Novartis Foundation Symposium
Edited by Gregory Bock, Maeve O'Connor, Joan Marsh

Functional relations between primate motor cortex cells and muscles: fixed and flexible

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Abstract. In behaving monkeys the effects of motor cortex cells on muscles are inferred from two quite different types of 'correlational' evidence: their co-activation and cross-correlation. Many precentral cells are *coactivated* with limb muscles, suggesting that they make a proportional contribution to muscle activity; however, such coactivation is typically quite flexible, and can be changed by operantly conditioning the dissociation of cell and muscle activity. *Cross-correlating* cells and muscles by spike-triggered averaging of the electromyogram (EMG) shows that certain cells produce short-latency post-spike facilitation of EMG; this correlational linkage is relatively fixed under different behavioural conditions and its time course suggests it is mediated by a corticomotoneuronal (CM) synaptic connection. CM cells typically facilitate a set of coactivated agonist muscles, and some also inhibit their antagonists.

The firing patterns of CM cells can differ significantly from those of their target muscles. During ramp-and-hold wrist responses most CM cells discharge a phasic burst that precedes target muscle onset and that contributes to changes in muscle activity. At low force levels many CM cells are activated without their target motor units. Conversely, many CM cells are paradoxically inactive during rapid forceful movements that vigorously activate their target muscles; they appear to be preferentially active during finely controlled movements. Thus CM cells, with a fixed correlational linkage to their target muscles, may be recruited without their target muscles, and vice versa.

1987 Motor areas of the cerebral cortex. Wiley, Chichester (Ciba Foundation Symposium 132) p 98–117

The classic work of others in this symposium has documented the direct effects that primate motor cortex can exert on motor neurons via the so-called corticomotoneuronal (CM) cells and has established much about their functional organization (Phillips & Porter 1964, 1977, Porter 1985). The size of maximal CM-excitatory postsynaptic potentials (CM-EPSPs) in forelimb motor neurons of the baboon (Clough et al 1968) relative to unitary CM-EPSPs (Asanuma et al 1979, Porter & Hore 1969) suggests that each motor neuron receives convergent monosynaptic input from a colony of 10–50 CM

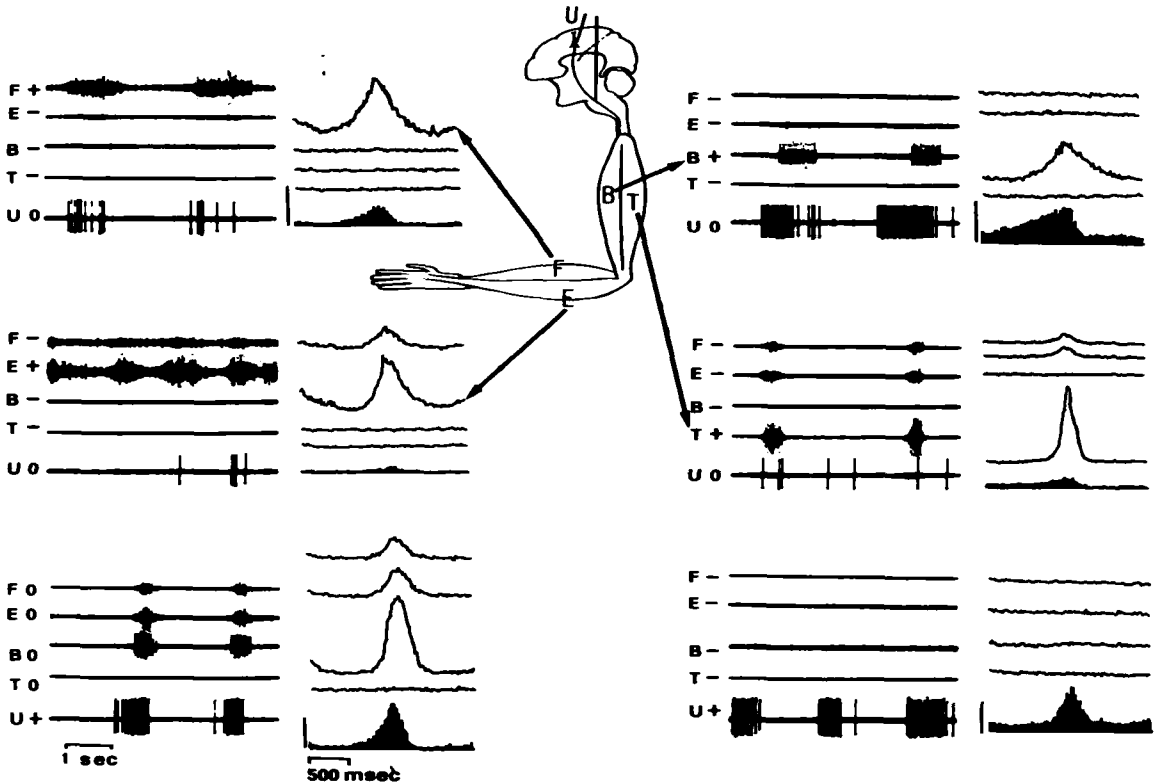


FIG. 1. Coactivation patterns of a motor cortex cell and forearm muscles. Records illustrate activity of flexor carpi radialis (F), extensor carpi radialis (E), biceps (B), triceps (T) and the cortical unit (U). The forearm was held fixed while isometric response patterns were operantly reinforced; the symbol after each letter indicates whether the reinforced pattern includes activation (+), or suppression (−) of that element, or did not include its activity (0). Each set shows sample trials (left) and averages (right) compiled for successive reinforced responses. (Redrawn from Fetz & Finocchio 1975.)

cells. These cells are distributed over relatively wide cortical regions (Landgren et al 1962, Jankowska et al 1975). Extensive divergence of terminals of single corticospinal cells is suggested by anatomical reconstruction (Shinoda et al 1981, Lawrence et al 1985) and electrophysiological evidence (Asanuma et al 1979).

Chronic unit recordings in behaving monkeys have further confirmed the role of motor cortex cells in the control of muscle activity. The close relation between the activity of pyramidal tract neurons and muscle force, first demonstrated by Evarts (1968), is now commonly considered to represent the typical behaviour of motor cortex cells. Further studies, too numerous to cite individually, showed that the activity of motor cortex cells may also be related to various other aspects of movement (cf. Thach 1978). Yet the observation that neuronal activity covaried with force—or any other movement parameter—was soon recognized as inconclusive evidence for a causal relationship between the two.

Coactivation of motor cortex cells and muscles

The question of causal involvement is illustrated by a study designed to determine whether motor cortex cells fired with particular sets of forelimb muscles (Fetz & Finocchio 1975). In these experiments the monkeys were trained to isometrically contract each of four representative forearm muscles in relative isolation. The cell illustrated in Fig. 1 was coactivated with isometric contractions of the flexors of the wrist and elbow (top left and right), but not the extensors of these joints (middle left and right). This neuron was also coactivated with the flexor muscles during active elbow flexion, and under isometric conditions when the monkey was rewarded for firing the cell in bursts (bottom left). Such consistent coactivation under different behavioural conditions would seem to suggest some sort of functional relationship. Yet when the monkey was preferentially rewarded for activating the cell without the muscles it readily dissociated their activity (bottom right). These results are representative of similar findings with other precentral neurons, and they illustrate two features of cell–muscle coactivation patterns: single motor cortical neurons were typically coactivated with multiple muscles, and their coactivation was quite flexible, subject to dissociation. Whether these cells had any causal effect on the associated muscles is not established by their coactivation (nor disproved by their dissociation).

Correlational linkages between cells and muscles

An independent means of confirming a causal relation between motor cortex cell and muscle activity is provided by the cross-correlation technique. Spike-triggered averages of forelimb muscle activity can detect the average post-

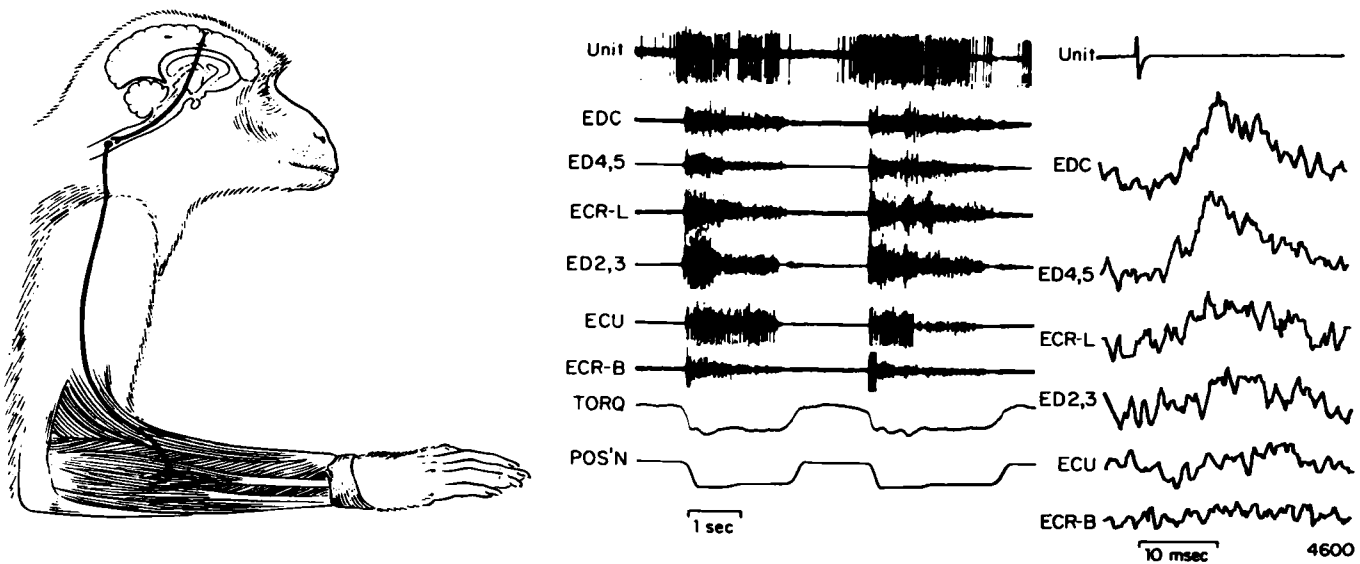


FIG. 2. Demonstration of correlational link between corticomotoneuronal (CM) cell and forelimb target muscles, probably mediated by corticomotoneuronal connections, as schematized at left. Responses of an extension-related CM cell during wrist movements against an elastic load (middle) show coactivated extensor muscles of the wrist (ECR-L; ECR-B; ECU) and the digits (EDC; ED4,5; ED2,3). Spike-triggered averages of rectified EMG (right) show post-spike facilitation in several target muscles. (Redrawn from Fetz & Cheney 1978.)

spike effects of certain motor cortex neurons on muscle activity (Fetz et al 1976, Fetz & Cheney 1978, 1980, Muir & Lemon 1983). Some neurons produce post-spike facilitation (PSF) whose magnitude and time course is consistent with mediation by monosynaptic connections (Fig. 2). Such cells may be identified as CM cells, where CM can be taken to imply an underlying corticomotoneuronal connection, or simply to identify a 'corticomotor cell' with a correlational linkage to its target muscles.

Single CM cells typically facilitate one or more of the coactivated forelimb muscles. The set of facilitated muscles, or *muscle field*, is usually a subset of the muscles that are coactivated synergistically during a movement. Monitoring six flexor and six extensor muscles of the wrist and fingers during alternating ramp-and-hold wrist movements, we found the average muscle field of extensor CM cells (2.5 muscles) to be slightly greater than that of flexor CM cells (2.1) (Fetz & Cheney 1980). Monitoring intrinsic hand as well as forearm muscles during a precision grip task, Buys et al (1986) found that their CM cells facilitated about 20–30% of the independent synergists. Their findings further suggested that distal muscle fields may be more restricted than proximal.

In contrast to the flexibility of the broad unit-muscle coactivation patterns, the correlational linkages revealed by spike-triggered averaging are relatively fixed. Spike-triggered averages compiled separately during the phasic and static component of a ramp-and-hold movement show PSF in the same muscles (Fetz et al 1976, Lemon et al 1986). Averages compiled during precision grip and power grip responses also reveal PSF in the same muscles, although their amplitudes were sometimes lower during the power grip (Buys et al 1986). To test for modulation of the PSF we trained monkeys to make alternating wrist movements in the horizontal plane with the wrist held in different postures (R.M. Martin & E.E. Fetz, unpublished work). With the wrist semi-prone the flexors and extensors were reciprocally activated as antagonists; with the wrist in a prone or supine position the ulnar flexors and extensors were synergistically coactivated, as were the radial flexors and extensors. Under these different movement conditions, CM cells continued to facilitate the same target muscles, with the same relative amplitudes.

These observations suggest that PSF is mediated by relatively direct synaptic linkages. Although the occurrence of PSF in a muscle is repeatable, its amplitude may change under different conditions. This modulation is understandable in terms of the underlying mechanisms. For multi-unit EMG recordings the PSF represents the net result of all the facilitated motor units. Any one motor unit would contribute in proportion to its post-spike firing probability convolved with its rectified action potential. The post-spike firing probability in turn is a function that is largely proportional to the derivative of the postsynaptic potential produced in the motor neuron (Fetz & Gustafsson 1983, Cope et al 1987). Thus the PSF amplitude could be modulated by recruitment of different motor units, which have different post-spike firing

probabilities and whose action potentials contribute differently to the net PSF. Therefore, changes in PSF amplitude are consistent with monosynaptic connections, and do not necessarily indicate the presence of a modulating interneuron. It seems relevant to note a case in which PSF appeared in new muscles: this was observed under the special conditions produced by a small, brief perturbation (Cheney & Fetz 1984); spike-triggered averages selectively compiled during the stretch-evoked muscle response revealed a significant increase in the PSF of target muscles, and additional PSF in muscles that showed no facilitation during the static hold period. These results may be explained by recruitment of higher threshold target motor units, or by enhanced postsynaptic potentials mediated disynaptically via spinal interneurons that are facilitated by synchronous input.

The question of synchrony between cortical neurons can be raised in conjunction with the wide muscle fields of CM cells. Could some of their postspike effects be mediated by synchronous firing with other CM cells? Direct evidence on the degree of synchrony has been obtained by cross-correlating the activity of simultaneously recorded neighbouring neurons. The cross-correlation peaks between motor cortex cells, when present, are typically broad (mean width:18 ms) (Smith & Fetz 1986). Cross-correlation peaks between pairs of CM cells with common target muscles can be somewhat sharper, but are still wider than required to mediate the post-spike effects (Cheney & Fetz 1985, W.S. Smith & E.E. Fetz, unpublished work). Thus, the clear PSF with sharp post-spike onsets can be confidently attributed to the output effects of the triggering cell rather than to its synchrony with other output cells.

In addition to post-spike facilitation, spike-triggered averages have also revealed post-spike suppression of muscles. In some cases the cell was coactivated with the muscles to which it had an inhibitory correlational linkage (Cheney et al 1985). More often, during ramp-and-hold responses cortical cells are reciprocally activated with the inhibited muscles, precluding spike-triggered averages. To reveal the correlational linkage of CM cells to antagonists of their target muscles, Kasser & Cheney (1985) used glutamate to generate spikes during the phase of movement in which the cell was normally inactive. This technique revealed that 40% of extensor CM cells and 18% of flexor CM cells had reciprocal inhibitory effects on the antagonists of their target muscles. The remaining CM cells had purely excitatory effects, and with one exception, facilitated only their coactivated target muscles.

Response patterns of CM cells and target muscles

The ability to identify CM cells in awake monkeys provides a model system in which the relative activation of connected elements can be compared under normal behavioural conditions. During active movements CM cell activity

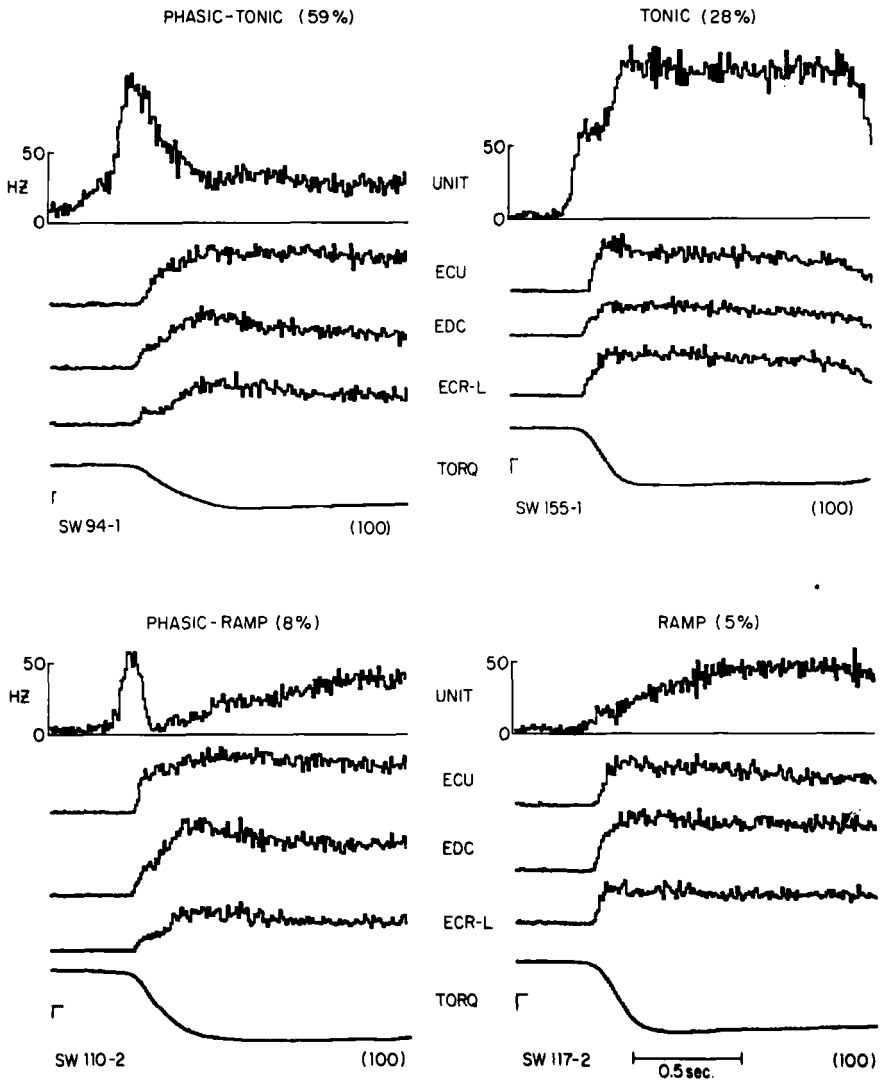


FIG. 3. Response patterns of CM cells during generation of isometric ramp-and-hold torque responses. Each set shows the time histogram of CM cell activity, averages of synergistic muscle activity and isometric torque. Titles give name and relative frequency of each type of CM cell. (From Cheney & Fetz 1980.)

does not simply mirror the activity of its target muscles. The differences in their discharge patterns reveal some significant distinctions between CM cells and motor units.

During simple ramp-and-hold wrist responses most of the CM cells exhibit

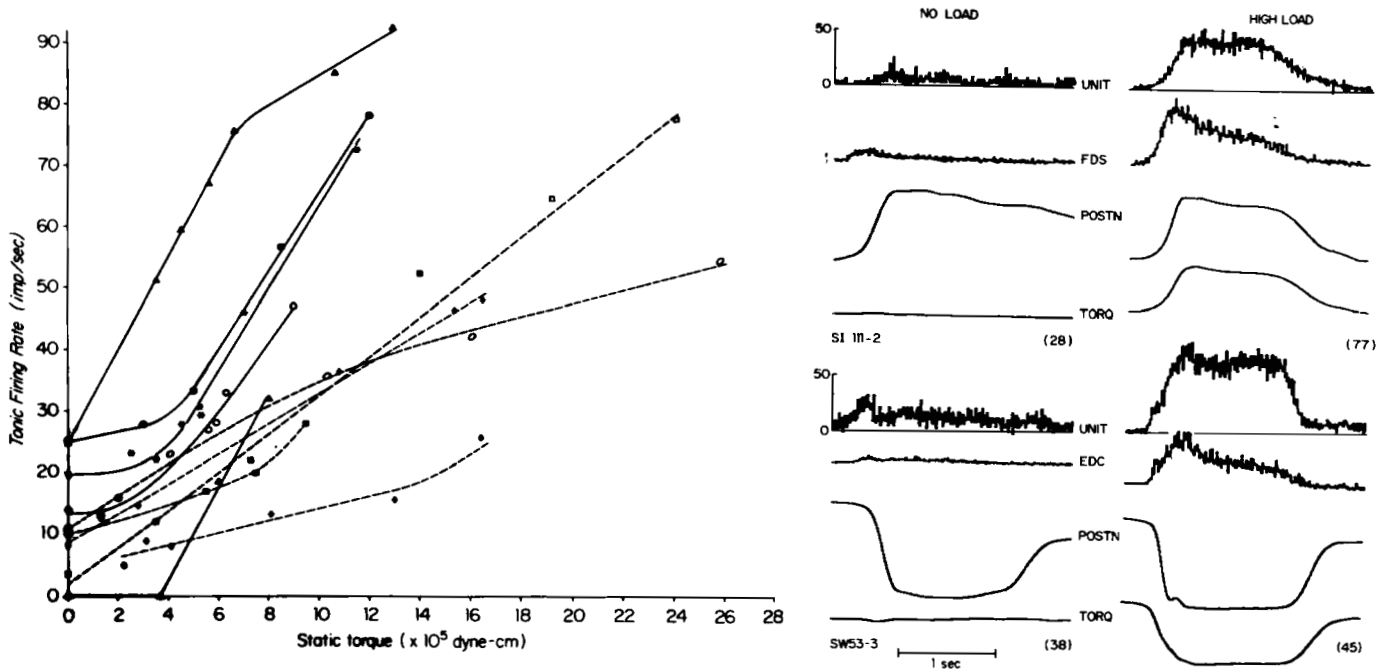


FIG. 4. Relation of CM cell discharge to active muscle torque. Examples of extension and flexion CM cells are shown at right for responses at two torque levels. Plot of tonic firing rate versus torque at left shows higher rate-torque slopes for extensor CM cells (solid lines) than flexor CM cells (dotted lines). (Graphs redrawn from Cheney & Fetz 1980.)

a phasic burst of discharge at the onset of muscle activity (Cheney & Fetz 1980) (Fig. 3). Such high frequency firing helps to bring the motor neurons to threshold. For those cells with inhibitory links to antagonist muscles this phasic discharge would simultaneously help to turn the antagonists off, and to inhibit their activation by stretch reflexes. Thus the cortical discharge pattern has a strong *phasic* component representing a *change* of muscle force. Physiologically this is dictated by the requirements for activating the relatively inert motor neurons, which require substantial input current to prod them to discharge. Interestingly, the firing patterns of rubromotoneuronal cells emphasize the phasic components of movement even more than CM cells (Cheney et al 1987).

During the static hold period of ramp-and-hold movements, when the force is maintained at a steady level, most CM cells (87%) fire at a constant rate; this *tonic* firing rate is an increasing function of the static *force* (Fig. 4). A small proportion of CM cells (13%) exhibit a gradually incrementing discharge frequency during the hold. These firing patterns of CM cells contrast with those of forearm motor units under the same conditions. Fifty-six per cent of motor units also fire tonically during the hold period, at rates proportional to static force, but 39% exhibit decrementing discharge (Palmer & Fetz 1985). It seems reasonable to speculate that the incrementing discharge of CM cells functions to counter the adaptation of motor neurons to steady input. Thus the contrast between the discharge patterns of CM cells and motor neurons can be understood in terms of the physiological properties of motor neurons and the inputs required to make them discharge appropriately.

It seems worth noting parenthetically that the representation of active force in CM cells is similar to the representation of peripheral stimuli in many sensory cortex cells. A passive ramp-and-hold joint rotation or cutaneous pressure typically evokes a phasic–tonic discharge in postcentral cortex cells. Thus, both motor and sensory cortex cells show an initial phasic component of discharge that codes a change in the peripheral event and a tonic discharge which codes its sustained intensity. The muscle field of CM cells is also obviously analogous to the receptive field of sensory cortex cells, in that both kinds of cortical cells represent the activity of a set of peripheral elements. Even the inhibitory component of the receptive field has its analogue in the reciprocal inhibitory linkages of CM cells to antagonists of their target muscles.

Dissociated activation of CM cells and target muscles

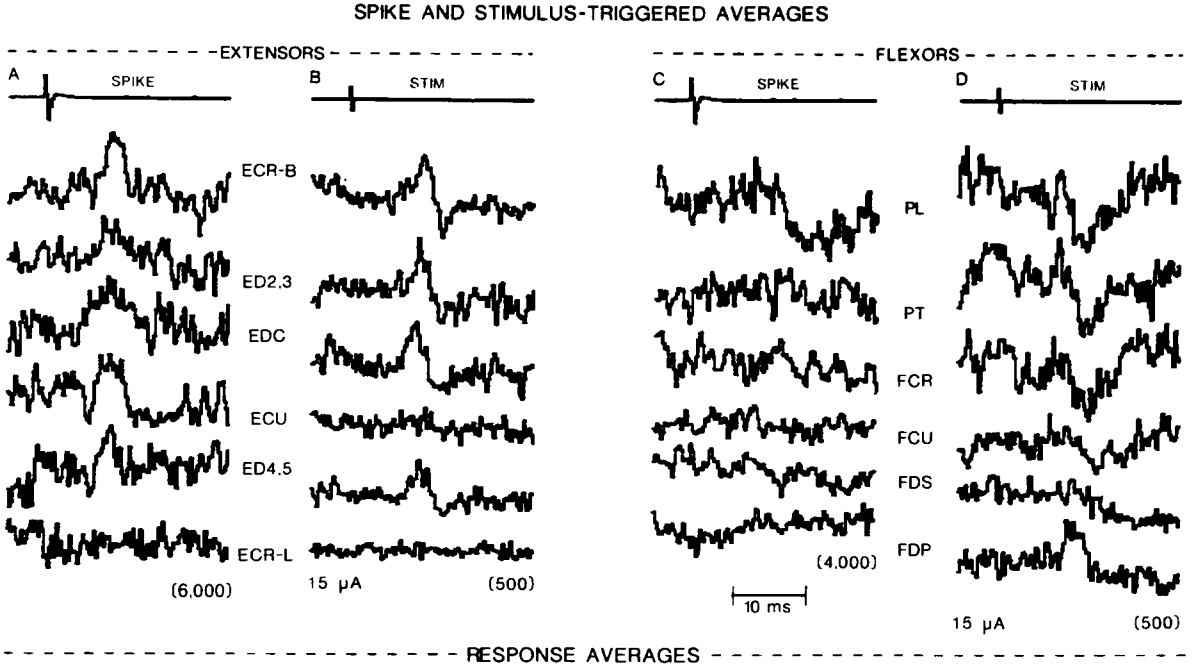
In addition to the differences in the response patterns of CM cells and their target motor units, there are circumstances in which each can be activated without the other. In general, CM cells appear to have a lower threshold for activation and they fire without their target muscles in three situations. First,

during ramp-and-hold movements most CM cells begin to increase their discharge well before the onset of activity in their target muscles. The mean onset time of phasic–tonic CM cells was 71 ms before their target muscles, and some began several hundred milliseconds earlier. As noted, this initial CM cell discharge would help to bring their target motor neurons to threshold. Secondly, during the static hold at low force levels, many CM cells are recruited into tonic activity without their target motor units. Whereas CM cells typically discharge at the lowest levels of active force, the motor units are recruited over a wider range of forces. Thirdly, many CM cells can be driven by adequate natural stimulation, which does not evoke responses in their target muscles (Cheney & Fetz 1984). Most CM cells respond to passive joint rotation that stretches their target muscles, and some respond to cutaneous stimulation. All these examples are of course consistent with the fact that CM-EPSPs are too small to produce obligatory responses in motor neurons, and they indicate that in the conscious primate motor cortex cells undergo a wider range of activities than is reflected peripherally in the muscles.

Perhaps more interesting is the evidence for the reverse dissociation: activation of target muscles without activation of the CM cells that facilitate them. Again three examples can be cited. During the ramp-and-hold movements some CM cells, particularly those without an initial burst, begin firing after their target muscles. For example, the mean onset time of the ramp cells was 100 ms after their target muscles. Secondly, during the static hold, a few CM cells were recruited at levels higher than their target muscles (Fig. 4); however, such high-threshold CM cells are seen rarely.

The most interesting case of muscle activation without CM cells occurs with rapid forceful movements. CM cells that fired strongly with moderate, well-controlled ramp-and-hold movements showed paradoxically meagre activity in relation to rapid alternating shaking of a manipulandum (Cheney & Fetz 1980). The latter ballistic movements involved considerably more intense activity of the cells' target muscles. This phenomenon has also been clearly demonstrated by Muir & Lemon (1983) for CM cells related to intrinsic hand muscles. When the monkey performed a precision grip response with thumb and forefinger, related CM cells were strongly activated; when the monkey performed a power grip task, involving even greater activity in the target muscles, the cells were relatively inactive.

Further evidence of such dissociation was obtained in studies in which CM cells were documented during both alternating ramp-and-hold movements and power grip responses (R.J. Kasser & P.D. Cheney, unpublished work). The CM cell in Fig. 5 facilitated several extensor muscles and fired with wrist extension during alternating ramp-and-hold responses, in which flexors and extensors were reciprocally activated. When the monkey performed a power grip by squeezing a pair of nylon bars, the extensors and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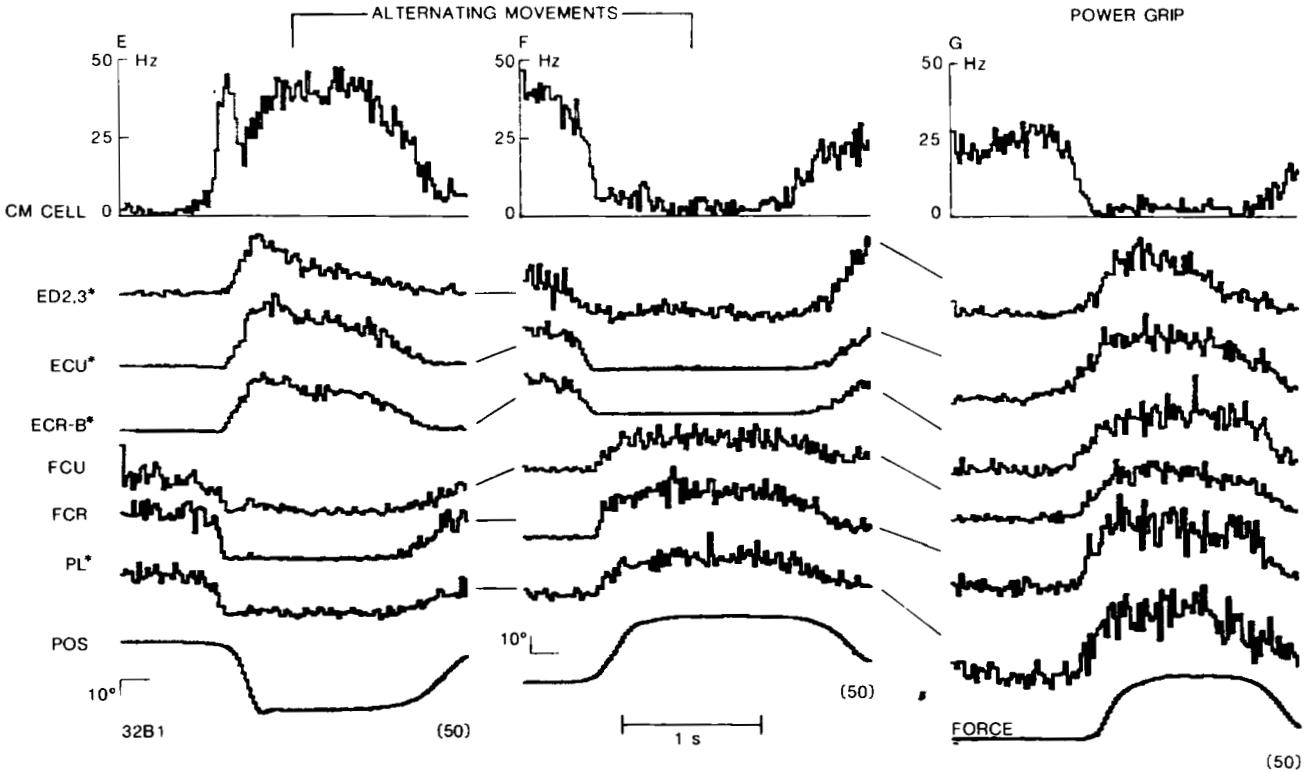

FIG. 5. Relation of a reciprocal CM cell to alternating wrist movements and power grip. Top records show reciprocal correlational linkages of the cell: post-spike facilitation of extensor muscles (A) and post-spike suppression of flexors (C). These reciprocal effects are further demonstrated by similar post-stimulus effects in averages triggered from single-pulse microstimuli delivered at the site of this CM cell (B,D). Response averages show that the CM cell was coactivated with its target muscles during alternating movements (E,F), and was suppressed during co-contraction of extensors and flexors in the power grip (G). Target muscles are indicated by asterisks. (From Cheney et al 1985.)

flexors co-contracted; during these co-contractions the activity of the CM cell dropped sharply, while its target muscles were vigorously active (bottom right). Such dissociation of CM cell and target muscle activity was observed in 14/23 of the CM cells tested under both conditions. An additional property of this cell provides a possible functional rationale for its behaviour: it had an inhibitory linkage to the flexor muscles, as revealed by spike-triggered averages of flexor EMG (top). Since the suppression of flexors is incompatible with their coactivation in the power grip, the neural mechanisms generating co-contraction of antagonists may exclude activation of such reciprocal CM cells. Support for this hypothesis can be found if one compares the correlational linkages of the CM cells to flexors and extensors with their relation to reciprocal responses versus co-contraction of these muscles. The reciprocal CM cells, which suppressed the antagonists of their target muscles, were less likely to be active during the power grip (4 of 13 cases) than the CM cells that produced pure facilitation (5 of 10 cases). It seems significant that the neural mechanisms that produce co-contraction of antagonists forgo the use of the reciprocal CM cells rather than inactivate the inhibitory interneurons.

Functional implications

The flexibility between CM cells and their target muscles allows a more extensive repertoire of responses than would be available with obligatory linkages. For example, the subthreshold effects of CM cells allow movements to be more specific than the muscle fields of the participating CM cells. A single muscle could be activated in isolation if its entire aggregrate of CM cells was recruited; even though many of these cells facilitate additional muscles, these wider effects would be more sparsely distributed and could remain subthreshold. Similarly, a movement involving coactivation of a group of muscles is unlikely to depend only on CM cells whose muscle fields match the activated muscles. *A priori*, the number of possible motor combinations clearly exceeds the number of CM cells available for each. It seems likely that a coordinated movement recruits a population of CM cells whose muscle fields include the activated muscles, but which may also include additional muscles. However, the above experiments suggest that significant constraints may pertain to the coactivation of physiological antagonists; CM cells with reciprocal correlational linkages seemed to be less involved in coactivation of antagonist muscles during performance of the power grip. Whether this observation is more related to the strength of the movement than to coactivation of the muscles remains to be determined by future experiments.

Acknowledgements

This work was supported in part by NIH grants NS 12542, RR 00166, NS 5082

and NSF grant BNS 82–16608. We thank our colleagues for permission to cite unpublished observations.

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DISCUSSION

Goldman-Rakic: You said that the corticomotoneuronal (CM) cells were in clusters. There is some evidence that callosum columns alternate with intra-hemispheric (associational) columns in the cortex. Have you tested whether anything different is being coded in the callosum as opposed to adjacent associational columns?

Fetz: Ours were all layer V cells and many were tested for corticospinal projections by pyramidal tract stimulation. I'm not sure how these CM cells would be distributed relative to callosal neurons. We did not stimulate the corpus callosum or the contralateral hemisphere to determine the response properties of callosal cells.

Thach: Fromm & Evarts (1981) attributed a fixed size principle to CM cells. They suggested that smaller cells are first recruited in movements of increasing power and larger ones are only added at the top. This and Roger Lemon's evidence shows that with certain kinds of power grip a cell that is recorded at smaller levels of force for other kinds of grip drops out. This would seem to be a

dramatic exception to the small-to-large recruitment order of the size principle.

Fetz: Yes, I agree that this property of CM cells is inconsistent with a size principle of recruitment for these cells. Fromm & Evarts (1981) did not really characterize the target projections of their precentral cells. So the cells that were preferentially recruited with the higher-force movements could also have been involved in activating peripheral or postural muscles that were activated only with the more intense movements.

Freund: Is there evidence for specialized task groups in the motor cortex? Thomas et al (1986) studied the selective activation of motor units located in different compartments of the first dorsal interosseous muscle during different mechanical requirements, such as stretching or adducting the forefinger.

Fetz: That hasn't been looked at directly, to my knowledge.

Porter: Some of the cells that Muir & Lemon (1983) recorded from need not have been activated at all in the tasks your monkeys were performing. Muir & Lemon were particularly interested in the use of individual digits and in the fractionation of muscle contraction associated with that.

Georgopoulos: Did you record any cells that would be activated specifically by co-contraction?

Cheney: We recorded from identified CM cells in monkeys during two tasks—alternating wrist movements and power grip. The alternating movement task involves a reciprocal pattern of activation of wrist flexor and extensor muscles whereas the power grip task involves coactivation of antagonist muscles. Of 51 CM cells for which we computed spike-triggered averages of both flexor and extensor muscles, only one cell, so far, has convincingly co-facilitated both flexors and extensors. However, in recordings from rubromotoneuronal cells under similar conditions we have found a significant population of co-facilitation cells (12 of 53 cells tested).

Georgopoulos: How then can you explain Dr Humphrey's observations?

Cheney: Humphrey & Reed (1983) found a class of cells in the convexity of the precentral gyrus (anterior MI) that were poorly modulated in relation to reciprocal patterns of flexor and extensor muscle activity associated with wrist movements but showed sustained increases in background discharge during coactivation of wrist flexor and extensor muscles. Coactivation was associated with stiffening at the wrist joint to oppose displacements produced by a continuous 1 Hz sinusoidal torque perturbation applied to the wrist. In addition, Humphrey and Reed were able to evoke co-excitation of flexor and extensor muscles by repetitive microstimulation applied to the cortical sites where these co-contraction related cells were found. On the basis of these findings they postulated that such cells may send excitatory terminals to motor neurons of both flexor and extensor muscles. Given the ubiquitous occurrence of antagonist muscle co-contraction, the existence of a unique class of cells specifically organized for co-contraction would seem to have considerable potential utility. However, microstimulation excites multiple corticospinal cells, not just one

cell, so the specific pattern of stimulus-evoked motor output that is observed is not necessarily characteristic of any individual cell. The existence of a zone in motor cortex containing cells that individually co-facilitate flexor and extensor muscles remains to be demonstrated at the level of single CM cells. We have found little evidence that individual CM cells are organized to produce co-facilitation. However, our recordings have been largely from the bank of the precentral gyrus, whereas Humphrey's co-contraction zone was on the convexity of the gyrus; so this issue needs to be examined further.

Calne: How stable is the system when you are recording from a cell, Dr Fetz?

Fetz: The monkeys make these movements under relatively stable conditions. The one disruption of input we studied involved torque perturbations of the wrist. We have not used interventions like cooling.

Thach: In those reaction-time experiments Meyer-Lohman et al (1977) showed that cooling the dentate delayed the onset of motor cortex activation of CM cells and also the onset of movement, as shown in the electromyogram (EMG). Presumably the motor cortex–motor neuronal linkage stays fixed and even if the activation of motor cortex and subsequently the EMG was delayed in time, that linkage would remain tight.

Would post-spike facilitation be a useful technique for looking at linkages further into the motor system—for example, at the potentially tight linkage between a cerebellar unit and a motor cortex unit via the thalamus?

Fetz: The probability of detecting post-spike enhancement through a disynaptic link is the product of the probabilities of the two monosynaptic links. Statistically, this tends to be extremely small. Nevertheless, the post-spike suppression indicates that disynaptic links *can* generate detectable effects. Several factors can raise the relative strength of disynaptic mediation: a large number of mediating interneurons, the fact that interneurons are fired more readily than motor neurons, and the enhancement of inhibitory postsynaptic potentials near firing threshold. Disynaptic mediation of *excitatory* effects from cortex to motor neurons in the primate is less probable. If this were a prominent pathway, we should see disynaptic EPSPs in the intracellular recordings. The synaptic potentials in thalamocortical cells from cerebellar nuclear cells are so large that this link should be detected by cross-correlation, if the connected units can be found and recorded simultaneously.

Calne: Rather than cooling the central nucleus, would it be easier to use a drug that takes the striatum out?

Porter: When the drug dose is high enough to abolish transmission through the system it often prevents movement.

Kuypers: You are dealing with cells concerned with movement, not with muscles, aren't you?

Fetz: One could interpret the function of the CM cells as facilitating movements that involve their target muscles. A common question is whether the CM cells are specifically related to those movements that are produced by coactiva-

tion of their target muscles. It seems unlikely that they would be exclusively involved in those particular movements and no others. Presumably they would also be active in movements that engage only subsets of their target muscles. Strictly speaking, the empirical evidence indicates that their role is to facilitate activity of their target muscles, and this may occur with a variety of movements.

Kuypers: If I transect the pyramidal tract the precision grip cannot be made, although the power grip can be executed. So I still tend towards the idea that the cells are dealing with movements rather than with muscles.

Fetz: Yes, the evidence suggests that the CM cells are preferentially active in fine movements, and less involved in powerful, rapid movements, although both engage their target muscles.

Rizzolatti: What is the definition of movement in this case? What is lacking for what you saw to be defined as movement?

Fetz: There *is* a wrist movement. I didn't mean to say that it is not a coordinated movement. The question is what is represented by the CM cells. One can interpret the experimental evidence either way. Single CM cells facilitate individual muscles or, more often, a group of target muscles, so in their correlational linkages they clearly represent muscles. When those target muscles are coactivated in a movement, you could also say the cell's activity represents the movement. I'm not sure how useful this distinction really is under these conditions.

Cheney: The issue of whether muscles or movements are represented by CM cells suffers from the implication that one or the other, but not both, must be represented. To the extent that every CM cell has an identifiable set of target muscles, one can argue that muscles are represented by individual cortical cells. It seems to me that the question of whether movements are also represented depends on whether the combinations of muscles facilitated by single cells (the cell's muscle field) form synergies that are functionally meaningful in the sense that activation of the synergy yields a purposeful movement or a distinct part of a purposeful movement. In this sense, cells with reciprocal or co-facilitation patterns of output effects on agonist and antagonist muscles might be thought of as representing movements. In addition, neurons that show strong modulation for one type of movement, for example, precision grip, but not another type, despite a similar pattern of activation of the cell's target muscles in the two movements, should also be considered as representing movements, since the neuron's discharge, in this case, would be movement-dependent. To test this issue further will require tasks that fractionate muscles into functionally meaningful combinations (synergies).

Lemon: An even better test might be to test two different fractionated movements which are different both in form and in the goal they are designed to achieve. If you could then see a difference in the activity of the population of CM cells projecting to the muscles of the hand, you would perhaps be nearer to an answer. The patterns of connectivity which you see by averaging should not

be confused with the behavioural relationship of the cell's activity to the activity of the muscles. One often finds muscles which are coactivated in a particular movement with a particular corticomotor cell, but the cells have no connection with these muscles. One has to be careful about drawing direct parallels between behaviour and connectivity in this kind of study.

Kuypers: If one cell is involved in that movement and the same muscle makes another movement, would you say that the cell is then probably not involved?

Cheney: I think we are finding that although a descending neuron's connections with motor neurons are relatively fixed, its activity must be considered movement- or task-dependent and not always predictable on the basis of the activity of its target muscles.

Porter: But is there any problem about that? Everyone seems to be saying that an instruction set generated somewhere in the brain selects from the motor cortex, and maybe from many other regions as well, certain descending connections that are to be activated. Their multiple innervation of a whole set of neuronal elements in the spinal cord leads to an output from the spinal cord. That output may be as limited, at least in the human hand muscles, as the activation under voluntary control of a single motor unit. Under other circumstances that output is directed to a wide population of muscles which are activated in what Paul Cheney called synergies. A given cortical cell may or may not be involved in the operation of that system, depending on what its contribution is to the total activation of the spinal cord.

Fetz: The movement may also be very specific and still involve CM cells whose output effects are less specific. For example, contracting a single muscle in isolation may recruit many CM cells with large muscle fields. Since their effects on additional target muscles can be subthreshold, the actual movement can be more specific than the muscle fields of the cells involved.

Strick: One can ask whether there is a CM cell branching pattern for every possible movement. Based on existing data, the answer would have to be no, there is not. Radial and ulnar deviations, for example, require coactivation of wrist flexors and extensors. However, no single cortical cells have been observed that branch to both wrist flexors and extensors.

Lemon: But if you don't search the cortex while the monkey is making this movement you may not find the cell that is related to the movement.

Porter: Pronation and supination are also complex movements involving many muscles, and these movements seem to be very dependent on the operation of corticospinal controls. I presume that another set of activations is required for the use of the muscles in pronation and supination.

Freund: This idea fits fairly well with the general scheme that the further upstream one looks, the more selective is the involvement of the neurons for certain aspects of the movement. If you cut the peripheral nerve no movement will be possible at all. If you cut the pyramidal tract or ablate the precentral motor strip, fractionated movements will disappear but some synergistic move-

ments will recover. In other areas further upstream (premotor, parietal) only some aspects of motor behaviour may be disturbed.

Porter: Dr Fetz, what are the likely conduction velocities of the fibres you studied? This might partly tell us whether slow as well as fast pyramidal tract axons can be involved in this sort of activity. Or are slow pyramidal tract axons, as many people earlier believed, innervating only the parts of the spinal cord that are concerned with activation in proximal muscles?

Fetz: The antidromic latencies of some of the CM cells in our studies were as long as 3.5 ms, representing the slowly conducting pyramidal tract fibres.

Porter: Yet you are confident that the latency of those post-spike facilitations is consistent with a monosynaptic action of those slow-conducting fibres?

Fetz: Yes, the slowly conducting CM cells produced post-spike facilitation at longer latencies—about 15–19 ms. Some of this delay must also represent longer conduction times in smaller motor neurons. We also saw some 'complex' facilitations that began too early to be mediated by monosynaptic action of the recorded cell.

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General discussion 1

Porter: We have covered a range of observations, from gross anatomical connectivity and the revelations that come from electrical or magnetic stimulation of the brain output system to more refined considerations of what individual elements within those systems may be contributing to the total output when a conscious animal is making some sort of learnt movement. A number of questions have not yet been answered. For example, one issue is the minute organization of the motor areas and whether the radial arrays of cells which are so evident in everyone's anatomical observations really have within them some sort of functional columnar organization. Or will the wide-ranging collaterals of the output cells from those radial arrays make us revise our views of columnar organization and vertical interactions within a radial column?

Lemon: The corticomotoneuronal (CM) projection to the hand muscles is relatively restricted. In our recently published study (Buys et al 1986), we recorded from a total of 58 identified CM cells, together with electromyograms (EMGs) from up to 10 muscles. All the muscles acted on the hand and fingers. Most of these cells showed facilitation in only two or three of the ten sampled muscles. Although the spike-triggered averaging technique is very good for this type of connectivity study, it is very difficult to make precise measures of amplitude and latency from averages of multi-unit EMG. A second problem is that the duration of post-spike facilitation (PSF) in such averages is much longer (mean 14 ms) than might be expected from a brief monosynaptic input to the motor neuron pool and, with durations of this order, oligosynaptic influences can certainly not be ruled out (Lemon et al 1986).

Recently Geert Mantel and I have been trying to get round this problem by making cross-correlations between spikes from single CM cells and the activity of single motor units from thenar muscles (mainly abductor pollicis brevis: AbPB). Recordings were made while the monkey carried out a precision grip movement.

Fig. 1 shows the set of results for one corticospinal cell. This cell discharged before the onset of the precision grip movement (arrowed in Fig. 1F) and it was at least partly coactivated with discharges of a single adductor pollicis (AdP) motor unit that became active during the hold phase of the grip (Fig. 1F). The spike-triggered averages of the rectified AdP surface EMG showed a clear PSF (Fig. 1A). Fig. 1B shows the result of the cross-correlation of 20000 pyramidal tract neuron (PTN) spikes with discharges of the motor unit. The correlogram shows a clear peak, with a latency of 17.4 ms and a half-width of 1.5 ms. The form and size of the correlation peak are strongly suggestive of monosynaptic

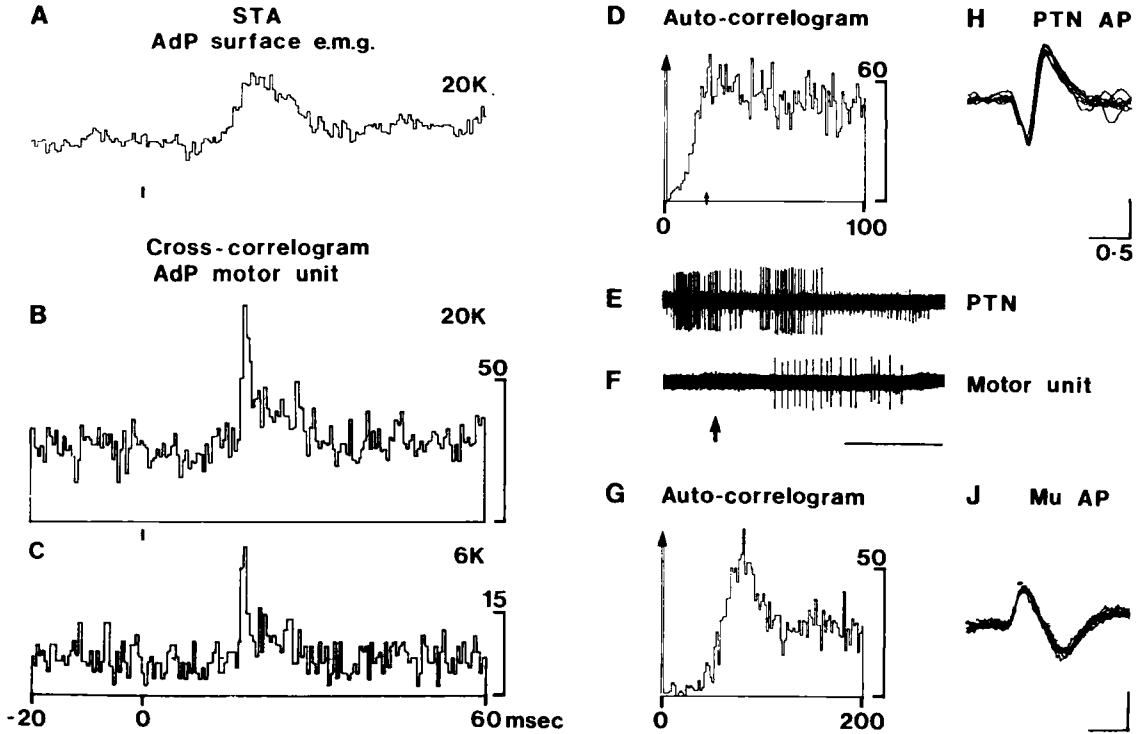

FIG. 1. (*Lemon*). A: post-spike facilitation (PSF) of multi-unit, surface EMG from adductor pollicis (AdP) by a single pyramidal tract neuron (PTN) revealed by a spike-triggered average (STA) of rectified EMG with respect to 20 000 PTN spikes. Spike discharges occurred at time zero (small vertical line). B: cross-correlogram of the same 20K PTN spikes (at time zero) with discharges of a single motor unit recorded from AdP. Bin width 500 μs. Bar at the right indicates number of motor unit discharges per bin. C: as in B, but with the exclusion of PTN trigger spikes preceded or succeeded by interspike intervals of < 20 ms. Note that the principal peak is still present in the correlogram. D and G: autocorrelograms of PTN and motor unit discharges respectively; bin width 1 ms and 2 ms respectively. E and F: recording of PTN and motor unit discharges during a single trial; PTN activity preceded the onset of precision grip (arrowed). Time bar 1s. H and J: superimposed plots of PTN and motor unit action potentials (Mu AP) respectively. Voltage calibrations are 100 μV in H and 200 μV in J.

action and, as far as we are aware, this represents the first direct experimental evidence for a CM input to a single motor unit in a conscious, moving monkey (Mantel & Lemon 1987). Most of the peaks we have observed were very brief (mean 1.9 ms); a few showed a 'tail' after the principal peak (e.g. Fig. 1B). The amplitude of the correlogram peak is usually expressed as the '*k* factor': the height of the peak divided by the baseline count. The *k* factors we have obtained from 30 correlograms with 12 different CM cells ranged from 1.2 to 3.0. Work in which both EPSPs and correlogram peaks have been studied (Gustafsson & Macrea 1984, Cope et al 1987) makes it possible to predict that peaks of this size probably originate from CM EPSPs with peak amplitudes of between 50 and 200 μV. The work by Redman & Walmsley (1983) on Ia synapses indicates that EPSPs of this magnitude could be produced by single synaptic contacts, as described by Lawrence et al (1985).

If a correlation peak was found between a given cortical cell and one motor unit in AbPB, a peak was generally found with most AbPB motor units. An example is shown in Fig. 2. This PTN produced PSF in the averaged surface EMG of AbPB (Fig. 2A), and correlation peaks were seen in correlograms made with all three discriminable motor units recorded in this muscle (Fig. 2B–D). Superimposed action potentials are shown in Fig. 2F–H. Inspection of the motor unit recordings showed that these potentials came from three *different* motor units, and this was confirmed by constructing motor unit-triggered averages (M.u.TA) of unrectified surface EMG; the resulting averages were all clearly different in form and amplitude (Fig. 2J–L).

The range of latencies for onset of correlation peaks in AbPB was 8.1–16.3 ms (mean 12.1 ms, $n = 27$). Different motor units, correlated with the same CM cell, had peaks with latencies varying by as much as 4 ms. This is probably due to differences in the conduction velocity of different motor units. This factor, combined with the temporal dispersion of the motor unit action potential in the surface EMG (compare Fig. 2F–H with J–L), probably explains the long duration of the facilitation observed in spike-triggered averages of surface EMG compared with the correlation peaks of individual motor units.

The motor neuron pools of the thenar muscles are arranged in long narrow columns in the C_8 and Th_1 spinal segments. Since we find positive correlations between single CM cells and most of the sampled AbPB motor units, we infer a longitudinal collateralization of corticospinal axons such as that described by Lawrence et al (1985).

Cheney: I would like to mention some of our recent work on the rubromotoneuronal system which is relevant to the issues we have considered here. Muir & Lemon (1983) reported that some corticospinal cells discharge intensely for precision grip but are relatively unmodulated for power grip, which involves all the fingers acting in concert. We have observed a similar specialization among some cells in the rubromotoneuronal system. Based on discharge relations to movement, we can define two populations of rubromotoneuronal cells: one is strongly modulated during a simple alternating wrist movement

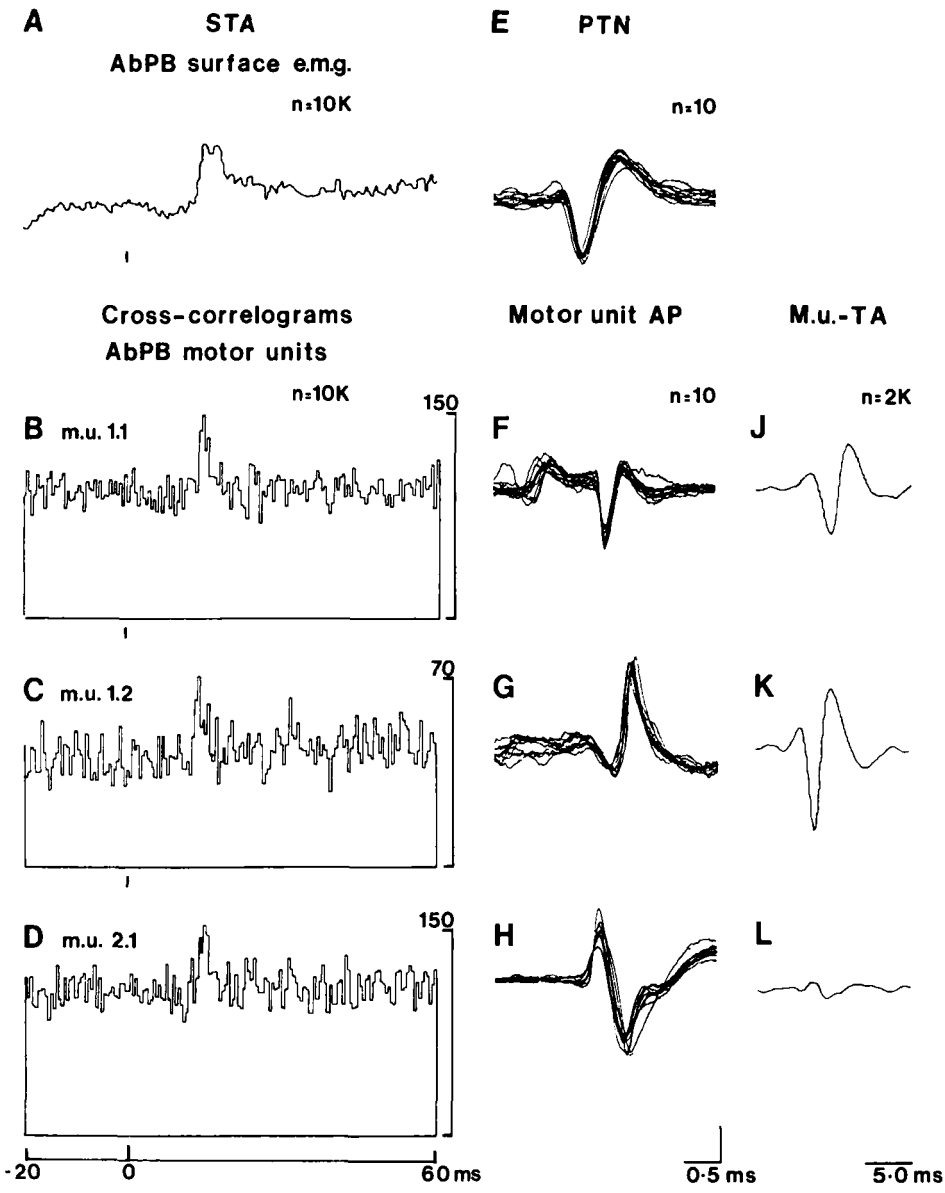

FIG. 2 (*Lemon*). A: spike-triggered average of abductor pollicis brevis (AbPB) surface EMG with respect to 10K spikes from a PTN. B–D: cross-correlograms between the same 10K PTN spikes (discharge at time zero) and discharges of three different motor units recorded from AbPB. E and F–H: 10 superimposed plots of action potentials recorded from the PTN and the three motor units respectively. Voltage calibration: 200 μV (F,G) and 500 μV (H). J–L: averages of unrectified, surface EMG of AbPB made with respect to 2000 action potentials of each individual motor unit. Note the differences in form of the resulting motor unit-triggered averages (M.u.TA).

task; the other shows little or no modulation during this task, despite producing strong post-spike facilitation of the forearm muscles involved in the task. On further testing, we found that the unmodulated cells were, in fact, strongly modulated in relation to a different task involving precision grip of a piece of food using the index finger and thumb. This represents another case in which target muscle activity was dissociated from that of the corresponding descending neuron, and again emphasizes that activation of descending neurons is dependent not only on muscle activity but also on the particular task being executed by those muscles.

Porter: Presumably those cells are being driven by some sort of descending connections with the red nucleus. Have you tried to see what happens to the discharges of rubromotoneuronal fibres when the cortex isn't driving them?

Cheney: The modulation of these rubromotoneuronal cells must be derived from either the cortex or the cerebellum, since those are the two major inputs to red nucleus. But we do not know which input is dominant under the conditions of our behavioural task.

Kuypers: The fibres from the motor cortex to the magnocellular or rather the rubrospinal red nucleus are limited in number, compared to the very large number of cerebellar interpositus fibres that terminate on those same neurons. Further, the cortical fibres have a tendency to terminate on the periphery of the dendritic tree, while the cerebellar fibres end on the dendrites and directly on the neuronal cell bodies. Therefore, the cerebellum must represent a very important driving source for these neurons.

Porter: Do you think the cerebellum takes the decision to move?

Kuypers: I do not know.

Marsden: One of the assumptions about the dissociation between firing of a pyramidal tract neuron and muscle activity under certain conditions is that exactly the same piece of muscle is involved in two separate movements. There is a good precedent for caution about that. Breakdown of the recruitment order and the size principle has been claimed to be demonstrated using the first dorsal interosseous muscle of the human hand as either an abductor or a flexor of the first finger. Reversal of recruitment order of motor units in the first dorsal interosseous can be demonstrated for those two movements and it was assumed that there was a breakdown in the size principle. It has been pointed out that different parts of that muscle are used to undertake that movement. Measurement of the activity of the whole muscle may be giving an incorrect answer if mechanically different parts of the muscle are being used. I don't know how you sort that out.

Kuypers: That is a very interesting observation. It would indicate that a muscle as defined anatomically is perhaps not a true muscle, and that an anatomical muscle actually consists of several 'functional muscles' which are used in different movements. Under such circumstances cortical neurons may be dealing with movements which are brought about by different 'functional muscles'.

Goldman-Rakic: I wonder whether you are really testing the essential function which the cortex has been specialized to do? The motor cortex is probably involved in fine digit control, but is it engaged at a monitoring level, as opposed to performing its quintessential function of integrating information from the environment and deciding to perform an action? The behavioural tests that we neuroscientists have to use to study cortical function in animals sometimes seem to bypass the voluntary aspect.

Thach: As you say, most of our monkeys are over-trained on the simple movement that we study. It becomes very stereotyped and automatic. The cerebellum plays a role in initiating these movements; whether it does so when the movement is less trained and more 'elective' is open to question.

Calne: Beevor has used an analogy between motor control in a ship and motor control in the brain. Everybody knows where the engine room is but nobody knows where the captain is. It seems to me that we have a lot of good engineers and people who understand the mechanism for turning the rudder but this is all execution. We still don't know anything about where or how the captain makes decisions. If one gets back to the concept of parallel processing in relation to control, some decision-making is still needed to integrate the parallel processing. Why is the cortex regarded as having the quintessential role of decision-making?

Lemon: I wish I knew the answer. The studies related to connectivity are only useful in the sense that they allow us to look at the cortical output. Beyond that you might say that studies of functional connectivity are not much use at all. However, if we are to understand which functions are localized in the cortex, we must first decide to study a particular group of cells which have a particular target in the animal's limb. Until we have made that step we cannot hope to see exactly what those particular cells are contributing to *their target muscles and to movement.* To poke an electrode into the cortex and see how the activity of a completely unidentified cell changes with a particular type of movement or whatever function you decide to study is, in my view, a lost cause.

Calne: What you are studying is what you are able to study—if an experiment to analyse the function of the cerebral cortex is possible, that is the experiment you do. That still leaves this big gap of the quintessential role of the motor cortex and its relationship with other components of the motor system. There has been major emphasis on cortical function but not so much on cortical relationships with other parts of the brain. From clinical evidence we know that these other parts clearly have an important role to play in both the execution and the initiation of movement.

Porter: We may come back to some of those matters later. We know what the motor neuron does. We are working towards an understanding of the way in which signals directed to the motor neuron, to make it do what it does, are organized in the brain. One of the output systems that is approachable by the electrophysiologists and that has some relevance to the clinical questions must be the part of the cortex that is most directly connected to the motor neuron

population. Tom Thach will tell us later about some of the other connections that are of interest clinically.

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