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EXCITATION OF THE CORTICOSPINAL TRACT BY ELECTROMAGNETIC AND ELECTRICAL STIMULATION OF THE SCALP IN THE MACAQUE MONKEY

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SUMMARY

1. The responses evoked by non-invasive electromagnetic and surface anodal electrical stimulation of the scalp (scalp stimulation) have been studied in the monkey. Conventional recording and stimulating electrodes, placed in the corticospinal pathway in the hand area of the left motor cortex, left medullary pyramid and the right spinal dorsolateral funiculus (DLF), allowed comparison of the actions of non-invasive stimuli and conventional electrical stimulation.

2. Responses to electromagnetic stimulation (with the coil tangential to the skull) were studied in four anaesthetized monkeys. In each case short-latency descending volleys were recorded in the contralateral DLF at threshold. In two animals later responses were also seen at higher stimulus intensities. Both early and late responses were of corticospinal origin since they could be completely collided by appropriately timed stimulation of the pyramidal tract. The latency of the early response in the DLF indicated that it resulted from direct activation of corticospinal neurones: its latency was the same as the latency of the antidromic action potentials evoked in the motor cortex from the recording site in the DLF.

3. Scalp stimulation, which was also investigated in three of the monkeys, evoked short-latency volleys at threshold and at higher stimulus intensities these were followed by later waves. The short-latency volleys could be collided from the pyramid and, at threshold, had latencies compatible with direct activation of corticospinal neurones. The longer latency volleys were also identified as corticospinal in origin.

4. The latency of the early volley evoked by electromagnetic stimulation remained constant with increasing stimulus intensities. In contrast, with scalp stimulation above threshold the latency of the early volleys decreased considerably, indicating remote activation of the corticospinal pathway below the level of the motor cortex. In two monkeys both collision and latency data suggest activation of the corticospinal pathway as far caudal as the medulla.

5. The majority of fast corticospinal fibres could be excited by scalp stimulation with intensities of 20% of maximum stimulator output. Electromagnetic

stimulation at maximum stimulator output elicited a volley of between 70 and 90% of the size of the maximal volley evoked from the pyramidal electrodes.

6. Electromagnetic stimulation was also investigated in one awake monkey during the performance of a precision grip task. Short-latency EMG responses were evoked in hand and forearm muscles. The onsets of these responses were approximately 0·8 ms longer than the responses evoked by electrical stimulation of the pyramid. Furthermore, they were comparable in latency to the fastest post-spike facilitation produced in the same muscles by identified cortico-motoneuronal cells.

7. It is concluded that in the monkey, both electromagnetic and scalp stimulation of the motor cortex can activate corticospinal neurones directly, but that supra-threshold scalp stimuli can activate corticospinal fibres deep to the cortex. These results are discussed in the context of the actions of non-invasive stimulation of the brain in man.

INTRODUCTION

The non-invasive methods of electromagnetic (Barker, Jalinous & Freeston, 1985) and percutaneous electrical (Merton & Morton, 1980) stimulation of the human brain to evoke motor responses are now widely used in research laboratories and in clinical practice (Berardelli, Inghilleri, Manfredi, Zamponi, Cecconi & Dolce, 1987; Ingram, Thompson & Swash, 1988; Koh & Eyre, 1988; Day, Dressler, Maertens de Nordhout, Marsden, Nakashima, Rothwell & Thompson, 1989; Eyre, Gibson, Koh, Miller, O'Sullivan & Ramesh, 1989). The actions of these stimuli upon the cerebral cortex and descending motor pathways are not fully understood. In man, both types of stimulation are assumed to excite activity in the corticospinal pathway on the basis of short central conduction times (Boyd, Rothwell, Cowan, Webb, Morley, Asselman & Marsden, 1986; Rothwell, Thompson, Day, Dick, Kachi, Cowan & Marsden, 1987) and this is supported by preliminary studies in the monkey (Amassian, Quirk & Stewart, 1978*a*; Edgley, Eyre, Lemon & Miller, 1989, 1990).

In man surface anodal stimulation of the scalp evokes EMG responses in contracting hand and forearm muscles at latencies 1–2 ms shorter than with electromagnetic stimulation (Hess, Mills & Murray, 1987; Rothwell *et al.* 1987; Day *et al.* 1989). On the basis of EMG and single motor unit recordings, Hess *et al.* (1987) and Day *et al.* (1989) have argued that scalp stimuli activate corticospinal neurones directly and that electromagnetic stimulation most readily activates the cortico-spinal pathway indirectly through trans-synaptic pathways. They have drawn the analogy between the action of surface anodal scalp stimuli in man and anodal stimulation of the exposed pial surface of the motor cortex in anaesthetized subhuman primates (Patton & Amassian, 1954; Kernell & Wu, 1967; Phillips & Porter, 1977; Amassian, Stewart, Quirk & Rosenthal, 1987*b*). Such stimuli can activate the initial segment of corticospinal neurones to produce a direct 'D' wave and, at higher strengths, can induce indirect 'I' waves of presumed trans-synaptic origin. It has been proposed that the latency difference of muscle responses to scalp and electromagnetic stimulation in man arises because the former elicits both D and I waves, whereas the latter most readily evoked I waves.

At present there is little direct evidence to confirm the now widely accepted assumption of predominantly trans-synaptic action of electromagnetic stimulation

on corticospinal neurones and activation at the initial segment of these neurones by surface anodal scalp stimuli. The aims of the present investigation were therefore to determine whether corticospinal neurones are activated directly or trans-synaptically be these stimuli.

Abstracts of this work have been published previously (Edgley *et al.* 1989, 1990).

METHODS

The study was performed on five adult macaque monkeys (three *M. fascicularis*, one *M. nemestrina* and one *M. mulatta*) weighing between 6 and 8 kg. Four acute experiments were performed on anaesthetized animals; in three of these electromagnetic and scalp stimulation (Digitimer D180) were compared directly and in the other only electromagnetic stimuli were used. In the first acute experiment electromagnetic stimuli were applied using a Cadwell MES-2 instrument; in two subsequent experiments a standard Novametrix Magstim 200 was used, and in the final experiment a modified version of this instrument which gave 50% more power was used. The effect of electromagnetic stimulation during voluntary movement was investigated in one conscious monkey using a standard Novametrix Magstim 200 instrument.

Acute experiments

Anaesthesia was induced with ketamine (10 mg kg^{-1}) and, after cannulation of a femoral vein, was maintained by continuous intravenous infusion of alfentanil (150 mg kg^{-1} h^{-1}) combined with midazolam (1 mg kg^{-1} h^{-1}). Tracheal and arterial cannulae were inserted to allow ventilation and blood pressure monitoring, respectively. In three animals a laminectomy to expose the cervical enlargement (C3–Th3) was performed. In the fourth, the upper segments of the lumbosacral enlargement (Th12–L3) were similarly exposed. The dura was opened and the exposed spinal cord was immersed in a pool of mineral oil maintained at 36–37·5 °C. Rectal temperature was maintained within the same limits. When surgery was complete the animals were paralysed with Flaxedil (20 mg kg^{-1} initial dose, subsequently 20 mg kg^{-1} h^{-1}) and ventilated. Deep anaesthesia was maintained throughout the experiment and this was verified by ensuring that neither heart rate nor blood pressure, which were monitored continuously, were altered by high-intensity peripheral nerve stimulation. At regular intervals the eyes were checked for the absence of corneal reflexes and pupillary dilation. Arterial blood samples were taken at regular intervals for blood-gas analysis.

Varnish-insulated tungsten stimulating electrodes (tip impedance 20–50 kΩ at 1 kHz) were positioned stereotaxically 5 mm apart in the left pyramid, at antero-posterior levels of A+2 and P−3. Correct placement was verified during the experiment by recording antidromic field potentials from the motor cortex which had low thresholds (20–50 μA; Lemon, Mantel & Muir, 1986) and subsequently by post-mortem histological analysis. Stimulation at the pyramid allowed the rapidly conducting component of the corticospinal outflow to be completely activated (Phillips & Porter, 1964). Two metal ring electrodes (outer diameter 8 mm) were sewn to the scalp at the vertex and over the left motor cortex for delivery of surface anodal scalp stimuli. For electromagnetic stimulation, the coil was placed tangentially just above the scalp and it was then fixed in the position in which response in the DLF could be obtained at the lowest threshold. Recordings from the spinal cord were made with silver ball electrodes placed on the right dorsolateral funiculus (DLF) of the cord 1·0–1·5 mm lateral to the dorsal root entry zone. In some experiments recordings from within the DLF were made with varnish-insulated tungsten electrodes. For both surface and depth recordings, a silver reference electrode was placed on muscles close to the cord. Recordings were made with a differential preamplifier in which the inputs could be muted for a few milliseconds during application of the stimuli (Barker, Eyre, Kenyon, Koh, Miller & Wraith, 1987). This greatly reduced the size of the stimulus artifacts and allowed volleys occurring within 1 ms of stimulus onset to be recorded. In one experiment killed-end recordings were made from the spinal cord following section of the DLF between two ball electrodes.

All signals were recorded on magnetic tape for off-line averaging and analysis, using a Cambridge Electronic Design 1401 programmable interface. Latencies were measured from stimulus onset to the peak of the first inflexion of the response and amplitudes were measured from the baseline to

the peak of the response. In each experiment, recording electrodes were inserted into the motor cortex, and antidromic conduction delays from the pyramid and from the spinal recording locations were determined.

Chronic experiment

One monkey was trained to perform a precision grip task with the thumb and index finger of the right hand for food rewards (Lemon *et al.* 1986). Electromagnetic stimuli were delivered during the performance of the motor task with the coil placed approximately 5 cm above the monkey's head and oriented tangentially. The monkey showed no averse reaction to the electromagnetic stimuli and continued to perform the precision grip task and to consume food rewards throughout the session. Surface EMGs were recorded from the right forearm: flexor digitorum superficialis (FDS) and extensor digitorum communis (EDC), and from the right hand: abductor pollicis brevis (AbPB) and 1st dorsal interosseous (1DI). All signals were recorded on magnetic tape for later off-line analysis.

After four recording sessions the monkey was deeply anaesthetized with halothane (1–2 %) in a 80 % N_2O, 20 % O_2 mixture. Two varnish-insulated tungsten electrodes were positioned in the left medullary pyramid using a method similar to that employed in the acute experiments. These electrodes were led to a small connector fixed to the skull. Several days after implantation of these electrodes, two further recording sessions were performed. During these sessions both electromagnetic stimulation and electrical stimulation through the pyramid electrodes (using shock strengths of 100–300 μA) were applied. Finally, at a second operation with the same full anaesthetic procedure described above, this animal was prepared for single-unit recording from the motor cortex (for details, see Lemon *et al.* 1986). The effects of electromagnetic and pyramidal stimulation were investigated in two further sessions.

Histology

At the end of the experiments the animals were killed by an overdose of midazolam and alfentanil (acute experiments) or sodium pentobarbitone (chronic) and then perfused through the aorta. Conduction distances were measured between the pyramidal and spinal recording and stimulation sites.

RESULTS

Observations in anaesthetized monkeys

Direct electrical stimulation of corticospinal tract

To compare the latencies of responses to electromagnetic and electrical stimulation of the scalp with the absolute conduction delays in the corticospinal pathway, this pathway was stimulated directly at several points. The conduction delays over the pathway from the cortex to the relevant spinal segments studied was determined by measurement of the latency of the antidromic response evoked in the hand area of the contralateral motor cortex by electrical stimulation of the DLF at the spinal recording site. With the stimulating electrode in the DLF at Th1, this was 1·79 ms (Fig. 1*A*). In all experiments it was possible to verify this conduction time by addition of the latencies of orthodromic DLF responses and antidromic cortical responses evoked by stimulation of the pyramidal tract ipsilateral to the motor cortex (1·02 and 0·78 ms in Fig. 1*C* and *B*, respectively). Electrical stimuli applied between the implanted pyramidal electrodes evoked a fast descending volley in the contralateral DLF (Fig. 1*C*). In all monkeys these volleys had thresholds of less than 50 μA and were maximal at about 300 μA (Fig. 1*D*). With increasing stimulus intensities the response latencies remained effectively constant (Fig. 6*C*). Accurate placement of the pyramidal electrodes was confirmed by post-mortem histology (Fig. 1*E*).

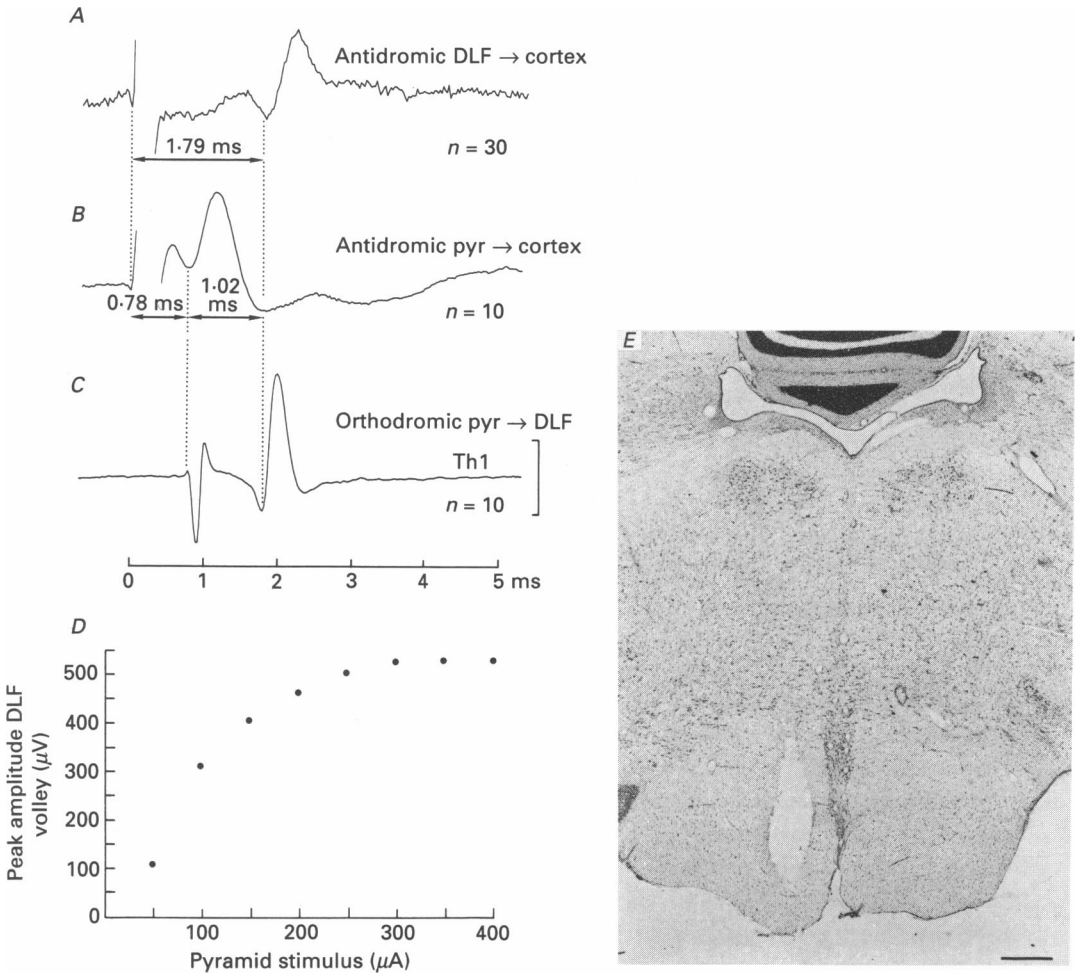


Fig. 1. *A–C*, conduction times in the corticospinal tract. *A*, averages of the antidromic responses evoked in the primary motor cortex by stimulation of the contralateral dorsolateral funiculus (DLF). Responses were recorded by a low-impedance intracortical electrode in the hand area of the motor cortex to single shocks (300 μA, 0·2 ms) delivered through a tungsten stimulating electrode in the DLF at the Th1 level. The latency of this response equalled the sum of the latencies of the responses shown in *B* and *C*. *B* is the antidromic response, recorded at the same cortical site and excited by stimulation of the pyramidal (pyr) tract, and *C* is the orthodromic volley set up by these same stimuli and recorded from the surface of the DLF at Th1. Pyramidal shock strength: 200 μA. This average has been moved to the right by an amount equal to the onset of the antidromic response in *B*. Calibration: *A*, 25 μV; *B*, 100 μV; *C*, 250 μV. In this and subsequent figures the number of sweeps contributing to the average is given by *n*. Negativity is upwards in all records. *D*, peak amplitudes of the orthodromic DLF volley evoked by shocks delivered to the pyramidal tract with the strengths indicated on the abscissa. In all experiments the volley amplitude saturated at or below 300 μA, which was taken to indicate maximal activation of the rapidly conducting corticospinal fibres. *E*, photomicrograph of section taken at the rostral medulla to demonstrate the location of the tip of the pyramidal tract-stimulating electrodes implanted in this monkey. Calibration bar: 1 mm.

Estimates of conduction velocity for this fast corticospinal volley were obtained from recording made in the DLF at two different segmental levels or between pyramid and DLF. The values obtained ranged from 66 to 72 m s^{-1}.

Electromagnetic stimulation

In each experiment electromagnetic stimulation evoked at threshold short-latency descending volleys in the DLF (early responses: E in Fig. 2*A*). Despite the use of a preamplifier with muted inputs, recordings of these volleys as they passed through the pyramid could not be made because of the magnitude of the stimulus artifact. Placement of the coil over the vertex of the skull was critical and small changes in the orientation of the coil could lead to large changes in the size of the response. In all four monkeys the optimal orientation was achieved with the coil placed tangential to the skull with the geometric centre of the coil 5–10 mm from the mid-line and over the left motor cortex. The coil was clamped at this position.

The threshold (*T*) for evoked volleys in the contralateral DLF was 30–40 % of the maximum output of all the three electromagnetic stimulators used. The amplitude of the early responses (E) grew with increasing intensity of stimulation (Fig. 2*A* and *C*). In two monkeys the responses were still increasing at the maximum output of the stimulator, but in the other two, responses reached a plateau at 80–90 % of maximum output (Fig. 2*C*). In the first three experiments, the responses evoked by electromagnetic stimulation were smaller than the maximum volley produced by pyramidal tract stimulation, with values of 65–75 % of the pyramidal response (Fig. 2*B* and *C*), indicating subtotal activation of the corticospinal tract. In the last experiment, using a more powerful stimulator (see Methods), electromagnetic stimulation evoked responses almost as large (90 %) as those from the pyramid.

In two experiments electromagnetic stimulation with Novametrix stimulators evoked late, rather labile volleys (L_1 and L_2 in Fig. 2*A*). These late responses were smaller than the early (E) volley and only appeared to stronger stimuli (65 % and 40 % or maximum output for the standard and more powerful Novametrix stimulators, respectively). In terms of threshold these values amounted to 2·2*T* and 1·5*T*, respectively. The latencies of both early and late responses evoked by electromagnetic stimulation at different intensities did not vary (Fig. 2*D* and Table 1.). There was a longer interval between the early (E) wave and the first late (L_1) wave than between L_1 and the second late wave (L_2).

The early descending volley set up by electromagnetic stimulation was verified as corticospinal by complete collision with volleys evoked by maximal electrical stimulation of the pyramid. In all cases the responses to electromagnetic stimulation were abolished with appropriately timed pyramidal volley (Fig. 3). Figure 3*A* and *B* shows the responses to pyramidal and electromagnetic stimuli when delivered separately. The response to the latter was completely collided when both stimuli were delivered simultaneously (Fig. 3*C*). It should be noted that the pyramidal volley used for collision is not visible in Fig. 3*C*, because it occurred during the period in which the preamplifier was muted. Complete collision occurred over the period in which the pyramidal stimulus preceded the electromagnetic stimulus by less than 1·5 ms or followed it by less than 0·5 ms (Fig. 3*D*).

Comparison of the latency of the early descending volleys evoked by electro-

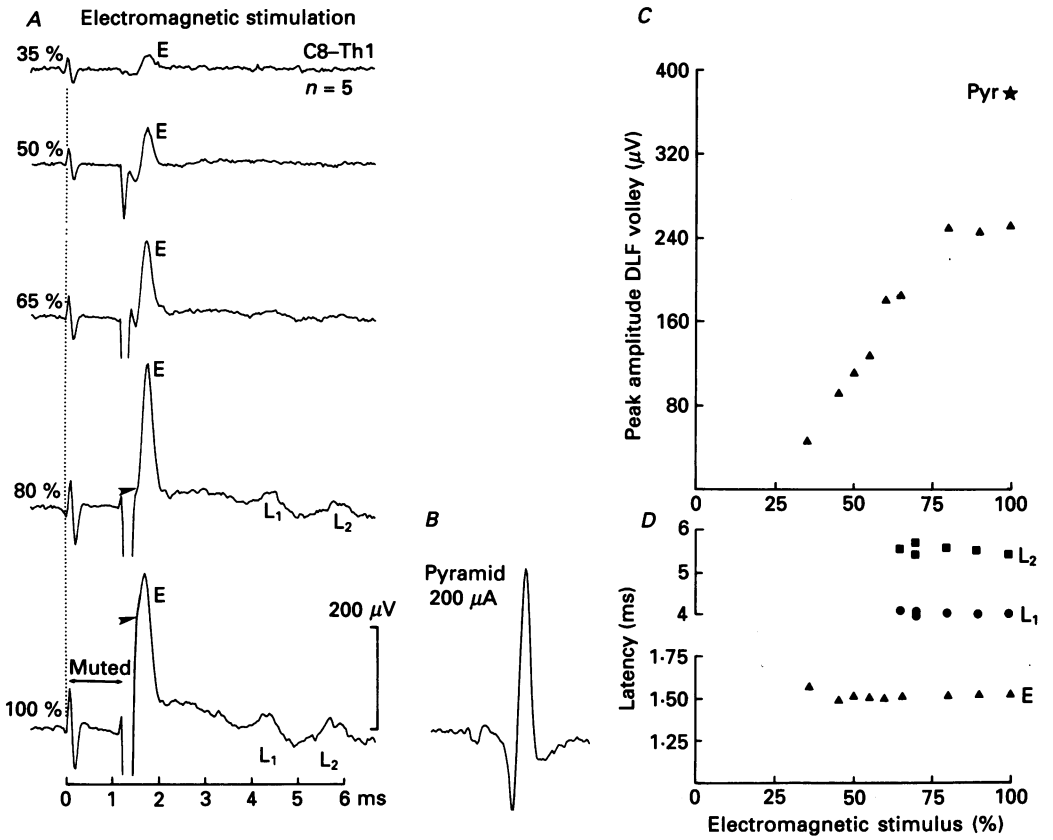


Fig. 2. *A*, averages of responses recorded from the surface of the DLF at the C8/Th1 border (right side) to electromagnetic stimulation of the cortex. The different stimulation strengths used are given as percentages of the stimulator's maximum output. Threshold was 30% and in this and the following figures the stimulus strengths are also given in multiples of the threshold for the first response (*T*). Weak shocks (35–65%; 1·2–2·2*T*) elicited only an early wave (E), while stronger shocks (75%, 2·5*T*) produced two additional later responses (L_1 and L_2). The stimulus artifact was suppressed by using a preamplifier with muted inputs in which the input leads were uncoupled for the period marked 'Muted', from the onset of the stimulus pulse until 1 ms later. The response was partially contaminated by the artifact at higher strengths (80 and 100%); the onset of the response is arrowed in each case. *B* shows, for comparison, the maximal orthodromic volley recorded from the same DLF electrodes to stimulation of the pyramid. Same gain as *A*. Negativity is upwards in *A* and *B*. *C*, the amplitude of the early volley measured from the prestimulus baseline level to the negative peak of the volley, evoked by electromagnetic stimuli of different strengths. In this experiment the volley size saturated at around 66% of the maximal pyramidal volley (Pyr ★). Each point is based on averages of five to ten responses. *D*, the latency of the early (E) and later waves (L_1 and L_2) remained constant at increasing stimulus strengths. Note the difference in the ordinate scales. All data from the same experiment.

magnetic stimulation with the delays determined using electrical stimulation of the corticospinal tract revealed a close correspondence (see Fig. 6*B*). Since the electromagnetically evoked orthodromic volleys had latencies similar to the antidromic volleys evoked by stimuli delivered at the spinal recording site, it is concluded that the electromagnetic stimuli activated corticospinal neurones directly.

TABLE 1. Latencies of late responses to electromagnetic and scalp stimulation

	Electromagnetic*	Scalp
At threshold	35%	7·5%
Early to first late response (L_1)	2·6 ms	2·5 ms
Between late responses (L_1–L_2)	1·4 ms	1·8 ms
At higher stimulus intensity	100%	25%
Early to first late response (L_1)	2.5 ms	2·7 ms
Between late responses (L_1–L_2)	1·4 ms	1·6 ms

* Novametrix standard stimulator.

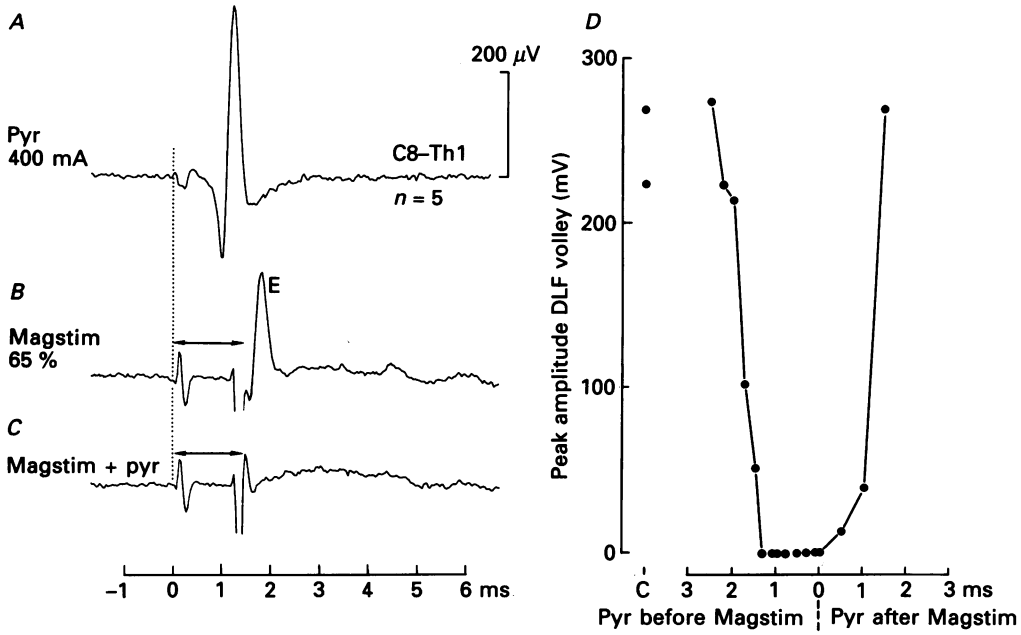


Fig. 3. *A–C*, collision of the early volley (E) evoked by electromagnetic stimulation (Magstim) at 65% (2·2*T*) by simultaneous supramaximal stimulation of the pyramidal tract (Pyr). *A*, shows the response recorded from the surface of the DLF to pyramidal stimulation alone, *B* the response to electromagnetic stimulation alone, while *C* shows that, when both stimuli were given simultaneously, the early volley was completely collided. In both *B* and *C* the preamplifier was muted for the period indicated by the arrows. This obscured the pyramidal volley in *C*, although its falling edge can just be seen after the artifact. Negativity is upwards in *A–C*. *D*, peak amplitude of the early volley evoked electromagnetic stimulation (65%) when preceded or succeeded by a supramaximal pyramidal shock. The collision period was brief (1·5 ms before to 1·5 ms after). Control (C) values for responses evoked by electromagnetic stimulation alone are shown on the left. Amplitudes measured from averages of responses to five shocks. Same experiment as *A–C*.

Scalp stimulation

In all three acute experiments in which this was tested, short-latency volleys in the ipsilateral pyramid and the contralateral DLF were evoked by scalp stimuli of relatively low intensity (Fig. 4*A* and *B*). With 50 μS pulses, the threshold for these volleys was 2·5–7·7% of maximum stimulator output. Increasing the stimulus

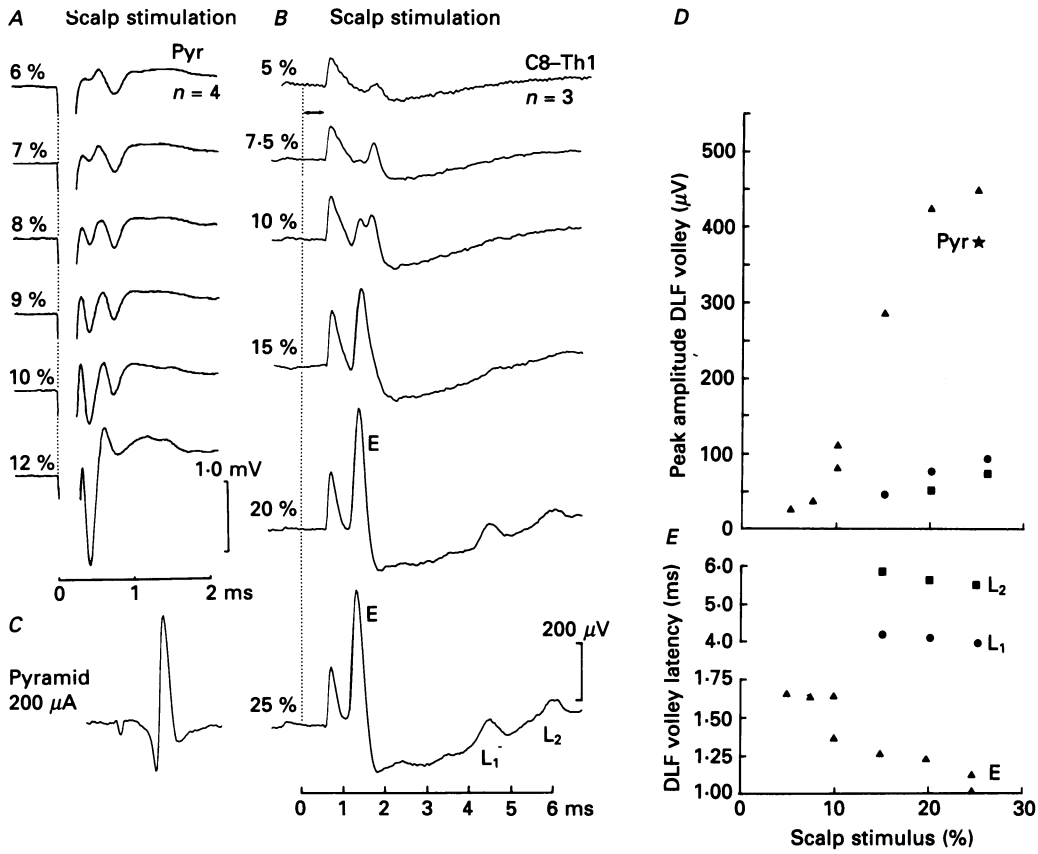


Fig. 4. *A*, responses to scalp stimulation (50 μS pulse) recorded differentially from tungsten electrodes in the left pyramidal tract at different stimulus intensities, given as percentage of the stimulator's maximum output. The 6% shocks (1·2*T*) elicited a small wave, on which an earlier wave was superimposed at 8% (1·6*T*) or higher. The first component was much larger than the second at higher strengths. Positivity is upwards. *B*, responses to scalp stimulation recorded from the surface of the right (contralateral) DLF at C8–Th1 in the same experiment as in *A*. The bifid appearance of the early (E) wave is apparent with stimulus intensities of 10% (2*T*); the E wave saturated at intensities of 20–25% (4–5*T*). At 15% (3*T*) late waves (L_1 and L_2) began to appear. *C* shows, for comparison, the maximal orthodromic volley recorded from the same DLF electrodes to stimulation of the pyramid. Same gain and timescale as *B*. Negativity is upwards. *D*, plot of peak amplitude of the E (▲), L_1 (●) and L_2 (■) DLF volleys against scalp stimulus strength. Above 20%, the E volley was slightly larger than the maximal pyramidal volley (Pyr ★). *E*, latencies of the E, L_1 and L_2 volleys at increasing scalp stimulus strengths. Note the difference in the ordinate scales. The sudden shortening in latency of the E wave is due to the appearance of the early component at 10% strength. All data from the same experiment.

intensity led to a large increase in the amplitude of the evoked response, which reached a plateau between 15 and 30% of maximum stimulator output (Fig. 4*D*). In two experiments, one of which is illustrated in Fig. 4, the amplitude of the early volley just exceeded that of the maximum pyramidal volley (Fig. 4*C*); in the third experiment they were of equal amplitude.

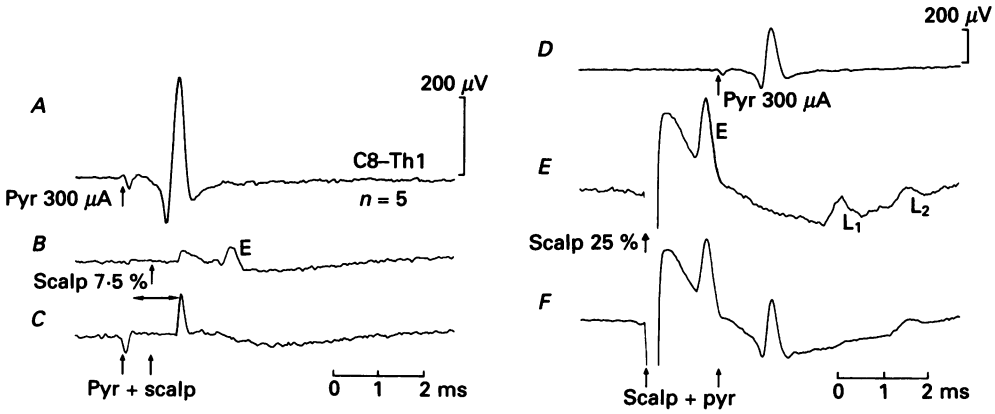
Further evidence that scalp stimulation could activate all large corticospinal fibres was provided by the observation that the volley evoked from the pyramidal electrodes could be abolished by a preceding scalp stimulus.

As with electromagnetic stimulation, increasing the stimulus intensity evoked later responses (Fig. 4*B*, L_1 and L_2); the thresholds for these waves were between 5 and 15% of stimulator output. The relative timing of the early and late waves was similar to that found for electromagnetic stimulation (Table 1).

A striking and consistent feature of the early volley evoked by scalp stimulation was the marked reduction in latency with increasing stimulus intensity (E in Fig. 4*E*). At threshold the latency of the early volley was similar to the conduction delay over the corticospinal pathway measured by direct electrical stimulation, indicating activation of the corticospinal neurones at a level close to the soma (Fig. 6*A*). Collision evidence, presented below, confirmed the corticospinal origin of the early volley. With increasing intensity of scalp stimulation, the latency of this volley decreased substantially, by 0·57–0·96 ms, values which approach the conduction delay from cortex to pyramid. Both DLF and pyramidal recordings showed that, as well as a small continuous shortening in latency, abrupt jumps in latency also occurred (Fig. 4*A*, *B* and *E*). The pyramidal recordings (Fig. 4*A*) clearly show that the early wave had two components, one at 0·6 ms (corresponding to the shortest cortex–pyramid delay in this monkey) and the other, which appeared with stronger stimuli (> 8%; 1·6*T*), at 0·3 ms. This higher-threshold component dominated the volley at higher strengths (Fig. 4*A*, 12% shock; Fig. 4*B*, 15 20, and 25% shocks). It would appear that the increment in stimulus intensity reaches threshold for activation of the corticospinal pathway at a site remote to the cortex, hence the latency 'jumps' to a lower value.

Figure 5*A–C* demonstrates the collision of the early wave evoked by low-intensity scalp stimulation (7·5% of maximum stimulator output; 1·5*T*). The timing of the pyramidal stimuli required to achieve collision of the early volley was different for threshold and stronger scalp stimuli (Fig. 5*G*). Thus with 7·5% shocks, the early volley was abolished when the pyramidal stimulus preceded the scalp stimulus by 1·5 ms, whereas with greater stimulus intensity (25%; 5*T*) the early volley was maximally reduced when the pyramidal stimulus preceded the cortical by less than 0·25 ms, indicating a site of collision further along the corticospinal pathway.

Fig. 5. *A–C*, collision of the early (E) volley evoked by weak scalp stimulation. Responses to supramaximal pyramid (Pyr) and 7·5% (1·5*T*) scalp stimulation alone are shown in *A* and *B*, respectively, while *C* shows that when both stimuli were given simultaneously, the E volley was completely collided. Timing of the stimuli indicated by the vertical arrows. In both *B* and *C* the preamplifier was muted for the period indicated by the horizontal arrow. Negativity is upwards. *D–F*, collision of the late (L_1) volley evoked by stronger intensity scalp stimulation (25%; 5*T*). The pyramidal shock (shown alone in *D*) was timed to precede the L_1 volley (shown in *E*), which was completely collided when both stimuli were applied (*F*). Negativity is upward. *G*, collision of the E volley evoked by scalp stimulation at 7·5% (●; right ordinate scale) and 25% (▲; left ordinate scale). Scalp shocks were preceded or succeeded by a supramaximal pyramidal shock. Collision occurred 1·0–1·5 ms earlier for the volley evoked by the weaker shocks. Control (C) values for responses evoked by scalp shocks alone are shown on the left of each plot. *H*. Collision of L_1 volley by pyramidal stimulation.



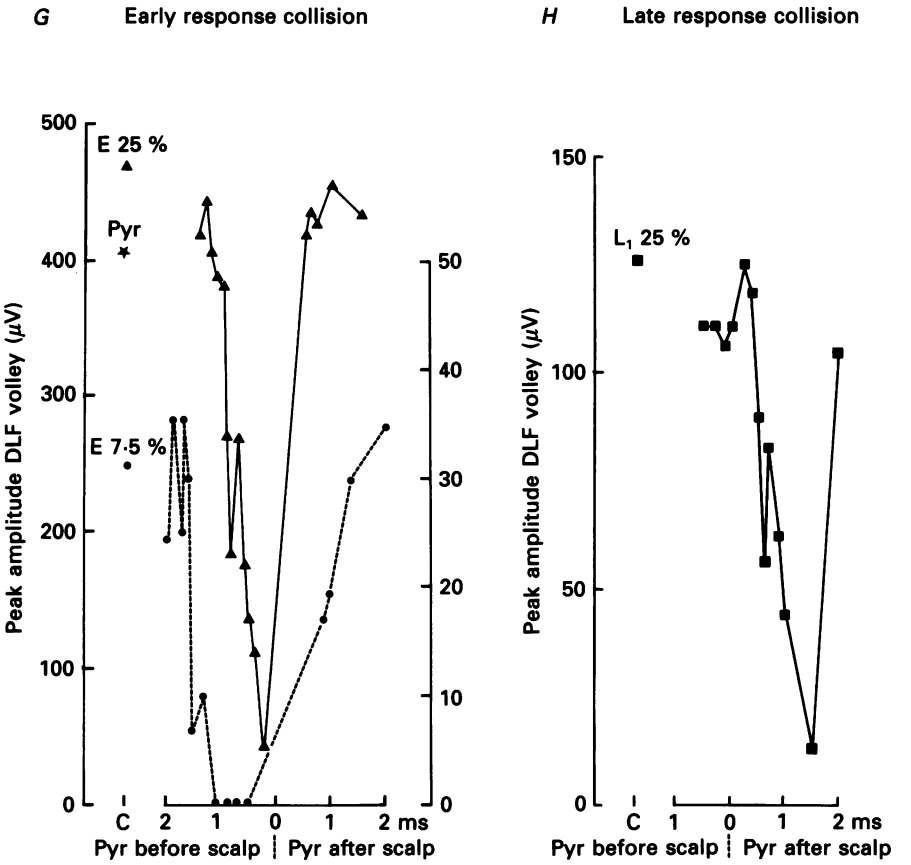


Fig. 5(*A–H*). For legend see facing page.

Complete collision of volleys evoked by scalp stimuli stronger than 20% (4*T*) was not observed. Figure 5*D–F* shows that the later waves evoked by such stimuli were also corticospinal in origin; collision of the L_1 wave is shown in Fig. 5*H*.

The sites at which the corticospinal pathway was activated could be estimated from the latency of the early volleys evoked by suprathreshold scalp stimuli. The comparisons of Fig. 6*B* suggest that the most caudal site of activation is either just rostral to, or at the level of, the medullary pyramid. Figure 6*C* demonstrates that the first latency jump occurred when the amplitude of the scalp-evoked volleys was a relatively small proportion of the maximal pyramidal volley. The relative invariance of the response latency to pyramidal and electromagnetic stimuli is also shown. A comparison of the volleys evoked in the same experiment by electromagnetic and scalp stimulation is shown in Fig. 6*A*. These volleys were recorded from the DLF at the level of the lumbar enlargement; the longer latency of the descending volleys at this spinal level allowed the fastest corticospinal volleys to be recorded without contamination by stimulus artifacts. Electromagnetic stimuli elicited an early (E) volley with essentially the same latency at two quite different strengths (50 and 100% full output; 1·7 and 3·3*T*), while there was shortening of the E wave by 0·96 ms when the scalp stimulus was increased from 8 to 25%. At the end of this experiment, killed-end recordings of the same volleys were obtained and their latencies were identical to those demonstrated in Fig. 6*A*.

A further indication that scalp stimuli could excite the corticospinal tract deep to the cortex comes from the observation that responses could be evoked in the DLF ipsilateral to the stimulated cortical hemisphere. These volleys were recorded by tungsten electrodes within the corticospinal tract. They were not due to volume conduction from the contralateral DLF, since there were no responses to supramaximal stimulation of the pyramid ipsilateral to the spinal recording site. Ipsilateral pyramidal stimulation failed to collide these volleys.

Fig. 6. *A*, comparison of volleys evoked by pyramidal (Pyr), electromagnetic (Magstim) and scalp stimulation (Scalp). Surface records from right DLF at upper lumbar (L1–L2) segments. Electromagnetic stimulation elicited an E wave with similar latency at both 50 and 100% of stimulator output (1·4*T* and 2·8*T*). Note that the preamplifier inputs were muted during these recordings. A volley of similar latency was produced by weak (8%; 1·6*T*) scalp stimulation. All these volleys had the same latency as the pyramidal volley (top), when this record was shifted to the right by the cortex–pyramid conduction delay (0·7 ms). Strong scalp stimuli (25%; 5*T*) produced an E wave at a much shorter latency (lowest average). Negativity upwards. *B*, timing of volleys in one monkey. DLF records at the C8–Th1 border. The upper two lines show that the latencies of the orthodromic and antidromic volleys from motor cortex to DLF were similar. These were evoked by surface anodal stimulation of the exposed cortex and by electrical stimulation in the DLF. Sum of conduction times from cortex to pyramid and from pyramid to DLF approach those of the overall ortho- and antidromic delays. Electromagnetic stimulation at 100% elicited a response slightly shorter than that for cortex-DLF (1·58 ms *vs.* 1·71 ms), and, while weak (5%) scalp stimulation elicited a volley with a comparable latency (1·68 ms), strong shocks shortened this to 1·0 ms (lowest line). *C*, amplitude–latency plot for the early volley elicited by scalp (●), pyramidal (▲) and electromagnetic (■) stimulation. Pyramidal and electromagnetic stimulation elicited volleys which had consistent latencies at all strengths. The maximum strength used is indicated for each type of stimulus. Scalp stimulation produced responses which shortened with suprathreshold stimuli. Two jumps in latency are evident, the first of which occurred with stimuli which elicited submaximal responses.

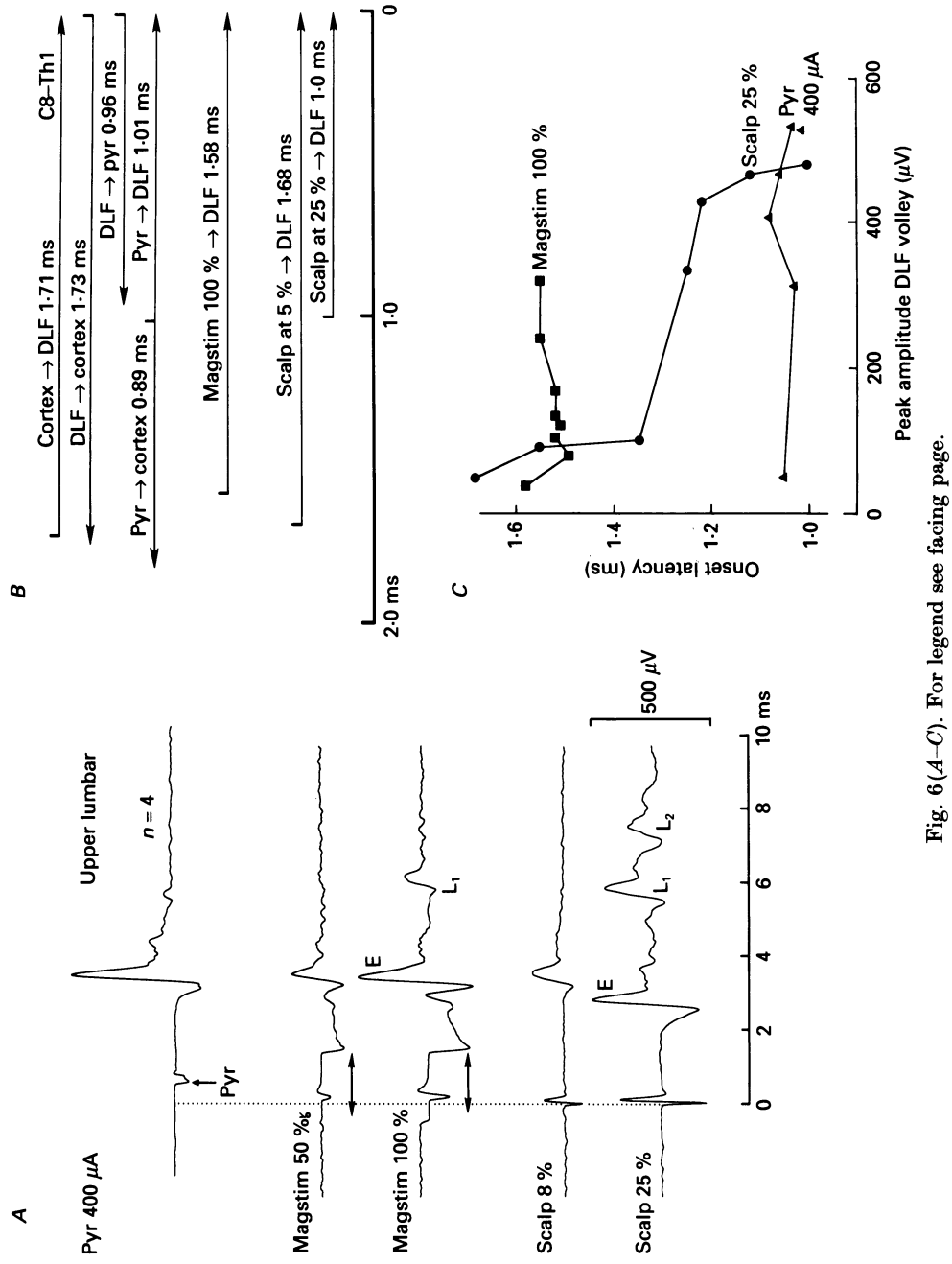


Fig. 6 (*A–C*). For legend see facing page.

Electromagnetic stimulation in the conscious monkey

The effects of electromagnetic stimulation were tested while the monkey performed a task involving precision grip movements between finger and thumb. Volleys were recorded differentially from electrodes implanted in the pyramidal tract and EMG responses were recorded from hand and forearm muscles.

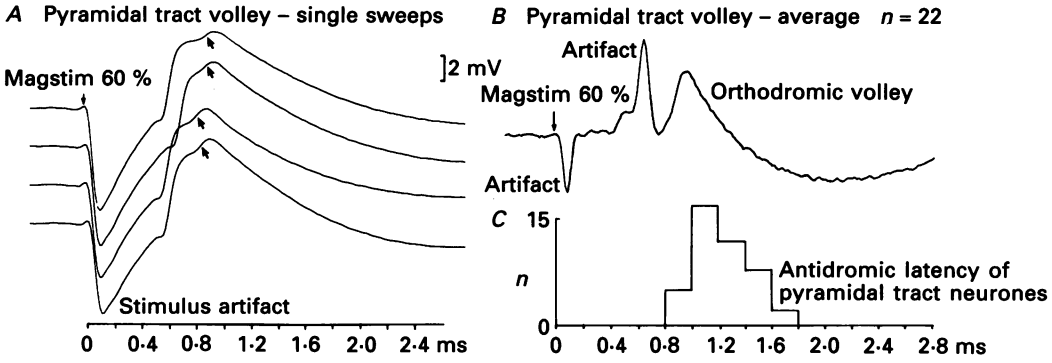


Fig. 7. Short-latency volleys evoked by electromagnetic stimulation (Magstim) and recorded from the pyramidal tract in a conscious monkey. *A*, four successive single sweeps. Despite the use of a preamplifier with muted inputs, a large artifact preceded a small volley (arrows), recorded differentially between two tungsten electrodes implanted in the pyramidal tract. *B*, the average of twenty-two sweeps where artifact subtraction has been used. The latency of this orthodromic volley (0·8 ms) corresponded closely to the latency at which pyramidal tract neurones could be antidromically excited from these same electrodes (histogram for forty-four neurones in *C*). Positivity is upwards in *A* and *B*.

Pyramidal tract recordings are shown in Fig. 7*A*. Because of the proximity of the recording electrodes to the stimulating coil large artifacts dominate the recordings, although small responses can be observed (arrows). Following averaging and subtraction of the artifact an orthodromic response becomes apparent (Fig. 7*B*). This volley was probably corticospinal because its latency (0·8 ms) corresponded with the latencies for antidromic activation of corticospinal neurones by these pyramidal electrodes in the same monkey (Fig. 6*C*). These neurones were sampled following the implantation of a recording chamber (see Methods).

Electromagnetic stimulation evoked short-latency EMG responses in both hand and forearm muscles. As shown in Fig. 8*A*, stimuli were delivered at the onset of a precision grip movement, when there was a sharp increase in force exerted by both index finger and thumb. The threshold for these responses was 25–35 % of maximum stimulator output. Typical EMG responses are shown in Fig. 8*B*. The mean latencies of these responses were 10·4 ms (S.D. ±0·7 ms) in abductor pollicis brevis (AbPB) and 7·7 ms (S.D. ±0·9 ms) in extensor digitorum communis (EDC). Responses evoked in the same muscles by single-pulse stimuli delivered through the pyramidal electrodes are also shown; their form closely resembled those induced by electromagnetic stimulation. Pyramidal responses had onset latencies of 9·7 ms (S.D. ±0·8 ms) and 6·0 ms (S.D. ±0·6 ms), in AbPB and EDC, respectively. Responses evoked from the pyramid

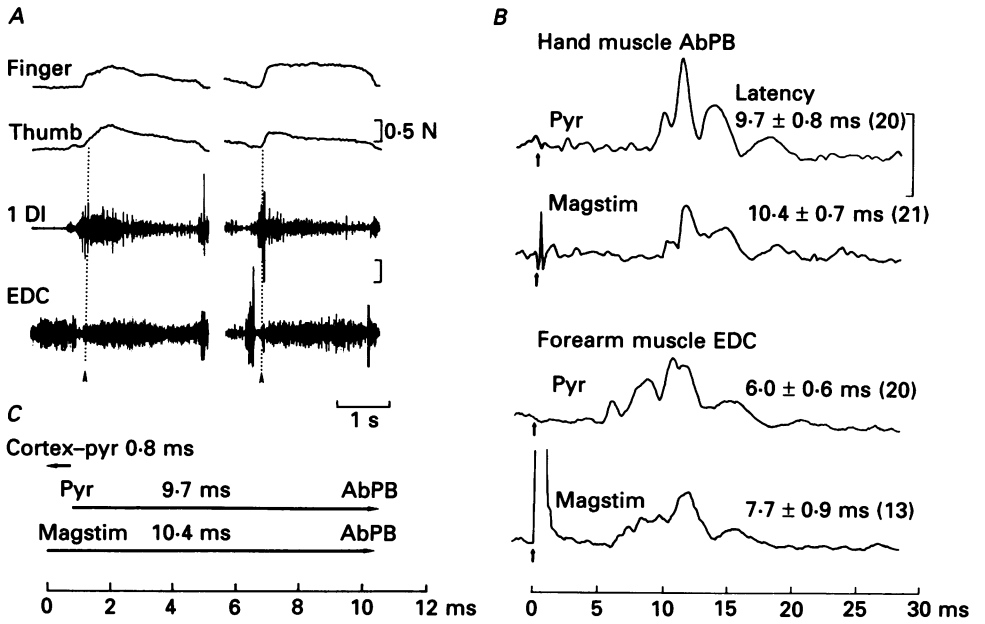


Fig. 8. EMG responses evoked by electromagnetic stimulation in hand and forearm muscles in the conscious monkey. *A*, stimuli were delivered during performance of a trained precision grip task, in which the monkey was required to exert a steady force on two levers with its index finger and thumb (top traces). Stimuli (arrowed) were timed to occur with the onset of force at the beginning of randomly selected trials, two of which are shown. Raw EMG records from the first dorsal interosseus (1DI) and extensor digitorum communis (EDC) are shown. Calibration: 1 mV for 1DI, 2 mV for EDC. *B*, averaged rectified EMG from AbPB and EDC. Electromagnetic stimulation (65%) produced short-latency responses which were slightly longer than responses recorded during the same session by single stimuli delivered to the pyramidal tract (duration 0·2 ms, strength 200 μA). Both types of stimuli were delivered during force onset. Stimulus onset is arrowed. Averages of thirty-two sweeps. Mean onset latencies (±S.D.) are given beside the records, together with the number of averages measured (in parentheses). *C*, latency of the EMG response evoked by electromagnetic stimulation in a hand muscle (AbPB) was 10·4 ms, which represented the sum of the latency for pyramidal response in the same muscle (9·7 ms) together with the conduction time from cortex to pyramid, taken as being equal to the latency of the antidromic volley recorded in the cortex after pyramidal stimulation (0·8 ms).

should have briefer latencies than those from the cortex because of the shorter conduction distance. The additional delay can be estimated from the shortest latency of antidromic activation of corticospinal neurones from the same pyramidal electrode, as shown in Fig. 8*C*. A histogram of these latencies, taken from the same animal, is given in Fig. 7*C*; the minimum latency was 0·8 ms.

There was concern that the magnetic field might induce currents in the implanted tungsten electrodes. This is excluded, however, since the latencies of the earliest responses to electromagnetic stimulation remained constant during the three phases of the experiment: in the intact animal before surgery, following implantation of pyramidal electrodes and after implantation of a stainless-steel chamber and headpiece for head restraint during chronic single-unit recording.

An alternative and more direct estimate of the total conduction time in the pathway from corticospinal neurones to muscle fibres in an awake monkey can be obtained from the latencies of post-spike facilitation produced by corticospinal neurones in the EMG of their target muscles (see Lemon *et al.* 1986). Subsequent to the electromagnetic stimulation experiments, recordings were made from corticospinal neurones in this monkey and the shortest latencies of post-spike facilitation in intrinsic hand muscles were 9·3–11·7 ms (mean 10·8 ms, $n = 5$). The similarity between these latencies and those of responses to electromagnetic stimulation confirms that the latter activated corticospinal neurones directly.

DISCUSSION

With the increasing use of electromagnetic and scalp stimulation for research and clinical diagnostic investigation, the mode of action of the stimuli upon the cerebral cortex needs to be critically examined. The present study suggests that at threshold these stimuli can activate the corticospinal pathway directly, in both anaesthetized and conscious monkeys. These experiments have demonstrated that in the anaesthetized monkey both types of stimuli evoke early and multiple late volleys, which can be recorded from the contralateral DLF and which can be collided by appropriately timed maximal corticospinal volleys elicited by stimulation of the medullary pyramid. The short period (1·0–1·5 ms) over which the pyramidal shock could collide the early component of the corticospinal volley indicates that collision takes place in rapidly conducting corticospinal axons with short refractory periods. These observations provide the first unequivocal evidence for activation of the fast-conducting fibres of the corticospinal tract by non-invasive stimulation of the brain.

The latency and form of the early responses evoked by threshold electromagnetic and scalp stimulation correspond with those of the direct response (D wave) first described by Patton & Amassian (1954). At higher intensities both types of stimulus evoke later volleys, the timing of which corresponds closely to the indirect, presumed trans-synaptic activation of corticospinal tract neurones (I waves, Patton & Amassian, 1954; Kernell & Wu, 1967). Similar late waves were observed with scalp stimulation by Boyd *et al.* (1986). Kernell & Wu (1967) found that surface anodal stimulation of the exposed baboon motor cortex elicited a series of I waves with intervals of 1–2 ms, which closely correspond to the intervals between late responses in the present study (see Table 1). The interval between the early and first late response in the present study (2·5–2·7 ms) is longer than the D–I_1 interval found by Kernell and Wu (1967) and it is most likely that the first late response in the present study corresponds to their I_2 wave, which had a lower threshold than I_1. The observations of Amassian *et al.* (1987*a*) of I waves alone at threshold with a tangentially orientated coil have not been confirmed in the present study. On the contrary, the present results indicate that electromagnetic stimulation can activate corticospinal neurones directly in both conscious and anaesthetized monkeys.

The relative efficacy of electromagnetic and surface anodal scalp stimulation can be estimated by comparing the magnitude of the maximum volleys evoked with the volley set up by supramaximal stimulation of the medullary pyramid (Figs 2*C* and 4*D*). From these data we conclude that the fast component of the corticospinal tract

in the monkey cannot be fully activated by electromagnetic stimulation with the Cadwell and standard Novametrix stimulators (up to 75% of the maximal pyramidal volley), although the more powerful Novametrix instrument could activate almost all of the fibres (up to 90% of the maximal pyramidal volley). In contrast, scalp stimulation achieved full activation at less than 30% of its output (50 μs pulses), corresponding to a shock strength of about 225 V.

At threshold both types of stimulus evoked early responses with latencies identical to that of the antidromic volley recorded in the motor cortex following stimulation of the DLF. It follows that at threshold, the early response represents activation of corticospinal tract neurones within the cerebral cortex, most probably at the level of the initial segment (Jankowska, Padel & Tanaka, 1975). Whereas with increasing intensities, the latency of the early responses evoked by electromagnetic stimulation remained constant, the latencies of those elicited by scalp stimulation shortened considerably. In all three monkeys in which this was studied, the shortening began with stimuli as low as 1·5 times threshold and well below the intensity at which maximum corticospinal activation was achieved (Fig. 6*C*). The minimum absolute latencies observed approached, and in one case were less than, the latencies of responses to stimulation of the medullary pyramid (Fig. 6*A* and *B*). Given the conduction velocity of corticospinal fibres observed in this study 66–72 m s^{-1}), a shortening of 1 ms represents a site of activation 66–72 mm below the grey matter of the sensorimotor cortex, i.e. at, or caudal to, the medullary pyramid. The sudden rather than continuous reduction in latency suggests that above a certain intensity, the current path is particularly effective for activating the deeper parts of the corticospinal tract. This effect might be due to changes in the orientation of the fibres in relation to the current path, for example at the cerebral peduncle or the pyramidal decussation.

It is important to note that the early responses evoked by high-intensity (25%) scalp stimulation could be almost completely collided by a pyramidal volley at a condition–test interval which was about 1 ms less than that observed with volleys evoked close to threshold (7·5% of output, see Fig. 5*G*). The spread of the stimulus is confirmed in part by the observations in one monkey that scalp stimulation evoked a volley at short latency in the *ipsilateral* DLF which could not be collided by a volley from the ipsilateral medullary pyramid. Bilateral activation of corticospinal fibres would be expected if the scalp stimulus was acting at the level of the pons or pyramid, where the left and right corticospinal tracts lie in close proximity.

The incomplete collision of responses evoked by strong scalp stimulation (25%; Fig. 5*G*) may reflect the activation of other fast descending fibres by these stimuli, as might be expected if the stimulus were acting at brain stem levels. This could be supported by the observation that at only 25–30% of full output, scalp stimuli elicited volleys which were larger than the maximal pyramidal volley (Fig. 4*D*).

Differences in the site of activation of the corticospinal pathway obtained at high intensity with the two forms of stimulation are not surprising considering the currents they are proposed to induce. Branston & Tofts (1990) have demonstrated that electromagnetic stimulation results in induced current profiles that lie parallel (tangential) to the surface of the skull. The magnitude of the magnetic field and thus presumably the current density diminishes in a direction perpendicular to the brain

surface initially in proportion to the square and then the cube of the distance from the centre of the coil (see Muncaster, 1982). For surface anodal electrical stimulation of the pial surface the current profiles lie predominantly perpendicular to the brain surface and the threshold for discharge of corticospinal neurones is proportional to the square of the distance from the anode (Phillips & Porter, 1977; Amassian *et al.* 1987*b*).

There are obvious differences in size and shape of the human and macaque skull. The human cortex is also more deeply folded, so that the orientation of corticospinal neurones with respect to the stimulating coil will be different in the two species. Nevertheless, the present results in the monkey are relevant to the interpretation of observations in human subjects using both forms of stimulation. The characteristics of the DLF volleys evoked by surface anodal electrical stimulation in the present study are comparable to those recorded by Boyd *et al.* (1986) in human subjects. For example, they report a shortening of the D wave by up to 0·8 ms with a bifid appearance as the stimulus intensity is increased (cf. Fig. 4). The shortening of 0·8 ms in latency and the conduction velocity calculated by these authors (50–74 m s^{-1}) implies a separation of at least 40 mm between the sites of activation at low and high current intensities. Finally, there is some evidence that electromagnetic stimulation in man can elicit a D wave (A. Berardelli, personal communication).

Most of the evidence relating to the action of non-invasive brain stimuli has been derived from studies of the timing of whole EMG and single motor unit responses. This evidence is essentially indirect and is complicated by factors governing the excitability of the α-motoneurones. Day *et al.* (1989) have argued that anodal scalp stimulation excites corticospinal neurones directly at the level of the motor cortex. They concluded that electromagnetic stimulation acts principally through trans-synaptic excitation of the corticospinal neurone, because a given motor unit was activated by electromagnetic stimulation up to 2 ms later than by anodal scalp stimulation. However, the shortest-latency category of motor unit responses, described by Day *et al.* (1989) as P0, represented the shortest latencies obtained with anodal scalp stimulation. It is not clear whether these responses were evoked at threshold or at higher stimulus intensity. This point is crucial since both whole EMG and single motor unit responses exhibited latency shortening of up to 1·5 ms with increasing stimulus intensities (Figs 3 and 11 of Day *et al.* 1989; see also Calancie, Nordin, Mallin & Hagbarth, 1987). An alternative interpretation of these results is that the shortest latency responses (P0) resulted from activation of the corticospinal tract below the level of the cortex while the electromagnetic stimuli acted at the cortex (latency category P1, Day *et al.* 1989). It is not known in man how large the corticospinal volleys must be before overt responses can be observed in actively discharging motoneurones, although in the conscious monkey large pyramidal shocks are required to excite some active hand motoneurones (W. Werner & R. N. Lemon, unpublished observations). It follows that at the intensities of scalp stimulation required to activate a given motor unit, the site of activation could already be deep to the cortex (see Fig. 6*C*). A further argument for a cortical rather than a deep site of activation by surface anodal stimulation in man has been that responses in different muscles are dependent upon the precise location of the anode, and this is thought to reflect the topographic representation of different body parts.

However, it is unclear whether the topographical representation of these responses is preserved with suprathreshold stimuli (Lemon, 1988).

Several studies have claimed a trans-synaptic action of electromagnetic stimuli, because the EMG responses evoked could be conditioned by the level of cortical excitability. The conditioning influences have included the degree and type of voluntary contraction (Hess *et al.* 1987; Datta, Harrison & Stephens, 1989), and long-latency cortical activation by muscle stretch (Day, Marsden & Rothwell, 1989). However, all of these conditioning procedures will affect the level of excitability of both the initial segment of the corticospinal neurones *and* cortical interneurones (Brooks & Eccles, 1947; Edisen, 1956; Amassian *et al.* 1987*b*). These conditioning procedures would be unlikely to affect the excitability of corticospinal axonal nodes in subcortical white matter and this offers an alternative explanation for the insensitivity of scalp-evoked responses to the level of cortical activity.

The present experiments show that both types of non-invasive stimulus can excite corticospinal neurones directly in the monkey, and, with higher stimulus intensities, scalp stimulation can activate the corticospinal pathway as far caudal as the medulla. It is probable that both types of stimulus evoke comparable responses in man.

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