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Patterns of Facilitation and Suppression of Antagonist Forelimb Muscles From Motor Cortex Sites in the Awake Monkey

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SUMMARY AND CONCLUSIONS

1. Patterns of excitatory and inhibitory effects were produced in antagonistic forelimb muscles by single intracortical microstimuli (S-ICMS) applied to motor cortex sites in macaque monkeys performing ramp-and-hold wrist movements. Stimulus-triggered averages (stimulus-TAs) of rectified electromyographic (EMG) activity revealed poststimulus facilitation and/or suppression in identified flexor and extensor muscles of the wrist and fingers. At 22 cortical sites the action potentials of single cells were also recorded and used to compute spike-triggered averages (spike-TAs) of covarying muscles. The set of muscles activated during the movement in which the cell was active are referred to here as "agonists"; those muscles active during wrist movement in the opposite direction are called "antagonists." (At sites where cells were not isolated the muscles showing poststimulus facilitation were called agonists.)

2. Poststimulus effects in agonist muscles typically consisted of facilitation in a subset of the agonists. For 48 sites from which poststimulus effects were tested on both flexors and extensors, the following combinations of effects were observed: *1*) pure facilitation of agonist muscles with no effect on antagonists; *2*) facilitation of both agonists and antagonists; *3*) facilitation of agonist muscles with reciprocal suppression of antagonists; *4*) "mixed" facilitation and suppression of synergist muscles; and *5*) pure suppression of some muscles with no effect on their antagonists. The suppression effects appeared most commonly in flexor muscles; conversely, facilitation was generally stronger in extensors.

3. Cortical sites eliciting pure suppression of flexor muscles with no facilitation of extensor muscles were found in two monkeys. These purely suppressive effects were observed not only in stimulus-TAs but also in spike-TAs computed from single cells at these sites. Some of these cells increased their activity during wrist extension (but had no detectable effect on the extensor muscles); others discharged during flexion.

4. Several observations suggest that the cortically evoked suppression is mediated by polysynaptic relays. The mean onset latency of the postspike suppression (7.4 ms) produced by inhibitory cells was longer than the mean onset latency of postspike facilitation (6.7 ms) produced by CM cells. Similarly, the mean onset latency of poststimulus suppression (8.9 ms) was longer than that of poststimulus facilitation (8.0 ms). Moreover, suppression was usually weaker than facilitation in the spike-TAs, as well as in stimulus-TAs compiled for the same stimulus intensity.

5. As found for poststimulus facilitation (7), the pattern of poststimulus suppression matched the corresponding postspike pattern computed for certain cells at sites of stimulation. This finding suggests that motor cortex cells form functional aggregates of output cells that affect the same or similar sets of target motoneurons and inhibitory interneurons. Such grouping was supported by spike-TAs compiled for neighboring cortical cells that produced the same profile of postspike suppression of muscle activity.

6. The effects evoked by single and repetitive ICMS from the same cortical sites were compared to assess the contribution of temporal summation. In many cases the profile of subthreshold poststimulus facilitation evoked by S-ICMS resembled the EMG activity evoked by repetitive ICMS. However, trains of stimuli could also activate muscles not directly affected by S-ICMS, thus suggesting that repetitive ICMS may recruit additional pathways by temporal summation.

INTRODUCTION

The excitatory effects of single motor cortex cells on forelimb muscles can be documented by computing spike-triggered averages (spike-TAs) of electromyographic (EMG) activity (10); the appearance of clear postspike facilitation of average muscle activity identifies corticomotoneuronal (CM) cells and indicates the distribution of effects among the synergistically acting agonist muscles. Most wrist-related CM cells produced postspike facilitation in more than one of the wrist and finger muscles, thus suggesting divergent effects on multiple target muscles.

The use of single intracortical microstimuli (S-ICMS) during wrist movements in conjunction with stimulus-triggered averages (stimulus-TAs) of EMG activity similarly reveals the statistical effects elicited in different forelimb muscles by stimulus pulses. Microstimulation at the site of CM cells produced profiles of poststimulus facilitation that matched those of postspike facilitation for the CM cell recorded at that site (7). However, the magnitude of poststimulus facilitation was several times greater than that of postspike facilitation, thus suggesting that CM cells form functional aggregates in which each cell facilitates similar or identical target muscles. Such grouping was further supported by the finding that neighboring CM cells often produced similar profiles of postspike facilitation of agonist muscle activity (7).

Many movements, including the alternating wrist movement used in these experiments, involve contraction of agonist muscles and simultaneous relaxation of antagonist muscles; therefore, it is of considerable interest to determine whether CM cells may affect antagonist as well as agonist motoneurons. Since CM cells are typically inactive during the phase of alternating wrist movement in which antagonist muscles are active, it is normally not possible to test their effect on antagonist muscles using spike-TA. However, spikes evoked by local injection of glutamate may show reciprocal effects on antagonists (8, 9, 15). Alternatively, one can stimulate these cells electrically during both flexion and extension and use stimulus-TAs to reveal their effect on the activity of agonist and antagonist muscles. With this technique we found several patterns of precentral action on agonist and antagonist forelimb muscles.

METHODS

The recording, stimulation, and analysis techniques used in this study were the same as those described in the companion paper (7). The identification of the forearm muscles has also been described (7, 10). Data in this paper were obtained from five rhesus macaques. In 22 cases, microstimuli were applied at recording sites where cells had shown postspike effects in spike-TAs; the other 26 stimulus sites were histologically confirmed to be in gray matter, but not necessarily near CM cells. Stimulus-TAs were compiled from single biphasic microstimuli (5 or 10 μA, 0.2-ms negative pulse followed by 0.2-ms positive pulse). Digitizing rate for all spike- and stimulus-TAs in this paper was 4 kHz. S-ICMS was delivered at a rate of 5–15/s, during the phase of wrist movements in which the averaged muscles were active. In some cases repetitive ICMS (300–400 Hz) was also applied, and the profile of evoked EMG activity across muscles was compared with effects of S-ICMS obtained in stimulus-TAs.

The magnitudes of postspike and poststimulus suppression were calculated by the same formula used to calculate mean percent facilitation (7) except that the comparison interval encompassed the suppression. Thus

$$\text{mean \% suppression} = \frac{\text{mean suppression height} - \text{mean baseline}}{\text{mean baseline}} \times 100$$

RESULTS

We documented the output effects evoked by S-ICMS at 48 motor cortex sites on both flexor and extensor muscles of the wrist and fingers; the chosen sites all produced subthreshold poststimulus facilitation and/or suppression in stimulus-TAs. CM cells, which produced clear postspike facilitation of their target muscles, were recorded at 19 of these sites. The spikes of these CM cells were monitored at various times during and after

TABLE 1. *Patterns of effects on forelimb muscles from S-ICMS*

	With Cells	Without Cells	Total
Pure facilitation: flexors	3	3	6
Pure facilitation: extensors	5	3	8
Facilitation with reciprocal inhibition	4	3	7
Pure inhibition: flexors	3	4	7
Pure inhibition: extensors	0	2	2
Mixed facilitation and suppression	6	7	13
Facilitation of flexors and extensors	1	4	5
Total	22	26	48

Number of sites from which indicated poststimulus effects were evoked in flexor and extensor muscles. For sites "with cells," spike-TAs showed postspike effects that were similar to poststimulus effects. Results obtained from five monkeys.

stimulation to confirm the viability and proximity of the recorded cell. Stimulus-TAs of wrist flexor- and extensor-muscle activity revealed several types of motor cortex action upon agonist and antagonist muscles during alternating wrist movements (Table 1).

Facilitation of agonist muscles with no effect on antagonists

At 14 cortical sites microstimuli evoked poststimulus facilitation in one set of muscles, called the "agonists," and produced no effect in their antagonists. Figure 1 illustrates an

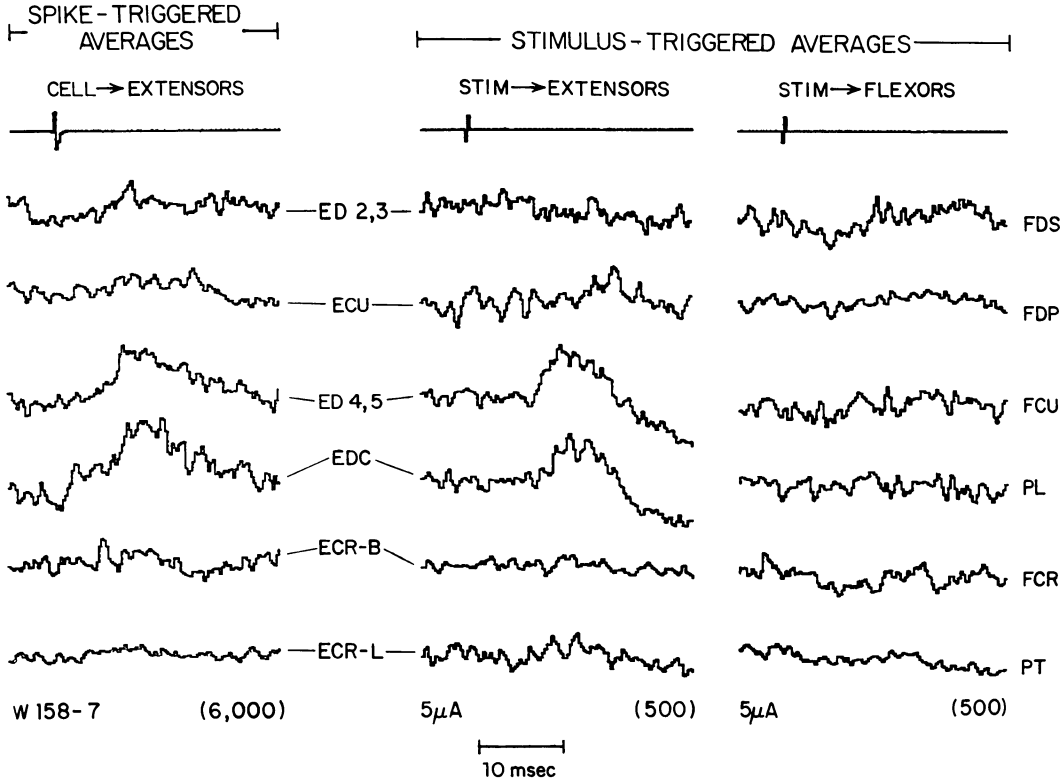


FIG. 1. Cortical facilitation of agonist muscles with no effect on antagonists. *Top record* in each column indicates time of triggering event (spike or stimulus); *lower records* are averages of rectified EMG of six synergist muscles. Spike-TAs for CM cell W158-7 (*left column*) reveal postspike facilitation in ED4,5 and EDC with a mean percent increase of 6.1 and 5.0%, respectively. *Middle* and *right columns* are stimulus-TAs of six extensors and six flexors computed for 5-μA stimuli applied to the recording site of cell W158-7. Poststimulus facilitation of ED4,5 and EDC (MPI = 16.3 and 15.9%) matches the profile of postspike facilitation. Stimuli applied during flexion evoked no effects in flexor muscles. Number of events averaged in this and subsequent figures is given in *parentheses*.

example of such a site at which a CM cell was also recorded. This cell fired with a phasic-tonic pattern (6) in association with wrist extension, and facilitated two target muscles, EDC and ED4,5. (The fluctuations in the spike-TAs of the other extensors were not sufficiently strong and consistent to be interpreted as spike-related effects.) S-ICMS of 5 μA delivered through the electrode during identical extension movements were used to compile the stimulus-TA shown in the middle column of Fig. 1. Poststimulus facilitation was evoked in EDC and ED4,5 but negligible effects appeared in the other muscles. The peak-to-noise ratios in the two sets of averages are comparable even though the spike-TAs were compiled from 12 times as many trigger events. Direct calculation showed the mean percent increase above base line of poststimulus facilitation to be three times greater than postspike facilitation of the same muscles; this suggests that S-ICMS evoked activity in a population of corticospinal cells affecting the same muscles (7).

This CM cell was inactive during the flexion movement, so spike-TAs of flexor muscle activity could not be compiled. However, microstimulation during flexion movements was used to test the output effects of these cells on antagonist muscles. Stimulus-TAs of wrist flexors (right-hand column of Fig. 1) were compiled from 5-μA S-ICMS applied to the same cortical site during flexion. None of the six wrist flexors showed any clear, repeatable, stimulus-related effect.

A similar pattern of effects, namely, poststimulus facilitation of agonist muscles without any effect on antagonists, was obtained at a total of eight cortical sites where CM cells had been recorded (five extension and three flexion cells). At six additional cortical sites, where no CM cells were recorded, S-ICMS similarly facilitated some muscles but did not affect their antagonists. Pure facilitation was evoked in extensors from eight sites and in flexors from six sites.

Facilitation of agonists with reciprocal inhibition of antagonists

At some cortical sites tested with stimulus-TA, facilitation of agonist muscles was coupled with reciprocal inhibition of antagonists. Figure 2 illustrates such a pattern. An extension-related CM cell at this site produced

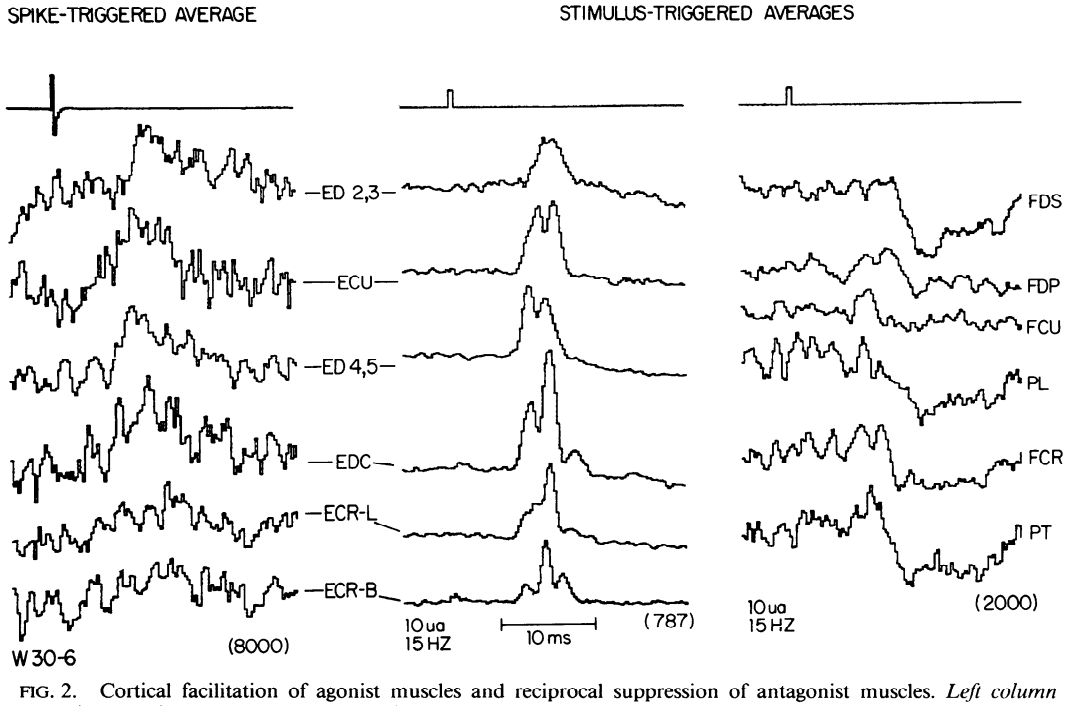


FIG. 2. Cortical facilitation of agonist muscles and reciprocal suppression of antagonist muscles. *Left column* shows spike-TAs for CM cell W30-6, revealing clear postspike facilitation in ED2,3, ECU, ED4,5, and EDC. *Middle* and *right columns* show stimulus-TAs for extensors and flexors, respectively, computed for 10-μA stimuli applied to the cortical site of this CM cell. Note poststimulus suppression of FDS, PL, FCR, and PT.

clear postspike facilitation in four extensor muscles (left column, ED2,3, ECU, ED4,5, EDC). Marginal effects also appeared in ECR-L and ECR-B. S-ICMS of 10 μA at this site produced strong poststimulus facilitation in the wrist extensor muscles (middle column). Stimulus-TAs of flexor EMG activity during wrist flexion revealed poststimulus suppression in several flexor muscles (right column). The clearest and strongest suppression appeared in FDS (−16.0%), PL (−8.3%), FCR (−8.7%), and PT (−9.12%); the effect in FDP, though marginal, also suggests suppression. The suppression was weaker than the poststimulus facilitation of agonists, as evidenced by the lower peak-to-noise level and the larger number of events averaged. The mean percent suppression was −10.5% in the four flexor muscles affected most strongly compared with a mean percent facilitation of +63.8% in the four most strongly facilitated extensors. The average onset latency of poststimulus suppression in the four flexors was 11.1 ms, compared with an average latency of 7.2 ms for onset of poststimulus facilitation.

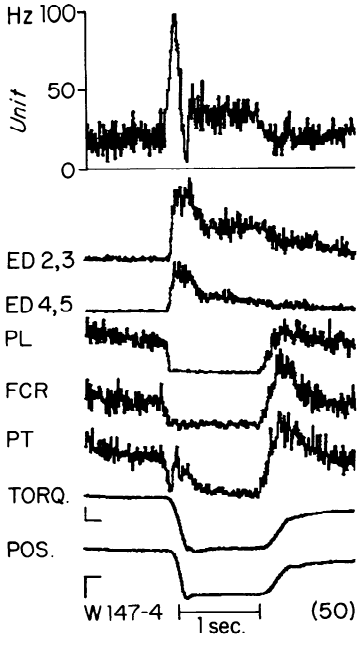


FIG. 3. Response pattern of precentral cell that produced only postspike suppression of antagonist muscles (cf. Fig. 4). Response averages show firing rate of cell and wrist flexor and extensor muscle EMGs during the alternating wrist movement. *Records* from top: histogram of cell firing rate, averages of full-wave rectified EMG activity; averages of wrist torque and position (extension down). Histogram bin width was 15 ms.

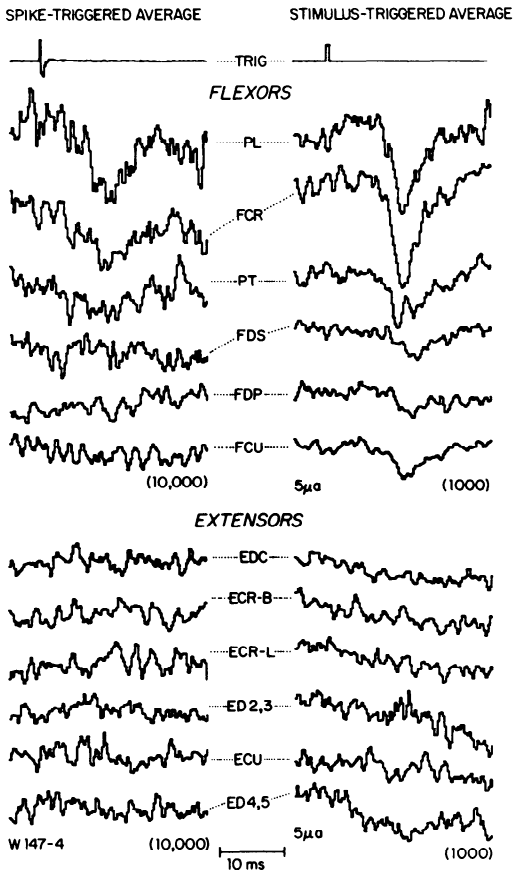


FIG. 4. Suppression of flexor muscle activity with no effect on extensors from cell whose activity is shown in Fig. 3. *Left column* shows spike-TAs of six flexor muscles and six extensor muscles. Note postspike suppression in PL and FCR and absence of any effect in extensor muscles. *Right column* shows corresponding stimulus-TAs of flexors and extensors computed for 5-μA S-ICMS applied at the same cortical site. Poststimulus suppression appeared most clearly in PL and FCR, and also in PT and FCU. None of the extensors shows a clear poststimulus effect.

Such a reciprocal pattern of facilitation and suppression of wrist extensor and flexor muscles was evoked from 7 of 48 cortical sites. CM cells were recorded at four of these sites. Reciprocal suppression was seen more frequently in flexor muscles (five sites) than extensors (two sites).

Suppression of muscles with no effect on their antagonists

At most cortical sites, the effects evoked by ICMS included facilitation of some fore-

limb muscles. An unexpected finding was that stimulation of certain cortical sites only suppressed muscle activity, and had no observed excitatory effect on any muscles. Moreover, at three of these sites we recorded cortical cells that also produced only postspike suppression in spike-TAs. The response pattern of one such cell, illustrated in Fig. 3, was phasic-tonic during the ramp-and-hold extension of the wrist, much like phasic-tonic CM cells that facilitate extensors (6). Unlike CM cells, however, this neuron also remained active during flexion, thus allowing spike-TAs to be computed for both flexor and extensor muscles (Fig. 4). None of the six wrist extensors showed any spike-related effect, whereas the spike-TAs of flexors revealed clear postspike suppression in PL and FCR. This postspike suppression emerged clearly after 10,000 events were averaged, in contrast to postspike facilitation, which is often evident in spike-TAs of 2,000 events. Figure 4 also shows the stimulus-TAs for flexor and extensor muscles for 5-μA S-ICMS applied at the site of the recorded cell. In stimulus-TAs of 1,000 events the flexors PL and FCR were most strongly suppressed; a weaker poststimulus suppression also appeared in the remaining flexors. For PL and FCR the mean poststimulus suppression (−20.8%) was five times larger than the mean postspike suppression (−4.6%). The stimulus-TAs of extensors show no clear effect in any extensor muscle, in agreement with the spike-TA.

The organization of cells in this region is further revealed by two cells recorded simultaneously at a neighboring cortical site (625 μm anterior and medial to the cell in Fig. 4). Both cells covaried with wrist flexion as shown by the response averages in Fig. 5; their steady increase in activity during the hold period resembles the inverse of the decrementing flexor EMG activity. The spike- and stimulus-TAs (Fig. 6) show an inhibitory effect on several flexors. The left column shows that cell 1 produced postspike suppression in PL (−1.2%) and FCR (−2.3%); this suppression was reproducible and built up continuously throughout the average. FDS showed a possible facilitation, but this effect was labile. No significant effect was evident in the remaining three flexor muscles. Cell 2 produced a similar pattern of postspike suppression in PL (−2.7%) and FCR (−3.7%). Stimulus-TAs computed at this cortical site confirmed these inhibitory effects. For 5-μA stimuli the flexors showed the strongest poststimulus suppression in PL (−23.0%) and FCR (−23.2%). In addition, there was weaker poststimulus suppression in FCU (−15.9%) and PT (−18%). Again, 5-μA stimuli delivered during extension evoked no poststimulus effect in the extensor muscles.

The recruitment of additional output cells

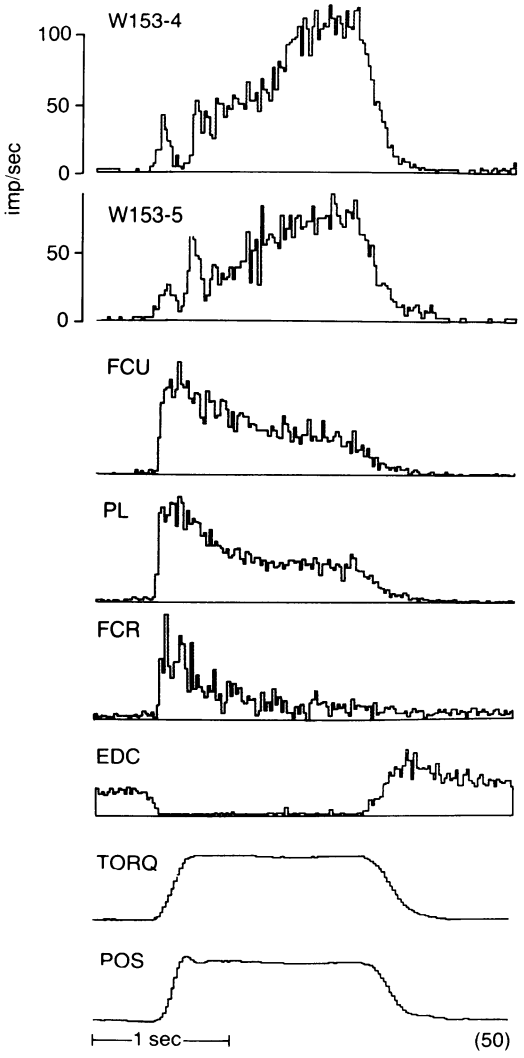


FIG. 5. Response averages of two cells that inhibited flexors (cf. Fig. 6) and were active during wrist flexion. Other traces show averaged EMG activity of indicated muscles, torque, and position. Cells were recorded simultaneously and separated on the basis of clear difference in action potentials.

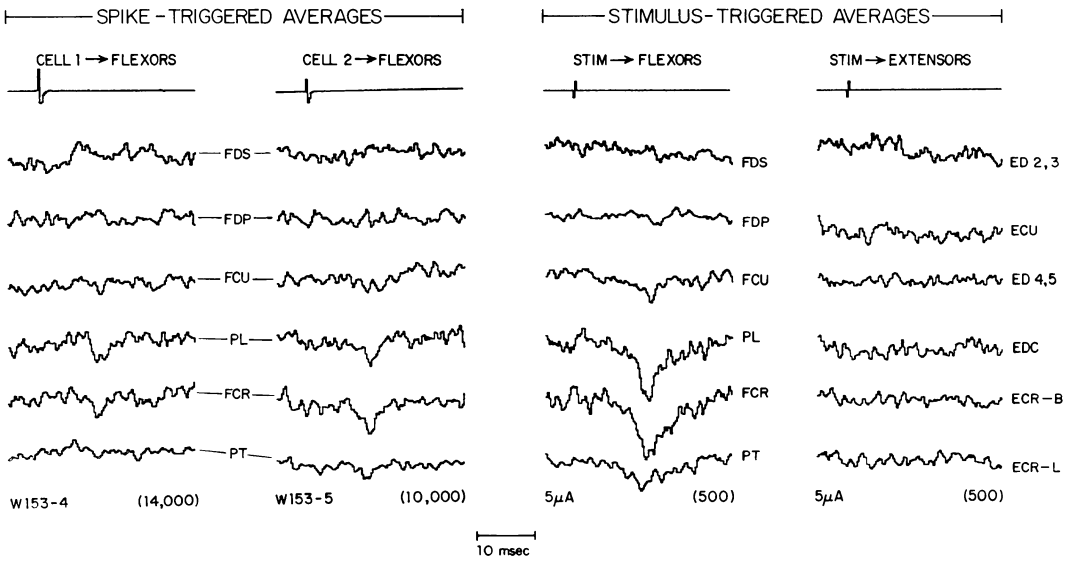


FIG. 6. Suppression of flexor muscles from two neighboring cortical cells. Spike-TAs for cells 1 and 2 (*left*) were compiled from pulses triggered from each waveform. Stimulus-TAs (*right*) were computed for 5-μA stimuli applied to the recording site. Strongest poststimulus suppression appeared in PL and FCR, matching pattern of postspike suppression. No effect was evident in extensors.

from this site was tested by S-ICMS of increasing intensity; the magnitude of poststimulus suppression of flexor muscles increased with stimulus intensity, as shown in Fig. 7. These curves resemble comparable plots for poststimulus facilitation as a function of stimulus strength (Fig. 6 in Ref. 7).

Pure suppression effects were obtained at three sites in two different monkeys (cf. Fig. 2 in Ref. 8; Fig. 11, below) where cortical inhibitory cells were also observed to fire with the inhibited muscles; pure suppression was evoked from six additional sites where spike-TAs were not compiled. Pure suppression was evoked more often in flexor muscles (seven sites) than extensors (two sites).

Other effects on agonist and antagonist muscles

At 13 sites, S-ICMS produced "mixed" effects, namely facilitation of some muscles and suppression of other coactivated muscles. Usually, one set of muscles (flexors or extensors) exhibited only facilitation while the antagonist set exhibited mixed effects. At six of these sites we recorded CM cells, whose target muscles were also facilitated by the stimulus. An example of mixed facilitation and suppression of flexor muscles is illustrated in Fig. 10.

At five cortical sites S-ICMS evoked facilitation in both flexors and extensors; one of these was a site of a CM cell.

Latency of cortically evoked suppression

For those inhibitory sites where inhibitory cells were also recorded, it was possible to compare the postspike and poststimulus suppression of the same muscles. The scatterplot of Fig. 8 compares the onset latencies of postspike suppression with latencies of the corresponding poststimulus suppression. The mean onset latency of postspike suppression was 7.4 ± 1.5 ms (n = 17, ±SD), whereas that of poststimulus suppression was 8.9 ± 1.0 ms. The mean difference between the onset latencies of poststimulus and postspike suppression, 1.5 ms, is comparable to the 1.3-ms difference in mean latency of poststimulus and postspike facilitation observed previously (7).

Comparison of single and repetitive ICMS

In these experiments we used S-ICMS during movement to evoke subthreshold output effects on active muscles to compare the

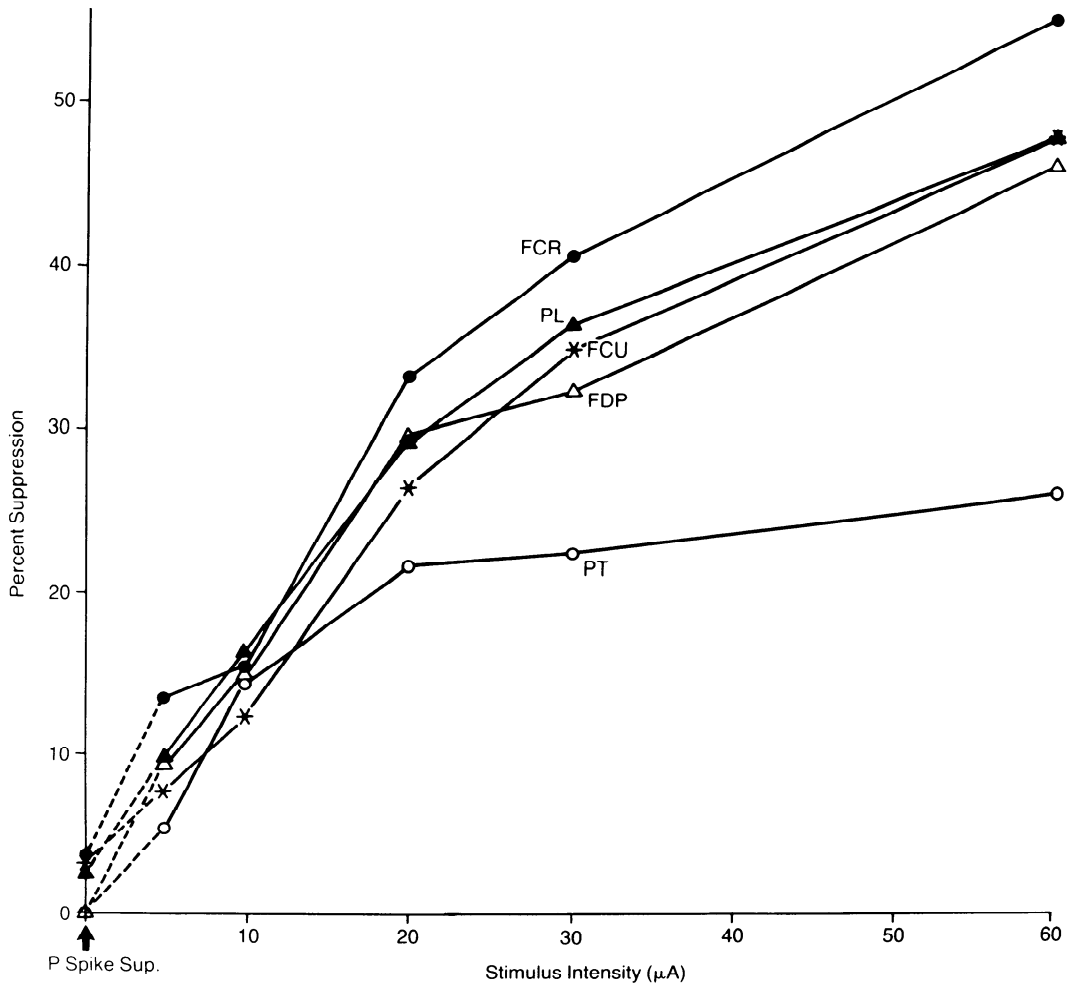
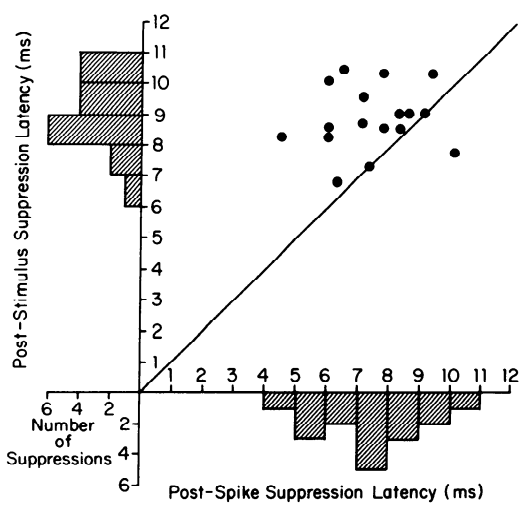


FIG. 7. Magnitude of poststimulus suppression as a function of stimulus intensity for site illustrated in Figs. 5 and 6. These stimulus-TAs were compiled off-line; also shown on the *ordinate* are magnitudes of mean postspike suppression in spike-TAs compiled on-line.



effects that follow the action potentials of recorded cortical cells. Repetitive ICMS is used commonly to evoke suprathreshold responses in the absence of movement (1, 3, 16, 20); repetitive ICMS elicits more potent output effects by virtue of temporal summation (2, 13). To evaluate the consequences of temporal summation, we compared the effects evoked by single and repetitive ICMS at the same sites. These often produced similar

FIG. 8. Comparison of onset latencies of postspike and poststimulus suppression of same muscles. Postspike suppression was obtained from spike-TAs for cells that fired with inhibited muscles; poststimulus suppression was obtained with S-ICMS at same site. Histograms summarize number of latencies in each interval.

profiles of effects; in particular, the muscle that showed greatest poststimulus facilitation in stimulus-TAs usually had the lowest threshold for overt activity evoked by repetitive ICMS.

An example of similar profiles of excitatory effects evoked by CM cell spikes, S-ICMS, and repetitive ICMS is illustrated in Fig. 9. The subthreshold poststimulus facilitation evoked by a single 5-μA stimulus during active extension is matched by suprathreshold EMG responses evoked by repetitive ICMS at 400/s during rest. The antagonist muscles showed no subthreshold effect in stimulus-TAs of 10 μA and were not appreciably activated by repetitive ICMS. Such consistent profiles of effects were seen commonly, but not always.

Figure 10 illustrates an example of different profiles of activity evoked by single and repetitive ICMS at the same site. The S-ICMS evoked a mixed pattern of facilitation

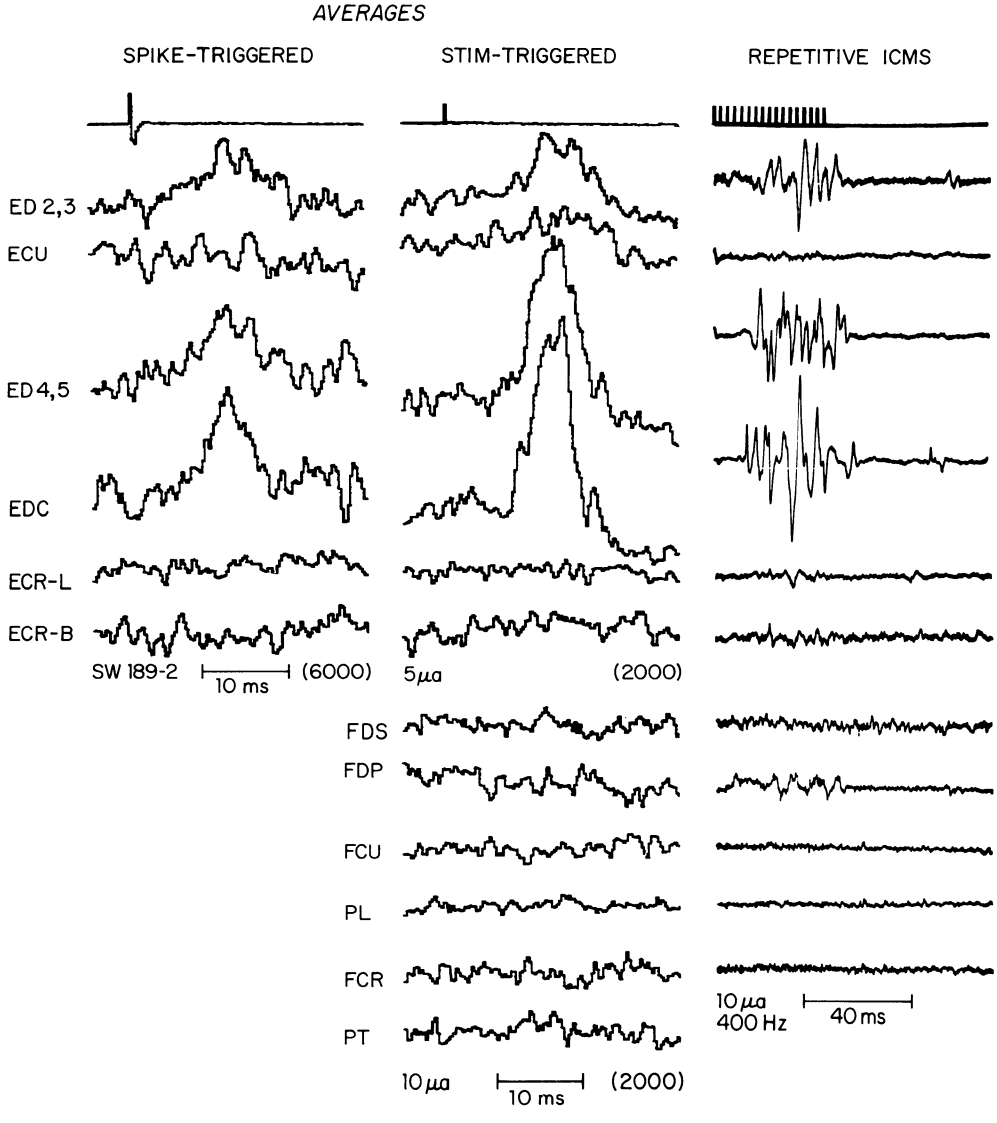


FIG. 9. Comparison of responses evoked in resting muscles by repetitive ICMS (*right*) and subthreshold effects on active muscles detected in spike-TA (*left*) and in stimulus-TA (*middle*). This illustrates reasonably good agreement in relative magnitude of evoked effects. Note different time scale and longer latency for repetitive ICMS.

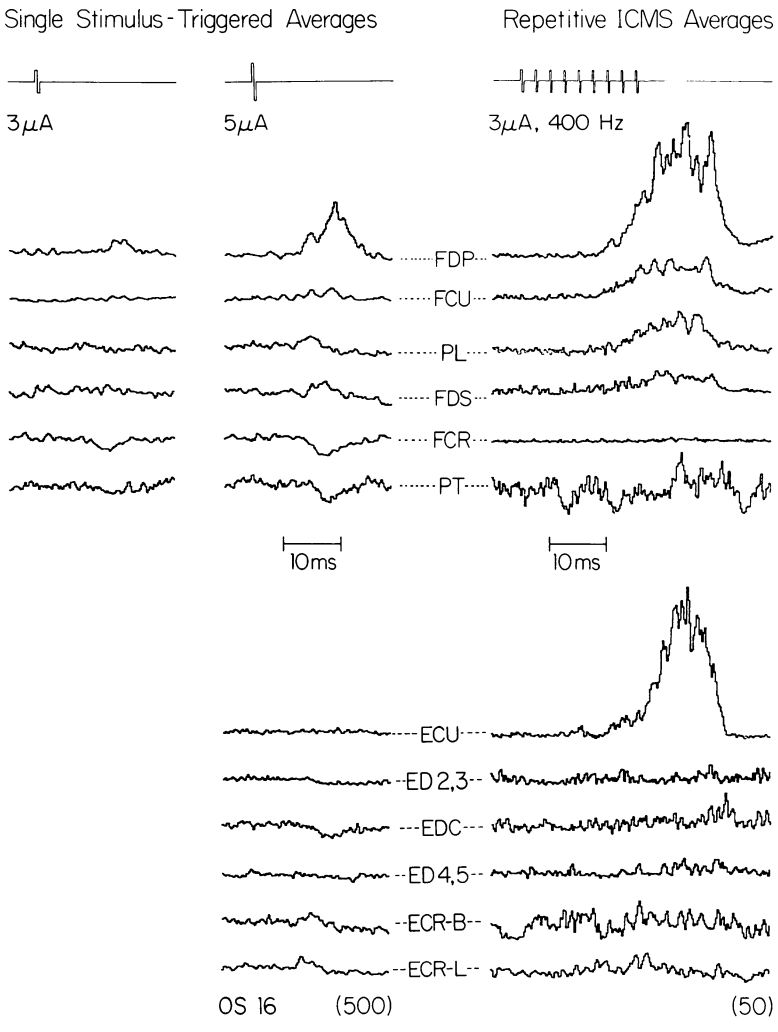


FIG. 10. Comparison of averaged EMG activity evoked by S-ICMS and repetitive ICMS from the same site. Stimulus-TAs (*left*) were compiled during active muscle contraction for S-ICMS at 3 and 5 μA. Averages of muscle activity evoked with monkey at rest by repetitive ICMS at 3 μA (*right*) show excitation of additional muscles, particularly ECU.

and suppression in the flexor muscles, as detected in the stimulus-TAs compiled during flexion (top left). With the monkey at rest, repetitive ICMS (3 μA) evoked clear excitation in several flexors but could not reveal any suppression because there was no background EMG to suppress (top right). Repetitive ICMS also evoked potent activation of an extensor muscle, ECU (bottom right); however, this muscle showed no evidence of poststimulus facilitation in stimulus-TAs compiled during extension (bottom left). Even though the S-ICMS (5 μA) was stronger than the repetitive ICMS (3 μA) and was applied during extensor muscle activity, it did not reveal the excitatory linkages recruited by repetitive stimulation.

The effectiveness of repetitive ICMS in suppressing ongoing muscle activity is illustrated in Fig. 11. A short train of stimuli (400 Hz, 10 μA) applied during the flexion hold period suppressed the EMG activity of three flexor muscles (top left). These muscles also exhibited poststimulus suppression after S-ICMS (top right). In addition, repetitive ICMS excited several extensors during this

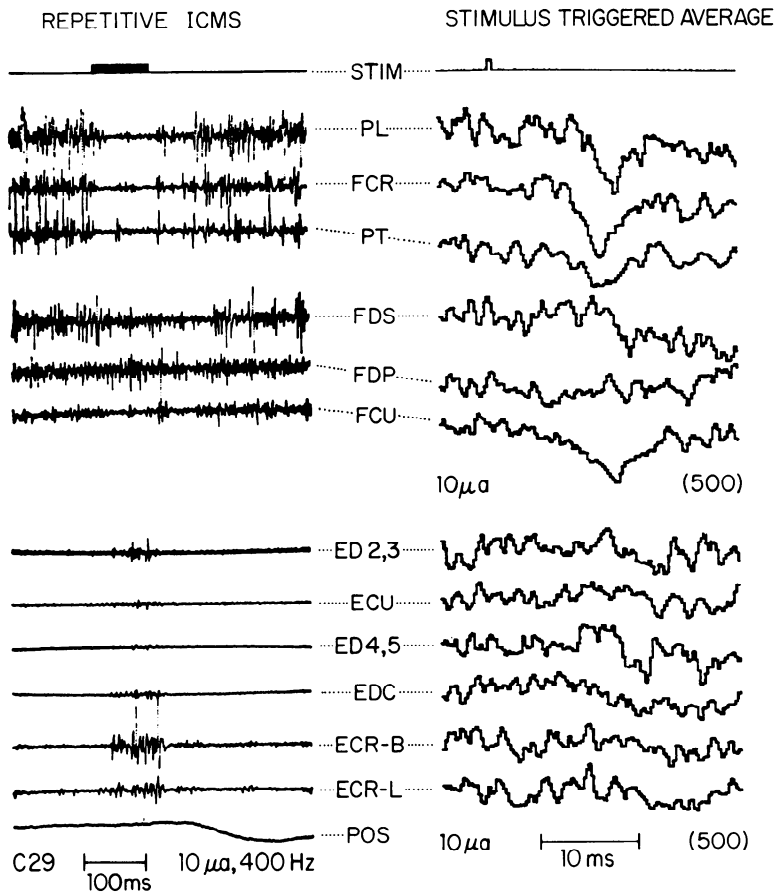


FIG. 11. Effect of repetitive and single ICMS at a cortical site that produced poststimulus suppression of flexor muscles (PL, FCR, PT, and FCU) but negligible effect on extensor muscles in stimulus-TAs (*right*). During the flexion movement, repetitive stimulation (10 μA for 100 ms at 400 Hz) nearly silenced the EMG in PL, FCR, and PT and evoked discharge of motor units in most extensor muscles. These muscle responses were sufficient to cause a transient extension of the wrist as indicated by deflection in position trace.

flexion phase of movement when their activity is normally suppressed. These evoked EMG responses were potent enough to displace the wrist toward extension, as evidenced by the downward deflection of the position record. By comparison, S-ICMS at 10 μA evoked no poststimulus facilitation in the extensors even though the stimulus-TAs of extensors were compiled during extensor activation. Thus, in this monkey repetitive ICMS evoked a pattern of activity that did not appear in stimulus-TAs computed for the same cortical site. Such discrepancies were encountered often enough to suggest that repetitive ICMS may recruit circuits that are not engaged by single stimuli.

DISCUSSION

Patterns of cortical action on forelimb muscles

Figure 12 schematically illustrates some major features of the organization of corticospinal connections to forelimb motoneurons suggested by these findings. The correlational linkages between cortical cells and contralateral forelimb muscles observed in spike- and/or stimulus-TAs are represented by the simplest synaptic connections to the relevant motoneuron pools. We observed three basic patterns of cortical action on flexor and extensor muscles in the monkey during alternating wrist movements. The first

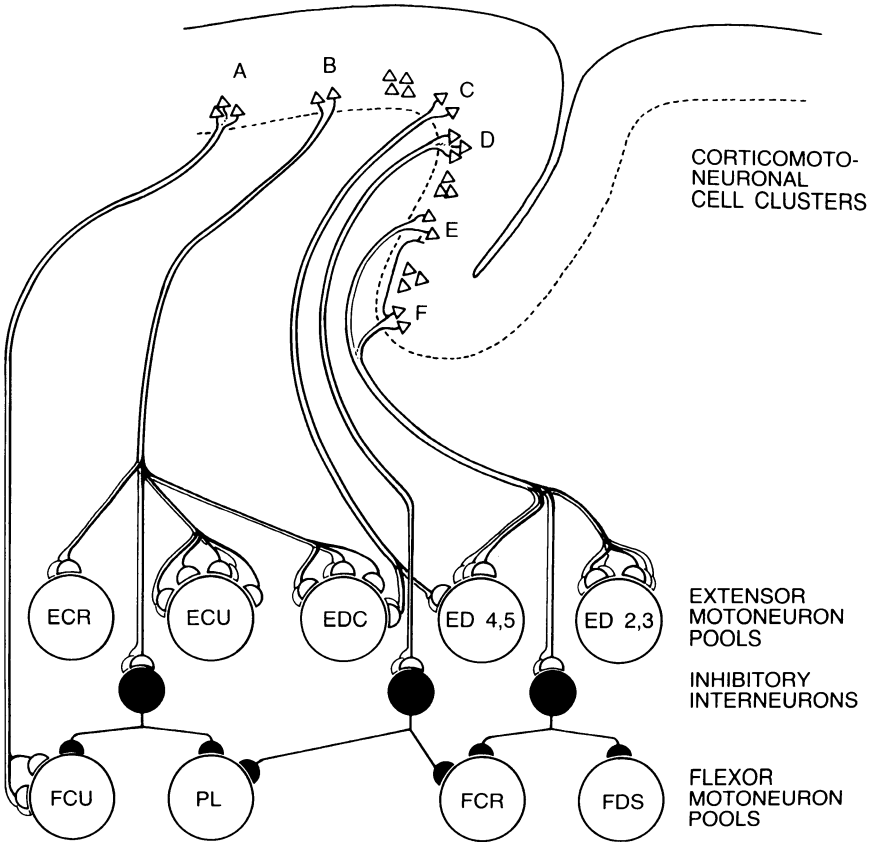


FIG. 12. Diagram of simplest circuits that may mediate the three basic patterns of cortical cell influence on wrist flexor and extensor motoneurons. Correlational evidence indicates that cells may facilitate agonist muscles with no effect on antagonist muscles (*A, C*); facilitate agonist muscles and simultaneously suppress antagonist muscles through a reciprocal inhibitory pathway (*B, E,* and *F*); and suppress certain muscles with no effect on their antagonists (*D*). Clustering and interconnection of cells with common targets is also suggested by these experiments.

pattern is facilitation of the agonist muscles with no effect on antagonists; this is represented by connections of cells *A* and *C*. The second pattern is facilitation of agonists with suppression of antagonists, which could be mediated by connections like those of cells *B, E,* and *F*. Third is pure suppression of some muscles with no effect on their antagonists, as illustrated by cell *D*. In addition, a mixed pattern of suppression and facilitation of synergist muscles was also seen in some stimulus-TAs. Such "mixed" patterns could represent activation of a combination of neighboring cortical cell aggregates (e.g., *A* and *B*), each mediating one of the simpler basic patterns illustrated in Fig. 12.

The concept of reciprocal organization in the corticospinal projection to motoneurons was first supported by Sherrington (21), who showed that stimulating the cortical surface could evoke contraction of a group of synergist muscles and simultaneous relaxation of the antagonists. Reciprocal effects evoked by repetitive cortical stimulation have been demonstrated in dissected ankle muscles (5) and monosynaptic reflexes (3, 23). Schmidt and McIntosh (20) observed simultaneous facilitation and inhibition of different, possibly antagonistic, divisions of the trapezius muscle in the awake monkey. Asanuma and Ward (4) found that the efferent zone causing contraction of a muscle was not coextensive with that causing relaxation of the antagonist. Subsequently, Thompson and Fernandez (23) demonstrated reciprocal inhibition of hindlimb monosynaptic reflexes by repetitive

ICMS from some cortical sites in the cat, but found more sites from which facilitation could be evoked with no apparent inhibition, or inhibition with no apparent facilitation. Using minimal surface stimuli, Jankowska, Padel, and Tanaka (12, 13) mapped the cortical areas from which monosynaptic excitatory postsynaptic potentials (EPSPs) and disynaptic inhibitory postsynaptic potentials (IPSPs) could be evoked in identified hindlimb motoneurons of the monkey; areas producing EPSPs in extensor motoneurons overlapped extensively, but not entirely, with areas producing IPSPs in flexors of the same joint. Our results with S-ICMS suggest that primate forelimb motor cortex also has sites whose stimulation elicits only facilitation, only inhibition, or facilitation coupled with reciprocal inhibition of antagonists. Such effects from S-ICMS are unlikely to involve responses mediated by temporal summation, and often resemble postspike effects produced by single cells recorded at the stimulus site.

Two of the output patterns, pure facilitation of agonists and facilitation combined with reciprocal inhibition of antagonists, have now been demonstrated to be produced by single CM cells (8, 9, 15). Using glutamate to activate CM cells during both flexion and extension, Cheney et al. (8, 9) found that some CM cells produced postspike suppression in antagonists of their target muscles. Of 49 CM cells that facilitated agonist muscles, 14 (28%) also suppressed the antagonists (15).

A new class of purely inhibitory motor cortex neurons is illustrated by the cells in Figs. 3–6, all of which inhibited flexors but had no observed effect on any extensors. Some sharply increased their activity during the extension and therefore contributed to the concurrent suppression of flexors (Fig. 3; the cell in Fig. 11, recorded from another monkey, had a similar response average: cf. Fig. 2 in Ref. 8). More surprising was the pair of cells that fired briskly during flexion (Fig. 5) but inhibited the coactivated flexor muscles (Fig. 6). The absence of any effect from this zone on extensor muscles is confirmed in the stimulus-TAs (Fig. 6). It appears, therefore, that the sole action of some cortical cells during movement is to inhibit muscles rather than facilitate them. Of course, our EMG electrodes may have failed to sample some facilitated motor units, in which case these could represent reciprocal inhibitory effects.

Effects on flexor vs. extensor muscles

Precentral motor cortex appears to affect forelimb flexor muscles somewhat differently than it affects extensor muscles. We noted previously that extensor CM cells had stronger postspike facilitation and larger muscle fields than did flexor CM cells (10, 15). Moreover, the firing rate of extensor CM cells increased more rapidly with wrist torque than did the activity of flexor CM cells (6). The present experiments reveal further asymmetries insofar as inhibitory effects were evoked more often in flexor muscles than in extensors; seven of the nine pure inhibitory sites affected flexors, and five of the seven cases of reciprocal suppression appeared in flexors. Kasser and Cheney (15) also found that reciprocal postspike suppression from CM cells is preferentially directed toward flexor muscles. Forty percent of their extension CM cells reciprocally suppressed flexor muscles, whereas only 15% of flexion-related CM cells reciprocally suppressed extensor muscles. Moreover, the number of flexor muscles suppressed per reciprocal CM cell was 2.6, compared with 1.3 for extensor muscles.

Differences between flexor and extensor responses to cortical stimuli were also reported by Preston et al. (19). Using corticospinal volleys to condition monosynaptic reflexes in the "pyramidal" baboon, they found cortical inhibition to be more prominent in proximal forelimb flexor muscles. Noting that these flexors serve as antigravity muscles during quadrupedal standing, they proposed that the initiation of voluntary movement during a quadrupedal standing posture involves cortical inhibition of flexors to produce a shift from forelimb flexor- (antigravity) muscle activity to extensor-muscle activity. For distal forelimb muscles, they observed a net cortical facilitation of flexor and extensor reflexes. These results are compatible with our observations that flexors may be facilitated as well as inhibited; under their experimental conditions direct excitatory effects on flexors could predominate over inhibitory effects.

Another functional correlate of the smaller muscle fields of flexor CM cells and the greater proportion of flexor inhibition may be the primate's greater capacity to fractionate digital flexion movements. CM cells are particularly active during a precision grip (17), which involves selective flexion of specific fingers.

Mediation of cortical suppression

For reasons discussed previously (7, 9, 10) we concluded that strong postspike facilitation with short latency and sharply defined onset is probably mediated by monosynaptic CM connections. Effects mediated via interneurons would be expected to produce weaker and temporally more dispersed correlations between the cortical cell and motor units, because a disynaptic correlation is the convolution of two monosynaptic correlations (10). It is now clear that postspike suppression of EMG can also be detected by spike-TAs compiled under normal conditions (Figs. 4 and 7) and for CM cells activated by glutamate (9, 15). These observations raise questions concerning the synaptic linkages mediating the postspike effects.

In most cases postspike suppression was weaker than postspike facilitation; more trigger events were usually required to reveal a clear inhibitory effect (Fig. 2). Moreover, the mean onset latencies of suppression were longer than facilitation latencies, for both postspike (9, 15) and poststimulus effects. These results and analysis of alternative explanations (15) suggest that inhibitory interneurons mediate the reciprocal inhibition from cortex. A likely interneuron mediating inhibition is the segmental "Ia-inhibitory interneuron." In the primate, Jankowska et al. (13) demonstrated convergent monosynaptic excitation from Ia-afferents and corticospinal cells on common inhibitory interneurons, identified as Ia-inhibitory interneurons by their suppression via conditioning ventral root volleys. These Ia-inhibitory interneurons generate unitary IPSPs comparable in size (with the motoneuron at rest) to the size of unitary Ia EPSPs (14).

The relative efficacy of direct excitation vs. disynaptic inhibition would depend on the sizes of underlying postsynaptic potentials (11). The relative magnitude of monosynaptic EPSPs and disynaptic IPSPs in spike-TAs from muscle afferents were documented by Watt et al. (24). The mean amplitude of their unitary Ia EPSPs (65.5 μV) was 13 times greater than the amplitudes of their presumed disynaptic IPSPs (4.9 μV). However, under normal behavioral conditions, several factors could enhance the relative effectiveness of disynaptic IPSPs, making them more comparable to effects of monosynaptic EPSPs. The relevant interneurons are likely to be more excitable during reciprocal movements than in the anesthetized preparation. Indeed, the strength of reciprocal Ia inhibition has been shown to increase with voluntary contraction in humans (22). Second, in active motoneurons the effective size of an IPSP increases with depolarization (11, 14); thus an IPSP that is comparable in size to an EPSP when measured at rest may be several times larger near threshold, where it exerts a proportional influence on firing probability. Finally, the net magnitude of disynaptic inhibitory effects would be proportional to the number of inhibitory interneurons, which could be sufficient to balance fewer but stronger direct excitatory linkages. These factors could tend to enhance the relative strength of disynaptic inhibitory correlations.

The present experiments suggest that the intervening inhibitory interneurons may be excited by two types of corticospinal cells: reciprocal CM cells, whose activity simultaneously facilitates their target muscles, and pure inhibitory cells, which had no observed excitatory output. Since the activity of all CM cells increases with active force (6), the reciprocal CM cells may well contribute to the correlated increase in reciprocal Ia inhibition (22).

Cortical clustering of comparable output cells

Evidence presented in the previous paper (7) suggests that cortical cells with a similar distribution of excitatory output effects may be grouped as aggregates or clusters in the cortex. The pattern of poststimulus facilitation elicited from a cortical site matched the profile of postspike facilitation from individual CM cells at that site. Furthermore, neighboring CM cells produced similar patterns of postspike facilitation in agonist wrist muscles. Similar grouping of cells with reciprocal effects on flexors and extensors was suggested

by the observation that the pattern of postspike suppression and facilitation obtained from single CM cells activated by glutamate could also be evoked with greater intensity by S-ICMS at the same site (8). We now report similar evidence for cortical cells that produced pure suppression of muscle activity. Again, the pattern of postspike suppression resembled the pattern of poststimulus suppression evoked by minimal S-ICMS except that the magnitude of poststimulus suppression was greater than that of postspike suppression (Figs. 4 and 6). With increasing stimulus intensity the poststimulus suppression became larger and more widespread (Fig. 7), thus reflecting increases in the underlying postsynaptic potentials (11). The similarity in distribution of suppression suggests that the corticospinal cells activated by S-ICMS targeted similar spinal inhibitory interneurons, or interneurons with similar target motoneurons.

Recordings from neighboring cortical cells confirmed that different cells of a suppression group produce similar patterns of postspike suppression. The three neighboring cells in Figs. 4 and 6 produced postspike suppression of PL and FCR. The interactions between these cells are of interest because they bear on the possibility that these effects may be mediated by synchronized firing of cells. Cross-correlation of the two simultaneously recorded cells did show evidence of a broad correlogram peak about the origin, suggestive of common synaptic input. However, the width of this peak (14 ms) and its magnitude (10% above base line) were incompatible with the hypothesis that the postspike suppression of these cells was mediated entirely by synchronization with another inhibitory cell (such as the neighboring one in Fig. 4). Moreover, this mechanism would involve a trisynaptic linkage, which is highly unlikely to produce clear effects in spike-TAs (10).

Our correlational evidence for clustering of cortical cells with common target cells is consistent with previous observations suggesting functional grouping of cortical output cells (1, 16). A more detailed analysis of the differences between cells within a group and the interaction between groups would further help to elucidate the mechanisms by which motor cortex cells control patterns of muscle activity.

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