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Functional Relations Between Primate Motor Cortex Cells and Forelimb Muscles: Coactivation and Cross-Correlation Patterns

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INTRODUCTION

A more complete understanding of the neural basis of learning and memory will depend in part on further knowledge about the neural mechanisms underlying voluntary movements. Before we can begin to analyze the neural events that mediate the effects of reinforcers and stimuli on operant behavior, we need to know more about the way the nervous system generates and controls simple motor responses.

In higher mammals, the cerebral cortex clearly plays a major role in the control and performance of appropriate movements. Clues about the behavioral functions subserved by different regions of cortex may be obtained by their ablation or stimulation (5). Specific hypotheses about the relationship between cortical cells and behavior may be further elucidated by recording activity of single units in animals trained to make relevant responses, as illustrated by the contributions of others in this symposium. This chapter will review recent studies of the functional relationships between precentral motor cortex cells and forelimb muscles; their coactivation was investigated by operantly conditioning response patterns in these elements, and their interaction was tested by cross-correlation techniques.

That many motor cortex cells discharge during voluntary limb movement has now been well established, but the specific parameters of movements, which are coded in precentral cell activity, remain to be elucidated satisfactorily. Experiments have shown

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that precentral cell activity may be related to active force (3,4,6,7,13,15,16,18), direction of movement (7,9,13–15,18), contraction of muscles (7,9,12,13,18), and preparation for responding (17,18), not to mention their sensory responses to passive limb movements and cutaneous stimulation (9,12,14). In a recent study, comparing the relations between motor cortex cells and three different behavioral variables, Thach (18) concluded that "all the types of neurons that were looked for were found, in nearly equal numbers." One may hope that this baffling variety of relationships is due, in part, to complexities in the arrangement of forelimb muscles, and that some clarification might come from further analysis of the functional relations between these cells and their relevant muscles. Documenting the response patterns of motor cortex cells during complex movement sequences is somewhat analogous to observing the responses of sensory cortex cells to complex stimulus patterns. Just as the functional organization of sensory systems has been elucidated by systematically comparing the response properties and receptive fields of cells at successive levels and relating these to peripheral receptors, so also might the functional organization of cells in motor systems be clarified by analyzing their relation to specific muscles.

OPERANTLY CONDITIONED RESPONSE PATTERNS OF MUSCLES AND PRECENTRAL CELLS

To investigate the coactivation of single motor cortex cells with isolated contraction of different forelimb muscles, we have recorded their activity in monkeys trained to contract different sets of forelimb muscles isometrically (12). The four muscles chosen were a flexor and an extensor of the wrist and of the elbow. Their activity was recorded over several months with implanted pairs of EMG electrodes. The activity of the same cortical units and limb muscles was also documented during active elbow movements, as illustrated for one precentral cell in Figure 8-1. This motor cortex cell fired before active elbow flexion and preceded the activity of the agonist muscle, the biceps. The fact that both wrist muscles were also coactivated with elbow flexion illustrates a basic problem in relating cell and muscle activity during a single movement sequence. Most movements involve coactivation of many muscles, making it impossible to known which ones, if any, the unit may be affecting.

To resolve further which of these forearm muscles the unit was consistently related to, the monkey was operantly reinforced for contracting each of the four muscles in relative isolation. With the arm held fixed, this cell fired with isometric contractions of both the biceps and flexor carpi radialis, that is, the flexors of the elbow and wrist (Fig. 8-2); the unit was inactive during contraction of the wrist and elbow extensor muscles. This result illustrates a property of other precentral cells recorded in this region under these conditions: most cells fired with isometric activation of more than one of the muscles. Some cells were activated with both the biceps and triceps, and others fired with all four muscles.

To explore the relationship between this unit and the forelimb muscles further, the monkey was also rewarded for activating the cell in "operant bursts" and was allowed to coactivate any of the muscles. Under these conditions, the monkey activated the biceps and both wrist muscles with operant bursts of the unit (Fig. 8-2*e*). Such a pattern was representative of results obtained with other cells whose activity was operantly rewarded: usually, the monkey coactivated several muscles with operant bursts. The set of coactivated muscles—the so-called "motor field"—could be quite different for

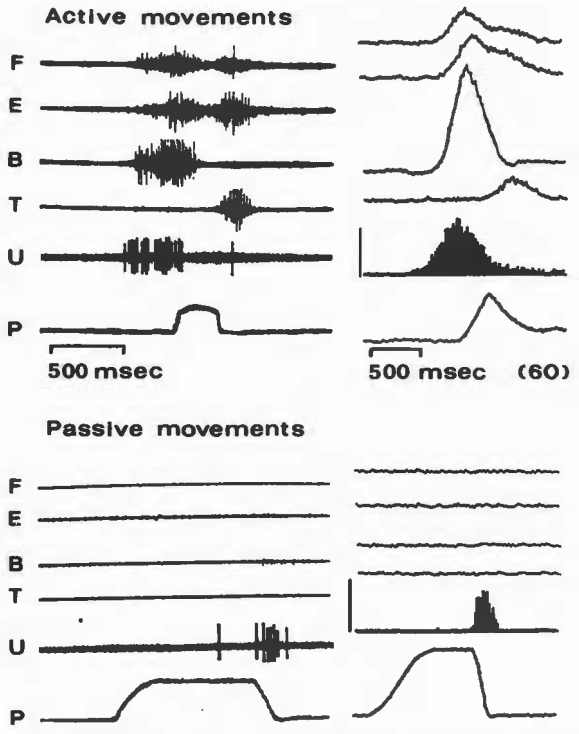

Figure 8-1. Responses of precentral unit and arm muscles during active and passive elbow movements. Muscles recorded with implanted EMG electrodes are, from top, flexor carpi radialis (F), extensor carpi radialis (E), biceps (B), and triceps (T). Precentral unit activity (U) and elbow position (P) recorded with potentiometer at the pivot point of the forearm cast. Single trials are shown at left and response averages compiled over 60 responses at right. With the forearm held in a cast, this cell responded before active elbow flexion and responded to passive elbow extension. The adequate natural stimulus for the cell was passive elbow extension and passive wrist flexion. Vertical bars calibrate a firing rate of 50 impulses per second. (From Fetz and Finocchio, ref. 12.)

adjacent motor cortex cells in the same cortical region (8,12). Indeed, some precentral cells were activated in operant bursts without any observed muscle activity or movements (9,12).

In other experiments, monkeys were operantly rewarded for activating motor cortex cells under relatively unrestrained conditions to determine which limb movements might be associated with cell activity (9). For some cells, operant bursts were associated with specific joint movements; however, many other cells were associated with more generalized and variable movements, with no obvious relation between the cell and any particular component of the movements. Thus, although operant reinforcement of cell activity may be a convenient technique for eliciting the movements associated with dif-

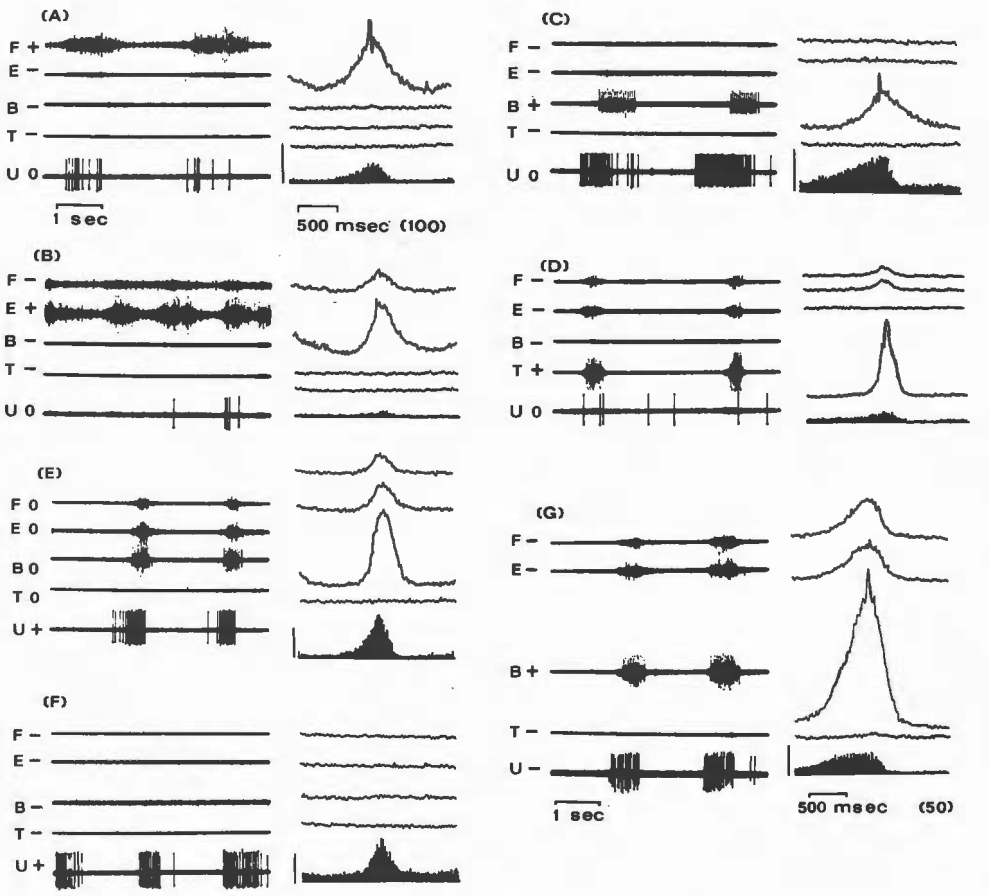

Figure 8-2. Operantly conditioned response patterns of the unit in Figure 8-1 and forearm muscles under isometric conditions. Responses at left show successive reinforced patterns, and response averages at right show reinforced responses. The elbow was held fixed at an angle of 90° and the wrist at an angle of 180°. The muscles and unit are labeled as in Figure 8-1. A + indicates elements whose activation was rewarded; a − indicates elements whose simultaneous suppression was required; 0 indicates elements whose activity was not included in the reinforcement contingency. (*a*), (*b*), (*c*), (*d*) Differential reinforcement of isolated bursts of EMG activity in each arm muscle, with no contingency on cortical unit. (*e*) Operant unit bursts were reinforced with no contingency on the muscles. (*f*) Reinforcement of operant unit bursts and simultaneous muscle suppression. (*g*) Responses when isolated biceps activity and unit suppression were reinforced. Vertical bar calibrates firing rate of 50/sec. Response averages include 100 events for (*a*) through (*d*) and 5 responses (*e*) through (*g*). (From Fetz and Finocchio, ref. 12.)

ferent cells, such movements sometimes turned out to involve complex and variable sequences. However, when the same unit was continuously reinforced over many minutes, certain components of these movements often dropped out, until relatively specific movements were repeatedly emitted with each burst.

Observing the same unit-muscle pairs during different responses revealed a considerable variability in patterns of unit-muscle coactivation, which was strongly dependent on the behavioral conditions. Some cells were consistently coactivated with a given muscle

under isometric conditions, but did not fire with that muscle, or were in fact suppressed when the muscle was activated during limb movements. Activity of the cell shown in Figure 8-2 provides an example. This cell was activated with the extensor carpi radialis (ECR) during elbow movements and during operant unit bursts but did not fire during isometric contractions of the ECR muscle. This indicates that unit-muscle correlations may depend considerably on the behavioral circumstances, and they should be tested under a variety of conditions to determine those which are the most consistent.

As discussed elsewhere, we might consider the "strongest" unit-muscle correlations to be those that involve the most intense coactivation of cell and muscle activity and those that appear most consistently under different behavioral conditions (8,12). However, even the strongest unit-muscle correlations could be changed by operantly reinforcing their dissociation. Thus, for the cell used in Figure 8-2, the unit-biceps correlation, which appeared during isometric biceps activity, unit reinforcement, and active elbow flexion, could be dissociated when the monkey was reinforced for activating the cell and suppressing all muscle activity (Fig. 8-2*f*). Similar dissociation was achieved for all precentral cells tested in this study and appeared to be as easy to condition as the isolated muscle activity. Thus, operant reinforcement of the dissociation revealed a degree of plasticity in these correlations which was not apparent when either the units, or the muscles, or the movements were the reinforced responses. In retrospect, this result might not be considered surprising since the effect of a single precentral cell—even one that has direct corticomotoneuronal connections—is subthreshold for firing the motoneuron and could, in principle, be easily overridden by the combined effects of other descending pathways. Nevertheless, the fact that these cells and motor units can be so independently activated does reveal an unexpected degree of flexibility in their relationships. When the reverse dissociation—biceps activation and unit suppression—was attempted (Fig. 8-2*g*), the monkey produced more intense biceps bursts but did not consistently suppress unit activity. Failure to shape this reverse dissociation may well have been due to behavioral causes such as fatigue or satiation.

In addition to relatively simple patterns of coactivation of units with muscles, some precentral cells exhibited more complex firing patterns. As an example, Figure 8-3 shows the response pattern of a non-PT neuron which exhibited a biphasic sequence of suppression as muscle activity increased, followed by activation as muscle activity was decreasing. This temporal pattern is most clearly evident in relation to the ECR muscle (Fig. 8-3*b*), but a similar sequence was apparent with each of the other muscles as well. The fact that this cell showed a similar response pattern with all four muscles may be interpreted in several ways. This cell's activity might be thought to be related to a common component of each response, such as orienting to the feeder. However, this did not appear to be the case, since free food delivery did not evoke activation of the cell, and since the suppression of cell activity began well before onset of muscle activity. Moreover, other cells in the same cortical region showed similar "off" response patterns with certain muscles, but not with other muscles. A second alternative is that this cell was simply coactivated with some other unrecorded muscle in another part of the body which underwent a similar response sequence. Such a hypothesis could conceivably be tested by recording activity of every muscle, but this becomes practically impossible. Besides being experimentally untestable, the notion that the response pattern of every motor cortex cell must mirror the response of some muscle is ultimately theoretically sterile. A single class of cells provides no basis for explaining how response patterns may be initiated and controlled. A third and perhaps more interesting alternative is that

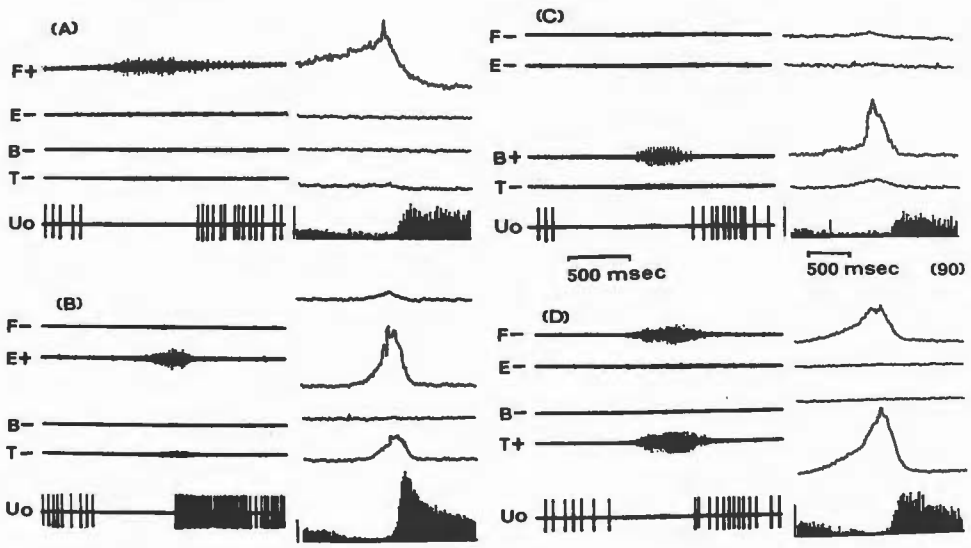

Figure 8-3. Response patterns of precentral non-PT neuron with isometric contractions of different forearm muscles. Single trials are illustrated at left, and response averages over 90 successive reinforced responses are shown at right. This unit exhibited a similar pattern of suppression and excitation with each of the muscles. (From Fetz and Finocchio, ref. 12.)

some cortical cells may have higher-order relationships to muscle activation—both temporally, in being related to changes in muscle activity, and spatially, in being related to more than one muscle. The biphasic pattern of this cell, then, might indicate that it could be related to turning muscle activity off; the fact that the pattern was similar for all four muscles suggests that it may be more related to the occurrence of a response than its topography. Such speculations are clearly tentative until convincingly confirmed. The point is that the last two alternatives cannot be resolved without some independent means, other than covariation, to establish causal relationships between cell and muscle activity.

CROSS-CORRELATION PATTERNS

To determine whether causal connections between precentral cells and forelimb muscles might be detected by cross-correlation techniques, we have used spike-triggered averages (STAs) of rectified EMG activity as a convenient approximation to true cross-correlations. Such STAs have revealed that action potentials of certain precentral neurons are followed by a transient postspike facilitation (PSF) of average motor unit activity in certain forelimb muscles. The latency and the time course of most PSF are consistent with their mediation by direct corticomotoneuronal (CM) connections, so we have referred to these precentral cells as CM cells.

In these experiments, monkeys were trained to alternately flex and extend the wrist against elastic loads. To provide periods of tonic coactivation of cells and agonist forelimb muscles, the ramp-and-hold movements involved a static hold period of at least 1 second (Fig. 8-4). Wrist and finger muscles were identified by their relative locations

and their response to intramuscular stimulation through the implanted pairs of recording electrodes. Action potentials of precentral cells that discharged tonically during either flexion or extension were used to compile STAs of full-wave rectified EMG activity of covarying agonists. For example, the cell shown in Figure 8-4 fired consistently during extension of the wrist and was recorded with six extensor muscles. STAs of two of the six covarying muscles (EDC and ED4,5) showed clear postspike facilitation. Two additional muscles (ECR-L and ED2,3) also showed evidence of a weaker augmentation of EMG activity after the spike. Averages of the remaining two muscles showed no significant spike-related effects in the number of events averaged.

The flexion-related cell shown in Figure 8-5 illustrates some further features of these cells. STAs show that action potentials of this cell were followed by postspike facilitation in all three implanted flexor muscles, as well as the flexor EMG recorded by surface electrodes. The remarkable response pattern of this cell is shown in the response averages (upper right). This unit exhibited an intense peak of activity at movement onset followed by a pause and a gradually increasing ramp of activity during the static hold period. Such a "phasic-ramp" pattern was characteristic of 8% of the CM cells (3). It illustrates the fact that the firing pattern of some CM cells may differ appreciably from the average activity of the muscles that they facilitate. Clearly, this cell had a particularly potent effect at movement onset when its firing was highest. This cell also illustrates the fact that the postspike facilitation was independent of triggering at onset

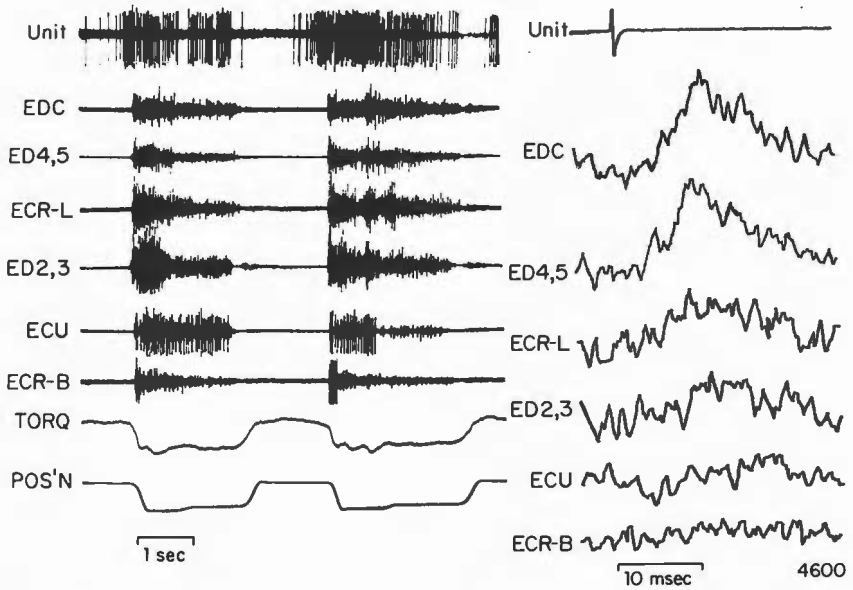

Figure 8-4. Responses of precentral CM cell that covaried with wrist extension and facilitated activity of extensor muscles. Responses at left show activity of unit and six coactivated extensor muscles, torque, and position. Muscles whose activity was recorded with implanted electrodes included extensors of the digits (EDC: ED4,5; Ed2,3) and extensors of the wrist (ECR-L; ECR-B; ECU). Spike-triggered averages at right indicate averages of full-wave rectified EMG activity from 4600 action potentials. Bin width was 250 μsec, and the analysis period included 5 msec before and 25 msec after triggering action potential. (From Fetz and Cheney, ref. 10.)

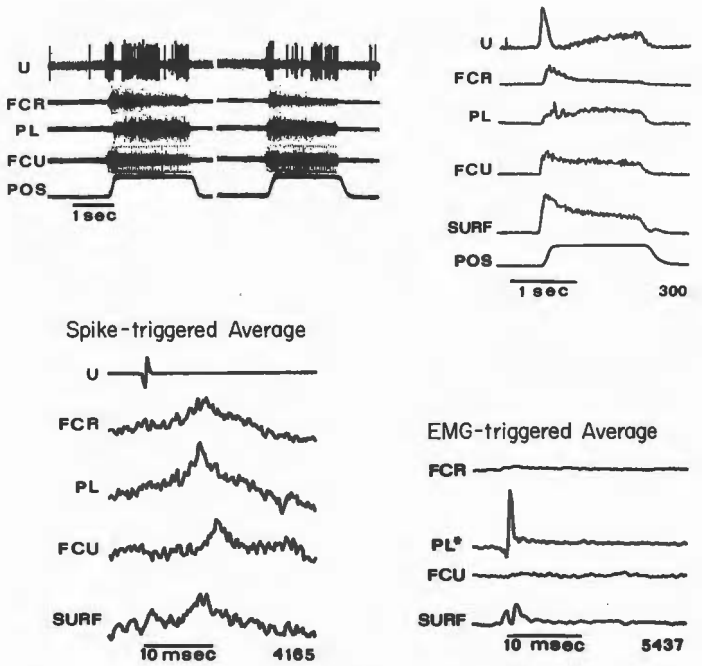

Figure 8-5. Precentral CM cell related to wrist flexion. Top left illustrates examples of two flexion responses showing EMG of flexor carpi radialis (FCR), palmaris longus (PL), and flexor carpi ulnaris (FCU) and wrist position (POS). Response averages at top right illustrate average pattern of unit and muscle activity during 300 successive flexion responses. The muscle activity of implanted muscles and surface-recorded EMG activity was full-wave rectified. Spike-triggered average at lower left was compiled for 4165 action potentials occurring during the tonic hold period, that is, excluding spikes during the phasic peak of unit activity. The EMG-triggered average at lower right shown an average of the rectified EMG activity triggered from motor units in PL. (From Fetz and Cheney, ref. 10.)

of movement, when muscle activity is increasing. The STAs (lower left) were compiled only from action potentials occurring during the tonic hold period, when muscle activity was relatively constant.

To confirm the independence of the EMG records, muscle activity was routinely cross-correlated by compiling EMG-triggered averages. As shown in Figure 8-5 (lower right), an average triggered from motor units in the PL muscle showed no evidence of common pickup of the same units in either of the adjacent muscles, FCR or FCU; the peak in the surface record indicates that the surface electrodes over PL did record some units in common. Similar averages triggered from each of the other muscles confirmed that the implanted electrodes had indeed recorded independent motor units. Such controls were routinely done when multiple PSFs were observed. In a few cases, EMG-triggered averages revealed evidence of common pickup; in those cases, one of the potentially redundant EMG records was eliminated from the data base.

When STAs were compiled simultaneously from several agonist muscles, the cells that produced PSF generally facilitated more than one muscle. Of 370 precentral neurons, which covaried strongly with either flexion or extension, and which were used to compile STAs of five or six nonredundant covarying forelimb muscles, less than half (43%) produced any evidence of PSF. Of those that produced PSF, 70% facilitated more than one muscle. This suggests that the set of facilitated muscles, that is, the cell's "muscle field," typically includes more than one synergist forelimb muscle. Whether the PSF is mediated by monosynaptic corticomotoneuronal connections remains to be proved. If it is, the muscle field would represent the set of target muscles whose motoneurons are contacted by terminals of the CM cell (1). In any case, the muscle field is a measure of the extent of facilitation of different muscles correlated with action potentials of single motor cortex cells.

CONCLUSION

In summary, the functional relations between motor cortex cells and muscles have been elucidated in different ways by their coactivation and their cross-correlation patterns. When specific patterns of cell and muscle activity were operantly reinforced, single motor cortex cells were found to be coactivated with several different muscles; moreover, the coactivation of a given unit-muscle pair could be quite flexible, depending on the behavioral conditions. Even "strong" unit-muscle correlations, which appeared consistently during a variety of different response patterns, could be dissociated by differential reinforcement of unit activity and muscle suppression (12).

In contrast to the widespread and variable coactivation patterns, the cross-correlation patterns, that is, the short latency postspike facilitation of EMG activity revealed by STAs, provides more secure evidence for a causal relation between cell and muscle activity. Whether or not they are mediated by monosynaptic connections, PSF provides a direct measure of the output effects on muscle activity correlated with action potentials of the precentral cell. The set of facilitated muscles, or "muscle field," usually included more than one of the covarying forelimb muscles. However, even CM cells were coactivated with more muscles than they facilitated, and many other precentral cells were coactivated with muscles that they did not facilitate. Interestingly, the firing patterns of CM cells were sometimes distinctly different from the activity of their facilitated target muscles.

Clearly, the most challenging work lies just ahead, namely, to combine the operant conditioning and STA techniques and to investigate further the interdependence, if any, of the covariation and cross-correlation patterns. For example, to test the mediation of the PSF it would be important to determine whether it is a function of different response patterns. To test the independence of CM cells and their target muscles, it would be interesting to see if their activity can be bidirectionally dissociated.

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