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SELECTIVE EXCITATION OF CORTICOFUGAL NEURONES BY SURFACE-ANODAL STIMULATION OF THE BABOON'S MOTOR CORTEX

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Understanding of the precise mode of action of a focal electrical stimulus on the complex systems of neurones embedded in the conducting medium of the cerebral cortex is still far from complete (Liddell, 1953). The first demonstration that the resulting corticofugal discharges contained a direct component, due to electrical stimulation of corticofugal cells, and an indirect component due to stimulation of corticofugal cells by way of other intracortical neuronal systems, was given by Patton & Amassian (1954). Evidence of direct electrical and of indirect synaptic excitation of cortical pyramidal neurones was found in intracellular records by Phillips (1956). Also, in stimulating the cerebellar cortex, Granit & Phillips (1957) found that the Purkinje cells could be excited both directly and indirectly. In both types of cortex those corticofugal neurones which were situated on the convexity of a gyrus or of a folium were stimulated by smaller currents if the focal cortical stimulus was made anodal. The threshold for focal cathodal stimulation was higher, and the stimulus stirred up more complex effects.

This paper extends these investigations to the motor cortex of a primate, the common African baboon (*Papio* sp.). The method of intracellular recording from pyramidal neurones was not used because the time, labour and material needed to collect enough observations would have been prohibitive, and because it seemed unlikely that the modes of direct and synaptic excitation of these neurones would differ materially from those already seen in the cat. Critical distinction between direct and indirect stimulation of cells demands minimal stimulus, with minimal spread in the cortex, to elicit the minimal, most circumscribed response. Since the electrical threshold for movement is higher than the threshold

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for cortical cellular excitation in the baboon (Landgren, Phillips & Porter, 1962*a*) as in the cat (Phillips, 1956; Hern & Phillips, 1959), movement itself cannot be used as the index of minimal corticofugal discharge. Instead, we have used, first, single-fibre records from the axons of the lateral corticospinal tract, and secondly, minimal synaptic potentials in spinal motoneurones innervating the forearm and hand, to measure the nature and timing of the corticofugal discharges evoked by minimal focal stimulation of the arm area. A preliminary report of the experiments with synaptic potentials has been published (Hern, Landgren & Phillips, 1960). We confirm that surface-anodal shocks can stimulate the corticofugal cells selectively. In the succeeding papers (Landgren, Phillips & Porter, 1962*a*, *b*) we have described the use of this method of selective stimulation of corticofugal cells in an investigation of the cortico-motoneural excitatory pathway (Bernhard, Bohm & Petersén, 1953) and of the simplest inhibitory pathway connecting the cortical pyramidal neurones with the motoneurones of the forearm and hand.

METHODS

Preparation. The subjects were twenty-four young baboons of either sex, weighing between 3 and 7 kg. The following details were all found to be important for success, and represent our final technique. To minimize excitement and struggling anaesthesia was induced in a dark box with 20–30 % oxygen in nitrous oxide, with 3 % chloroform added from a calibrated vaporizer ('Chlorotec', Cyprane Ltd.). After the animal was removed from the box the same mixture was continued by mask, and an intraperitoneal dose of pentobarbitone, 20 mg/kg, was injected. Chloroform was gradually reduced to zero during the 3 min following the injection, but nitrous oxide and oxygen were continued throughout the operation; when the trachea had been cannulated the mixture was supplied from a bag to an inspiratory–expiratory valve system attached to the cannula. A polythene cannula was inserted into the right saphenous vein. During the operation anaesthesia was deepened when necessary by addition of 0·5–1·0 % chloroform or by intravenous injection of soluble hexobarbitone 10 mg/kg. If necessary 'dextran' was injected intravenously, but it was seldom needed in later experiments. The vertebral spines and laminae were exposed from C2 to approximately D5 and the wound was tightly packed to control oozing of blood. The skull overlying the right arm area was next opened. Then the left radial nerve was uncovered at the elbow and the left ulnar and median nerves just above the elbow. These nerves were cut and fitted with nylon sleeves containing paired silver rings, about 1 cm apart, which encircled the nerves. The sleeves were stitched into the nerve beds and the wounds closed. Thus prepared the nerves remained in good condition, as was shown by the survival of Group Ia monosynaptic potentials and antidromic motoneurone responses for as long as necessary, up to 20 hr. The head was then fixed in a Horsley–Clarke holder belonging to the recording frame but detached from it and mounted on the operating table. The dura was reflected from the motor area: a cylindrical Perspex 'top hat' was fixed into the scalp wound, by a 'purse-string' round its flanged base, and filled with warm mineral oil through a rectangular opening in the side facing the occiput. The nitrous oxide was disconnected when the preparation was transferred to the recording frame, where the head-holder was clamped with the head flexed at right angles to the spine, which was held horizontal (prone) by self-tapping screws driven into the ischial tuberosities and clamps on the

iliac crests. The spines and laminae were removed bilaterally from C4 to C7 or T1 inclusive before the final fixation by two forceps-type clamps; a single long one gripping all the exposed thoracic spines and a short one gripping the spine of C2.

Stimulation and charting of cortex. The cortex was accessible to stimulation through the rectangular opening 3·0 × 1·5 cm in the occipital (uppermost) side of the oil-filled Perspex 'hat', and could be seen and photographed through the oil and the hat's plane polished crown. In the earlier experiments a grid of ten independently-sprung ball-pointed Ag-AgCl electrodes was held against the cortex by a three-dimensional slide mechanism. One ball at a time could be made cathodal or anodal with reference to an earthed chlorided plate sewn into the scalp on the other side of the head. By shifting the whole grid, 20, 30 or 40 points could be tested. It was difficult to avoid blood vessels. Electrode positions were charted on photographs available during the experiment.

Greatly increased mobility has been achieved with an instrument kindly built for us by Dr E. H. J. Schuster (Fig. 1). A single ball-tipped chlorided silver electrode, *e* (tip diameter 0·5–0·8 mm) is moved over the cortical surface by the 'joystick' *j*, and applied to the brain surface or lifted off it by rotating the head of the 'joystick'. As the 'joystick' moves a pencil moves over a map, giving 2·5 × magnification. Photography of the brain is unnecessary. Three conspicuous vascular intersections are plotted as reference points on each map, and the central, superior pre-central and inferior pre-central sulci are drawn by the pencil as these sulci are traced with the tip of the electrode. All the maps from one experiment can afterwards be accurately superimposed by using the reference marks as guides.

The square-wave stimulator has been described already (Kay, Phillips & Teal, 1958). To allow photographic superimposition of many sweeps when using repetitive stimuli, one channel has now been provided with an alternative oscillator controlled by the time-marking and sweep-triggering system, so that the shocks of repetitive trains occur at the same points on the sweeps. The stimulating current was always measured by recording, on one of the four oscillograph beams, the amplified voltage drop across a 1000 Ω resistor in series with the brain.

Recording from the lateral corticospinal tract. Extracellular records were made from 69 pyramidal fibres (six baboons). Pyrex capillaries about 50 μ in outside diameter, tapering to 5–10 μ tip diameter, were filled with 4 M-NaCl solution, or with silver wire which just projected from the glass. Both types were good for recording waves in the tract, but we thought that the metal-filled capillaries yielded a better harvest of single-fibre spikes. Access to the dorsolateral white matter was gained by cutting a few dorsal root filaments. Sufficient control of cord pulsation was maintained by raising the dural edges with stitches fastened to the animal frame, and by light pressure on the cord with a saddle-shaped celluloid plate; by watching the vessels on the surface of the cord through a microscope we made sure that the circulation remained brisk. Probing of the tract through a hole in the plate was guided by the wave given by a volley sent down from the cortex by a short shock of strength about 2 mA (Fig. 3). At the end of the experiment an empty Pyrex capillary was driven into the same hole and at the same angle as the recording pipette, and broken off by crushing with watchmaker's forceps. After hardening in 10 % formaldehyde-saline the cord was sliced free-hand under the dissecting microscope with a razor blade and the slice containing the capillary photographed (Fig. 3). The tracks were always in the white matter.

Recording from motoneurones. Intracellular records were made from 163 motoneurones (eighteen baboons). Capillaries filled with 0·6 M-K_2SO_4 or 3 M-KCl were used. Their d.c. resistance in Ringer's solution was 10–20 MΩ. To reduce shock artifacts the second grid of the balanced cathode-follower input was connected to a chlorided silver-wire electrode, which was applied to the spinal cord near the point of entry of the micro-electrode. The cathode-follower output was connected to two amplifiers and oscilloscope beams: one direct-coupled and at low gain, for continuous measurement of membrane potential; the other condenser-coupled, at higher gain, for detection of minimal synaptic action. Its

response to a rectangular input at the cathode follower grid is shown in Fig. 9. The input capacitance of the cathode-follower probe was less than 3 pF, and grid current less than 4×10^{-11} A.

To control cord pulsation sufficiently to allow intracellular recording in the cervical region it is essential to open both pleural cavities. The collapsed lungs were ventilated with warmed, wet air at 60–70 c/min, at a small tidal volume which kept them away from the

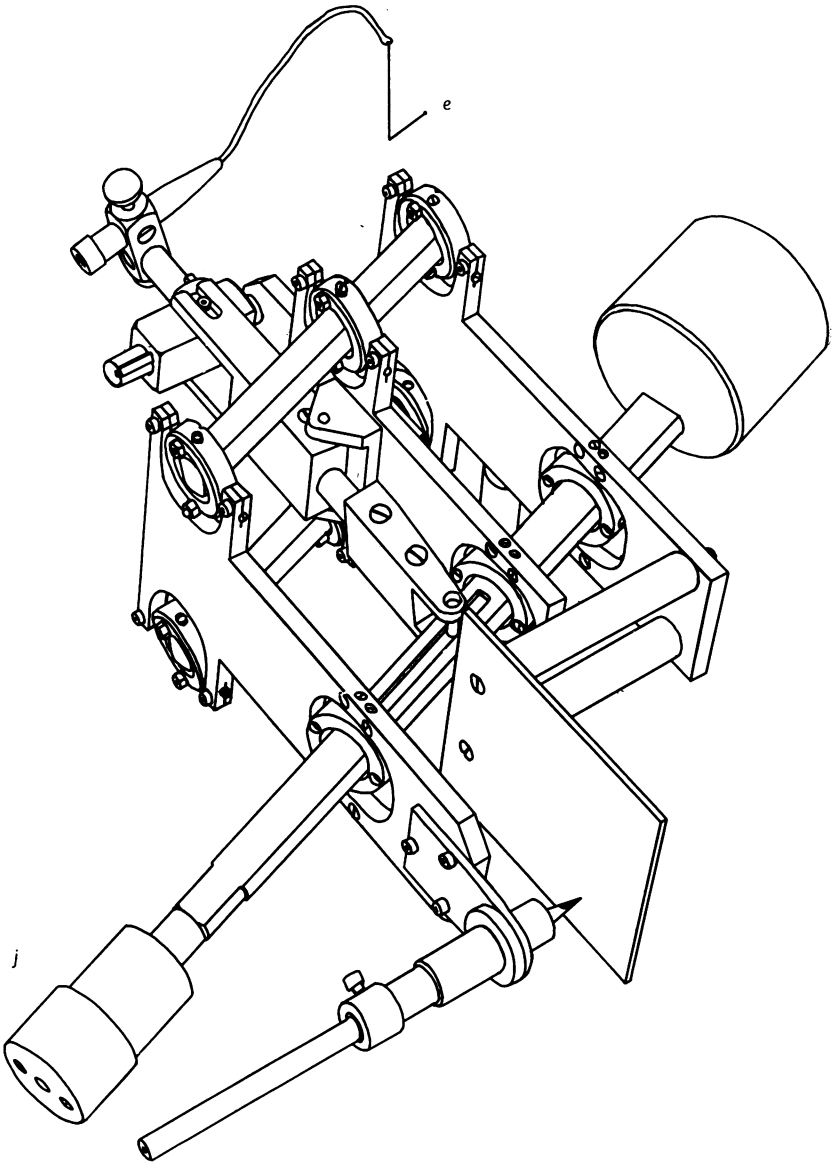

Fig. 1. Instrument for charting the brain surface (E. H. J. Schuster), set up for operation in a vertical plane. *e*, ball-pointed electrode; *j*, joystick.

chest wall. This abolished respiratory efforts. Whenever ventilation was discontinued in order to test the state of the blood by the response of the respiratory centre, respiratory efforts were resumed in 5–20 sec.

Narcosis was kept deliberately shallow, so that the motoneurones showed some synaptic 'noise' (Brock, Coombs & Eccles, 1952). When this became excessive, hexobarbitone (*ca.* 10 mg/kg) was injected into the saphenous cannula. This was usually necessary about once per hour.

Rectal temperature was kept between 36 and 39° C.

RESULTS

Motor responses to focal surface-anodal (S+) and surface-cathodal (S−) stimulation of cortex

In previous mapping experiments on the baboon's brain focal cathodal stimulation was used exclusively (Liddell & Phillips, 1950, 1951, 1952). In their pioneer work on the dog, however, Fritsch & Hitzig (1870) were impressed by the superiority of the surface anode, and Livingston & Phillips (1957) found in the cat that in the forelimb region of cortex the surface-anodal motor threshold was generally the lower. It was therefore important to compare motor maps and thresholds in the baboon's arm area as a preliminary to the investigation of unit responses. For these experiments the limb nerves were not cut. Figure 2 shows the results in four experiments. It shows that the thresholds for minimal flick movement of thumb and index in answer to 5·0 msec anodal and cathodal pulses were of the same order, about 1·0–3·0 mA according to the prevailing level of anaesthesia (Liddell & Phillips, 1951). Only in one experiment (Fig. 2*c*) was the surface-anodal threshold a little lower than the cathodal. The lowest-threshold area for anodal stimulation was always centred on the Rolandic fissure, and the centre of the 'cathodal' area always lay in a precentral direction and overlapped the 'anodal' area.

Pyramidal-tract waves generated by surface-anodal and surface-cathodal stimulation

Figure 3*b* (bottom) shows the typical wave recorded by a silver-filled or electrolyte-filled Pyrex capillary from the lateral corticospinal tract in the cervical cord. To reduce temporal scatter of pyramidal impulses short shocks (0·2 msec) were used for setting up the waves. The initial positive-going phase is assumed to signal the approach of pyramidal impulses and the sharp change-over into the negative-going phase presumably gives the instant of their arrival at the recording point. Figure 3 is taken from the only experiment (one out of six) in which a wholly positive-going wave was recorded from the tract with this type of microelectrode (see Methods). For 7 hr the wave had kept the form shown in the lower part of the figure and the motor 'flick' response of thumb and index,

evoked by a long (5 msec) cortical pulse, had remained normal whenever tested. In the last half hour the wave became positive, and the motor response failed. After death the fixed cord slices showed haemorrhage in the dorsolateral column. The remaining five cords showed no haemorrhage, and, during life, negative waves. Thus the positive-going wave is the sign of an injured tract. In some preliminary experiments, in which a 200 μ enamelled silver wire electrode was used, the waves were always positive

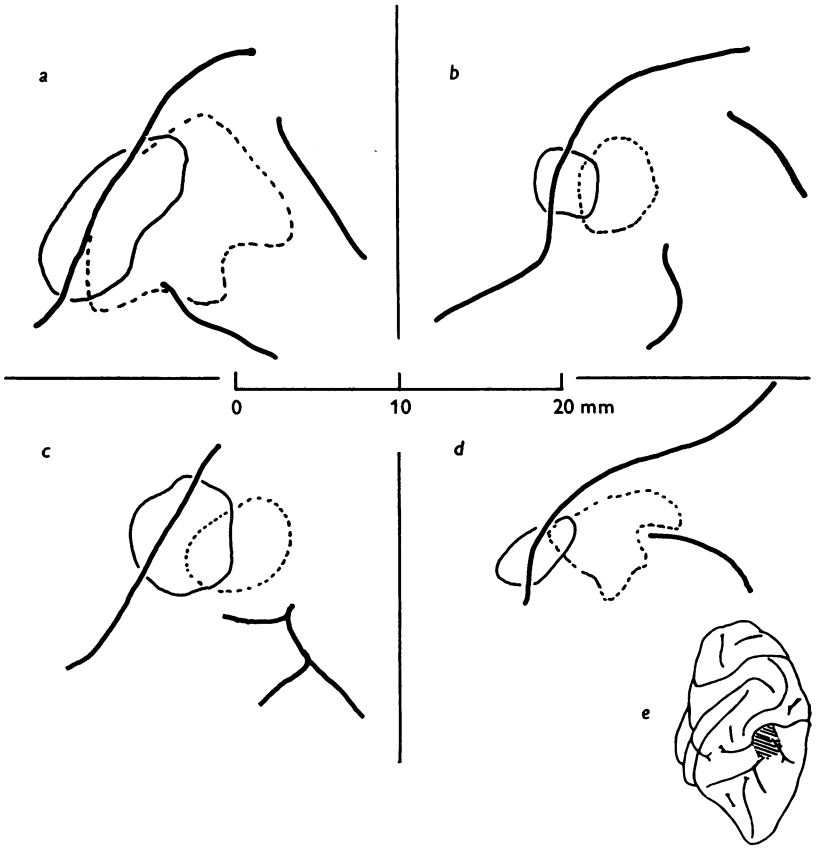

Fig. 2. Motor maps for flick movement of thumb and index finger. Surface anodal pulses (full lines); surface-cathodal pulses (interrupted lines). Pulse duration 5·0 msec. Diagrams *a*, *b*, *c*, *d*, show arm area of right hemisphere in different experiments. Orientation given by inset *e*, which shows dorsolateral view of right hemisphere held with frontal pole downwards (as in all experiments). That part of pre-central gyrus shown in *a*, *b*, *c*, and *d*, bounded by central, inferior pre-central and superior pre-central fissures, is stippled in *e*. Scale 20 mm for *a–d*.

a, Outlines at 1·9 mA (S+) and 1·8 mA (*S*−), thresholds 1·6 mA (*S*+) and 1·4 mA (*S*−) at centre of common area; *b*, 2·5 mA (*S*+) and 2·4 mA (*S*−); *c*, when anaesthetic was deep, 3·1 mA (*S*+) and 3·1 mA (*S*−); when lighter, 1·3 (*S*+) and 1·9 mA (*S*−); *d*, 3·0 mA (*S*+), 3·1 mA (*S*−).

(cf. Lance, 1954). Figure 3 shows clearly that the initial positivity of the 'uninjured' wave corresponds to the first part of the upstroke of the 'injured' wave; on this upstroke the approach of impulses is not sharply distinguished from their arrival. The advantage of the positive-negative wave for measuring the time of arrival of the volley is evident. Conduction distance has not been measured and conduction velocities have not been calculated.

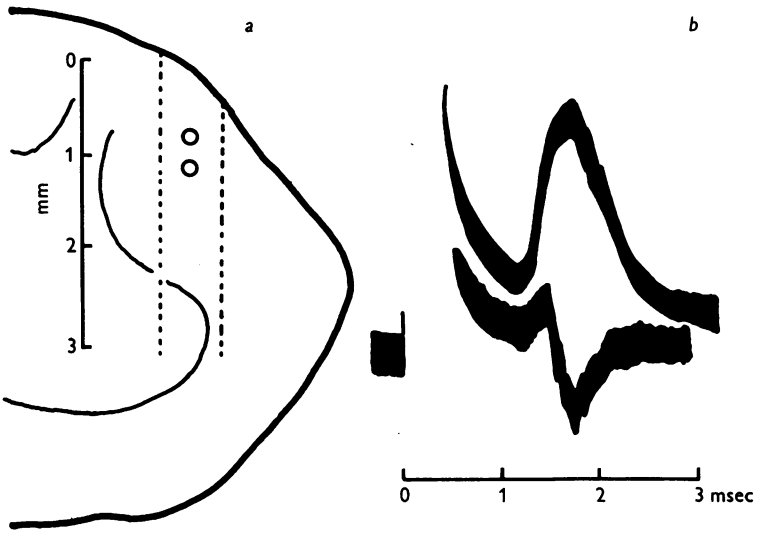

Fig. 3.*a*. Tracing of left half of slice of spinal cord, C5–6. Interrupted lines show direction of punctures and medial and lateral limits of electrode tracks set by diameter of window in celluloid saddle. Wave amplitude greatest in region of circles. Wave almost absent at depth corresponding to edge of ventral horn.

b. Below, positive-negative wave recorded at depth shown by upper circle near beginning of experiment; shocks to cortex $S+$, 0·2 msec, 4·1 mA. Above, positive wave recorded at depth shown by lower circle at end of experiment. Shocks $S+$, 0·2 msec, 4·2 mA (see text). (Superimposed sweeps, traced to common time scale.) Voltage scales unequal and not shown: amplitude of lower wave is less than 0·5 mV, and upper wave about 0·5 mV. Positivity indicated by upward deflexion in this and all other records.

The wave increases in size as a 0·2 msec cortical pulse, $S+$ or $S-$, is strengthened from about 1·5 mA to about 5 mA, the strongest current used in any of these experiments. I waves (Patton & Amassian, 1954) have not been observed on slower sweeps in response to single shocks, so that even the strongest of these shocks was not excessive. Only if shocks of at least 2·5 mA have been repeated at 200–250 c/s have small I waves been seen following the latter volleys. Three to five such shocks have caused movement of thumb and index only if narcosis was so light that

there were also spontaneous movements. Their relative motor inefficiency stands in contrast to the effect of single, weaker, 5 msec pulses.

There have been no large systematic differences betwen the tract waves evoked by $S+$ and $S-$ stimuli. The latency was often 0·3–0·4 msec longer in the $S-$ cases. The characteristically different effects of $S+$ and $S-$ stimulation are not seen in the wave experiments; it will be shown that the differences revealed by more sensitive detectors of corticofugal discharge tend to be obliterated when one employs currents strong enough to evoke the massed discharge needed for the appearance of the wave.

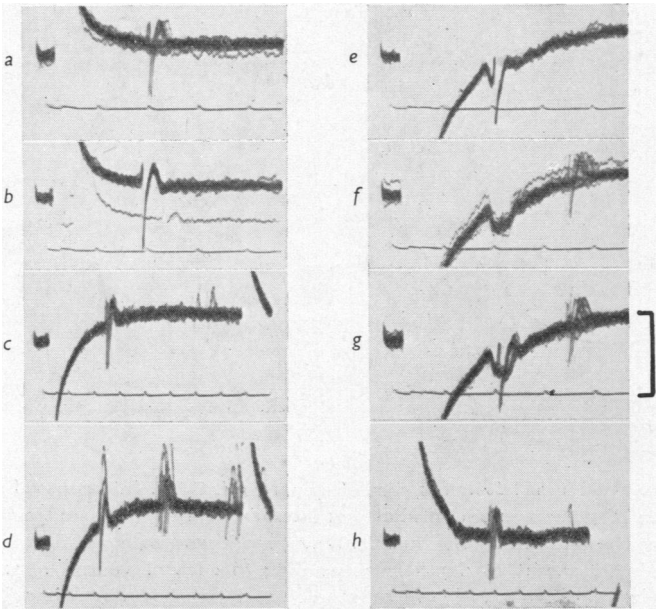

Fig. 4. Responses of pyramidal fibre to surface-anodal and surface-cathodal shocks, recorded at level of C5–6 junction. Each record is of about 20 superimposed sweeps.

Surface-anodal: *a*, 0·2 msec, threshold 1·8 mA, latency variable, about 1·85 msec; *b*, 0·2 msec, 2·0 mA, latency constant 1·8 msec; *c*, 8·0 msec, 0·95 mA, regular response, latency about 2·2 msec; *d*, 8·0 msec, 1·3 mA, fires three impulses, first with latency of about 1·9 msec.

Surface-cathodal: *e*, *f*, *g*, 0·2 msec; all shocks over 4·3 mA (see text); strength adjusted to give: *e*, tract wave; fibre impulse regular, latency 1·82 msec; *f*, tract wave; fibre impulse erratic, latency about 3·35 msec; *g*, tract wave; alternating early or late firing of fibre, latency 1·87 or 3·3 msec; *h*, 8·0 msec, 2·6 mA. Latency about 3·5 msec. Time msec, calibration 0·5 mV.

Unitary pyramidal impulses generated by $S+$ and $S-$ stimulation

The spikes recorded from the lateral corticospinal tract were often triphasic potentials of the type illustrated in Fig. 4; these usually survived

well. Sometimes they became positive, and then soon died; these fibres were presumably injured, although the tract wave remained negative-going.

Figure 4 shows the different responses given by a pyramidal neurone to $S+$ and $S-$ stimulation at various strengths. The tract wave was not very prominent when the cortex was stimulated at the point nearest to this cell, i.e. at which the least current was required. The threshold was high, 1·8 mA at 0·2 msec for $S+$ (cf. Landgren *et al.* 1962*b*). At this strength (record *a*), firing was not invariable, and latency a little erratic; the impulse arrived at the C6 segment about 1·85 msec after the cortical shock. Strengthening the current to 2·0 mA (record *b*) made firing and latency regular. In record *c* a long pulse was strong enough at 0·95 mA to guarantee a regular impulse at 2·2 msec latency. When the pulse was strengthened to 1·3 mA a first impulse always arrived at C6 at about 1·9 msec, and second and third impulses followed the first in many trials (record *d*). For $S-$ shocks the threshold was over 4·3 mA. Records *e*, *f*, *g* show alternative modes of response to three different stimulus strengths greater than 4·3 mA. The strongest shocks (record *e*) gave an invariably early impulse, latency 1·82 msec, during the small tract wave. A weaker shock in record *f* gave the tract wave and an occasional late impulse, latency about 3·35 msec. And record *g*, with intermediate strength, shows alternation between these two modes of response. It was observed at the time of experiment that when the early spike fired, the late spike missed, and vice versa. Finally, record *h* shows that for a long $S-$ pulse the threshold (2·6 mA) is more than twice that for the long $S+$ pulse (0·95 mA, record *c*) and the latency more than 1 msec longer (3·5 msec instead of 2·2 msec).

These are typical results. For surface-cathodal stimulation the threshold is from about 1·5 to more than 5 times higher than for surface-anodal; the lower the $S+$ threshold, the greater the difference between $S+$ and $S-$ thresholds.

Synaptic actions on motoneurones of C7 – T1 segments evoked by S+ and S– cortical stimuli

Figure 5 illustrates an experiment on a radial nerve motoneurone of the forearm. The motoneurone was identified by antidromic stimulation of the radial nerve (Fig. 5*c*). In all these experiments the membrane potential level was recorded in every sweep, and antidromic impulses were recorded at frequent intervals as a control of the condition of the motoneurone. The cortex was stimulated with long pulses. The map shows part of the arm area (orientation as in Fig. 2); the area from which $S+$ evokes excitatory synaptic action on this motoneurone with near-threshold stimulation is adjacent to the central sulcus (broken line), while the area for $S-$, for

which the threshold current is slightly larger, spreads pre-centrally (full line). At Point 1 (the lowest-threshold point) 0·3 mA, $S+$, gives a short-latency synaptic potential and $S-$, 0·25 mA, gives nothing. At point 2, which is at the edge of the $S+$ area and near the centre of the $S-$ area, $S+$ at 0·4 mA gives a minimal synaptic action. $S-$ at the same strength gives a larger, delayed synaptic action. In cats surface-cathodal pulses caused 'break' discharges by impaled pyramidal neurones (Phillips, 1956), and the delayed synaptic wave in the right middle record of Fig. 5 might be supposed to signal such a discharge. The bottom record, in which the pulse was further lengthened, disproves this explanation. The experiment is

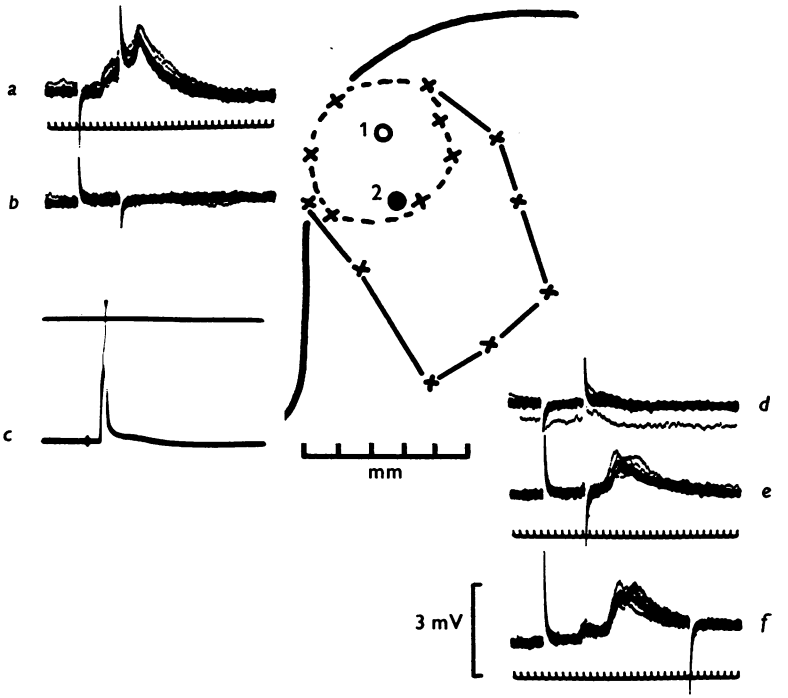

Fig. 5. Map showing cortical areas which when stimulated with 6·0 msec pulses produced excitatory post-synaptic potentials in a test radial motoneurone. Orientation as in Fig. 2. Interrupted outline, $S+$, 0·35 mA. Full outline: $S-$, 0·4 mA. Point 1 is near centre of $S+$ area and fringe of $S-$ area; point 2 is near centre of $S-$ area and fringe of $S+$ area.

Records: *a*, point 1, $S+$, 0·30 mA gives short latency synaptic potential; *b*, point 1, $S-$, 0·25 mA gives no response; *d*, point 2, $S+$, 0·40 mA gives minimal response; *e*, point 2, $S-$, 0·40 mA gives long latency synaptic potential; *f*, as in *e*, but pulse duration increased to show that response is not an 'off' response to break of current. *c*, Identification of motoneurone by antidromic stimulation of radial nerve. Membrane potential −72 mV, action potential +10 mV. KCl-filled micro-electrode. Time 1000 c/s for all records. All records are of 20 or more superimposed sweeps.

typical in that cathodal stimulation is effective from a larger, forward-spreading area; at the lowest-threshold point anodal stimulation gives a good response where nearly-equal cathodal stimulation gives no response. The depolarization in the anodally-evoked response is about 2 mV. The membrane potential was −72 mV; the depolarization needed to discharge the motoneurone would be about 15 mV.

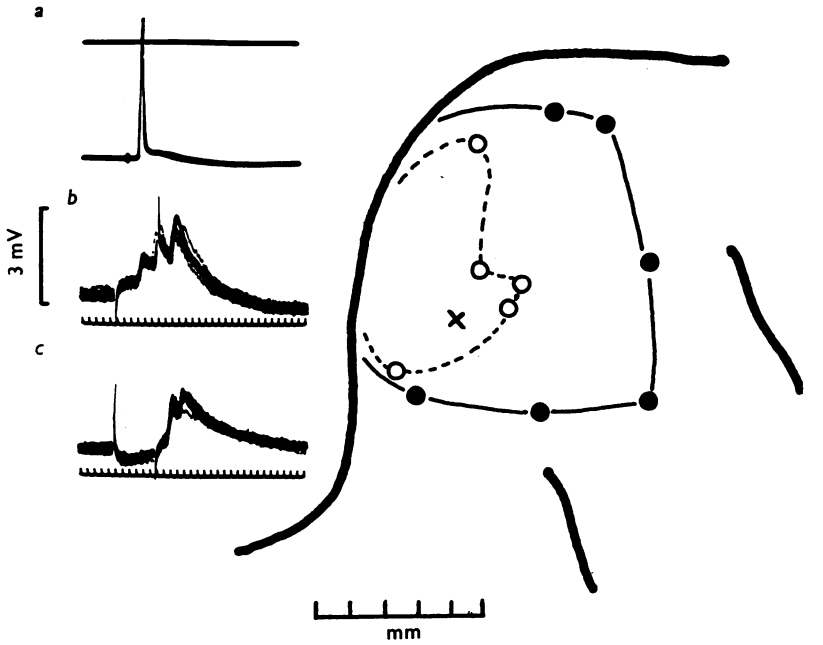

Fig. 6. Median motoneurone. Map shows right pre-central areas from which synaptic potentials could be evoked with 5 msec pulses: Interrupted line, $S+$, 0·4 mA; full line, $S-$, 0·5 mA. Scale in mm. Records: *a*, antidromic impulses (superimposed sweeps) recorded after completion of map. Membrane potential −70 mV, action potential +12 mV. *b*, $S+$ pulses, 0·55 mA, and *c*, $S-$ pulses, 0·50 mA, applied to point × within $S+$ field. Membrane potential −60 to −62 mV.

Figure 6 shows a similar experiment on a motoneurone of the median nerve. It is shown chiefly to illustrate the remarkable series of peaks on the synaptic potential evoked by the $S+$ shock. In view of the repetitive response of pyramidal cells to long pulses (e.g. Fig. 4*d*), it is likely that these represent discrete synaptic actions of repetitive pyramidal impulses (Landgren *et al.* 1962*a*). Such peaks are less evident in Fig. 5.

When shocks are strengthened beyond near-threshold values, the differences between the responses to $S+$ and $S-$ stimulation are obscured. In Fig. 7 the cortical $S+$ threshold for minimal synaptic action on a median

motoneurone was 0·5 mA. There was no response to $S-$ shocks below 1·0 mA. Above this strength $S-$ shocks evoked larger synaptic potentials than did $S+$ shocks of roughly equal strength; latency was similar for both at the highest strength. Membrane potential was -76 mV; the largest of these synaptic potentials was 14·5 mV, and was still below the level for generating an impulse in the motoneurone.

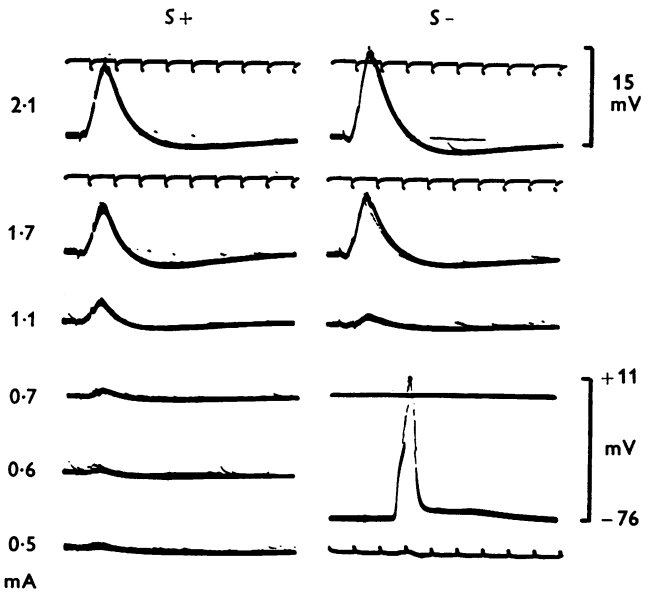

Fig. 7. Median motoneurone. $S+$ and $S-$ cortical pulses, to show similar effects with stronger pulses of 5·0 msec duration. Bottom right, antidromic impulse. Membrane potential -76 mV, action potential $+11$ mV. Time, 1000 c/s. Left, $S+$ at strengths indicated; weaker shocks (not shown) had no effect. Right, $S-$. Weaker shock (not shown) was ineffective. Time, 100 c/s.

The most dramatic difference between $S+$ and $S-$ stimulation is, however, revealed when these 5 msec pulses are repeated. Figure 8 compares, on an ulnar motoneurone, the effects of repetition at 44 c/s for 1·4 sec. At the top left of the figure single $S+$ shocks, 0·7 mA, gave a synaptic potential with a rhythm impressed on its upstroke (cf. Fig. 6), and with peak depolarization of about 7·5 mV. Repetition at 44 c/s (top two lines) gave a series of similar synaptic potentials, and when stimulation ceased the last synaptic potential subsided like the response to a single shock: the membrane showed no mark of pyramidal after-discharge. With $S-$ the result was absolutely different. Single pulses, although slightly stronger (1·0 mA), gave a slightly smaller depolarization (6 mV), and without the regular rhythm on the upstroke. On repetition the synaptic potentials

grew to 15 mV and became notched on both up- and downstrokes. Twelve impulses were discharged during the 1·4 sec period of stimulation. (Their after-potentials can be seen on the record. The simultaneous low-gain record, which showed the spikes, has been omitted for reasons of space.) When stimulation ceased there were no further impulses from the motoneurone, but its membrane received prolonged subliminal synaptic bombardment from the corticofugal after-discharge.

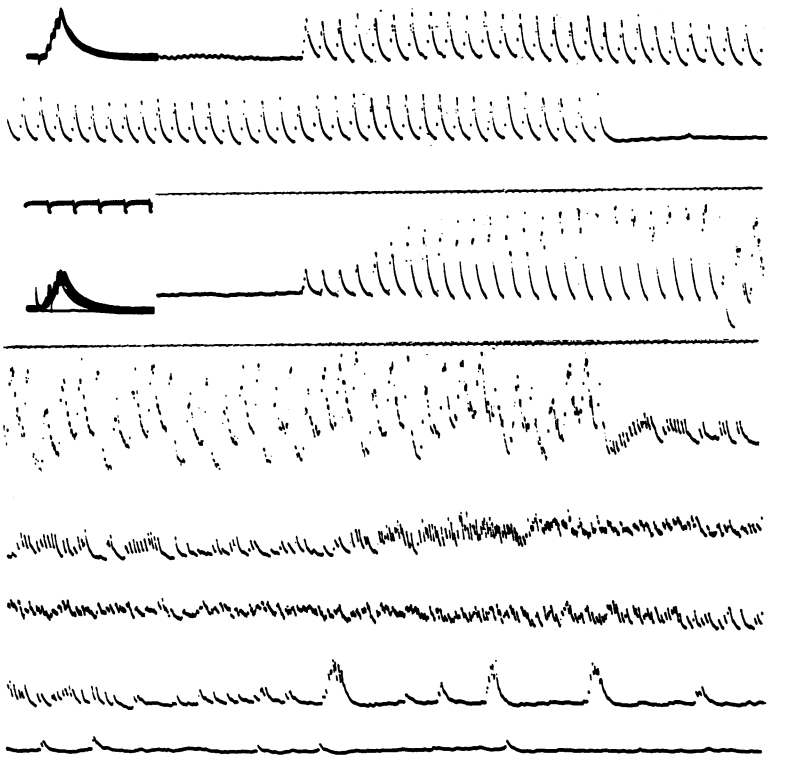

Fig. 8. Ulnar motoneurone. Membrane potential −69 to −74 mV. To show different actions of repetitive $S+$ and $S-$ stimulation at 44 c/s for 1·4 sec. Top two lines: $S+$, 5·0 msec, 0·7 mA. Top left, superimposed records showing response to single shocks (repeated at 1·0 c/s). Note ripple on upstroke of synaptic potential. Peak depolarization about 7·5 mV. The same shocks were then repeated at 44 c/s, synaptic potentials being recorded on moving paper. Note similarity of individual synaptic potentials and absence of after-discharge. Remainder of figure: $S-$, 5·0 msec, 1·0 mA. Stimulation at 1·0 c/s (superimposed sweeps) gives peak depolarization of about 6·0 mV. Repetition at 44 c/s for 1·4 sec gives growth (from 3·0 to 15·0 mV) and complication of synaptic potentials. Impulses discharged whenever firing level (−58 mV) reached. Note prolonged cortical after-discharge, revealed by irregular synaptic potentials. Time 100 c/s for sweeps, and small 100 c/s marks for continuous record.

Figure 9 is shown to illustrate a complex situation that requires further analysis. When motoneurones are depolarized, inhibitory synaptic potentials increase in amplitude (Coombs, Eccles & Fatt, 1955). At the end of the experiment on this radial motoneurone its membrane potential had fallen to -53 mV. Surface-cathodal shocks (right) then caused excitatory synaptic action starting 3·0 msec after the beginning of the cortical shock. Surface-anodal shocks gave a small initial excitatory action, and a larger inhibitory action beginning about 1·0 msec later. Other experiments showing this invariable sequence of excitatory and inhibitory actions are presented in another paper (Landgren *et al.* 1962*a*). The point to be made

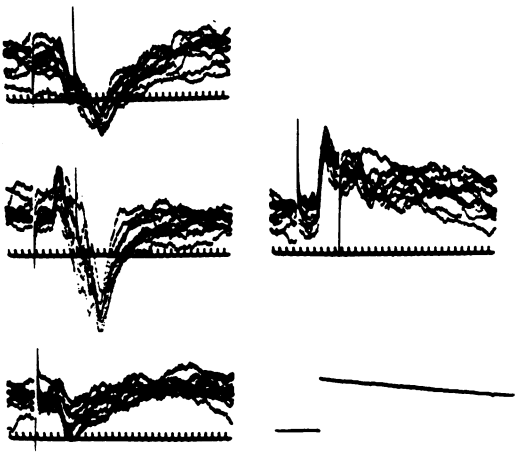

Fig. 9. Radial motoneurone. K_2SO_4 electrode. Records taken near end of experiment on this cell, when membrane potential had fallen to -53 mV, to show different responses from $S+$ and $S-$ stimulation of same point, 3·5 mm medial to lowest-threshold point for $S+$ stimuli. $S+$ stimulus gives small excitatory synaptic action followed by larger inhibitory action. $S-$ gives larger excitatory action. Left (above downwards): $S+$, long pulse, 0·42 mA, latency of IPSP = 3·9 msec; $S+$, long pulse, 0·75 mA, latency of EPSP = 2·8 msec, IPSP = 3·8 msec; $S+$, short pulse, 0·75 mA, latency of IPSP = 3·7 msec. Right: $S-$, long pulse, 0·63 mA, latency of EPSP = 3·0 msec. Time, 1000 c/s. Bottom right, response of recording system to 1·5 mV rectangular voltage step.

here is that the effect of cortical shocks on spinal motoneurones is often likely to be mixed. The cortical $S+$ and $S-$ shocks, applied at the same point, have clearly excited different corticofugal discharges which have produced opposite synaptic actions on this motoneurone. The depolarized state of this cell probably favoured the revelation of the inhibitory effect. Mixed effects on other motoneurones are also likely. In future experiments the deliberate use of depolarizing currents, passed through the intracel-

lular electrode, will be needed to uncover any inhibitory actions, and to show the extent to which apparently 'pure' excitatory actions may in fact be mixed.

DISCUSSION

The action of focal surface-anodal stimuli in evoking, at lower threshold than cathodal stimuli, responses of short and regular latency is already familiar in cat's pyramidal neurones (Phillips, 1956) and cerebellar Purkinje cells (Granit & Phillips, 1957). These lowest threshold cells, with the greatest differences between $S+$ and $S-$ thresholds, were all situated on the convexity of a gyrus or folium. Since the recording micro-electrode was in the cortex, the depth and approximate position of the recording site was known. In the present experiments, the discharge of pyramidal cells was detected by a micro-electrode in the spinal cord, recording extracellularly from pyramidal axons or intracellularly from spinal motoneurones. There was thus no direct evidence of the intracortical location of the pyramidal cells. It may be assumed, however, that the lowest threshold responses were due to stimulation of cells on the convexity of the precentral gyrus. It was in these lowest-threshold cells that the largest differences between $S+$ and $S-$ thresholds and latencies were found.

The shorter, fixed latency of the discharge set up by a brief $S+$ current pulse, and the regular rhythmic firing during the passage of a longer pulse, are in favour of the view that these responses are due to a flow of outward current through the excitable membrane of the 'pace-maker' region of the pyramidal cell (Phillips, 1961). Analogous results have been obtained in experiments on receptor organs, and have also been interpreted in terms of stimulation by an outward current through the axon close to the receptor organ. Thus Maruhashi, Mizuguchi & Tasaki (1952) recorded from single axons attached to tactile receptors in toad's skin. They found that anodal polarization of the skin overlying the receptor (the cathode being elsewhere on the outer surface of skin) caused repetitive firing of the axon. When the current was reversed there was no discharge of impulses during the polarization, but if the current was strong enough there was (as in pyramidal cells, Phillips, 1956) an impulse at the break. They concluded that surface-anodal polarization or sensory stimulation both generated outward current across the axonal membrane. In experiments on lateral line organs in *Xenopus laevis*, Murray (1956) found that an inward current flowing across the skin (surface-anodal) caused an acceleration of the 'resting' discharge of impulses, an outward current caused a slowing. He gave reasons for supposing that the inward current hyperpolarizes the axon terminals but depolarizes the proximal part of the non-myelinated axon or the first node of Ranvier. It is probable that when the

cerebral cortex is stimulated with a surface anode, the apical dendrites of the pyramidal cells on the convexity of the gyrus, those with their long axes normal to the surface, will be hyperpolarized and the axons of the same cells will be depolarized. It is also likely that horizontally-running axons in the outer layers of the cortex, and intracortical neurones in these layers, will be subjected to the depressant action of anodal polarization. This should contribute further to the narrowing of the effect of surface anodal stimulation on the corticofugal axons, with the reduction to a minimum of the coexcitation of intracortical systems bringing synaptic excitation to bear upon the pyramidal cells.

On the other hand, surface-cathodal stimulation should be specially favourable for the excitation of systems of axons and neurones in the outer cortical layers. The results of such stimulation, producing responses with longer, more variable, and sometimes alternative preferred latencies, are most simply interpreted in terms of indirect excitation of pyramidal cells in this way. The fact that the optimal foci for surface-cathodal stimulation always lie in a precentral direction from the optimal foci for surface-anodal stimulation suggests that there are intracortical pathways running backwards towards the pyramidal neurones of the motor cortex, and that these pathways can be stimulated most effectively where they converge towards the pyramidal cells. The surface-cathodal foci were always within area 4, which extends 10 mm forward from the central sulcus in these brains (T. P. S. Powell, personal communication). Further, if surface-anodal stimulation at its optimal focus excites pyramidal axons, surface-cathodal stimulation at the same focus would be expected to depress them. Such depression would presumably be less if the focal cathode were moved forward, away from the optimal anodal focus.

The effect of surface-cathodal stimulation in stirring up prolonged intracortical neuronal activity, in contrast with the 'dead-beat' action of surface-anodal shocks on pyramidal discharge, is most strikingly illustrated in Fig. 8. There can be little doubt that the build-up and after-discharge associated with surface-cathodal stimulation are due to activation of intracortical mechanisms. For if they were due to interneuronal reverberation at the spinal level, generated by pyramidal impulses, such intraspinal reverberation would be expected whatever the polarity of the cortical stimulus giving rise to the pyramidal impulses. The prolonged intracortical activity seen in response to repetitive cathodal stimulation is an epileptoid phenomenon, causing pyramidal discharges which exert subliminal effects on the spinal motoneurone.

We conclude that weak surface-anodal stimulation selectively excites the corticofugal neurones or their axons leaving the cortex. This technical possibility allows, in effect, a by-passing of the complexities of the

intact cortex without attempted surgical simplification, e.g. by laminar thermocoagulation (Dusser de Barenne, 1934), which must destroy the apical dendrites of the deepest pyramidal cells as well as destroying the cells and fibres of the outer cortical layers. The method may be of practical usefulness in cortical regions other than the motor. In other papers (Landgren *et al.* 1962*a*, *b*) it is exploited in an investigation of the simplest pyramidal pathways to motoneurones of the forearm and hand.

SUMMARY

1. The arm area of the motor cortex of the baboon has been stimulated with rectangular current pulses of 5 msec duration. A focal electrode applied to the cortical surface has been made anodal or cathodal with respect to an indifferent, remote electrode.

2. The threshold currents for minimal movement of the hand are similar with single surface-anodal or surface-cathodal pulses. The minimal cortical areas are different: surface-anodal stimulation is effective near the edge of the central fissure, surface-cathodal stimulation is effective from an overlapping area lying pre-centrally.

3. Leading from single pyramidal fibres in the lateral corticospinal tract, and using minimal synaptic potentials in C7-T1 motoneurones as an index of minimal corticofugal discharge, we have found that the threshold for surface-anodal stimulation is lower than that for surface-cathodal stimulation. The difference is the greater the lower the surface-anodal threshold.

4. Responses to surface-cathodal stimulation have longer and variable latency. Their optimal cortical foci lie pre-centrally from the optimal foci for surface-anodal stimulation.

5. Repetitive surface-anodal stimulation elicits a series of similar cortical discharges, without after-discharge. By contrast, repetitive surface-cathodal stimulation elicits discharges of increasing size and complexity; prolonged cortical after-discharge outlasts the period of stimulation.

6. It is concluded that, with stimuli strong enough to excite minimal corticofugal discharges, surface anodal stimuli directly excite the impulse-generating or 'pace-maker' regions of the pyramidal cells. Surface-cathodal stimuli excite the pyramidal cells indirectly, by cortical synaptic mechanisms.

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