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ELECTRIC AND MAGNETIC STIMULATION OF HUMAN MOTOR CORTEX: SURFACE EMG AND SINGLE MOTOR UNIT RESPONSES

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SUMMARY

1. The effects of different forms of brain stimulation on the discharge pattern of single motor units were examined using the post-stimulus time histogram (PSTH) technique and by recording the compound surface electromyographic (EMG) responses in the first dorsal interosseous (FDI) muscle. Electrical and magnetic methods were used to stimulate the brain through the intact scalp of seven normal subjects. Electrical stimuli were applied either with the anode over the lateral central scalp and the cathode at the vertex (anodal stimulation) or with the anode at the vertex and the cathode lateral (cathodal stimulation). Magnetic stimulation used a 9 cm diameter coil centred at the vertex; current in the coil flowed either clockwise or anticlockwise when viewed from above.

2. Supramotor threshold stimuli produced one or more narrow (< 2 ms) peaks of increased firing in the PSTH of all thirty-two units studied. Anodal stimulation always produced an early peak. The latencies of the peaks produced by other forms of stimulation, or by high intensities of anodal stimulation, were grouped into four time bands relative to this early peak, at intervals of −0·5 to 0·5, 1–2, 2·5–3·5 and 4–5·5 ms later. Peaks occurring within these intervals are referred to as *P*0 (the earliest anodal), *P*1, *P*2 and *P*3 respectively.

3. At threshold, anodal stimulation evoked only the *P*0 peak; at higher intensities, the *P*2 or more commonly the *P*3 peak also was recruited. The size of the *P*0 peak appeared to saturate at high intensities.

4. In five of six subjects, cathodal stimulation behaved like anodal stimulation, except that there was a lower threshold for recruitment of the *P*2 or *P*3 peak relative to that of the *P*0 peak. In the other subject, the *P*3 peak was recruited before the *P*0 peak.

5. Clockwise magnetic stimulation, at threshold, often produced several peaks. These always included a *P*1 peak, and usually a *P*3 peak. A *P*0 peak in the PSTH was never produced by a clockwise stimulation at intensities which we could explore with the technique.

6. Anticlockwise magnetic stimulation never recruited a *P*1 peak; in most subjects a *P*3 peak was recruited first and at higher intensities was accompanied by *P*0 or *P*2 peaks.

7. On most occasions when more than one peak was observed in a PSTH, the unit fired in only one of the preferred intervals after each shock. However, double firing was seen in five units when high intensities of stimulation were used. The intervals between the two discharges was the same as the intervals between peaks in the PSTH.

8. Surface EMG responses in the FDI muscle behaved in a way predictable from the behaviour of the single motor units which had been studied.

9. These results are discussed in terms of the D and I wave hypothesis proposed for responses of pyramidal tract neurones to surface anodal stimulation of the exposed motor cortex in primates.

INTRODUCTION

Electrical (Merton & Morton, 1980) and magnetic (Barker, Jalinous & Freeston, 1985) methods of stimulating the human brain through the scalp have been available for several years. Despite its apparently gross nature, the electrical method seems to activate the motor cortex of man in a manner very similar to that described for direct stimulation of the exposed cortex in non-human primates (see Day, Dick, Marsden & Thompson, 1986; Day, Thompson, Dick, Nakashima & Marsden, 1987*c*; Day, Rothwell, Thompson, Dick, Cowan, Berardelli & Marsden 1987*b*). The aim of this paper is to present further data to support this interpretation by examining the effects of anodal and cathodal stimuli, and to contrast these data with those obtained using the magnetic stimulator. The outcome is that different forms of stimulation preferentially activate different neuronal elements in the brain. Parts of these data have been presented to the Physiological Society (Day *et al.* 1986; Day, Maertens de Noordhout, Marsden, Nakashima, Rothwell & Thompson, 1987*a*; Day, Dressler, Maertens de Noordhout, Marsden, Rothwell & Thompson, 1988).

METHODS

Subjects were seven normal volunteers, including the authors, aged between 28 and 36 years. All gave informed consent for the procedures used. The project had the approval of the local ethical committee. None of the subjects experienced any lasting side effects after participating in the experiments.

Stimulators

The electrical stimulator was a prototype of the commercially available Digitimer D180 stimulator which was kindly built for us by Mr H. B. Morton. Peak output voltage was 750 V, with typical maximum peak currents of up to 1 A decaying with a time constant of 50 μs. Stimulus intensity is expressed on a linear scale as a percentage of the maximum output of the device. Stimuli were given via two 9 mm diameter Ag–AgCl electrodes fixed with collodion glue at the vertex of the scalp and 7 cm laterally on a line joining the vertex and external auditory meatus. The terms 'anodal' and 'cathodal' stimuli refer to which of the output leads was connected to the lateral electrode position.

Magnetic stimulation was performed using a device kindly made for us by Drs A. Barker, R. Jalinous and I. L. Freeston of the University of Sheffield. The characteristics of this stimulator have been described in detail elsewhere (Barker *et al.* 1985; Hess, Mills & Murray, 1987). The device is now available commercially as the Novametrix Magstim 200. We used a 9 cm diameter coil centred at the vertex with the inducing current flowing either clockwise or anticlockwise as viewed from above. Intensities are expressed as a percentage of the maximum output of the device.

Recording surface EMG

All recordings were made from the first dorsal interosseous muscle (FDI) of the right hand. Surface EMGs were obtained via two 9 mm diameter Ag–AgCl electrodes with the active electrode over the motor point of the muscle and the reference on the metacarpophalangeal joint of the index finger. EMGs were preamplified (Devices, type 3160), bandpass filtered (−3 dB at 0·8 Hz and 2·5 Hz) and amplified (Devices, type 3120). During stimulation, subjects maintained an isometric contraction of 10% maximum voluntary effort in FDI by abducting their index finger against a strain gauge attached to the proximal interphalangeal joint of the index finger.

Single unit studies

Single motor units were recorded via conventional concentric needle electrodes (Dantec type 13L58) and amplified as above with filters set 3 dB down at 80 Hz and 2·5 kHz. A total of thirty-two units were studied in seven different subjects. Thirty of the units were studied using anodal cortical stimulation, sixteen using cathodal stimulation, seventeen using clockwise magnetic stimulation and eight using anticlockwise stimulation. Most units were examined using more than one form of stimulation, usually at several different intensities. The units studied all were recruited at low force levels (less than 10% maximum) and fired tonically for periods of greater than 10 min. Audio and visual feedback was provided to aid the subject in the task. The time of occurrence of a particular motor unit potential was detected by a pulse height window discriminator designed by Mr H. C. Bertoya. If the height of the potential fell within two adjustable voltage levels then a +5 V pulse was produced after a fixed delay of 2 ms. This delay has been compensated for in the figures and text.

In order to construct a post-stimulus time histogram (PSTH) of the unit firing, subjects were instructed to fire the unit voluntarily at about 10–15 Hz with the aid of audio feedback. At random intervals from 4·5 to 6·0 s, a cortical stimulus was given and the time of unit firing stored. The response to each stimulus was viewed on a digital storage oscilloscope so that a check could be made on the shape of the potential which triggered the unit discriminator. Trials in which spurious triggering occurred were excluded from the final PSTH. The PSTHs were collected with a bin width of 0·25 ms and contained the responses from 100 trials. In some early experiments (not illustrated, although included in the final combined data), the bin width was 0·1 ms or 0·5 ms. All data from single unit studies was recorded on magnetic tape using a Racal 7DS FM recorder with a frequency response from DC to 2·5 kHz to allow further analysis of the data.

The following criteria were used when measuring the peaks in the PSTH: (i) a peak was defined as occurring if there were four or more counts in two adjacent time bins after 100 stimuli. The probability of seeing a peak of this size by chance alone depends on the firing rate of the motor unit, the number of trials collected and the number and duration of the PSTH bins. In the present experiments, we were interested in peaks occurring in FDI within a 15 ms time period from 20–35 ms after the cortical shock. With a unit firing rate of 10 Hz and bin widths of 0·25 ms, the probability of four or more counts appearing in two adjacent time bins within this time period is about one in every twenty histograms collected. (ii) The onset of a peak was taken as the first bin in which there were two or more counts. (iii) A peak was defined as ending when the next two adjacent bins contained a total of one or no counts. (iv) If a peak was abnormally wide and had a bimodal distribution it was interpreted as two peaks which were closely adjacent such that the counts never dropped to zero between each peak; the middle time bin was taken as the end of the first peak and the start of the second. (v) The latency of a peak was defined as the onset latency plus half its width.

RESULTS

Relative timing of the PSTH peaks of single motor units produced by different forms of cortical stimulation

Figure 1 illustrates the response of a typical single unit in the FDI muscle following three different types of cortical stimulation. Each PSTH was constructed from the responses to 100 stimuli given 10 ms before the start of the sweep. As noted previously (Day *et al.* 1987*a*; Day *et al.* 1988), the most striking difference between

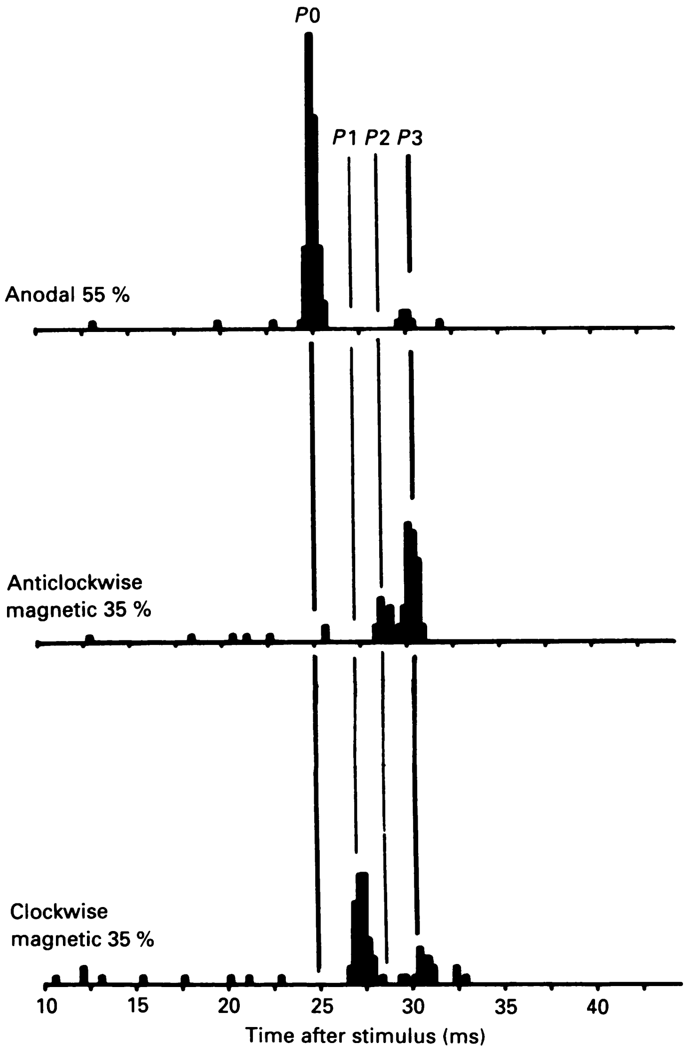

Fig. 1. Post-stimulus time histograms from a single motor unit in FDI studied using anodal (top), anticlockwise magnetic (middle) and clockwise magnetic (bottom) stimulation. Each histogram was constructed from the responses to 100 stimuli given 10 ms before the start of each record. Stimulus intensity is given as a percentage of the maximum output of each stimulator. The histogram peaks have been labelled *P*0, *P*1, *P*2 and *P*3 (continuous vertical lines) according to their latency after the stimulus (see text).

the PSTHs was that the latency of increased probability of firing was not the same with each type of stimulation. The earliest response occurred about 25 ms after the shock when anodal stimulation was given; responses to clockwise magnetic stimulation began some 2 ms later, and responses to anticlockwise stimulation about 1·5 ms later still.

At the intensities used here, each type of stimulation increased the firing probability of the unit over two discrete time intervals. The second peak in the PSTH began 5 ms after the first when anodal stimuli were given, 3 ms after the first when clockwise magnetic stimuli were given, and only 1·5 ms after the first when anticlockwise stimuli were applied. The latency of this second peak was therefore approximately the same (30 ms) for all three types of stimulation.

The timing of individual peaks in the PSTH, produced by different forms of stimulation, relative to the earliest peak produced by anodal stimulation, varied slightly from unit to unit and from subject to subject. Despite this, when the latency of these peaks relative to the earliest anodal peak was plotted, a certain grouping was evident (Fig. 2*A*). No matter what the form of stimulation, PSTH peaks for these twenty-five units tended to occur in one (or more) of four separate time bands. In Fig. 2*B*, the data of Fig. 2*A* has been broken down into four groups according to whether anodal, cathodal, clockwise or anticlockwise stimulation was used. The earliest peaks of probability produced by anodal stimulation was defined as *P*0. Peaks produced by other forms of stimulation that fell within ±0·5 ms of the anodal peak were similarly designated *P*0. Cathodal stimuli, and on two occasions anticlockwise magnetic stimuli, produced a peak at this time. Peaks occurring within the second interval which spanned a time band from 1·0 to 2·0 ms later than *P*0 are referred to as *P*1. Only clockwise magnetic stimuli produced a PSTH peak at this timing. The third (*P*2) and fourth (*P*3) intervals spanned time bands of 2·5–3·5 ms and 4·0–5·5 ms after *P*0 and were filled by peaks evoked by all forms of stimuli.

Most of the units illustrated in Fig. 2 were studied at more than one intensity. The latencies plotted are only those for peaks at the highest intensity of stimulation used in each case. The effect of intensity on the size and number of peaks in the PSTH is summarized below.

Electrical stimulation at different intensities

Anodal stimulation

The effect of anodal stimulation was studied in thirty units and the results confirm those published in previous studies (Day *et al.* 1987*b*). An example of unit behaviour at three different intensities of anodal stimulation is shown in Fig. 3. Low intensity stimulation produced a single peak of increased firing in the PSTH 22·5 ms after the shock (*P*0). As the intensity was increased, a second peak appeared with a latency about 5 ms longer than the first (*P*3). At the highest intensity the PSTH became more complex. The *P*3 peak was small, but was now preceded by a large peak (*P*2) starting only some 3·5 ms after *P*0. A further late peak, 6·75 ms after the first also was evident (this peak at 6·75 ms was not incorporated in Fig. 2 since it appeared only in this unit and one other, both studied at high intensities).

With anodal stimulation the earliest peak (*P*0) had the lowest threshold and an average duration of 1·48±0·4 ms (mean±1 S.E.M.). The absolute latency to unit firing, measured from the time of the cortical shock to the time at which a unit triggered the window discriminator, was 22·5±0·4 ms (mean±S.E.M.), with a range of 19·3–30·3 ms. Eighteen units were examined using intensities sufficient to produce multiple peaks in the PSTH. In fourteen of these the *P*3 peak, and in three the *P*2, was recruited after the *P*0. Only one unit (illustrated in Fig. 3) clearly showed both a *P*2 and *P*3 peak. No units had a *P*1 peak in the PSTH when anodal stimulation was used.

Examination of the *P*0 peak in the unit shown in Fig. 3 appears to indicate that

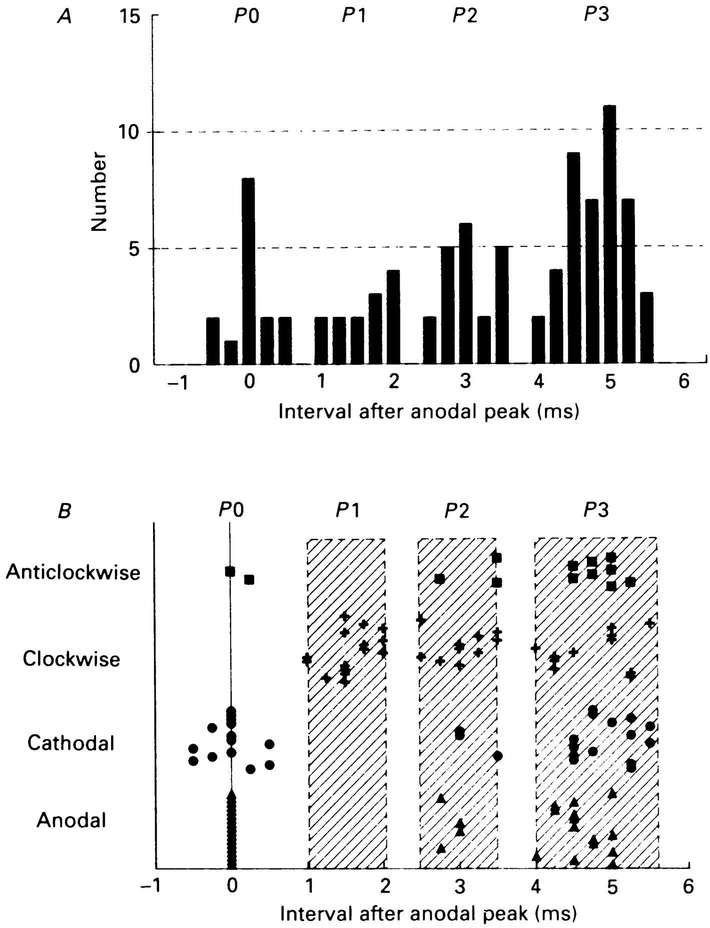

Fig. 2. *A*, histogram showing relative latencies of PSTH peaks in twenty-five different units compiled from data using anodal, cathodal, clockwise and anticlockwise magnetic stimulation. Peak latencies were expressed relative to the time of the earliest anodal peak ($t = 0$ ms) in each unit. The ordinate plots the number of units in which a peak occurred at a given interval. Four preferred latencies are visible: at the time of the first anodal peak ($-5{\cdot}0$ to $+0{\cdot}5$ ms) and at 1–2, 2·5–3·5 and 4–5·5 ms later. These are labelled *P0*, *P1*, *P2*, and *P3* respectively. Anodal peaks at *P0* are not included in the histogram, since they were the standard against which the other peaks were measured. *B* same data as in *A*, displayed according to the type of stimulation. The abscissa again plots the latency of each peak relative to the (first) anodal peak (vertical line at $t = 0$ ms); the hatched areas correspond to the time intervals spanned by the peaks in *A*. Each horizontal row of the graph plots data from the PSTH of a single unit grouped according to the method of stimulation. For example, the bottom nineteen rows are from eighteen different units studied using anodal stimulation. By definition, these units all fired in the *P0* interval at $t = 0$ ms; they also fired in the *P2* or *P3* interval. It should be noted that seven of the total number of units studied did not contribute data to this figure. To be included in the figure, units must have been studied with anodal stimulation. In addition, if only anodal shocks were given, two (or more) peaks must have been evident in the PSTH.

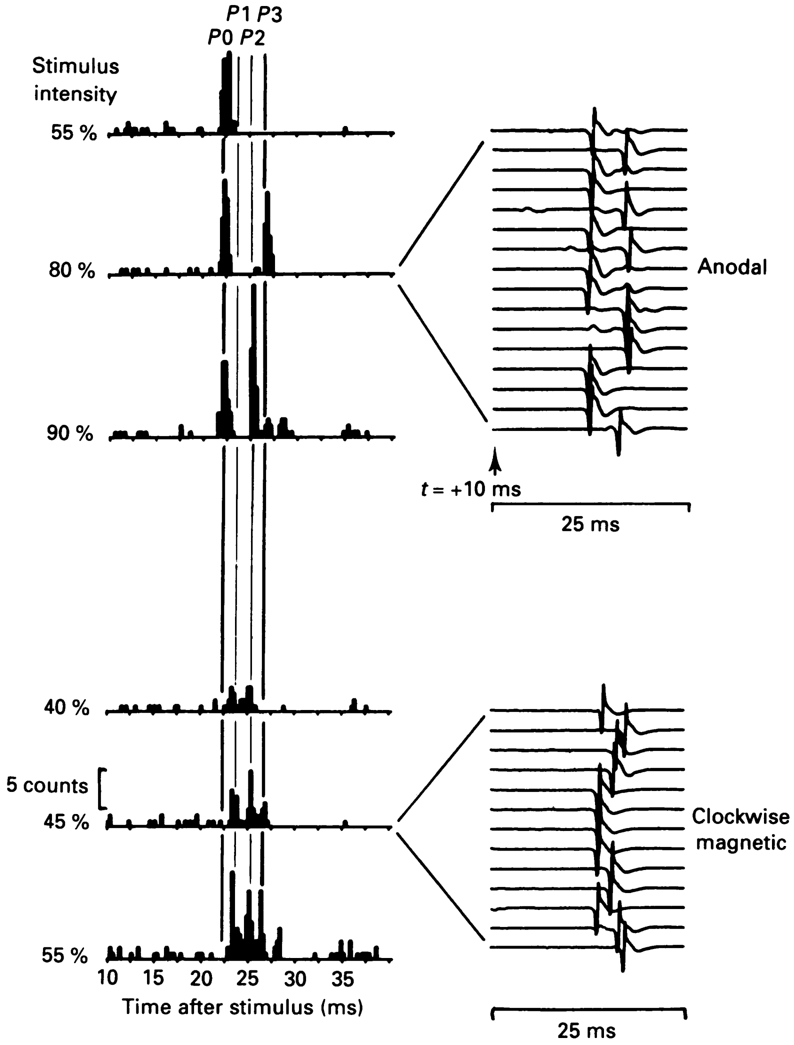

Fig. 3. PSTH data (left column) recorded from the same subject after different intensities of anodal (upper half) and clockwise magnetic (lower half) stimulation. All traces start 10 ms after stimulation. The same motor unit was studied throughout. The earliest PSTH peak following anodal stimulation occurs 1·25 ms before the earliest magnetic peak. With anodal stimulation at 55 % only a single (*P*0) peak is evident; at 80 % a later peak occurs some 5 ms later (*P*3); at 90 % this peak is much smaller and is preceded by another peak (*P*2). Magnetic stimulation at 40 % appears to produce two peaks (*P*1, *P*2) and three peaks at higher intensities. The raster plots in the right column show part of the raw data from which the PSTHs at 80 % anodal and 45 % magnetic were constructed. They show that the single unit discharges at particular intervals after each shock. This unit never fired twice in response to a single shock in the trials making up these histograms (but see later).

the number of counts in the *P*0 interval was approximately constant for all three intensities of stimulation. Even when later peaks were recruited at intensities of 80 and 90%, the first peak was unchanged, as if it has saturated at a lower intensity. Six of the fifteen units which were studied using two or more stimulus intensities appeared to exhibit this behaviour. The relationship between the size of the initial peak in the PSTH and strength of shock for each of these fifteen units is shown in Fig. 4. Spread of data has been reduced by expressing stimulation intensity as a percentage of the threshold level needed to produce a just-identifiable response in each unit. The size of the initial peak appeared to saturate in those units in which a large range of stimulus intensities could be studied, for example the unit identified by an arrow in Fig. 4.

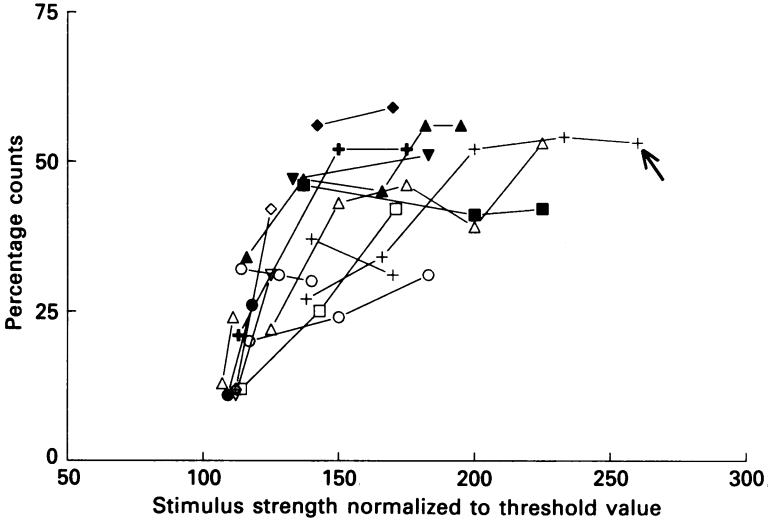

Fig. 4. Relation between size of first peak in the PSTH of fifteen motor units and the intensity of anodal stimulation. The size of the peak is expressed as the percentage of trials in which the unit discharged in the time interval defined by the *P*0 peak. Stimulus intensity is expressed as a percentage of the threshold needed to produce a just-recognizable PSTH peak after twenty to thirty trials. The size of the peak appears to saturate in some units at high intensities of stimulation (e.g. unit identified by arrow).

The maximal size of the PSTH peak gives some indication of the size of the maximum compound EPSP evoked by a descending volley. Since the largest stimuli produced firing of a motor unit within the *P*0 interval on approximately 50% of trials, the estimated size of the maximum compound excitatory postsynaptic potential (EPSP) would be about 5 mV (see also Ashby & Zilm, 1982). This is larger than our previous estimate of 3 mV on a smaller sample of six units (Day *et al.* 1987*b*) and is approximately twice that of the mean maximal corticomotoneuronal EPSP in motoneurones supplying ulnar innervated hand muscles in the baboon (Clough, Kernell & Phillips, 1968).

The trials on which a unit fired in the *P*0 interval were not randomly distributed (see also Calancie, Nordin, Wallin & Hagbarth, 1987). The probability of firing depended on the timing of the cortical shock relative to the on-going interdischarge

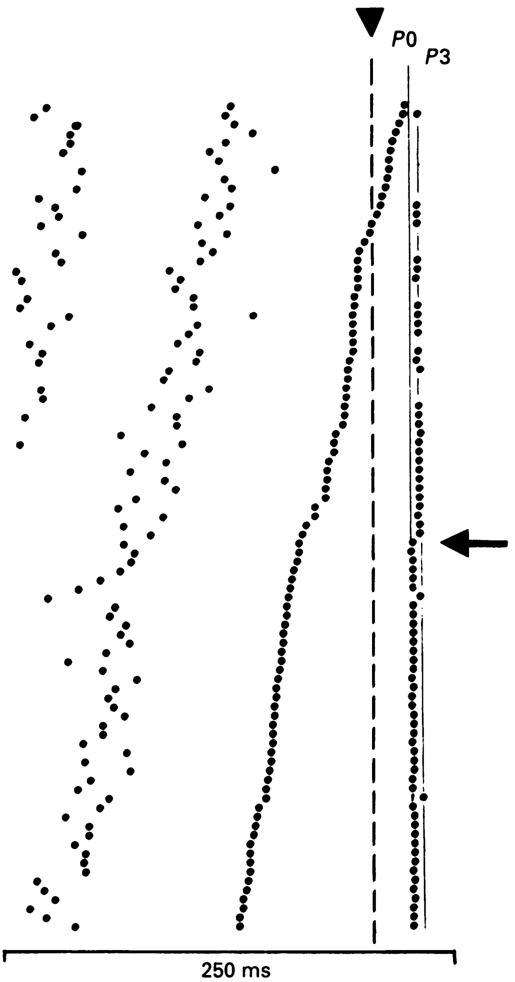

Fig. 5. Raster plot of the timing of discharge (represented by the symbol ▼) of a single FDI unit (data from same unit illustrated in Fig. 3) in the 200 ms before and the 50 ms after an anodal cortical shock of 80% maximum (vertical broken line). Each horizontal row represents data from a single trial. The rows have been ordered according to the time of the last spontaneous spike preceding or just after the cortical stimulus. In the bottom half of the figure (below arrow), the last spontaneous spike preceded the stimulus by 40 ms or more, and on all but two occasions the latency of the response to the cortical stimulus was approximately 22·5 ms; on the other two it was about 27 ms. These latencies correspond to the *P*0 and *P*3 intervals in the PSTH of Fig. 3 and are indicated by the continuous vertical lines to the right of the figure. In the upper half of the figure, the last spontaneous spike occurred less than 40 ms before the stimulus or even after it. In these trials responses to the cortical shock occurred less frequently and, when discharged by the stimulus, the unit fired only in the *P*3 interval.

interval of the unit. This phenomenon is shown in the raster plot of Fig. 5, which contains data from the individual trials making up the histogram of the unit shown in Fig. 3. Each horizontal line of the raster represents a single trial and each dot the occurrence of a unit discharge. The trials are aligned to the cortical stimulus (vertical line). During the experiment, the timing of the anodal shock was random with respect to the on-going discharge of a unit, but in this figure, the trials have been reordered according to the time of occurrence of unit discharge prior to or just after the cortical shock. Trials in which the shock was given just before or after an on-going spike are at the top of the figure; trials in which the shock was given 40–100 ms after the last spike are at the bottom. As can be seen in the histogram of Fig. 3, this unit discharged either 22·5 or 27 ms after the shock. These timings are labelled in Fig. 5 as *P*0 and *P*3. When the cortical shock was given 50 ms or more after a preceding spike (trials below the arrow), the unit almost always discharged in the *P*0 interval. If the shock was given less than 40 ms after a preceding spike (trials above the arrow), the unit discharged either in the *P*3 interval or not at all.

Cathodal stimulation

Single unit responses to cathodal stimulation were very similar in many respects to those obtained using anodal shocks. PSTH peaks were produced in the *P*0, *P*2 and *P*3 intervals in similar proportions to anodal stimulation. Fourteen of the sixteen units were studied with both anodal and cathodal stimulation; in these units, the duration of the *P*0 peak was the same with each type of shock (anodal, 1·43 ± 0·07 ms; cathodal, 1·41 ± 0·08 ms). Five of the six subjects studied had a higher threshold for cathodal than anodal activation of a single unit. In these subjects, just-suprathreshold cathodal stimulation produced a single early peak (*P*0) of increased firing in the PSTH. Only if the stimulus intensity was raised did a second peak (usually *P*3 or sometimes *P*2) occur. Although this behaviour was similar to that seen with anodal stimuli, there was one crucial difference: the relative thresholds for production of the *P*0 and *P*3 (or *P*2) peaks were much closer when cathodal shocks were given. In the unit illustrated in Fig. 6, counts only appeared in the bins of the *P*3 peak when the anodal stimulus intensity was 83% above threshold, whilst two counts filled these bins with cathodal shocks of only 10% suprathreshold and the *P*3 peak was quite evident with shocks of 27% suprathreshold. The same behaviour was observed in all the other units studied in these five subjects.

The remaining subject had a slightly lower threshold for cathodal stimulation. In four units which were studied, cathodal shocks first produced the *P*3 peak; the *P*0 peak was recruited only as the intensity was raised.

Magnetic stimulation at different intensities

As with electrical stimulation, magnetic stimuli were capable of producing one or more peaks of increased firing probability in the PSTH of single motor units. An example of the response to clockwise magnetic stimulation is shown in the bottom half of Fig. 3. This is the same unit whose response to anodal shocks is illustrated in the top half of Fig. 3, so that the PSTH to both forms of stimulation can be compared directly. There are two differences between the histograms. First, the latency to the earliest peak of probability of firing was longer when magnetic stimuli were given. Second, the PSTH following magnetic stimuli was more complex, especially at low stimulus intensities. In five of the seventeen units studied with magnetic stimulation, several peaks in the PSTH were evident (Fig. 3) even at just-suprathreshold intensities, whereas anodal stimuli at intensities just above threshold always produced a single peak (*P*0).

As noted above, there were two differences between clockwise and anticlockwise forms of magnetic stimulation. The threshold intensity was lower, and the peaks in the PSTH which clockwise stimulation evoked sometimes were different from those using anticlockwise stimuli. In fifteen of seventeen units studied using clockwise stimulation, the shortest latency peak evoked in the PSTH was the *P*1 peak. In the remaining two units, it was the *P*2 peak. Eight of these units also were studied using anticlockwise stimulation. In no case was a clear *P*1 peak evoked. In four units, the *P*3 peak was the earliest we observed; in two others the *P*3 was the earliest at low intensities, but was preceded by a *P*0 or a *P*2 peak at higher intensities. In the two remaining units, the earliest peak at all intensities was a *P*0 in one case and a *P*2 in the other.

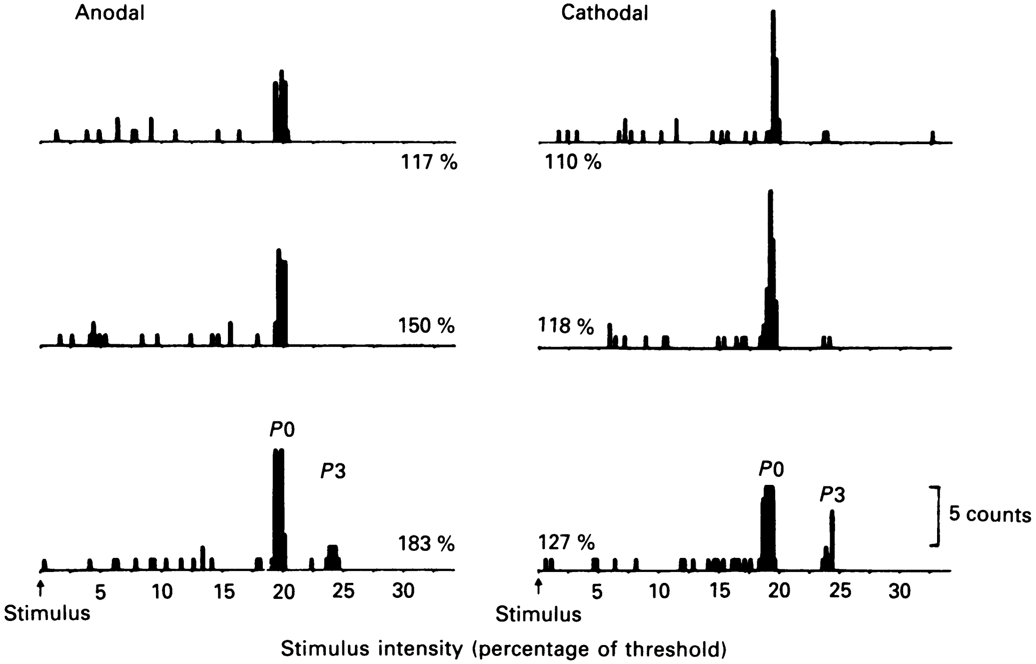

Fig. 6. PSTHs from the same motor unit in FDI studied using three different intensities of anodal (left column) and cathodal (right column) stimulation. The stimulus was given at the start of each record. Intensities are expressed as a percentage of the threshold value needed to produce a just-identifiable peak in twenty to thirty trials. At high intensities, two peaks of increased firing are visible in the PSTH and are labelled *P*0 and *P*3. The *P*3 peak appears clearly with cathodal stimuli of only 127% threshold, whereas anodal stimuli of 183% are necessary before a similar sized peak is evident.

Because of the presence of several closely spaced peaks in the PSTHs to magnetic stimulation, it was not always possible to measure with certainty the total duration of each peak. The only reliable estimate we could make was that of the *P*1 peak in eleven units studied using clockwise stimulation. In this sample, the peak width was 1·7 ± 0·2 ms, which was slightly, but not significantly ($p > 0{\cdot}05$), longer than that of the *P*0 peak using anodal stimulation.

Multiple firing of single motor units following a single cortical stimulus

The presence of multiple peaks in the PSTH of single motor units following a magnetic or electrical cortical shock raises the question of whether a unit ever fired twice in response to a single stimulus. In a previous paper (Day *et al.* 1987*b*), we argued that since the peak twitch force produced by a single cortical stimulus can greatly exceed the peak twitch produced by a supramaximal peripheral nerve shock (see also Marsden, Merton & Morton, 1983), some units must fire more than once after cortical stimulation. This was borne out by the results of collision experiments, in which a single supramaximal antidromic peripheral nerve volley failed to obliterate an orthodromic volley set up by a single cortical shock. In the present series of experiments double firing was observed directly in five units, all of which could be studied reliably at high stimulation intensities. An additional example of a single unit firing twice can be seen in Fig. 1 of Gandevia & Rothwell (1987).

Figure 7 illustrated the most completely documented example of the phenomenon. On rare occasions, this unit produced double discharges during the course of a tonic voluntary contraction. A record of such a doublet is shown in the top part of the figure. In this instance, the interdischarge interval was 4·2 ms. Note the long interdischarge interval which followed the doublet. The form and amplitude of the second spike of the doublet is somewhat different from that of the first, presumably because of slowing (or even block) of the fine terminal branches innervating this unit (Bawa & Calancie, 1983). Magnetic stimuli at 50% and above and electric anodal stimuli at 60% and above also could evoke similar doublets. The interdischarge interval was 5 ms when anodal stimuli were given and 3·2 ms for magnetic stimuli. These intervals corresponded closely to interpeak intervals in the PSTH of the unit. In this particular unit it was also possible to show that the tendency for multiple firing increased as the stimulus strength was raised. With magnetic stimuli of 50%, only three doublets were observed out of 100 trials. At 55%, eight doublets were seen after only fifty trials.

Fig. 7. Example of double firing of a single motor unit in FDI. *A*, during weak voluntary contraction; *B* and *C*, following anodal electrical or clockwise magnetic cortical stimulation. The four rows on the left of part *A* should be read continuously from left to right and top to bottom. They are part of a continuous record of the unit firing during a weak voluntary contraction. In the third row, there is a spontaneous doublet firing, followed by a long interdischarge interval. The doublet has been expanded in the sweep on the right. In the left of part *B* are two PSTHs recorded from this unit following anodal stimulation at 60% or clockwise magnetic stimulation at 55%. Each starts 10 ms after the stimulus was given. Two peaks are evident in the anodal PSTH; three in the magnetic PSTH. These peaks correspond to the *P*0 and *P*3 (anodal) and the *P*1, *P*2 and *P*3 peaks (magnetic) as defined in Fig. 2. During construction of these histograms, those trials in which the unit fired twice were excluded. However, examples of occasions on which the unit did fire twice to either anodal or magnetic stimulation are shown in the right-hand panel of Fig. 7*B*. The interval between these doublets was 5 ms after anodal and 3·2 ms after magnetic stimulation. In the left of part *C* are shown the three trials (out of 100) in which the unit fired a doublet after magnetic stimulation at 50%. On the right are the eight trials (out of the first fifty) in which a doublet was seen at the higher intensity of 55%.

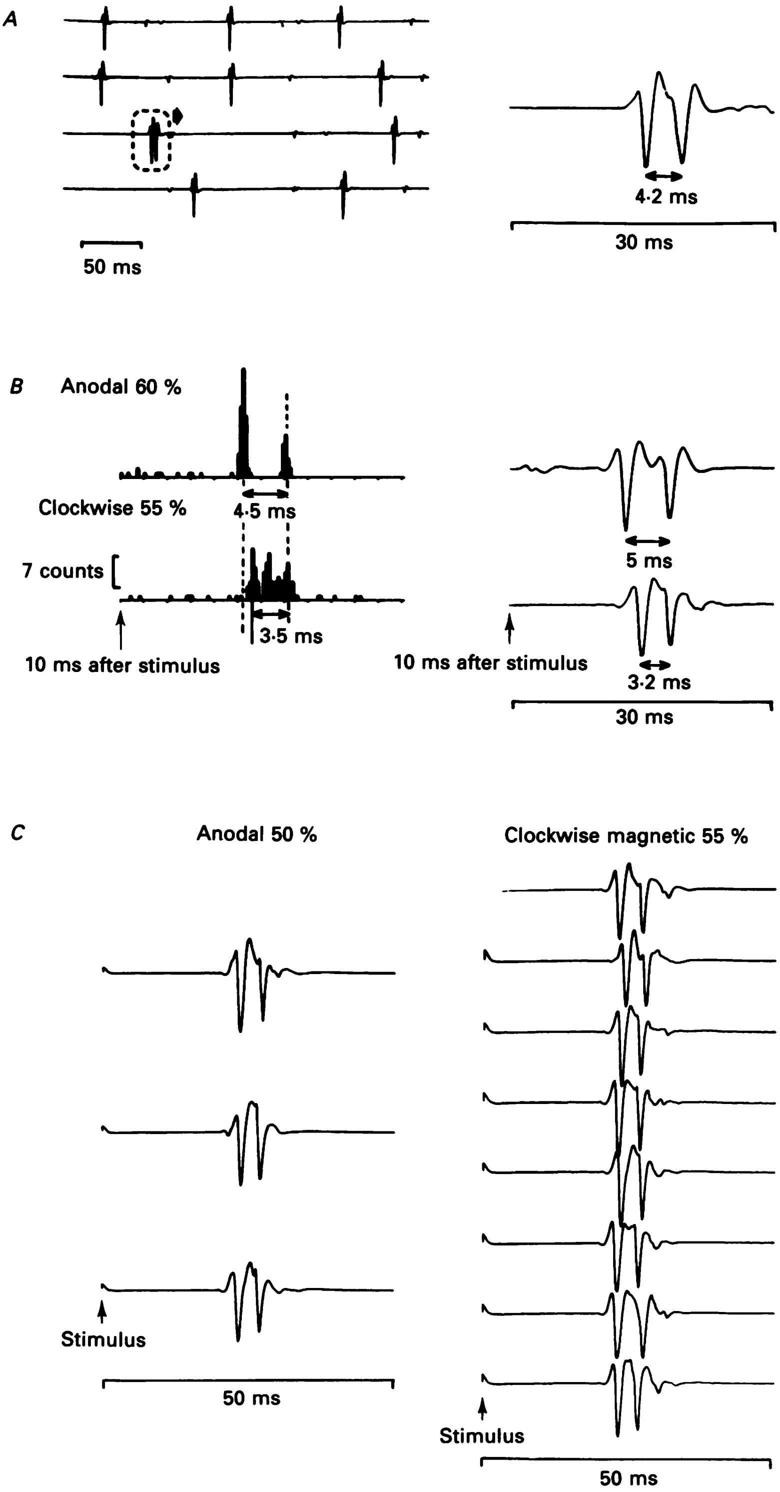

Fig. 7. For legend see facing page.

Surface EMG responses in FDI to different forms of cortical stimulation: relationship of PSTH peaks to surface EMG waveforms

Surface EMG responses in small hand muscles have been analysed in detail previously (Rothwell, Thompson, Day, Dick, Kachi, Cowan & Marsden, 1987; Hess *et al.* 1987; Day *et al.* 1988). The purpose of presenting surface EMG data here is to emphasize the close correspondence between these responses and the single unit responses described above.

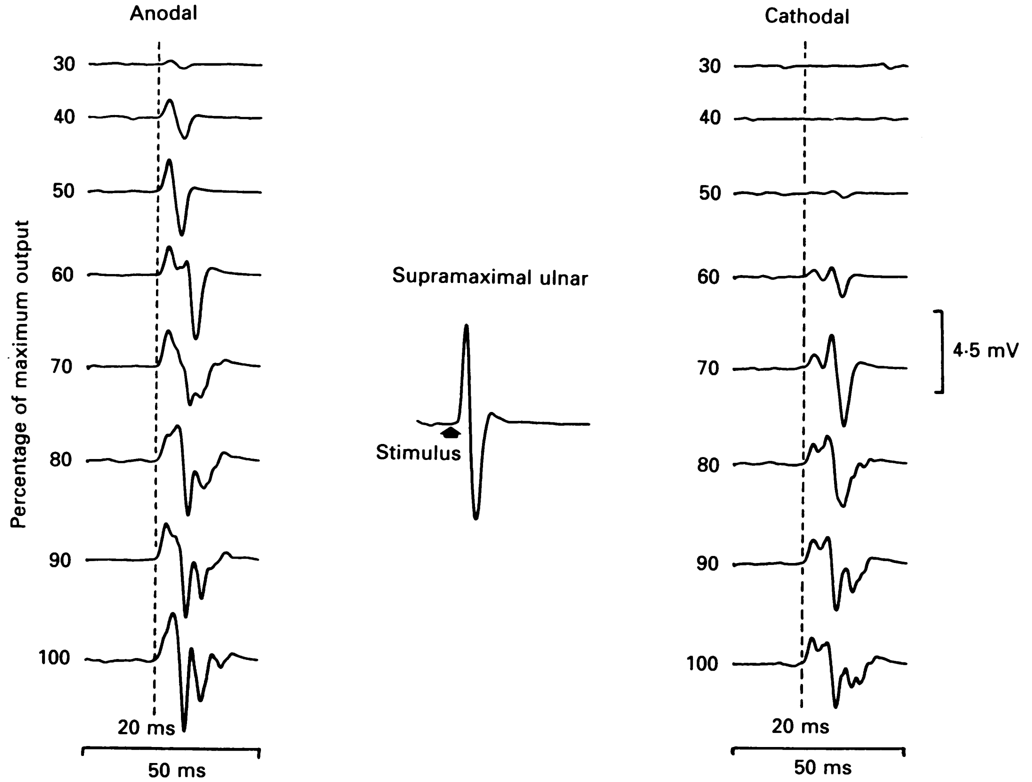

Fig. 8. Comparison of surface EMG responses from FDI following anodal (left column) and cathodal (right column) stimulation at different intensities. The middle trace shows the response to supramaximal stimulation of the ulnar nerve at the wrist. Intensities of cortical stimulation are given as a percentage of the maximum output of the stimulator. Traces are the average of five trials each. Note the more complex, polyphasic responses to just-suprathreshold cathodal stimulation (compare 40 or 50% anodal with 60% cathodal). Note that the low frequency cut-off for these EMG records was 80 Hz, rather than the more usual 0·8 Hz. Inflexions in the trace become clearer when low-frequency components are removed. Dashed vertical line represents 20 ms elapsed time.

Electrical stimulation

In six of seven subjects, the response latency was the same for both anodal and cathodal stimulation, irrespective of intensity. However, there were two differences in the form of the response, as shown for the subject illustrated in Fig. 8. (1) As with the single unit data, the threshold was lower with anodal than cathodal stimulation.

The mean threshold difference between anodal and cathodal stimulation was 21 % of the output of the stimulator (range 10–30 %); (2) the EMG response at just-suprathreshold intensities was longer and more polyphasic when cathodal stimuli were given (compare responses at 60 % cathodal and 40 % anodal). The total duration of the EMG responses at intensities of 25 % above threshold were longer for cathodal than anodal stimulation in five of the subjects (mean (±S.E.M.): anodal duration, 11·1 ± 1·4 ms; cathodal, 15·2 ± 1·5 ms) but where the same at 50 % suprathreshold (anodal, 14·5 ± 1·7 ms; cathodal, 15·5 ± 1·5 ms). This increase in complexity of surface EMG responses mirrors the tendency of cathodal stimuli to produce several peaks of increased firing in the PSTH of single units at low intensities of stimulation.

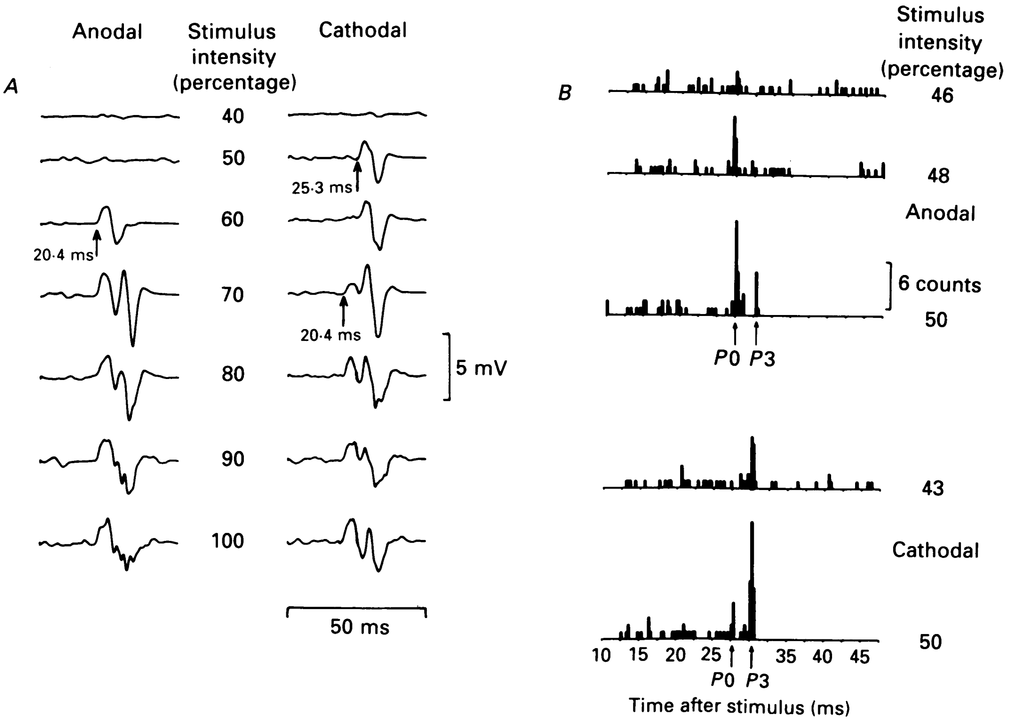

Fig. 9. Surface EMG (*A*) and PSTH data (*B*) from the subject with the anomalous response to cathodal stimulation. His surface EMG responses in FDI (*A*) had a lower threshold to cathodal (right column) than anodal (left column) stimulation, and at just-suprathreshold intensities had a latency some 5 ms longer when cathodal shocks were given. The latency difference disappeared at high intensities. The same behaviour can be seen in the PSTHs recorded from a single unit in the same muscle (*B*). The top three histograms were constructed after different intensities of anodal stimulation; the bottom two after cathodal stimulation. Each histogram begins 10 ms after the stimulus. The threshold for an anodal response was 46 %, whereas a clear peak was visible with a cathodal intensity of only 43 %. The first recruited cathodal peak occurred in the *P*3 interval. At the higher intensity (50 %) a *P*0 peak was visible.

The surface EMG responses were quite different in the subject whose single data also differed from the rest of the group. In this subject, the cathodal threshold for surface EMG responses, as with his single unit data, was lower than the anodal threshold. In addition at low intensities of stimulation the latency of cathodal responses was 5 ms or so longer than that of anodal responses. At moderate intensities, the cathodal latency jumped to equal that of the anodal response (see Fig. 9). The latency change corresponds to the order of recruitment of peaks in the PSTH for this subject (the *P*3 appeared at lower and the *P*0 at higher intensities of cathodal stimulation).

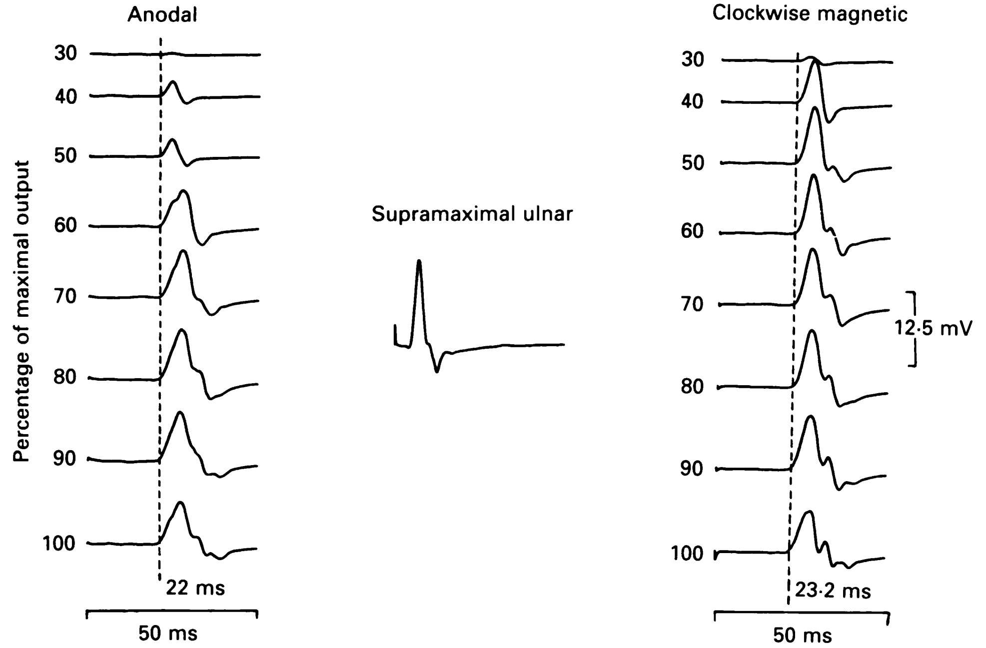

Fig. 10. Comparison of surface EMG responses in FDI to anodal (left column) and clockwise magnetic (right column) stimulation at different intensities. The middle trace shows the response to supramaximal stimulation of the ulnar nerve at the wrist. Intensities are expressed as a percentage of the maximal output of each stimulator. The onset latency was 1·2 ms later when magnetic stimuli were given. Traces are the average of five trials each. Stimuli were given at the start of the sweep in each case.

Magnetic stimulation

Figure 10 compares typical surface EMG responses to anodal and clockwise magnetic stimulation in a single subject; combined data from six subjects is shown in Fig. 11. The main difference between the responses was latency. On average, the latency difference over the intensity range 60 to 80% was 1·7 ms, which is very similar to the latency difference between *P*0 and *P*1 peaks of the PSTH. At higher intensities of stimulation, the average latency difference decreased slightly. The reason for this was that at 90 and 100% the response latency to clockwise magnetic stimulation in some subjects jumped to equal that of anodal stimulation (see also Amassian, Cadwell, Cracco & Maccabee, 1987*a*). This is illustrated for one subject in Fig. 11*D*. Inclusion of these trials in the total data reduced the average latency for magnetic response at high intensity.

Figure 11*C* shows that at most intensities, the duration of the surface EMG was longer when anodal shocks were given. This is comparable to the single unit data showing that the range of unit firing was from *P*0 to *P*3 (i.e. about 5 ms) with anodal stimuli, whereas it was only from *P*1 to *P*3 with clockwise magnetic stimulation. Interestingly, anodal surface responses had a shorter duration at just-suprathreshold intensities, corresponding to the fact that such stimuli give only a *P*0 peak in the PSTH whereas magnetic shocks often rise to multiple peaks at low intensities of stimulation.

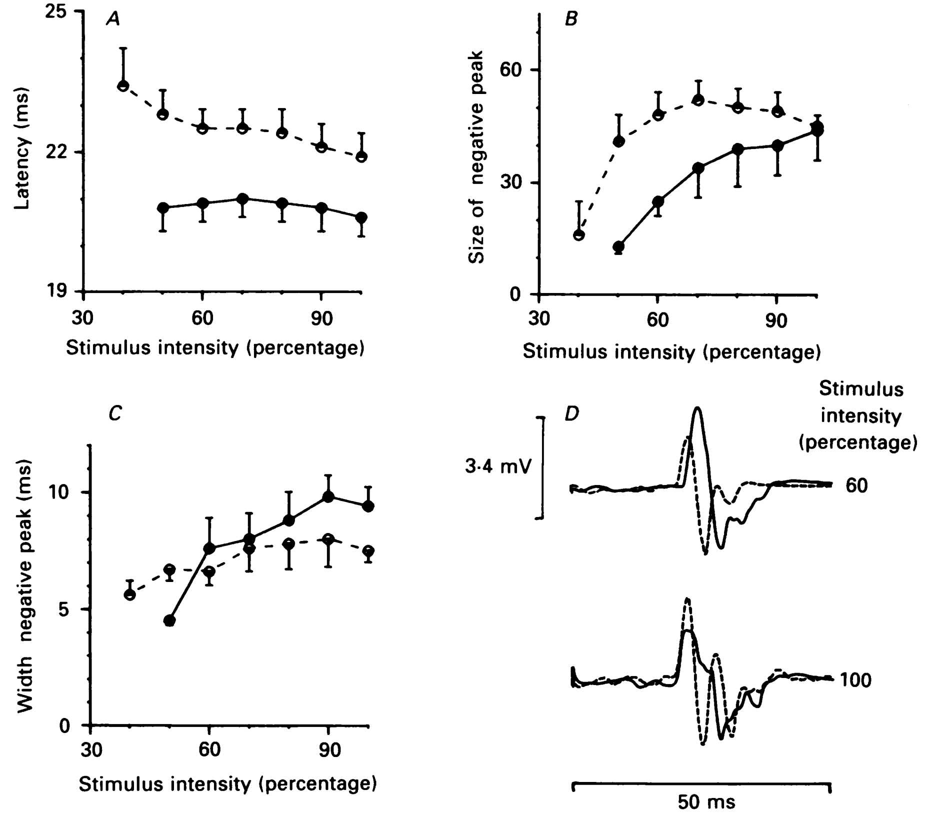

Fig. 11. Comparison of various features of the surface EMG responses in FDI to clockwise magnetic (continuous lines) and anodal (dashed lines) stimulation. Graphs in *A*, *B* and *C* are the average (± 1 S.E.M.) data from five subjects and show the relation with stimulus intensity (abscissa) of: latency (*A*); size of the negative peak, expressed as a percentage of the maximum M wave in FDI following supramaximal stimulation of the ulnar nerve at the wrist (*B*); width of the negative peak from onset to first zero crossing (*C*). *D*, single surface EMG records from one subject at anodal and clockwise magnetic intensities of 60 and 100% of the maximal output of the stimulators. At 60%, the onset latency to anodal stimulation is 1–2 ms later than magnetic; at 100%, the latencies in this subject were equal.

Data comparing surface EMG responses to clockwise and anticlockwise magnetic stimulation have been presented recently (Day *et al.* 1988). The latency difference between surface EMG responses at just-suprathreshold intensities was 3 ms or so, which is comparable with the interval between the *P*1 and *P*3 peaks which are recruited preferentially in PSTHs by similar intensities of stimulation. In the present series we also measured the duration of the negative peak of the surface EMG response in five subjects. At 25 % suprathreshold, the duration of responses following clockwise stimulation was 5·6 ± 0·3 ms, whereas it was only 4·4 ± 0·6 ms following anticlockwise stimulation (Student's paired *t* test, $P < 0.05$). At 50 % suprathreshold, the durations were the same (clockwise, 6·0 ± 0·6 ms; anticlockwise, 5·9 ± 0·3 ms). This data is compatible with single unit results. At just-suprathreshold intensities, clockwise stimulation almost always produced a *P*1 peak and often a *P*2 and/or *P*3 peak. In contrast, anticlockwise stimulation usually evoked only a *P*3 peak. Hence the range of times over which single units might discharge was longer with clockwise stimulation and might therefore have contributed to the wider surface EMG potentials at these low intensities. At higher intensities the difference disappeared.

DISCUSSION

Interpretation of PSTH peaks

The present results confirm previous findings (Calancie *et al.* 1987; Day *et al.* 1987*b*,*c*; Zidar, Trontelj & Mihelin, 1987; Day *et al.* 1988) that a single electrical or magnetic stimulus to the brain can produce multiple peaks of increased firing probability in the PSTH of single motor units. Following the reasoning of Fetz and Gustaffson (1983), who showed that double EPSPs separated in time by some 5 ms can give rise to two separate peaks, we have suggested that the multiple peaks observed in our PSTHs are due to the arrival of several EPSPs at the motoneuronal membrane (Day *et al.* 1987 *b*,*c*). An alternative explanation is that a single long-duration EPSP could have been interrupted by one or more shorter IPSPs. Certainly, stimulation of the motor cortex can give rise to inhibitory postsynaptic potentials (IPSPs) at spinal motoneurones (Landgren, Phillips & Porter, 1962; see also Cowan, Day, Marsden & Rothwell, 1986). In the non-human primate, EPSPs produced by motor cortex stimulation are primarily monosynaptic and can be terminated by the later arrival of disynaptic IPSPs. Such an action would be expected to 'sharpen up' peaks in the PSTH. However, arrival of IPSPs is unlikely to be the sole reason for the existence of multiple peaks in our PSTHs, since under certain conditions it was possible to observe a single late peak at threshold intensities of stimulation with an early peak appearing only at higher intensities. Also, both early and late peaks have relatively similar durations. This is most easily explained on the basis of arrival of two similar EPSPs, but would be difficult to fit into the hypothesis of a single long EPSP.

PSTH peaks following electrical stimulation

Previously it has been suggested (Day *et al.* 1987*b*) that anodal stimulation through the scalp produces effects very like those described for anodal stimulation of the exposed motor cortex of monkeys and apes (see Phillips & Porter, 1977). That is, a single scalp shock gives rise to several descending volleys in the pyramidal tract by direct (D) and indirect (I) activation of the same pyramidal tract neurones (Patton & Amassian, 1954; Kernell & Wu, 1967*a*). These D and I volleys (Patton & Amassian, 1954) generate multiple EPSPs (and IPSPs) in spinal motoneurones

(Kernell & Wu, 1967*b*) which in turn generate multiple peaks in the PSTH of single motor units. Although I volleys show a small amount of temporal dispersion, intracellular recording of the resulting compound EPSP almost always reveal clear inflexions on the rising phase (e.g. Kernell & Wu, 1967*b*, Figs 1–4; Hern, Landgren, Phillips & Porter, 1962, Fig. 6; Jankowska, Padel & Tanaka, 1975*b*, Fig. 10; Clough *et al.* 1968; Fig. 1). These are believed to correspond to arrival of each separate EPSP at the spinal motoneurone. Since the form of the PSTH reflects the differential of the time course of the compound EPSP, these inflexions probably are sufficient to give rise to separate peaks of increased motoneuronal firing probability. Thus our hypothesis is that the *P*0, *P*1, *P*2 and *P*3 peaks correspond to arrival at spinal motoneurones of EPSPs generated by D, I_1, I_2 and I_3 waves in the pyramidal tract.

Anodal stimulation could discharge a single motor unit at times corresponding to the *P*0, *P*2 and *P*3 peaks. According to the hypothesis outlined above, the *P*0 peak would reflect excitation produced by a pyramidal D wave volley. The duration of the *P*0 peak in the PSTH, which is thought, for these large effects, to reflect the rise time of the underlying EPSP (see for example Ashby & Zilm, 1982; Fetz & Gustafsson, 1983), was narrow ($< 1{\cdot}5$ ms). This is similar to the rise time of the group I monosynaptic EPSP in leg motoneurones estimated using the same technique by Mao, Ashby, Wang & McCrea (1984) and is therefore consistent with a monosynaptic connection from cortex to spinal α-motoneurones. The number of counts in the *P*0 peak grew rapidly as the stimulation intensity was raised. At intensities of more than 50% above threshold the size of this peak tended to saturate. Similar saturation of monosynaptic EPSPs was observed by Phillips & Porter (1964) in experiments using intracellular recording from spinal motoneurones in baboons.

The later PSTH peaks were only seen after high intensity anodal shocks and lay in the *P*2 and *P*3 intervals. This would be consistent with the higher threshold of I wave compared with D wave recruitment in acute monkey experiments (Patton & Amassian, 1954). It is of interest that in most cases, it was the *P*3 peak which was recruited first, rather than the *P*2 or *P*1 peak. This fits with Kernell & Wu's (1967*a*) observation that there is a threshold difference amongst I waves. The first I wave to be recruited often was the I_3 wave and only rarely the I_2. The I_1 wave was seen solely at very high intensities. The interval D–I_3 was of the order of 4 ms and the D–I_2 interval about 2·5 ms (see Fig. 5 in Kernell & Wu, 1967*a*). These values approximate those for the *P*0–*P*2 and *P*0–*P*3 interval in our PSTH peaks.

Cathodal stimuli produced multiple peaks in the PSTH of single units at the same latencies as those following anodal stimulation. However, there was one difference between the two forms of stimulation: with cathodal stimuli, the late PSTH peaks generally appeared at a lower intensity relative to the threshold of the early peak. The differences between anodal and cathodal stimulation, therefore, were evident only at intensities close to the threshold for eliciting movement. If the later peaks in the PSTH are produced by EPSPs from I waves in the pyramidal tract, then the fact that these later peaks are recruited at lower intensities (relative to those required to elicit a D wave) by cathodal compared to anodal shocks, is consistent with the known lower threshold for I wave production when cathodal stimuli are applied to the surface of the brain in a monkey (Hern, Landgren, Phillips & Porter 1962).

PSTH peaks following magnetic stimulation

The question arises as to whether the peaks in the PSTH evoked by magnetic stimulation are produced by the same D and I wave mechanism that we suggest is responsible for the electrically evoked peaks. Given that correspondence in timing of peaks does not guarantee correspondence of mechanism, the question must remain open. As a basis for future work we propose the following: the $P1$ PSTH peak produced by *clockwise* magnetic stimulation is due to the arrival of an EPSP from an I_1 volley in the corticospinal tract and the later peaks represent EPSPs released by I_2 and I_3 volleys. Low intensity *anticlockwise* magnetic stimulation recruited only the late P_3 peak in the PSTH without any earlier peaks being evident. This would mean that the currents induced by anticlockwise stimulation at low intensities could produce only an I_3 wave in those pyramidal tract fibres destined for the arm and hand.

Unlike electrical stimulation, therefore, magnetic stimulation of the arm area of motor cortex does not easily produce a D wave (and hence the earliest $P0$ PSTH peak) in the corticospinal tract. Similar results were noted by Amassian, Quirk & Stewart (1987*b*) who recorded the descending volley from the pyramidal tract after magnetic and electrical scalp stimulation in the monkey. They found that magnetic stimulation, with the coil in a position similar to that used in our experiments, failed to produce volleys at a timing corresponding to the anodal D wave. In contrast, waves were seen at timings corresponding to the anodal I waves. Again, it was not clear whether the I waves were produced by the same mechanism when electrical or magnetic stimuli were given, although the implicit assumption was that this was the case.

The finding that a $P3$ peak (I_3 wave) could be obtained on its own with anticlockwise magnetic stimulation excludes the possibility that the I waves are generated by a short reverberating circuit of cortical neurones which produce the synaptic inputs for all I waves in sequence (e.g. Kernell & Wu, 1967*a*). Another possibility is that the I waves might be produced by a single large and long-lasting EPSP at the pyramidal tract neuronal membrane (Phillips, 1987). The neurone would respond to this sustained input by discharging repetitively, due to the intrinsic pacemaker properties of its membrane, at I wave intervals. If the EPSP was rather slow in rising, this might account for the production of a late I_3 wave rather than the I_1 or I_2 waves, although it is difficult to see why this time interval should be relatively fixed within the I_3 (or $P3$, at a motor unit level) interval. Intrinsic noise in the cortex might be expected to make the EPSP rise faster on some occasions than on others, giving a more continuous distribution of initial firing intervals than seen with anticlockwise stimulation. The explanation that we favour is that the I_3 wave is generated via a different chain of cortical neurones to those responsible for the I_1 wave and that these chains are differentially sensitive to clockwise and anticlockwise current flow.

Factors contributing to the differences between electrical and magnetic stimulation

The important result is that the central conduction times from cortex to spinal motoneurones and the threshold to elicit a response depends critically on the type of stimulus used. It appears that the different modes of brain stimulation activated the motor cortex in different ways and that different classes of neurones are preferentially activated by these various stimuli. Some explanation is required as to why this might be the case.

Three major factors influence which neurones are excited by these stimuli (see Ranck, 1975; Phillips & Porter, 1977): (i) The distance of the neurone from the stimulating site and its electrical excitability. (ii) The orientation of the axis of the neurone relative to the lines of stimulating current. A voltage gradient parallel to the long axis of the neurone is the most favourable. (iii) The direction of current flow along these lines relative to the direction of orthodromic propagation of impulses in that neurone. A complicating factor in applying these principles concerns the folding of the cerebral cortex. The orientation of different groups of cortical neurones relative to the skull surface changes continually down the wall and base of the central sulcus. Nevertheless, at threshold intensities when the most striking differences between the various forms of stimuli were evident, all forms of stimulation are likely to activate those neurones nearest the stimulating electrode, that is, those on the convexity of the precentral gyrus. For this restricted region of the motor cortex, the orientation of a given type of neurone is relatively constant, and it is likely that the orientation of the pyramidal tract neurones at this site in man is perpendicular to the skull as it is in the baboon (Phillips & Porter, 1977).

Considering (ii) above, the lines of stimulating current in the brain should be quite different for electrical and magnetic stimulation. Electrical stimulation, with one electrode over the vertex and the other on the side of the head, will have both vertical (i.e. parallel to the long axis of the pyramidal tract neurone) and horizontal (i.e. perpendicular to the long axis of the pyramidal tract neurone) components. For this reason, electrical stimulation, with its vertical component of current flow will favour direct excitation of the pyramidal tract neurone. In contrast, magnetic stimulation probably induces current flow in an annulus under the stimulating coil which is predominantly in the horizontal plane. Accordingly, magnetic stimulation would be best suited for stimulating horizontally oriented neurones within the cortex (such as interneurones, pyramidal tract axon collaterals and afferent axons from cortical and subcortical sites), but not the vertically oriented pyramidal tract neurones. This may explain why, with the coil position used here, we were unable to produce a D wave with clockwise magnetic stimulation. In this respect, magnetic stimulation might be analogous to intracortical stimulation (Landau, Bishop & Clare, 1965; Asanuma & Sakata, 1967; Jankowska, Padel & Tanaka, 1975*a*) in producing synaptic activation of pyramidal tract neurones and I waves in the pyramidal tract.

Palmer & Fetz (1985) have recorded single motor unit PSTHs in forearm muscles following intracortical microstimulation (ICMS) in the monkey. Unlike the present data using magnetic stimulation, single pulse ICMS only appeared to produce a single peak in the PSTHs. In Figs 3 and 4 of Palmer & Fetz (1985), double peaks may have been produced, but these are not as clear as those described in the present paper. This may be because the stimulus employed by Palmer & Fetz (1985) was much weaker than that produced by magnetic stimulation. The amount of PSTH facilitation was barely twice that of background noise and was not followed by any reduction in the on-going motor unit activity, whereas in our experiments, the PSTH peaks often were ten or more times the background firing probability and were followed by a clear silence of the motor unit discharge.

Finally, changing the polarity of the stimulus had important effects (point (iii) above). For example, comparing anodal and cathodal stimulation, the lines of current must remain constant irrespective of polarity, while the direction of current flow will be reversed. According to Phillips and Porter (1977), anodal stimulation would hyperpolarize the dendrites and depolarize the axon of the vertically oriented pyramidal tract neurones and thus be effective in activating these neurones directly at some site along its axon. Cathodal stimulation, in contrast, would tend to depolarize the dendrites of pyramidal tract neurones and hyperpolarize the axon, making conditions less favourable for direct excitation, while depolarization of neurones in more superficial layers of the cortex would favour indirect activation. This may explain why the stimulus intensity required to produce a D wave is greater for cathodal stimulation. A. similar argument may be used to account for the differences between clockwise and anticlockwise magnetic stimulation. At threshold, clockwise stimulation produced a $P1$ peak in the PSTH (I_1 wave) and anticlockwise stimulation a $P3$ peak in the PSTH (I_3 wave) and never a $P1$ peak. Presumably the neurones that are activated to produce a $P1$ peak project in such a direction as to make them preferentially accessible to clockwise current flow in the coil. This difference may also indicate a spatial asymmetry of the afferent inputs to pyramidal tract neurones.

Multiple firing of single motor units

In the majority of instances in which multiple peaks were observed in the PSTH, the unit under study would fire only on one of the possible peaks after a cortical electrical stimulus was given. It has been suggested previously that double firing of some motor units must contribute to the large peak twitch force recorded at high stimulus strengths (see Day *et al.* 1987*b*) although other authors have failed to observe such a phenomenon when studying single motor units (Calancie *et al.* 1987; Hess *et al.* 1987). In the present experiments, motor units sometimes were observed to fire twice on those rare occasions when with high stimulus intensities it was possible to visualize their behaviour without contamination from other nearby units.

At first sight it would seem that a very large input would be needed to make a motoneurone fire twice within an interval as short as 4–5 ms. This may be possible, given the known temporal summation of pyramidal EPSPs at the motoneurone cell membrane (Phillips & Porter, 1964). On the other hand, the simple model may be quite misleading at such short intervals. For example, in man, doublet firing of some, but not all, single motor units can occur relatively frequently even during small, steady, voluntary or reflexive muscle contractions (see Bawa & Calancie, 1983). The reason for this probably relates to the 'delayed depolarization' or the 'post-spike hump' described in cat and rat motoneurones (Kernell, 1964; Nelson & Burke, 1967; Calvin & Schwindt, 1972). In some motoneurones, especially if studied at minimal steady firing rates, each spike is followed by a delayed depolarization of about 3–7 mV, lasting of the order of 2·5–6 ms (Kernell, 1964). In the cat, delayed depolarization summates approximately linearly with Ia EPSPs arriving at the motoneurone (Nelson & Burke, 1967). Similarly, in one carefully studied unit of the present series, the interval between double firing was similar to the interval between peaks in the PSTH. Thus, arrival of a second EPSP, summating with the post-spike hump, may have brought the motoneurone to threshold shortly after the unit had fired its first impulse.

Correlation with surface EMG responses

The FDI muscle is relatively isolated and its surface EMG responses to cortical stimulation can be relatively uncontaminated by other EMG activity, especially if nearby hand muscles are relaxed. Probably because of this, the form of the surface EMG response is well predicted by extrapolation from single unit behaviour. The latency differences, complexity and duration of surface compound EMG responses to electrical and magnetic stimulation all are consistent with single unit behaviour. This observation implies that many of the motor units in the whole muscle behave in the same way as the small sample that have been analysed in this paper.

In conclusion, despite the apparently gross nature of the methods for stimulating the human motor cortex through the intact scalp, it appears that different neuronal elements within the brain can be activated selectively by different forms of stimulation. These differences are most pronounced at just-suprathreshold intensities of stimulation and tend to disappear at high levels. In this paper we have proposed, at least for the FDI muscle, that the data can be most parsimoniously explained using the D and I wave hypothesis of pyramidal neurone activation. To what extent other mechanisms are involved in the segmentation of responses to brain stimulation, and to what extent the responses in other muscles of the body are similar, is as yet unclear. Finally, if our reasoning on the mechanism of action of the magnetic stimulator is correct than it will be clear that the output characteristics of the magnetic stimulator used in these experiments might well influence the responses which are seen.

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REFERENCES

AMASSIAN, V. E., CADWELL, J., CRACCO, R. Q. & MACCABEE, P. (1987*a*). Focal cerebral and peripheral nerve stimulation in man with the magnetic coil. *Journal of Physiology* **390**, 24*P*.

AMASSIAN, V. E., QUIRK, G. S. & STEWART, M. (1987*b*). Magnetic coil versus electrical stimulation of monkey motor cortex. *Journal of Physiology* **394**, 119*P*.

ASANUMA, H. & SAKATA, H. (1967). Functional organization of a cortical efferent system examined with focal depth stimulation in cats. *Journal of Neurophysiology* **30**, 35–54.

ASHBY, P. & ZILM, D. (1982). Relationship between EPSP shape and cross-correlation profile explored by computer stimulation for studies on human motoneurons. *Experimental Brain Research* **47**, 33–40.

BARKER, A. T., JALINOUS, R. & FREESTON, I. L. (1985). Non-invasive magnetic stimulation of the human motor cortex. *Lancet* **ii**, 1106–1107.

BAWA, P. & CALANCIE, B. (1983). Repetitive doublets in human flexor carpi radialis muscle. *Journal of Physiology* **339**, 123–132.

CALANCIE, B., NORDIN, M., WALLIN, U. & HAGBARTH, K. E. (1987). Motor-unit responses in human wrist flexor and extensor muscles to transcranial cortical stimuli. *Journal of Neurophysiology* **58**, 1168–1185.

CALVIN, W. H. & SCHWINDT, P. (1972). Steps in production of motoneuron spikes during rhythmic firing. *Journal of Neurophysiology* **35**, 297–309.

CLOUGH, J. F. M., KERNELL, D. & PHILLIPS, C. G. (1968). The distribution of monosynaptic excitation from the pyramidal tract and from primary spindle afferents to motoneurones of the baboon's hand and forearm. *Journal of Physiology* **198**, 145–166.

COWAN, J. M. A., DAY, B. L., MARSDEN, C. D. & ROTHWELL, J. C. (1986). The effect of percutaneous motor cortex stimulation on H-reflexes in the muscles of the arm and leg in man. *Journal of Physiology* **377**, 333–347.

DAY, B. L., DICK, J. P. R., MARSDEN, C. D. & THOMPSON, P. D. (1986). Differences between electrical and magnetic stimulation of the human brain. *Journal of Physiology* **378**, 36*P*.

DAY, B. L., DRESSLER, D., MAERTENS DE NOORDHOUT, A., MARSDEN, C. D., ROTHWELL, J. C. & THOMPSON, P. D. (1988). Magnetic stimulation of the human brain can activate different neuronal elements when the magnetic field direction is reversed. *Journal of Physiology* **401**, 46*P*.

DAY, B. L., MAERTENS DE NOORDHOUT, A., MARSDEN, C. D., NAKASHIMA, K., ROTHWELL, J. C. & THOMPSON, P. D. (1987*a*). A comparison of the effects of cathodal and anodal stimulation of the human motor cortex through the intact scalp. *Journal of Physiology* **394** 118*P*.

DAY, B. L., ROTHWELL, J. C., THOMPSON, P. D., DICK, J. P. R., COWAN, J. M. A., BERARDELLI, A. & MARSDEN, C. D. (1987*b*). Motor cortex stimulation in intact man. II. Multiple descending volleys. *Brain* **110**, 1191–1209.

DAY, B. L., THOMPSON, P. D., DICK, J. P. R., NAKASHIMA, K. & MARSDEN, C. D. (1987*c*). Different sites of action of electrical and magnetic stimulation of the human brain. *Neuroscience Letters* **75**, 101–106.

FETZ, E. E. & GUSTAFSSON, B. (1983). Relation between shapes of post-synaptic potentials and changes in firing probability of cat motoneurones. *Journal of Physiology* **341**, 387–410.

GANDEVIA, S. C. & ROTHWELL, J. C. (1987). Knowledge of motor commands and the recruitment of human motoneurons. *Brain* **110**, 1117–1130.

HERN, J. E. C., LANDGREN, S., PHILLIPS, C. G. & PORTER. R. (1962). Selective excitation of corticofugal neurones by surface-anodal stimulation of the babbon's motor cortex. *Journal of Physiology* **161**, 73–90.

HESS, C. W., MILLS, K. R. & MURRAY, N. M. F. (1987). Responses in small hand muscles from magnetic stimulation of the human brain. *Journal of Physiology* **388**, 397–419.

JANKOWSKA, E., PADEL, Y. & TANAKA, R. (1975*a*). The mode of activation of pyramidal tract cells by intracortical stimuli. *Journal of Physiology* **249**, 617–636.

JANKOWSKA, E., PADEL, Y. & TANAKA, R. (1975*b*). Projections of pyramidal tract cells to α-motoneurones innervating hind-limb muscles in the monkey. *Journal of Physiology* **249**, 637–667.

KERNELL, D. (1964). The delayed depolarisation in cat and rat motoneurones. In *Progress in Brain Research*, vol. 12, ed. ECCLES, J. C. & SCHADE, J. P., pp. 42–55. Amsterdam: Elsevier.

KERNELL, D. & WU, CHIEN-PING, (1967*a*). Responses of the pyramidal tract to stimulation of the baboon's motor cortex. *Journal of Physiology* **191**, 653–672.

KERNELL, D. & WU, CHIEN-PING, (1967*b*). Post-synaptic effects of cortical stimulation on the forelimb motoneurones in the baboon. *Journal of Physiology* **191**, 673–690.

LANDAU, W. M., BISHOP, G. H. & CLARE, M. H. (1965). Site of excitation in stimulation of the motor cortex. *Journal of Neurophysiology* **28**, 1206–1222.

LANDGREN, S., PHILLIPS, C. G. & PORTER, R. (1962). Minimal synaptic actions of pyramidal impulses on some alpha motoneurones of the baboon's hand and forearm. *Journal of Physiology* **161**, 91–111.

MAO, C. C., ASHBY, P., WANG, M. & MCCREA, D. (1984). Synaptic connections from large muscle afferents to the motoneurons of various leg muscles in man. *Experimental Brain Research* **56**, 341–350.

MARSDEN, C. D., MERTON, P. A. & MORTON, H. B. (1983). Direct electrical stimulation of corticospinal pathways through the intact scalp in human subjects. *Advances in Neurology* **39**, 387–391.

MERTON, P. A. & MORTON, H. B. (1980). Stimulation of the cerebral cortex in the intact human subject. *Nature* **285**, 227.

NELSON, P. G. & BURKE, R. E. (1967). Delayed depolarization in cat motoneurons. *Experimental Neurology* **17**, 16–26.

PALMER, S. S. & FETZ, E. E. (1985). Effects of single intracortical microstimuli in motor cortex on activity of identified forearm motor units in behaving monkeys. *Journal of Neurophysiology* **54**, 1194–1211.

PATTON, H. D. & AMASSSIAN, V. E. (1954). Single and multiple unit analysis of cortical stage of pyramidal tract activation. *Journal of Neurophysiology* **17**, 345–363.

PHILLIPS, C. G. (1987). Epicortical electrical mapping of motor areas in primates. In *Motor Areas of Cerebral Cortex*, ed. BOCK, G., O'CONNOR, M. & MARSH, J. pp. 5–20. London: John Wiley.

PHILLIPS, C. G. & PORTER, R. (1964). The pyramidal projection to motoneurones of some muscle groups of the baboon's forelimb. In *Progress in Brain Research*, vol. 12, ed. ECCLES, J. C. & SCHADE, J. P. pp. 222–242. Amsterdam: Elsevier.

PHILLIPS, C. G. & PORTER, R. (1977). *Corticospinal Neurones: Their Role in Movement*. London: Academic Press.

RANCK, J. B. (1975). Which elements are excited in electrical stimulation of mammalian central nervous system: A review. *Brain Research* **98**, 417–440.

ROTHWELL, J. C., THOMPSON, P. D., DAY, B. L., DICK, J. P. R., KACHI, T., COWAN, J. M. A. & MARSDEN, C. D. (1987). Motor cortical stimulation in intact man. I. General characteristics of EMG responses in different muscles. *Brain* **110**, 1173–1190.

ZIDAR, J., TRONTELJ, J. V. & MIHELIN, M. (1987). Percutaneous stimulation of human corticospinal tract: a single fibre EMG study of individual motor unit responses. *Brain Research* **422**, 196–199.