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CORTICOSPINAL PROJECTIONS TO UPPER LIMB MOTONEURONES IN HUMANS

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SUMMARY

1. Magnetic stimulation was applied over the motor cortex in forty-five normal human subjects and peristimulus time histograms (PSTHs) of the discharges of single motor units were used to record changes in the firing probability of individual spinal motoneurones of contralateral upper limb muscles. Recordings were obtained from 153 motor units from fourteen upper limb muscles.

2. For the majority of motor units the initial effect was a short latency facilitation. The estimated central conduction velocities and the rise times of the underlying excitatory postsynaptic potentials (EPSPs) were compatible with monosynaptic facilitation by a fast corticospinal pathway. In some motor units the initial effect was a short latency inhibition. Other units showed no statistically significant changes in firing probability. The proportion of the tested motor units in each of these categories depended on the muscle. All of the sampled units of first dorsal interosseous (1DI) showed short latency facilitation, as did the majority of units in the forearm and the biceps brachii. More than half of the sampled motor units of triceps brachii and deltoid showed either no effect or were inhibited.

3. To compare the *net* short latency actions of the neurones activated by magnetic stimulation on various motoneurone pools, the magnitude of the short latency facilitation or inhibition in a given motor unit was normalized to the magnitude of the short latency facilitation in the 1DI motor unit of the same subject at the same stimulus intensity, and these data were pooled for a number of subjects.

4. 1DI motoneurones received strong net facilitation (estimated mean EPSP amplitude $2{\cdot}9 \pm 0{\cdot}2$ mV), the motoneurones of forearm muscles and biceps brachii received weaker net facilitation and triceps brachii and deltoid received no net effect.

5. It is concluded that the short latency corticospinal projections to upper limb motoneurones in humans have a distinct pattern which is similar to that in other primates.

INTRODUCTION

The projections of individual cortical neurones to spinal motoneurones have been identified in primates using spike-triggered averages. Some motor cortex neurones, ('corticomotoneuronal' cells), produce transient post-spike facilitation in target muscles with a duration and latency suggesting monosynaptic connections to spinal

motoneurones (Fetz & Cheney, 1980). Post-spike facilitation is stronger for hand muscles than for forearm muscles (Lemon, Mantel & Muir, 1986), probably reflecting greater independence of these muscles in discrete movements. Some cortical cells produce post-spike suppression of EMG activity, which is thought to be mediated disynaptically by spinal inhibitory interneurones (Kasser & Cheney, 1985; Lemon *et al.* 1986).

Anodal stimulation over the cortical surface excites large populations of cortical neurones. The composite postsynaptic potentials (PSPs) in motoneurones reflect the net synaptic actions on motoneurones of these corticospinal neurones and thus the 'interest' of the cortex in the control of various muscles. Phillips & Porter (1964) reported that motoneurones of distal muscles of the baboon's forelimb received stronger monosynaptic facilitation than did motoneurones of proximal muscles, and that more biceps than triceps motoneurones showed monosynaptic excitation.

Surface anodal stimulation over the motor cortex in intact, awake human subjects produces short latency EMG responses in contralateral limb muscles (Merton & Morton, 1980; Rothwell, Thompson, Day, Dick, Kachi, Cowan & Marsden, 1987) at latencies consistent with the activation of rapidly conducting corticospinal neurones (Rothwell *et al.* 1987). The estimated rise times of the excitatory postsynaptic potentials (EPSPs) generated in motoneurones are short, suggesting that the corticospinal neurones activated by anodal stimulation in man make monosynaptic connections with spinal motoneurones (Zidar, Trontelj & Mihelin, 1987; Day, Dressler, Maertens de Noordhout, Marsden, Makashima, Rothwell & Thompson, 1989).

The human motor cortex can also be stimulated without the discomfort produced by anodal stimulation, by using a rapidly changing magnetic field to generate electric currents in the brain. Magnetic stimulation over the motor cortex produces short latency contractions of contralateral muscles, similar to those produced by anodal stimulation (Barker, Freeston, Jalinous, Merton & Morton, 1985; Hess, Mills & Murray, 1987; Mills, Murray & Hess, 1987). The responses to magnetic stimulation have latencies that are 1–2 ms longer than the responses to anodal stimulation (Hess *et al.* 1987). Hess *et al.* (1987) and Day *et al.* (1989) have argued that the latency difference occurs because anodal stimulation activates corticospinal neurones directly, whereas magnetic stimulation activates the corticospinal pathway transsynaptically. However, Edgley, Eyre, Lemon & Miller (1990) postulate that the initial facilitation following magnetic stimulation in man results from direct activation of cortical neurones, and that the earlier facilitation observed following anodal stimulation is due to excitation of corticospinal fibres deeper in the brain.

Anodal cortical stimulation produces a distinct pattern of muscle activation in normal human subjects (Rossini, Marciani, Caramia, Roma & Zarola, 1985; Cowan, Day, Marsden & Rothwell, 1986; Rothwell *et al.* 1987; Beneke, Meyer, Gohmann & Conrad, 1988). When surface recordings are made from various muscles, distal upper limb muscles are recruited more readily than proximal muscles, and the amplitudes of the evoked muscle action potentials are larger for distal than proximal muscles. Surface recordings of EMG activity in response to magnetic stimulation in normal subjects have shown a similar pattern (Brouwer & Ashby, 1990).

Surface recordings of evoked EMG, however, cannot provide reliable information

about the projections of cortical neurones to motoneurones in man. Inhibitory projections cannot be detected in this way, and the amount of background activity of motoneurones affects the amplitude of the response to anodal (Rothwell *et al.* 1987; Beneke *et al.* 1988) and magnetic (Hess *et al.* 1987) stimulation.

In this study, magnetic stimulation was used to activate large populations of cortical neurones. The characteristics of the short latency PSPs generated in the motoneurones of various upper limb muscles were derived from peristimulus time histograms (PSTHs) of repetitively discharging motor units. The area of a peak of increased firing probability in a PSTH was used to estimate the amplitude of the composite EPSP and the duration of the peak was used to estimate its rise time (Ashby & Zilm, 1982; Fetz & Gustafsson, 1983; Cope, Fetz & Matsumura, 1987). The amplitudes of PSPs in motoneurones of each muscle were compared to the amplitude of the EPSP in a first dorsal interosseus (1DI) motoneurone of that subject at the same recording session using the same stimulus parameters. It is assumed that the relative sizes of the PSPs in various motoneurones reflect the number of projections (and/or boutons) from the cortex to the motoneurone and thus the 'interest' of the cortex in that motoneurone pool.

METHODS

Studies were carried out on forty-five normal subjects, who provided informed consent. Recordings were made from fourteen upper limb muscles on the non-dominant side: anterior, middle, and posterior deltoid, long head of biceps brachii, long, medial and lateral heads of triceps brachii, extensor carpi radialis (ECR), extensor carpi ulnaris (ECU), extensor digitorum communis (EDC), flexor carpi radialis (FCR), flexor carpi ulnaris (FCU), flexor digitorum sublimus (FDS), and first dorsal interosseous (1DI).

A concentric needle electrode (Dantec 13L49, recording surface area = 0·07 mm^2) was inserted into the muscle to be studied and positioned close to a motor unit which was activated by gentle voluntary contraction. The subjects were asked to perform a variety of movements to ensure that the recorded unit belonged unambiguously to a given muscle. The action potentials of this motor unit were extracted with a window discriminator and displayed on a storage oscilloscope via a delay line. The trigger pulse was generated at the peak of the selected motor unit action potential, so the time to peak was measured and all latencies were corrected for the rise time of the motor unit action potential. Subjects were instructed to keep the unit firing steadily at a rate of 5–10 Hz with the aid of visual and auditory feedback of the motor unit's discharge.

A brief, rapidly changing magnetic field was generated with a Cadwell MES-10 magnetic stimulator. When this stimulator is triggered, a current is discharged through a 14-turn stimulating coil (inside diameter 7·5 cm, outside diameter 9 cm). This generates a magnetic flux (maximum 2 T at 100% according to the manufacturers specifications) which in turn induces currents in conductive materials in the vicinity of the coil, in the form of a damped sinusoid with a first peak at about 5 μs. The stimulating coil was placed flat on the scalp, over the motor cortex, centred over a point marked on the scalp, midway between Cz and C4 (Cz–C4) or midway between Cz and C3 (Cz–C3), with the inducing current flowing clockwise (as viewed from above) at Cz–C4, and counterclockwise at Cz–C3. A minimum of 100 stimuli, at 3 s intervals, were delivered to the hemisphere contralateral to the recording site. For experiments in which the effects of magnetic stimulation on the motoneurones of various muscles were to be compared, the stimulus intensity was standardized to just below the level which resulted in a muscle twitch in the voluntarily contracted 1DI. This is called 'standardized intensity'. Stronger or weaker stimuli were used to examine the effect of varying stimulus intensity (but these data were not used in the comparisons between the motoneurones of different muscles).

A laboratory computer was used to generate peristimulus time histograms (PSTHs), with bin width 1 ms. A 100 ms pre-stimulus period was used to determine the mean background firing probability of the motor unit (which was between 0·5 and 1 counts per bin when firing frequency

was 5–10 Hz), after frequency histograms had shown that the variation of bin contents in the pre-stimulus portion was roughly Gaussian.

A 'satisfactory recording' was defined as a run in which the unit's spike train had been recorded without contamination during 100 stimuli. A 'period of increased firing probability' was accepted if the mean firing probability in one or more bins exceeded the mean background firing probability plus two standard deviations. A running smooth of two bins was used to define the beginning and end of a peak and hence its width. The area of the peak of increased firing probability above the mean background level (expressed as 'extra counts per 1000 stimuli') provided an estimate of the magnitude of the underlying composite EPSPs produced by the corticospinal volley. To avoid including random 'peaks' which occur in the pre- and post-stimulus periods, a period of increased firing probability as defined above was still rejected if the total number of extra counts per 1000 stimuli in a peak was less than 35 (see Mao, Ashby, Wang & McCrea, 1984).

A 'period of decreased firing probability' was accepted if the mean firing probability of sections of five consecutive bins was significantly less than the background mean firing probability of the 100 ms pre-stimulus period using Student's t test and $t > 2$. The area of the period of decreased firing probability was expressed as 'fewer counts per 1000 stimuli'. This method of analysis differs from that used for EPSPs because the reduction in firing probability is limited at zero and cannot be shown to be less than two standard deviations from the mean unless extremely long runs are used.The width of a period of decreased firing probability was defined from the centre of the last five-bin segment that was significantly less than the pre-stimulus mean.

The initial changes in firing probability occurring at 'short latency' were analysed separately. The latency of a response depends on the subject's height, and the distance of the particular muscle from the spinal cord. For 1DI, responses occurring with a latency of < 30 ms were accepted as 'short latency'. For more proximal muscles, such as biceps and triceps, the response had to be about 5–10 ms shorter and for deltoid, 10–15 ms shorter than the latency of the 1DI response in that subject. Only the initial peak or trough was analysed (as an EPSP is represented by a peak followed by a trough, and an IPSP by a trough followed by a peak). If there was no response at the appropriate time the response was scored zero (i.e. the value of the pre-stimulus background). Responses which occurred at longer latencies, but which were still less than voluntary reaction time (100 ms), were analysed separately.

The percentage of motor units of a given motoneurone pool showing short latency facilitation, inhibition or no response provided a qualitative description of the projections to that motoneurone pool. This does not take into account differences in the strength of the facilitation or inhibition. An estimate of the 'net action' of the corticospinal projections to a given motoneurone pool was obtained in the following way. Changes in the firing probability of a motor unit (expressed as positive numbers for extra counts per 1000 stimuli, or negative numbers for fewer counts per 1000 stimuli), were expressed as a percentage of the changes in the firing probability of the 1DI motor unit obtained in the same subject, at the same stimulus intensity, at the same recording session. The means of these values from a number of subjects were determined for each muscle studied. In some initial studies, changes in the firing probability of motor units in the wrist flexors (FCU, FDS) and wrist extensors (ECU, ECR) were normalized to those in the FCR and the EDC respectively. These data could not be related to 1DI in the same manner, but, as the percentage of sampled units showing facilitation or inhibition is valid, these data are included. Student's t tests were used for the statistical analysis.

The central conduction velocity of the pathway producing short latency facilitation of 1DI motoneurones was estimated as follows. The direct muscle response (M wave) and recurrent response (F wave) were recorded from the 1DI with surface electrodes, following supramaximal stimulation of the α-motoneurone axons in the ulnar nerve at the wrist. The peripheral conduction time was estimated from 1/2 (latency of F wave $-$ 1 ms (turnaround time) + latency of M wave), and an additional 1 ms was allowed for the synaptic delay between the corticospinal pathway and the α-motoneurone.

RESULTS

A total of 153 satisfactory recordings were obtained from forty-five subjects, aged 20–52, during stimulation at standardized intensities.

Short latency responses

Magnetic stimulation resulted in short latency facilitation or inhibition in the majority of units. Examples are shown in Figs 1 and 4. The results are summarized in Tables 1 and 2. The proportion of sampled motor units of a given motoneurone pool showing short latency facilitation, inhibition or no response is shown in Fig. 2 and the *net* short latency effect normalized to the response in 1DI (see Methods) is shown in Fig. 3. The responses of certain representative motoneurone pools are presented in more detail below.

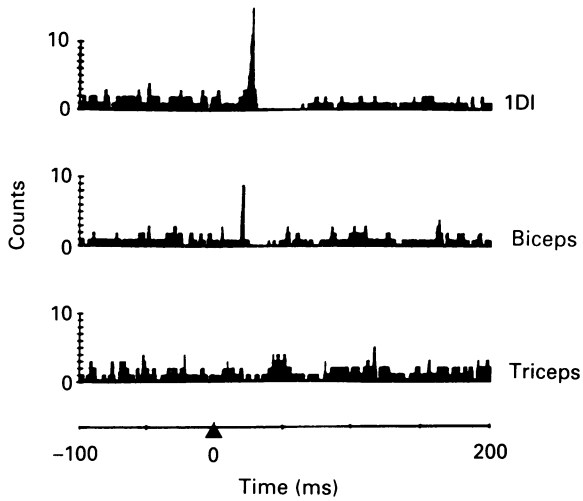

Fig. 1. PSTH of single motor units in the left 1DI (top), biceps (middle), and lateral head of triceps (bottom) in one subject, in response to magnetic stimuli applied over the right motor cortex (Cz–C4) at 29% of the maximum stimulator intensity. The stimulus was delivered at time zero. There is a large short latency peak of increased firing probability in the 1DI motor unit (latency = 23 ms, extra counts per 1000 stimuli = 276), a smaller peak in the biceps motor unit (latency 14 ms, extra counts = 119), and no short latency peak in the triceps motor unit, although there is a later peak (latency = 40 ms, extra counts = 135).

Projections to 1DI

Strong short latency facilitation was observed in all of the forty-three 1DI units recorded from thirty-eight subjects. An example is shown in Fig. 1. The mean area of the peaks of 1DI was 286 ± 20 (mean $\pm$ S.E.M.) extra counts per 1000 stimuli. In one subject, the mean latency of ten F waves was 31·5 ms, and the M wave was 4 ms, giving a peripheral conduction time of 18·25 ms. This was subtracted from the latency of the facilitation in 1DI (24 ms), to obtain the central conduction time (5·75 ms). Based on a 27 cm distance from Cz–C3 to C7 in this subject, central conduction velocity was calculated to be 47 m/s. (If a further 1 ms delay is subtracted from the central conduction time to allow for trans-synaptic activation of the corticospinal neurone, the central conduction velocity becomes 57 m/s.)

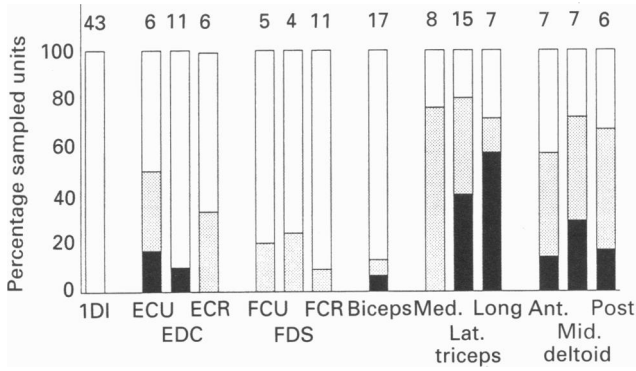

Fig. 2. Graph showing the proportions of sampled motor units which were facilitated (open bars), inhibited (filled bars) or showed no response (shaded bars) at short latency following magnetic stimulation at standardized intensity. All of the 1DI motor units sampled showed short latency facilitation. The majority of forearm motor units and biceps motor units were facilitated. The majority of triceps and deltoid motor units showed no response or were inhibited. The number of motor units investigated is shown at the top of each column.

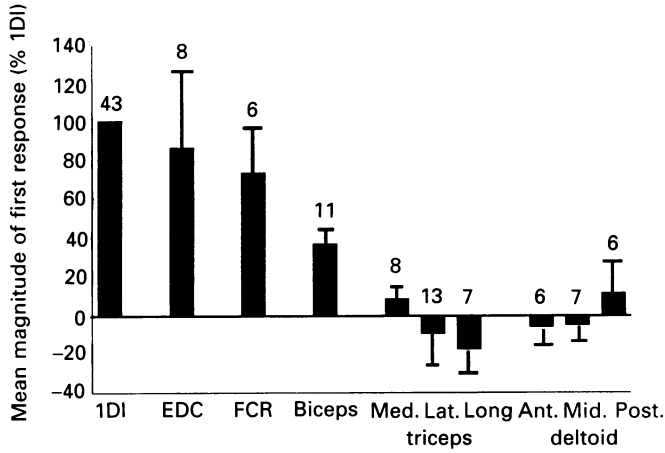

Fig. 3. Net short latency actions of magnetic stimulation over the cortex on motoneurones of various upper limb muscles. The changes in firing probability (in extra or fewer counts per 1000 stimuli) have been normalized to those of the 1DI for that subject (see Methods). The means of these values are shown with the standard error of the mean. 1DI, EDC and FCR received the strongest net facilitation. Short latency facilitation of motoneurones of more proximal muscles (such as biceps) was weaker. Motoneurones of some proximal muscles received no net facilitation. The number of motor units investigated is indicated at the top of each column.

Projections to forearm muscles

Magnetic stimulation produced short latency facilitation of the majority of EDC and FCR units (Fig. 2) although the net facilitatory action was weaker than for 1DI (EDC 86%, FCR 73%) (Fig. 3). There was facilitation of the majority of units in the other forearm muscles examined (Fig. 2). The net facilitatory action was somewhat weaker than for EDC or FCR units. The values are given in Table 2.

Projections to biceps

The majority of biceps motor units were facilitated at short latency (Fig. 2). The net facilitation of biceps units was weaker than that of distal muscles (Fig. 3).

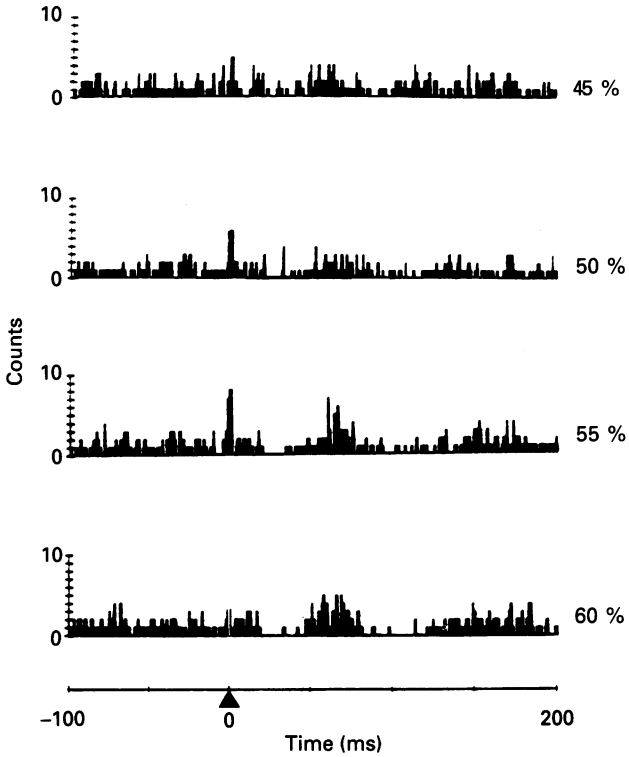

Fig. 4. PSTHs of the same single motor unit in the lateral head of the right triceps in response to magnetic stimuli applied over the left motor cortex (Cz–C3) at intensities 45, 50, 55 and 60 % of the maximum stimulator intensity. The stimulus was delivered at time zero (arrow), and peaks occurring in the top three histograms at time zero are due to stimulus artifact. There is a period of decreased firing probability in each histogram with a latency of about 20 ms and magnitude (top down) of 49, 83, 130 and 143 fewer counts per 1000 stimuli.

Projections to triceps

In contrast to biceps, the initial response in triceps motor units was often inhibitory. For example, six of fifteen units in the lateral head of triceps showed initial inhibition, six showed no effect, and three showed weak facilitation (Fig. 2). The magnitude of the net action of the cortical stimulus on the motoneurones of the lateral head of triceps, related to the magnitude of the facilitation in 1DI in these subjects using the same stimulus, was −10 %. The majority of the units of the long head of triceps were also inhibited.

The lack of facilitation could not be attributed to inadequate stimulation. Figure 4 shows four recordings obtained from the same lateral triceps motor unit, during magnetic stimulation at intensities of 45, 50, 55, and 60 % of maximum. At all four

TABLE 1. Short latency effects produced in various upper limb motor units by magnetic stimulation over the contralateral cortex

Muscle	N	Response	n_1	Mean latency (ms)	Mean duration (ms)	% 1DI	n_2
1DI	38	+	43	22·2 ± 0·4 (18–30)	5·5 ± 0·3 (2–9)	100	43
		0	0	—	—	—	—
		−	0	—	—	—	—
		Tot.	43			Net 100	43
EDC	9	+	10	18·3 ± 0·8 (16–22)	5·2 ± 0·5 (3–8)	118·4	7
		0	0	—	—	—	—
		−	1	23·0	8·0	−138	1
		Tot.	11			Net 86·3	8
FCR	9	+	10	16·7 ± 0·8 (14–22)	4·9 ± 0·5 (3–7)	88·0	5
		0	1	—	—	0	1
		−	0	—	—	—	—
		Tot.	11			Net 73·3	6
Biceps	14	+	14	17·7 ± 0·8 (10–24)	3·2 ± 0·3 (1–5)	36·9	11
		0	2	—	—	—	—
		−	1	20·0	11·0	—	—
		Tot.	17			Net 36·9	11
Triceps (med. head)	8	+	2	14·0 ± 1·0 (13–15)	3·0 ± 1·0 (2–4)	34·2	2
		0	6	—	—	0	6
		−	0	—	—	—	—
		Tot.	8			Net 8·1	8
Triceps (lat. head)	14	+	3	15·3 ± 1·2 (13–17)	3·0 ± 0·6 (2–4)	37·5	3
		0	6	—	—	0	6
		−	6	17·0 ± 0·6 (15–19)	16·3 ± 2·3 (9–21)	−59·6	4
		Tot.	15			Net −9·7	13
Triceps (long head)	7	+	2	15·0	3·0 ± 1·0 (2–4)	30·3	2
		0	1	—	—	0	1
		−	4	15·0 ± 1·8 (12–20)	10·0	−42·5	4
		Tot.	7			Net −15·6	7
Deltoid (ant.)	7	+	3	10·7 ± 0·3 (10–11)	3·0 ± 1·0 (2–5)	12·0	2
		0	3	—	—	0	3
		−	1	15·0	12·0	−62	1
		Tot.	7			Net −6·3	6
Deltoid (mid.)	7	+	1	13·0	3·0	22	1
		0	4	—	—	0	4
		−	2	16·0 ± 3·0 (13–19)	10·5 ± 3·5	−29·5	2
		Tot.	7			Net −5·3	7
Deltoid (post.)	7	+	2	18·5 ± 3·5 (15–22)	4·0 ± 2·0 (2–6)	50·5	2
		0	3	—	—	0	3
		−	1	16·0	9·0	−32	1
		Tot.	6			Net 11·5	6

Column 1 shows the tested muscle. Column 2 shows the number of subjects (N) from which the data were obtained. Column 3 shows the initial short latency responses of the motor units examined: '+' indicates facilitation, '0' no short latency response, and '−' inhibition. Column 4

TABLE 1. (*cont.*)

shows n_1, the number of motor units examined in each muscle at the standardized intensity. Totals (Tot.) are given for each muscle. Columns 5 and 6 show the mean latency and duration of the facilitation or inhibition with ranges, where appropriate, in parentheses. Column 7 shows the magnitude of the responses, normalized to the response obtained in 1DI in the same subject at the same stimulus intensity. Normalized data are displayed separately according to response (+, 0, or −), and as the net response for that muscle (+, 0, and − all included). Column 8 shows the total number of motor units for which a comparable 1DI recording was available, n_2. All means are shown ± S.E.M.

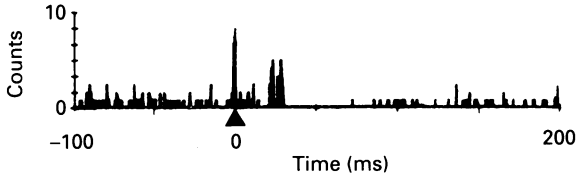

Fig. 5. PSTH of a single motor unit in the left 1DI in response to magnetic stimuli applied over Cz–C4 at 38% intensity. Stimuli were applied at time zero (stimulus artifact appears at this time). Two peaks of increased firing probability appear at short latency: the first at 21 ms (duration = 3 ms, extra counts per 1000 stimuli = 110), the second at 24 ms (duration = 4 ms, extra counts = 120).

stimulus intensities the first effect was inhibition. This increased in magnitude with increasing stimulus intensity.

Projections to deltoid

Deltoid motor units also often showed short latency inhibition (Fig. 2). The net action of the cortical stimulus on the motoneurones of the anterior deltoid was −6% 1DI and of the middle deltoid was −5% 1DI (Fig. 3).

Multiple short latency peaks

It is recognized that the rather wide bin width (1 ms) used in the these studies has the advantage of allowing peaks to be visualized on PSTHs constructed with a small number of sweeps, but can cause multiple periods of facilitation to coalesce. Nevertheless, in some instances the short latency facilitation was composed of double or multiple peaks (Fig. 5). Multiple peaks (2–4 ms apart) were observed in 8/43 1DI units, 2/10 EDC units, 3/11 FCR units, and 4/17 biceps units.

Longer latency responses

In a number of units a later period of increased firing probability was observed (Table 3). These responses were most prominent in triceps; an example from a triceps unit is shown in Fig. 1. These late peaks were not simply due to the recurrence of motor unit firing synchronized by a strong short latency facilitation (periodicity effect), as they could occur without the prior facilitation (e.g. Fig. 1, bottom), and, when following an early facilitation, occurred 25–30 ms after the early responses although the motor units had interspike intervals of 100–200 ms. Nor were the late peaks just a rebound following a period of decreased firing probability, as they

TABLE 2. Short latency effects produced in forearm muscle motor units by magnetic stimulation over the contralateral cortex

Muscle	N	Response	n_1	Mean latency (ms)	Mean duration (ms)	% EDC or FCR	n_2	% 1DI
EDC	9	+	10	18·3±0·8 (16–22)	5·2±0·5 (3–8)	100·0	11	
		0	0	—	—	—	—	
		−	1	23·0	8·0	—	—	
		Tot.	11					86·3
ECR	5	+	5	18·2±0·4 (17–19)	6·2±1·6 (4–12)	40·0	4	
		0	1	—	—	0	1	
		−	0	—	—	—	—	
		Tot.	6			Net 32·0	5	
ECU	5	+	3	17·0±1·5 (15–20)	7·3±0·3 (7–8)	63·7	3	
		0	2	—	—	0	1	
		−	1	20·0	12·0	−108·0	1	
		Tot.	6			Net 16·6	5	
FCR	9	+	10	16·7±0·8 (14–22)	4·9±0·5 (3–7)	100	6	
		0	1	—	—	—	—	
		−	0	—	—	—	—	
		Tot.	11					73·3
FCU	5	+	4	16·5±0·7 (15–18)	5·5±0·9 (3–7)	68·5	4	
		0	1	—	—	0	1	
		−	0	—	—	—	—	
		Tot.	5			Net 54·8	5	
FDS	4	+	3	21·0±1·5 (18–23)	3·7±1·2 (2–6)	68·3	3	
		0	1	—	—	0	1	
		−	0	—	—	—	—	
		Tot.	4			Net 51·3	4	

Columns 1–6 as for Table 1. Column 7 shows the magnitude of responses normalized to the response obtained in the EDC motor unit in the same subject for wrist/finger extensors, and in the FCR motor unit in the same subject for wrist/finger flexors. Normalized data are displayed according to response and as net response. n_2 = total number of motor units for which a comparable EDC or FCR recording was available. Column 9 shows the magnitude of the responses in EDC and FCR, normalized to the magnitude of the 1DI responses in the same subjects. All means shown ± 1 S.E.M.

occurred without a prior period of decreased firing probability in 1/5 biceps, 9/21 triceps, and 4/10 deltoid units (e.g. Fig. 1, bottom). In addition, in 2/2 FCR, 1/5 biceps, 6/21 triceps and 3/10 deltoid units, the late facilitation was larger than any previous inhibition and therefore was unlikely to be due entirely to a rebound effect. The difference in latency between the first and the later response was not related to the distance of the muscle from the spinal cord.

TABLE 3. Long latency facilitation produced in various upper limb motor units by magnetic stimulation over the contralateral cortex

Muscle	n_1/n	Initial response		Latency (ms) Range	Latency (ms) Mean	Duration (ms) Range	Duration (ms) Mean	Magnitude (% 1DI)	n_2
1DI	12/43	+	12	54–90	70·3±3·1	2—22	5·4±1·6	81·5	12
		0	0	—		—		—	
		−	0	—		—		—	
EDC	6/11	+	5	29–83	61·2±9·9	2–10	5·2±1·6	19·1	3
		0	0	—		—		—	
		−	1	38	38·0	20	20·0	255·0	1
FCR	2/11	+	2	29–65	47·0±18	3	3·0	46·9	1
		0	0	—		—		—	
		−	0	—		—		—	
Biceps	5/17	+	3	43–55	48·3±3·5	1–4	2·7±0·9	28·7	1
		0	1	53·0	53·0	2	2·0	—	
		−	1	53·0	53·0	3	3·0	—	
Triceps	21/30	+	4	46–54	47·5±2·3	1–12	6·5±2·5	66·0	4
		0	9	44–87	53·2±4·5	2–10	6·8±1·2	34·0	9
		−	8	41–58	47·8±2·0	3–11	6·9±1·1	48·4	7
Deltoid	10/20	+	3	41–54	47·3±3·8	2–7	4·0±1·5	19·8	3
		0	4	35–47	41·0±2·5	1–4	2·3±0·6	14·6	3
		−	3	39–45	42·0±1·7	3–4	3·3±0·3	33·1	3

Column 2 shows n_1, the number of motor units which were facilitated at a longer latency, in relation to n, the number of motor units sampled. Column 3 shows the short latency responses of those motor units: '+' indicates facilitation, '0' no short latency response, '−' inhibition. The last three columns show the latency, duration and magnitude of the longer latency facilitation, separated according to which initial response it followed. Magnitude is normalized to a percentage of the short latency response to identical stimuli, obtained in the 1DI motor unit in the same subject. n_2 = total number of motor units for which a comparable 1DI recording was available. All means are shown ± 1 S.E.M.

DISCUSSION

Short latency facilitation

The motoneurones of 1DI received strong short latency facilitation. The average amplitude of the underlying composite EPSP was estimated to be 2·9±0·2 mV (mean±S.E.M.), assuming that the membrane potential of a repetitively discharging human motoneurone follows a linear ramp trajectory between action potentials, and that the maximum excursion from threshold is approximately 10 mV. This value is slightly less than previous estimates (3–5 mV) of the EPSPs evoked in 1DI by suprathreshold stimuli (Day, Rothwell, Thompson, Dick, Cowan, Berardelli & Marsden, 1987; Day *et al.* 1989), but of course depends on the stimulus strength, here set just below that which produced a visible contraction of the voluntarily activated 1DI.

The conduction velocity of the pathway mediating the short latency facilitation is rapid (estimated to be about 47 m/s to motoneurones of 1DI). This is slightly slower than estimates of the conduction velocity of pathways activated by anodal

stimulation of the cortex in humans (60–70 m/s: Rothwell *et al.* 1987; 50–80 m/s: Levy, York, McCaffrey & Tanzer, 1984; 50–74 m/s: Boyd, Rothwell, Cowan, Webb, Morley, Asselman & Marsden, 1986), but probably represents conduction in the fast corticospinal pathway.

The rise times of the underlying composite EPSPs responsible for the short latency facilitations, estimated from the mean widths of the PSTH peaks were 3–5·5 ms. This is consistent with monosynaptic facilitation of spinal motoneurones taking the following into consideration. (1) The peaks represent composite EPSPs from a number of corticomotoneuronal cells with axons having different conduction velocities. (2) There is likely to be slight variation in the time at which the action potential of a given motor unit generates a trigger pulse from the window discriminator, caused by neuromuscular 'jitter' (Stalberg & Trontelj, 1979) and by slight changes in the configuration of the action potential due to occasional superimposition of other low amplitude units or to slight movement of the recording electrode during the 5 min of data collection. (3) The peaks may represent more than one corticospinal EPSP. One millisecond bin widths were used (to allow the projections to be identified with as few stimuli as possible). In these circumstances, multiple facilitations at short intervals may appear as one peak (Day *et al.* 1989). From this evidence and from the fact that the responses are predominantly contralateral (Brouwer & Ashby, 1990) it is concluded that the short latency facilitation of contralateral motoneurones from magnetic stimulation results from the activation of 'fast' corticospinal neurones which make monosynaptic connections with motoneurones.

Short latency inhibition

In some motoneurones, the short latency effect of magnetic stimulation was inhibition. The mean latency of this inhibition was $2{\cdot}06 \pm 0{\cdot}8$ ms longer than the mean latency of the facilitation observed in motor units of the same muscles (pooled data from a number of different subjects). In primates, pyramidal tract neurones have been shown to inhibit spinal motoneurones; the difference in onset between EPSPs and IPSPs has been reported to be 1·2–1·5 ms (Landgren, Phillips & Porter, 1962; Phillips & Porter, 1964), which is compatible with a disynaptic linkage. This may also be the case in humans. Inhibition occurred more often in the motoneurones of proximal than distal muscles (Fig. 2), and was seen most frequently in triceps motor units. The absence of facilitation in these motor units was not due to inadequate stimulus intensity, since the inhibition persisted and became more pronounced when the stimulus intensity was increased (Fig. 4).

Distribution of short latency effects

It is likely that magnetic stimulation applied with the large diameter coil used in this study excites a large area of cortex and a large number of corticospinal neurones. If so, the effects observed in any one motoneurone represent the net synaptic actions from these many corticospinal neurones. Strong facilitation implies that many corticospinal neurones have short latency projections to that motoneurone (and presumably to other species of motoneurone, in various functional combinations). The absence of short latency facilitation implies that there are few corticospinal

neurones with direct facilitatory projections to that motoneurone. Thus the pattern can be considered to reflect the overall 'interest' of the cortex in direct activation of various motoneurone pools.

Before accepting that the observed pattern reflects the differential strengths of the projections to different motoneurone pools, a number of artifacts must be excluded. First, it is unlikely that there was selective activation of certain corticospinal neurones because of the position of the stimulator. Hess *et al.* (1987) found that precise coil position was not critical to either the amplitudes or latencies of compound muscle action potentials recorded in small muscles of the hand. Brouwer & Ashby (1990), using the same large coil used in the present study, showed that the pattern of muscle activation and the order in which muscles were recruited by increasing the stimulus intensity were not altered by moving the stimulating coil to various scalp positions within several centimeters. The representations of biceps and triceps on the cortex are known to be close together in monkeys (Asanuma & Rosen, 1972; Kwan, MacKay, Murphy & Wong, 1978) and humans (Penfield & Boldry, 1937) so that it is unlikely that the differential actions on these particular muscles result from selective stimulation of certain areas of the cortex. Second, because the overall pattern (e.g. greater facilitation of 1DI than deltoid) was similar in all subjects, it is unlikely to be accounted for by the specific microanatomical orientation of the gyri, which could be expected to vary slightly from subject to subject. Third, it is possible that the observed pattern could reflect a greater tendency for recurrent activation of corticospinal neurones projecting to some motoneurones than to others. This, however, is not consistent with the observed incidence of separated multiple peaks, which was somewhat higher in biceps (24%) than in 1DI (19%). Fourth, a PSTH peak resulting from monosynaptic facilitation could be reduced in size by subsequent disynaptic inhibition, causing the strength of the facilitatory projections to be underestimated. Thus, the pattern may, in part, represent differences in the amount of inhibition. However, there were examples in which the facilitation of motor units was not followed by inhibition yet the same pattern was present. In addition, the complete absence of short latency facilitation cannot be attributed to disynaptic inhibition, as the inhibition would start later than any monosynaptic facilitation.

Finally, as magnetic stimulation appears to activate corticospinal neurones at the initial segment (Edgley *et al.* 1990), the pattern of corticospinal cells brought to threshold by a stimulus might depend on their level of excitability. However, the pattern of short latency facilitation following the stimulation of corticospinal axons by anodal stimulation (Rothwell *et al.* 1987; Beneke *et al.* 1988) is similar to that identified here. This implies that the pattern represents corticospinal projections to motoneurones. Similarly detailed studies of PSPs generated by anodal stimulation would be necessary to confirm this.

It is concluded that the short latency facilitation produced by magnetic stimulation results from the activation of rapidly conducting corticospinal neurones with monosynaptic projections to motoneurones. The pattern represents the net effect of stimulating many corticospinal neurones non-specifically, but reveals that there are more corticospinal neurones projecting to (and/or more excitatory synaptic boutons on) motoneurones of distal hand muscles than on motoneurones of proximal

arm muscles. This contrasts somewhat with the recent findings of Colebatch, Rothwell, Day, Thompson & Marsden (1990), who suggested that there are corticomotoneuronal projections to the deltoid muscle, of a strength comparable to the strength of projections to small hand muscles. In their studies, the responses to suprathreshold magnetic stimulation, of deltoid and pectoralis major motor units were compared in the same subjects. However, responses in 1DI motor units in the same subjects to similar stimuli were not recorded.

The distribution of the corticospinal projections in man observed here is similar to the projections described for other primates. In the baboon (Phillips & Porter, 1964; Clough, Kernell & Phillips, 1968) and the monkey (Lemon *et al.* 1986), monosynaptic facilitation is greater to motoneurones of distal muscles than proximal muscles, with the facilitation of intrinsic hand muscles being greater than that of forearm muscles. In the baboon, more motoneurones of elbow flexors than elbow extensors receive short latency facilitation, and over half of triceps motoneurones receive disynaptic inhibition or later (polysynaptic) facilitation (Phillips & Porter, 1964). The occurrence of inhibition predominantly in motoneurones of proximal muscles has also been described in monkeys (Bernhard & Bohm, 1954).

The differential distribution of short latency corticospinal projections to human motoneurones implies that lesions of the short latency corticospinal pathway might result in a similarly specific distribution of weakness. The pattern of weakness observed in hemiplegic patients is consistent with this expectation. In the upper limb, this weakness involves distal more than proximal muscles, and the elbow flexors are relatively more weakened than the elbow extensors (Colebatch, Gandevia & Spira, 1986).

Longer latency effects

A later period of increased firing probability, which was not simply a rebound after a period of decreased firing probability, nor the recurrent firing of the motor unit synchronized by a strong facilitation, occurred in a number of motor units. These responses were of longer latency than the 'medium latency excitation' described for proximal arm muscles by Colebatch *et al.* (1990), which was postulated to be due to activity in small diameter corticospinal fibres, or an indirect polysynaptic route. The differences in the latencies between the first and the later facilitations were not related to the distance of the muscle from the spinal cord, and thus did not appear to result from feedback from limb receptors. These periods of increased firing probability were generally of longer duration than the short latency responses, reflecting longer rise times of the underlying EPSPs. A slower conducting, oligosynaptic pathway could mediate this response. Differences in the distribution of the later effects of cortical stimulation on motoneurones have also been observed in primates. In monkeys, a phase of facilitation later than the monosynaptic response was found to be more pronounced in nerves to proximal arm muscles than in those to distal hand muscles (Bernhard & Bohm, 1954) and, in accordance with the present findings, greater in elbow extensor than elbow flexor motoneurones (Preston, Shende & Uemura, 1967).

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