was difficult to measure the delay of the response because the beginning of the discharge was superimposed on the end of the shock artifact which lasted for 20 msec. However, in some areas far from the cathode a delay up to 50–60 msec was recorded.

When the cathode was in the standard position and the anode almost anywhere, the distribution of the electrical activity was as follows (Fig. 4). The slow potentials and the synchronous waves were recorded at distances of not more than 4–5 mm from the cathode. Asynchronous activity was recorded from the rest of the motor area and around it, near the anode, and in the nearest part of the premotor area. This activity appeared a little later than that near the cathode. No action potentials at all could be recorded from the sensory area or from the contralateral motor area.

When the strength of stimulation was just above threshold there were only slow waves with spikes becoming synchronous near the cathode, and a small synchronous response near the anode; just below threshold slow waves were

recorded, but these were smaller than those usually associated with the fast discharges.

Relationship between movements and electrical activity of the cortex

The first movement was observed when the slow negative wave had reached nearly two-thirds of its maximum value and the synchronization of the spikes

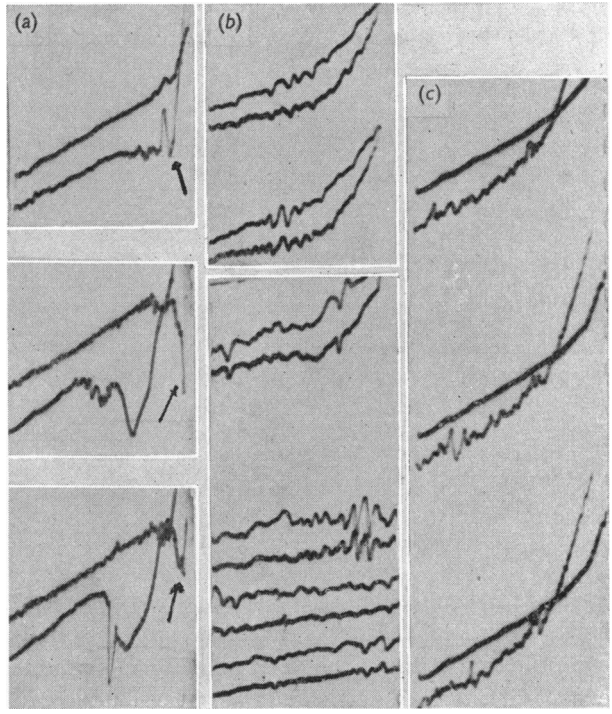

Fig. 4. Stimulation applied to the two ends of the motor area. Strength 1·3 times threshold; frequency 4/sec. Movement observed: flexion of the contralateral foot. Duration of time base 150 msec: d.c. gain 5 mm = 10 mV; a.c. gain 1 cm = 50 mV. Negativity downwards. Read from right to left; stimuli on right. Action potentials recorded at various distances from cathode: (*a*) Upper record 15 mm, lower record 2 mm away; 2nd electrode 2 cm away backwards. Three discharges following stimuli after 4, 12 and 14·5 sec of stimulation. The lower record shows a slow negative wave of increasing amplitude and spikes which synchronize progressively till a complete synchronous wave appears at the bottom. (The shape of the slow wave is altered by interference of the a.c. recording at high gain for the fast potentials; the correct shape is shown in Fig. 5.) A negative spike precedes the slow wave (arrowed). The upper record shows only a fast discharge of increasing duration. (*b*) Record from the premotor area. Upper record in front of the cathode, lower record 2 cm below. First and second stimulus shown after 20 sec of stimulation, third after 40 sec. Asynchronous discharges, similar to each other, but often not in phase, and of increasing duration (at the end over 450 msec). (*c*) Record taken 2 mm from the anode (lower record) and from the sensory area (upper record). Three consecutive stimuli are shown after 40 sec of stimulation. Fast activity only near the anode; no activity at all over the sensory area.

was almost complete. When the stimulus was just above threshold this happened 12–19 sec after the first shock. This delay was found to coincide closely with that of the first movement.

The first action potentials, however, appeared at a much earlier stage. For example in one experiment the first spikes appeared at 4 sec, the first clearly synchronized wave at 12 sec and the first movement 13–19 sec after the beginning of stimulation. The muscles involved in the first movement seemed to be correlated only with the area from which the slow waves and synchronous potentials were recorded.

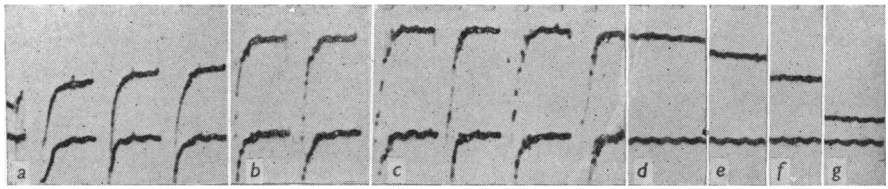

Fig. 5. Temporal summation of slow potentials in the zone near the cathode (upper record) and lack of this phenomenon farther away on the motor area (lower record). Read from left to right. Negativity upwards. Stimulation with saw-tooth pulses; frequency 12/sec; strength 1·3 times threshold. Cathode on the upper end; anode, earthed, over the middle of the motor area. Recording in d.c. gain 1 mm = 0·5 mV. Between *a* and *b*, nine stimuli; between *b* and *c*, eleven stimuli; between *c* and *d*, *d* and *e*, *e* and *f*, *f* and *g*, 0·5 sec.

Stimulation with bi-temporal electrodes

With a frequency of stimulation of 250/sec and a strength between 2 and 3 times the cortical threshold, there was extensive contraction of the muscular system mainly on the side of the cathode. Weaker shocks produced almost no movements, except of the face and shoulders. The generalized contraction, however, was not maintained for long, and except for the face, neck and shoulders had completely disappeared after 2–3 sec.

During the muscular contraction some slow pendular movements of the limbs with or without the trunk were sometimes observed just as if a clonic seizure were about to start: this, however, did not happen and instead there was relaxation during or immediately after the passage of current.

Bi-temporal stimulation at frequencies of 4, 8 (Fig. 6), 20 and 250/sec and with a strength of up to 3 times threshold produced a small asynchronous discharge of spikes near the cathode and an even smaller one near the anode; there were no slow waves and no tendency towards synchronization, neither was there any electrical activity in the other areas. When the strength was increased to up to 5 times threshold, fast activity was recorded also from distant areas; it was about one-third of the size of the discharge near the cathode. The time required for building up the discharge and the general

characteristics were very much the same as for the asynchronous activity recorded during stimulation of the motor area.

When a frequency of stimulation of 250/sec was used, it was not possible to record during the stimulation itself; the discharge following the last stimulus

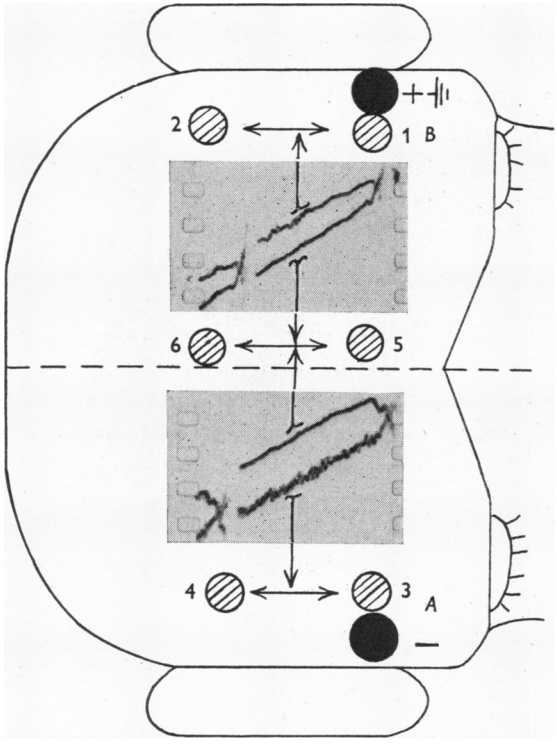

Fig. 6. Bi-temporal stimulating electrodes (A^-, B^+ earthed). Recording from three pairs of electrodes: 1–2 (1 at 2 mm from B^+), 3–4 (3 at 2 mm from A^-), and 5–6 on top of the head. Frequency of stimulation 8/sec; strength 3 times threshold. Duration of time base 150 msec. Some action potentials, asynchronous and prolonged in 3–4, smaller and with a delayed start in 1–2, nothing in 5–6. Read from right to left; stimuli on left.

was similar to that discussed above, and was limited to the area near the two stimulating electrodes.

The peripheral effects were different when the frequency of stimulation was below 25/sec. The muscular system contracted roughly as before when the strength of stimulation had reached about 3 times the cortical threshold; no relaxation was observed though, even when the strength had been increased to up to 5 times the cortical threshold.

DISCUSSION

Stimulation of the cerebral cortex through electrodes placed on the surface of the head had a double purpose: (1) To investigate the spread of excitation along the cortex under the best physiological conditions. This is not achieved with the exposed cortex: even if drying is avoided by means of a layer of paraffin oil and if the temperature is maintained at a constant level, it is impossible to compensate for the loss of the c.s.f. pressure. Moreover, any electrodes applied directly to the surface of the cerebral cortex are a constant source of mechanical stimulation and injury. (2) To test whether it is possible to stimulate in this way across the brain (as, for instance, with bi-temporal electrodes) without causing such widespread excitation as to mask any changes due to subcortical action.

According to Chang (1951*a*) a single electrical shock through electrodes fixed into the exposed cortex elicits a large negative spike followed by a prolonged negative wave lasting more than 800 msec. The first potential is always present, but the second one occurs when the stimulation is sufficiently strong, and increases with the strength of stimulus. With an even stronger stimulus a positive spike precedes the negative potential and another positive spike follows it. Generally, when the excitation spreads, positive potentials, as well as negative spikes, are recorded from the site of stimulation; these suggest the arrival of disturbances from different areas (McCulloch, 1949).

Stimulation from outside the skull gives responses with the same general pattern: a negative spike appears first, followed by a prolonged negative wave, surmounted by fast negative potentials when it has become sufficiently large. All this resembles closely the electrical activity first recorded from the spinal ventral roots by Barron & Matthews (1938): these authors even observed, in mammals, the negative spike preceding the slow synaptic potentials, but reported that these findings were not constant. On the cortex the negative spikes can almost always be seen; the subsequent positive deflexion is found not only when the strength of stimulation is increased, but also after repetitive stimuli; e.g. with 1·6 times threshold and a frequency of 8/sec it started 12–15 sec after the beginning of stimulation and later progressively increased.

Chang (1951*a*) concluded that the slow negative wave is due to the cortical internuncials, and that the first negative spike is the immediate response of the dendrites and axons of the first layer of the cortex: in fact he reported that this spike spreads more over the surface layers, while the slow potential appears to progress mainly in the deeper cell layers. This suggests a close resemblance between the organization of the cortex and that of the spinal cord.

The positive variations require a different interpretation, and will be discussed later.

A new fact observed during the present work is the tendency of the fast activity on top of the slow wave to synchronize increasingly during repetitive stimulation. This result presents a further similarity to what has been found in the spinal cord (Gualtierotti, 1953) and could accordingly be interpreted as due to ephaptic interchanges among a number of active cells in the internuncials.

The slow negative wave and spikes occur only in the region of the cortex directly excited: in other parts only fast activity has been recorded. This activity is similar to the conducted discharges recorded from motor pathways, far from the nuclei in which the discharges originated. Thus motor nuclei from which spikes only can be recorded might not actually be excited, but only passively invaded by a stream of impulses; in fact this activity is accompanied by no peripheral signs of cortical excitation; it is present over the whole motor area, but the muscles involved in the electrically induced movements correspond only to a small region of excitation. It can be assumed therefore that these spikes originate either from short association fibres or groups of cells not concerned in the motor function; however, since no slow synaptic potentials are recorded, it seems more likely that no cells are involved.

When the stimulation is kept up for a long time, there is a spread of muscular contraction. Normally this spread is limited to a homogeneous cyto-architectonic field and does not travel along the commissural fibres. No action potentials can therefore be recorded from the corresponding areas of the opposite side. Such a spread may however occur, as is demonstrated by the contralateral movements induced by strong and prolonged stimulation; the same thing happens spontaneously in epileptic seizures during which a great number of cells discharge together; in this case the activity is carried far along the white matter, and also to and from other parts of the brain, midbrain and cerebellum (McCulloch, 1949). However, there exist powerful barriers to prevent this happening under normal physiological conditions.

If these conclusions hold good, some other results of neuronography, for instance, will have to be revised; actual excitation must be distinguished from the mere passage of impulses. Thus it might be possible to follow the course of the conditioning wave which precedes excitation as it spreads through structures not directly involved.

During the present work, no attempt has been made to investigate the part, if any, played in building up the cerebral activity by the proprioceptive impulses coming from the contracting muscles. Hyde & Gellhorn (1949) report that the muscular response to stimulation of the motor cortex is larger before than after deafferentation. Since, however, in the first period of stimulation the cortical response does not vary much in duration, there can be no great spread of activation caused by these impulses then. This is also proved by the fact that the contraction of the appropriate group of muscles increases in strength, but other muscles are not recruited. Nevertheless, the proprio-

ceptive influence may play a major role in the spread of excitation to other motor foci, and in the change in excitability of the ones primarily involved, during the late part of a period of prolonged stimulation.

As the physiological spread of excitation increased, other nervous structures began in turn to activate the primary area. This afferent activity appeared as a positive spike (McCulloch, 1949) and was recorded, in one instance, 14 sec after the beginning of stimulation (frequency 4/sec, strength 1·6 times threshold) with a delay of 50–60 msec compared with a maximum delay of 20 msec for the action potentials. A similar spike was visible in the cortex after prolonged bi-temporal stimulation.

The area of the cortex excited during a long period of stimulation or during consecutive bursts of stimulation remained nearly constant: also there was none of the deviation of response found by authors who have worked on the exposed cortex (Bosma & Gellhorn, 1947). Since such a deviation was observed in the present experiments if there was no rest of 3–4 min between consecutive stimulations, it can be assumed that there is some long-lasting change in the cortex after it has been excited. This has been proved by Chang (1951*b*) who found that after a single shock there was a short refractory period, followed by a prolonged depression, which was proportional to the intensity of stimulation and the number of cortical neurones excited. With an exposed cortex mechanical injury, cold, etc., might very easily cause an increased afferent inflow or subliminal stimulation as an adjunct to the electrical one. Thus the various cells might start discharging or not according to the summated effect of the stimuli and all these other factors; it is not necessary therefore to think of complicated connexions among different foci or multiple actions of a single focus to explain variations in the peripheral effect. After eliminating all the secondary causes, the pattern of the peripheral response is repeatable, provided that the only remaining conditioning action, the one due to electrical stimulation, is given time to disappear.

No great handicap was found in the use of external electrodes: it was possible to stimulate such a small area that the movements obtained were as restricted as when the exposed cortex was used (Ruch, Chang & Ward, 1947).

The delay between the beginning of stimulation and the first muscular contraction was caused by the building up of the action potentials in the appropriate parts of the cortex: at first asynchronous activity appeared, while the slow negative wave was increasing. No muscular contraction took place during this phase, which lasted for some seconds when frequency of stimulation was low. At a certain level of negativity, synchronization occurred and the movements started. It is difficult to say which phenomenon, whether the height of the negative wave or the synchronization of the fast activity, was mainly associated with this. However, it is suggested that discharges below a certain size fail to pass the synapses between the motor nuclei of the cortex

and spinal cord; as soon as the slow negative wave and superimposed synchronous spike have reached a sufficient amplitude, transmission occurs. The fact that the muscular contraction developed smoothly can be explained by the asynchronizing action of the spinal cord nuclei; this may be observed for instance during strychninization: a group of asynchronous impulses is discharged along the motor pathways at the peak of the negative deflexion of the synchronous wave in the cord due to strychnine (Bremer & Bonnet, 1948).

Further experiments are required to explain the shift of the stimulated focus along the motor area as the frequency changes: up to now, in fact, no adequate technique has been devised to record the electrical response of the cortex during stimulation in the range of frequencies (between 30 and 100/sec) in which this change took place. Similar shifts, however, have been described by Hyde & Gellhorn (1951) on changing the frequency of stimulation.

Analysis of the movements showed that they were of two kinds: the ispilateral ones, with a low threshold, caused by direct excitation of the peripheral nervous system; and the contralateral ones with a higher threshold, cortically induced. A full report of this is published elsewhere (Spencer Paterson, 1952).

Some of the main features of the cortically induced movements have been already discussed; namely the initial delay, the absence of deviation of response and the variations with frequency. Of special interest is the second delay between the first discrete movement and the later more widespread contractions: this suggests a step-like increase in the excited area, after a previously existing block has been removed. It could be said tentatively that this spread was facilitated by the fast electrical activity which was recorded over a wide area; but further work on this is needed. The third stage of the spread seems to involve both the connecting fibres of the same side and the commissural fibres, since at this stage contralateral movements also appear.

Stimulation across the brain with bi-temporal electrodes did not excite the cortex directly, since, if the conclusions reached above are true, the asynchronous volleys of potentials seen mainly under the cathode were not an index of actual cortical activation. In any case, these potentials were only recorded in a very limited area around the cathode and anode. Thus it can be assumed that currents passing through the whole thickness of the cortex do not excite it, but that the most effective currents are those passing parallel to its surface.

SUMMARY

1. During stimulation of the motor cortex of baboons through external electrodes discrete contralateral movements appeared at a certain strength; the movements involved were different according to the frequency of stimulation. With stimuli at less than 10/sec the movements followed the frequency of stimulation, but this did not happen at higher frequencies.

2. There was always a delay between the beginning of stimulation and the onset of peripheral effects, and also between the first contraction and the spread to other muscles.

3. In consecutive periods of stimulation no deviation of response was ever observed, provided that there were intervals of at least 2–3 min between them.

4. Near the cathode the electrical response appeared as a discharge of fast potentials on top of a slow negative wave; a negative spike preceded these two electrical changes. In the motor area far from the cathode and in the premotor area discharges of fast potentials, of increasing duration, only appeared. In the sensory area and in the contralateral motor area no response was ever recorded.

5. During repetitive stimulation temporal summation of the slow activity and synchronization of the fast activity were recorded.

6. The first muscular movement analysed by film recording was observed when the slow negative wave had reached nearly two-thirds of its maximum value and the synchronization of the spikes was almost complete: the muscles involved were correlated only with the area from which the slow waves and synchronous potentials were recorded.

7. During stimulation with bi-temporal electrodes at a frequency of 250/sec and a strength between 2 and 3 times the cortical threshold, a transitory contraction of most of the muscular system took place, which disappeared after 2–3 sec of stimulation.

8. The recorded potentials were found to be similar to those obtained on the exposed cortex and to resemble closely the synaptic potentials and action potentials recorded from the spinal ventral roots.

9. The first negative spike has been interpreted as the immediate response of dendrites and axons of the first layer of the cortex, while the slow negative wave and spikes are due to internuncials.

10. The tendency of the fast activity to synchronize was taken as a further similarity to the spinal cord.

11. Fast activity alone, recorded far from the cathode, was not thought to be an index of excitation of the motor centres in the area involved: in fact this activity was not accompanied by peripheral signs of cortical excitation.

12. The delay between the beginning of stimulation and the first muscular contraction was caused by the building up of the action potentials in the appropriate part of the cortex.

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