Journal of Physiology (1990), **425**, *pp.* 283–299
With 10 *figures*
Printed in Great Britain

CORTICOSPINAL VOLLEYS EVOKED BY ANODAL AND CATHODAL STIMULATION OF THE HUMAN MOTOR CORTEX

BY DAVID BURKE, RICHARD G. HICKS AND JOHN P. H. STEPHEN

From the Department of Clinical Neurophysiology, Institute of Neurological Sciences and Department of Orthopaedic Surgery, The Prince Henry and Prince of Wales Hospitals and School of Medicine, University of New South Wales, Sydney 2036, Australia

(*Received 24 November 1989*)

SUMMARY

1. In fifteen neurologically normal subjects, corticospinal volleys evoked by transcranial stimulation of the motor cortex were recorded from the spinal cord using epidural electrodes in the high-thoracic and low-thoracic regions during surgery to correct scoliosis.

2. Anodal stimulation at the vertex produced complex corticospinal volleys that could be recorded at both sites, with multiple waves analogous to the D and I waves documented in animal experiments. These volleys were of higher amplitude when the cathode was 7 cm lateral to the vertex rather than 7 cm anterior. There were no differences in conduction time between the two recording sites for D and I waves, when these waves could be identified at the low-thoracic site.

3. Anodal stimuli of 150 V commonly produced a descending volley containing a single peak at both recording sites. Modest increases in stimulus intensity to 225–375 V produced a peak 0·8 ms in advance of the wave of lowest threshold in thirteen subjects and, in seven subjects, further increases produced an additional peak 1·7 ms in advance of the first-recruited wave. The early peaks increased in size with stimulus intensity, replacing the first-recruited wave. These results suggest that the site of impulse initiation with electrical stimulation of the motor cortex shifts from superficial cortex to deep structures, approximately 5 and 10–11 cm below the cortex. These sites are probably the internal capsule and the cerebral peduncle.

4. With cathode at the vertex and anode over the 'hand area', the response of lowest threshold occurred at the latency of the anodal D wave but could not be recorded at the low-thoracic site, suggesting that it was generated by the anode over the 'hand area'. Slightly higher intensities induced a 'cathodal D wave' and still higher intensities produced late peaks at latencies of anodal I waves. These cathodal D and I waves involved axons innervating lumbar segments. There was no evidence that cathodal stimulation preferentially produced I waves. Cathodal stimulation at the vertex with the anode 7 cm anteriorly produced similar results: D waves were produced at relatively low intensities, but I waves appeared at relatively high stimulus intensities, if at all.

5. It is concluded that the 'D and I waves hypothesis' adequately explains the

EMG responses to anodal stimulation of the leg areas of the motor cortex, although the explanation for latency shortenings with voluntary effort or increased stimulus intensity must take into account different sites of D wave initiation in addition to temporal summation of D and I waves in the target motoneurone pool. The present results do not support the D and I wave hypothesis when the leg areas of motor cortex are stimulated by cathodal pulses delivered through the intact skull.

INTRODUCTION

The motor responses produced by electrical stimulation of the human motor cortex through the scalp have been interpreted on the basis of animal studies in which electrical stimuli were applied directly to the exposed precentral motor cortex (for example, Day, Rothwell, Thompson, Dick, Cowan, Berardelli & Marsden, 1987). In cat, monkey, baboon and man (Patton & Amassian, 1954; Landau, Bishop & Clare, 1965; Kernell & Wu, 1967; Katayama, Tsubokawa, Maejima, Hirayama & Yamamoto, 1988), anodal stimulation of the motor cortex evokes a series of descending waves in the corticospinal tract (see also Lance & Manning, 1954). The wave of lowest threshold and shortest latency (the 'D wave') is produced by direct activation of corticospinal neurones, with impulse initiation presumed to occur at the axon hillock, initial segment or first node of Ranvier (Hern, Landgren, Phillips & Porter, 1962; see also Phillips & Porter, 1977; Amassian, Stewart, Quirk & Rosenthal, 1987). The later waves are of higher threshold and at least some of them result from synaptic activation of corticospinal neurones due to stimulation of cortical interneurones (i.e. indirect activation – hence, 'I waves'). Thus, these waves represent reactivation of the population of corticospinal neurones that participated in the D wave (Kernell & Wu, 1967), rather than volleys in more slowly conducting axons, and as a result I waves may be suppressed by tetanic stimulation of the cortex (Lance & Manning, 1954).

The threshold current required to activate corticospinal axons is higher for cathodal stimulation than anodal stimulation (see Phillips & Porter, 1977). Theoretically, the direction of current flow produced by cathodal stimulation in a vertically oriented population of corticospinal neurones would favour hyperpolarization in the region of the axon hillock, preventing D wave generation, while exciting superficial horizontal layers of the cortex and hence favouring transsynaptic activation of corticospinal neurones (Phillips & Porter, 1977; Amassian *et al.* 1987). Accordingly, Day, Dressler, Maertens de Noordhout, Marsden, Nakashima, Rothwell & Thompson (1989) have recently presented indirect evidence that cathodal stimulation of the human motor cortex at low intensity preferentially generates I waves in corticospinal neurones while anodal stimulation preferentially generates D waves.

Direct stimulation of the motor cortex using a ball electrode applied to the pia differs from stimulation through skin and bone, as is necessary in intact human subjects. Given the convolutions of the cortex it is likely that many corticospinal neurones will not be oriented vertically to the scalp surface, and the relevance of the 'D and I wave hypothesis' to studies on intact human subjects is open to conjecture. Nevertheless, two lines of evidence support the applicability of this

model to the human situation. Firstly, a limited number of recordings made from the human spinal cord during spinal surgery have demonstrated presumed D and I waves in response to stimulation of the motor cortex through the scalp (Boyd, Rothwell, Cowan, Webb, Morley, Asselman & Marsden, 1986; Pelosi, Caruso & Balbi, 1988; Inghilleri, Berardelli, Cruccu, Priori & Manfredi, 1989). Secondly, the different responses evoked by anodal and cathodal electrical stimulation and by clockwise and anticlockwise magnetic stimulation can be adequately explained using the D and I wave hypothesis (Day *et al.* 1987, 1989).

The present study addresses the site of stimulation of corticospinal neurones as stimulus intensity is increased using anodal and cathodal stimulation of the leg area of the motor cortex. Corticospinal volleys evoked by stimulation of the human motor cortex through the scalp were recorded from the spinal cord during spinal surgery on neurologically normal patients. The results indicate that, while the D and I wave hypothesis is adequate for anodal stimulation, it is probably not so for cathodal stimulation of the leg area. With modest increases in stimulus intensity the site of impulse initiation for the D wave moves deeper in an apparently stepwise manner, suggesting that the scalp stimulation preferentially accesses specific deep structures some 5 or 10 cm below the cortex.

METHODS

Recordings were obtained as part of neurophysiological monitoring of spinal cord function in fifteen neurologically normal patients undergoing Cotrel-Dubousset instrumentation for congenital or idiopathic scoliosis. Fourteen of the patients were aged 11–21 years and the fifteenth was aged 67. All patients but one were female. Informed consent was obtained from the patient and/or parents for the operation and the neurophysiological procedures.

The patients were anaesthetized with a mixture of nitrous oxide and oxygen supplemented by halothane or isoflurane, paralysed using pancuronium and artificially ventilated. They lay prone throughout the operation. Recordings were made from the high-thoracic and low-thoracic regions using electrodes inserted into the epidural space after adequate operative exposure. The electrodes were inserted through the posterior interspinous ligament into the epidural space over the posterior surface of the spinal cord, passed cephalad for a few centimetres and secured in position by a suture. In seven patients a monopolar recording was made from the high-thoracic region, using a reference electrode inserted into the paraspinal muscles. The recording from the low-thoracic region was made using a bipolar epidural electrode (interelectrode distance 2·5 cm). In the remaining patients a bipolar electrode was also used at the high-thoracic site. The largest part of the cervical enlargement of the spinal cord is at the level of the fifth and sixth vertebrae: the high-thoracic electrode was usually just caudal to this level. The lumbar segments of the adult human spinal cord lie opposite the tenth and eleventh thoracic vertebrae: the low-thoracic electrode was at this level.

The motor cortex was stimulated using two silver–silver chloride cup electrodes cemented to the cleaned but otherwise unprepared scalp with collodion and filled with electrode gel. Routinely, the anode was placed at the vertex and the cathode 7 cm lateral to the vertex. In this position anodal stimulation at the vertex would excite the regions of the motor cortex supplying mid-line truncal and leg areas (e.g. Gandevia & Rothwell, 1987; Rothwell, Thompson, Day, Dick, Kachi, Cowan & Marsden, 1987; Gandevia, 1989). Anodal stimulation at the lateral electrode would activate one of the upper limb areas of the motor cortex (e.g. Day *et al.* 1987, 1989; Rothwell *et al.* 1987). Electrical stimuli were delivered using an isolated stimulator with low output impedance (Digitimer, D180A; Welwyn Garden City, Herts), capable of delivering a capacitatively coupled discharge of up to 1500 V through a time constant of 50 or 100 μs. In ten subjects, the time constant was 50 μs, in four it was 100 μs and, in one subject, both were used. Qualitatively similar results were obtained with the two time constants. In the present study, stimulus voltage did not exceed 750 V. Calibration testing on the D180A confirmed a linear relationship between the stimulus level as indicated by the

intensity dial and the stimulus actually delivered by the D180A. The mean rise time of the pulses delivered by the stimulator was 5·5 μs. The stimulator was triggered manually, at a rate not exceeding once every 3 s.

In addition, in all experiments, both tibial nerves were stimulated simultaneously in the popliteal fossae using the two isolated stimulators of a microprocessor-based EMG/Evoked Potential machine (Medelec MS92B, Old Woking, Surrey). The intensity of these peripheral nerve stimuli was supramaximal for the antidromic nerve action potential recorded at the ankle. The ascending somatosensory volley was recorded from the spinal cord using the same epidural electrodes. The somatosensory stimuli were delivered either in sequences separate from the motor cortical stimuli or simultaneously with the motor cortical stimuli. In the latter case the stimulators and averaging sweep of the MS92B were triggered by the Digitimer.

The evoked epidural volleys were amplified, filtered, monitored and averaged, using automatic artifact rejection. The sweep duration was 10 or 20 ms (sampling rate 50 or 25 kHz) for each channel. The technique of exponential averaging was used routinely so that a continuously updated average was available for monitoring purposes. Six bandpass filter settings were available, using four high-pass filters: 2, 20, 200 and 500 Hz. To define the descending corticospinal volleys, duplicate averages of ten to twenty-five responses were recorded. This was also usually sufficient to define the ascending somatosensory volley when both the motor cortical and peripheral nerve stimuli were delivered simultaneously. When the somatosensory stimuli were delivered in isolation, duplicate averages of thirty-two to sixty-four sweeps were recorded.

Throughout this paper, the term 'D wave' is applied to the peak of lowest threshold using anodal stimulation at the vertex. Earlier peaks appearing at higher threshold are referred to as part of the 'D wave complex'. Consistent peaks occurring at longer latency than the D wave are referred to as 'I waves'. Latencies were measured from stimulus delivery to the onset of the corticospinal volley (defined as the onset of the first negative deflection) and to the peaks of each subsequent negative wave. These measures are referred to as onset latency and peak latency. Of necessity, only peak latencies were measured for I waves.

RESULTS

The routine configuration of the stimulating electrodes, used in all fifteen subjects, was anode at the vertex with cathode 7 cm lateral to the vertex. The maximal stimulus levels used in different subjects were between 375 and 750 V, and with these intensities descending corticospinal volleys could be recorded in all fifteen subjects. At the high-thoracic level, the evoked corticospinal volley consisted of up to seven or eight separate peaks in each subject, the peak-to-peak amplitude of the D wave complex being 6–74 μV (mean 25 μV). In fourteen of the fifteen subjects, an evoked corticospinal volley was recorded at the low-thoracic level but it was smaller than the volley at the high-thoracic level in each subject, on average by a factor of 3:1 ($P = 0{\cdot}001$; two-tailed t test for paired data). In two of the fifteen subjects, the corticospinal volley was of low amplitude (1·5 μV) at the low-thoracic site. The inability to record a distal volley in one subject and the low amplitude in two additional subjects probably resulted from a relatively caudal placement of the epidural electrode. In the remaining twelve subjects, the evoked volley at the low-thoracic electrode consisted of two to seven separate peaks, the maximal amplitude of the initial components being 4–20 μV (mean 9·8 μV). In two subjects stimulus artifact obscured the onset of the corticospinal volley at the high-thoracic electrode even when low stimulus intensities were used, and in these subjects relevant latencies were measured to the negative peaks of the components.

Particularly with high stimulus intensities and with the 100 μs time constant, stimulus artifact obscured the onset of the evoked volley when the high-pass filter was 20 Hz. In four subjects in whom the onset of the corticospinal volley could be

clearly defined using the 20 Hz filter, the effects of different bandpass settings on the evoked volley were studied (Fig. 1). When the high-pass filter was raised from 20 to 200 Hz, the onset latency of the potential decreased by on average 0·3 ms but there was no further shift when the high-pass filter was increased to 500 Hz. There were

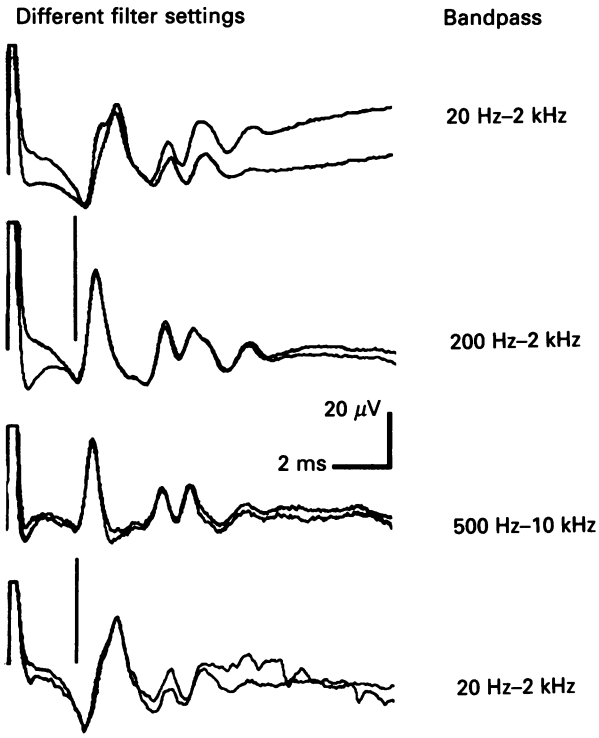

Fig. 1. The effect of different filter settings on corticospinal volleys evoked by a vertex–anodal stimulus of 450 V (time constant 50 μs), recorded at the high-thoracic site. Duplicate averages of twenty-five responses are superimposed for each bandpass filter setting. The cathode was 7 cm lateral to the vertex.

more prominent changes in the peak of the initial negative component of the volley, with the latency to peak decreasing by 0·7 ms when the 200 Hz high-pass filter was introduced, and by an additional 0·1 ms when the 500 Hz filter was introduced. With the 500 Hz filter, different components were more readily identified with fewer sweeps in the average. As a routine, the bandpass adopted for the present study was therefore 500 Hz–10 kHz.

D wave complex

With anode at the vertex and cathode 7 cm laterally, motor cortex stimulation at relatively low intensities (usually 150 V) evoked a descending volley containing a single peak with a mean latency to peak of 4·0 ms (S.D. 0·77 ms) at the high-thoracic electrode (Figs 2–4). This peak was termed the 'D wave'. In thirteen subjects, modest increases in stimulus intensity (to only 225–375 V in eleven of the thirteen) shortened the latency of onset of the D wave complex due to the appearance of an earlier peak. With further increases in stimulus intensity, this earlier peak increased

in size, and the peak of lowest threshold usually decreased in size. In two subjects the early high-threshold wave completely replaced the D wave of lowest threshold (Fig. 2; see also Figs 9 and 10 for similar results using an anteriorly placed cathode). In seven subjects, stimulus intensities of 375–600 V recruited a third peak to the D

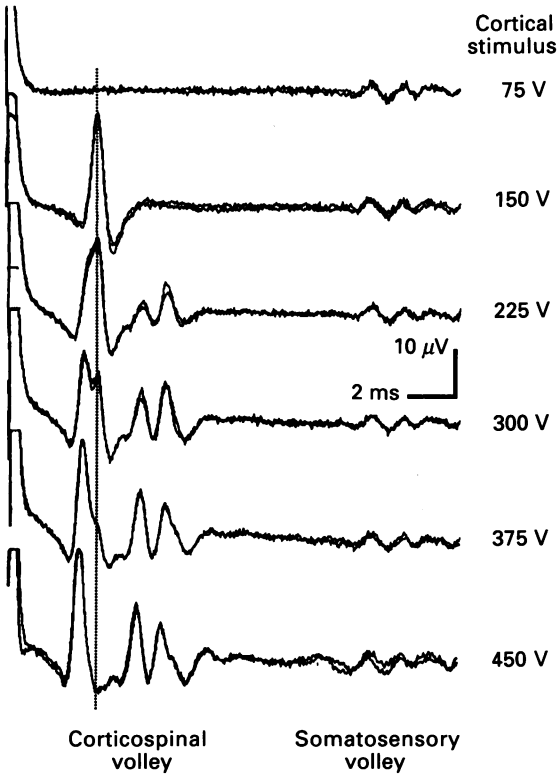

Fig. 2. The effect of increasing stimulus intensity (time constant 50 μs) on the corticospinal volley recorded at the high-thoracic site. Electrode configuration: anode at vertex, cathode 7 cm lateral to vertex. Duplicate averages of twenty-five sweeps are superimposed for each stimulus intensity. The low-amplitude polyphasic deflection to the right of each trace represents the ascending somatosensory volley set up by bilateral stimulation of the tibial nerves in the popliteal fossae. The cortical and somatosensory stimuli were delivered simultaneously, at the onset of the sweeps. The dotted vertical line indicates the D wave. Note that this peak is completely replaced at 450 V by an earlier peak that began to appear at 225 V.

wave complex, resulting in further shortening in the latency of onset of the complex (Fig. 3, see also Figs 7 and 9). The appearance of second or third peaks in the D wave recorded at the high-thoracic site was paralleled by the appearance of comparable peaks at the low-thoracic site (Fig. 4; see also Figs 6 and 9), indicating that the early high-threshold peaks were directed to the lower limbs, and were not some peculiar artifact due to cathodal stimulation of the hand area. The shortening in latency at the high-thoracic electrode was paralleled by a comparable shortening of latency at the low-thoracic electrode (Fig. 4), indicating that similar populations of corticospinal axons were responsible for the multiple peaks in the D wave complex. The disappearance of the D wave of lowest threshold in two subjects (Figs 2 and 9) and the

decrease in amplitude of this wave in other subjects (see, for example, Fig. 7) suggest that the same population of corticospinal axons was stimulated at a lower level when high stimulus intensities were used.

As illustrated in Figs 3 and 5, the second peak recruited into the D wave preceded

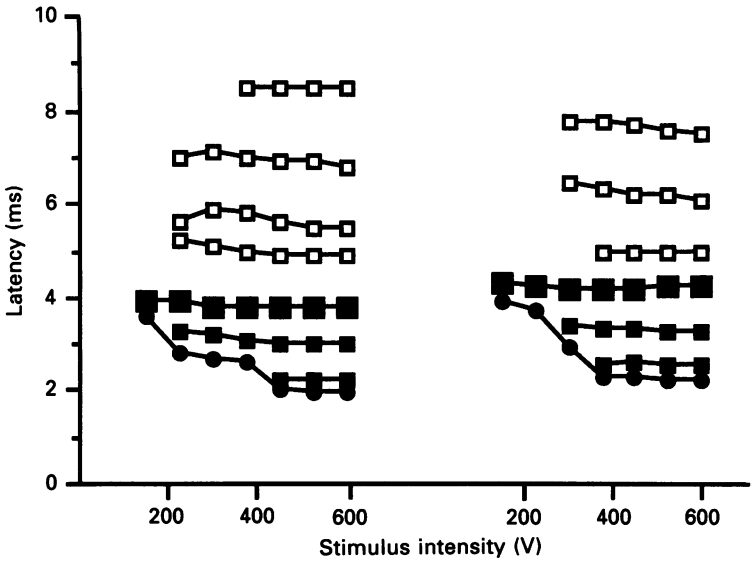

Fig. 3. The effect of increasing stimulus intensity (time constant 50 μs) on the latencies of different components of the corticospinal volley recorded at the high-thoracic level in two subjects (anode at vertex; cathode 7 cm lateral to vertex). Stimuli at 75 V failed to evoke a corticospinal volley in either subject. The onset latency of the corticospinal volley is indicated by ●. The peak latency of the wave of lowest threshold (the D wave) is indicated by large filled squares, and the earlier negative peaks of higher threshold in the D wave complex by small filled squares. The peak latencies of presumed I waves are indicated by □.

the first by, on average, 0·8 ms. The third peak, recruited into the D wave complex at relatively high intensities, occurred an additional 0·9 ms in advance of the second peak. The shortening of latency of the D wave complex as stimulus intensity increased occurred relatively abruptly in some subjects, almost in a stepwise manner, as additional peaks were recruited into the complex (Fig. 3). In other subjects, latency shortened as the late-recruited peaks emerged from the original D wave (Fig. 4) but then stabilized at a constant interval in advance of the original D wave.

I waves

With cortical stimulation using the anode at the vertex and cathode 7 cm laterally, the D wave complex at the high-thoracic electrode was followed by a series of smaller peaks, presumably 'I waves', on average, three in the first 5 ms following the D wave (Figs 2 and 5). In nine subjects, comparable peaks could be recognized at the low-thoracic electrode and followed the initial (D wave) complex by comparable latencies (Fig. 6). However, not all deflections at the two recording sites could be matched, presumably because some axons terminated between the two recording sites.

The interval between successive I waves was approximately 1 ms (Fig. 5). The

latency to peak of the I waves remained relatively constant as stimulus intensity was raised, generally varying by < 0·2 ms (Figs 2 and 3). The first deflection occurred within 1·5 ms (mean 0·94 ms) of the lowest-threshold component of the D wave complex and was seen in all subjects (Fig. 5). It was usually one of the first late waves to appear as stimulus intensity was increased (Fig. 3, left and Fig. 7) but this was not so in all subjects (Fig. 3, right). Its size varied in different subjects from a small but consistent deflection (Fig. 2) to a major peak (Fig. 7).

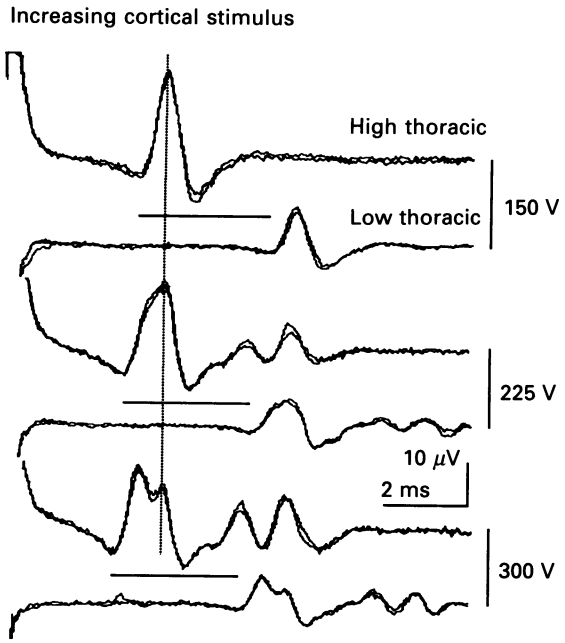

Fig. 4. The effect of increasing stimulus intensity on the conduction time between the high-thoracic and low-thoracic recording sites (anode at vertex; cathode 7 cm lateral to vertex; time constant 50 μs). Same subject as in Fig. 2. At 150 V, a single peak is seen at the high-thoracic and low-thoracic sites. At 225 V the D wave at both sites is distorted by an earlier peak which is better seen at 300 V. I waves are visible at 225 V at both recording sites and are more distinct at 300 V. The dotted vertical line indicates the peak of the initial D wave. The horizontal lines indicate the conduction time between the two recording sites for the onset of the volley.

In ten subjects a sufficient range of stimulus intensities was used to allow measurement of the absolute and relative thresholds for different I waves. The mean stimulus intensity (±S.D.) at which I waves appeared were: I_1, 375±132 V ($n = 10$); I_2, 420±133 V ($n = 10$); I_3, 466±123 V ($n = 9$); I_4, 488±97 V ($n = 4$). For each I wave, there was a wide range of threshold intensity: for I_1 and I_2, 225–600 V; for I_3, 300–675 V. In five subjects the thresholds for I_1 and I_2 were the same. In four subjects, I_1 had the lowest threshold of all four waves, and in one subject, I_2 had the lowest threshold. Analysis of variance revealed a significant difference in threshold for different I waves in the ten subjects ($P = 0{\cdot}0014$). The thresholds for I_1 and I_2 were not significantly different, but the thresholds for I_3 and I_4 differed from those for I_1 and I_2 in the same subjects at the 5% level.

Vertex anodal stimulation with different cathodal sites

In three subjects stimuli were delivered with the anode at the vertex and with the cathode 7 cm lateral and, in a separate sequence, 7 cm anterior to the vertex. In each subject the amplitude of the evoked D wave at all stimulus intensities between 150

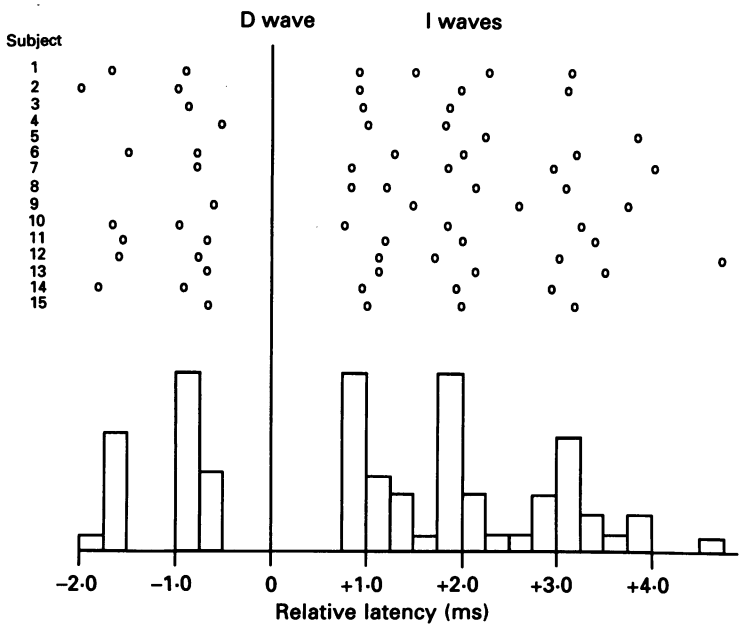

Fig. 5. The latency of the various peaks in the corticospinal volleys of each subject, expressed relative to the initial D wave (for each subject, anode at vertex; cathode 7 cm lateral). For each subject, the most complex reproducible volley has been measured, usually that obtained with the most intense stimulus (range 375–600 V). The initial peaks in the D wave complex fall into two latency distributions 0·8 and 1·7 ms in advance of the D wave. The late waves, termed I waves, are more variable, but the histogram (bin width 0·25 ms) indicates a sequence of peaks with means of 1·0, 2·0, 3·1 and 3·8 ms for the intervals 0·5–1·5, 1·5–2·5, 2·5–3·5 and 3·5–4·5 ms, respectively. Consistent late waves with latencies longer than 5 ms have not been plotted.

and 600 V was smaller with the anteriorly situated cathode and the amplitude and number of I waves were less. The amplitude of the largest component of the D wave complex at the high-thoracic level was on average 10 μV with the anterior cathode and 30 μV with the lateral cathode. Similar differences were seen in the low-thoracic recording.

Cathodal stimulation at the vertex

In six subjects the polarity of the stimulating leads was reversed so that cathodal pulses were delivered at the vertex, the anode being 7 cm lateral (over the 'hand area'). Such stimuli activated corticospinal volleys, some of which were directed to the lower limbs (Fig. 6). The amplitudes of the D wave components were between one-third and one-half of those produced by anodal stimulation, but the volleys were as complex and most of the components occurred at similar latencies.

The threshold for corticospinal volleys was the same as that for vertex–anodal stimulation (212 ± 74 V; $n = 6$), and the threshold volleys had the same latency (Fig. 7). However, the volley evoked with the cathode at the vertex was of lower amplitude and could not be recorded at the low-thoracic region (Fig. 8*A*), possibly

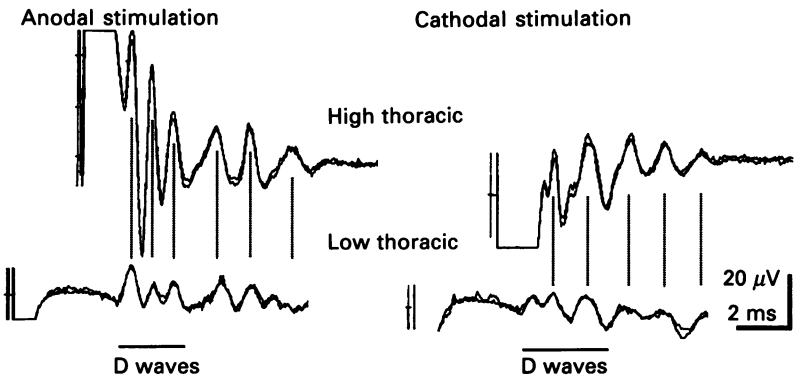

Fig. 6. Conduction times for the corticospinal volleys set up by anodal and cathodal stimulation at the vertex between the high- and low-thoracic recording sites. Stimulating electrodes at vertex and 7 cm lateral to vertex (time constant 50 μs). Stimulus intensity 600 V. The volleys have been aligned according to corresponding peaks, because stimulus artifact distorts the latency of onset. With anodal stimulation the initial three peaks represent the D wave complex. The subsequent two I waves correspond well, but the third I wave at the high-thoracic site cannot be matched with an equivalent wave at the low-thoracic site. With cathodal stimulation there is good matching between individual peaks at the two recording sites, allowing for stimulus artifact interfering with the definition of the first peak at the high-thoracic level. The first three peaks represent the D wave complex. The last three peaks represent I waves.

because it was initiated by anodal stimulation over the 'hand area'. With stronger stimuli, the 'cathodal D wave' became broad with a dominant peak 0·2–0·6 ms later than the equivalent peak recorded when the anode was at the vertex (Fig. 8*B*, left; see also Fig. 9). As with vertex–anodal stimuli, the presumed D wave complex contained early peaks that grew with stimulus intensity to dominate the D wave complex. By contrast with the first-recruited 'D wave', these earlier waves occurred at the same latency whether the anode or the cathode was at the vertex. As shown in Fig. 6, these earlier components of the presumed D wave complex propagated to the low-thoracic region.

There was no evidence that cathodal stimulation preferentially generated late waves with latencies comparable to the I waves of vertex–anodal stimulation. I waves did appear with higher stimulus intensities than required for the D wave (Fig. 7), at similar latencies as with vertex anodal stimulation (Fig. 8*B*, right panel), and conducted over the thoracic region with the same velocities as the early waves (Fig. 6, right panel). Although the cathodal D wave complex was less intense than the anodal D wave complex, cathodal I waves were often of similar amplitude to anodal I waves. In these six subjects, the evoked I waves were not necessarily the same as with anodal stimuli although I_1 could be recorded in all subjects. There was a significant difference ($P = 0{\cdot}0335$; two-tailed t test for paired data) in the thresholds

for I waves with anodal and cathodal stimulation: anodal required a mean intensity of 400 ± 155 V; cathodal a mean intensity of 488 ± 205 V.

These results suggest that the responses of lowest threshold were generated under the anode whether that electrode was at the vertex or over the 'hand area', and

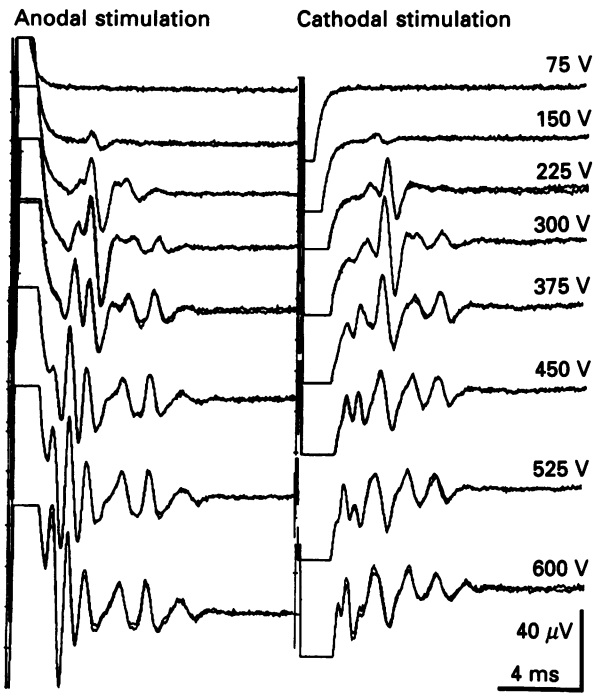

Fig. 7. The effects of increasing intensity of anodal and cathodal stimulation at the vertex on the corticospinal volley recorded at the high-thoracic site. Stimulating electrodes at vertex and 7 cm lateral to vertex (time constant 50 μs). Same subject as in Fig. 6. With vertex–anodal stimulation, the D wave appears at 150 V, but with increasing stimulus intensity, earlier peaks emerge and come to dominate the D wave complex. With vertex–cathodal stimulation (anode over the 'hand area') a D wave is recorded at 150 V, but at 225 V, the D wave complex consists of two peaks, the largest of which occurs 0·2 ms later than the D wave at 150 V. With cathodal stimulation, consistent I waves do not appear until stimulus intensity reaches 300 V.

therefore that the sites of impulse initiation were relatively superficial. Slightly stronger stimulus intensities evoked a 'cathodal D wave' directed to lumbar segments, at longer latency than the 'anodal D wave', presumably reflecting a different but still relatively superficial site of impulse initiation. With further increases in stimulus intensity, the short-latency high-threshold components of the D wave complex appeared with both vertex–anodal and vertex–cathodal stimulation, at similar short latencies, presumably initiated at similar deep subcortical sites.

Anodal and cathodal stimulation using electrodes at vertex and 7 cm anterior

To eliminate the stimulation of upper limb areas of the motor cortex, the effects of vertex–anodal and vertex–cathodal stimulation were compared in three subjects

using electrodes at the vertex and 7 cm anterior to the vertex (Figs 9 and 10). The low-threshold non-propagating D wave due to anodal stimulation of the 'hand area' was not seen when the anode was anterior to the vertex, but otherwise the results were similar. In the three subjects, stimulus intensities were raised from 75 to 675 V

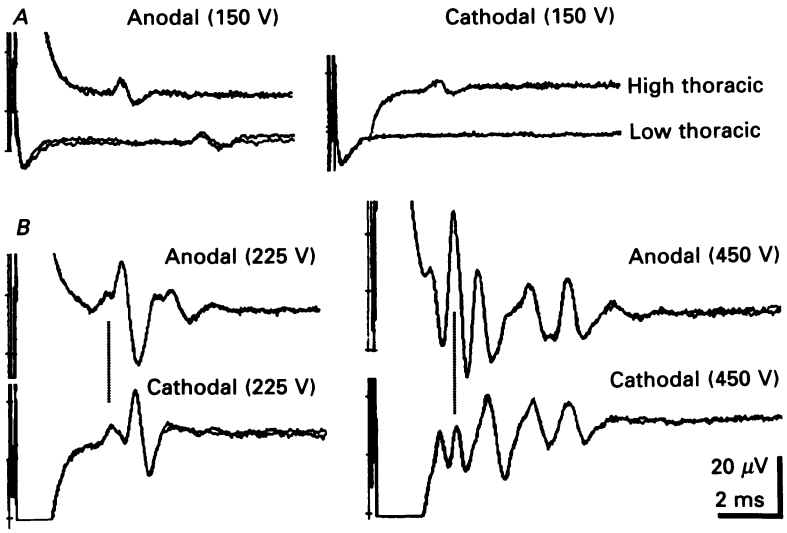

Fig. 8. Contrasting effects of anodal and cathodal stimulation at the vertex. Stimulating electrodes at vertex and 7 cm lateral to vertex (time constant 50 μs). Same subject as in Fig. 7. *A*, anodal stimulation at 150 V produces a D wave that conducts to the low-thoracic site, but cathodal stimulation at 150 V (anode over the 'hand area') produces a D wave that does not propagate to the low-thoracic level. The latencies of the waves at the high-thoracic site are identical. *B*, the volleys recorded at the high-thoracic level using anodal and cathodal stimulation at 225 and 450 V are aligned. In the left panel, the latency of the major peak in the D wave complex with cathodal stimulation is 0·2 ms longer than the latency of the major peak with anodal stimulation, but the earlier peak in the complex has the same latency. Note that I waves are produced by anodal but not cathodal stimulation. At 450 V, stimulus artifact distorts the initial peak in the D wave complex with anodal and cathodal stimulation, but the second peaks have the same latency. The third peaks (corresponding to the dominant peaks with the 225 V stimuli) have different latencies. The I waves produced by anodal and cathodal simulation have similar latencies.

in 75 V increments. Anodal and cathodal stimulation at 675 V produced a D wave complex containing two or three peaks, the earliest of which was obscured by stimulus artifact in the high-thoracic recording (Figs 9 and 10). The thresholds for the D waves were 150–300 V, and were slightly higher for two of the three subjects with vertex cathodal stimuli (150 V for anodal and 225 V for cathodal in Fig. 10; 225 V for both in Fig. 9; 225 V for anodal and 300 V for cathodal in the third subject). The cathodal D wave was broad, almost bifid, and of lower amplitude than with anodal stimulation at least when the intensity of the stimulus was low (Figs 9 and 10). The first subcomponent of the bifid peak was produced by threshold stimulation, and occurred at the latency of the anodal D wave. However with modest increases in stimulus intensity the later subcomponent of the D wave became dominant. With cathodal stimulation, I waves were not detectable at either

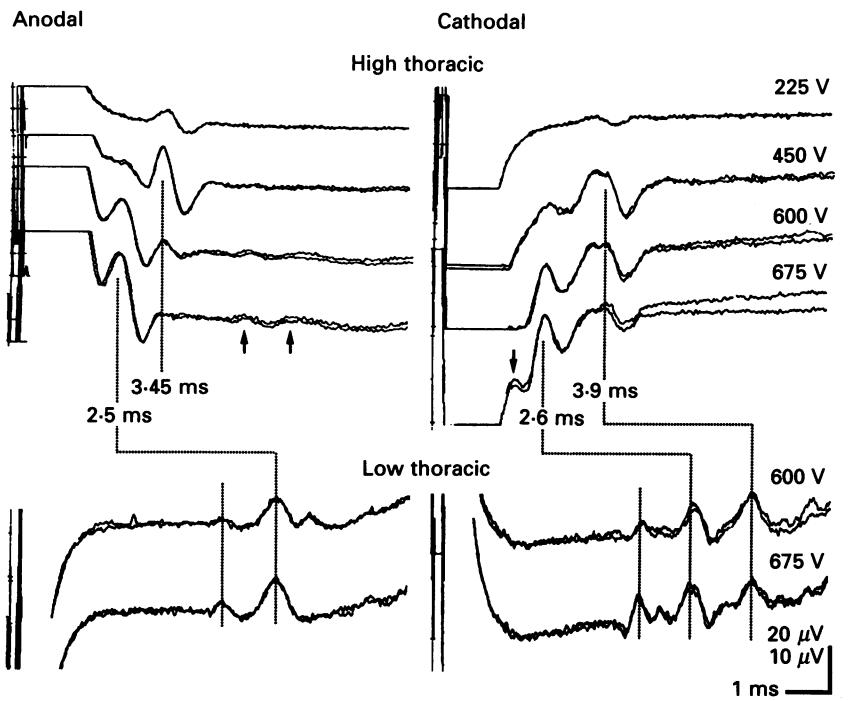

Fig. 9. Contrasting effects of vertex–anodal and vertex–cathodal stimulation using electrodes at the vertex and 7 cm *anterior* to the vertex (stimulus time constant 50 μs). Both forms of stimulation activate corticospinal axons innervating lumbar segments. At 150 V, neither anodal nor cathodal stimulation produced a recordable volley. With increasing stimulus intensity, both anodal and cathodal, the D wave complex develops peaks in advance of the initial D wave and, with anodal stimulation, these peaks completely replace the initial D wave at 675 V. Stimulus artifact obscures the earliest peak of the D wave complex at the high-thoracic site, particularly with anodal stimulation, but not at the low-thoracic site. I waves (upward vertical arrows) were seen with anodal stimulation at 600 V but cannot be identified with cathodal stimulation at 675 V. Downward vertical arrow with cathodal stimulation indicates the earliest peak of the D wave complex. With anodal stimulation, artifact obscures the comparable peak at the high-thoracic site.

recording site in two subjects although anodal stimuli produced I waves (see Fig. 9). In the third subject I waves appeared at a relatively modest stimulus intensity, but these stimuli also produced a high-threshold early wave in the D wave complex (see vertical arrow in Fig. 10).

DISCUSSION

The present results suggest that, while anodal stimulation at the vertex evokes D and I waves analogous to those documented in animals (Patton & Amassian, 1954; Landau *et al.* 1965; Kernell & Wu, 1967), the site of initiation of D wave shifts from superficial site within the cortex to deep subcortical levels as stimulus intensity is increased. No evidence was found that vertex–cathodal stimulation preferentially activates I waves (see Day *et al.* 1989).

Site of D wave initiation

Low-threshold anodal stimulation at the vertex induced a corticospinal volley that propagated to the low-thoracic region. When the anode was over the 'hand area' of the motor cortex, the volley evoked by low-threshold stimuli did not propagate to

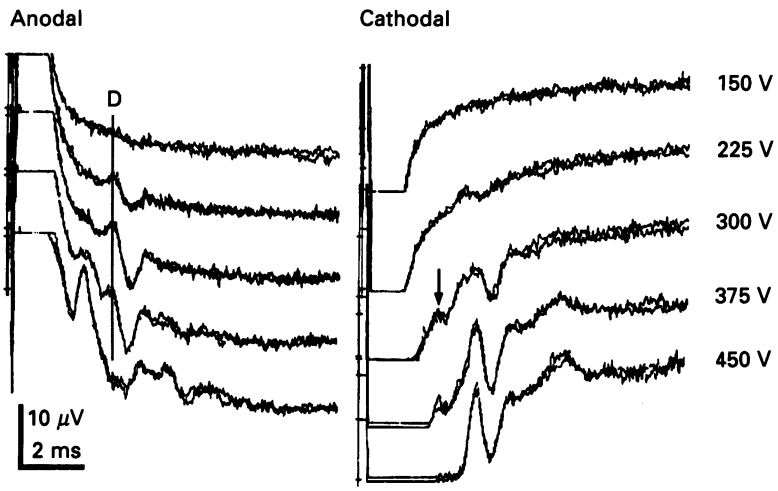

Fig. 10. Contrasting effects of vertex–anodal and vertex–cathodal stimulation using electrodes at the vertex and 7 cm *anterior* to the vertex (stimulus time constant 100 μs). Volleys recorded at the high-thoracic electrode. With anodal stimulation a small D wave appears at 150 V (indicated by dotted vertical line), but this low-threshold wave is completely replaced at 450 V by an earlier wave that appears at 300 V. With cathodal stimulation, a similar early peak (indicated by vertical arrow) precedes the D wave of lowest threshold; it also begins to appear at 300 V. I waves appear with anodal stimulation at 225 V (I_1), with I_2 at 375 V and I_3 at 450 V. With cathodal stimulation, two I waves (I_1 and I_3) appear at 300 V.

the lumbar segments. This suggests that weak anodal stimulation activates corticospinal neurones at a relatively superficial level, under the site of stimulation. However, the appearance of earlier peaks in the D wave complex and the tendency for these peaks to replace the original D wave as stimulus intensity was increased suggests that stronger stimuli activate corticospinal axons at deeper subcortical levels.

The shift in latency of the D wave did not occur in the progressive fashion expected if impulse initiation occurred at progressively deeper nodes of Ranvier. The different components of the D wave complex were separated by discrete intervals of 0·8 and 0·9 ms. This suggests that corticospinal axons have at least three sites at which they are preferentially susceptible to electrical stimuli delivered to the scalp: superficial cortex, 0·8 ms deeper and a further 0·9 ms deeper.

The conduction velocity of the fastest human corticospinal axons is approximately 65 m/s within the spinal cord (Boyd *et al.* 1986; Inghilleri, Berardelli, Cioni, Cruccu, Meglio & Manfredi, 1988; Pelosi *et al.* 1988; Inghilleri *et al.* 1989). If the most cephalad parts of the axon have this same conduction velocity, a latency decrease of 0·8 ms corresponds to 5 cm. This implies that D wave initiation shifts from superficial

cortex to a site of relative electrical accessibility 5 cm deep to the cortex and then to a second site 10–11 cm deep to cortex. Such sites are probably the internal capsule and the cerebral peduncle. In agreement with this view, Edgley, Eyre, Lemon & Miller (1990) suggest that, in the monkey, the site of activation of corticospinal axons can shift from a superficial cortical level to 'a level approaching the medullary pyramid' as the intensity of transcranial electrical stimulation is increased.

I waves

The present study extends previous descriptions of I waves in human subjects by documenting their pattern of appearance with graded stimuli and demonstrating conduction of these volleys to lumbar segments (cf. Boyd *et al.* 1986; Inghilleri *et al.* 1989). Many of the I waves could be matched at the two recording sites and it was confirmed that these waves had much the same conduction time between the recording sites as the D wave. Though slower conducting axons could have contributed to some peaks (see Lance & Manning, 1954; Kernell & Wu, 1967), it is also possible that the 'unmatched' waves represent activity in axons directed to intervening segments of the spinal cord. Kernell & Wu (1967) reported that the earliest I wave (I_1) occurred at a higher threshold than later I waves (see also Day *et al.* 1989). This was not confirmed in the present study.

The small (generally $< 0{\cdot}2$ ms) changes in latency of individual I waves with increasing stimulus intensity occurred mainly as the wave increased in size, presumably as more corticospinal axons were recruited into the compound potential. The constancy of I wave latency is similar to that reported by Kernell & Wu (1967), and supports the cortical origin of these waves.

Cathodal stimulation

In the present study, cathodal stimulation did not induce I waves preferentially though I waves could be recorded with stimulus intensities that were higher than required for the presumed D wave. The site of initiation of the cathodal D wave is likely to be under the cathode because it involved axons innervating lumbar segments. At threshold, its latency was similar to that of the anodal D wave but, with modest increases in stimulus intensity, the latency of the dominant component was 0·2–0·4 ms longer than that of the anodal D wave. This difference in latency is probably too small to invoke trans-synaptic activation, as has been suggested for I waves (Patton & Amassian, 1954; Kernell & Wu, 1967; Phillips & Porter, 1977). Presumably the later peak in the cathodal D wave resulted from direct activation of corticospinal neurones at a superficial level, perhaps at their dendrites. In agreement with the data of Day *et al.* (1989), the I waves evoked by cathodal stimulation had similar latencies as the I waves evoked by anodal stimulation. In the present study, the major differences between anodal and cathodal stimulation of the leg area were a higher threshold for truly cathodal stimulation, D components of slightly longer latency, and a generally less intense D wave complex. The similarities between anodal and cathodal stimulation were the early peaks in the D wave complex (see previous section) and I waves of comparable latency and amplitude.

The failure of cathodal stimulation to produce I waves preferentially is reminiscent of the failure of magnetic stimulation of the monkey cortex to generate I waves

(Edgley, Eyre, Lemon & Miller, 1989, 1990). These 'negative' findings suggest that it would be prudent to retain reservations about the D and I wave hypothesis for intact human subjects. As implied in the studies of Edgley *et al.* (1989, 1990), the different response latencies seen with anodal and cathodal electrical stimulation and with clockwise and counterclockwise magnetic stimulation might result from direct activation of the corticospinal neurone and its axon at different levels.

Whether the present conclusions are applicable to transcranial stimulation of the arm and hand areas of motor cortex is conjectural. Pyramidal neurones are likely to be oriented differently with respect to the scalp in different regions of the motor cortex. Specific studies on the 'hand area' are required to determine whether the D and I wave hypothesis is valid for transcranial stimulation of this region of motor cortex.

The concept of 'central motor conduction time'

In clinical studies it has proved valuable to estimate 'central motor conduction time' by subtracting the latency of the EMG potential produced by spinal stimulation from the latency of the EMG potential produced by cortical stimulation (for a critical review, see Gandevia, 1989). The derived estimate includes time for corticospinal conduction, synaptic activation and conduction to the anterior roots, at which level spinal stimulation is believed to activate α-motor axons. For the upper limb, central motor conduction time is generally about 5 ms. The brevity of the 'central motor conduction time' is part of the evidence that the initial EPSP generated in spinal motoneurones by transcranial stimulation of the human motor cortex is monosynaptic (Day *et al.* 1987; Rothwell *et al.* 1987), much as in non-human primates (Phillips & Porter, 1977). This particular piece of evidence is less convincing when one considers that modest increases in stimulus intensity can decrease the latency of the descending volley by more than that required for one or two interneurones.

Plassman & Gandevia (1989) have demonstrated that, with high-voltage electrical stimulation over the spinal cord, impulse initiation can occur far from the spinal cord, even in the brachial plexus. This could falsely decrease the measured peripheral conduction time and, thereby, increase 'central motor conduction time'. The present study demonstrates that motor cortical stimulation using moderate stimulus intensities can result in latencies that are shorter by 1·7 ms, presumably because of a shift in the site of impulse initiation. The extent of the possible latency shortening is large compared to the overall 'conduction time' ($\sim$ 5 ms). Clearly, caution is required in the performance and interpretation of this clinical test.

This study was supported by the National Health and Medical Research Council of Australia and The Prince Henry Hospital Centenary Foundation. The authors are grateful to Dr S. C. Gandevia and Professor J. W. Lance for reviewing the manuscript.

REFERENCES

AMASSIAN, V. E., STEWART, M., QUIRK, G. J. & ROSENTHAL, J. L. (1987). Physiological basis of motor effects of a transient stimulus to cerebral cortex. *Neurosurgery* **20**, 74–93.

BOYD, S. G., ROTHWELL, J. C., COWAN, J. M. A., WEBB, P. J., MORLEY, T., ASSELMAN, P. & MARSDEN, C. D. (1986). A method of monitoring function in corticospinal pathways during

scoliosis surgery with a note on motor conduction velocities. *Journal of Neurology, Neurosurgery, and Psychiatry* **49**, 251–257.

DAY, B. L., DRESSLER, D., MAERTENS DE NOORDHOUT, A., MARSDEN, C. D., NAKASHIMA, K., ROTHWELL, J. C. & THOMPSON, P. D. (1989). Electric and magnetic stimulation of human motor cortex: surface EMG and single motor unit responses. *Journal of Physiology* **412**, 449–473.

DAY, B. L., ROTHWELL, J. C., THOMPSON, P. D., DICK, J. P. R., COWAN, J. M. A., BERARDELLI, A. & MARSDEN, C. D. (1987). Motor cortex stimulation in intact man. 2. Multiple descending volleys. *Brain* **110**, 1191–1209.

EDGLEY, S. A., EYRE, J. A., LEMON, R. N. & MILLER, J. S. G. (1989). Direct activation of corticospinal neurones by electromagnetic stimulation in anaesthetized and conscious monkeys. *Journal of Physiology* **414**, 8*P*.

EDGLEY, S. A., EYRE, J. A., LEMON, R. N. & MILLER, J. S. G. (1990). At what level is the corticospinal pathway excited by electromagnetic and percutaneous electrical stimulation of the brain? Evidence from the anaesthetized macaque monkey. *Journal of Physiology* **420**, 47*P*.

GANDEVIA, S. C. (1989). Human motor cortical output studied with transcranial stimulation. *Current Opinion in Neurology and Neurosurgery* **2**, 782–787.

GANDEVIA, S. C. & ROTHWELL, J. C. (1987). Activation of the human diaphragm from the motor cortex. *Journal of Physiology* **384**, 109–118.

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

INGHILLERI, M., BERARDELLI, A., CIONI, B., CRUCCU, G., MEGLIO, M. & MANFREDI, M. (1988). The conduction velocity of the corticospinal tract in man. In *Non-Invasive Stimulation of Brain and Spinal Cord: Fundamentals and Clinical Applications*, ed. ROSSINI, P. M. & MARSDEN, C D., pp. 123–130. Alan R. Liss, New York.

INGHILLERI, M., BERARDELLI, A., CRUCCU, G., PRIORI, A. & MANFREDI, M. (1989). Corticospinal potentials after transcranial stimulation in humans. *Journal of Neurology, Neurosurgery, and Psychiatry* **52**, 970–974.

KATAYAMA, Y., TSUBOKAWA, T., MAEJIMA, S., HIRAYAMA, T. & YAMAMOTO, T. (1988). Corticospinal direct response in humans: identification of the motor cortex during intracranial surgery under general anaesthesia. *Journal of Neurology, Neurosurgery, and Psychiatry* **51**, 50–59.

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

LANCE, J. W. & MANNING, R. L. (1954). Origin of the pyramidal tract in the cat. *Journal of Physiology* **124**, 385–399.

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.

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

PELOSI, L., CARUSO, G. & BALBI, P. (1988). Characteristics of spinal potentials to transcranial motor cortex stimulation: intraoperative recording. In *Non-Invasive Stimulation of Brain and Spinal Cord: Fundamentals and Clinical Applications*, ed. ROSSINI, P. M. & MARSDEN, C. D., pp. 297–304. Alan R. Liss, New York.

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

PLASSMAN, B. L. & GANDEVIA, S. C. (1989). High-voltage stimulation over the human spinal cord: sources of latency variation. *Journal of Neurology, Neurosurgery, and Psychiatry* **52**, 213–217.

ROTHWELL, J. C., THOMPSON, P. D., DAY, B. L., DICK, J. P. R., KACHI, T., COWAN, J. M. A. & MARSDEN, C. D. (1987). Motor cortex stimulation in intact man. 1. General characteristics of EMG responses in different muscles. *Brain* **110**, 1173–1190.