Transcranial electrical stimulation of the motor cortex in man: further evidence for the site of activation

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1. The motor cortex was stimulated electrically (vertex anode; cathode 6 cm lateral) in neurologically normal subjects undergoing surgery for scoliosis, and the evoked corticospinal volleys were recorded from the spinal cord using epidural electrodes.

2. Stimuli >330 V produced a complex D-wave volley containing three separate peaks, with high-threshold components, 0·8 ms (D_2) and 1·6 ms (D_3), in advance of the lowest-threshold component (D_1). As stimuli increased up to 1500 V, D_3 replaced the later components completely, but there was no further latency 'jump'.

3. Brainstem stimulation using electrodes over each mastoid process produced a descending volley that had the same latencies as D_3. At threshold, stimulation of the brainstem or spinal cord attenuated the D wave evoked by simultaneous cortical stimulation.

4. It is concluded that transcranial electrical stimulation of the motor cortex at high intensities can access corticospinal neurones at the pyramidal decussation, and that stimulation of the brainstem (and the spinal cord) preferentially accesses corticospinal axons. At threshold, motor cortex stimulation probably activates corticospinal neurones at or near the cerebral cortex.

Despite its widespread use, it is still not clear which elements in the brain are excited by either transcranial electrical or magnetic stimulation over the motor cortex. Until 1985, it was generally supposed that transcranial electrical stimulation of the motor cortex activated descending corticospinal fibres in much the same way as unipolar surface anodal stimulation of the exposed cortex of the monkey. That is, an anode applied to the surface of the cortex was believed to induce electrical current flow which entered the dendritic tree of pyramidal cells, flowed through the soma and then left the cell at the initial segment region where excitation took place.

However, the introduction of transcranial magnetic stimulation posed a problem with this interpretation. When magnetic stimulation was used, the EMG responses in intrinsic hand muscles always occurred 1–2 ms later than those seen in the same muscles after electrical stimulation. In their original reports of the technique, Hess, Mills & Murray (1986) suggested that the difference in latency arose because electrical stimulation excited neural elements deeper in the brain than magnetic stimulation, while Day, Dick, Marsden & Thompson (1986) proposed that the latency difference arose because magnetic stimulation activated pyramidal neurones trans-synaptically rather than directly at the initial segment or proximal nodes of the descending axons. The same two theories are still debated even now, some eight years later (see Edgley, Eyre, Lemon & Miller, 1990; Burke, Hicks, Gandevia, Stephen, Woodforth & Crawford, 1993).

In recent years, a great deal of work, particularly in animal experiments, has supported the notion that electrical stimulation may activate corticospinal fibres deep within the brain. In the anaesthetized monkey, direct recordings from the pyramidal tract have shown that transcranial electrical stimulation over the motor cortex can activate fibres deep within the cranium, at the pyramidal decussation (Edgley *et al.* 1990). These findings have received some support recently from observations of Burke, Hicks & Stephen (1990) who recorded the descending volleys from the spinal cord using epidural electrodes in patients undergoing surgery for scoliosis. They found that, at moderate intensities of electrical

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stimulation, the site of activation spread in two discrete jumps from an initial, presumed cortical level to points 0·8 ms and 1·7 ms distal, equivalent to 5 cm and 10–11 cm deeper (assuming a corticospinal conduction velocity of 60–65 m s^{-1}). Such points might correspond to the cerebral peduncle and pyramidal decussation, respectively. Having shown that transcranial electrical stimulation can activate elements very deep within the brain, the question is whether activity arising from stimulation of descending fibres within the brainstem is sufficient to produce EMG responses in conscious man, when weak or modest stimulus intensities are used.

The purpose of this paper is to provide further evidence for the site of activation of descending pathways after transcranial electrical stimulation over the motor cortex in man. These results may help elucidate the reasons for the discrete jumps in latency with electrical stimulation and, in addition, they have implications for the potential sites at which the more common technique of magnetic stimulation may activate motor cortical structures.

Some of the results have been published in abstract form (Rothwell, Burke, Hicks, Stephen, Woodforth & Crawford, 1993).

METHODS

The corticospinal volleys evoked by transcranial electrical stimulation of the motor cortex were recorded in fifteen neurologically normal subjects (ten female, five male; aged 12–24 years) undergoing surgery to correct scoliosis. The subjects gave informed consent to the operative, anaesthetic and experimental procedures, which were performed with the approval of the appropriate institutional ethics committee. Most of the stimulating and recording techniques have been described in previous papers (Burke *et al.* 1990; Ugawa, Rothwell, Day, Thompson & Marsden, 1991; Hicks, Burke, Stephen, Woodforth & Crawford, 1992).

The motor cortex was stimulated using an anode at the vertex and a cathode on one side, 7 cm lateral to the vertex. Capacitively coupled pulses of up to 1500 V (time constant, 100 μs) were delivered from a Digitimer D180A (Welwyn Garden City, Herts, UK) stimulator at a rate of less than one every 3 s. The evoked volleys were recorded from the spinal cord using bipolar cardiac pacing electrodes inserted into the epidural space at two levels, high and low thoracic, and then advanced rostrally by the surgeon so that the recording surfaces would be adjacent to the upper-limb and lower-limb spinal segments, and this was confirmed in two patients by intraoperative X-rays. The recorded corticospinal volleys were amplified and filtered (bandwidth 0·5–5 kHz), and ten

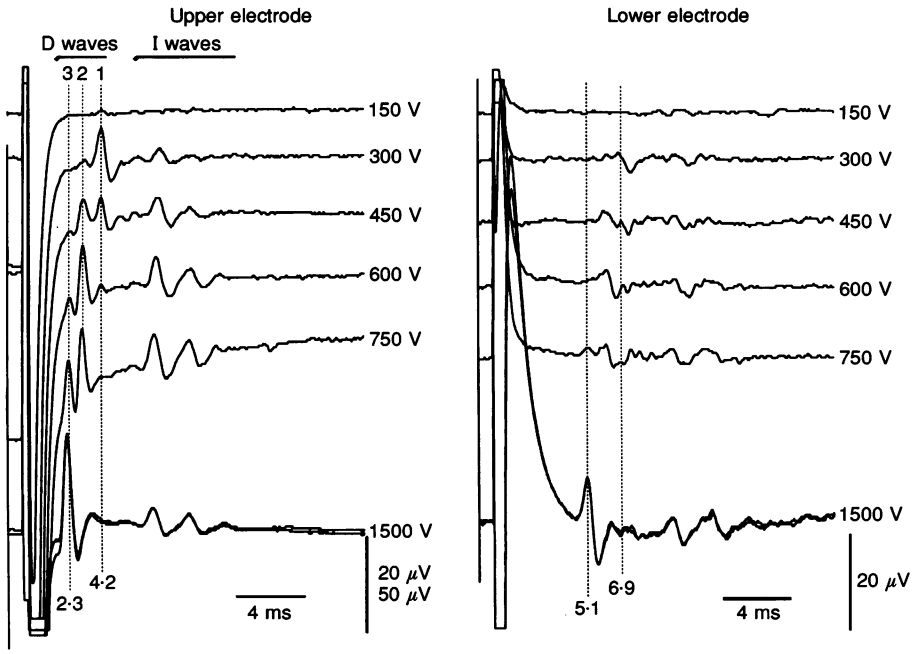

Figure 1. Cortical stimulation using increasingly strong stimulus intensities
Epidural recordings from the low-cervical and low-thoracic levels (female, aged 14). The stimulus artifact begins 1 ms after the start of the sweep. Two averages are superimposed for the 1500 V stimulus. Note the gradual recruitment of earlier D-wave components as the stimulus intensity is increased, and the progressive increase in the size and number of I waves. In the recordings from the upper electrode, the 50 μV vertical calibration applies only to the responses at 1500 V. The dotted lines indicate successive D-wave components and their respective peak latencies. In this and subsequent figures, each trace is the average of ten responses.

sweeps were averaged for each observation using a Medelec Sapphire 4ME (Old Woking, Surrey, UK). The averaged waveforms were stored on disk.

The brainstem was stimulated through two electrodes fixed on either side of the scalp about 5 cm lateral to the inion over the mastoid process (Ugawa *et al.* 1991). The polarity of stimulation was adjusted to produce the smallest stimulus artifact in the epidural recording electrodes. In six experiments, the brainstem was stimulated using the D180A stimulator. In an additional five experiments, the brainstem or cervical spinal cord was stimulated using the stimulators of the Sapphire 4ME, in order to assess whether the antidromically transmitted volley collided with the corticofugal volley set up by motor cortex stimulation.

RESULTS

Stimulation over the motor cortex

In all subjects, it was possible to confirm previous observations (Burke *et al.* 1990) that, at threshold, cortical stimulation produced a single descending volley (Fig. 1). This volley reached the low-cervical region within ~4 ms, i.e. at a latency consistent with direct activation of corticospinal neurones or their axons. As the intensity was increased, this volley increased in size and was accompanied by other volleys which occurred at preferred time intervals both before and after the original volley. Simultaneous recordings from two electrodes showed that the conduction velocities of these volleys within the spinal cord were virtually identical, consistent with the view that there were multiple volleys in the same population of axons. This can be appreciated in the lower traces of Fig. 1, in which the intervals between D_3 and each of the three major I waves are identical at the two recording sites. As the intensity of stimulation was increased, the original low-threshold volley gradually diminished and disappeared (Figs 1 and 2), indicating that the high-threshold early volleys involved the same axons as the low-threshold volley.

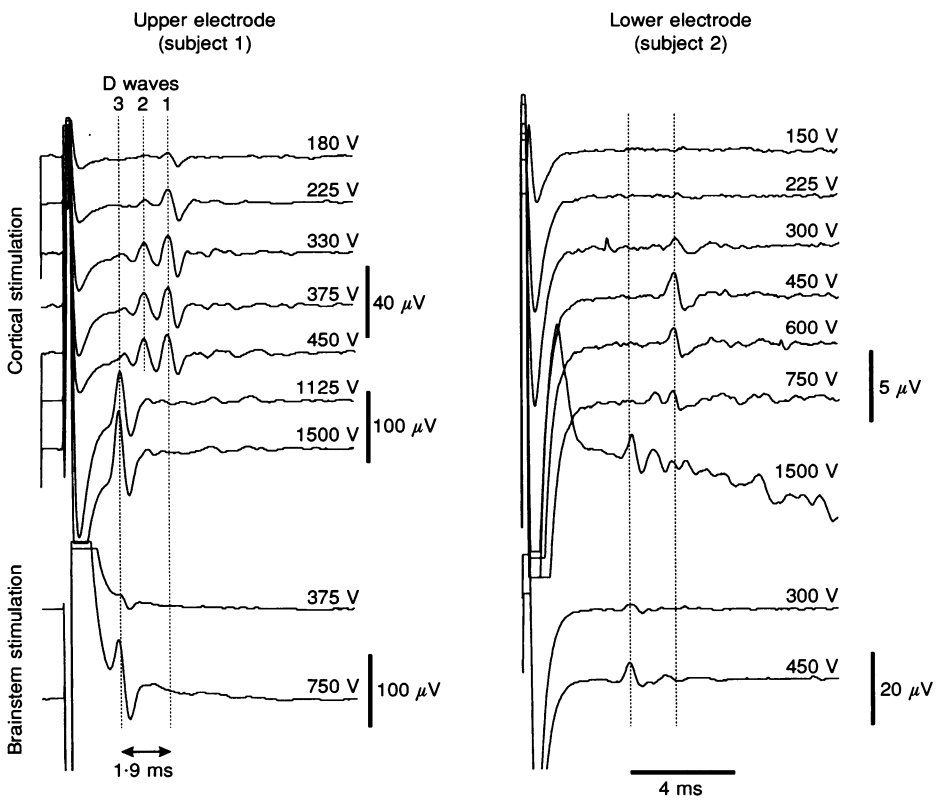

Figure 2. Responses to cortical and brainstem stimulation
Averaged epidural recordings from the low-cervical and the low-thoracic levels in two subjects (subject 1: female, aged 14; subject 2: male, aged 12), in response to different stimulus intensities. For subject 1, the stimulus was given 1 ms after the onset of the sweep; for subject 2, the stimulus occurred at the onset of the sweep. Gradually increasing intensities of cortical stimulation recruited three D-wave components (D_1, D_2, D_3) with a latency shift from D_1 to D_3 of 1·9 ms in subject 1. Brainstem stimulation evoked a volley which had the same latency as the D_3 component resulting from cortical stimulation. Note the absence of late activity with brainstem stimulation except for a small wave at 450 V in subject 2 (bottom trace on right).

The initial wave probably equates to the D wave observed in animal experiments, and may be initiated at cortical or just-subcortical levels. In the present paper this wave will be termed the D_1 wave. As the intensity of stimulation increased, the site of activation of corticospinal fibres shifted deeper into the brain in all subjects, in two stages, giving rise to two earlier waves, D_2 and D_3, with threshold latencies of, on average, 0·8 ms (range 0·5–1·0 ms) and 1·6 ms (range 1·1–2·0 ms) in advance of D_1, respectively. The waves which follow the original D_1 wave are thought to be I waves set up indirectly by trans-synaptic activation of corticospinal neurones (see Burke *et al.* 1990; Rothwell *et al.* 1991; Hicks *et al.* 1992).

The present study presents three new observations on the nature of the D waves. First, in twelve of fifteen subjects it was possible to obtain recordings at the maximal intensity available from the stimulator (1·5 kV). Even with such intense stimuli, the latency of the complex D wave never decreased by more than 2 ms. In other words, the D_3 was the earliest volley that could be generated with this stimulating montage: there was no suggestion that the site of stimulation could spread more caudally than the point from which D_3 arose. Second, with strong stimulation, it was clear that as the D_2 and D_3 components increased in size, the original D_1 wave decreased in size and eventually disappeared, and that the same process then occurred with D_2 such that, at 750–1500 V (in eight of twelve subjects), D_3 was the only definite D-wave component (Figs 1 and 2). It can therefore be concluded that D_1, D_2 and D_3 are volleys in the same population of corticofugal axons, differing in latency because they arise from three different sites on the corticospinal pathway. This conclusion has been drawn previously (Burke *et al.* 1990), but on data that were less conclusive. Third, there was no evidence for activity of other pathways of slower velocity or for activation of the same pathway at levels other than those corresponding to the D_1, D_2 and D_3 waves. Nevertheless, as can be seen for D_3 in Fig. 1, there

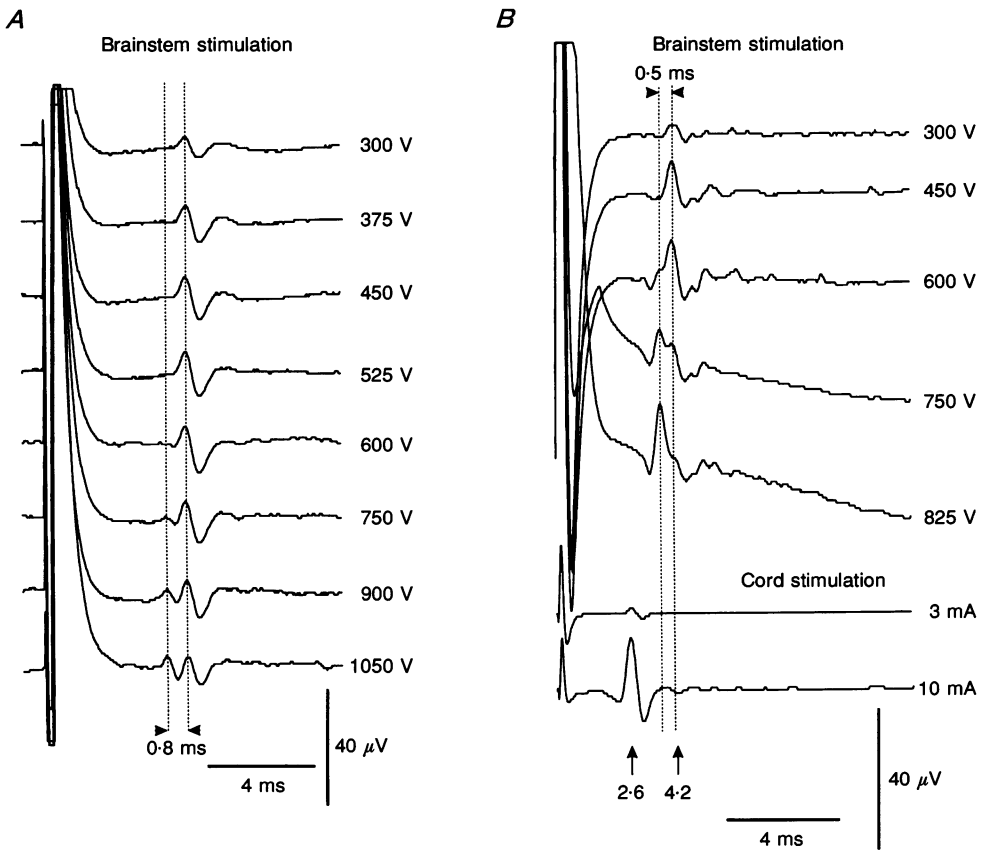

Figure 3. Brainstem stimulation
Averaged epidural recordings from the low-thoracic level in two patients (males, aged 18 in *A* and 12 in *B*) showing responses to different stimulus intensities. In *B*, the lowest two traces are responses to direct spinal cord stimulation through the low-cervical electrode. There is a jump in latency of 0·8 ms (*A*) and 0·5 ms (*B*), beginning at 750 V in *A* and 600 V in *B*. There is no late activity in *A* but there is in *B*. Direct stimulation of the cord in *B* evoked a single early volley. Vertical arrows in *B* indicate the latencies of the volley evoked by cord stimulation and of the lowest-threshold component to brainstem stimulation.

was often a slight shortening of the latency to peak of these D-wave components as their amplitude increased. This change could result from recruitment of slightly faster axons into the compound potential as amplitude increased (which is unlikely given that larger axons should have lower thresholds) or caudal displacement of the site of activation of corticospinal axons to successively deeper nodes of Ranvier (which is a well-documented phenomenon in conduction studies on peripheral nerves).

Stimulation at the level of the brainstem

Brainstem stimulation evoked a descending volley in all six subjects when the high-voltage Digitimer stimulator was used. The size of the potential and its duration were similar to those of the D wave seen after cortical stimulation. The threshold for eliciting the volley was not systematically measured but ranged from < 200 to 300 V. With relatively weak intensities, the latency of the volley produced by brainstem stimulation and its conduction velocity down the cord were equal to those of the D_3 wave seen after cortical stimulation (Fig. 2). At high stimulus intensities (usually more than 1·5 times threshold), there was sometimes a slight decrease in the latency of the brainstem volley, much as occurred with the D-wave components to cortical stimulation. In most cases, the latency changed gradually, by only 0·1–0·2 ms. However, in two subjects, the latency decreased abruptly in a single step of 0·8 ms (Fig. 3*A*) or 0·5 ms (Fig. 3*B*). In Fig. 3*B*, it was established that this latency jump did not correspond to a stimulation site as low as the upper recording electrode (the low-cervical region). Stimulation at that electrode produced a response which was recorded at the lower electrode 1·08 ms earlier than the earliest volley after brainstem stimulation. Accordingly, the jump of 0·5 ms indicates a site caudal to the brainstem, one-third of the distance to the low-cervical region.

In three of the six subjects, there was no sign of any further descending activity after the initial brainstem volley, even when the amplitude of the brainstem-evoked volley approached the maximal amplitude of the D wave (Figs 2 and 3*A*). However, in the other three subjects, some late activity was then observable (see Figs 3*B* and 4). Because this late activity was not clear at both upper and lower electrodes, it was not possible to estimate its conduction velocity.

Collisions with the cortical volley

In one subject, it was possible to record volleys resulting from cortical stimulation (using the D180A) and brainstem stimulation (using the Sapphire 4ME) separately and together. (This was attempted in two additional subjects but an artifact-free brainstem volley could not be recorded with the stimulus strength available from the EMG machine.) In Fig. 4, when cortical stimulation was given alone it produced D_1 and I waves. Brainstem stimulation produced a volley with a latency about 2 ms earlier than

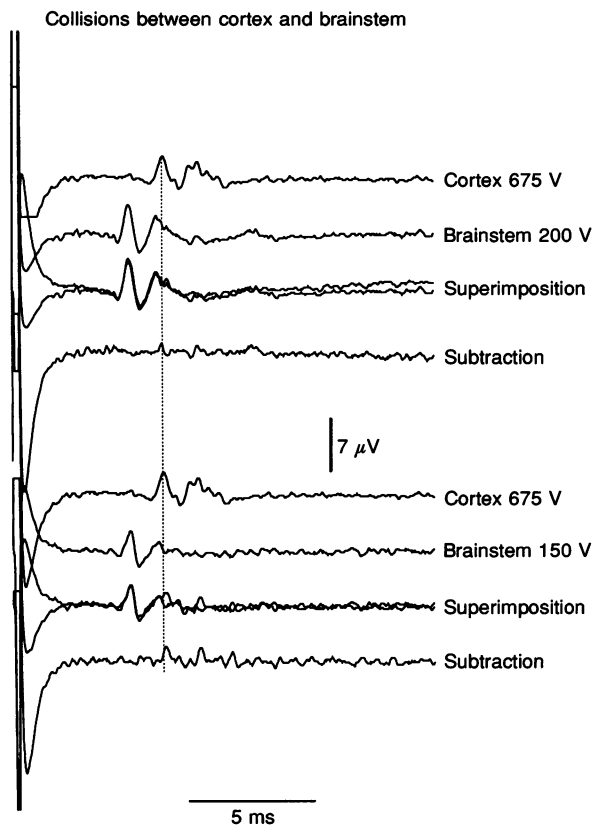

Figure 4. Collisions between volleys evoked by cortical and brainstem stimulation (female, aged 15)
Traces are average recordings from the low-thoracic site after separate stimulation of the cortex and the brainstem or of both sites simultaneously. In the upper panel, cortex stimulation at 675 V evoked a D wave (vertical dotted line) followed by later activity (first trace). Brainstem stimulation at 200 V evoked an earlier volley (second trace). When both stimuli were given together, the resulting volley was very similar to the volley produced by brainstem stimulation on its own. The third trace is a superimposition of the response to brainstem stimulation alone and the response to combined cortical and brainstem stimulation. The two traces superimpose almost completely. The fourth trace is a subtraction of the response to brainstem stimulation alone from the response to combined stimulation. In the lower panel, brainstem stimulation at 150 V produced a smaller descending volley with less complete collision. In the superimposed traces the response to combined stimulation produced additional activity at around the time of the vertical dotted line; this is clearer in the subtraction in the fourth trace.

the D_1 wave. When both cortical and brainstem stimuli were given at the same time, and the stimulus intensity to the brainstem was set at 200 V, the response to combined stimulation was almost exactly the same as the response to brainstem stimulation given alone. Presumably the antidromic volley produced by the brainstem shock had collided with the D and I volleys after cortical stimulation (see later). When the intensity of the brainstem shock was decreased to 150 V, any such collision was less than perfect, and there was extra descending activity when both stimuli were given together compared with when the brainstem shock was given alone.

In a further two patients, collisions were performed between volleys evoked by direct stimulation of the spinal cord through the upper recording electrode and stimulation of the cortex. This was undertaken because it proved difficult to stimulate the brainstem in some subjects using the stimulators of the EMG machine (see earlier). Figure 5 shows that, as the intensity of cord stimulation was increased, the collision with the volleys elicited by motor cortical stimulation became more and more complete. At 15 and 20 mA, the cord volley largely obliterated the motor cortical volley. The fact that the volley produced by brainstem or spinal cord stimulation could obliterate the volley produced by cortical stimulation implies that, at the intensities used, the brainstem/spinal cord shock activated the same set of descending axons as those activated by cortical stimulation. In the three experiments in which collision experiments could be performed successfully, corticospinal axons were among the axons of lowest threshold with both spinal stimulation and brainstem stimulation, as evidenced by the diminution of

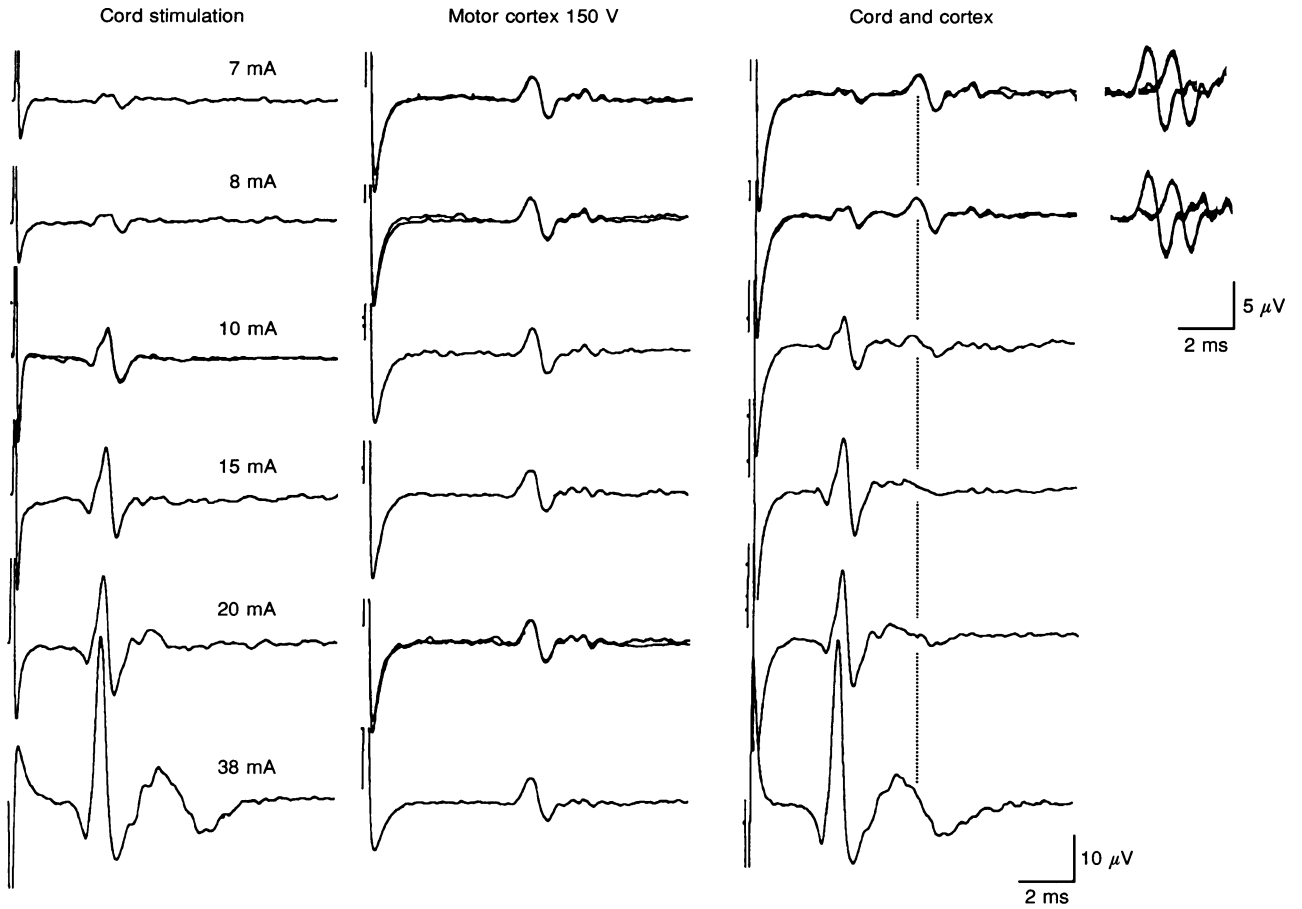

Figure 5. Collisions between volleys evoked by cortical and spinal cord stimulation (male, aged 13)

Low-thoracic recording of volleys set up by stimulation of either the spinal cord at the low-cervical region (left column) or the cortex (middle column) or both cord and cortex together (right column). The cord stimulus was increased from liminal (7 mA) to supramaximal (38 mA). The cortex stimulus was fixed at 150 V, and produced a D wave with some small I wave activity. The inset (top right) shows, at higher gain, the responses to cortex and combined stimulation for cord stimuli of 7 mA and 8 mA, illustrating that liminal cord stimulation decreases the size of the D wave. In the inset the traces have been superimposed with the responses to combined stimulation displaced ~1 ms to the right so that the small change in amplitude can be appreciated.

the corticospinal volley with liminal spinal or brainstem volleys (see the superimposed traces to the right of the third column in Fig. 5).

Strong brainstem or spinal stimuli obliterated the I wave components of the response to cortical stimulation. There are three possible explanations for this unexpected finding. (1) The late waves were not in corticospinal axons. (2) The late waves were in corticospinal axons not activated in the D wave. (3) The late waves were suppressed by antidromic activity not abolished by the D wave (possibly due to a form of recurrent inhibition). The present experiments do not provide definitive evidence on this issue.

DISCUSSION

These results illustrate three fundamental features of the corticospinal responses evoked by transcranial electrical stimulation over the human motor cortex. First, there is a limit to how deeply the site of activation can be displaced with increasing intensities of stimulation. Second, the most caudal site compares very closely with the site activated by brainstem stimulation. Third, collision experiments demonstrated that both brainstem and spinal stimulation activate corticospinal axons at threshold.

The descending volley produced by brainstem stimulation has never been recorded previously in human subjects. The volley travels at the same velocity as, and can occlude, that evoked by cortical stimulation. The implication is that a substantial proportion of the volley (at least that evoked near threshold) is produced by activity in the same axons as those activated by cortical stimulation. However, the brainstem volley differed from the volleys evoked by stimulation of the cortex in two ways. First, in four of six subjects, the response did not change greatly in latency as the intensity of stimulation was increased, and this suggests that the stimulus did not spread to activate descending pathways more caudally, within the spinal cord itself. Second, the brainstem volley was followed by later activity only when the stimulus was strong and the evoked volley approached the size of the maximal D wave to cortical stimulation.

Why are there latency jumps with electrical stimulation?

It is expected that latency would decrease as stimulus intensity increased such that activation occurred at successively deeper nodes of Ranvier and, indeed, a gradual drift in latency was seen in the present experiments. However, the relatively abrupt decreases in latency of about 0·8 ms suggest that there are sites of preferential accessibility of the corticospinal axon to electrical stimulation applied to the scalp, as postulated by Burke *et al.* (1990). It is noteworthy that these jumps began to occur with relatively modest stimulus intensities (D_2 at 300 V in Fig. 1 and 225 V in Fig. 2, left-hand panel; and D_3 at 450 V in Fig. 1 and 330 V in Fig. 2, left-hand panel) and that there were no further jumps even with a stimulus of 1500 V. This suggests that, in addition to the site of lowest threshold, there are two other special sites on the corticospinal tract within the cranial cavity.

As suggested for magnetic stimuli (Amassian, Eberle, Maccabee & Cracco, 1992; Maccabee, Amassian, Eberle & Cracco, 1993), such sites are likely to be where there are bends in the descending tract and/or electrical inhomogeneities in the surrounding medium, producing a change in impedance for current flow along the axons. Given the size of the latency jumps, the conduction velocities of human corticospinal axons and the results of Ugawa *et al.* (1990) and Thompson *et al.* (1991), see later, the two sites are likely to be the cerebral peduncle and the pyramidal decussation. The latter site was that from which electrically evoked volleys could be initiated in the monkey when stimulus intensity was 1·5 times threshold (Edgley *et al.* 1990). Such jumps do not occur with magnetic stimulation, presumably because the magnetic stimulus penetrates less deeply into cerebral tissue. Accordingly, it has been shown that, even with 100% of the output of the magnetic stimulator, there is no comparable jump in latency in the evoked corticospinal volley in monkey (Edgley *et al.* 1990) or in man (Burke *et al.* 1993).

In two of six subjects, there were latency jumps with brainstem stimulation when stimulus intensity was increased. The 'new' site of initiation was caudal to the brainstem but rostral to the epidural electrode at the low-cervical level. As a whole, the corticospinal tract undergoes no further 'bend' within the spinal cord, and it is possible that this spinal site of 'preferential accessibility' in the two subjects was the upper end of the cervical enlargement. Perhaps at this point, changes in the geometry of the spinal cord produce inhomogeneities in the electrical currents flowing around the corticospinal axons. Presumably this site cannot be accessed from the scalp using electrodes over the motor cortex.

Site of initiation of the volleys responsible for electrically and magnetically evoked EMG potentials

In conscious subjects, the responses evoked by brainstem stimulation in active muscles occur 2 ms earlier than those produced by cortical stimulation. This implies that the descending volley which produces the discharge of spinal motoneurones in conscious active subjects arrives 2 ms earlier after brainstem stimulation than after cortical stimulation. Since the present results show that the conduction velocity of the pathways activated by brainstem and cortical stimuli are equal, and that a substantial proportion of the fibres activated by each form of stimulation are shared, then the cortical volley (or,

at least, the component that actually triggers the motoneurone discharge) must be initiated 2 ms proximal to the brainstem volley. In most subjects, relatively weak stimulation of the brainstem produced only a single descending volley, and there was no evidence of any substantial jumps to shorter latencies. Where is this brainstem volley initiated?

On indirect evidence, Ugawa *et al.* (1990) suggested that brainstem stimulation activates the corticospinal pathways at the level of the pyramidal decussation. Thompson *et al.* (1991) recorded the descending volleys produced by electrical stimulation of the cortex from electrodes resting on the ventral surface of the brainstem. At threshold, the electrically evoked corticofugal volley reached the brainstem after a latency of about 2 ms. Since a threshold cortical volley occurs 2 ms after a brainstem volley, the implication is that the brainstem stimulus does indeed activate the descending pathways at the brainstem, probably at the pyramidal decussation (see above).

These arguments lead to the conclusion that cortical stimulation discharges spinal motoneurones with a volley initiated 2 ms proximal to the brainstem, the site of activation being within the cerebral cortex, perhaps close to or at the cell body of the corticospinal neurone. In the model of Iles & Lunn (1993), excitation with anodal stimulation occurred some ten nodes or more distal to the anode, and they therefore suggested that transcranial anodal stimulation excites axons several nodes deeper than the site of action of magnetic stimulation. On the other hand, the threshold D wave is very sensitive to the level of volatile anaesthesia (Hicks *et al.* 1992), consistent with its origin at or near the initial segment of the corticospinal neurone. Such a site of origin is also implicated by the finding that the D wave produced by magnetic stimulation has the same latency as the threshold D wave to anodal stimulation (Burke *et al.* 1993). If the anodal D wave arises from the cortex the remaining question is whether the volley which discharges spinal motoneurones is preceded by a smaller volley, perhaps initiated at a deeper level, but too small to discharge the motoneurones by itself. Neither single motor unit nor H-reflex studies have ever shown convincing signs of an early subthreshold volley preceding the triggering volley, but such studies have been based on < 100 and < 20 trials, respectively, and it is possible that, at the stimulus intensities used, a deep subcortical D-wave component was too small to be demonstrated with reliability. Either way, it can be concluded that, at threshold intensities used to stimulate the motor cortex of conscious man, activation of corticospinal pathways occurs at or near the cell body in the cerebral cortex.

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