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Effects of Single Intracortical Microstimuli in Motor Cortex on Activity of Identified Forearm Motor Units in Behaving Monkeys

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SUMMARY AND CONCLUSIONS

1. We examined the magnitude and extent of output effects elicited from focal cortical sites on the activity of individual motor units (MUs) by delivering single-pulse intracortical microstimuli (S-ICMS) (5–15 μA) during isometric wrist activity. Stimulation sites in the precentral gyrus (area 4) were chosen for study if stimulus-triggered averages (stimulus-TAs) of multiunit electromyograms (EMGs) revealed poststimulus facilitation (PStimF) of EMG activity in any of the coactivated wrist muscles. Single MUs were then isolated in the facilitated muscles with a remotely controlled tripolar microelectrode. MUs were identified by their signatures in their parent muscles (from MU-triggered averages of EMGs) and by their firing pattern during ramp-and-hold wrist responses (36).

2. One objective was to quantify the magnitude and time course of the effects on single MUs by compiling peristimulus histograms of MU firing. The cross-correlation histograms between S-ICMS and MU action potentials showed peaks with onset latencies of 8.8 ± 1.7 ms (mean ± SD, n = 64) and durations of 1.8 ± 1.2 ms (n = 104). The cumulative sums of the correlogram peaks resembled the rising phase of corticomotoneuronal excitatory postsynaptic potentials previously recorded in forelimb motoneurons (11, 30, 35). Comparison of correlogram peaks with stimulus-TAs of MU potentials suggests that the duration of PStimF of multiunit EMG (9, 10) can be accounted for, in approximately equal proportions, by *1*) the variation in firing time of single MUs (i.e., the width of the MU correlogram peaks), *2*) the width of single MU potentials, and *3*) the contribution of different MUs at different latencies. The sizes of the correlogram peaks relative to base line were larger than the PStimF of multiunit EMGs, and increased more rapidly with stimulus intensity, indicating appreciable cancellation in the multiunit records.

3. A second objective was to determine whether S-ICMS affected all the MUs of a facilitated muscle, or only a particular subset. Of 104 MUs sampled in facilitated muscles, 99 (95%) were found to be individually facilitated ($P < 0.05$). MU firing patterns during isometric ramp-and-hold torque responses were characterized as phasic, phasic-tonic, tonic, or decrementing (36); stimulation at a given cortical site was found to facilitate all four types of MUs. When more than one muscle showed PStimF from a site, MUs belonging to each of the facilitated muscles were facilitated individually by S-ICMS at that site.

4. Taken together, the data suggest that 5- to 15-μA S-ICMS pulses activate corticofugal cells that nonselectively facilitate most, if not all, motoneurons of a muscle; these cortical cells can also facilitate motoneurons belonging to more than one synergist muscle.

INTRODUCTION

To study cortical effects on muscles, investigators first applied repetitive electrical stimulation to the exposed motor cortex in anesthetized monkeys, and elicited contraction of multiple muscles (7, 14, 49). Intracortical sites were further resolved by using repetitive intracortical microstimulation (ICMS) to acti-

vate muscles (2) or single motor units (MUs) (1, 32). The spinal cord targets were ultimately resolved by intracellular recordings of cortically evoked synaptic potentials in motoneurons. Single-pulse surface stimulation of the primate cortex showed that "colonies" of the corticomotoneuronal (CM) cells excite particular motoneurons monosynaptically (24, 30, 38, 40). Jankowska et al. (24) found that corticomotoneuronal excitatory postsynaptic potentials (CM-EPSPs) in different motoneurons of the same hindlimb muscle were sometimes evoked from different cortical sites; since some cortical sites did not evoke CM-EPSPs in all the motoneurons of the same muscle, they suggested that individual CM cells may have selective effects on particular motoneurons within a pool (24).

In behaving animals, the activity of single cortical cells (15–17) or S-ICMS (9, 42) has been cross-correlated with forelimb electromyograms (EMGs). Spike-triggered averages (spike-TAs) of multiunit EMGs have shown that CM cells facilitate MUs in one or more coactivated "target" muscles. Averages triggered from S-ICMS delivered at the site of CM cells (stimulus-TAs) revealed poststimulus facilitation of the cell's target muscles, but produced a stronger effect, indicating that the stimuli recruited groups of corticospinal cells affecting these muscles (9).

The distribution of effects evoked by cortical stimuli and single cells was consistent with divergence of CM cells to motoneurons of different muscles (4, 15). Anatomical studies have also revealed divergent corticospinal terminals projecting to motor nuclei of different muscles (44), and making contact with multiple neighboring motoneurons (31). However, whether CM cells project selectively to specific motoneurons of a muscle remains to be determined. Ia-afferents appear to diverge to most, if not all, motoneurons of the homonymous muscle (34).

Some investigators have speculated that in humans cortical control of MUs may be "selective" (20, 33), suggesting that corticospinal cells may affect fast-twitch and/or phasically firing MUs preferentially. Qualitative differences in effects on slow- and fast-twitch MUs of cat triceps surae have been demonstrated from cutaneous afferents (26) and from the rubrospinal (6) and corticospinal (39) systems. In humans, too, cutaneous afferents have been shown to exert preferential excitatory effects on fast-twitch, high-threshold MUs (21). The specificity of monosynaptic connections from the cortex to motoneurons within a pool is relevant for understanding the mechanism underlying variable behavior of MUs in different volitional motor tasks (5, 22, 23, 37). The present study was designed to explore cortical output effects, elicited by S-ICMS applied during wrist muscle activity on single MUs of the forearm. We chose cortical sites where S-ICMS evoked poststimulus facilitation of multiunit EMG, and then sampled as many single MUs from the facilitated muscles as possible to determine whether these cortical output sites preferentially affected a subset of MUs. Single MUs were characterized by their signature in the MU-triggered average (MU-TA) of the parent muscle EMG, and by their firing pattern during ramp-and-hold torque trajectories (phasic-tonic, tonic, phasic, or decrementing) (36). In contrast to the predictions of the selective hypothesis, our results showed that MUs of all firing patterns were facilitated by S-ICMS applied in the motor cortex. Preliminary reports of some of these results have been presented elsewhere (19, 43).

METHODS

Surgical preparation

Chronic single-unit recording and ICMS were performed in four awake monkeys with a recording chamber implanted over the left precentral motor cortex, as described previously (16, 17). EMG wire electrodes were implanted in up to 12 forearm muscles, which were identified by their relative location and by the movements evoked by stimulation through the EMG electrodes (16, 36).

Electrophysiological data acquisition

ICMS and intracortical recording were done with the same tungsten microelectrodes. A remotely controlled switch relay (Wabash I.C. no. 815-241-L6, Wabash Relay and Electronics, Wabash, IN) connected the electrode to the preamplifier for cell recording or to the stimulator for ICMS. Low-intensity S-ICMS (5–15 μA) were delivered at selected cortical sites during extension or flexion activity; about 22 stimuli were delivered during the hold periods at a rate of 15/s. The S-ICMS pulses were generated by a Grass S88 stimulator driving two Grass stimulus-isolation units (model PSIU6) connected to deliver constant-current biphasic pulses. Current intensity was monitored by the voltage drop across a 10-kΩ resistor in series with the leads to the electrodes.

Synchronized pulses from the stimulator also triggered on-line averages of rectified EMG activity of coactivated flexor or extensor muscles. The stimulus-TAs lasted 30 ms, including 5 ms before and 25 ms after the trigger, and had a bin width of 250 μs. Intervals between stimuli were ~67 ms, too long for temporal summation; this ensured that the effects in the stimulus-TAs were evoked by single stimulus pulses. Stimulus-TAs usually comprised 500–1,000 samples. A poststimulus increase in the average rectified EMG, appearing as a transient peak in the stimulus-TA of multiunit EMG, was called poststimulus facilitation (PStimF) (9). The stimulus intensity chosen was usually the lowest that could elicit significant effects in stimulus-TAs of EMG. The same intensity was maintained for investigation of all single MUs of facilitated muscles.

Once the muscles facilitated from a particular cortical site were identified, a tripolar MU microelectrode (36) was positioned in the facilitated muscle(s) to record as many MUs as possible during the experimental session. MU-TAs of unrectified EMG were used to identify the MU's parent muscle, i.e., the muscle whose average revealed the MU potential as recorded by indwelling wire electrodes, called the MU *signature* (36). All isolated MUs with signatures in a facilitated muscle were recorded on analog tape, regardless of whether any MU facilitation was observed on-line.

Data analysis

PERISTIMULUS HISTOGRAMS AND CUMULATIVE SUMS. Peristimulus histograms (PSHs) of single MU discharge were compiled using discriminator acceptance pulses triggered from identified MUs. This cross-correlation histogram showed the number of MU spikes occurring at particular times relative to the micostimulus pulse, and provided a quantitative measure of the change in MU firing probability correlated with S-ICMS pulses. PSHs were compiled on-line, and more extensively off-line. Like the stimulus-TAs, the PSHs were 30 ms long, usually consisted of 500–1,000 samples, and had a bin width of 250 μs.

To calibrate the histograms, the number of counts per bin was converted to firing frequency. A bin with n counts in a histogram of N samples would represent a mean firing frequency (f) of

$$f = (n \text{ counts/bin}) \cdot (4 \times 10^3 \text{ bins/s}) \cdot (1/N \text{ samples})$$
$$= 4n \cdot 10^3/N \text{ imp/s} \quad (1)$$

A transient increase in firing probability in the PSH was called the correlogram peak. To help detect trends in noisy histograms, we used a derived function called a *cumulative sum* (13). Cumulative sums were compiled from PSHs by subtracting the mean base-line value from each bin value of the PSH and cumulatively summing these differences. The base-line interval used for calculating the mean base-line value was chosen to be the first 10 ms of the histogram, i.e., 5 ms before and 5 ms after the S-ICMS. In previous studies the mean onset latency of PStimF was 8.0 ± 1.2 ms (mean ± SD) (9), so this base-line interval safely preceded any possible evoked effects. Thus, the content of the nth bin of the cumulative sum is

$$c_j = \sum_{i=0}^{j} (n_i - \bar{n}) \quad (2)$$

where c_j is the cumulative sum value for bin j, n_i is the content of the ith bin of the PSH, and $\bar{n}$ is the mean base-line value.

The onset latency of MU facilitation was determined from the onset times of correlogram peaks, corrected for the delay in generating the window discriminator acceptance pulse after onset of the MU potential. This pulse delay was determined from the MU-TAs of the MU recording itself, and was the difference between the onsets of the MU action potential and the acceptance pulse. The corrected onset latency of MU facilitation after the cortical stimulus was obtained by subtracting this pulse delay from the onset time of the correlogram peak. The onset of the correlogram peak was defined as the first of a series of bins with values consistently above the mean base-line level (see below).

In a few figures, PSH bins were compacted by combining two adjacent bins. Compacting the bins reduces variance in the average associated with a small bin width, and helps visualize statistically significant effects that are obscured by noise. Such compacted histograms were used only for display; all statistical analysis was performed on uncompacted histograms, with 250-μs bins.

STATISTICAL ANALYSIS. To quantify the statistical significance of possible events in PSHs, the bin values were tested with the group comparison t test (48). A major assumption of this parametric test is that the variances of the test and comparison groups are equal. Modification of the statistical test for unequal variance by modifying the degrees of freedom (df) is explained below. The number of samples in the two groups need not be equal, and the two groups must be independent of one another.

A group comparison t test program (STATS) compared the bins in the base line, B (the first 10 ms of the histogram), with the bins in a comparison interval, C, chosen to be all the contiguous bins surrounding the peak bin containing counts that exceeded the mean base-line level. These intervals are illustrated in Fig. 1. The program calculated mean counts per bin in B and C, as well as their variances, number of bins, the B and C variance ratio (C/B), pooled variance, percent change of

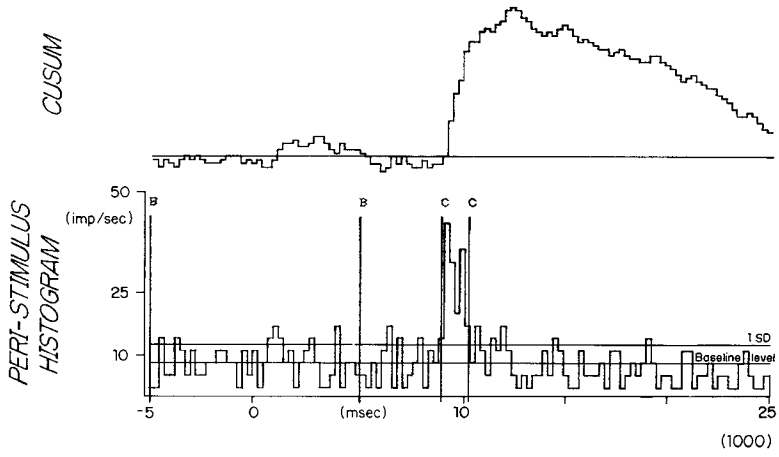


FIG. 1. Analysis of a PSH using the t test (group comparison t test). *Vertical lines* labeled B surround the bins used for the base-line group. Those labeled C surround the comparison group bins. The STATS program calculated the mean base-line level and 1 SD from base line. The mean base-line counts were 2/bin, corresponding to 8 imp/s. There were 1,000 samples in the histogram; in this and subsequent figures, the number of samples is given in parentheses.

comparison mean relative to base-line mean (percent increase), standard error, t value, df, and modified df (see below). The t value and df were calculated as

$$t = (\text{B mean} - \text{C mean})/\sqrt{[\text{pooled variance} \times (1/\text{B bins} + 1/\text{C bins})]} \quad (3)$$

$$\text{df} = (\text{B bins} - 1) + (\text{C bins} - 1)$$

(see Ref. 48). For example, the histogram in Fig. 1 was compiled from 1,000 samples. There was a mean of 2.0 counts/bin in the base line and 8.2 counts/bin during the correlogram peak, corresponding to a mean firing rate of 8.0 imp/s in the base line and 32.7 imp/s in the peak.

To quantify the increased firing probability in the correlogram peak, we computed the mean percent increase of firing probability in the comparison interval over the base-line firing. This value was defined as

$$\text{mean percent increase} = [(\text{C mean} - \text{B mean})/\text{B mean}] \times 100\% \quad (4)$$

The t test value and df were used to check for probability and statistical significance on a table of t. A single MU was considered to be facilitated if the correlogram peak had a statistically ($P < 0.05$) greater mean firing rate than the base-line firing rate.

A modified df value, compensating for unequal population variances (47), was used to determine the statistical significance of the t test value if $2 < (C/B) < 0.5$. In Fig. 1, a t value of 7.65 for modified df = 5 had a $P < 0.001$ of supporting the null hypothesis for a two-tailed test.

Anatomical reconstructions

For all four monkeys, the location of the central sulcus was determined initially by opening the dura when the recording chamber was implanted and photographing the cortical surface. The location of precentral sites was confirmed by recording activity of task-related cells. It sometimes helped to make a preliminary survey of motor effects elicited at different depths by high-frequency repetitive ICMS (biphasic 0.2-ms pulses; 5–20 μA; 400 Hz; 20- to 50-ms trains). At the end of recording sessions, the monkeys were killed and perfused with physiological saline followed by 10% formalin. Coordinates of the chamber were marked in the brain by India ink applied along tracks at several extreme coordinates. The cortical surface under the chamber was also photographed.

Figure 2 illustrates the locations of electrode tracks selected for use in this study. Data were obtained with S-ICMS pulses of 5–15 μA for all illustrated sites except one, which was stimulated with 20 μA. Sites stimulated with pulses of 20–30 μA were not included in the statistical analysis.

Summary of abbreviations used

MU-TA: motor unit-triggered average of multiunit EMG recorded with indwelling wire electrodes, triggered from MU action potentials recorded by microelectrode.

MU signature: waveform of motor-unit potential in the MU-TA of parent muscle EMG.

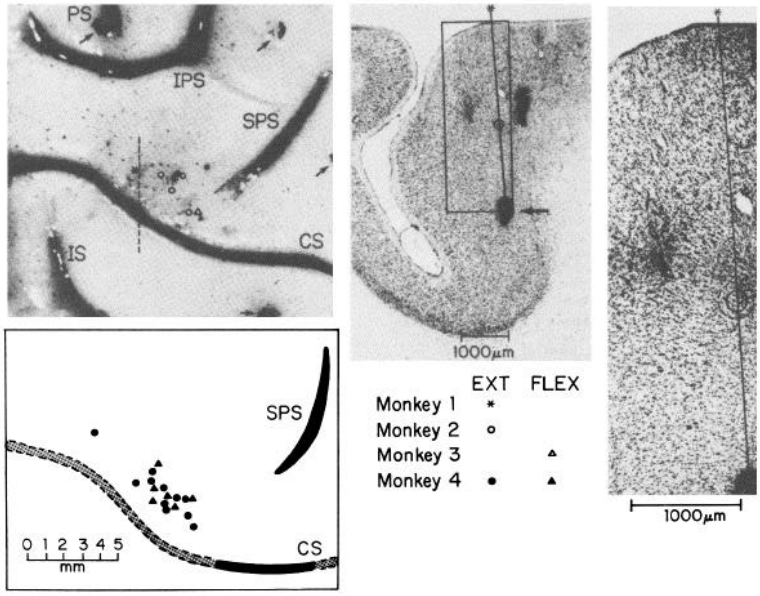


FIG. 2. The location of electrode penetrations relative to the central sulcus of 4 monkeys. Photograph shows location of electrode tracks on cortical surface of monkey *1*. A parasagittal section (*dashed line*) stained with cresyl violet is shown to the *right*. An electrode track (*asterisk* near *dashed line*) with a cortical output site (*encircled*) that facilitated single MUs of ED4,5 and ECR-L (illustrated in Fig. 11); this site was located relative to a deeper histological lesion (*heavy arrow*). *Solid circle*, estimated spread of 10 μA; *dashed circle*, spread of 20 μA (41). Sections were reconstructed in relation to India ink marks at selected chamber locations (*small arrows* on cortical surface). Electrode tracks from monkeys *2* and *3* are shown superimposed on the photograph of monkey *1*. Electrode tracks of monkey *4* are shown relative to the sulci (*darkened*) observed with a dural flap. The estimated location of the remaining sulcus is shown by *dashed lines* with *stippling*. CS, central sulcus; IPS, inferior precentral sulcus; IS, intraparietal sulcus; PS, principal sulcus; SPS, superior precentral sulcus. Tracks with PStimF of extensor (EXT) and flexor (FLEX) muscles are indicated separately.

S-ICMS: single-pulse intracortical microstimulation.

PSH: peristimulus histogram of motor-unit firing. Synonymous with cross-correlation histogram of S-ICMS with MU action potentials.

Stimulus-TA: stimulus-triggered average of multiunit EMG (or of motor-unit recording), triggered from S-ICMS.

PStimF: poststimulus facilitation of averaged rectified EMG in stimulus-TA.

RESULTS

PStimF of single MUs

After locating an effective output site in the motor cortex, where S-ICMS evoked facilitation of EMG in forelimb muscle(s), we recorded single MUs belonging to the facilitated muscle(s). Stimulus-TAs of MU activity and PSHs usually revealed effects on individual MUs. Figure 3 illustrates the effects of 10-μA S-ICMS at a site that clearly facilitated multiunit EMG in ECR-B and EDC, and also facilitated ECR-L to a lesser extent. The signature of this MU indicated that its parent muscle was ECR-B (Fig. 2 in Ref. 36). This ECR-B MU was facilitated by stimulus pulses of the same intensity applied at the same intracortical site. The corrected onset latency of the correlogram peak was 7.5 ms. In the averaged motor-unit record (third trace), the onset of facilitation occurred at approximately the same latency as onset of facilitation of the multiunit EMG in ECR-B (fourth trace). More commonly, the onset of facilitation of single MUs began after onset of multiunit activity (see below).

The shape and amplitude of PStimF revealed in stimulus-TAs of multiunit EMG activity depend on the various contributions of different facilitated MUs to the EMG. To evaluate the contribution of a *single* MU to the multiunit averages, it is useful to compare the features of stimulus-TAs of isolated MU records with averages of multiunit activity of

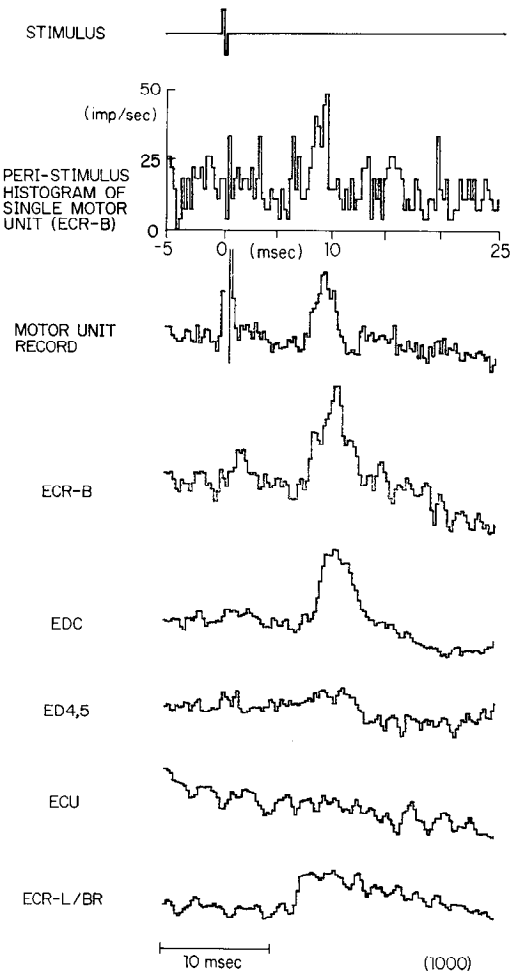


FIG. 3. Effects of S-ICMS on single ECR-B MU and multiunit EMG. From *top*: S-ICMS pulse, peristimulus histogram of ECR-B MU, stimulus-TAs of the rectified MU record and of the rectified EMG from ECR-B (the parent muscle), and synergist extensor muscles. S-ICMS of 10 μA at this site evoked strong PStimF of ECR-B and EDC, and weak PStimF of ECR-L/BR.

their parent muscles (Fig. 4 and Table 1). In 40 MU recordings the action potentials of a single MU entirely dominated the record. In stimulus-TAs of these MU records, the mean *onset latency* of the MU peak was 8.3 ± 1.4 ms (mean ± SD). In contrast, the mean onset latency of PStimF of the parent multiunit activity was shorter, 7.7 ± 1.0 ms. The shorter onset latency of multiunit facilitation was consistent with the expectation that some other MUs would probably be facilitated earlier than the single MU sampled. The mean *duration* of the single MU peak (rectified) was 4.0 ± 2.3 ms, compared with a mean duration of 6.4 ± 2.8 ms for the multiunit PStimF. Again, the longer duration of facilitation of multiunit activity was consistent with earlier and later facilitation of other MUs. Another factor contributing to the wider PStimF peaks in multiunit records is the fact that the MU signature (seen by the intramuscular EMG electrodes) was wider than the MU action potential seen by the microelectrode (compare traces *2* and *4* of Fig. 2 in Ref. 36).

The shape of the stimulus-TA of the MU record is strongly affected by the shape of the MU action potential. In contrast, the shape of

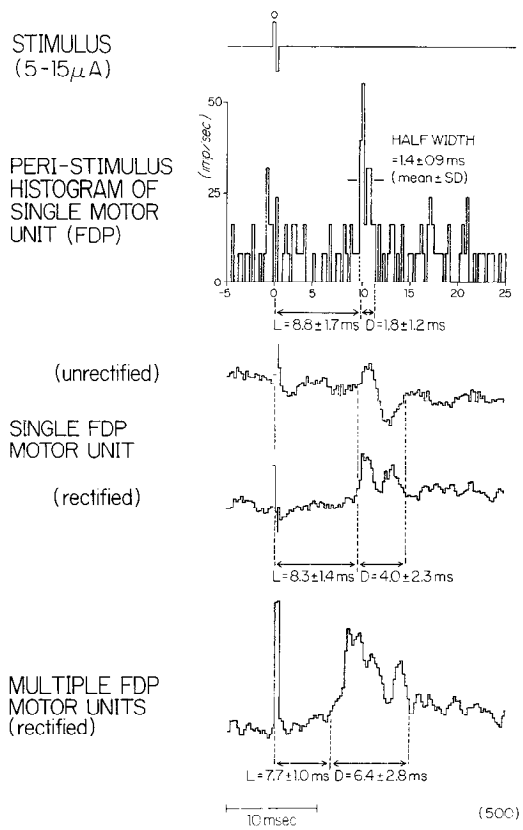


FIG. 4. Timing of PStimF of single MUs and multiunit activity. The latency and duration values on the figure are mean values of all data. The illustrated example shows the PSH of a FDP MU; the onset latency (L) of this correlogram peak was 8.5 ms; its duration (D) was 1 ms; and its half width (i.e., duration at one-half peak amplitude) was 1.25 ms. PStimF of the record of this single MU had a latency of 8.5 ms and a duration of 5.75 ms. PStimF of multiunit EMG had a latency of 5.75 and a duration of 9.75 ms.

TABLE 1. *Poststimulus effects on single MUs and multiunit EMG activity*

Averages	Measure	Mean, ms	SD	Range, ms	*n*
Correlogram peaks of single MU	Half width	1.4	0.9	0.25–4.75	104
	Duration	1.8	1.2	0.50–6.0	104
	Onset	8.8	1.7	5.75–13.75	64
Action potential of single MU	Duration	4.0	2.3	1.0–10.75	40
	Onset	8.3	1.4	6.0–11.75	40
Multiunit EMG	Duration	6.4	2.8	2.5–13.75	40
	Onset	7.7	1.0	5.75–9.75	40

the correlation peak of the PSH of MU firing is a more quantitative measure of the poststimulus change in MU firing probability. The *onset latencies* of the poststimulus correlogram peaks were calculated for 64 MUs for which correction factors could be obtained from MU-TAs (as explained in METHODS). The mean corrected onset latency of correlogram peaks was 8.8 ± 1.7 ms (n = 64); this was not statistically different from latencies determined directly from averages of the single MU records (8.3 ± 1.4 ms, n = 40). The mean *duration* of the correlogram peak, determined from PSHs of all recorded MUs (n = 104), was 1.8 ± 1.2 ms. The half width (the mean duration of the bins in the correlogram peaks that exceeded one-half of the absolute peak amplitude) was 1.4 ± 0.9 ms (n = 104). Thus, the dispersion in poststimulus firing times of single MUs averaged less than a third of the width of PStimF of multiunit EMG.

Effect of increasing S-ICMS intensity on facilitation of MUs

In previous studies (9, 10) the increase in PStimF with increases in the intensity of S-ICMS was used to infer corresponding increases in recruitment of corticofugal cells. In those data, the mean increase in PStimF was 23%/10μA, in good agreement with comparable measures of PStimF in the present data. In this study, increasing the intensity of S-ICMS also produced larger correlogram peaks providing a quantitative measure of the effect on firing probability of single MUs. Figure 5 illustrates the relation between S-ICMS intensity and mean percent increases in firing probability of EDC and ECR-B MUs. The slopes of the linear fits indicate that the correlogram peaks increased more rapidly than the PStimF of multiunit EMG. For the ECR-B MU, the average height of the correlogram peak increased by 289%/10 μA, compared with an increase of 22%/10μA for the PStimF peak of its parent muscle, for the same trials. Similarly, the slope for the EDC MU was greater for the correlogram peak (180%/10 μA) than the PStimF of the EDC muscle (5%/10 μA). Over

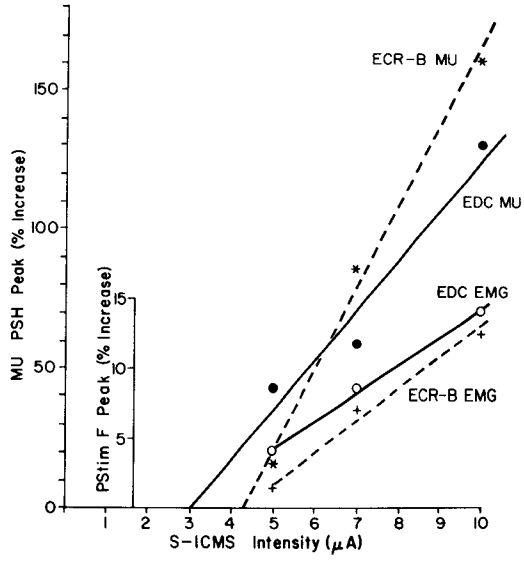


FIG. 5. Increase in poststimulus firing probability of single MUs (*larger ordinate scale*) and poststimulus facilitation of multiunit EMG (*shorter scale*) as function of cortical stimulus intensity (*abscissa*). Mean percent increase of MU firing rate over base line in PSH peaks is plotted for 2 MUs, facilitated from 2 different cortical sites. *Solid circles* represent EDC MU (site 76PAS); *asterisks*, ECR-B MU (site 53PAS2). The mean height of the PStimF peak as a percent of base line is shown for the EMG of the parent muscles for the same trials (note differences in *scales* at *left*). *Open circles*, EDC EMG; *plus signs*, ECR-B EMG. The correlogram peak in the PSHs of the EDC MU for S-ICMS intensities of 5, 7, and 10 μA, had onset latencies of 7.75, 7.0, and 7.5 ms, respectively, and durations of 1.25, 1.5, and 1.0 ms. The correlogram peak of the ECR-B MU had onset latencies of 9.25, 9.0, and 9.25 ms, respectively, and durations of 1.0, 2.75, and 2.25 ms.

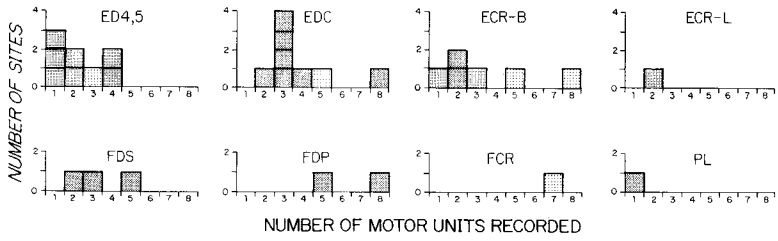


FIG. 6. Histograms showing the number of facilitated MUs recorded in different facilitated forelimb muscles. Each *square* represents the recording of n MUs in the same facilitated muscle, all tested by stimulating a particular cortical site. *Dark stippling,* all n MUs were facilitated ($P < 0.05$); *light stippling,* all but 1 MU were facilitated. The figure summarizes results from 23 different intracortical output sites in 4 monkeys (there are more than 23 squares because some sites affected multiple muscles).

this range of intensity, the latency and duration of correlogram peaks did not change appreciably.

Distribution of cortical effects among MUs

One hundred four MUs were tested with S-ICMS of 23 motor cortex output sites that facilitated their parent muscles; of these, 99 MUs (95%) were facilitated at $P < 0.05$; 81 (78%) were facilitated at $P < 0.02$; and 63 (61%) were facilitated at $P < 0.01$. For these comparisons, the intensity of S-ICMS used for the histograms of MU firing was identical to the intensity for stimulus-TAs of parent muscle EMGs. Figure 6 summarizes the number of single MUs affected in each muscle from the 23 cortical output sites. Each square represents a sample of n motor units tested from the same cortical site, where n is plotted on the abscissa; the shading indicates whether the S-ICMS facilitated all n MUs (dark shading) or $(n - 1)$ MUs (light stipple). As many as eight MUs were recorded in a single facilitated muscle, and sometimes all eight were affected (as for EDC and FDP).

Figure 7 illustrates a set of seven MUs recorded from FCR, and their responses to 10-μA S-ICMS. MUs 1 and 2 were recorded simultaneously, as were MUs 3 and 4, and MUs 5 and 6. The MU action potentials and their relative amplitudes are illustrated in the second line. Each MU had a unique signature in the FCR muscle (third line), confirming that the seven MUs were all different. The PSHs of MU firing are shown in the fifth line. All MUs except MU 5 showed statistically significant increases in firing probability after the 10-μA cortical stimulus. The timing and amplitude of these correlogram peaks, and their statistical significance, are given in Table 2.

Cortical facilitation of single MUs of different facilitated synergists

For five of the 23 cortical output sites, single MUs were sampled in more than one facilitated synergist muscle (Table 3). For some sites, different muscles were studied during the same recording session; for the rest, MUs of different muscles were sampled during two consecutive recording sessions. One site facil-

TABLE 2. *PSH characteristics for seven MUs recorded from FCR*

Unit	Firing Pattern	Onset Latency, ms	Peak Duration, ms	% Increase	t Value	P
1	D	9.0	2.0	152	6.91	0.001
2	PT	10.0	3.3	66	4.13	0.01
3	D	10.8	3.0	71	2.80	0.05
4	D	8.5	1.3	102	3.86	0.05
5	T	12.3	2.0	46	1.84	0.10 (NS)
6	T	7.0	1.0	105	3.00	0.01
7	T	7.3	2.3	91	3.91	0.001

Firing patterns were decrementing (D), phasic-tonic (PT), or tonic (T). Onset latency of correlogram peaks was determined from cumulative sums and corrected for the delay introduced by window discrimination. Percent increase is defined as (CM-BM)/BM, where CM is comparison mean and BM is base-line mean. NS, not significant.

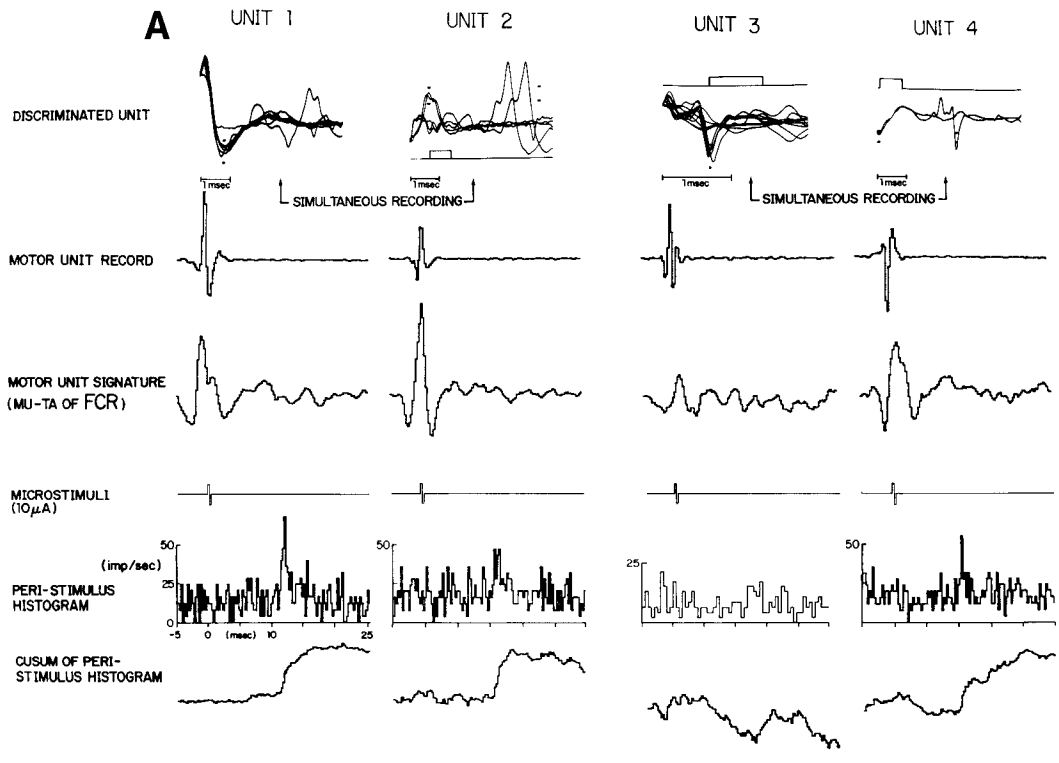


FIG. 7. Effects on 7 different FCR MUs evoked by 10-μA S-ICMS applied at an intracortical output site. MUs are numbered in order of recording. *A*: units 1–4 (*above*); *B*: units 5–7 (*facing page*). *Top line*, window discrimination of the MU action potentials; *dots* indicate the upper and lower window voltages. The photograph showing discrimination of MU 1 (*top line*) also shows MU 2, which did not pass through the window. Similarly, MU 1 is captured in the photograph of discrimination of MU 2, MU 3 in the photograph of discrimination of MU 4, MU 5 in discrimination of MU 6, and vice versa. The acceptance pulse, about 1 ms in duration, is illustrated with MUs 2–7. *Second and third lines* illustrate MU-TAs of the MU action potential and the MU signature, respectively. (Rank order of MU size, from largest to smallest peak-to-peak amplitude of their signature: 2, 1, 4, 7, 6, 3, 5.) *Fifth and sixth lines* show PSHs and cumulative sums, respectively. PSHs of MUs 3 and 6 have compacted bin widths of 500 μs.

itated MUs of two extensor muscles and suppressed MUs of two additional extensor muscles. (Note: poststimulus suppression of MU activity was occasionally observed, but was not systematically studied.)

Examples of MUs that belong to two different muscles, both facilitated from the same cortical site, are shown in Fig. 8. S-ICMS (10 μA) applied at this site produced strong facilitation of EDC and ECR-B, and moderate facilitation of ED4,5. During the first recording session four MUs were facilitated ($P < 0.05$); two from ED4,5 and two from ECR-B. MU-TAs confirmed that electrodes in the muscles adjacent to the parent muscle did not record these MUs. During a second recording session, four MUs were sampled in EDC and six in ECR-B; nine of these MUs were facilitated ($P < 0.05$), and the tenth MU showed some equivocal evidence of facilitation ($P < 0.10$).

Cortical facilitation of MUs with different firing patterns

In light of the four categories of MU firing patterns (phasic, phasic-tonic, tonic, or decrementing), it was of interest to determine whether certain MUs were preferentially facilitated by S-ICMS. Figure 9 illustrates the response patterns of the seven MUs illustrated in Fig. 7. MU 2 exhibited a phasic-tonic firing pattern; its highest firing frequency occurred closer to dT/dt_{max} than T_{max}. In contrast, the other MUs had their highest firing frequencies closer to the time of T_{max}, and showed tonic or decrementing firing patterns. Thus, stimulation at this site significantly facilitated dec-

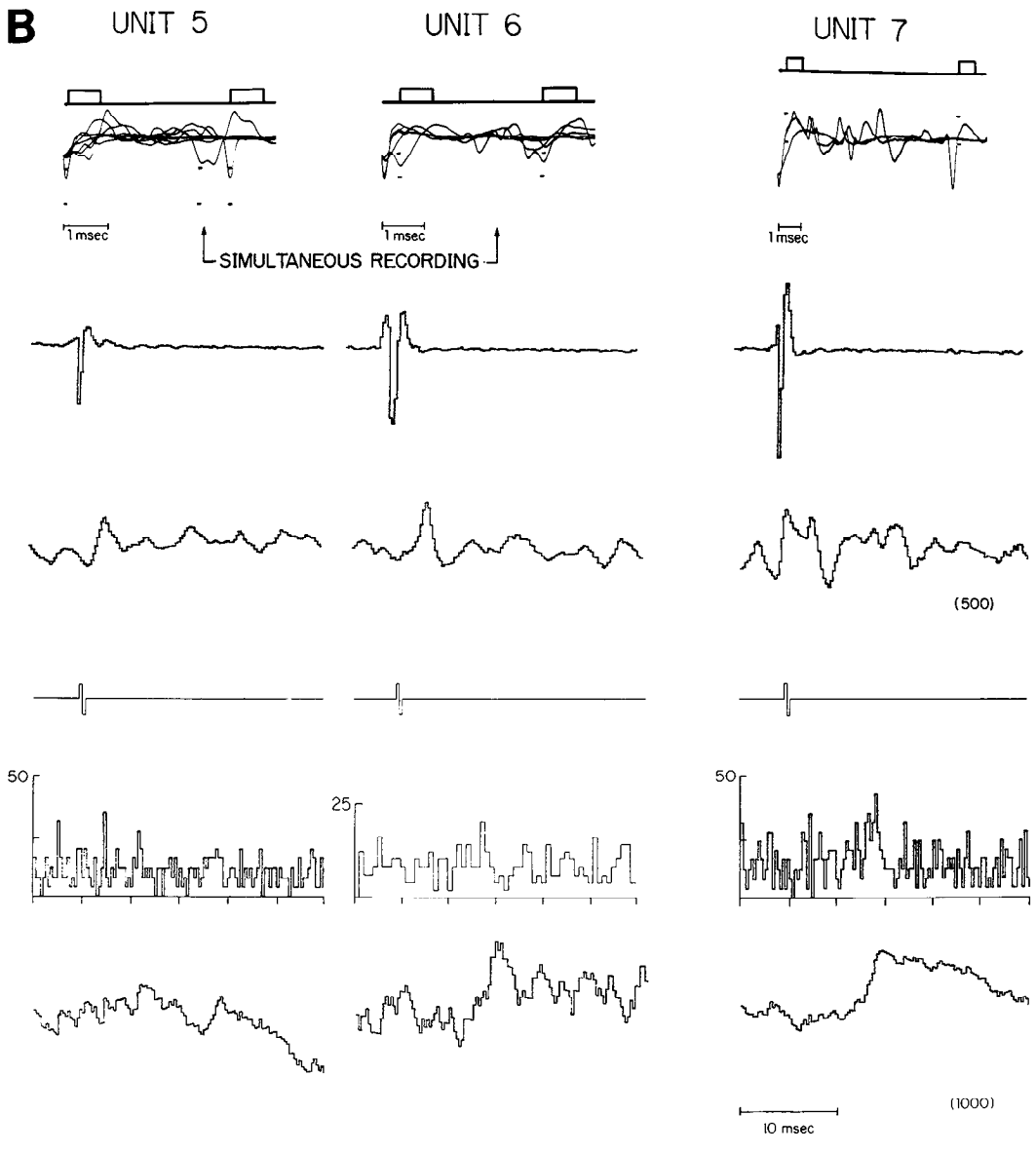


FIG. 7. (*Continued*)

rementing, phasic-tonic, and tonic MUs. The percent increase in firing rate during the correlogram peaks (Table 2) did not correlate in any obvious way with MU firing pattern.

To see whether these seven MUs were representative of all MUs that fired during this task, their response histograms were summed together after each was weighted in proportion to the peak-to-peak amplitude of its MU signature. The resulting sum, shown in Fig. 9 (bottom trace), closely resembled the response average of the rectified EMG recorded from the FCR muscle.

Figure 8 also illustrates facilitation of MUs with different firing patterns from a single cortical site (53PAS). Figure 8*A* shows the facilitation of three MUs of ECR-B (with phasic-tonic, decrementing, and tonic firing patterns) firing at torque levels of ~25% maximal behavioral contraction (MBC) (36). The facili-

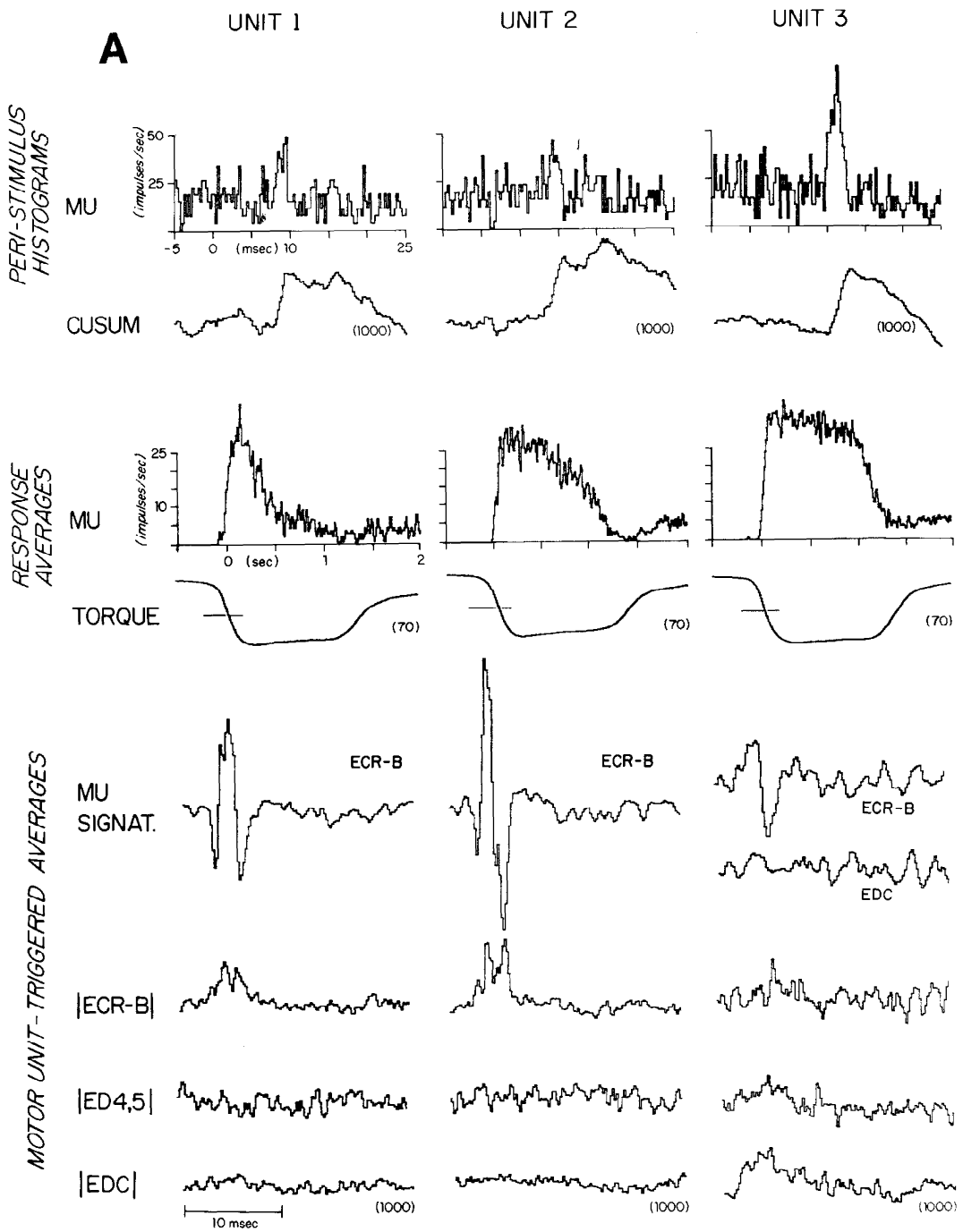


FIG. 8. Facilitation of 5 extensor MUs evoked by 10-μA S-ICMS at a single intracortical output site (53PAS). *A*: 3 ECR-B MUs with different firing patterns. MU 1, a phasic-tonic unit, fired maximally during the ramp phase, and had a low firing frequency during the hold period. MU 2, a decrementing unit, fired maximally at the beginning of the hold period and had a decreasing frequency during the hold. MU 3 was a tonic unit. The moderate static torque levels at which MUs 1, 2, and 3 were studied were 7.7, 8.6, and 9.5 x 10^5 dyn·cm, respectively. *B* (*facing page*): facilitation of MUs from other facilitated muscles. MU4 was an ED4,5 MU with a phasic-tonic firing pattern at a moderate torque level. Compacted bins of PSH were 500 μs. MU 4 was studied at a static torque level of 9 x 10^5 dyn·cm. MU5 was an EDC MU with a phasic firing pattern, recruited at torque level 19.9 x 10^5 dyn·cm. In this figure and Fig. 9, zero torque level is at the *broken horizontal line* through the torque average. MU SIGNAT., MU signature (unrectified EMG). *Bottom 3 traces* show MU-TAs of rectified EMG.

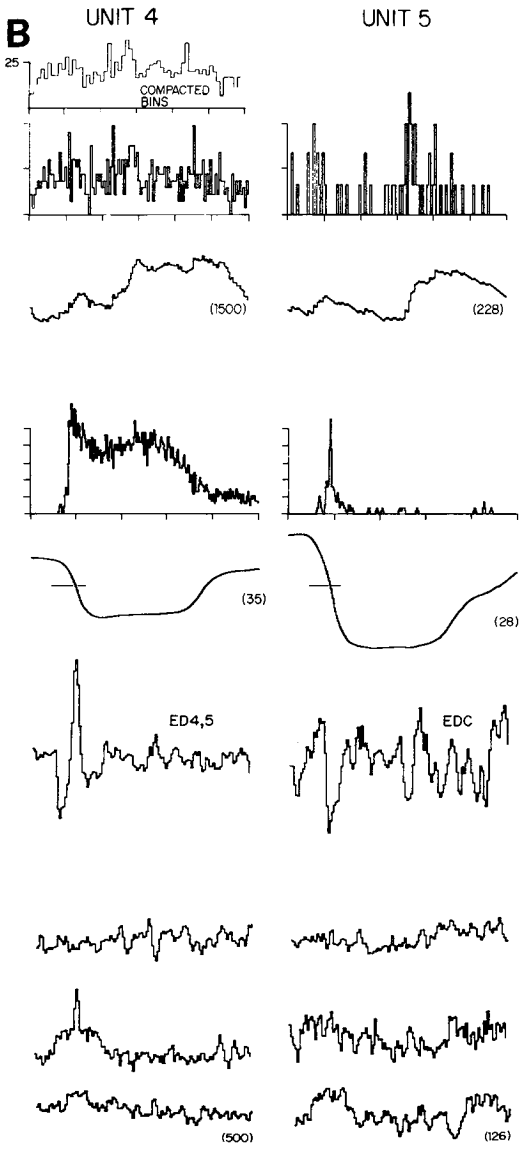


FIG. 8. (*Continued*)

tation of each of these MUs was highly significant ($P < 0.01$) (corrected onset latencies of the correlogram peaks were 7.0, 7.5, and 9.0 ms, respectively). Firing rate during the correlogram peaks increased by 82% for the phasic-tonic MU, 96% for the decrementing MU, and 140% for the tonic MU. Figure 8*B* illustrates two other MUs facilitated from this site: an ED4,5 phasic-tonic MU and an EDC phasic MU recruited at a high torque level (see below). The correlogram peak increased by 70% over base line for the ED4,5 MU and 393% for the EDC MU.

To determine whether the strength or onset latency of facilitation was systematically related to different MU firing patterns would require many more identified MUs recorded from the same muscle. Our preliminary data suggest that onset latency of facilitation was not clearly related to MU firing pattern. For three cortical sites (49PAS, 52PAS, 53PAS; cf. Tables 2 and 3, Fig. 8) the decrementing and tonic MUs were facilitated more strongly than the phasic-tonic MUs. However, the strength of facilitation may well be a function of activity, and more controlled delivery of stimuli during particular phases of activity are required to make meaningful comparisons.

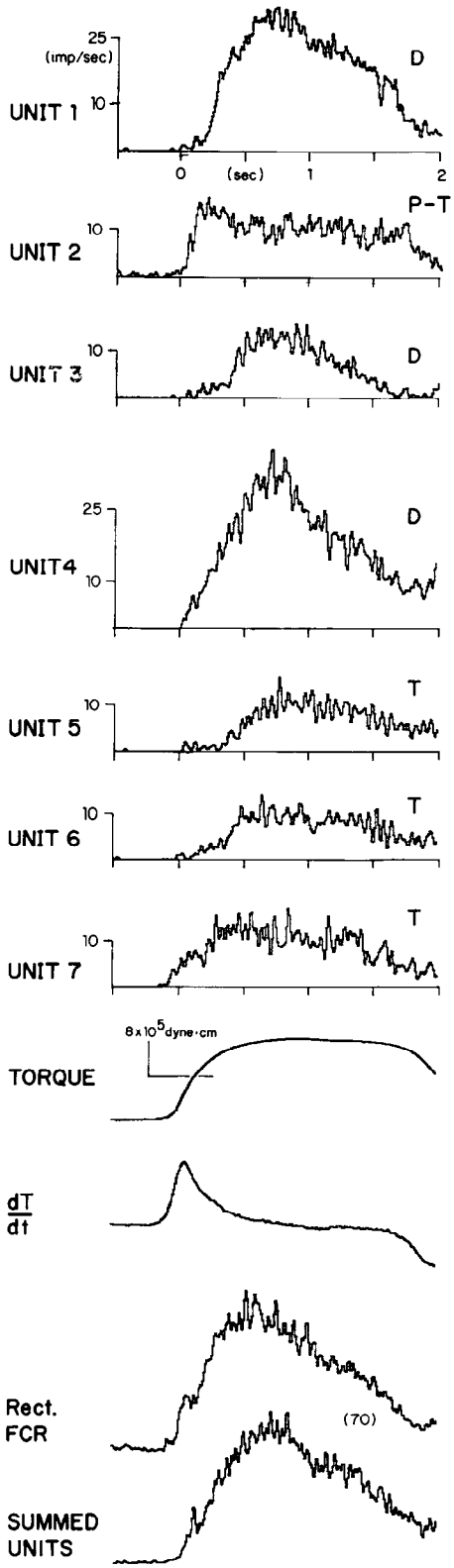
Cortical facilitation of MUs recruited at different torque levels

MUs recruited at high torque levels could not be studied extensively for several reasons. At high torques, the microelectrodes usually recorded many MUs, thus precluding reliable discrimination. Moreover, MUs recruited at high torque levels often fired phasically. The low net base-line firing rate throughout the

TABLE 3. *Facilitation or suppression of more than one facilitated synergist muscle by 10-μA S-ICMS at five cortical output sites*

Output Site	Muscles Facilitated or Suppressed	Ratio of MUs Affected per MUs Recorded	
		Session 1	Session 2
37TH	+ED4,5	+1/1	
	+EDC	+2/2	
	+ECU		
	+ECR-L		
49PAS	+ED4,5	+2/2	
	+ECR-L	+2/2	
	+EDC		
52PAS	+EDC	+1/1	+7/7
	+ED4,5	+4/4	
	−ECR-B		−1/2
	−ECR-L		−1/1
	+ECU		
53PAS	+ED4,5	+2/2	
	+ECR-B	+2/2	+5/6
	+EDC		+4/4
59PAS	+ED4,5	+1/1	
	+EDC		+4/5
	+ECR-B		
	+ECR-L		

+, Facilitation; −, suppression. Statistical significance ($P < 0.05$) was met by facilitation and suppression.



ramp-and-hold response made determination of statistical significance difficult because of the low number of counts contributing to the PSH. The EDC MU in Fig. 9 was recruited at a high torque level, and could be isolated reliably with time-amplitude window discrimination (36). This MU fired phasically, with maximum firing rate at dT/dt_{max}. A PSH compiled only from S-ICMS delivered during the ramp phase of movement showed a highly significant ($P < 0.01$) correlogram peak with an onset latency of 10.75 ms. The increase in firing during the correlogram peak (393%) was greater than that found for other MUs sampled from ECR-B and ED4,5 (see above). However, EDC multiunit activity was also facilitated more strongly from this site (47% over base line) than that of ED4,5 and ECR-B (14%).

DISCUSSION

Documenting the effects of S-ICMS on the firing rate of individual forelimb MUs has provided more quantitative and detailed evidence on the distribution of corticospinal effects than was previously available from stimulus-TAs of multiunit EMG activity. Prior studies under comparable behavioral conditions documented the distribution of output effects on multiple forelimb muscles (9, 10). The resulting poststimulus facilitation and suppression of EMG confirmed the existence of excitatory and inhibitory pathways, but quantitative interpretation of the averages was limited because MUs of unknown size and number contributed to the averages. In contrast, the poststimulus histograms of single MUs quantify the magnitude and time course of the poststimulus effect, and may be used to infer the shape of underlying postsynaptic potentials (PSPs) (18). Moreover, by sampling the responses of different MUs within the same muscle, we found that the cortical effects are exerted on most, if not all, MUs of the muscle.

FIG. 9. Response histograms of 7 MUs of FCR, and the response average of FCR multiunit activity during the flexion phase of the ramp-and-hold isometric response. The dT/dt trace was obtained by differentiating the torque trajectory. The *bottom trace* is a sum of PSHs of the 7 MUs, each weighted according to the peak-to-peak amplitude of its MU signature. The firing pattern of the MU is indicated at the right of each histogram (T, tonic; P-T, phasic-tonic; D, decrementing). All histograms were compiled of 70 samples, except for MU2 (56 samples).

Mechanism of PStimF

The cortical elements that could be activated by S-ICMS and the possible pathways mediating their effects on motoneurons are illustrated in Fig. 10. As indicated by the numbered circuits, the cortical stimulating electrode may *1*) directly activate local somas, *2*) directly activate local axon collaterals of distant somas, *3*) transsynaptically activate local somas, and *4*) transsynaptically activate distant somas. Activation of local somas (mechanisms *1* and *3*) is supported by empirical findings that the effects elicited by S-ICMS in motoneurons (4) and in EMGs recorded from synergist muscles (9, 10) were very similar to the effects elicited by the action potentials of cortical neurons recorded at the site of stimulation. Mechanism *2*, antidromic activation of distant cells, could also contribute to effects, but if present, does not recruit enough cells to affect additional muscles appreciably (9). Mechanism *4* would require reliable transsynaptic activation of cells at a distance; this mechanism may be enhanced by temporal summation produced by repetitive high-frequency ICMS. Indeed, the effects produced by repetitive ICMS can be more widespread than effects produced by S-ICMS at the same site (10). The effectiveness of transsynaptic activation of cells (mechanisms *2* and *4*) by S-ICMS would be proportional to the spatial summation of excitatory inputs; since the number of excitatory terminals activated by S-ICMS should decrease rapidly with distance (3), remote cells would be less likely to be activated transsynaptically than local cells. Thus, the cortical cells close to the electrode, whether activated directly or indirectly, probably made the predominant contribution to the output effects.

At the spinal level, the corticofugal effects may be mediated by various routes. The most direct path involves monosynaptic connections of corticomotoneuronal cells, and can either diverge to multiple motoneurons (pattern *A*) or project to specific subsets (pattern *B*); in addition, polysynaptic pathways via spinal interneurons or brain stem relays may also contribute (pattern *C*). Potential disynaptic circuits include corticospinal terminations onto spinal interneurons, collaterals to descending brain stem cells, such as rubromotoneuronal cells, or collaterals to other CM cells. Spike-TAs of EMG activity have confirmed the existence of single CM cells that produce divergent effects in multiple muscles, as well as other CM cells that specifically affect single muscles (15, 16). Either type of CM cell may still project selectively to specific MUs within its target muscle(s) (pattern *B*). As discussed below, the onset latencies of poststimulus effects are consistent with monosynaptic connections. Polysynaptic relays (pattern *C*) should produce later and wider correlogram peaks, due to cumulative delays and dispersion introduced by the interneuronal linkages (16). Our present results are consistent with the possibility that S-ICMS produces output facilitation mediated largely by local corticospinal cells that affect most, if not all, motoneurons of a muscle. However, the results do not preclude other combinations of the above mechanisms.

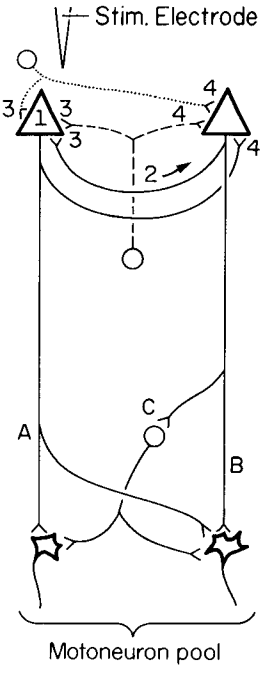


FIG. 10. Possible mechanisms mediating cortical facilitation of different MUs of the same muscle by intracortical microstimuli. Cortex: *1*) direct activation of local somas; *2*) direct activation of distant somas via axon collaterals; *3*) transsynaptic effects on local somas; *4*) transsynaptic effects on distant somas. *Dotted line*, intracortical cell; *dashed line*, thalamocortical or intercortical cell. Spinal cord or extrapyramidal system: *A*, divergent CM cell terminals; *B*, selective CM cell terminals; *C*, divergent interneuronal linkages.

Factors contributing to timing of PStimF

It is instructive to compare the temporal features of the three types of poststimulus effects used to identify excitatory corticospinal effects in behaving monkeys (Table 1 and Fig. 4). In order of increasing resolution of target elements, these are: stimulus-TAs of multiunit EMGs, stimulus-TAs of single MU potentials, and peristimulus histograms of MU firing. The three are interrelated; the stimulus-TA of single MU records is the convolution of the MU potential with the peristimulus histogram. The stimulus-TA of multiunit EMG is the sum of the effects in many single MUs. Accordingly, the PStimF of multiunit EMG had a significantly longer mean duration (6.4 ms) than the stimulus-TAs of single MUs (4.0 ms), which in turn were wider than the PSH peaks (1.8 ms). These data suggest that, on average, three factors contribute about equally to the dispersion of PStimF of multiunit EMG: the variance in firing latency of single MUs, the width of single MU action potentials, and the summed contribution of different MUs with different onset times.

Factors affecting the time course of correlogram peaks

The time course of the correlogram peak in the PSHs should be a function of the shape of the underlying EPSP in the motoneuron, and the amount of synaptic noise (18, 27–29). The mean duration of correlogram peaks observed in this study (Table 1) is closer to the expected rise time of CM-EPSPs than their duration. Intracellular recordings in primate motoneurons have revealed that cortical surface stimulation evokes CM-EPSPs in forelimb motoneurons with rise times of 1.5–2.5 ms and durations of 3–17 ms (11, 30, 35, 38). Our correlogram peaks had durations ranging from 0.5 to 6.0 ms. Most of the peak durations (90/104) were <3 ms, and only four peaks lasted as long as 5–6 ms.

In cat motoneurons, electrically evoked EPSPs larger than the synaptic noise produced correlogram peaks whose shapes resembled the derivatives of the underlying EPSPs (18). If our PSH peaks, obtained in behaving monkeys, also resemble the derivative of the CM-EPSP, the integral of this peak (i.e., the cumulative sum) should resemble the EPSP. This often seemed quite plausible for the rising

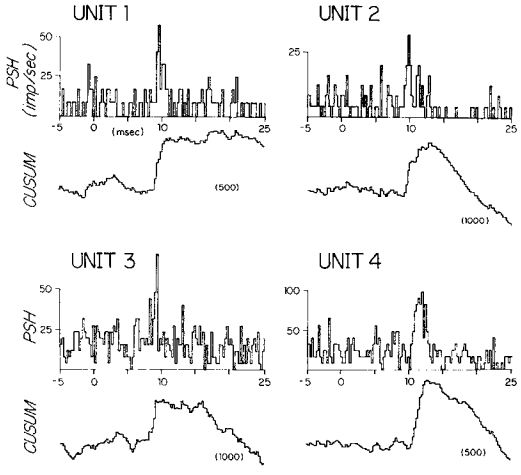


FIG. 11. Representative cumulative sums of PSHs of the firing of 4 different MUs. The integrated correlogram peaks often resemble CM-EPSPs (cf. Refs. 11 and 30). (See Fig. 2 for the cortical site that facilitated MU 2, a MU of ED4,5.)

phase of the cumulative sums, as illustrated in Fig. 11. The falling phase of the cumulative sums showed various rates of descent; some returned to base line, reflecting a trough following the correlogram peak, whereas others fell only slightly, if at all. The full time course of cumulative sums was sometimes 10–17 ms.

The fact that correlogram peaks were usually comparable in duration to CM-EPSP rise times is consistent with the mediation of MU facilitation by CM projections. Synaptic noise comparable in size to the EPSP may widen the correlogram peak beyond the EPSP rise time (18, 28), an effect that may explain some of the wider correlogram peaks. Corticospinal facilitation via polysynaptic connections would be expected to generate EPSPs and correlogram peaks wider and later than those mediated by direct connections (16, 27). However, we found no significant relation between the durations of correlogram peaks and their latency. The MUs with correlogram peaks > 3 ms had a mean onset latency of 8.7 ± 1.6 ms (n = 14), which was not significantly different from the mean onset latency of all MUs measured (8.8 ± 1.7 ms, n = 64). Conversely, the mean duration of the correlogram peak of 11 MUs with late (>10 ms) onset latencies (2.5 ± 1.3 ms; range 1.0–5.3 ms) did not differ significantly from the mean peak duration of

all MUs (1.8 ± 1.2 ms; range 0.5 to 6.0 ms; $n = 104$).

The onset latencies of correlogram peaks in most records were consistent with their mediation by CM projections. CM-EPSP latencies of 3.5–5.2 ms in baboons (31), plus peripheral conduction times of 3–6 ms from motoneuron to muscles, yield predicted latencies of 6.5–11.2 ms, in good agreement with latencies observed in our averages.

Cells and MUs activated by S-ICMS

The amount of current spread required to activate cortical cells and axons can be estimated on the basis of previous experiments (reviewed in Ref. 41). Using a strength-duration relation to normalize surface versus intracortical stimuli, Ranck (41) found an approximate log-log relation between current intensity and distance of effective current spread. A given current was calculated to activate myelinated axons more widely than cortical cells. Microstimuli of 15 μA were estimated to activate myelinated axons in a radius of 400 μm and cells within a radius of 140 μm.

Ranck's estimates of current spread (cf. Fig. 1 in Ref. 41) combined with Tower's (46) estimates of a neuronal packing density of 22 cells/10^6 μm^3 for monkey cortex predict the number of cells activated by S-ICMS. Approximately 25 cells would be activated for 5 μA S-ICMS, 140 cells for 10-μA S-ICMS, and 253 for 15-μA S-ICMS. Jones and Wise (25) found that corticospinal cells in area 4 of the cortex of squirrel and cynomolgus monkeys accounted for ~50% of the cells in layer V. Therefore, the number of corticospinal cells activated is probably less than half these estimated values.

The observed increase in firing probability of *single* MUs with increasing intensity of S-ICMS (Fig. 5) provides further insight into the recruitment of corticospinal cells. Stimulus-TAs of multiunit EMG activity showed PStimF that increased with increasing stimulus intensity (9). This increase could be mediated by several mechanisms: At the cortex, larger stimuli could activate marginally responsive cells more reliably and could also recruit additional corticospinal cells into activity. Similarly, at the spinal level the greater corticofugal volley could activate the same MUs more reliably and recruit additional MUs. Our results confirm that single MUs were more effectively activated by larger S-ICMS. The fact that the correlogram peak increased more rapidly than the PStimF of multiunit EMG with stimulus intensity is probably explained in large part by cancellation of MU potentials in the multiunit records. As additional MUs are recruited synchronously by the higher stimulus intensities, their waveforms would not sum linearly, due to cancellation of positive and negative components.

The increase in the correlogram peaks of single MUs would be expected to be proportional to increases in the underlying EPSPs. In cat motoneurons, the correlogram peak maxima (relative to base line) increased with EPSP amplitude by 2.4%/μV (18). This would correspond to an estimated increase of 0.8%/μV for the mean height of the peaks. Applying this factor to our data, a correlogram peak with a mean height of 1% over base line would be expected to correspond to an EPSP of 1.3 μV. The graphs in Fig. 5 would then predict an increase in EPSP amplitude with cortical stimulus intensity of 22.5–36.1 μV/μA.

In their study of CM-EPSPs in cervical motoneurons of the baboon, Phillips and Porter (38) showed that the amplitudes of representative CM-EPSPs increased almost linearly with cortical surface stimulation over the lower range of stimulus intensities. The slopes of these linear increases were in the range of 0.4 to 1.5 mV/mA. The difference between their slopes and our estimated values may be related to a more effective recruitment of corticospinal cells by intracortical stimuli than by surface stimuli of the same intensity. This difference is evident from comparisons of recruitment curves for intracortical (45) and surface (38) stimuli.

Divergent effects of S-ICMS on different muscles

Previous studies showed that single CM cells (16, 17) and S-ICMS (9) delivered near CM cells often facilitated a group of synergistic forelimb muscles. Those conclusions clearly depend on the independence of the EMG records, which was tested by cross-correlating the EMG activity. The fact that MU-TAs of EMG usually show a large signature in one muscle and are relatively flat for synergist muscles

(Fig. 2 in Ref. 36) confirms that multiunit EMG electrodes can be selective.

Our present results provide more direct confirmation that microstimulation of cortical output sites affects motoneurons of different muscles. MUs whose signature appeared in different facilitated muscles were each facilitated by S-ICMS applied at the same cortical site (cf. Table 3 and Fig. 8). The MU-TAs confirmed that the MU signatures appeared in only one EMG record and that their potentials did not contribute to EMGs of the other facilitated muscles.

Divergent effects on different motoneurons of a single muscle

To date, Jankowska et al. (24) have performed the most detailed analysis of corticomotoneuronal effects from different cortical sites on motoneurons of identified hindlimb muscles. At certain cortical sites, surface stimulation evoked CM-EPSPs in some, but not all, the motoneurons of a given pool. The motoneurons of a given muscle were monosynaptically excited from cortical sites that often overlapped, but were rarely identical. On the basis of these observations, Jankowska et al. proposed that CM cells may project selectively to specific hindlimb motoneurons within a pool.

Our results showed that almost all single MUs belonging to facilitated forelimb muscles were facilitated individually for the same site; 95% of the MUs sampled showed statistically significant ($P < 0.05$) evidence for facilitation. Moreover, MUs of every type of firing pattern were facilitated. The difference between these sets of observations may be explained by several differences in technique. The corticofugal elements evoked by cortical surface stimulation (24) may differ significantly from those evoked by S-ICMS. The ability of S-ICMS to recruit fibers as well as somas may result in activation of a larger group of functionally related cells. Second, our stimulus-TAs may detect polysynaptic as well as monosynaptic linkages, particularly when the stimuli evoke a synchronous descending volley of impulses. The results of Jankowska et al. (24) suggest that selective connections may exist on a finer level of resolution.

Hypotheses of "selective" CM projections to phasic MUs in humans (20, 33) have been based on relatively indirect evidence. Nonselective pyramidal tract projections to fast and slow MUs in monkeys are consistent with the findings of Chapman and Wiesendanger (8); after pyramidotomy, hypotonia of forelimb flexor muscles did not recover, thus suggesting that the tonic MUs generating postural tone are facilitated by the pyramidal tract. Nonselective MU facilitation is also consistent with findings that human MUs are recruited in a set order, regardless of whether the response is ballistic or slow, isometric or isotonic. Such observations led Desmedt and Godaux (12) to conclude that "the descending commands . . . are not allowed a free choice . . . among motoneurons." Our results would tend to confirm this conclusion for corticospinal pathways activated by ICMS.

In view of our limited samples of MUs within a single muscle, these conclusions must be considered preliminary. Although our cortical sites affected virtually all MUs of a muscle to some degree, a more extensive analysis could reveal preferentially stronger effects on particular types of MUs. Note again that these results were obtained with microstimuli, which activated groups of corticospinal cells. Whether individual CM cells of a particular class (9) selectively affect particular types of MUs (36) remains to be elucidated.

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