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Comparable Patterns of Muscle Facilitation Evoked by Individual Corticomotoneuronal (CM) Cells and by Single Intracortical Microstimuli in Primates: Evidence for Functional Groups of CM Cells

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SUMMARY AND CONCLUSIONS

1. We compared the averaged responses of forelimb muscles to action potentials of single motor cortex cells and to single intracortical microstimuli (S-ICMS). Activity of precentral neurons and 12 identified forelimb muscles (6 flexors and 6 extensors of wrist and fingers) was recorded in macaques while they performed alternating ramp-and-hold wrist movements. Action potentials of cells that covaried reliably with wrist flexion or extension were used to compile spike-triggered averages (spike-TAs) of rectified electromyographic (EMG) activity of six synergistically coactivated muscles. Cells whose spikes were followed by a clear postspike facilitation (PSF) of rectified muscle activity were designated corticomotoneuronal (CM) cells.

2. CM cells typically facilitated a subset of the coactivated muscles called the cell's target muscles. The relative strength of the PSF in different target muscles ranged from clear increases above base-line fluctuations to weak but significant effects. For each CM cell we characterized the "PSF profile" of facilitation across different muscles, defined as the relative strength of PSF in each of the coactivated agonist muscles.

3. After identifying the CM cell's target muscles, we delivered S-ICMS through the microelectrode at the same site. Biphasic stimuli were delivered during the same wrist movements in which the recorded CM cell had been active. Stimulus intensities were too weak (typically 5–10 μA) and their repetition rate too slow (5–15 Hz) to evoke muscle excitation evident in the raw EMG record. However, stimulus-triggered averages (stimulus-TAs) of the rectified EMGs of coactivated muscles revealed consistent patterns of poststimulus facilitation (PStimF).

4. In most cases the muscles facilitated by the CM cell in spike-TAs (n = 60) were also facilitated by S-ICMS in stimulus-TAs. At sites of CM cells the threshold stimulus intensities for evoking a statistically significant effect were between 0.5 and 2 μA. S-ICMS of 5 μA evoked PStimF that was, on the average, six times stronger than the PSF of the CM cell. The height of the facilitation peak relative to base-line fluctuations was 5–60 times greater for the stimuli than the spikes of the CM cell. The average onset latency of PStimF (8.0 $\pm$ 1.2 ms) was 1.3 ms longer than the mean latency of PSF (6.7 $\pm$ 1.4 ms).

5. At two-thirds of the cortical sites where both spike- and stimulus-TAs were computed (n = 30), the PStimF profile exactly matched the PSF profile. At the remaining sites, the rank order of facilitation differed by one muscle, typically the one showing the weakest PSF. In all cases, the muscle that was most strongly facilitated in the spike-TA was also most strongly affected in the stimulus-TA.

The fact that microstimuli evoked essentially the same profile of facilitation across muscles but produced more intense effects than spikes of the single CM cell suggests that the stimulus activated a group of CM cells with identical or common target muscles.

6. Neighboring CM cells encountered in the same cortical region typically had similar or identical muscle fields. A pair of simultaneously recorded CM cells produced PSF in the same target muscles, and their cross-correlogram showed evidence of a synaptic interconnection. However, spike-TAs selectively compiled from *non*synchronous spikes showed that each cell produced PSF independently of any synchronous spikes in the other. Taken together, these results suggest that neighboring CM cells with common target muscles may form functional clusters in precentral cortex that affect similar combinations of muscles.

INTRODUCTION

Electrical stimulation of motor cortex has been used with varying degrees of resolution to document output effects on limb muscles evoked from cortical sites. To evoke muscle contraction in anesthetized animals, repetitive stimulation is necessary to provide the requisite temporal summation (2, 4, 6, 23). The spread of current can be minimized by intracortical microstimulation (ICMS) (6), but the activation of fibers by ICMS and the temporal summation produced by repetitive ICMS limits the spatial resolution that can be obtained (4, 19, 25). To avoid the synchronous activation of a group of cells by electrical stimuli, spike-triggered averages (spike-TAs) have been used during normal wrist movements to detect the postspike effects correlated with action potentials of single cortical cells (14, 15, 27). Such spike-TAs can reveal subthreshold effects in multiple coactivated muscles.

In the primate, the minimal structural unit by which motor cortex can influence spinal motoneurons directly is the corticomotoneuronal neuron. Single α-motoneurons receive convergent monosynaptic input from a "colony" of corticomotoneuronal neurons (24, 30) distributed over a cortical area of several square millimeters (2). These regions have been mapped in detail for both forelimb (24, 30) and hindlimb (20) motoneurons in the primate. Such cortical projection areas for different motoneurons overlap widely and sometimes contain one or more low-threshold foci (2, 20). The cortical areas containing the "aggregate" of corticomotoneuronal colonies projecting to all motoneurons of a muscle also overlap extensively for different muscles (2, 20).

The divergence of synaptic terminations from single corticospinal cells to multiple motoneurons is equally important to understanding motor cortex organization. Such branching of corticomotoneuronal terminals to motoneurons of different muscles represents an upper limit to the specificity of direct action of single motor cortex neurons. Extensive divergence of corticospinal cell terminals has been demonstrated by antidromic activation of pyramidal tract neurons (PTNs) from different segmental levels (7) and by intraaxonal injection of horseradish peroxidase (HRP) (32). Using spike-TAs of electromyographic (EMG) activity in behaving monkeys, we found that discharges of some motor cortex cells are followed by an enhanced firing probability in motor units of several covarying muscles (13–15). The strength and timing of postspike facilitation (PSF) suggest that most are mediated by monosynaptic connections between the recorded cortical cell and the motoneurons of the facilitated motor units. Here the term CM cell refers to precentral cells whose action potentials are correlated with clear PSF (clear PSF includes moderate and strong PSF, as previously defined, Ref. 14). Most of these cells probably make corticomotoneuronal (CM) connections, although CM cell is used here to designate cells with clear correlational links to motoneurons. Most of the CM cells related to wrist movement facilitate several forelimb muscles that are synergistically activated during flexion or extension (3, 14).

The manner in which CM cells may be organized into functional groups is of considerable interest. Electrophysiological evidence supports the notion that precentral cells responsive to similar peripheral inputs are arranged in a column (6, 7, 23), and possible anatomic substrates for such a module have been reported (11, 22, 28). The possibility that the cells that have common output targets may be arranged in clusters is sug-

gested by the distribution of cortical neurons retrogradely labeled by HRP from different target sites (22, 28) and by antidromic stimulation from motor nuclei (7).

In the present experiments, the PSF of average EMG activity following impulses of CM cells was compared with the average poststimulus facilitation (PStimF) generated by single intracortical microstimuli (S-ICMS) delivered at the same cortical site. The stimuli usually facilitated the same muscles as the CM cell but evoked stronger effects, thus suggesting that the stimulus activated a group of CM cells with similar sets of target muscles.

METHODS

Surgical and training procedures

Data were collected from three rhesus macaques (*Macaca mulatta*) trained to perform ramp-and-hold wrist movements alternating between extension and flexion zones (9). A recording chamber enabling exploration of a 20-mm-diam area of cortex was centered over the hand area of the precentral gyrus. In some monkeys, PTNs could be identified by antidromic responses to stimuli delivered through a bipolar concentric stimulating electrode in the pyramidal tract (14).

Multi-unit EMG activity of 12 forearm muscles acting at the wrist and digits was recorded with pairs of multistranded stainless steel wires implanted in each muscle. The six extensors were extensors carpi ulnaris (ECU), digitorum communis (EDC), digitorum 2 and 3 (ED2,3), digitorum 4 and 5 (ED4,5), carpi radialis longus (ECR-L), and carpi radialis brevis (ECR-B); the six flexors were flexors carpi radialis (FCR), digitorum profundus (FDP), carpi ulnaris (FCU), digitorum sublimis (FDS), palmaris longus (PL), and pronator teres (PT).

For implantation of the electrodes the monkey was anesthetized, and the wire electrodes were inserted transcutaneously into the muscles by use of a hypodermic needle. The site of each muscle was identified by palpation, visualization of muscles through the skin, and measurements of the location of the muscle relative to definable landmarks such as the radial and ulnar epicondyles (see Fig. 2 in Ref. 14). The final position of each electrode pair was confirmed by movements evoked by trains of intramuscular stimuli (100/s) delivered through the EMG electrodes. When all electrode pairs were situated properly, the leads were taped to the arm with medical adhesive tape. Between recording sessions the monkey was seated in a restraining chair with a partition to prevent access to the electrode leads with the opposite arm. Under these conditions, each EMG implant provided stable recording for 3 to 4 wks.

The monkeys were trained in the ramp-and-hold task by rewarding them with applesauce for holding their wrists in a flexion or extension zone for 1–2 s. Movement away from the zero position (hand aligned with forearm) was opposed by a moderate elastic load proportional to displacement. The boundaries of the target zone for flexion were usually 25 and 35°; those for extension were 20–30°. Recording sessions usually consisted of the three or more hours during which the monkey performed reliably and accurately.

Averaging procedures

Our techniques for compiling spike- and stimulus-TAs of rectified EMG activity are diagrammed in Fig. 1. For spike-TAs, the action potentials of a single cortical neuron whose activity covaried reliably with wrist flexion or extension were used to trigger a six-channel averager (PDP8/E computer). The EMG activity of the six covarying forearm muscles was full-wave rectified and averaged over a 30-ms period, from 5 ms before the cortical spike to 25 ms after it, with a bin width of 250 μs. Representative records of unrectified EMG activity and full-wave rectified EMG activity for this 30-ms analysis period are illustrated in Fig. 1. When spike-TAs of 2,000 or more events revealed evidence of PSF in any mucle, the activity of that cell and all coactivated muscles was recorded on an analog tape recorder. After the recording periods, the microelectrode was connected to a constant-current stimulator through a remotely controlled reed relay switch (Fig. 1) to deliver S-ICMS to the same cortical site. Stimuli were biphasic, with each phase lasting 0.2 ms. For both spike- and stimulus-TAs, the electrode was positioned at the depth where the recorded action potential was maximal. To insure that stimulus- and spike-TAs would be comparable, we applied microstimuli only during the phase of movement in which the cortical cell had been active and during movements against the same loads used for the spike-TAs. To preclude temporal summation of stimulus effects, the stimulus pulses were separated by 67–200 ms (15–5 stimuli/s).

After stimulation, activity of the CM cell could nearly always be recorded again, thus confirming that the electrode had not moved and that the weak S-ICMS had not damaged cells near the electrode tip. Reidentification of the recorded cells was based on antidromic latency from pyramidal tract stimulation, their characteristic response patterns during the ramp-and-hold wrist movement (9), and the PSF profile (14).

Activities of the cortical cell, EMG of the implanted muscles, wrist torque, and wrist position were recorded on a 16-channel instrumentation

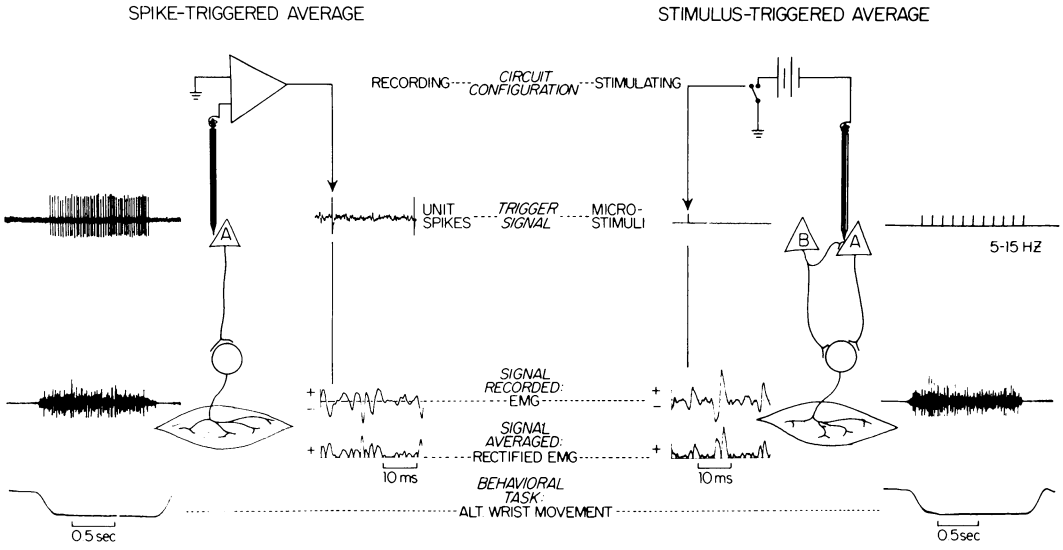


FIG. 1. Comparison of experimental conditions for compiling spike- and stimulus-TAs. For spike-TAs (*left*) the microelectrode recorded activity of a task-related cell. Sample record shows activity of an extension-related CM cell, an extensor muscle, and wrist position during one extension movement. For spike-TAs, rectangular pulses (1 V, 1 ms), initiated on rising phase of each spike, triggered the signal averager. Fast sweep shows unit spikes with raw EMG and full-wave rectified EMG. For stimulus-TAs (*right*), biphasic constant-current pulses were delivered at low frequency (5–15 Hz) through the same microelectrode. Stimuli were applied only during phase of movement in which previously recorded cell had been active. For both spike- and stimulus-TAs, full-wave rectified EMG activity was averaged over an interval from 5 ms before to 25 ms after the trigger event.

tape recorder; this allowed off-line computation of various averages on the same data samples (e.g., spike-TA, EMG-TA, response averages, selective spike-TA, etc.).

Quantitative measurement of PSF and PStimF

The strength of the PSF and PStimF was quantified in two ways. In most cases we computed a "mean percent facilitation," defined as

$$\text{mean percent facilitation} = \frac{\text{mean peak height} - \text{mean base line}}{\text{mean base line}} \times 100$$

The mean base line was the average of all bin values in the base-line interval from 5 ms before to 5 ms after the trigger, and mean peak height was the average value between onset and end of the facilitation peak (Fig. 2). (Our averager computed each bin value as the sum of the A/D samples divided by the number of samples; thus, the mean base line and mean peak height, as well as mean percent facilitation, were independent of sample size, except for statistical fluctuations.) The onset of the facilitation peak was the first bin that exceeded the maximum base-line fluctuations in a sustained direction. The end of facilitation was taken to be the last bin above onset level.

The percent facilitation could be computed for those averages whose numerical values were stored digitally on disks. For early experiments only graphic records of averages were available; for these we measured the "peak-to-noise ratio" (14). The height of the facilitation peak was measured relative to the extrapolated base-line level, and in the same record, base-line "noise" was measured as the average of the two largest peak-to-peak variations occurring before the onset of facilitation. Thus, the peak-to-noise ratio for a given average was the height of the facilitation peak above base line divided by the largest base-line fluctuations. As a function of the number of events averaged (n), the magnitude of random noise fluctuations would be expected to increase as the square root of n, whereas a signal locked with the trigger would increase as n. Thus, to compare the strength of facilitation in averages compiled for different numbers of events, we calculated the peak-to-noise ratio expected for comparable numbers of events on the assumption that the peak-to-noise ratio increases in proportion to the square root of the number of events averaged. This relation was confirmed to hold well for averages compiled for different numbers of events (between 3,000 and 15,000).

These two estimates of the relative magnitude of facilitation were highly correlated. When com-

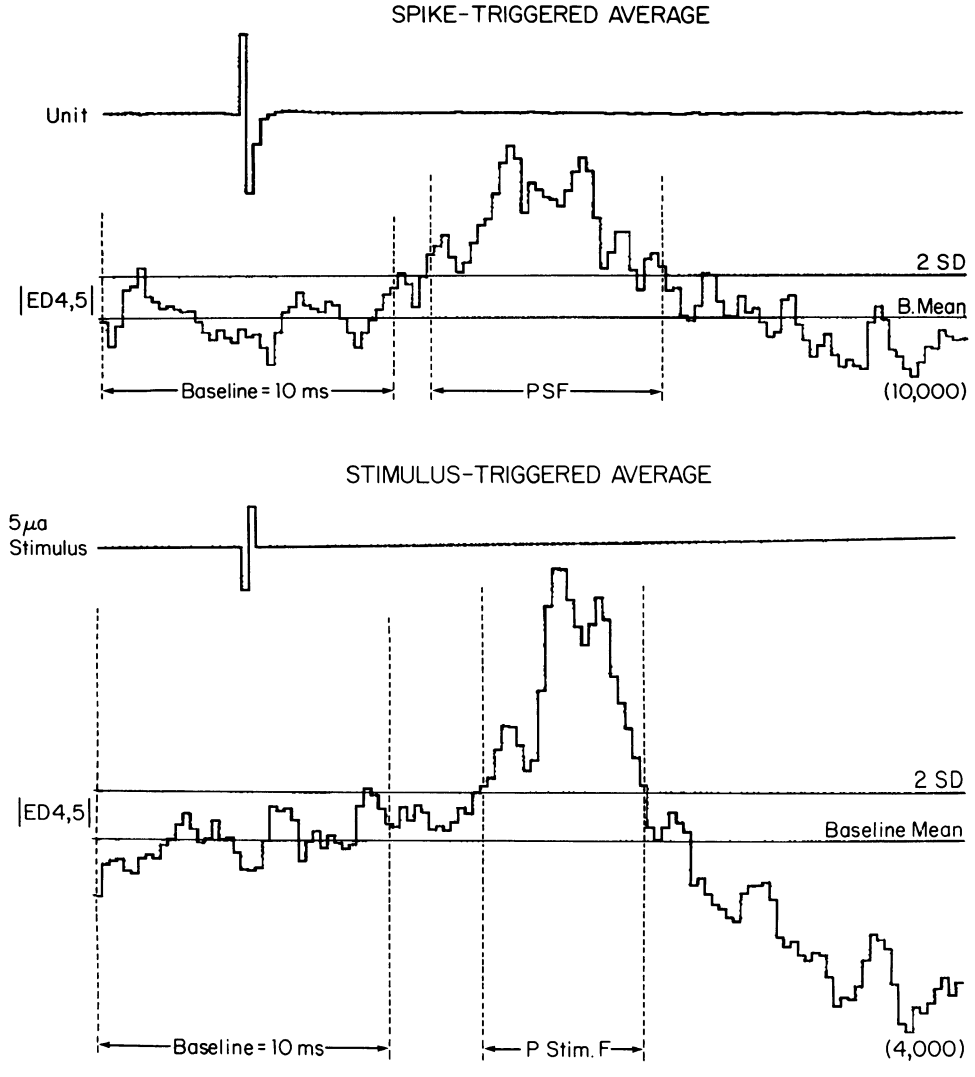


FIG. 2. Comparison of spike- and stimulus-TAs of EMG activity of an extensor muscle (ED4,5). *Top*: spike-TA compiled from 10,000 spikes of an extension-related CM cell (antidromic PT latency: 1.2 ms). *Bottom*: stimulus-TA compiled from 4,000 stimuli (5 μA) delivered at same cortical site. *Vertical lines* denote base-line interval (first 10 ms) and facilitation interval. *Horizontal lines* denote mean of base-line values and 2 SD above mean. In this and subsequent figures, number of events averaged is shown in *lower right*.

pared for 150 spike-TAs, the correlation coefficient between the peak-to-noise estimate and the percent facilitation was $r = 0.80$. In some cases the spike-TAs had sloping base lines because a significant proportion of trigger spikes occurred at the onset of movement when muscle activity was increasing. In these cases, the base-line ramp was subtracted before the magnitude of facilitation was measured.

As in previous experiments, EMG recordings from different muscles were tested for electrical cross talk by EMG-triggered averages (EMG-TAs). Motor unit potentials recorded in each individual muscle were used to trigger averages of full-wave rectified EMG activity of all the covarying muscles. Significant peaks appearing in averages of nontrigger muscles were interpreted as evidence that the electrode pair in that muscle could have recorded some motor unit potentials in common with the electrodes in the muscle triggering the averager. Some correlated peaks would be expected to be caused by synchronization of motor units as a result of common synaptic input; such physiological correlations may be as large as 15% (26, 29). Wherever cross talk of 15% or more occurred in

simultaneously facilitated muscles, the records were considered to be potentially redundant, and only one was retained as an independent recording.

RESULTS

Comparison of PSF and PStimF from single motor cortex sites

Figure 2 illustrates the PSF produced by an extensor CM cell in a finger extensor muscle (top) and the PStimF produced by a 5-μA stimulus delivered at the same site during comparable extension movements (bottom). For each record, the base line (first 10 ms) and facilitation intervals are indicated by vertical dotted lines. Onset of facilitation, defined as the first bin that exceeded base-line fluctuations in a sustained direction, here corresponds to the first bin exceeding 2 SDs above the base-line mean. In this case, the 5-μA stimulus produced a mean percent facilitation of 8.2% above base line, larger than that produced by the spike (3.1%). Moreover, the stimulus generated a clear effect in fewer sweeps. The peak-to-noise ratio was also greater for the PStimF than the PSF (6.5 vs. 1.7, respectively, after scaling for comparable numbers of sweeps). Thus by all measures the 5-μA stimulus clearly evoked a greater facilitation of muscle activity than did the spike.

Figure 3 compares the profiles of postspike and poststimulus facilitation obtained at a cortical site of a flexor CM cell. The spike-TA of five wrist flexor muscles revealed a clear PSF in a single muscle (FCU) and negligible spike-correlated effects in the other flexor muscles in this average of 10,000 events. Single 8-μA microstimuli delivered at this site evoked a similar profile of PStimF; the stimulus-TA shows facilitation restricted to FCU, with no effect in the other four muscles. Again, the stimuli evoked a stronger effect than the spikes of the CM cell; the mean percent facilitation was 3.4% after the spike compared with 15.7% after the 8-μA stimulus. In these records, the peak-to-noise ratio of the PSF and the PStimF appear similar; however, the spike-TA includes twenty times as many sweeps as the stimulus-TA. Thus the scaled peak-to-noise ratios actually differ by a factor of 4.5.

Increasing the stimulus intensity to 10 μA evoked even stronger facilitation in FCU (16.1%) but no additional effects in other muscles. At 20 μA, the S-ICMS facilitated FCU by 27.3% and evoked some additional effects in the other flexors. Decreasing the stimulus intensity to 5 μA (not shown) produced a facilitation of 2.5%; this was weaker than the PSF and suggests that some of the 5-μA S-ICMS did not activate the cell.

In most cases the facilitation effects appeared in more than one muscle. Figure 4 illustrates the profile of facilitation evoked by microstimuli applied near an extensor CM cell that facilitated three finger muscles: EDC, percent facilitation = 5.8%; ED4,5,

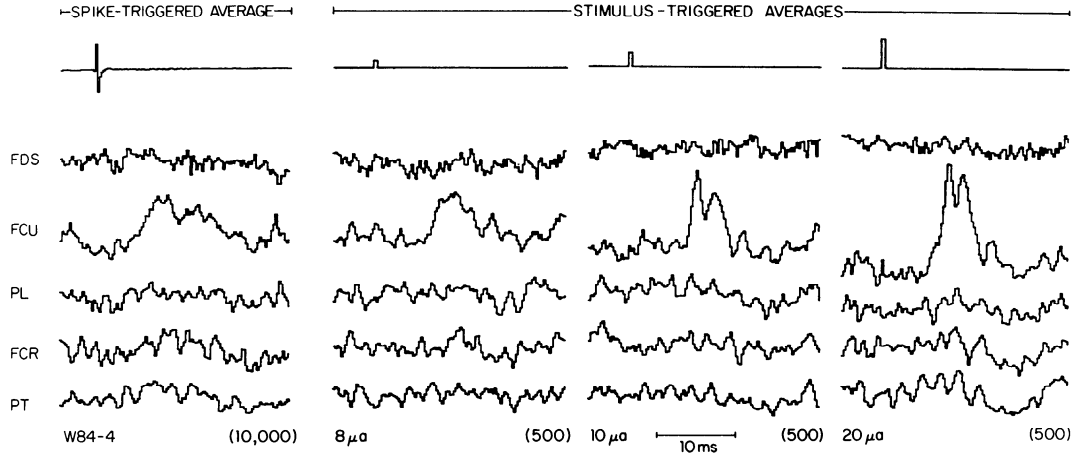


FIG. 3. Comparison of PSF and PStimF for a CM cell affecting a single muscle. Spike-TAs at *left*, compiled for 10,000 events, show PSF in only one flexor muscle (FCU). Stimulus-TAs for S-ICMS of 8, 10, and 20 μA each include 500 stimuli. Magnitude of facilitation is plotted in Fig. 6*B* (cell W84-4).

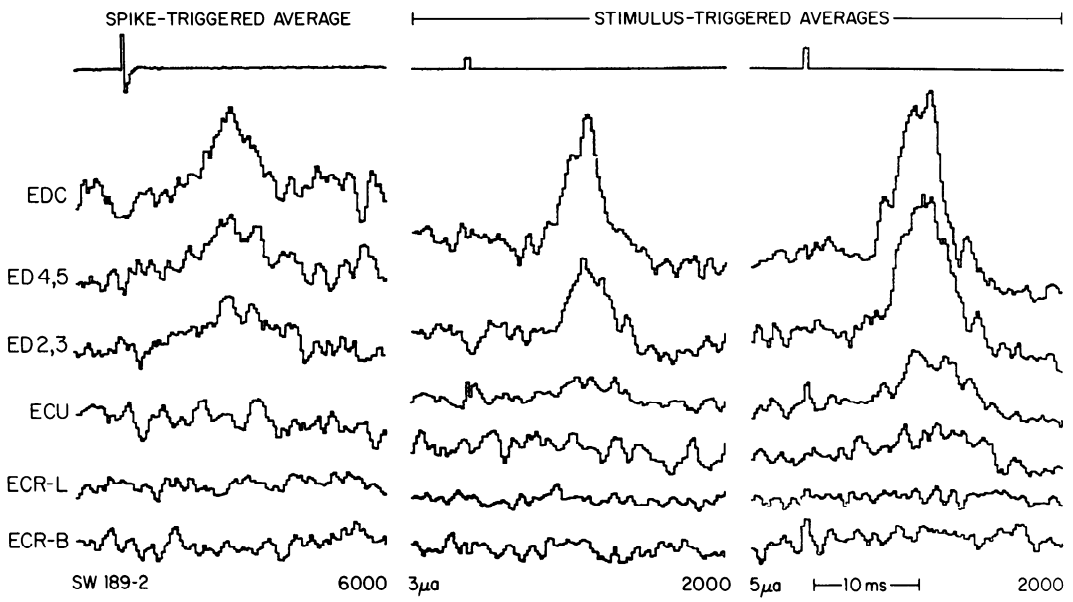


FIG. 4. Comparison of PSF and PStimF profiles for multiple muscles. This CM cell (SW189-2) facilitated three of six extensors (*left*), shown in decreasing strengths from top down. PStimF evoked by S-ICMS at 3 μA (*middle*) and 5 μA (*right*) exhibited same relative magnitude of facilitation.

4.1%; and ED2,3, 3.7%. S-ICMS at 3 and 5 μA evoked PStimF in the same muscles and with the same relative magnitudes of percent facilitation. Although the poststimulus profile of facilitation was identical to the postspike profile, the absolute magnitude of the PStimF was significantly greater. The average facilitation values for this cell, SW189-2, are plotted in Fig. 6*B*.

To illustrate the degree of independence of EMG recordings for the muscles in Fig. 4, the EMG-TAs compiled for these muscles are shown in Fig. 5. The large peaks in each set represent the triggering motor units; the associated records, showing the other muscles at the same scale, are relatively flat. Some of the broad, shallow bumps seen in several of the records would be expected from synchro-

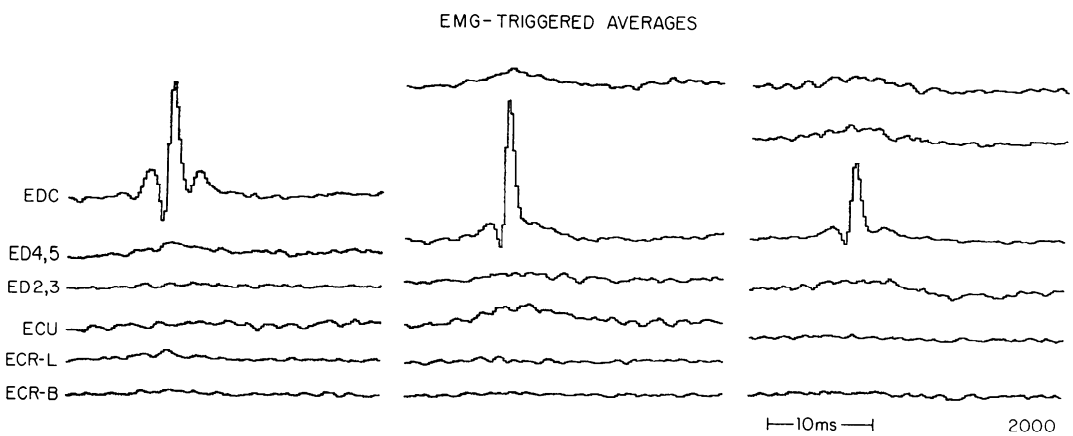


FIG. 5. EMG-TAs used to determine independence of muscle recordings for facilitated muscles in Fig. 4. Each set shows full-wave rectified EMG activity at same gain and in same sequence from top to bottom. Triggering motor units were obtained from EDC (*left*), ED4,5 (*middle*), and ED2,3 (*right*). None of associated broad peaks in nontriggering muscles exceeded 15% of peak in triggering muscle.

nization produced by common synaptic input (26, 29). The muscles of particular interest here are those most strongly facilitated in Fig. 4, EDC and ED4,5. The EMG-TAs on the left show a bump in ED4,5 which is 9% of the triggering peak in EDC; conversely, in the middle records the bump in EDC is 11% of the triggering peak in ED4,5. These values are below our 15% criterion for rejecting records as potentially redundant. Even if these peaks are attributed entirely to common pick-up of the same motor units, the relative amplitudes of these peaks indicate that the expected contamination of the facilitations by cross talk would be <15%, because the EMG-TAs were compiled from the same records as the spike-TAs.

Figure 6 plots the increase in the magnitude of PStimF with stimulus intensity for several representative cortical sites. For most sites the percent facilitation of the individual muscles increased together, as shown for the four target muscles of CM cell SW174-1 in Fig. 6*A*. The curves and the averages (inset) indicate that the facilitation evoked by 5-μA stimuli exceeded the PSF of the cell (plotted on the ordinate). Figure 6*B* plots the net facilitation evoked from six different cortical sites; for each point the mean percent facilitation evoked in all the target muscles of the CM cell recorded at that site was averaged to determine the net facilitation. (The highest stimulus intensities commonly evoked PStimF in additional muscles, but these were not included in the net facilitation.) Again, the magnitude of the stimulus-evoked facilitation is plotted as a function of stimulus intensity, and the points on the ordinate show the net PSF of the target muscles of the CM cell. The best linear fits to the solid curves suggest that the percent facilitation increased, on the average, by 23% per 10 μA.

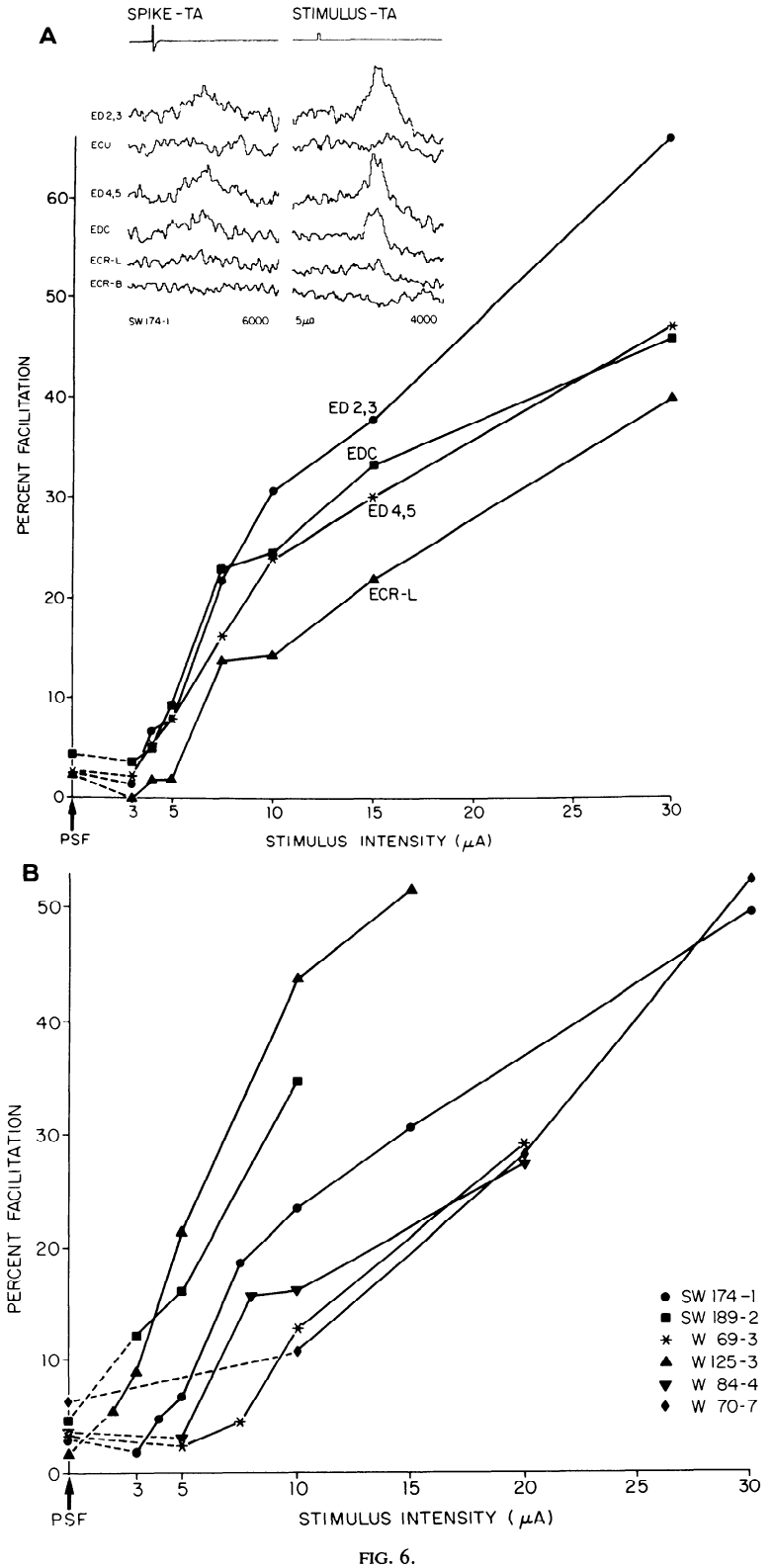
Quantitative comparison of PSF and PStimF

The histograms in Fig. 7 compare the profiles and relative magnitudes of PSF and PStimF at all 30 cortical sites examined. The top bars of each pair give the number of muscles exhibiting PSF in the spike-TA (left) and PStimF in the stimulus-TA (right) at the same site (e.g., first set at top shows that 5 of 6 muscles were facilitated by cell and stimulus). In most cases (26/30), the stimulus facilitated the same muscles as the CM cell. Moreover, the *profile* of facilitation, i.e., the rank order of the magnitude of facilitation in different muscles, was also similar for the CM cell and the stimulus. Heavy shading in the right column indicates a discrepancy in the relative order of the strength of facilitation across muscles in spike-TAs compared with stimulus-TAs (e.g., in first set at top, one muscle had a different rank order in relative PStimF strength compared with PSF strength). At 20 of 30 cortical sites examined, the profile of PStimF matched that of PSF. At the other 10 cortical sites, some discrepancies were noted between the PSF and PStimF profiles; most of these involved differences in the relative strength of facilitation, rather than differences in the muscles showing facilitation. Moreover, these discrepancies usually involved the muscles with the weakest facilitation. At every site, the muscle most strongly facilitated by the CM cell also showed the strongest PStimF.

Microstimuli of 5 μA or more usually evoked a more potent output effect than the CM cell alone (Figs. 2, 6, and 7). The relative magnitudes of PSF and PStimF are summarized by the downward bars in Fig. 7, which plot the mean peak-to-noise ratios for the spike-TAs (left) and stimulus-TAs (right). Each bar represents the mean values for all target muscles facilitated at that site. The measure of facilitation magnitude shown in Fig. 7 is the peak-to-noise ratio because this was available for all sites. The alternative measure, mean percent facilitation, quantifies the mean area under the facilitation peak relative to base line; those averages for which the mean percent facilitation could be computed showed similar differences between strength of spike- and stimulus-evoked facilitation. The mean percent facilitation produced by S-ICMS was greater than that of the PSF by a factor of 6.3 $\pm$ 5.6 SD (n = 33) for 5-μA stimuli, and by 10.9 $\pm$ 11.9 (n = 36) for 10-μA stimuli.

PSF from neighboring CM cells

The fact that PStimF was consistently larger than PSF for each muscle can be attributed to synchronous stimulation of other cells in addition to the single CM cell that provided triggers for the spike-TA. The fact that stimuli facilitated essentially the same


A
SPIKE-TA
STIMULUS-TA
ED2,3
ECU
ED4,5
EDC
ECR-L
ECR-B
SW174-1
6000
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4000
PERCENT FACILITATION
ED 2,3
EDC
ED 4,5
ECR-L
PSF
STIMULUS INTENSITY (μA)
B
PERCENT FACILITATION
SW 174-1
SW 189-2
W 69-3
W 125-3
W 84-4
W 70-7
PSF
STIMULUS INTENSITY (μA)

FIG. 6.

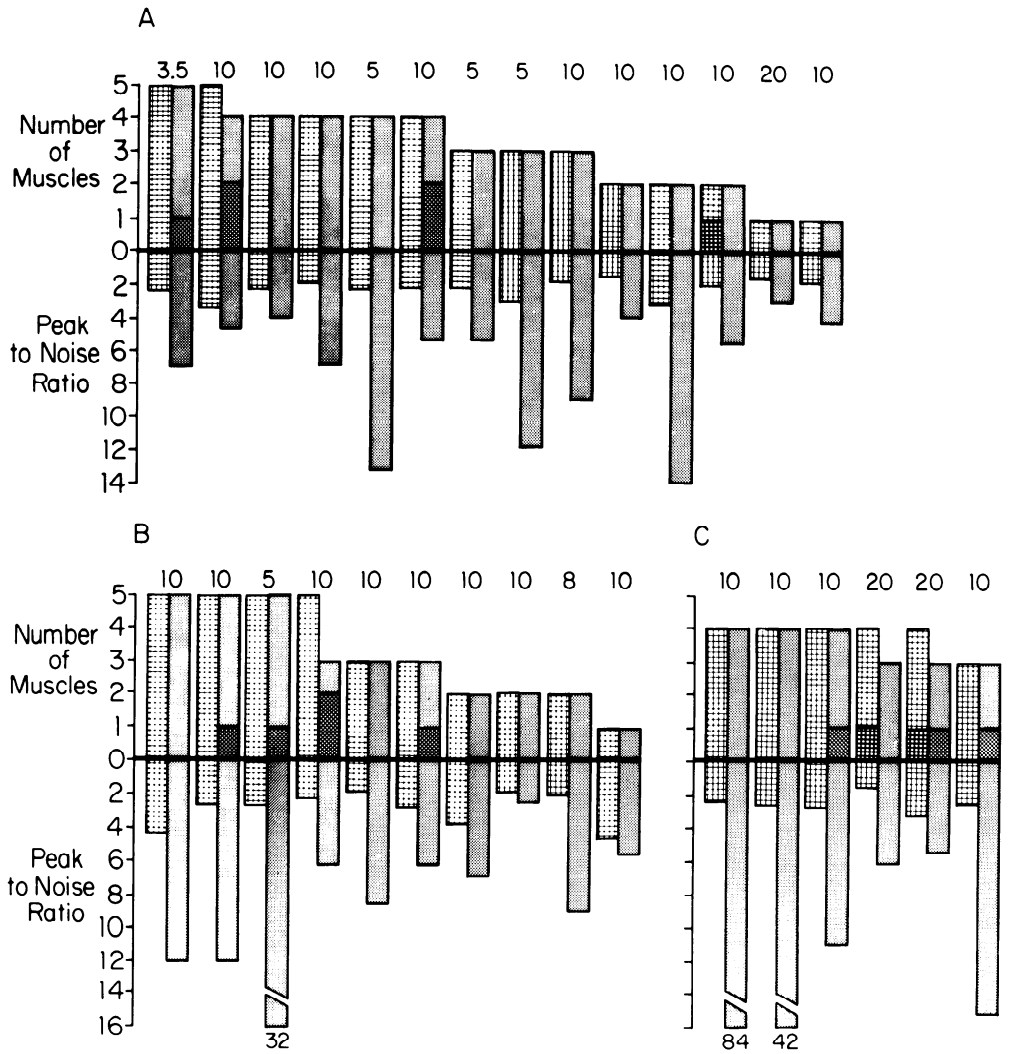

FIG. 7. Comparison of PSF and PStimF at 30 cortical sites where both were observed. Data are grouped according to number of independent synergist muscles tested: *A*, 6; *B*, 5; *C*, 4. Height of *upper bars* in each set gives number of muscles with PSF (*left*) and PStimF (*right*). *Heavy shaded portions of right bars* indicate number of muscles whose magnitude of PSF relative to other muscles was different from relative magnitude of their PStimF in corresponding stimulus-TA. *Heavy shaded portions of the left bars* indicate cases in which a muscle showed PSF but not PStimF. *Numbers* above *bars* give stimulus intensity in microamperes. Height of *lower bars* gives average peak-to-noise ratio of all postspike or poststimulus facilitations of affected muscles. Peak-to-noise ratios were normalized to same numbers of sweeps.

set of muscles as the CM cell suggests that these additional stimulated cells included PTNs affecting the same muscles. These additional cells could either be located in the vicinity of the recorded CM cell or be interconnected with it and activated via collaterals

FIG. 6. Magnitude of PStimF plotted as function of stimulus intensity. *A*: mean percent facilitation of four extensor target muscles of CM cell SW174-1. Values for PSF are shown along *ordinate*. *Inset* shows examples of spike-TA and stimulus-TA for this site. *B*: net percent facilitation of target muscles of six CM cells plotted as a function of stimulus intensity. Net percent facilitation is average of percent facilitation of all the cell's target muscles. Net PSF is plotted on *ordinate* for each cell.

(e.g., cell B in Fig. 1). Further evidence that neighboring CM cells *do* facilitate similar muscles was provided by spike-TAs computed from different CM cells in the same cortical region. In nine cases we recorded two neighboring CM cells with identified muscle fields. Their spatial separation averaged 420 μm $\pm$ 157 (SE); the CM cells of each pair typically exhibited different response patterns during the ramp-and-hold movement (10) and had different antidromic latencies to pyramidal tract stimulation. Their muscle fields were either identical (n = 2 pairs) or differed by one muscle (n = 6) or two (n = 1). The properties of these pairs of neighboring CM cells are summarized in Table 1.

Figure 8 illustrates the response patterns of a pair of neighboring CM cells whose activity was recorded simultaneously through the same microelectrode. Cell W69-3 showed a tonic firing pattern and cell W69-4 a phasic-tonic pattern (Fig. 8*A*). Figure 9 shows the spike-TAs of extensor muscles computed for each cell, as well as the stimulus-TA obtained at the same cortical site. Spikes of cell W69-3 were followed by clear facilitation in ED4,5 and ECU, a weaker facilitation in EDC, and the weakest facilitation in ECR. A possible marginal effect in ED2,3 was not considered significant. The spike-TA computed from cell W69-4 shows PSF in the same target muscles as cell W69-3. Furthermore, the order of relative magnitude of facilitation in different muscles was the same as that from cell W69-3. The stimulus-TA at this cortical site shows a similar profile of PStimF for the 10-μA stimulus.

These results confirm that neighboring CM cells can produce similar patterns of facilitation in covarying muscles and raise the question whether the PSF observed from one cell of the pair might be mediated by a strong synchronization with the other cell, rather than by direct CM connections. Indeed, the cross-correlation histogram of the two spike trains (Fig. 8*C*) indicates that the firing prob-

TABLE 1. *Muscle fields of neighboring CM cells*

CM Cells	PT Latency, ms	Separation, μm	Response Pattern	Muscle Field
SW100-1	1.1	209	P-T	FCU; (FDS/FCR); (PT)
SW100-2	nt		T	FCU; (FDS); PL
SW108-1	1.1	140	P-R	EDC; ED4,5; ECR
SW108-8	nt		P-T	EDC; ED4,5; (ECR); (ECU)
SW117-2	1.5	440	R	ED4,5; EDC; ECR
SW117-3	0.9		T	ED4,5; EDC; (ECR); ED2,3; ECU
W30-6	nt	466	T	ED2,3; ECU; EDC/ECR/ED4,5
W30-8	1.0		P-T	ED2,3; (ECU); EDC/ECR/ED4,5
W54-2	1.0	425	?	(FCU); (PL); (FCR/PT)
W54-3	1.3		P-T	FCU; PL; FCR/PT; FDP
W69-3	nt	0	T	ECU; ED4,5; EDC; (ECR)
W69-4	1.0		P-T	ECU; ED4,5; EDC; (ECR)
W114-2	1.0	1,378	P-T	FDP; FCU; PL; (FDS)
W114-3	1.0		P-R	FDP; FCU; PL; (FDS); (FCR/PT)
W114-10	nt	80	P-T	FCR/PT; (FDS)
W114-11	nt		P-T	FCR/PT
W158-7	nt	652	P-T	ED4,5; EDC; ECR; (ECU); ED2,3
W158-9	nt		P-R	ED4,5; EDC; ECR; (ECU)

These pairs of CM cells were recorded in same electrode tracks; separation of recording sites is subject to error, since some cells were recorded on separate days; nt, not adequately tested. Cells' response patterns during ramp-and-hold movements (19) were phasic-tonic (P-T), tonic (T), phasic-ramp (P-R), or ramp (R). The facilitated target muscles are listed under Muscle Field, with weakly facilitated muscles shown in parentheses. Diagonal slash (e.g., FDS/FCR) indicates that each muscle showed PSF but their electromyographic triggered averages indicated potential cross talk > 15%.

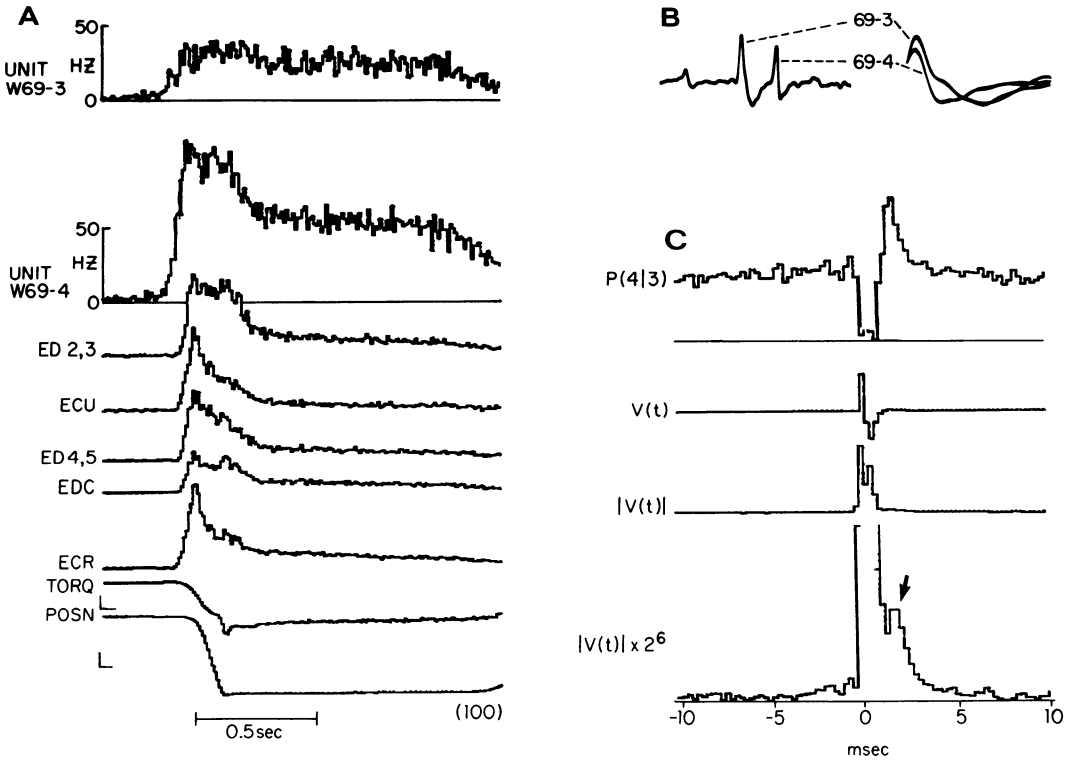

FIG. 8. Two CM cells (W69-3 and W69-4) recorded simultaneously at same cortical site. *A*: response averages of cell activity, wrist extensor muscles, wrist torque, and position (100 extension ramp-and-hold movements). *B*: extracellular action potentials of two cells shown in a single trace (*left*) and superimposed (*right*); spikes were separated on the basis of a clear difference in waveform. *C*: *top trace* shows cross-correlogram as probability of a spike in cell W69-4 before and after a spike in W69-3 (at origin). Dip at origin reflects refractory period of spike separator. Bin width was 250 μs. Trace V(t) shows average of unrectified cortical unit activity, including spikes of cells W69-3 and W69-4, triggered from spikes of W69-3. Trace |V(t)| shows average of same cortical cell activity as in V(t) after full-wave rectification. Bottom shows |V(t)| after a 64-fold increase in vertical gain; separation of second peak (*arrow*) indicates that refractory period in correlogram did not eliminate a synchronization peak. All records were compiled from occurrence of spikes in cell W69-3.

ability of the phasic-tonic cell (W69-4) was enhanced following the spikes of the tonic cell (W69-3).

Is it possible that only one cell of this pair actually affected the muscles and that the PSF associated with the other cell was mediated entirely by the correlation between cell spikes? Several factors are inconsistent with this possibility. First, the magnitude of the cross-correlogram peak is sufficient by itself to account for only 10% of the PSF of either cell. Second, the latency of the PSF from cell W69-3 should be 2 ms longer than that of cell W69-4 if it is mediated by the correlation between cells; in fact, the PSF latencies from cell W69-3 were the same as or shorter than corresponding latencies from cell W69-4. Third, and most conclusively, spike-TAs selectively triggered from only those spikes of one cell that were *not* temporally associated with spikes in the other cell *also* showed clear PSF (Fig. 10). Selective spike-TAs for the isolated spikes of cell W69-3 (Fig. 10*A*) show clear facilitation in the activity of ED4,5 and ECU, the same muscles that showed PSF in this cell's overall spike-TA (Fig. 9). Since the selective spike-TA includes only 1,823 events, it is understandable that some of the weaker PSFs apparent in the overall average of 10,000 events (EDC and ECR) are not clear in this average. Similarly, the isolated spikes of cell W69-4 (Fig. 10*C*) also produced PSF in ED4,5 and ECU, and weaker effects in EDC and ECR.

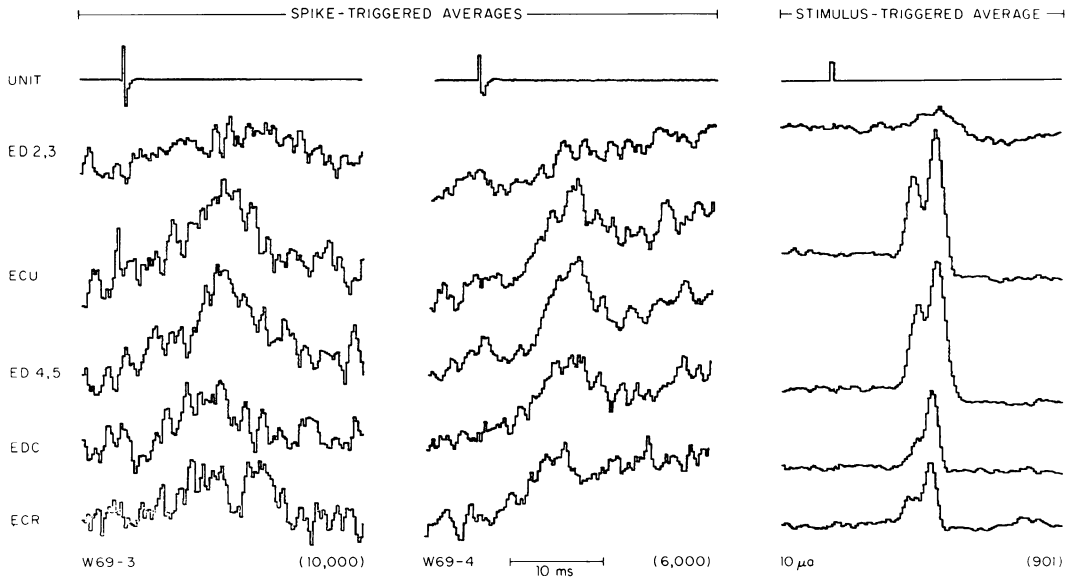

FIG. 9. Spike- and stimulus-TA of extensor muscle EMG activity for the pair of neighboring CM cells in Fig. 8. *Left,* spike-TA compiled for cell W69-3; *middle,* spike-TA for cell W69-4; *right,* stimulus-TA for 10-μA stimuli applied to cortical site where these cells were recorded.

This facilitation profile resembles that observed in the overall spike-TAs for this cell (Fig. 9). Thus, the spike-TAs selectively triggered from isolated spikes show that the PSF associated with each cell of this pair does not depend on the occurrence of synchronous spikes in the other cell.

The effect of coincident spikes in the two CM cells can be demonstrated directly by compiling spike-TAs specifically from action potentials in one cell that *were* associated with spikes in the other. As shown in Fig. 10, *B* and *D,* the spikes of each cell that were preceded within 5 ms by a spike in the other are associated with a greater PSF in the cells' target muscles than isolated spikes.

Onset latencies of PSF and PStimF

The onset latency of muscle facilitation was measured as the time after the trigger event when a sustained rise in the average EMG level first exceeded maximal base-line fluctuations (Fig. 2). Figure 11 plots the onset latencies of PSF vs. PStimF for all cases in which a muscle showed both for the same site. The PSF onset latencies ranged from 3.8 to 9.9 ms, with a mean and SD of 6.7 $\pm$ 1.4 ms. For the same sites the PStimF latency ranged from 6.3 to 11.0 ms, with a mean and SD of 8.0 $\pm$ 1.2 ms. For a given muscle the onset latency of PStimF minus that of PSF ranged from -2.0 to 5.4 ms. The latency of PStimF exceeded that of PSF by a mean of 1.3 $\pm$ 1.3 ms.

In general, onset latency decreased slightly with increasing stimulus intensity, although many exceptions were observed. For a sample of 19 PStimFs calculated for 5 and 15 μA from the same site, the mean onset latency was 9.0 ms at 5 μA compared with 8.3 ms for the same muscles at 15 μA.

To obtain further evidence on the mechanisms mediating the effects of ICMS, we also compared the PStimF evoked by stimulating the white matter with that evoked from intracortical sites. PStimF evoked from white matter sites generally had higher thresholds than that from intracortical sites, as noted previously (24). However, the onset latencies were similar to those for gray matter, and these latencies also decreased with stimulus intensity. For example, raising the stimulus intensity from 5 to 15 μA shortened the onset latency by a mean of 1.7 ms (n = 3) for white matter compared with 0.7 ms (n = 19) for gray matter.

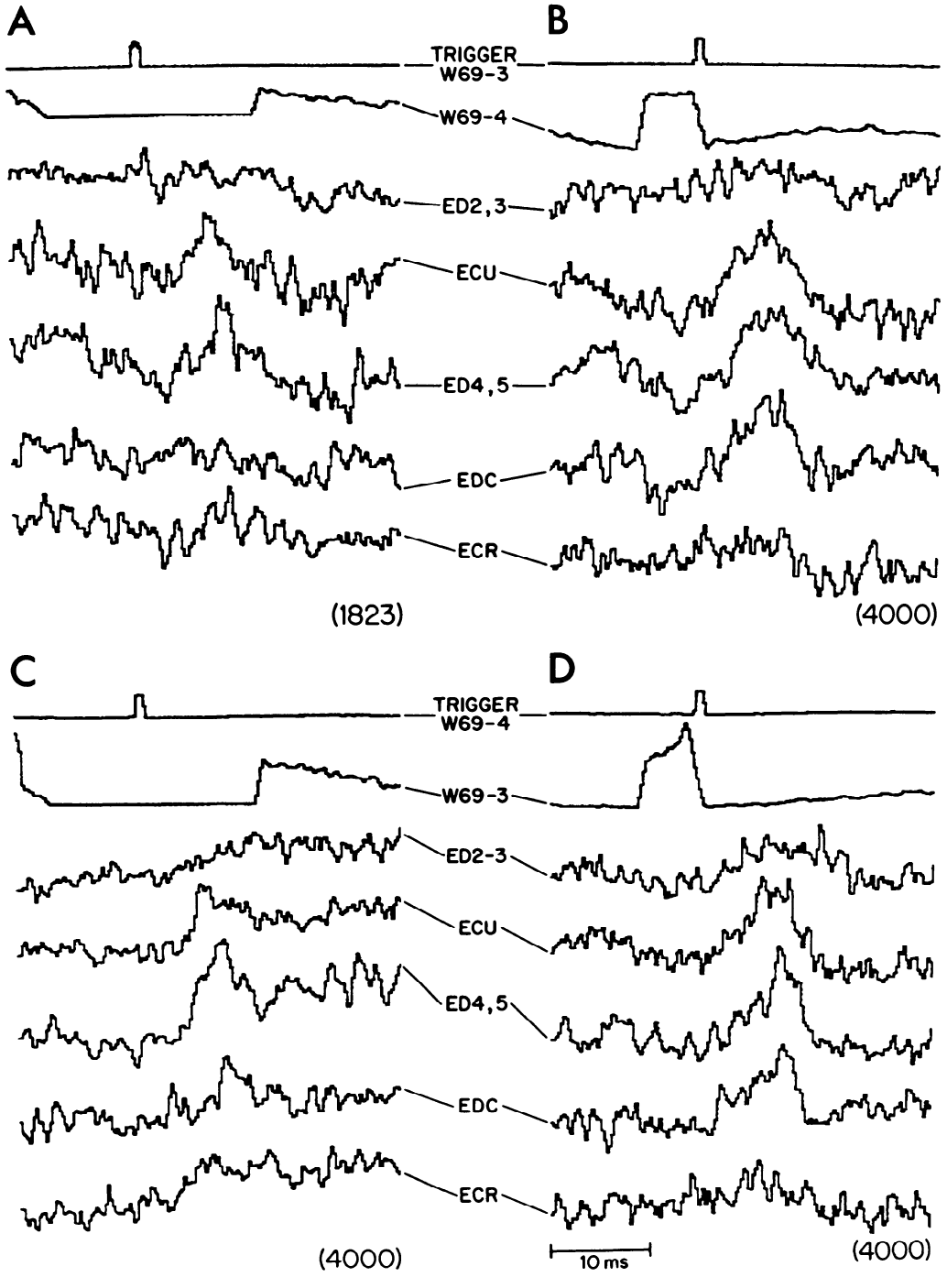

FIG. 10. PSF from associated and dissociated spikes of cells W69-3 and W69-4 (cf. Figs. 8 and 9). *A, C*: dissociated spikes were those action potentials separated by 5 ms or more from a spike in other cell of pair; *B, D*: associated spikes were those of one cell occurring 5 ms or less after a spike in other cell. Top trace in each set is average of pulses (1 ms duration) generated from spikes of trigger cell; second trace is average of pulses generated from spikes of other cell. (Vertical gain of top trace is greatly reduced compared with that of second trace.) Corresponding spike-TAs of full-wave rectified EMG activity of identified muscles are shown in remaining traces of each set.

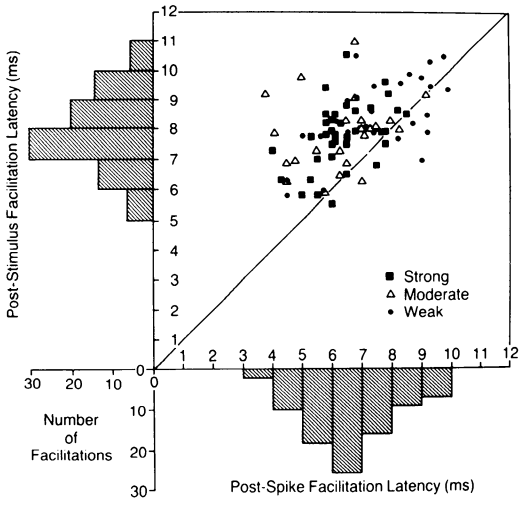

FIG. 11. Onset latencies of PSF vs. PStimF in averages computed for same cortical site. Histograms of each are plotted along axes. *Diagonal line* indicates loci of equal latencies. Symbols indicate strength of PSF; differences between mean latencies of PStimF and PSF were comparable for strong (1.4 ± 1.1 ms), moderate (1.6 ± 1.6 ms), and weak (1.0 ± 1.3 ms) PSF.

DISCUSSION

A comparison of effects produced by action potentials of single CM cells and by S-ICMS on forelimb muscle activity elucidates the mode of activation of cortical cells by microstimuli as well as the cortical organization of CM cells affecting related target muscles.

Effects of ICMS on cortical cells

ICMS has proven to be a useful technique for investigating the organization of efferent connections from motor cortex to motoneurons since minimal currents may be used (2, 6, 7, 23, 30). The fact that ICMS activates both somas and fibers at comparable thresholds (19, 21, 25, 31, 33), however, limits the degree to which the excited neural elements can be specified. ICMS could activate cortical neurons by three different mechanisms: *1*) direct stimulation of local somas via current spread; *2*) direct stimulation of local axons whose somas may be remote; and *3*) indirect, transsynaptic stimulation of neurons receiving sufficient convergence of excitatory input from the directly activated cells. Careful analysis of the mode of activation of PTNs by ICMS shows all three mechanisms to be significant (4, 25, 31, 33); with repetitive ICMS the transsynaptic activation of PTNs becomes increasingly dominant (4, 19). This precludes a precise description of the exact number and location of neuronal elements activated by ICMS. For example, estimates of the extent of effective current spread for direct activation of PTNs vary widely (2, 4, 19, 25). Also, estimates for cells may differ from those for axons and axon terminals. Furthermore, the distance from which a cell or axon can be directly excited from a point source may vary as a function of the cell's size (8, 31). These factors make it impossible to specify the nature and number of elements activated by ICMS or to define a precise boundary surrounding the microelectrode tip within which all cells will be activated. As a general rule, Asanuma and co-workers (4, 33) proposed that a 10-μA stimulus (0.2-ms pulse duration) will directly activate any cell whose action potential can be recorded with the same microelectrode.

Considering cortex to be an isotopic medium, one can estimate the extent of effective current spread from a point source by the expression

$$r_0 = \sqrt{i/k} \qquad (1)$$

where r_0 is the radius of the cortical volume containing the directly activated cells, i is the stimulus current, and k is a proportionality constant (31, 33). Using minimal, intermediate, and maximum estimated values of k, the number of small and large PTNs activated by different intensities of ICMS can be calculated from estimates of cell density in layer V of cortex (22, 30) as Anderson et al. (2) have done for higher intensities of ICMS. These estimates (Table 2) cover a wide range of possible numbers of cells directly activated by ICMS. Our evidence would suggest that the value of 3,000 is an overestimate because it predicts a threshold of 4 μA for short-latency effects mediated by large PTNs; yet our thresholds for evoking PStimF range from 0.5 to 2 μA, similar to those reported by others for axons and cells (17, 19, 21, 31). These estimates of current spread suggest that a 10-μA ICMS will directly activate 1–12 large PTNs and 180–2,168 small PTNs. However, because these measurements of current spread are derived empirically from large PTNs, we cannot be certain that they apply as well to the more numerous small PTNs.

TABLE 2. *Number of PTNs activated by different intensities of ICMS*

Stimulus Intensity, μA	Minimal k, k = 250 μA/mm²		Intermediate k, k = 1,350 μA/mm²		Maximal k, k = 3,000 μA/mm²	
	Large	Small	Large	Small	Large	Small
3	3	650	1	120	1	54
5	6	1,084	1	201	1	90
10	12	2,168	2	402	1	180
15	18	3,252	3	603	2	270
20	24	4,336	4	804	2	360

Estimates based on evidence of Andersen et al. (2). Large and Small refer to size of pyramidal tract neurons.

Current from ICMS will activate axons as well as somas because their electrical thresholds are comparable (19, 21). Other cells receiving a sufficient number of excitatory fibers activated synchronously would also be activated transsynaptically; the number of cortical cells excited transsynaptically by S-ICMS should decrease with distance from the stimulus site. Therefore, the descending volley elicited by ICMS could consist of both direct and indirect components. Such components have been demonstrated by direct recording of pyramidal tract waves evoked by ICMS (19, 25). Jankowska et al. (19) found that at most sites where ICMS was applied, PTNs were activated indirectly, although for one-third of the stimulus sites the descending volley had latencies consistent with direct activation of PTNs. Asanuma and colleagues (25, 33) have suggested that the direct component is the dominant factor for evoking muscle activity when the right stimulus parameters are used. Both groups agree that with repetitive stimulation, the indirect component of the descending volley becomes significantly larger than the direct component (4, 19). Therefore, some effects evoked by repetitive ICMS may be mediated predominantly by indirect activation of corticospinal circuits. In our stimulus-TAs the S-ICMS were separated by intervals too long for temporal summation, so the PStimF represents the effect of a single stimulus. Comparing the effects of single and repetitive ICMS at the same site, we sometimes found that repetitive stimulation produced additional effects (10).

In our experiments the PStimF evoked from sites of CM cells was probably mediated by the recorded CM cell plus some neighbors that were activated directly because of their proximity to the stimulating electrode and/or activated transsynaptically. In a given muscle the size of PStimF increased when stimulus intensity was increased from threshold. At ~15 μA, facilitation often began to appear in additional muscles. The above intermediate estimates of current spread would suggest that the cortical projection area containing CM cells with common muscle fields has a radius of ~280 μm.

The relative magnitudes of PStimF and PSF might be used to estimate the number of corticospinal cells stimulated, given certain assumptions. Assuming that the PStimF increases in proportion to the number of PTNs excited and that the PSF of the recorded CM cell approximates the mean effect of the group, one can divide the PStimF magnitude by the PSF magnitude to obtain a rough estimate of the number of PTNs stimulated. Numerous sources of variance would make individual facilitation ratios relatively unreliable, but the average of a large number of comparisons may come closer to meeting these assumptions. For 33 comparisons, a 5-μA stimulus evoked facilitation 6.3 times greater than the PSF of the single CM cell at that site, thus suggesting that 5 μA activated ~6 PTNs. This estimate agrees with the number of large PTNs estimated to be directly affected by 5 μA for minimal k values (Table 2). Of course, not all the PTNs are likely to be CM cells; some may contribute to PStimF through polysynaptic linkages whose effectiveness could be enhanced by the synchronous descending volley. Moreover, not all CM cells activated by the stimulus need to have somas located near the stimulating electrode; a distant CM cell activated via its axon

collateral would also contribute cortical output.

Latency of PStimF

The mechanisms mediating these facilitations are further elucidated by their latencies. For a CM cell, the latency between the axon hillock spike and PSF onset would equal the conduction times of the action potentials along the axons of the CM cell and the motoneuron plus two synaptic delays. The latency of PStimF would equal the sum of these same delays and any delays in activating the cortical cells. The utilization time for directly activating somas or axons would be ~200 μs, and the minimum time for transsynaptic activation of PTNs is ~0.8 ms (8). With these assumptions, a PStimF latency that exceeds the corresponding PSF latency by <1 ms would be consistent with direct activation of CM cells. The observed latency difference of PSF and PStimF ranged from −2.0 to +5.4 ms and averaged 1.3 ms. These larger differences may reflect several mechanisms. *1*) Conceivably, PStimF may be mediated entirely by transsynaptic activation of CM cells, thereby adding an additional synaptic delay. This seems unlikely, however, because S-ICMS was always applied to the site of maximum CM spike amplitude, which should have assured direct activation of the recorded CM cells. *2*) PSF latency may be artifactually shortened by delays between initiation of a spike at the axon hillock and recording of the extracellular action potential. A delay of up to 0.4 ms could occur before the spike amplitude reaches detectable levels. In contrast, PStimF latencies were measured from the onset of the stimulus trigger pulse, and thus they include the utilization times before action potentials are initiated in the corticofugal cells. *3*) In some cases PSF latency may also be shortened by strong synchronization between the activity of different CM cells. A contribution to the PSF mediated by another CM cell sending a collateral to the recorded cell should begin at a latency shortened by the conduction time along the collateral plus a synaptic delay (14). In such a case the S-ICMS could also evoke facilitation by stimulating that collateral, and the latency of the resulting PStimF would again include the collateral conduction time as well as the axonal utilization time. These mechanisms may partly explain the difference in latency between PStimF and PSF.

CM cell arrangement within the cortex

The fact that the profile of PStimF was identical or very similar to that of PSF of CM cells at the same cortical site suggests that the group of cells activated by the stimulus affects the same set of target muscles as the recorded cell. If neighboring CM cells commonly had different target muscles, more of the stimulus-TAs should have revealed facilitation in additional muscles or produced a different rank order of facilitation magnitude compared with spike-TAs. At most of the cortical sites examined, the profile of PSF matched that of PStimF; the rest showed minor discrepancies, usually in the order of relative magnitude of facilitation of the same set of muscles. At four cortical sites, PStimF did not occur in a muscle that did show PSF. In these cases the muscle may have received facilitation only from the recorded cell but not its neighbors; the number of stimulus events may have been insufficient to reveal an isolated effect from the recorded cell, but adequate to reveal the common effect of the group.

Our results suggest that the CM cells in the vicinity of the electrode tip, whether activated directly or transsynaptically by ICMS, have very similar target muscles. The extent to which PStimF is mediated by activation of CM cells remote from the site of stimulation is unknown, although we expect it to be small for the reasons discussed above. Direct confirmation that neighboring CM cells do have similar muscle fields was provided by spike-TAs of CM cells that were recorded simultaneously (Figs. 9 and 10) or successively (Table 1). The PSF profiles of such cell pairs were usually similar.

The degree of interaction between neighboring CM cells is of considerable interest because it bears on their functional organization. Previous cross-correlations of simultaneously recorded and coactivated precentral cell pairs showed negligible correlogram peaks (13). Using computer separation of action-potential waveforms, Allum et al. (1) compiled correlograms with features suggesting excitatory and inhibitory interactions. The

spike activity of our simultaneously recorded CM cells did show a weak correlogram peak (Fig. 8). However, averages selectively triggered from those spikes of one CM cell that were not associated with spikes in the other cell confirmed that each cell produced PSF independent of activity in the other cell (Fig. 10). Although these two cells produced a similar profile of PSF, they had different response patterns during wrist movement; one was tonic and the other was phasic-tonic (9). The cross-correlogram peak, if mediated by a connection between the cells, would indicate that the tonic cell sent an excitatory collateral to the phasic-tonic cell.

Some features of the functional organization of CM cells suggested by these observations are diagrammed in Fig. 12. A basic feature is that some CM cells send divergent terminals to more than one target motoneuron pool. This is consistent with anatomic (32) and electrophysiological (7) evidence for divergent collaterals of corticospinal axons to diverse motoneuron groups. Thus, different CM cells facilitate different combinations of muscles, and each muscle would be part of the muscle field of many different CM cells.

This diagram also indicates that neighboring CM cells have similar or identical target muscles, as symbolized by two representative CM cells in each group. A relevant question is whether neighboring cells with similar target muscles form distinct aggregations separated by gaps containing no CM cells. Such clustering of corticospinal neurons retrogradely labeled by HRP has been described in the primate (11, 22, 28); large HRP injections in the ventral horn revealed clusters of 4–20 corticospinal cells occupying a 0.5- to 1-mm-diam area of layer V. Similar grouping of PTNs has been suggested by acute electrophysiological recording (2, 6, 7, 18, 23, 24). Moreover, neighboring PTNs have been shown to project to similar motoneuron pools (7). Our results are consistent with such clustering insofar as the PStimF profile resembled the corresponding PSF profile, even with increasing stimulus intensity. Comparable grouping of cortical cells with similar inhibitory as well as excitatory outputs is described in the subsequent study (10).

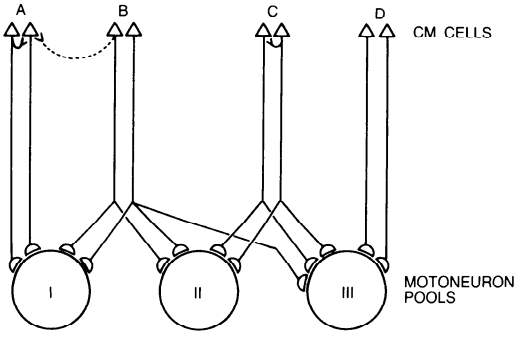

FIG. 12. Diagram of CM cell organization consistent with experimental observations. Correlational linkages are represented by monosynaptic connections. Groups of CM cells with similar muscle fields are located together in cortex.

Thus, neighboring CM cells with similar target muscles may form functional projection groups. The synaptic organization of such projection groups could be of considerable consequence to the cortical control of muscle activity. Cross-correlational evidence suggests some interaction between related CM cells within a group, as suggested by the solid collaterals in Fig. 12. Extensive collateral interactions between different projection groups (symbolized by the dotted connection from group *B* to *A*) seems less likely because stimulation of such collaterals (at site *A*, for example) would produce PStimF of other muscles (e.g., II) in addition to the target muscles of the recorded CM cell, and such an effect was rarely observed. We therefore conclude that during movement the coordinated activation of different output groups is more likely to involve coordinated inputs from other areas than extensive direct interactions between output cells with different target muscles.

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