Postspike Facilitation of Forelimb Muscle Activity by Primate Corticomotoneuronal Cells

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SUMMARY AND CONCLUSIONS

1. In macaque monkeys making ramp-and-hold wrist movements against elastic loads we recorded activity of task-related motor cortex cells and specific wrist and finger muscles. EMG electrode pairs were implanted in six flexor and six extensor muscles identified by their anatomical location in the forelimb and by characteristic movements evoked by intramuscular stimulation. For precentral cortex cells that discharged during the wrist movements we compiled spike-triggered averages (STAs) of full-wave rectified EMG activity of five to six coactivated muscles.

2. Eighteen percent of the STAs compiled from selected cells showed evidence of postspike facilitation (PSF) of average EMG activity. Such PSF began after the cortical spike (mean onset latency, 6.7 ms), reached a peak (mean peak latency, 10.2 ms), and declined again to prespike base-line levels (mean decay time, 7.0 ms). Seventy-eight percent of the STAs showed no spike-related features, and 4% exhibited complex features.

3. The strength of the PSF was qualitatively rated as strong, moderate, or weak on the basis of clarity relative to base-line fluctuations. When quantified, strong PSF had the largest peak amplitudes relative to mean base-line levels and relative to maximal base-line fluctuations. Strong PSF had slightly shorter onset latency and longer duration than moderate or weak PSF.

4. In some monkeys the cells' projection into the pyramidal tract was tested by the collision technique. Fast pyramidal tract neurons (PTNs) produced mainly PSF with the shortest onset latencies, but also gave rise to PSF with longer latencies; slow PTNs produced PSF with longer latencies.

5. Pairs of spikes with brief interspike intervals were found to be particularly effective in generating PSF. STAs triggered from two action potentials separated by very short interspike intervals showed a net facilitation exceeding the linear sum of the PSF of isolated action potentials.

6. Most cells produced PSF in more than one of the coactivated forelimb muscles. To eliminate any possibility of redundant recording of the same facilitated motor units through different electrodes, EMG activity was cross-correlated and those records with evidence of significant cross talk were excluded from the data base. Of 370 task-related neurons recorded with five to six independent muscles, 27% produced strong or moderate PSF in at least one muscle. Half of these produced clear PSF in more than one muscle. The cell's muscle field, i.e., the set of facilitated muscles, typically comprised a subset of the coactivated synergist muscles. The mean number of facilitated muscles was 2.5 for extensor cells and 2.1 for flexor cells.

7. The excitatory effects on forelimb extensor muscles tended to be stronger and more widespread than on flexor muscles. The proportion of task-related cells showing clear PSF was larger for extensor cells (37%) than flexor cells (22%). Moreover, the ratio of strong to weak PSF was twice as great for extensor cells (1.2) as for flexor cells (0.6). Finger extensor muscles were more strongly facilitated than wrist extensor muscles or flexor muscles.

8. The strength, latency, and time course of most PSF suggest they are mediated by monosynaptic corticomotoneuronal (CM) connections, although a contribution through indirect linkages cannot be excluded. Taking the strong and moderate PSF as evidence of CM connections, the present results indicate that CM cells commonly distribute divergent terminals to motoneurons of more than one muscle. The larger muscle fields of extensor cells may reflect a greater divergence of terminals than flexor cells.

INTRODUCTION

The primate's ability to control and co-ordinate its forelimb muscles depends critically on cells in precentral motor cortex, including some neurons that affect motoneurons directly. Such corticomotoneuronal (CM) cells are uniquely situated to transmit impulses directly from cerebral cortex to motoneurons, and convergent lines of evidence suggest that they are essential for the independent control of distal forelimb muscles (21, 29, 31).

The functional organization of CM connections has been substantially elucidated by electrophysiological experiments in anesthetized primates. Monosynaptic excitatory postsynaptic potentials (EPSPs) may be evoked by cortical stimulation in both hindlimb (2, 14, 26, 33, 34, 39) and forelimb (5, 15, 19, 20, 30) motoneurons, with similar characteristics for lumbar and cervical CM EPSPs (27). Phillips and colleagues (5, 19, 20, 30) showed that in the baboon virtually every motoneuron of distal forelimb muscles receives convergent input from a "colony" of CM cells whose somata may be distributed over several square millimeters of cortex. Systematically mapping the cortical areas from which minimal CM EPSPs could be evoked in single hindlimb motoneurons, Jankowska et al. (14) found these areas to be irregular, sometimes unconnected patches. Such areas often overlapped for motoneurons of different muscles, including antagonists; moreover, different motoneurons of the same pool could receive input from CM cells in different areas. In the anesthetized baboon, motoneurons of distal forelimb muscles exhibited maximal CM EPSPs of 1.5–3 mV,

comparable in size to their maximal Ia EPSPs (5, 19, 30). In hindlimb motoneurons, minimal or unitary CM EPSPs have been found to be about 100 μV or less (2, 14, 33).

While it is thus clear that many CM cells may converge onto single motoneurons, less is known about the possible divergence of single CM cells to different target motoneurons. Since cortical stimulation and lesions both involve many corticofugal cells, they cannot resolve the terminal distribution of individual neurons (13, 31). Antidromic activation of single pyramidal tract neurons (PTNs) from different spinal levels has been used to determine the location of their terminals with increasing degrees of precision (2, 37). In the monkey, Shinoda et al. (37) found that 30% of PTNs could be antidromically activated from both cervical ventral horn and thoracic levels, suggesting that these corticospinal cells may affect diverse groups of segmental cells. Asanuma et al. (2) investigated the areas of "passage" and "termination" of single PTN axons in lumbar motor nuclei and found that 4 of 10 PTNs terminated in more than one motoneuron pool.

Such detailed electroanatomical mapping experiments require anesthetized animals, thus precluding observation of the cells' normal firing patterns. In different experiments, using awake monkeys trained to perform appropriate motor responses, the activity of precentral motor cortex cells has been related to a variety of movement parameters (7, 10, 11, 31). While such studies typically find that the response patterns of some neurons are consistent with particular hypotheses, the functional significance of the recorded activity often remains uncertain because the destination of the cells' output is unknown. For example, in a previous study designed to investigate functional relations between single motor cortex cells and specific forearm muscles, many precentral cells covaried with more than one set of muscles (10); when the monkeys generated bursts of precentral unit activity, they often coactivated several muscles, and when different muscles were activated isometrically or during arm movements, most of the precentral cells fired with several different groups of muscles. Whether such cell activity actually contributed causally to the con-

comitant muscle activity cannot be proved on the basis of their covariation patterns, no matter how strong or consistent. Indeed, some unit-muscle correlations varied drastically under different behavioral conditions, and even the most consistent correlations could be changed by operantly reinforcing their dissociation (10). Since coactivation of a cell and muscle is neither necessary nor sufficient evidence for a causal connection, some independent means of establishing a causal link between cell and muscle activity in behaving animals is desirable.

The technique of spike-triggered averaging (STA) has proved a convenient means of documenting the output effects of single cells on their postsynaptic targets. STAs of motoneuron membrane potentials have revealed the unitary EPSPs evoked by single muscle afferent fibers (22, 23, 38, 40) and motor cortex cells (2). In behaving monkeys the effect of certain precentral cortex cells on the activity of covarying forelimb muscles has also been documented by STAs of rectified EMG activity (3, 8, 9). For some motor cortex cells STAs reveal a transient postspike facilitation (PSF) of average EMG activity of specific covarying muscles. Since the latency and time course of the stronger PSF are consistent with their mediation by monosynaptic connections, we have referred to these neurons as CM cells (4, 8, 9); in the present context we use the term CM cell to designate a motor cortex cell with sufficiently strong correlational linkages to motoneurons to enhance clearly their firing probability. We here provide further evidence concerning the features of such PSF and the extent to which single precentral cells may facilitate different wrist and finger muscles. The accompanying paper (4) documents the firing patterns of such CM cells in relation to their target muscles and to different levels of active force.

METHODS

Activity of single units in precentral cortex of six rhesus macaques was recorded with tungsten microelectrodes. As previously described (8–10), recording mounts allowed exploration of a 20-mm-diameter circle, centered over precentral arm area (4 mm anterior to bregma, 18 mm lateral). During recording, the monkey's head was restrained via flexible nylon rods threaded into cap nuts cemented to the occipital skull. In three monkeys, the projection of the cells' axons into the pyramidal tract could be tested by antidromic responses to stimulation through a bipolar electrode. Antidromic response and latency were usually determined by the collision technique (cf. Fig. 9).

EMG activity of 12 or more specific forelimb muscles was recorded differentially via indwelling pairs of stranded stainless steel wires (AS-632 Bioflex insulated wire, Cooner Sales Co., Chatsworth, CA). In two monkeys the EMG electrodes were implanted surgically and led subcutaneously to a connector plug on the skull. In four monkeys the wires were inserted into each muscle belly transcutaneously with hypodermic needles, and the external wires and terminal connectors were taped to the upper arm. The latter implants could be left in place for several weeks; they were easier to apply and remove and caused less surgical trauma and subsequent infection than the subcutaneous implants. Forearm muscles were identified by their relative anatomic location and the characteristic wrist and finger movements elicited by trains of low-intensity intramuscular stimuli (100–500 μA, 100/s, 100-ms trains). Electromyographic activity of the following muscles was routinely recorded: extensor carpi ulnaris (ECU), extensor digitorum communis (EDC), extensor digitorum two and three (ED2,3), extensor digitorum four and five (ED4,5), extensor carpi radialis longus (ECR-L), extensor carpi radialis brevis (ECR-B), flexor carpi radialis (FCR), flexor digitorum profundus (FDP), flexor carpi ulnaris (FCU), palmaris longus (PL), pronator teres (PT), and flexor digitorum sublimis (FDS). Figure 1 illustrates the relative locations of these muscles in the macaque forearm.

Behavioral training

During recording sessions, monkeys sat in a primate chair inside a sound-attenuating chamber. Both forearms were restrained by formfitting casts and the right hand was placed with fingers extended between padded plates. The plates could rotate about a vertical shaft whose axis coincided with the flexion-extension axis of the wrist. The angular position and torque about the shaft could be monitored as described in the following paper (4). A servo system provided controllable resistance to active movements, usually simulating an elastic load, proportional to wrist displacement from a center position.

The rewarded behavior consisted of alternate flexions and extensions of the wrist into electronically detected hold zones (10–15° in the extension direction and 20–25° in flexion). To
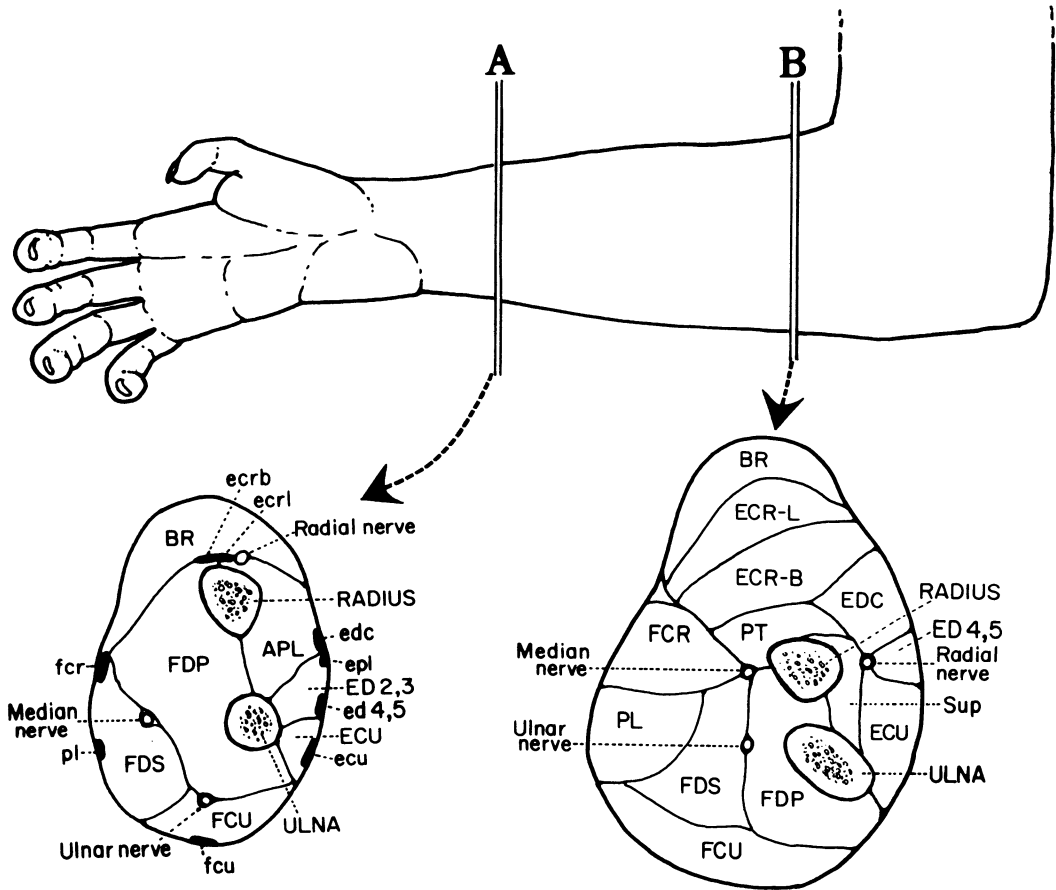
FIG. 1. Relative locations of wrist and finger muscles in right forearm of macaque. Cross-sections were traced from photographs of transverse sections of a frozen forearm. Identification of muscles and tendons in each section was confirmed by the wrist and finger movements produced by pulling muscles and tendons in the thawed intact forearm; the distal insertions of muscles shown in cross-section could also be confirmed by peripheral dissection. In addition to muscles named in the text, diagrams show brachioradialis (BR), abductor pollicis longus (APL), and supinator (Sup). Muscle tendons are shown in black and identified by lowercase labels.

provide periods of tonic coactivation of cells and muscles, the monkey was required to hold the wrist in each zone for 1–2 s. Lights indicated the direction to move and tones were sounded when the wrist was in the appropriate hold zone; a buzzer indicated successful completion of hold, and applesauce was delivered on a fixed ratio (1:1–1:3) schedule.

Averaging procedures

Units were sought during wrist movements against moderate loads. For task-related cells on-line STAs of full-wave rectified EMG activity were compiled simultaneously for the set of covarying muscles. If the STA of any muscle revealed signs of PSF in averages of 2,000 events, we recorded the activity of that unit, the EMG

of the six covarying muscles, and wrist position and torque. A Honeywell 7600 tape recorder stored unit activity at 5-kHz bandwidth and EMG at 3-kHz bandwidth. Averages compiled off-line usually confirmed those compiled on-line with regard to the muscles exhibiting PSF. The EMG activity was full-wave rectified (but unfiltered) in order to minimize cancellation of positive and negative components of motor-unit action potentials that might appear at variable latencies. Figure 2 illustrates the STA technique. Comparing STAs of rectified and unrectified EMG of the same facilitated muscles, we often found clearer postspike effects averaging rectified EMG, presumably because the variance in latency of the facilitated motor-unit potentials exceeded their width, resulting in
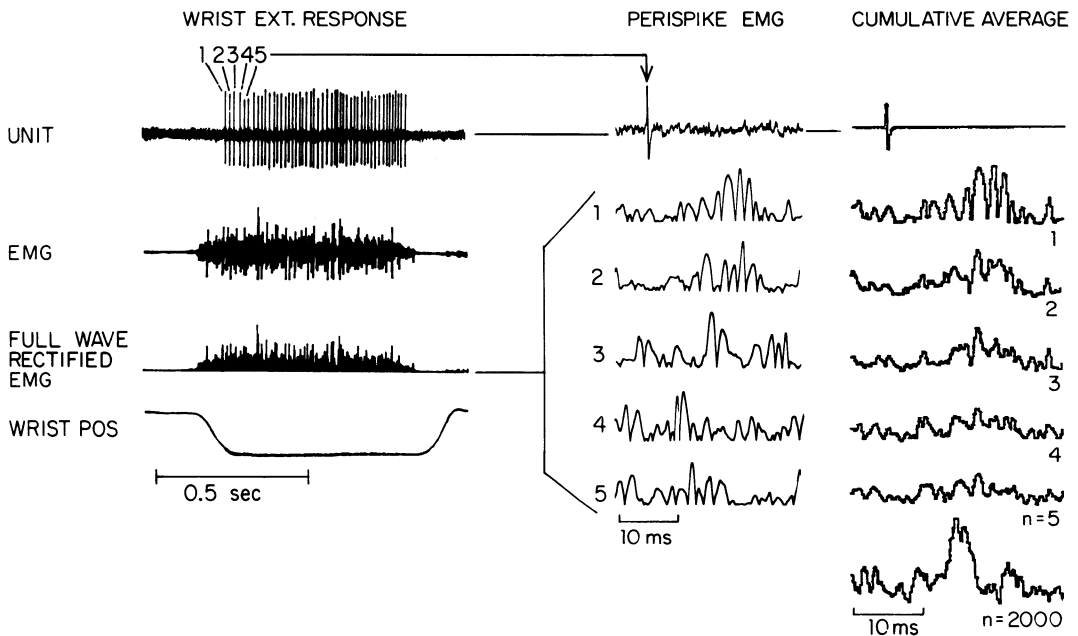
FIG. 2. Spike-triggered averaging technique used to detect postspike effects. The single response at left illustrates normal and rectified EMG of one agonist muscle. The middle column illustrates the perispike-rectified EMG for the first five action potentials, and the column at right shows cumulative STAs for the first n spikes, where $n = 1, 2 \ldots 5$, and 2,000.

some cancellation. However, in certain cases the STAs of unrectified EMG showed larger postspike fluctuations than STAs of rectified EMG; this can occur if the amplitudes of uncorrelated units appreciably exceed the amplitude of the facilitated unit. We also found that STAs of rectified EMG were more sensitive in detecting effects than postspike time histograms of pulses triggered from the EMG.

In initial experiments, STAs were compiled with a LAB 8/E advanced averager; later we used a more efficient program, written by D. Kalk, which compiled events for every spike, including those falling within the analysis interval of preceding spikes. In order to provide a prespike baseline, the analysis interval of the STAs typically included 5 ms before to 25 ms after the spike; bin width was 250 μs. We took particular care to insure that only one and the same cortical unit was used to provide triggers by monitoring its action potentials on an expanded sweep of an oscilloscope; the sweep was initiated on the rising edge of the action potential and the beam was brightened by the triggering pulses. The desirability of long-term recording from single units biased our sample substantially toward neurons with large, stable action potentials.

To test the possibility of cross talk in EMG recordings, we also compiled similar averages

of rectified EMG activity, triggered from the motor units of each individual muscle. The trigger threshold was set sufficiently low to trigger the averager from all of the recorded motor units of one muscle, and the full-wave rectified EMG of every coactivated muscle was averaged.

To better define the time course of the wrist movements, we also compiled response averages of unit and muscle activity, position, and torque. These are aligned at onset of movement and typically included 500 ms before to 1,500 ms after movement onset. Bin width of the response averages was 10 or 20 ms.

RESULTS

Postspike facilitation revealed by spike-triggered averages

STAs of rectified EMG activity of co-activated forelimb muscles were compiled for 370 precentral cortex cells whose activity covaried clearly with wrist flexion or extension. For each cell the activity of five or six different synergistic muscles was recorded and averaged, yielding a total of 2,083 STAs (each comprising at least 2,000 events).
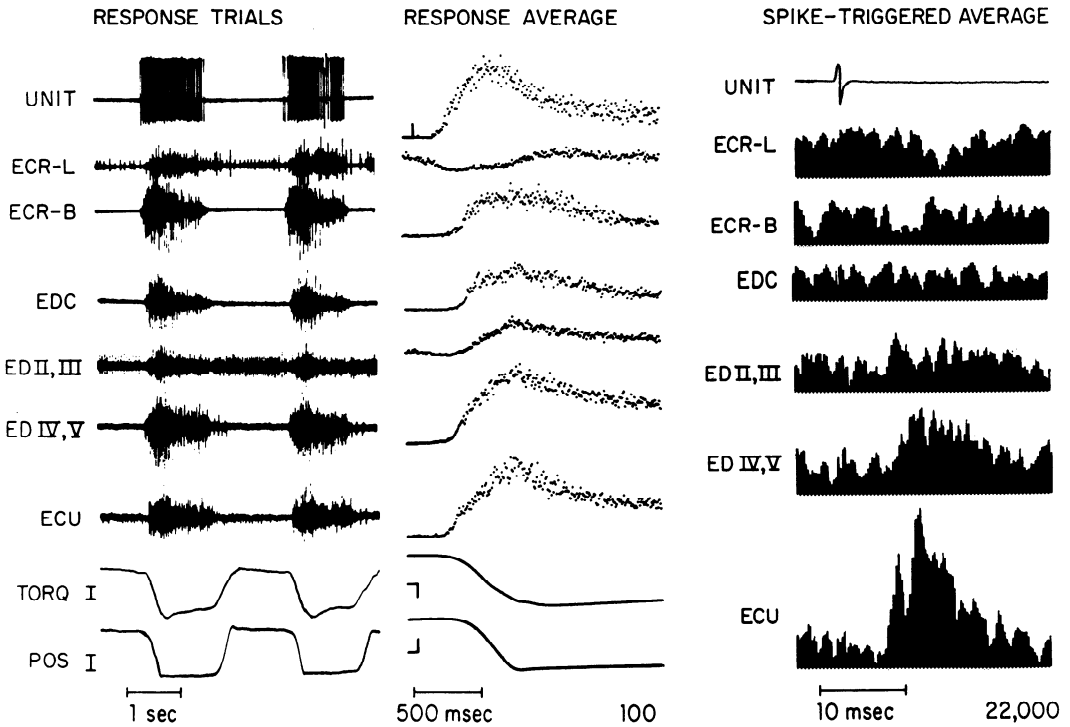
FIG. 3. Responses of extension-related cell showing strong PSF in ECU muscle. Examples of original recording at left illustrate activity of unit and six forearm extensor muscles, wrist torque (T), and position (P) (extension down). Response average in center was compiled for 100 successive extension movements and was triggered from onset of extension. This cell exhibited a phasic burst during movement onset in addition to its tonic discharge during the static hold. STAs at right show action potential of unit at top and averages of full-wave rectified EMG activity of each muscle. The STAs were shaded for clarity; the base line was stippled to indicate that it does not represent the zero level of muscle activity. In this and subsequent figures, number of events averaged is shown in lower right (unit *SI 86-4*).

Of these, 383 (18%) showed evidence of a transient PSF of averaged EMG activity. Such PSFs were defined as an increase in averaged EMG activity above base-line fluctuations beginning after the cortical spike; after reaching a peak, they declined again to prespike levels. Excluded by this definition were infrequent instances in which the average EMG level increased or decreased steadily throughout the analysis interval; such sloping base lines were probably due to preferential sampling during changing levels of EMG activity. Also excluded were rare STAs (4%) that showed clear but complex features involving distinct fluctuations in average EMG beginning before or within 3 ms of the cortical spike. Eleven STAs exhibited postspike reduction of average EMG comparable in magnitude to PSF. The vast majority (78%) of STAs

showed no evidence of any consistent spike-related fluctuations in average EMG.

Figure 3 illustrates responses of a cell related to wrist extension, recorded with six coactivated extensor muscles of wrist and fingers. The STAs reveal an increase in the average level of ECU activity (lower right). This PSF began abruptly 6.0 ms after the cortical spike, rose to a peak in 3.5 ms, and returned to baseline thereafter. A smaller but clear PSF is also evident in ED4,5, with a slightly longer onset latency (7.3 ms). The STAs of the other muscles showed no features interpreted as PSF.

For this cell the effects revealed by averaging an increasing number of events are illustrated in Fig. 4. The facilitation of ECU was already evident in the STA of 1,000 events and became increasingly clear as more events were averaged. The PSF
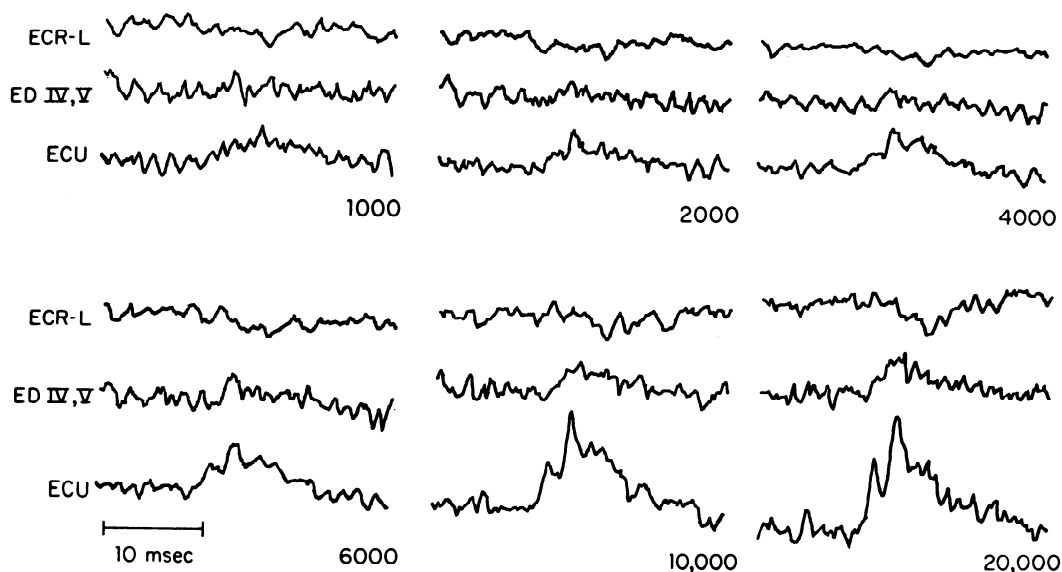
FIG. 4. Appearance of PSF in STAs of different numbers of events for the unit illustrated in Fig. 3. ECU and ED4,5 muscles showed PSF in STAs of 1,000 and 6,000 events, respectively. In contrast, the possible postspike suppression in the ECR-L record appeared in 20,000 events. (As indicated in Fig. 3, the ECR-L electrodes recorded some motor units active during flexion—probably in brachioradialis.) Triggering action potential occurred 5 ms after beginning of sweeps. The double peak that is evident in the larger ECU averages appeared in STAs of unrectified EMG as a biphasic waveform, suggesting that these peaks may represent components of the same motor unit (*SI 86-4*).

in ED4,5 began to appear in 6,000 sweeps and became clear by 10,000. By comparison, the ECR-L record shows a possible postspike suppression, which became evident only in averages of 20,000 events. Most of the cells that exhibited PSF did so in averages of 2,000–4,000 events; larger numbers of events were often averaged to define the PSF time course more clearly. In certain cases a postspike fluctuation appeared in STAs of less than 1,000 events, but then diminished or disappeared as more events were included; such cases were not counted as PSF, which by definition required a distinct peak in STAs of at least 2,000 events. For many cells, several consecutive STAs were compiled to confirm the reproducibility of PSF.

The cell illustrated in Fig. 5 was recorded in another monkey. This unit also covaried with extension but, in contrast to the previous cell, fired tonically during the hold period and exhibited no phasic response at movement onset. STAs of 4,000 events revealed a clear PSF in three extensor muscles, ED4,5, EDC, and ECR-L, with onset

latencies of 5.8, 5.8, and 6.5 ms, respectively; averaging more events confirmed the existence of additional weaker PSF in ED2,3 and ECR-B.

Although STAs were routinely compiled for an analysis interval of 30 ms, we often averaged over longer intervals to check for other spike-related fluctuations at earlier and later times. Figure 6 illustrates the typical finding: the clearest spike-correlated event was a transient augmentation occurring in the 20-ms interval following the action potential. The smaller fluctuations in base line before and after the spike varied randomly with independent samples and did not increase systematically with the number of events averaged. Since STAs with longer analysis periods required considerably more time to compile and since they resolved the temporal features of the PSF less clearly, we chose the 30-ms epoch for routine analysis.

Properties of PSF

The clarity of individual PSFs varied over a considerable range, from those with pronounced peaks to those representing a

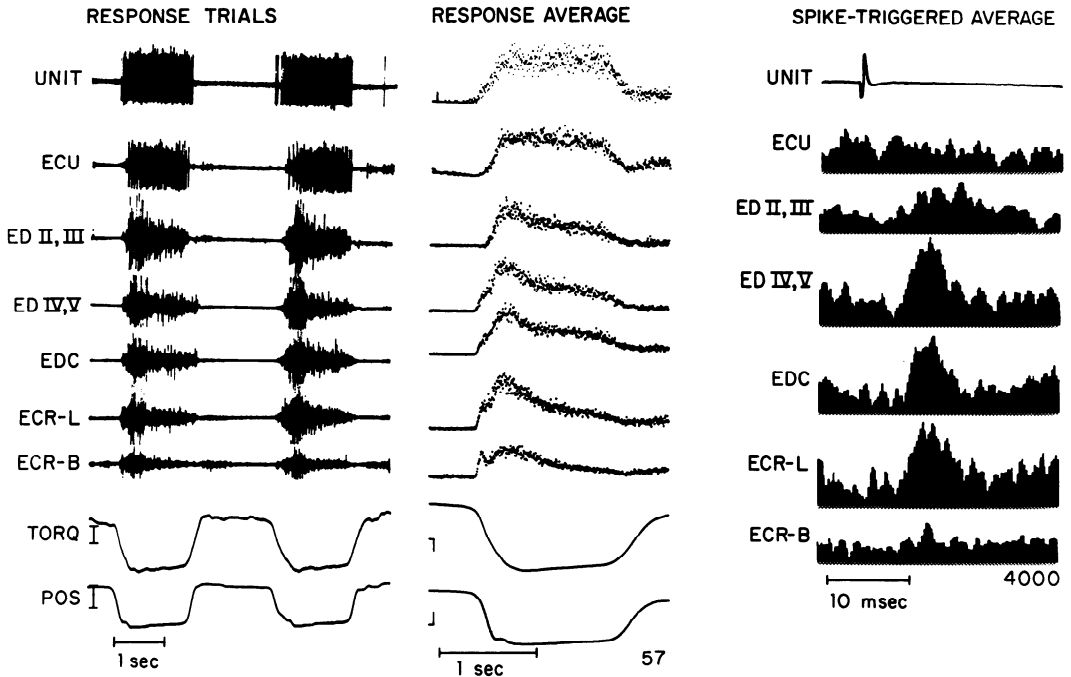RESPONSE TRIALS RESPONSE AVERAGE SPIKE-TRIGGERED AVERAGE

FIG. 5. Responses of extension-related CM cell (*SW 53-3*) with strong PSF in three muscles. This unit fired tonically throughout the hold period, without any additional phasic response at movement onset. STAs (right) show clear PSF in ED4,5, EDC, and ECR-L in averages of 4,000 events.

slight but significant augmentation. To check for systematic differences between these extremes, we qualitatively categorized each PSF as strong, moderate, or weak. Strong PSFs rose sharply from base line and were usually clearly defined in STAs of several thousand events (e.g., EDC, Fig. 5); weak PSFs had smaller amplitudes relative to

TABLE 1. *Characteristics of postspike facilitation*

	Strong (53)	Moderate (53)	Weak (58)	O^+ (55)
Peak/noise ratio	4.3 ± 1.5	2.8 ± 0.7	1.8 ± 0.5	1.2 ± 0.3
Percent peak facilitation	12.4 ± 8.3	9.2 ± 5.1	5.7 ± 3.3	4.2 ± 1.9

	Strong	Moderate	Weak	Overall Mean
Onset latency	6.1 ± 1.6 (106)	7.2 ± 2.6 (109)	7.8 ± 3.4 (131)	6.7 ± 2.9 (346)
Rise time	3.7 ± 1.4 (106)	3.1 ± 1.8 (109)	2.9 ± 0.9 (131)	3.2 ± 1.8 (346)
Peak latency	9.4 ± 1.9 (106)	10.3 ± 2.9 (109)	10.8 ± 3.6 (131)	10.2 ± 3.0 (346)
Decay time	7.7 ± 3.0 (106)	7.3 ± 2.9 (108)	6.2 ± 2.8 (129)	7.0 ± 3.0 (343)

Values are means ± SD for the number of PSFs given in parentheses. Representative samples of weak, moderate, and strong PSFs were separately analyzed. Percent peak facilitation and peak-to-noise ratio are defined in text; the O^+ category represents augmentation below criterion for PSF. Onset latency, rise time, peak latency, and decay time, as defined in text, are given in milliseconds.

base-line fluctuations, and their confirmation often required averaging larger numbers of events (e.g., ECR-B, Fig. 5); moderate PSFs lay between (e.g., ED2,3, Fig. 5).

While the relative "strength" of each PSF was qualitatively estimated, a more quantitative measure was obtained for over 50 representative samples of each. To quantify the magnitude of the PSF peak relative to base-line fluctuations, the height of the PSF peak above the mean base-line level was divided by the peak-to-peak base-line noise (defined as the mean of the three largest peak-to-peak fluctuations in prespike base line). As shown in Table 1, this measure of "peak-to-noise ratio" averaged 4.3 for strong PSF, 2.8 for moderate, and 1.8 for weak. Such a peak-to-noise ratio was also computed for a fourth category of postspike increases that were too weak to be confidently identified as PSF, but that nevertheless suggested a possible augmentation following the spike; these submarginal "facilitations" had an average peak-to-noise ratio of 1.2.

Another measure of the strength of PSF is the height of the PSF peak relative to the mean base-line level on which it appeared; such a "percent peak facilitation" was calculated for some representative STAs. Since any number of uncorrelated motor units could contribute to the average base line level and since a given motor unit contributes to the STA in proportion to its motor-unit potential, this measure remains somewhat arbitrary. In any case, the mean percent peak facilitation was 12.4% for strong PSF, 9.2% for moderate, 5.7% for weak (and 4.2% for submarginal augmentation). Since the PSF peak occurs at one particular time after the spike, the overall average facilitation is perhaps better represented by the mean height of the entire PSF relative to the base-line level. The mean height of the PSF could either be computed from its integral or estimated from the peak, knowing the PSF shape. If the PSF is assumed to rise and fall linearly, its mean height would be about 29% of the peak height; thus, the average facilitation would be estimated to be about 3.6% for strong PSFs.

To quantify the time course of each PSF, we measured its onset latency after the cortical spike, its rise time to peak, and decay time back to base line. The PSF onset
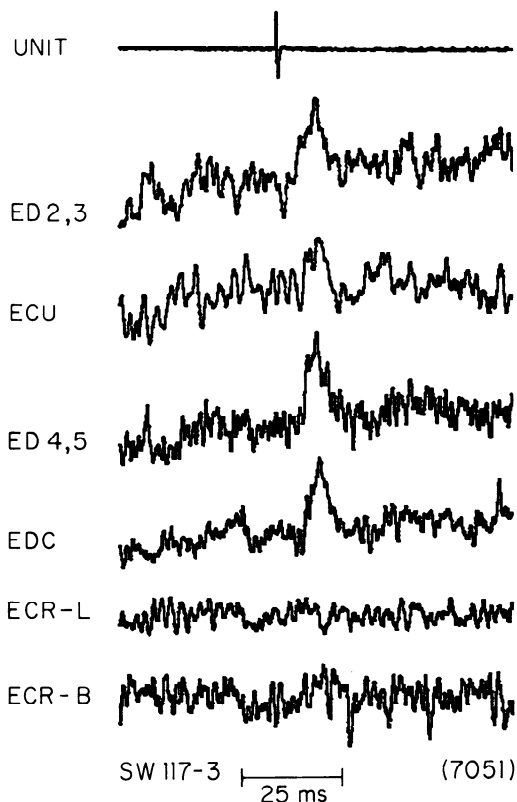

FIG. 6. STA with a 100-ms analysis inverval, including 40 ms preceding and 60 ms following the cell's action potential. Four of the six muscles exhibited PSF in the first 25 ms following the spike; no other spike-related fluctuations were evident. This unit (*SW 117-3*) was confirmed to be a PTN, with an antidromic response latency of 0.9 ms.

latency was defined as the time from the start of the cortical spike to the first sustained increase of average EMG above the largest base-line fluctuations. The histogram in Fig. 7 plots the onset latencies of strong, moderate, and weak PSF: the great majority began between 3.5 and 10 ms after the cortical spike, with an overall mean of 6.7 ms. Most of the PSFs with latencies greater than 9 ms were moderate or weak; the average onset time for the strong PSF (6.1 ± 1.6 ms) was slightly shorter than the mean onset latency of moderate (7.2 ± 2.6 ms) or weak (7.8 ± 3.4 ms) PSF. When a single cell was associated with PSF in several muscles, their onset times tended to be closer together than would be expected on a purely random basis. Figure 8 illustrates the PSF onset times for representative CM
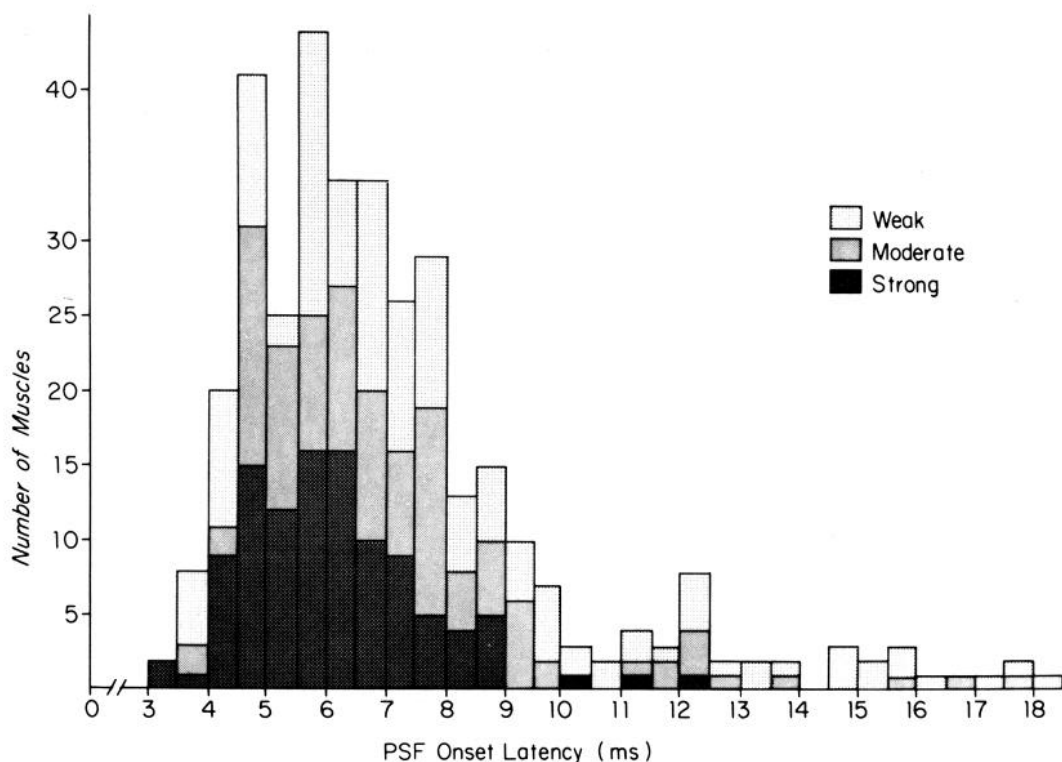
FIG. 7.   Onset latencies of PSF relative to action potential of cortical neurons. Strong, moderate, and weak facilitations showed similar distribution of latencies, except that strong facilitation appeared less frequently above 9 ms. Excluded from the histogram were cells associated with complex features, including three with PSF latencies below 3 ms.
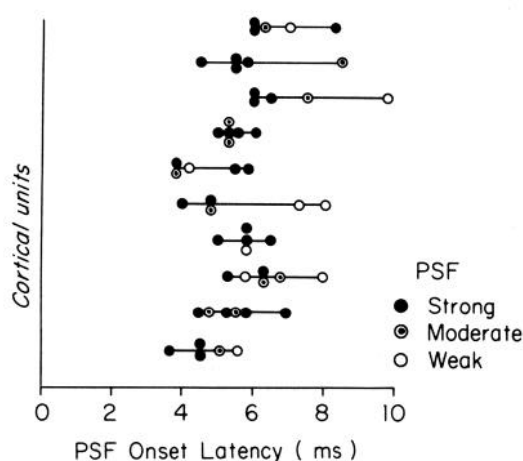

FIG. 8.   Relative onset latencies of PSF in different muscles facilitated by single CM cells. Each connected set of dots indicates the onset times and strength of PSF associated with one cell.

cells that produced PSF in five or six muscles; for individual cells these latencies varied less than randomly selected values, but their scatter does reflect substantially different conduction times to each muscle.

To quantify the PSF waveforms further we also measured their rise times (the time between onset and peak) and their decay times (the time between peak and return to base-line levels). Rise times were similar for strong, moderate, and weak PSFs, with a slight tendency for stronger PSFs to have longer rise times (Table 1). However, the rise times of all types of PSF were within a standard deviation of each other and of the overall average rise time of 3.2 ± 1.8 ms. Similarly, the average decay time was slightly longer for strong PSF than for weak, with the overall mean decay being 7.0 ± 3.0 ms. A useful measure of
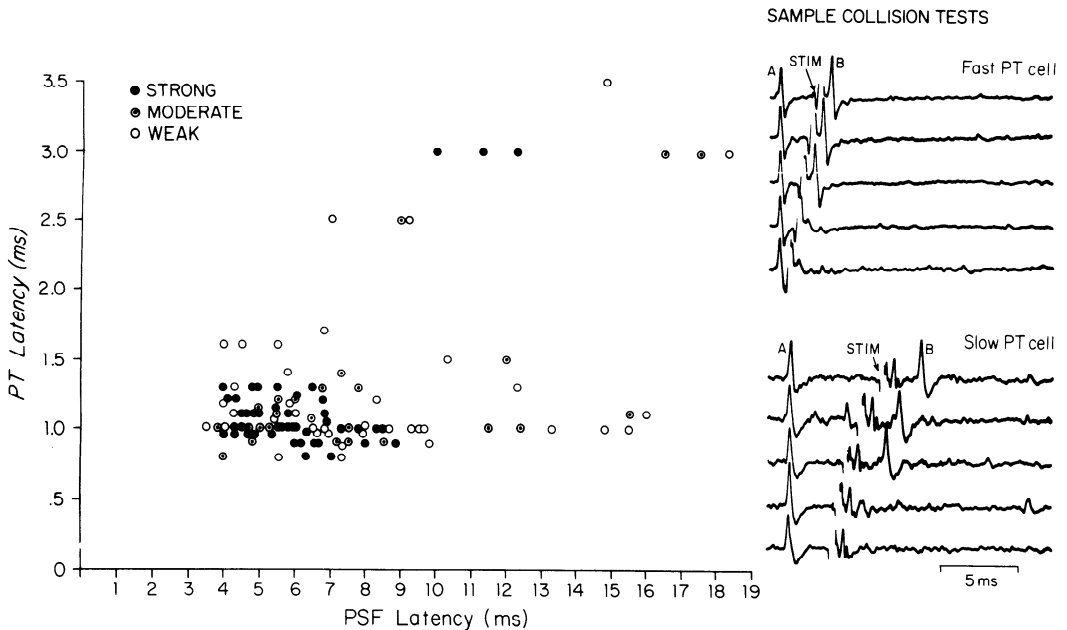
FIG. 9. Relation between PSF latency and antidromic PT latency. Collision tests used to identify PT projection are illustrated at right for a fast and slow PTN. PT stimulus was triggered at decreasing intervals following a spontaneous action potential. PT latency was measured from onset of stimulus to onset of antidromic action potential. Plot of PT latency versus PSF latency is shown for strong, moderate, and weak PSF.

the time of greatest EMG facilitation is the latency of the PSF peak after the cortical spike. On the average, the PSF peaks occurred 10.2 ± 3.0 ms after the cortical spikes.

Relation between PSF latency and pyramidal tract latency

In some monkeys, stimulating electrodes were implanted in the medullary pyramidal tract (PT) to test the cells' axonal projections through the pyramids. Responses were confirmed to be antidromic by the collision technique, as illustrated in Fig. 9 for a fast and a slow PTN that exhibited PSF. When tested, the great majority of cells exhibiting PSF responded antidromically to PT stimulation. Most of the confirmed PTNs were fast PTNs, probably due to preferential sampling of cells with stable action potentials. A few PSF cells failed to respond antidromically at the stimulus intensities employed (up to 10 times threshold for the A-wave). However, this does not prove that

they were not PTNs; in one monkey relatively few precentral cells responded to PT stimulation, probably due to a misplacement or malfunction of the PT electrode. Thus, failure to evoke antidromic responses cannot prove the absence of a descending projection; on the other hand, the occurrence of an antidromic response does confirm a descending projection. Of 82 identified PTNs whose activity covaried strongly with wrist movements and that were analyzed with five or six covarying muscles, 45 (55%) exhibited PSF in at least one muscle.

For the PTNs that exhibited PSF, Fig. 9 shows the relation between their antidromic PT latency and the onset of the associated PSF. In general, the fast PTNs, with antidromic latencies below 2 ms, produced primarily short-latency PSF, while the slow PTNs produced PSF with longer latency. Conversely, the short PSF latencies were all associated with fast PTNs, while the longer PSF latencies could occur with both slow and fast PTNs.

Enhanced effectiveness of brief interspike intervals

Intracellular recording in motoneurons has revealed that a pair of CM EPSPs evoked by cortical stimuli separated by brief intervals may not sum linearly; the size of the second CM EPSP may be considerably enhanced compared with that of the first (19, 26, 27, 30, 32, 39). We looked for comparable evidence of nonlinear summation of the PSF produced by pairs of action potentials of single cortical cells. Normally, the briefest interspike intervals tended to occur during the phasic peaks of unit activity at movement onset; since motoneurons would also be subject to greater excitation at that time, any observed increase in the size of the PSF at movement onset could not be attributed unequivocally to the brief intervals between spikes of a recorded cell. On the other hand, the tonic discharge during the static hold phase normally included relatively few interspike intervals below

10 ms. However, in one instance, a CM cell exhibited unusually brief intervals between spikes, apparently due to injury by the microelectrode. This fortuitous occurrence provided evidence that high-frequency discharge may be particularly effective in producing PSF. Figure 10 illustrates the STAs compiled separately for action potentials preceded by longer and shorter interspike intervals. Averages triggered only from spikes preceded by intervals greater than 20 ms revealed a shallow PSF in three extensor muscles (Fig. 10, left). A second set of averages, triggered from spikes that had been preceded by another within 6-8 ms, revealed a greater PSF; this increased amplitude is largely attributable to algebraic summation of the individual PSF. However, averages selectively triggered from those spikes preceded by very brief interspike intervals of less than 3 ms showed pronounced PSF whose amplitude was greater than the algebraic sum. These sets of STAs were compiled off-line
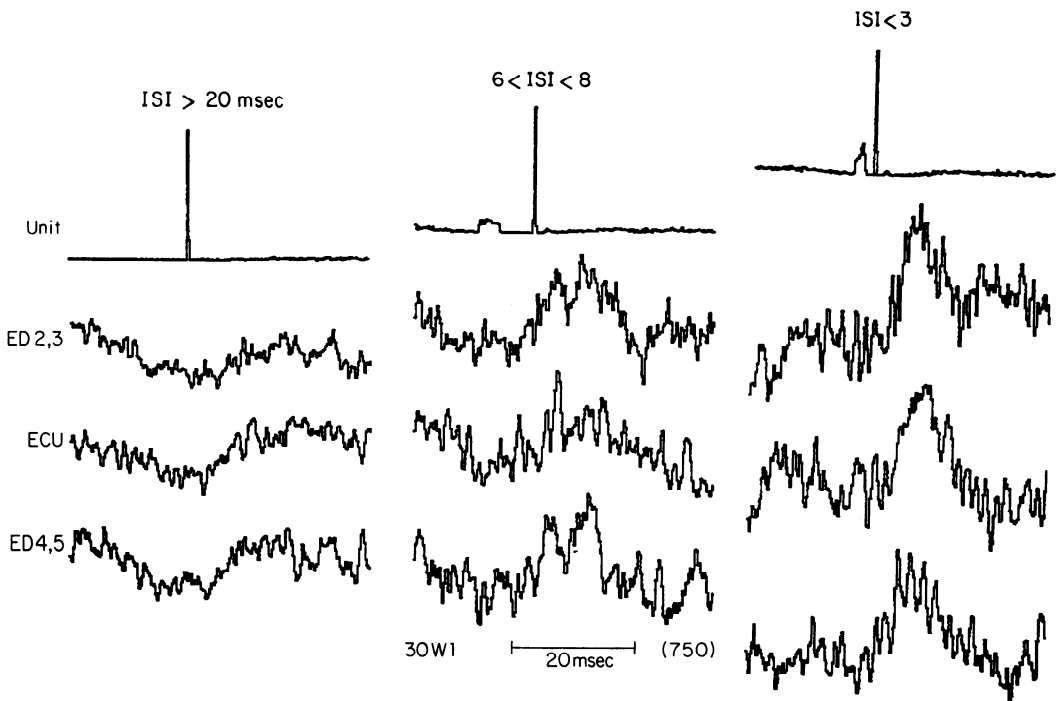

FIG. 10. PSF produced by pairs of action potentials separated by different intervals. STAs were selectively triggered from action potentials preceded by interspike intervals greater than 20 ms (left), between 6 and 8 ms (center), and less than 3 ms (right). In this case the analysis interval was 50 ms (−20 to +30 ms), and the number of events averaged for each was 750.

for equal numbers of events from the same section of tape-recorded activity. Thus, the differences in size of the PSF do not seem to be related simply to different levels of average EMG activity. This nonlinear summation of facilitation suggests that brief intervals may be particularly effective in contributing to PSF.

Distribution of PSF in different muscles

Most of the precentral cells that showed PSF were associated with facilitation of more than one muscle. Such multiple PSFs usually had different onset latencies (Fig. 8) and waveforms, suggesting that they were produced by different motor units. Nevertheless, it was important to determine in each case whether the appearance of PSF in multiple muscles could have been due to redundant recording of the same facilitated motor units with different electrode pairs. We therefore cross-correlated EMG activity by compiling EMG-triggered averages, using all the recorded motor units of a given muscle as triggers and averaging the rectified

EMG activity recorded by other leads. Figure 11 illustrates such EMG-triggered averages for the muscles facilitated by the cell in Fig. 5. In each set the muscle used to trigger the averager can be identified by a prominent peak, produced by summation of the triggering motor units. If other electrodes had recorded any of these same motor units at a distance, similar peaks would appear in their averaged records. This was observed infrequently; usually, leads in adjacent muscles showed negligible signs of cross talk. At very high gains the EMG-triggered averages of synergist muscles commonly showed evidence of motor-unit synchronization, as would be expected from shared synaptic input (16, 24, 28); such synchronization peaks were considerably broader than the motor-unit potential and could, therefore, be readily distinguished from the sharper peaks due to redundant recording of the same motor units. In several cases, adjacent muscles that had yielded similar PSF in STAs did show sufficient evidence of cross talk in the EMG-
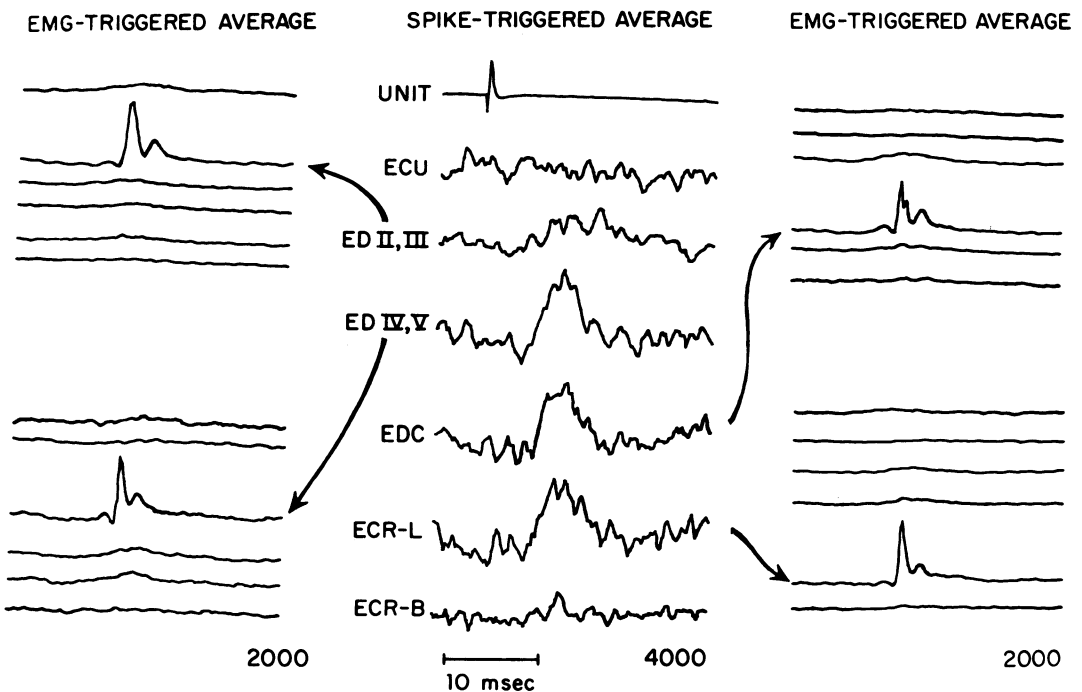

FIG. 11. EMG-triggered averages for muscles facilitated in common by the same cell (cf. Fig. 5). EMG-triggered averages (left and right columns) show muscles in the same sequence as the STA (center). For each set, the muscle providing triggers is indicated by arrows.
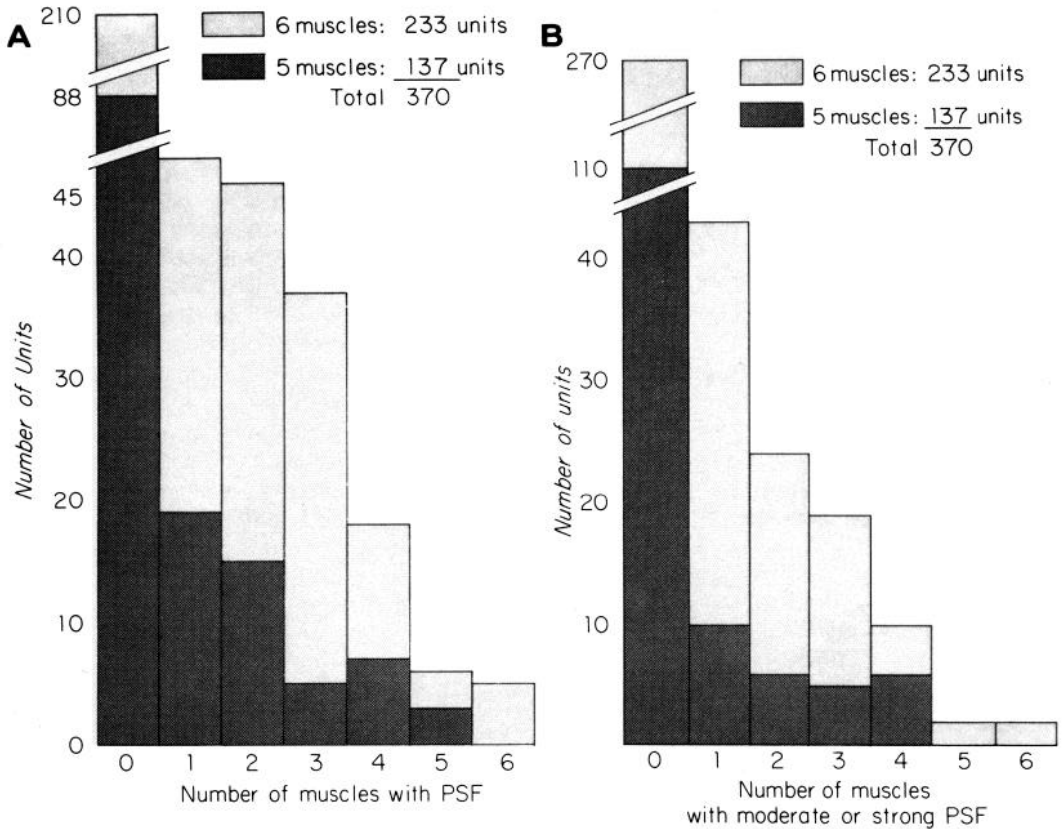
FIG. 12. Number of facilitated muscles when STAs of five or six different muscles were simultaneously compiled. Only nonredundant muscle recordings were included. *A*: histogram for all PSF; *B*: histogram for only strong and moderate PSF, counting weak PSF as no effect.

triggered averages to raise questions of mediation by the same motor units. In those cases, all but one of the potentially redundant EMG records were excluded from the data base.

The number of independent muscles that exhibited PSF was determined for 370 task-related precentral neurons, each recorded and averaged with five or six covarying wrist and finger muscles. These cells represent a selected subset of all observed precentral neurons–namely, those that covaried strongly with wrist flexion or extension; most were active during the static hold period. Other neurons, which were weakly or variably related to the wrist movements or which fired only phasically at movement onset, tended not to exhibit PSF. Figure 12*A* plots the number of nonredundant muscles

exhibiting any PSF, whether strong, moderate, or weak. Over half of the selected precentral cells that fired during wrist extension or flexion showed no PSF in any of the covarying agonist muscles in STAs of at least 2,000 events. Of the cortical cells that did produce some PSF, over two-thirds were associated with facilitation of two or more muscles. The mean number of facilitated muscles per cell was 2.4.

Since the weak PSF may have questionable significance, a separate count of the number of muscles clearly facilitated was obtained by considering all weak PSFs to represent a negligible effect. The results, plotted in Fig. 12*B*, show that 27% of the task-related cells were associated with moderate or strong PSF in at least one muscle. Of these, over half produced clear
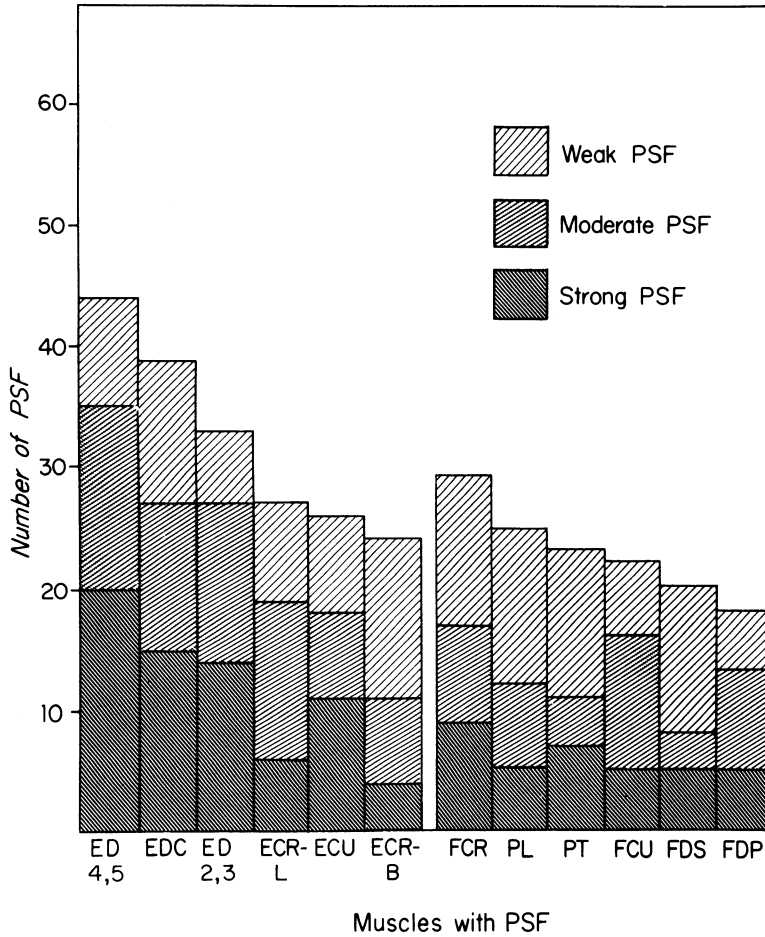
FIG. 13. Number of strong, moderate, and weak PSF observed in different forelimb muscles. Data for 78 extension cells and 66 flexion cells.

PSF in two or more muscles; the mean number of clearly facilitated muscles per cell was 2.1.

As a group, extensor muscles tended to be more strongly and more frequently facilitated than flexor muscles. The proportion of STAs showing PSF was slightly greater for extensors (223/951 = 23%) than for flexors (166/1066 = 16%). Correspondingly, a larger proportion of the task-related extensor cells was associated with clear PSF (37%) than of flexor cells (22%). The percentages of strong, moderate, and weak PSF were 36, 35, and 29%, respectively, for extensor muscles, compared with 26, 30, and 44% for flexor muscles. Thus, the ratio of strong to

weak PSF was twice as great for extensor muscles (1.2) as for flexor muscles (0.6). Figure 13 plots the number of strong, moderate, and weak PSF observed in each forelimb muscle. PSF appeared more often in the extensors of the fingers (ED4,5, EDC, and ED2,3) than in extensors of the wrist (ECU, ECR-L, and ECR-B). No significant difference was observed between the amount of facilitation of flexors of the fingers (FDP and FDS) and wrist (FCU, PL, and FCR). For this sample the mean number of facilitated muscles per cell was 2.5 for extensor cells ($n = 78$) and 2.1 for flexor cells ($n = 66$). Thus, the excitatory effects of precentral cells on forelimb extensor

muscles tended to be more potent and more widespread than on flexor muscles, a difference observed in all monkeys.

DISCUSSION

Mediation of PSF

Using action potentials of single motor cortex cells to compile STAs of rectified forelimb muscle activity, we found that the most common spike-related effect was a postspike facilitation of average EMG activity. Unlike random fluctuations, the PSF could be replicated in successive STAs and become clearer with increasing numbers of events averaged. Such PSF had a mean onset latency of 6.7 ms after the cortical spike, reached a peak at about 10 ms, and declined again thereafter, suggesting that they represent output effects of the recorded cell. The fact that microstimuli applied near these cells evoked a similar pattern of poststimulus facilitation (3) confirms the existence of output connections from these sites. The extent to which these PSFs are mediated by direct monosynaptic connections or by indirect polysynaptic pathways cannot be conclusively resolved by cross-correlation alone. It seems reasonable to assume that the strongest PSFs probably represent the effects of CM cells, but possible contribution of indirect connections to the PSF must also be considered (40). Definitive confirmation of monosynaptic connections between the recorded cells and motoneurons of facilitated muscles would require demonstration that these cells produced CM EPSPs in the relevant motoneurons. Short of such final proof, the present evidence can nevertheless be evaluated in terms of various possible mediating pathways. Figure 14 illustrates the three circuits that would be expected to make the most significant contributions to a correlation between action potentials of a recorded cortical cell (C) and motoneuron (M), namely, a direct corticomotoneuronal connection, and two disynaptic circuits involving a third neuron (A), which contacts M. Cell A could either be serially interposed between C and M, or send a collateral to C as well as to M. The spike-correlated effects produced by each configuration would have certain distinguishing characteristics with

regard to latency, shape, and relative amplitude.

The onset latencies of the PSF produced by monosynaptic connection would be the sum of conduction times in the axons of the PTN and motoneuron plus two synaptic delays. Onset latencies of PSF produced by indirect circuits would largely overlap these, but could be longer (serial circuit) or shorter (collateral circuit). Since the motoneuron conduction time introduces a significant source of variance to the latency of peripherally measured effects, only latencies shorter than minimal conduction times can be interpreted as evidence of indirect mediation via collateral circuits. The latencies of most PSFs were consistent with known conduction times in PTNs and forelimb motoneurons. In macaques, stimulating the PT at a point halfway between cortex and cervical cord evoked antidromic responses with latencies as brief as 0.7 ms (6, 12), and even 0.6 ms (6). Assuming a utilization time of 0.2 ms, the total conduction time of the fastest PTNs from cortex to cervical levels would be 1.0 ms. With a synaptic delay of 0.3 ms, the fastest CM cells in the macaque could evoke unitary EPSPs in cervical motoneurons beginning 1.3 ms after the cortical action potentials. Conduction over the remaining pathway from motoneurons to muscles could take as little as 2.5 ms. Thus, we estimate that the fastest monosynaptic pathways would yield a muscle response 3.8 ms after the cortical spike. The great majority of PSF latencies were longer (Fig. 7). A few examples of spike-correlated facilitation beginning at shorter latencies were also observed. The "complex" features in some STAs involved broad peaks in several muscles at the time of the cortical spike, beginning before the spike, as if the recorded cell received strong input from many CM cells. With these relatively rare exceptions, all of the observed PSF latencies are consistent with the known conduction times of PTNs and forelimb motoneurons.

When tested for PT projection, the majority of cells producing PSF were PTNs. Moreover, their antidromic latencies were significantly related to the onset latency of PSF (Fig. 9). Slow PTNs generated PSF with longer latencies, while fast PTNs
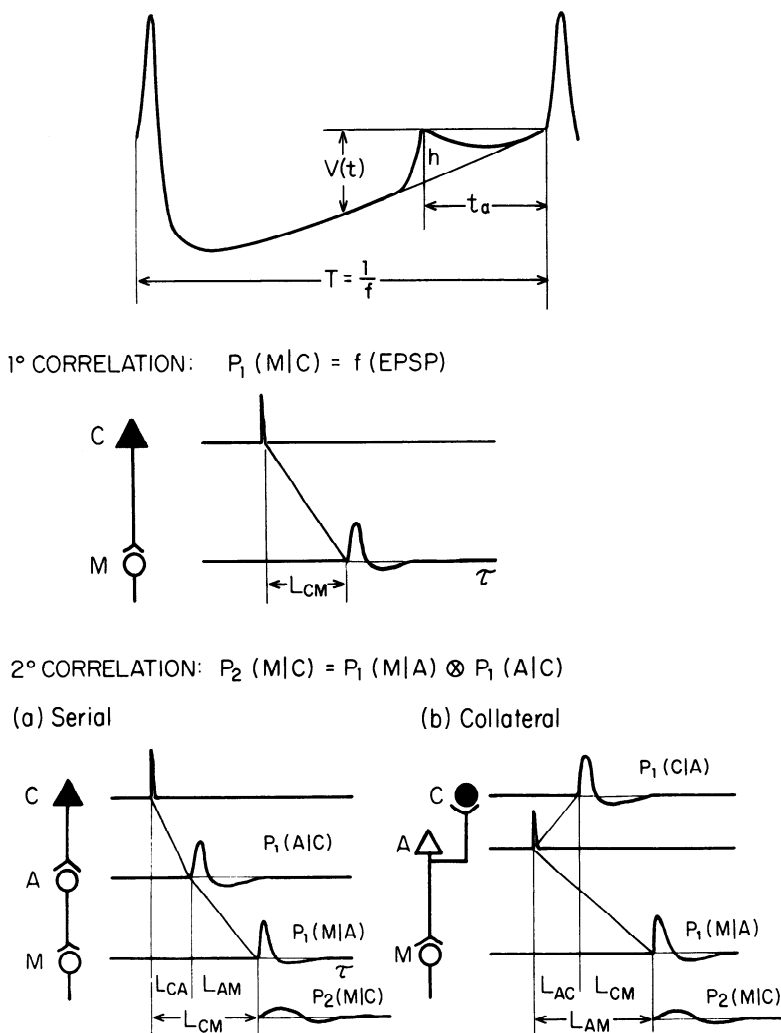
$V(t)$

h

t_a

$T = \frac{1}{f}$

1° CORRELATION: $P_1 (M|C) = f (EPSP)$

C

M

L_{CM}

τ

2° CORRELATION: $P_2 (M|C) = P_1 (M|A) \otimes P_1 (A|C)$

(a) Serial

(b) Collateral

C

A

M

$P_1 (A|C)$

$P_1 (M|A)$

τ

L_{CA} L_{AM}

L_{CM}

$P_2 (M|C)$

C

A

M

$P_1 (C|A)$

$P_1 (M|A)$

L_{AC} L_{CM}

L_{AM}

$P_2 (M|C)$

FIG. 14. *Top*: schematic representation of EPSP superimposed on membrane potential of active motoneuron. T, interval between motoneuron action potentials; $V(t)$, difference between membrane potential and threshold. h, height of EPSP peak; t_a = time during which EPSP may trigger motoneuron action potential. *Bottom*: connections between cells which could potentially contribute to correlations between recorded cortical cell C, and motoneuron, M. The first-order correlation, produced by a direct CM connection, is indicated as a peak occurring at latency L_{CM} after the cortical spike. Second-order correlations are mediated by a third neuron, A, which contacts the motoneuron and receives input from C (serial circuit) or sends a collateral to C (collateral circuit). Diagrams at right illustrate expected first- and second-order correlation peaks and their relative onset latencies.

generated mainly short PSF latencies. The longer PSF latencies associated with fast PTNs may be due to longer conduction times of the facilitated motoneurons. When a single cortical cell produced PSFs in several muscles, their latencies varied less than those of the overall population, but sufficiently to suggest involvement of different sizes of motor units. A few cortical cells were correlated with PSF, but did not respond antidromically to PT stimulation at the intensities tested; whether they might have responded at greater stimulus intensities or with a different placement of the PT electrodes remains an open question. Since lack of antidromic response may well have been due to several causes, such evidence does not prove that these cells were not

PTNs. The strengths and latencies of PSFs associated with these few cells did not differ markedly from those observed with confirmed PTNs.

Shape of PSF

The observed PSFs exhibited a variety of shapes. By definition, all PSFs declined again to prespike levels after reaching a peak, so they would not have resulted from summing nonstationary EMG activity, as occurs at movement onset. Preferential sampling when muscle activity is increasing would produce a steadily rising level of average EMG activity thoughout the analysis interval. The fact that the PSFs occur independently of any events at movement onset was also proved by compiling STAs triggered only from action potentials occurring during the static hold periods. Such averages revealed patterns of PSF similar to those compiled for all spikes (8).

The shapes of the observed PSF would be determined by several factors, including the number of individual motor units facilitated, the waveform of their muscle-unit potentials, and the shape of their postspike firing probability. The contribution of a single motor unit to the PSF would be the convolution of its rectified waveform with its postspike firing probability.

The postspike firing probability of a single motoneuron is its cross-correlogram with the cortical cell, and represents the conditional probability $P(M|C,t)$ that the motoneuron M fires at time t, given a spike in cell C at time $t = 0$. Each of the circuit configurations in Fig. 14 would make a different contribution to this postspike firing probability. A monosynaptic CM connection between the cortical cell and motoneuron would produce a first-order cross-correlogram, $P_1(M|C,t)$, whose time course would be related to the shape of the CM EPSP. Several possible relations between EPSPs and correlogram peaks have been proposed on theoretical grounds, namely, that the cross-correlogram produced by a monosynaptic connection resembles the EPSP (25, 40), or its temporal derivative (17, 18), or some combination of the two (16). Direct comparison in invertebrate motoneurons suggests that when EPSPs produce correlogram peaks they resemble

each other (22). In cat motoneurons, however, postsynaptic potentials evoked by muscle afferents produced cross-correlogram peaks resembling the EPSP derivative, slightly delayed (E. E. Fetz and B. G. Gustafsson, unpublished observations).

The effect of an EPSP on motoneuron firing probably can be qualitatively estimated. Consider an EPSP of height h superimposed on the membrane trajectory of an active motoneuron, as illustrated in Fig. 14. Such an EPSP would initiate an action potential only during the time t_a, when $V(t)$, the difference between threshold and the membrane potential, is less than h. The time t_a depends on the rate at which the membrane potential approaches threshold, since $dV/dt = h/t_a$. If the motoneuron fires tonically at rate $f = 1/T$, the proportion of time the EPSPs could reach threshold is $t_a/T = hf(dV/dt)^{-1}$. Thus, if the unitary EPSP has amplitude h = 100 μV and the motoneuron fires at rate $f = 20$/s, with membrane potential slope of $dV/dt = 0.5$ V/s (35), the EPSP would initiate an action potential 0.4% of the time. This would mean that 2,000 randomly timed EPSPs would include about eight that activate the motoneuron. Although the remaining EPSPs would also contribute to the membrane current driving the motoneuron, they would not contribute to a correlogram peak.

This model suggests that the EPSPs occurring during t_a would initiate action potentials during their rising phase. Moreover, by advancing the occurrence of action potentials, they would reduce the number of action potentials during their falling phase. Observed from the point of view of events synchronized with the EPSPs, such as the spikes of the presynaptic cell, the firing probability of the motoneuron would be augmented during the rise of the EPSP and decreased during its fall. In other words, the CM EPSP produced by the cortical spikes would generate a postspike firing probability resembling its temporal derivative.

In contrast to the first-order correlation between C and M produced by a monosynaptic connection, the two indirect circuits, via neuron A, would produce a second-order correlation. In both cases, the conditional probability $P_2(M|C,t)$ that M

fires at time t, given a spike in C, is the convolution of the two first-order correlations between the connected cells:

$$P_2(M|C,t) = \int_{-\infty}^{t} P_1(M|A,\tau)P_1(A|C,t-\tau)d\tau$$

The peak of such a second-order correlation would be smaller and more dispersed than the peaks of the underlying first-order correlations. To estimate the relative magnitude of such second-order correlations, consider the simplified case in which both first-order correlation peaks are represented by square waves of height H and duration D. In that case, the shape of the resultant second-order correlation would be triangular, with a maximum height of H^2D, a duration of 2D, and an area of $(HD)^2$. Moreover, the onset latency of the second-order peak would be the sum (or difference) of the latencies of the first-order peaks for the serial (or collateral) circuit. Thus, if the monosynaptic connections from A to M and between C and A both produce correlation peaks with areas on the order of 4×10^{-3}, the resulting second-order correlation between C and M would have a net area of 1.6×10^{-5}. This would produce one correlated firing of M for 60,000 spikes in C.

In fact, the net postspike firing probability produced by indirect circuits could be larger than this estimate, since the net effect of all disynaptic linkages is the sum of such second-order correlations over the set of all potentially mediating neurons, {A}. Moreover, synaptic linkages between neurons C and A may be more effective than connections to motoneurons, leading to a higher correlation $P_1(A|C)$. STAs of 14,000 to 20,000 events can detect postspike suppression (cf. Fig. 4), which is probably mediated disynaptically. Such higher order correlations thus require another order of magnitude of events in the STA to be detected.

A fourth circuit configuration that has been suggested to generate correlations between C and M is a common input to the recorded cell (C) and to an unrecorded CM cell (A) from a common input neuron (B). Such a circuit would lead to a third order correlation between C and M, namely, the convolution of three first-order correlations. The magnitude of such a contribution would be similar to that of trisynaptic serial circuits and would probably be negligible.

The synchronization of motor cortex cells, which may be produced by collateral connection or by common inputs, has been directly investigated by cross-correlating activity of task-related neighboring cells. As documented previously (8), in a sample of 12 pairs of strongly covarying precentral cells (not necessarily PTNs) that responded to similar passive and active movements, no evidence of a correlogram peak was obtained in averages of 10,000 events. This would indicate that synaptic linkages between neighboring coactivated motor cortex cells are generally too weak to produce pronounced synchronization between spikes, a result consistent with intracellular analysis (1). More recently, however, we have observed a significant exception: a pair of CM cells, both of which produced PSF in the same set of muscles and whose correlogram exhibited a weak asymmetric peak (consistent with a collateral from one cell to the other). Analysis of the strength and timing of the PSF of each cell indicated that motor-unit facilitation was too strong and began too early to be mediated via the correlation between the CM cells. To obtain more definitive evidence, STAs were compiled off-line from those action potentials of each cell that were not preceded or followed by spikes of the other cell; these STAs revealed the same distribution of PSF. Thus, although a weak correlation between these two CM cells existed, this was not necessary to produce the PSF of either cell. This observation does indicate, however, that both monosynaptic and polysynaptic circuits between CM cells and motoneurons may exist simultaneously, producing a net correlation that represents the combined contribution of each circuit.

The above considerations suggest that direct connections would probably make the dominant contribution to the PSF. Irrespective of their mediation, however, the PSFs represent an empirical measure of the increased postspike firing probability of motor units correlated with the action potentials of single motor cortex cells. In that sense, the PSFs provide a more direct measure of the functional consequences of a cell's activity than could be deduced from its

postsynaptic connections alone—even if such anatomical connections could ever be completely known, and could be used to predict correlational linkages. Monosynaptic CM connections probably range in effectiveness from the most potent to those too weak to produce any detectable correlogram peak (cf. Ref. 22). Thus, the PSF may help identify those motor cortex cells with sufficiently potent functional connections to generate enhanced postspike probability of motor-unit firing. It seems likely that cortical cells with the strongest correlational linkages probably have the most direct anatomical connections. In contrast, the weaker spike-correlated effects may represent, to a debatable degree, the consequences of direct or indirect anatomical connections.

Distribution of PSF

CM cells typically produced PSF in a set of muscles that may be called the cells' "muscle field" (8, 9). Usually, many more forelimb muscles were coactivated with each cell during wrist movement than were facilitated. The extent of facilitated motor units probably exceeds the number detected by our limited sample of five to six muscles. Each set of EMG electrodes recorded activity of perhaps 10–20 motor units, a small fraction of the total in each muscle. The observation that cortical stimulation may evoke CM EPSPs in some but not all motoneurons of a hindlimb muscle (14) suggests that CM cells can selectively affect specific motoneurons within the pool; if this is common for the forelimb as well, the muscles without PSF might have contained unrecorded facilitated motor units. Moreover, motor units in additional forearm muscles that were not sampled might also have shown postspike effects. To preclude the possibility of overestimating the number of facilitated muscles by redundant recording of the same motor units, we excluded EMG records whose cross-correlation showed evidence of cross talk. This may have eliminated some PSF produced in independent muscles. Thus it seems more likely that the number of target muscles was underestimated due to limited sampling than overestimated as a result of redundant motor-unit recording or correlations between precentral cells (8).

Assuming that the strong PSF may be interpreted as evidence of anatomical CM connections, these results have implications for the functional organization of CM connections to forelimb motoneurons. The fact that single CM cells typically facilitated more than one muscle suggests a divergent effect on different motoneuron pools, consistent with recent electroanatomical evidence that single PTNs may be activated from different motor nuclei (2, 37). The observation that extensor CM cells had somewhat larger muscle fields and tended to produce stronger PSF than flexor cells is consistent with the larger CM EPSPs observed in motoneurons of forelimb extensors, such as EDC (5, 30). Maximal CM EPSPs may be larger in extensor motoneurons because their average unitary CM EPSPs are larger or because they receive convergent input from more CM cells. Our finding that single extensor CM cells tend to produce stronger and more widespread PSF than do flexor CM cells may also be due to larger unitary CM EPSPs or to greater divergence of terminals. Our observation that in each monkey a greater proportion of the extensor-related cells produced clear PSF tends to support the possibility that forelimb extensor motoneurons have larger CM colonies than do flexor motoneurons.

In conclusion, the PSF would seem to provide a more secure basis for deducing causal linkages between precentral cells and muscles than their coactivation patterns. In these wrist movements, many more muscles were coactivated than were facilitated by any given CM cell. Moreover, as shown in the accompanying paper (4), the response pattern of a CM cell may differ drastically from the response pattern of its target muscles.

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