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CHAPTER 11

Neural mechanisms underlying corticospinal and rubrospinal control of limb movements

Paul D. Cheney[1], Eberhard E. Fetz[2] and Klaus Mewes[1]

[1] *Department of Physiology and Ralph L. Smith Research Center, University of Kansas Medical Center, Kansas City, KS 66103 and* [2] *Department of Physiology and Biophysics, University of Washington, Seattle, WA, 98195, U.S.A.*

Introduction

Commands for movements of the limbs are transmitted from the brain to the spinal cord through descending systems. Some neurons of these systems contact motoneurons directly and will be referred to as premotor neurons. The anatomical organization, synaptic effects and discharge properties of premotor neurons are of central importance to understanding how the brain controls movement. This paper reviews our current understanding of the organization and functional properties of descending systems and recent advances that have come from single unit recording in awake monkeys using new techniques that reveal the synaptic connections of single premotor neurons with motoneurons of agonist and antagonist muscles. Emphasis will be placed on the role of descending systems in the control of limb movements, although it is recognized that locomotion and other motor behaviors involving axial, head and/or facial muscles may involve similar principles. Emphasis will also be on motor control in primates although relevant data from the cat and other species will be included where no primate data is available.

Identification of descending systems controlling limb movements

In the history of work on motor function of the CNS, a variety of techniques have been used to identify brain structures projecting to motoneurons. Fritsch and Hitzig (1870) first evoked muscle contractions by applying electrical stimulation to the motor area of cerebral cortex in the dog. Recording movements evoked by gross electrical stimulation of the brain surface was followed by more elaborate techniques such as measurement of the actual forces produced in isolated muscles by focal surface stimulation of the cortex (Chang et al., 1947). The historical progression toward using more refined and sensitive methods to detect cortical output ultimately led in the 1960's to recording synaptic potentials evoked in motoneurons from electrical stimulation of the cerebral cortex or subcortical structures (Phillips and Porter, 1977). Most recently, considerable progress has been made in developing microstimulation techniques for more refined and discrete activation of descending neurons (Asanuma and Sakata, 1967). This effort has culminated with methods capable of detecting the excitatory and inhibitory effects of single neurons on muscle activity in the awake animal during task performance (Fetz et al., 1976; Cheney, 1980; Fetz and Cheney, 1980; Buys et al., 1986).

Paralleling these electrophysiological developments, anatomical studies became increasingly more refined and sensitive. Degeneration methods provided the first clear evidence concerning the origin of various spinally projecting neurons

(Brodal, 1981). However, the application of various neuroanatomical tracers such as horseradish peroxidase (HRP) has yielded enormous progress in understanding the origin and organization of descending systems.

Holstege (this volume, Chapter 14) has divided spinal cord projecting descending systems into two categories: somatic and limbic. This subdivision recognizes not only the traditional somatic descending systems but also substantial recent evidence for another group of descending systems which arise from limbic structures (Holstege, 1987). Traditional descending systems include the corticospinal, rubrospinal, reticulospinal, vestibulospinal, tectospinal and interstitiospinal systems (Fig. 1). These systems are known to: 1) exert powerful, relatively direct excitatory and inhibitory synaptic effects on motoneurons, 2) exhibit somatotopic organization (except the reticulospinal system), and 3) be highly modulated in relation to the kinematic features of movement. Limbic descending systems arise from locus coeruleus, raphe nuclei, and hypothalamic nuclei. These neurons are also labelled by spinal cord injections of the retrograde tracer HRP. Similarly the spinal terminations of these neurons can be labelled by the anterograde tracer ^{3}H-leucine (Holstege, this volume). Like the somatic descending systems, the limbic systems also terminate among motoneurons but are believed to influence motoneuron excitability in a more tonic fashion related to behavioral state and/or to exert some trophic influence over motoneurons and spinal cord circuitry. This paper will focus on the somatic descending systems involved in the control of muscle contraction and movement parameters.

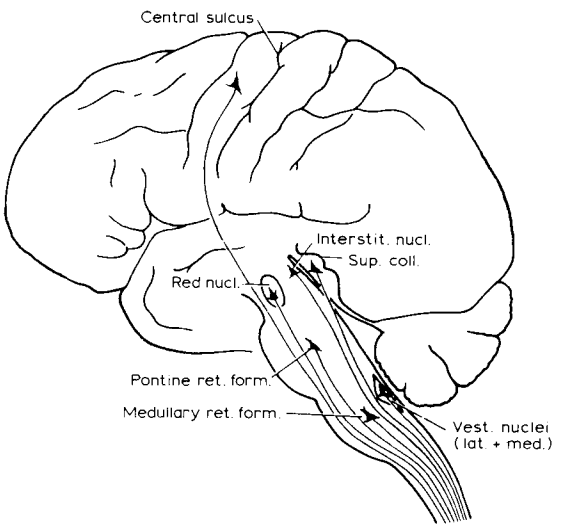

Fig. 1. Origin of brain descending systems containing neurons that contact spinal motoneurons. (Modified from Brodal, 1981)

It is clear that not all descending systems are equipotent in their access to motoneuron pools of the limb when viewed along a continuum extending from most distal to proximal and finally to most axial. This was recognized very early in mapping studies of motor cortex, which revealed that distal muscles, although much smaller in mass than more proximal and axial muscles, were represented by a much larger area of cortex. The classic studies of Lawrence and Kuypers (1968a,b) also showed that deficits from lesions of the pyramidal tract (corticospinal) and rubrospinal system are most severe and lasting for movements of the distal extremity whereas deficits from lesions of the reticulospinal and vestibulospinal systems are most severe for movements involving proximal and axial muscles. Based on these findings and the different anatomical locations of these tracts in the spinal cord, Lawrence and Kuypers divided descending systems into a dorso-lateral component, which included the corticospinal and rubrospinal systems, and a ventro-medial component which included the reticulospinal and vestibulospinal systems. One of the basic findings of their studies was that lesions of the corticospinal system resulted in permanent loss of relatively independent finger movements (RIFMs) and severe distal weakness; however, the monkey could maintain an upright posture, run and climb the side of the cage with little or no difficulty. Deficits from corticospinal lesions were less severe if the rubrospinal system was intact. Similarly, deficits from rubrospinal system lesions were virtually unnoticeable if the corticospinal system was intact. In contrast, lesions of the ventro-medial system rendered the monkey immobile and unable to maintain an upright posture.

In this respect, such lesions were much more disabling than those of the dorso-lateral system.

This lesion work and other anatomical and electrophysiological studies emphasize the importance of the dorso-lateral descending systems in the control of distal musculature and the mediolateral systems in the control of proximal and axial muscles. Consequently, studies on descending control of limb movements, appropriately, have focussed on the corticospinal and rubrospinal tracts. However, it should be noted that the reticulospinal and vestibulospinal systems also make synaptic linkages with motoneurons of distal limb muscles (see later section of this paper) and their involvement in limb movements should not be overlooked.

Categories of limb movements

The limbs participate in a wide range of movements which can be classified in terms of the various control problems they present to the neural apparatus. The following factors may all be of significance in determining underlying neural mechanisms and shaping the relevant motor program (Cheney, 1985):

1. Movement speed: slow (ramp) versus ballistic (Delong and Strick, 1974).
2. The number of joints involved: simple (1 joint) versus compound (coordination of two or more joints).
3. The type of feedback guidance: somesthetic, vestibular, auditory, visual or some combination of these.
4. Movement complexity: for instance the number of discrete steps in a movement sequence (Roland et al., 1980) and whether movement targets are remembered or visible.
5. The mechanism by which the movement is stopped: self terminated or externally terminated.
6. Accuracy constraints.
7. Muscle groups involved: 1) distal versus proximal/axial, 2) flexors versus extensors, and 3) fast versus slow muscles (Preston et al., 1967; Burke et al., 1970).
8. The degree of learning and mental concentration required, ranging from the most automatic or stereotyped (e.g., respiration and locomotion) to the least automatic such as playing the piano (Phillips and Porter, 1977).

Of all these factors, the subdivision of movements on a continuous scale from most automatic to least automatic seems particularly useful. This distinction was first proposed by Hughlings Jackson (as cited in Phillips and Porter, 1977) and seems to be a key factor in determining the involvement of various descending systems in movement. For example, lesions of the corticospinal system in monkeys interfere with the use of the hand for skilled movements such as removing a food morsel from a narrow well but the same monkeys show no obvious deficit in using the hand for more automatic locomotor movements such as running or climbing the side of the cage (Tower, 1940). In evolution, the forebrain has come to occupy a position of supreme importance for executing the least automatic, most skilled movements. Accordingly, the severity of deficits in skilled movements following lesions of the pyramidal system increases with the size of the forebrain (Phillips and Porter, 1977).

Synaptic linkage from descending premotor neurons to spinal motoneurons

The synaptic linkage between neurons of descending systems and alpha motoneurons has been investigated using: 1) intracellular recording of EPSPs and IPSPs evoked by stimulation of descending systems (Table I), and 2) facilitation or suppression of the muscle spindle Ia monosynaptic reflexes after stimulation of a descending system (Table I; Preston et al., 1967; Asanuma and Sakata, 1967). Intracellular recordings provide precise timing and magnitude information about EPSPs and IPSPs associated with different descending systems. However, because impaling individual motoneurons is technically difficult, only limited intracellular data is available on the distribution of premotor EPSPs and IPSPs to dif-

TABLE I

Summary of results from studies of synaptic effects from premotor descending systems on motoneurons

Primate	Forearm digits		Wrist		Elbow		Shoulder		Hindlimb digits		Ankle		Knee		Hip		Neck	Axial	Facial
	F	E	F	E	F	E	F	E	F	E	F	E	F	E	F	E			
Corticospinal																			
Intracellular	+m	+m	+m/−	+m/−	+m/−	−/+m			+m	+m	+m/−	+m/−	+m/−	+m/−		+m			
Ia conditioning	+m	+m	+m/−	+m/−	−/+	+/−					+m/−	+m	+m/−	−d	+m/−	−d			
Spike trig. ave.	+/−	+/−	+/−	+/−															
Rubrospinal																			
Intracellular									+m		+m	+m/− (fdl) −d/+ (gsol)							
Spike trig. ave	+/−	++/−	+/−	++/−															
Reticulospinal*																			
Intracellular											+m/−	+m/−	+m	+m					
Vestibulospinal*																			
Intracellular										0		+m		+m					

Cat	Forearm digits		Wrist		Elbow		Shoulder		Hindlimb digits		Ankle		Knee		Hip		Neck	Axial	Facial
	F	E	F	E	F	E	F	E	F	E	F	E	F	E	F	E			
Corticospinal																			
Intracellular	+d	−/+d	+d/−t	+d/−t	+d/−t	+d/−t −d,t	+d	−/+d										+d, −d	
Ia conditioning	+	+	+/−	+/−	+/−	−slow +/− (fast)					+d	−d (slow) +/− (fast)	+d	−d	+d/−	−d			
Rubrospinal																			
Intracellular			+d/−		d/−t	+d/−t			−	+d/−	+d/−	−sol +mg −/+fdl +−pl	+d/−	+d/−	+d/−	+d/−			+m
Reticulospinal																			
Intracellular	+m 38%	+m/− 38%	+m/− 38%	+m/− 38%	+m/− 78%	+m/− 50%			+m/− 50%	+m/− 70%	+m/− 86%	m/− 85%	+m/− 60%	−d/+ 50%		+m/−d 60%	+m 85% −m 68%	+m 72% −m −d
Vestibulospinal																			
Intracellular	+p/−p	+p/−p	+p/−p	+p/−p	+p/−p	+p/−p			−p	+m	−d	+m +p	−d	+m +p		+m +p	+m −m	+m −m

m = monosynaptic, d = disynaptic, t = trisynaptic, p = polysynaptic, + = excitatory, − = inhibitory, +/− = mixed with predominant effect listed first, % = % of motoneurons receiving effects. Methods used to examine synaptic effects on motoneurons include intracellular recording, Ia reflex conditioning and spike triggered averaging of EMG activity (SpTA). Excitatory and inhibitory components of mixed effects are probably generated by different premotor neurons. All inhibitory effects probably have a minimal disynaptic linkage. Data from Alstermark and Sasaki (1985), Alstermark et al. (1985), Baev (1971), Burke et al. (1970), Clough et al. (1968), Grillner et al. (1971), Hongo et al. (1969), Illert et al. (1976a,b), Illert and Wiedemann (1984), Jankowska et al. (1975), Landgren et al. (1962a,b), Peterson et al. (1978, 1979), Peterson (1979), Phillips and Porter (1964), Preston (1961), Preston et al. (1967), Shapovalov (1972), Shapovalov et al. (1971, 1973), Wilson et al. (1970), Wilson and Yoshida (1969), Yu et al. (1972). SpTA data from Cheney et al. (1988), Fetz and Cheney (1980), and Kaser and Cheney (1985).

ferent motoneuron pools. Monosynaptic reflex testing also provides relatively precise timing information on synaptic events. However, unlike intracellular recording, which yields detailed information about synaptic input to a single motoneuron, monosynaptic reflex testing provides a measure of the net effect of the stimulated premotor neurons on an entire population of motoneurons, for example motoneurons of a specific muscle.

Table I summarizes results from existing studies of the distribution of synaptic effects from premotor descending systems to motoneurons of different muscles in cats and primates – the two most widely studied species. The data was derived from both intracellular and monosynaptic reflex testing experiments. For comparison, data derived from recent work using the technique of spike-triggered averaging of EMG activity in awake monkeys is included. This new approach to examining the correlational linkages from single premotor cells to motoneurons will be considered in detail in later sections. Despite the critical role of descending systems in the control of limb movements, quantitative detail about the synaptic connections of these systems is relatively sketchy, especially in primates. Nevertheless, some generalizations concerning the synaptic effects of descending systems on motoneurons have emerged:

1. In primates, all descending systems make monosynaptic connections with at least some motoneurons. The proportion of motoneurons receiving monosynaptic corticospinal or rubrospinal input is 100% for the most distal muscles and diminishes for more proximal muscles. (Clough et al., 1968; Phillips and Porter, 1977). The magnitudes of corticospinal EPSPs vary in a parallel manner for motoneurons of distal and proximal muscles. Conversely, the incidence of monosynaptic input to motoneurons of proximal and axial muscles is greater for the ventro-medial descending systems than dorso-lateral systems.
2. In the cat, the dorso-lateral descending systems have a minimum disynaptic linkage to motoneurons, although some monosynaptic connections to muscles of the digits have been reported (Enberg, 1963; McCurdy et al., 1984). In the rat, about half of distal forelimb and hindlimb motoneurons receive monosynaptic input from the corticospinal system (Elger et al., 1977; Janzen et al., 1977). These connections may be related to the greater development of independent digits in the rat than in the cat and the rat's greater skill in their use.
3. The fast or slow nature of a muscle, and perhaps individual motor units within a muscle seems to be an important factor determining the synaptic action of the rubrospinal and corticospinal systems (Burke et al., 1970; Preston et al., 1967). Fast, phasic muscles such as the medial gastrocnemius are facilitated from cortex, whereas slow postural muscles such as soleus are predominantly inhibited. Within the gastrocneumius muscle, fast and slow motor units are also distinguished by the corticospinal and rubrospinal systems with fast units receiving facilitation and slow ones inhibition (Burke et al., 1970).
4. Information on unitary EPSPs from neurons of descending systems has been limited and fragmentary. Asanuma and Rosen (1972) reported an individual corticospinal EPSP of 100 μV. This experiment is technically much more difficult than the detection of individual EPSPs in motoneurons from muscle afferents partly because the identity of the premotor neuron's target muscles is uncertain. More systematic information on the magnitude and distribution of individual EPSPs and IPSPs, analogous to that which exists for spindle afferent postsynaptic potentials would clearly be of interest. The synaptic effects of individual corticospinal neurons on single motor units have been detected with cross-correlation techniques (Mantel and Lemon, 1987; Fortier et al., 1989).
5. As is clear from Table I, large gaps exist in our knowledge of input to motoneurons from

descending systems, particularly in the primate. For example, only corticospinal input has been investigated for forelimb muscles in the primate. In view of the large number of monkeys required for intracellular experiments, it seems unlikely that significant new studies can be expected. However, while not providing the same level of quantitative information about synaptic effects, spike-triggered averaging of EMG activity does yield detailed information about the sign, magnitude and distribution of synaptic effects on motoneurons and in conjunction with response properties of the same cells, provides a powerful approach toward achieving a more complete knowledge of premotor descending control of different muscles.

Spike-triggered averaging of EMG activity: Method for identifying the output properties of single premotor neurons

Rationale and procedure

The introduction of recording from single neurons in awake animals by Jasper et al. (1958) and its application to issues related to the cortical control of movement by Evarts (1966) has brought about great progress in understanding the functional role of descending systems. However, this approach has always been limited by the lack of information about the axonal projections of individual neurons. Ideally, the discharge of a particular premotor neuron should be interpreted in relation to its synaptic effects on motoneurons of its target muscles. With the introduction of spike-triggered averaging of EMG activity in awake animals, it has become possible to examine for the first time, not only the movement related discharge of single premotor neurons, but also the organization of their output effects on the activity of agonist and antagonist motoneurons.

To identify, in awake monkeys, cortical premotor cells with a functional linkage to motoneurons, Fetz and Cheney (1980) developed the method of spike-triggered averaging of rectified EMG activity. The rationale for this method is as follows. Premotor neurons with a direct excitatory synaptic linkage to motoneurons will produce individual EPSPs at a fixed latency following discharge of the premotor cell. The magnitude of these EPSPs will be too small to reliably discharge the motoneuron with each occurrence. Nevertheless, the EPSPs will depolarize the membrane, bringing the motoneuron closer to firing threshold and transiently increasing its firing probability. EMG activity is the sum of the spike trains of a population of motor units within a muscle. Since the neuromuscular junction normally has a high safety factor characterized by a one-to-one relationship between motoneuron and muscle fiber action potentials, motor unit spike trains provide an accurate reflection of the firing of spinal motoneurons. Therefore, the synaptic effect of a single premotor cell on motoneuron firing probability can be detected by averaging the EMG activity associated with many premotor cell spikes. These events are illustrated in Fig. 2 for the effects of a single muscle spindle Ia afferent on the firing probability of a target motoneuron and average EMG activity of the corresponding muscle.

Further details of the spike-triggered averaging procedure are illustrated in Fig. 3. In this case, the discharge of a single cortical neuron was recorded in relation to the extension phase of a ramp-and-hold wrist movement. EMG activity was full-wave rectified and the 30 ms segments extending from 5 ms before the trigger spike to 25 ms after the spike were digitized at 4 KHz and averaged. The EMG associated with each of the first five spikes in the record is shown (perispike EMG) along with the cumulative average of these EMG segments. Note that the prominent waveforms occurring about 10 ms after the first cortical spike are largely lost after the EMG segments associated with the first five spikes are averaged. However, an average of 2,000 spike events shows a clear peak beginning at a latency of 6 ms. Such a transient increase in average EMG activity is referred to as postspike facilitation (PSpF) and is interpreted as evidence of an underlying synaptic linkage between the trig-

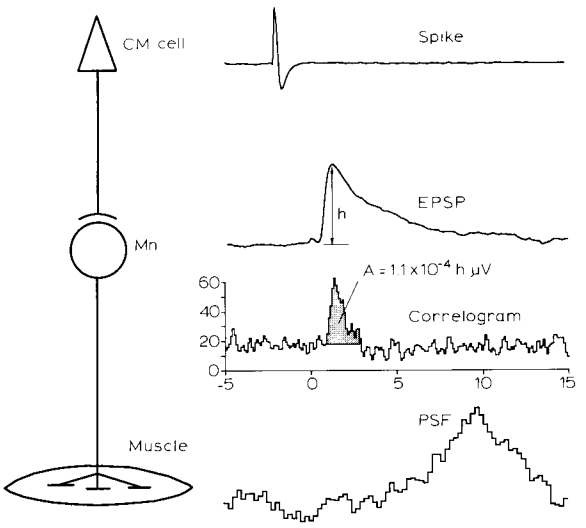

Fig. 2. Events mediating the postspike effects of a premotoneuronal cell connected monosynaptically to motoneurons. Spike discharges are followed by unitary EPSPs and an increase in motor unit firing probability reflecting the derivative of the EPSP. PSpF in the corresponding average of rectified EMG activity is delayed by conduction time from the spinal cord to the muscle. The area of the correlogram peak was found to be proportional to the height of the EPSP. The time course of PSpF is greater than the correlogram peak for a single motor unit because: 1) PSpF is the sum of facilitation in several motor units with different conduction velocities, and 2) the duration of the motor unit potential waveform contributes to PSpF. Data shown is for a muscle spindle Ia afferent (Cope et al., 1987). Figure from Fetz et al. (1989)

ger neuron and motoneurons. Cortical neurons yielding PSpF are referred to as corticomotoneuronal or CM cells; red nucleus neurons yielding PSpF are referred to as rubromotoneuronal or RM cells.

The strength of the spike-triggered averaging method is that it can be applied in awake animals enabling the identification of cells that are causally involved in producing muscle activity. The response properties of these motor output neurons can then be investigated during specific motor tasks. The response properties of these neurons are particularly important in understanding the contribution of descending systems to movement. Thus, the spike-triggered averaging method enables parallel investigation of the synaptic organization of premotor cells with motoneurons and investigation of relations between cell discharge and specific kinematic parameters of movement.

Spike-triggered averaging of rectified EMG activity is capable of revealing a cell's correlational linkages with motoneurons. However, compared to spike-triggered averages of intracellularly recorded synaptic potentials, it provides less precise information about the timing of synaptic events and, hence, the number of synapses in the linkage. Moreover, although postspike effects can be quantified to provide some measure of the relative strength of an underlying synaptic effect, the magnitudes of PSpF must be interpreted with caution. For example, PSpF from a premotor neuron that facilitated a small fraction of recorded motor units strongly might be similar in magnitude to PSpF from a neuron that facilitated a large fraction of the recorded motor units weakly. Cross correlating premotor cell discharge with single motor units avoids these ambiguities and provides a more exact and interpretable measure of the strength of a synaptic effect. However, recording isolated motor units is more difficult, and the probability of finding an effect may be low if the motor unit field of a premotor neuron is small.

Reliability and reproducibility of postspike effects

Identifying features in spike-triggered averages can sometimes be difficult, and a variety of approaches have been used to assess their reliability. A conceptually simple but statistically rigorous approach would be to compile several consecutive averages (five or more) all with the same number of trigger events (Kasser and Cheney, 1985). The effects in these averages could then be tested statistically by comparing them to averages computed under the same conditions but with random triggers (Fig. 4). Although this might be ideal from a statistical viewpoint, it requires an extensive amount of redundant data, which cannot always

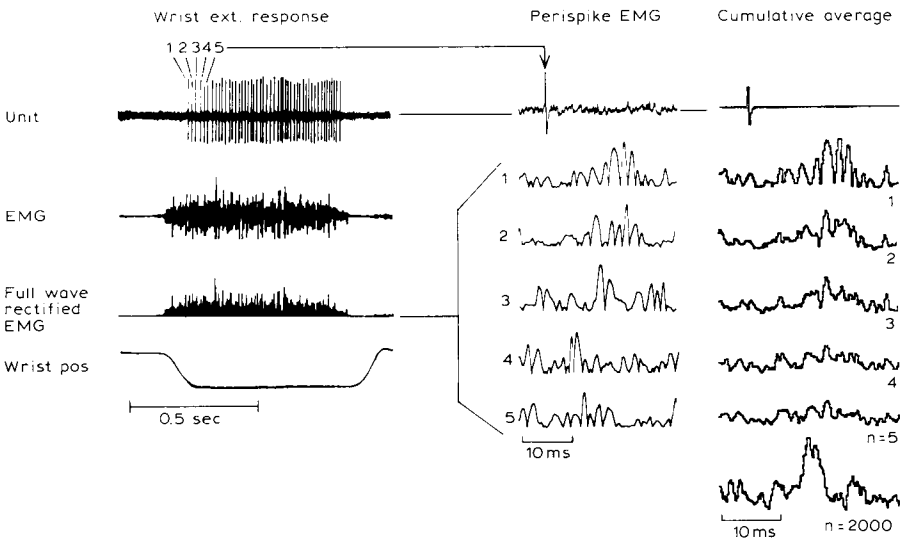

Fig. 3. Spike-triggered averaging procedure used to detect postspike effects from single premotor neurons. Spikes associated with movement are used to trigger averages of rectified EMG activity. The response at the left illustrates the discharge of a cortical cell and normal and rectified EMG activity of one agonist muscle associated with wrist extension. Thirty millisecond segments of EMG activity associated with each premotor cell spike are averaged. The cumulative average of EMG segments associated with the first five cell spikes are shown in the column at the right. Although no clear effects are present after five sweeps, the average of 2000 events shows a clear, transient postspike facilitation. (From Fetz and Cheney, 1980)

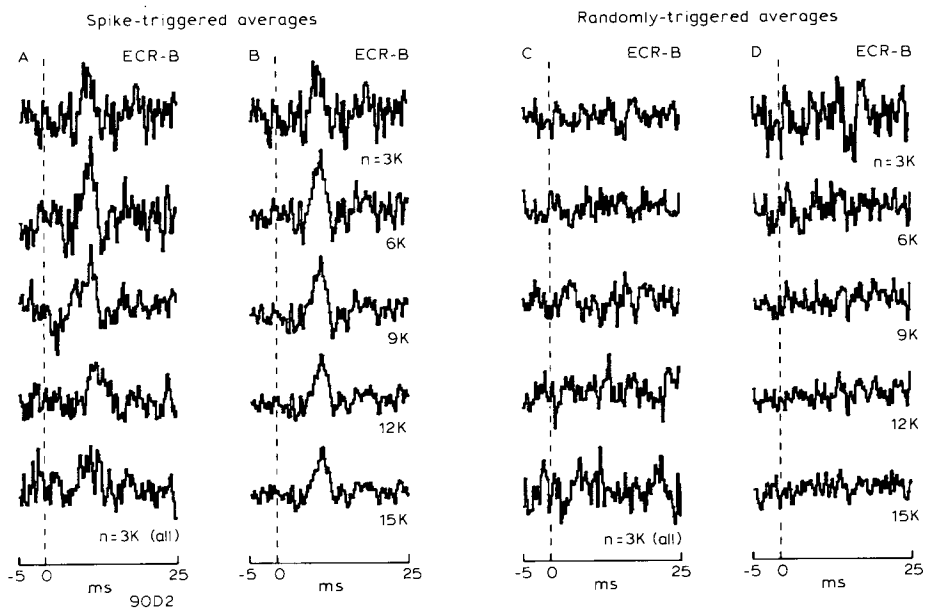

Fig. 4. CM cell spike-triggered averages and randomly-triggered averages of the same agonist muscle. Columns A and C show five consecutive averages of 3000 trigger events. Columns B and D show the cumulative averages of the records in A and C. Note the presence of clear PSpF in each 3K spike-triggered average and the absence of a clear effect in the randomly-triggered average. Also note the continuous improvement in signal-to-noise ratio with increasing numbers of trigger events. (From Kasser and Cheney, 1985)

be obtained during actual recording. Furthermore, this procedure seriously limits recording time available to complete a diverse protocol of tests. As a compromise, a similar but abbreviated approach to analysis of significance can be applied. The reproducibility of an effect must be demonstrated by showing that: 1) it appears in at least two consecutive averages of 2000 trigger events or more, or, more commonly, 2) that the signal to noise ratio of an effect improves as more sweeps are averaged (Botteron and Cheney, 1989). Statistical significance of facilitated or suppressed segments of a particular average is assessed by *t*-test comparisons with points in the baseline segment preceding the trigger spike (Fetz and Cheney, 1980; Kasser and Cheney, 1985). The onset and termination of an effect is measured as the point where the smoothed envelope of an effect crosses a line representing one or two standard deviations of the baseline points (Fig. 5). All averages are based on at least 2000 trigger events, although the number of trigger events is usually much higher.

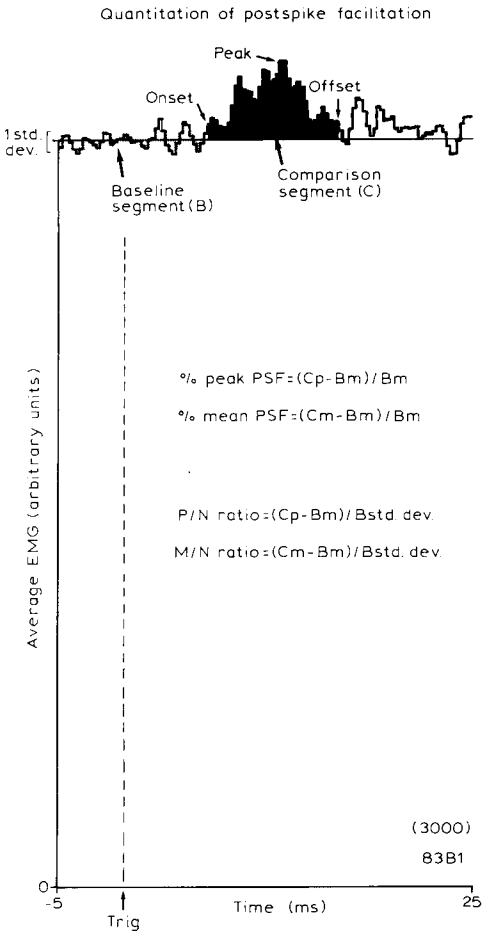

Fig. 5. Methods of quantifying postspike and poststimulus effects. The change from baseline of the facilitated or suppressed segment may be expressed as a percent of baseline or as a signal-to-noise ratio. In both cases, magnitude may be measured as either a peak or mean value. Bm = baseline mean, Cp = peak value, Cm = mean value in C segment. A related approach to quantifying postspike effects is to calculate a ratio of the peak effect to base line (referred to as k value) or the mean effect to base line (referred to as k′) (Mantel and Lemon, 1987)

Quantifying postspike effects

Postspike effects in averages of rectified EMG activity can be quantified by two different methods (Fig. 5). One measure expresses the increase or decrease in average EMG activity as a percent of baseline; the other expresses the increase or decrease as a signal-to-noise ratio. In both cases, facilitation and suppression can be measured as a peak or a mean of the facilitated or suppressed points. Signal-to-noise measures have the advantage of being independent of baseline level making comparisons of the strength of effects under widely varying conditions possible (Cheney and Mewes, 1985). Postspike effects in averages of EMG activity seem to obey the principle that applies generally to signal averaging: signal-to-noise ratio increases in proportion to the square root of the number of sweeps or trigger events. This has been directly validated for both PSpF and PSpS. For example, in Fig. 4, the peak-to-noise ratio of PSpF at 12,000 trigger events is double that at 3000 trigger events. Quantitative comparisons using signal-to-noise ratio measures must be normalized to a standard number of trigger events using the proportionality between magnitude and square root of the number of trigger events.

Detection of inhibitory effects with spike-triggered averaging of EMG activity

The utility of the spike-triggered averaging technique extends beyond the detection of ex-

citatory synaptic effects. Cheney et al. (1982) and Kasser and Cheney (1985) first showed that postspike suppression (PSpS) of antagonist muscles from CM cells is detectable with spike-triggered averaging of rectified EMG activity. Fig. 6 is an example of PSpS from a cortical cell whose discharge increased during wrist flexion. Spike-triggered averages show clear facilitation of multiple agonist muscles (extensors) and reciprocal suppression of the antagonists. FCR was strongly suppressed at a latency slightly longer than the PSpF of the extensors. Additional flexors showed weaker but clear PSpS. The average magnitude of PSpS is about half that of PSpF and the onset latency of PSpS is about 3 ms longer than that of PSpF. These findings are consistent with involvement of interneurons in mediation of PSpS. Kasser and Cheney (1985) concluded that PSpS is probably mediated by collaterals of CM cells to Ia inhibitory interneurons, since corticospinal input to these interneurons is well established (Jankowska and Tanaka, 1974; Jankowska et al., 1976). CM cell collaterals to other cortical cells with direct inhibitory synapses on motoneurons is unlikely because monosynaptic IPSPs from motor cortex have never been reported. Therefore, detection of effects with spike-triggered averaging of EMG activity is not limited to monosynaptic linkages but also includes less direct linkages. Additional non-obligatory synapses, however, will weaken the strength of the primary correlation peak and will broaden its time course (Fetz and Cheney, 1980). Consequently, the clearest effects will generally be those mediated by monosynaptic linkages. Comparison of PSpF with reciprocal PSpS confirms this view (Kasser and Cheney, 1985).

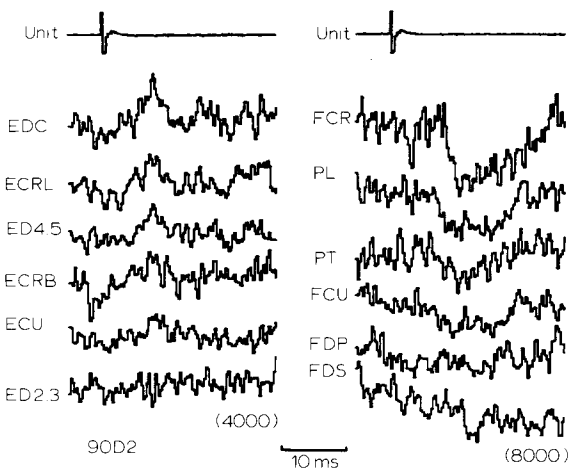

Fig. 6. Spike-triggered averages for a reciprocally organized CM cell. This cell produced clear PSpF in multiple extensor muscles and clear PSpS in multiple flexor muscles. (Kasser and Cheney, unpublished)

The fact that disynaptic inhibitory linkages are detectable with spike-triggered averaging raises the question of detectability of disynaptic excitatory events. Preliminary studies of postspike effects from cells in motor thalamus of the monkey show some cases of clear, reproducible PSpF (Fig. 7, from unpublished work of Mewes and Cheney). Since cells of motor thalamus are known to project monosynaptically to pyramidal tract cells, the minimum synaptic linkage to motoneurons is disynaptic (Amassian and Weiner, 1966; Araki and Endo, 1976; Purpura et al., 1964). Therefore, disynaptic excitatory linkages are also clearly detectable with spike-triggered averaging of EMG activity. Sensitivity capable of revealing non-monosynaptic linkages is an asset in so far as it enables identification of cells, such as those in motor thalamus, that provide input to premotor neurons of descending systems and ultimately have powerful effects on muscle activity. The relations of these cells to movement and to the discharge of premotor neurons to which they project can then be investigated knowing that the cells are causally involved in the movement. The contribution of disynaptic linkages to PSpF from CM and RM cells must also be considered possible.

Interpretation of cross correlograms in relation to underlying EPSPs

Postspike effects are generated only from EPSPs that cause the motoneuron to fire or IPSPs that prevent motoneuron firing. It should be noted that spike-triggered averaging of EMG activity requires that both the trigger neuron and muscle are simultaneously active. In this case, the postsynaptic potentials from the trigger cell will be superimposed on motoneuron membrane trajectories associated with repetitive firing in which voltage threshold for spike initiation is approached as a

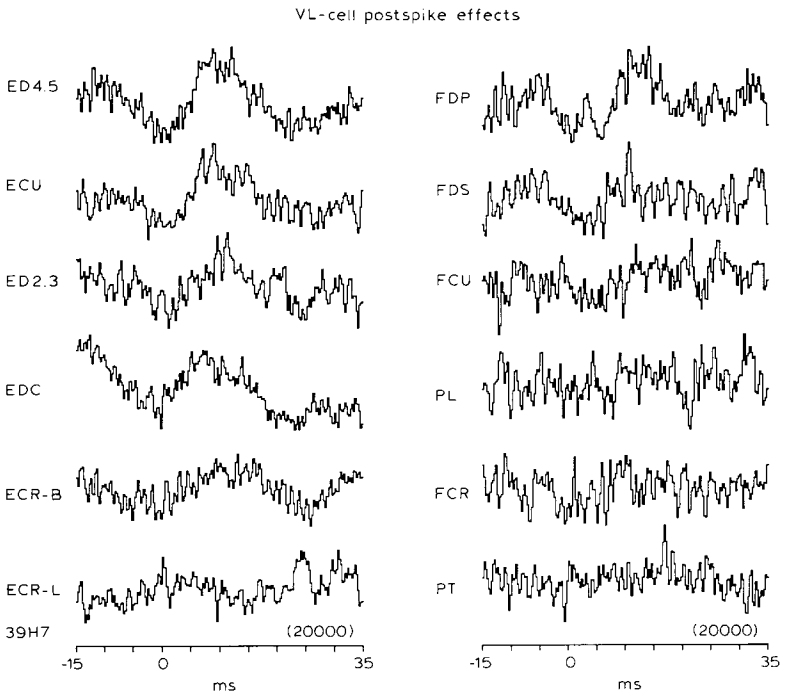

Fig. 7. Postspike facilitation of multiple extensor muscles from a cell in motor thalamus of a monkey. Minimum linkage for these effects is disynaptic. Number of trigger events in parentheses. (Mewes and Cheney, unpublished)

ramp trajectory (Fig. 8). Only EPSPs that depolarize the motoneuron to threshold or IPSPs that prevent its depolarization to threshold will contribute to postspike effects observed in averages of EMG activity. Since the motoneuron membrane potential moves toward threshold during the rising phase of an EPSP, the increased firing probability of a motoneuron is associated primarily with the rise of the EPSP. The advanced occurrence of these spikes in the correlogram peak leaves a subsequent trough, that is, a period of reduced firing probability. Consequently, the changes in firing probability of a motoneuron associated with the EPSP reflect primarily the derivative of the EPSP rather than the EPSP itself (Fetz and Cheney, 1980). The trough will be shallower than the peak because the interval from which spikes are drawn is longer than the rising phase of the EPSP. These predictions were directly confirmed in cat motoneurons: the increase in motoneuron firing probability following electrical stimulation of Ia afferents in the peripheral nerve coincided with the rising phase of the compound EPSP (Fetz and Gustafsson, 1983). The mean half-width of correlogram peaks (0.65 ms) agreed closely with the mean half width of the EPSP derivatives (0.55 ms) but not with the mean half width of the EPSPs (4.31 ms). Large EPSPs always produced correlogram peaks that best matched their derivatives, whereas small EPSPs in the presence of synaptic noise often produced correlogram peaks that were wider than their derivatives. The duration of correlogram peaks for single motor units from CM cells spikes (Mantel and Lemon, 1987) and microstimuli applied in the vicinity of CM cells (Palmer and Fetz, 1985b) also had durations consistent with the derivative of the CM -EPSP rather than the EPSP itself.

More recently, Cope et al. (1987) examined the shapes of correlogram peaks produced by the smaller amplitude, fast rising unitary EPSPs evoked from single Ia afferent fibers. Again, the dura-

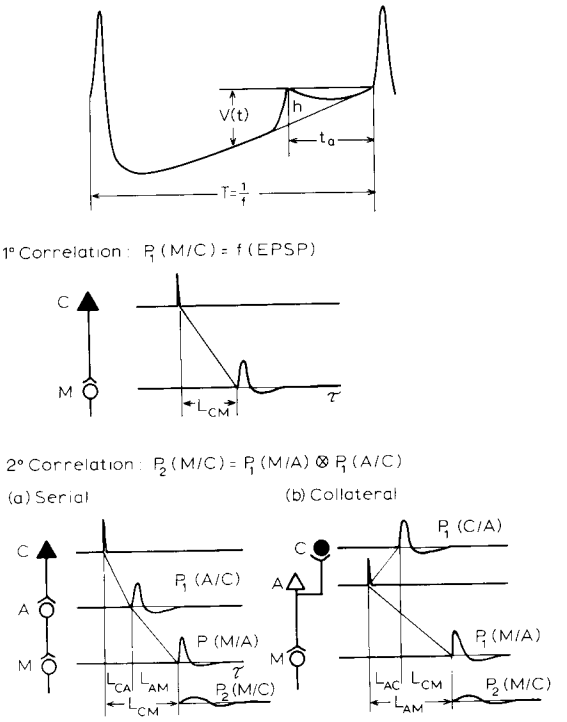

Fig. 8. Relation between synaptic connections and cross-correlogram features. *Top*: schematic representation of EPSP superimposed on membrane potential of a repetitively firing motoneuron; t_a = time during which EPSP may trigger a motoneuron action potential. *Bottom*: neural connections which could yield PSpF. Monosynaptic connection produces primary correlation; disynaptic links produce secondary correlations that is the convolution of underlying primary correlations (From Fetz and Cheney, 1980)

tion of the correlogram peak could be accounted for largely by a component proportional to the derivative of the EPSP (Fig. 2). The correlogram peak area was best correlated with EPSP amplitude. In SpTAs of multiunit EMG activity, the onset of PSpF is delayed from the onset of the motoneuron correlogram peak due to conduction time to the muscle. PSpF is also much broader than the motor unit correlogram peak because of contributions from the motor unit potentials themselves (about 4 ms) and contributions resulting from the summation of potentials from multiple facilitated motor units with different conduction times to the periphery.

IPSPs produced primary correlogram troughs followed by compensatory peaks (Fetz and Gustafsson, 1983). Again, this is consistent with the ramp trajectory of membrane potential toward threshold in a repetitively firing motoneuron. The IPSP delays the occurrence of spikes, forming a correlogram trough followed by a compensatory peak. These delayed spikes will tend to collect at a later point forming the compensatory peak. Unlike correlogram peaks associated with EPSPs, correlogram troughs associated with IPSPs were wider than the IPSP derivatives and did not correspond to any linear combination of the shape of the IPSPs or its derivative. Another significant difference between EPSPs and IPSPs is the increase in magnitude of the IPSP near threshold; this means that IPSPs having the same amplitude as EPSPs when measured at rest actually have a three-fold greater effect when the motoneuron is firing.

Contribution of discharge synchrony to postspike effects

A question raised frequently concerning the interpretation of spike-triggered averages is the degree to which postspike effects may be mediated by other cells that are synchronized with the trigger cell. For example, a cell lacking axonal connections with motoneurons could, nevertheless, show PSpF if its discharge was sufficiently synchronized with a true premotor cell. Synchrony might result from collateral synaptic input (Fig. 8b) or from shared input from the same afferent axons. PSpFs resulting from synchrony with a true premotor cell arising from axon collaterals or common synaptic input constitute second and third order correlations respectively (Fetz and Cheney, 1980). Such higher order correlations are the convolution of the individual primary correlations in the circuit. In the case of collateral synaptic input to a non-premotor cell (C in Fig. 8b), the primary correlations are between cell C and A (the actual premotor cell) and between A and the motoneuron

(M). Common synaptic input to A and C (not illustrated) would involve primary correlations between C and the afferent input cell, from the afferent input cell to a true premotor cell (A), and finally from the premotor cell to the motoneuron. In each case, the increase in probability of firing of the motoneuron associated with the spikes of the non-premotor cell is the product of the primary correlations in the circuit. PSpF resulting from such indirect neuronal circuits should be weaker and broader than that from monosynaptic linkages.

Smith and Fetz (1989) recently quantified the contribution of synchrony between neighboring cortical neurons, including CM cells, to PSpF. Thirty-five percent of 217 cortical cell pairs exhibited correlogram peaks that straddled the origin, consistent with common synaptic input. Fifteen cell pairs with common synaptic input were combinations of a non-CM with a CM cell. Despite the presence of a clear correlogram peak between the CM cell and non-CM cell, none of the 15 non-CM cells showed significant postspike effects. This demonstrates that synchrony of discharge arising from common synaptic input is insufficient to mediate PSpF from a cell lacking axonal connections with motoneurons.

For CM cells facilitating the same muscles, the contribution of synchrony to PSpF was evaluated by computing spike-triggered averages from cells after eliminating the synchronized spikes as triggers (Fig. 9). The records in the left column were all compiled with the spikes of Cell A as the trigger. Record (a) shows the distribution of spikes from cell B relative to spikes of Cell A aligned at zero time (cross-correlogram of A on B). The solid line is the correlogram after eliminating the triggers that were synchronized with spikes of Cell B; the dotted line shows the correlogram peak of synchronized spikes without any spike selection. After eliminating synchronized spikes, PSpF from each cell was observed in the same muscles and was in all respects similar to the control averages computed from all the cell's spikes (compare b and c). The contribution of synchronized spikes is revealed by subtracting the SpTAs obtained from non-synchronized spikes from the corresponding control SpTA (b from c). The difference between control and selected SpTAs is essentially flat (f). Records in the column under Cell B show the correlogram of cell B on A before and after eliminating synchronized spikes and the corresponding control PSpF and spike selected PSpF. Again, synchrony made virtually no contribution to PSpF. As a further test of the contribution of synchrony, the cross-correlogram containing the synchronized spikes was convolved with the PSpF of the CM cell (records d and e for cell A). The peak in the convolution was much smaller than the peak of the PSpF and had a time course matching the broad shoulders of the PSpF but lacking the sharply defined center peak of the PSpF.

Some important conclusions can be drawn from these findings. First, the contribution of one CM cell to the PSpF of a synchronized CM cell seems to be negligible and not a major concern in using spike-triggered averaging of EMG activity to identify CM cells or the distribution of their effects to motoneurons of different muscles. Second, the contribution that synchrony does make is largely to the broad, gradually changing shoulders of the PSpF rather than to the primary PSpF peak itself. This may account for the early onset of some PSpFs.

The modest contribution of synchrony to PSpF may seem to contradict evidence of clear PSpF from cells in motor thalamus (Fig. 7) and clear PSpS of antagonist muscles (Fig. 6), both of which must be mediated by a minimum disynaptic linkage. However, the strength of synapses in indirect linkages and the number of interneurons are important factors in determining whether significant features in correlations will be detected. Stimulus-triggered averages from thalamic cells may reveal effects mediated by synaptic linkages through motor cortex, and through red nucleus, via potent connections of interpositus axons. Nevertheless, it remains clear that the characteristics of most PSpFs are consistent with mediation by a monosynaptic linkage. The later components

of PSpF, however, might receive a contribution from disynaptic linkages.

Spike-triggered averages of unrectified EMG activity

Normally EMG activity is rectified before averaging to avoid possible cancellation of negative and positive components of motor unit potentials and to eliminate any ambiguity between excitatory and inhibitory events. However, Botteron and Cheney (1989) recently showed that postspike effects are also clearly detectable in averages of unrectified EMG activity. Of 110 muscles showing PSpFs in averages of rectified EMG activity, 49 (45%) also showed clear postspike effects in corresponding averages of

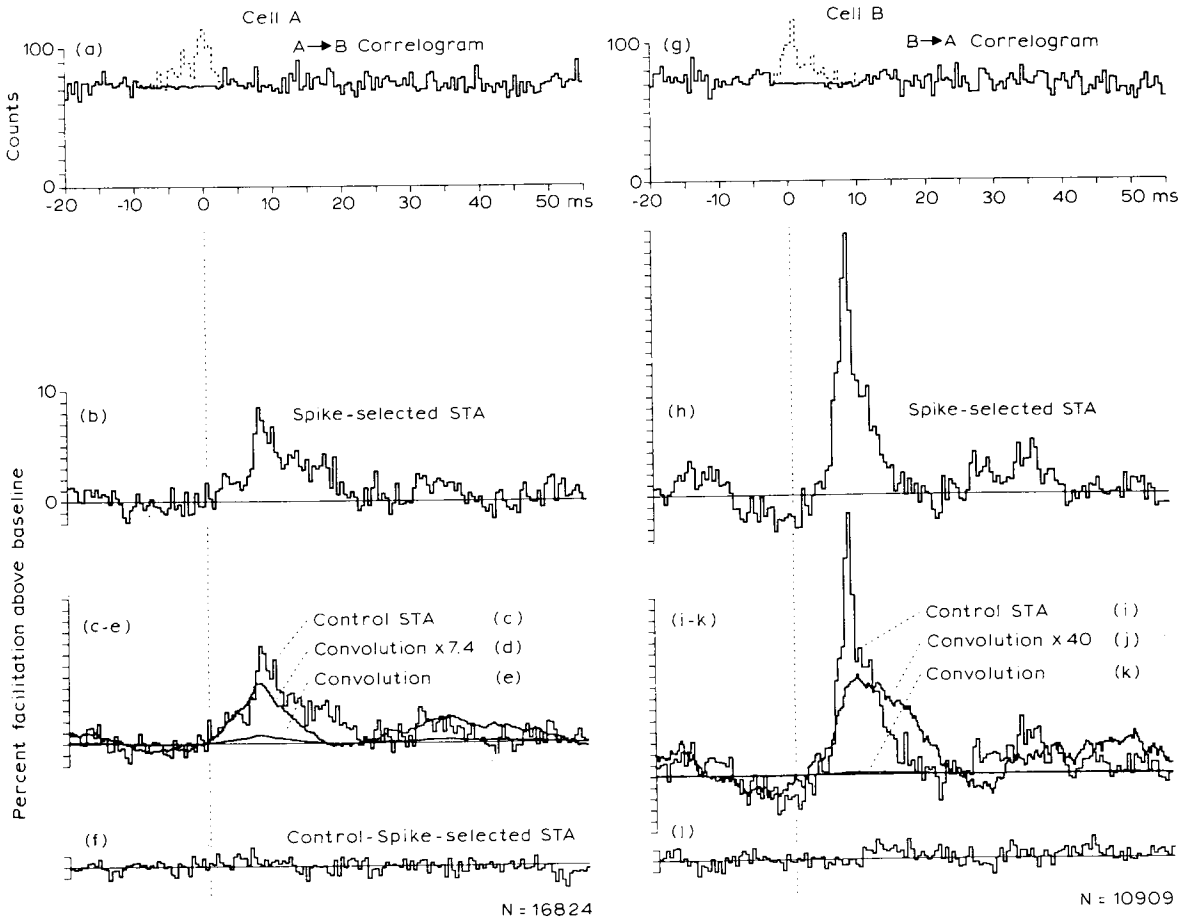

Fig. 9. Contribution of spike synchrony to PSpF. Analysis for a pair of simultaneously recorded CM cells. Effect of synchrony was evaluated by two methods. First, by eliminating the synchronized spikes as trigger events and comparing spike selected and control spike-triggered averages. Second, by convolving the cross-correlogram of cell B using A as the reference with the spike selected spike-triggered average from cell A. Same analysis was performed for Cell A using B as a reference. (a,g): cross-correlograms of Cell B with A as a reference (left) and Cell A with B as a reference (right). Dotted lines are correlograms including all spikes; solid lines are correlograms with synchronized spikes excluded. Spike selected averages (b, h) match control averages (c, i) indicating little or no contribution of synchronized spikes to PSpF. (f,l): control spike-triggered average minus spike selected average. Convolution represents the component of spike-triggered average expected from synchronized spikes of the other cell. The convolution peak corresponds with the broad component of the PSpF and has an early onset latency. The magnitude of the convolution peaks were 1/7 and 1/40 the magnitude of the broad component corresponding PSpFs. (From Smith and Fetz, 1989)

unrectified EMG activity. Remarkably, clear postspike effects in unrectified EMGs were also found in association with 50% of the cases of CM cell suppression of muscle activity (Fig. 10). The waveform that emerges from the unrectified EMG in association with PSpF is the average of the waveforms of all the facilitated motor unit potentials displaced in time according to their onset latency. Similarly, the waveform in the average of unrectified EMG activity associated with PSpS is the inverse of the suppressed motor unit potentials. Although effects in unrectified EMGs are some times clearer than in averages of rectified EMGs, cancellation of effects by summation of the positive and negative components of different motor unit potentials was confirmed as a serious problem leading, in some cases, to complete loss of effects. Nevertheless, averages of unrectified EMGs were useful in clarifying the nature of some postspike effects that were classified as complex based on latencies that were too short to be consistent with underlying anatomical connections. Effects in averages of unrectified EMGs had appropriate latencies and these cells could then be confidently classified as premotor cells.

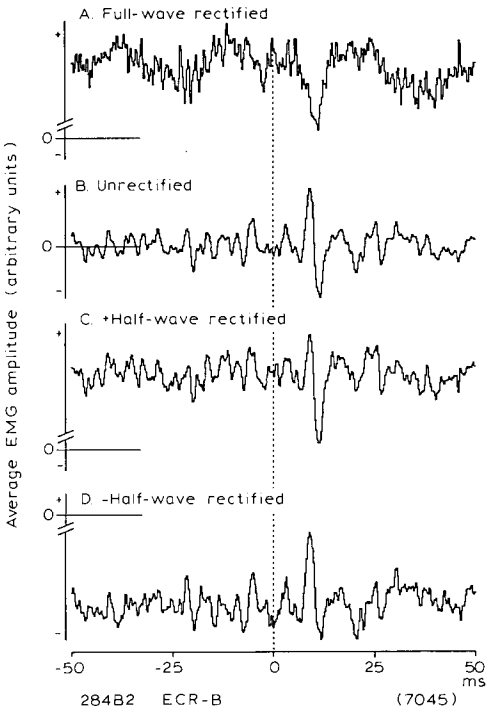

Fig. 10. Effect in unrectified EMG associated with PSpS. Waveforms of opposite polarity in half-wave rectified EMGs are not overlapping and cancellation does not occur. Waveforms in unrectified averages are the inverse of the suppressed motor unit potentials. (Botteron and Cheney, 1989)

Cross-correlations between premotor neurons and single motor units

Spike-triggered averaging of multinunit EMG activity with indwelling multistranded stainless steel wires benefits from broad sampling of the motor units within a muscle. This might enhance the probability of detecting postspike effects in cases of a restricted distribution of synapses from a premotor cell within a motoneuron pool. In addition, averaging the EMG signal itself prolongs the PSpF and enhances detection because the individual facilitated motor unit potentials usually straddle many sampling points. However, while this may account for some of the success of the method, it also introduces complications that render quantifying effects more difficult. Furthermore, PSpF in averages of EMG activity provides no information about the extent of facilitation of individual motor units within the muscle. These limitations can be addressed by computing cross-correlograms between the discharges of single premotor neurons and individual motor units within a muscle. Using this approach, Mantel and Lemon (1987) found clear peaks in the cross-correlograms of single CM cells and individual motor units in a target muscle. Fig. 11 is an example of a CM cell that produced clear PSpF in an average of surface EMG from abductor pollicis brevis (record A). Cross-correlations revealed that the cell also facilitated all three of the single motor units recorded with the same CM cell. The cross-correlogram peaks for individual motor units are weaker and narrower (mean half-width = 1.9 ms) than the PSpF of surface EMG. Of 31 motor units tested with 11 CM cells, 27 showed significant

facilitation. Similar proportions of facilitated motor units were found by Fortier et al. (1989). These results suggest a relatively broad distribution of terminals to different motoneurons within the motoneuron pool. This conclusion is further supported by the findings of Palmer and Fetz (1985b) who cross-correlated single motor unit activity with single intracortical microstimuli (S-ICMS). As many as 8 single motor units from an individual facilitated forearm muscle were tested for effects from S-ICMS at 23 cortical output sites. Overall, 95% (99 of 104) of motor units tested were facilitated by low intensity S-ICMS, again suggesting a broad distribution of terminals from CM cells to different motoneurons within a pool.

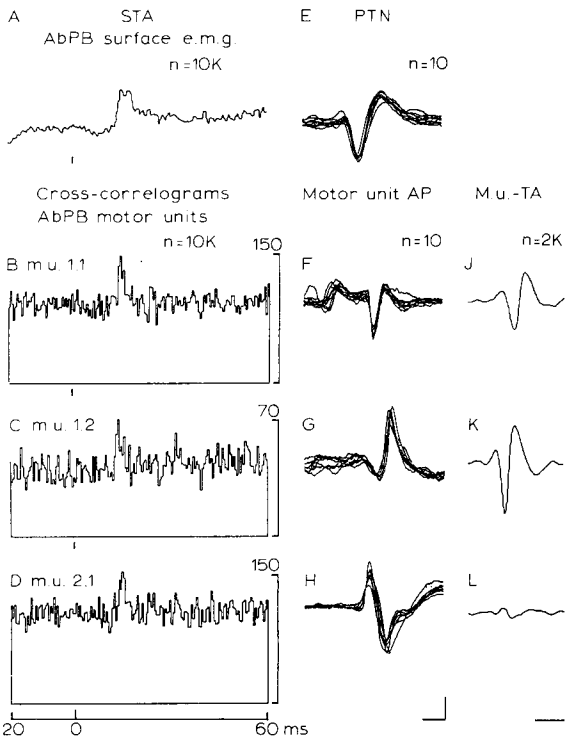

Fig. 11. Cross-correlograms of three single motor units in Abductor pollicis brevis (AbPB) triggered from a CM cell. (A). Spike-triggered average of rectified EMG activity. (B, C and D): Cross correlation functions for three AbPB motor units with reference to the discharge of a CM cell at zero time. (E). Spike waveform of the CM cell. (F, G and H): spike waveforms of the three motor units. (J, K and L): average spike waveforms of the three motor units. (From Mantel and Lemon, 1987)

Characteristics of PSpF and PSpS from single premotor neurons

Spike-triggered averaging of EMG activity has been used to analyze the output effects of single corticospinal and rubrospinal neurons on wrist and digit muscles in the monkey (Cheney et al., 1988; Fetz and Cheney, 1980; Lemon and Muir, 1983; Lemon et al., 1986; Mewes and Cheney, 1986). The sign and distribution of synaptic effects on motoneurons of agonist and antagonist muscles have been investigated under similar conditions for both CM and RM cells. Agonist muscles are defined as those which are coactivated with the cell during voluntary movement. To activate CM cells that are normally silent during the antagonist phase of movement, Kasser and Cheney (1983) developed a double barrelled microelectrode suitable for combined recording and glutamate iontophoresis in the awake monkey. Discharge during the antagonist phase of movement was evoked with glutamate. Spikes were then gated during either flexion or extension and used as triggers for compiling averages of the corresponding muscles. RM cells always showed a sustained background discharge throughout the alternating wrist movement cycle. Consequently, the output effects of these cells on antagonist muscles could be tested without using glutamate iontophoresis.

The characteristics of PSpF and PSpS studied with the same methods and under the same behavioral conditions are detailed in Table II. As expected, the latency of RM postspike effects are shorter than those of CM cell effects by about one millisecond. Since the conduction velocities of CM and RM cells are similar (Landgren et al., 1962a,b; Shapovalov et al., 1971; Shapovalov, 1973), this difference can be attributed to the shorter conduction distance to motoneurons for RM cells. It is also worth noting that for both CM and RM cells, the latency of PSpS is about 3 ms longer than the latency of PSpF. As discussed above, this suggests mediation of suppression by non-monosynaptic pathways. Disynaptic inhibition from Ia afferents to antagonist motoneurons has a latency that is

TABLE II

Characteristics of postspike effects from CM and RM cells

Postspike effects	CM	RM
Onset latency		
PSpF	6.3 ± 1.6	5.9 ± 1.9
PSpS	10.1 ± 2.8	9.3 ± 3.0
Peak magnitude (% of baseline)		
PSpF	7.0 ± 6.6	4.1 ± 2.0
PSpS	4.1 ± 2.4	4.0 ± 2.3
Number muscles with PSpF/cell	3.0	3.0
Number muscles with PSpS/cell	1.3	2.1

CM cell data from Kasser and Cheney (1985); RM cell data from work of Mewes and Cheney.

about one millisecond longer than excitation (Jankowska and Roberts, 1972). The three millisecond latency difference between PSpF and PSpS, therefore, seems somewhat long and remains unexplained. Nevertheless, it is known that corticospinal and rubrospinal neurons terminate on Ia inhibitory interneurons, and this seems to be a likely pathway for PSpS.

CM and RM cells facilitated not one but an average of three muscles of the five to six coactivated forearm agonists tested. The distribution of PSpS was more restricted for both CM and RM cells; this may be related to the fact that PSpS is weaker and more difficult to detect (Table II). It should be noted that three facilitated muscles per CM or RM cell holds for cells related to alternating wrist movements involving simple coactivation of forearm wrist and digit muscles. Cells related to more discrete tasks, such as precision grip between the thumb and index finger, show more restricted muscle fields (Lemon et al., 1986).

Functional output patterns of PSpF and PSpS from single premotor neurons

The output effects of CM and RM cells on motoneurons of agonist and antagonist muscles are organized in functionally meaningful patterns. Three fundamental categories of output effects on agonist and antagonist muscles can be identified – pure facilitation, reciprocal and cofacilitation (Fig. 12; Data compiled from: Kasser and Cheney, 1985; Smith and Fetz, unpublished work; Mewes and Cheney, unpublished work). Pure facilitation cells facilitated agonist muscles but had no detectable effect on the antagonists. Just over half of the CM cells and 39% of the RM cells were of this type. Reciprocal cells facilitated the agonists and simultaneously suppressed the antagonists. Thirty percent of CM cells and 27% of RM cells were of this type. Cofacilitation cells were common in the RM cell population (18%) but only a few examples were identified in CM cell recordings.

The reciprocal and cofacilitation cell types are particularly noteworthy because they represent clear examples of ways in which descending systems are functionally organized for specific types of movements. Reciprocally organized cells are well suited for mediating the reciprocal pattern of extensor and flexor muscle activation associated

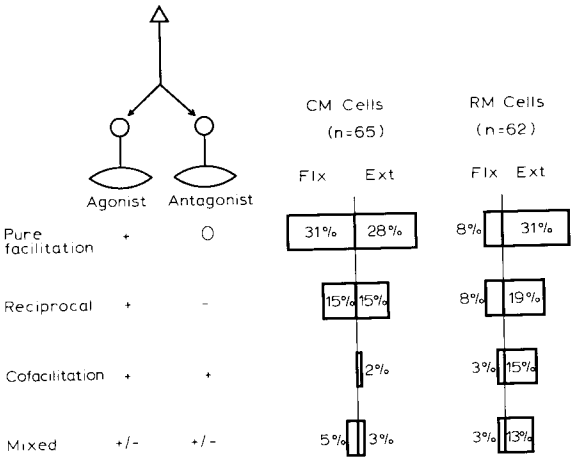

Fig. 12. Projection patterns of CM and RM cell output types to flexor and extensor muscles. Pure facilitation cells facilitated agonist muscles and had no effect on antagonists; reciprocal cells facilitated agonists and reciprocally suppressed the antagonists; cofacilitation cells simultaneously facilitated both flexor and extensor muscles; and mixed cells facilitated some agonists and suppressed others. Note that RM cells preferentially facilitate extensor muscles but CM cells are equally divided between those that facilitate extensors and flexors. (From Fetz et al., 1989)

with alternating movements. Similarly, the cofacilitation pattern is well suited for responses such as power grip that involve coactivation of forearm flexors and extensors to stabilize the wrist. Cofacilitation cells may also help bring motoneurons to threshold, independent of the direction of movement. Some additional minor categories of cells produced: 1) mixed effects, that is, facilitation and suppression in different synergist muscles, 2) pure suppression of antagonist muscles with no effects on agonists, and 3) inverse effects – facilitation of antagonists coupled, in some cases, with suppression of agonists.

In addition to these functional patterns of CM and RM cell output organization, other preferences in the distribution of PSpF and PSpS were observed. Most striking was the preferential facilitation of extensor muscles by RM cells (Fig. 12). Whereas CM cells were equally divided between those that facilitated either flexor or extensor muscles, 78% of RM cells facilitated extensors either exclusively or predominantly. This strong preference in favor of facilitation of extensors was also present in the microstimulation data. Even at sites where individual cells facilitated flexor muscles, stimulation predominantly facilitated extensor muscles (Mewes et al., 1987).

Although the number of CM cells facilitating flexor and extensor muscles was not different, the magnitude of PSpF in extensors was greater than that in flexors, and a similar tendency existed for RM cells (Cheney et al., 1988).

Beyond these preferences, individual CM and RM cells did not show a strong bias favoring facilitation of a specific muscle or combination of muscles. No particular muscle or combination of muscles was facilitated with any greater probability than others, although a weak tendency for stronger and more frequent facilitation of EDC was evident.

Modules of output organization in descending systems

Maps of topographic representation

Premotor neurons of most descending systems are not arranged randomly but rather show ordered representation of the peripheral muscular apparatus at two different levels. On a large scale, premotor neurons are arranged in an orderly fashion such that neurons controlling adjacent body parts occupy contiguous areas of the cortical or brainstem region. The existence of such a topographic organization for motor cortex has been known since the earliest stimulation experiments. More recently, movements evoked by applying electrical stimuli to the surface of motor cortex have been mapped in detail for a variety of species including humans and these general maps are well known (Phillips and Porter, 1977). A broad orderly representation of the contralateral musculature exists in motor cortex of all primate species. The basic pattern of organization is one in which the foot is represented most medially in the precentral gyrus followed laterally by more proximal muscles of the leg, the trunk, arm, hand and, most laterally, the representation of the face and tongue. An important feature of such maps is the disproportionately large representation devoted to muscles used in skilled movements of the face and hands compared to that devoted to control of large proximal muscles used in postural control and locomotion. Kwan et al. (1978) presented a variation of this motor map based on movement relations of arm neurons and microstimulation findings in the monkey. They concluded that muscles of the arm are represented in a radial pattern in the cortex with hand muscles at the center, wrist muscles in a band encircling the hand representation, elbow muscles next and finally shoulder muscles in the most peripheral band. Clear topographic organization has also been established for the rubrospinal and vestibulospinal systems, but as yet, none has been established for the reticulospinal system (Brodal, 1981).

The maps of motor representation derived from these studies have been very useful in understanding the coarse features of descending system organization; but how much variability exists in the maps from one subject to the another? Topographic maps provide only a general picture of the organization. Detailed features of the organization

will vary across subjects and to an even greater extent across species. For example, from the topographic maps of red nucleus it is only possible to conclude that the arm representation is located dorso medially and the leg representation ventolaterally. Further details may vary and must be established on an individual basis. Similarly, in motor cortex the relative location of representation for major body parts, for example, the hand, is consistent across subjects but the relative locations from which specific movements of the hand and digits can be elicited with electrical stimulation of cortex will vary in different subjects. The amount of cortical area from which a particular movement can be evoked with intracortical microstimulation may also vary in different subjects. Such variations may reflect the history of the subject's use of that movement. Nudo and Merzenich (unpublished data) showed that the area of motor cortex in monkeys from which movements of the hand and digits could be evoked with microstimulation enlarged after several days of performing a skilled movement of the hand. Therefore, the details of cortical motor maps show plasticity and may become remodelled adaptively as a function of use.

Columnar organization in motor cortex?

As Phillips and Porter (1977) pointed out, the most elemental unit of output organization from motor cortex is the single spinal cord-projecting premotor neuron – the CM cell. However, do these neurons form higher order functional aggregates in which all cells of the aggregate share common features? In motor cortex, a further consideration is whether the common features extend across cortical lamina to form columns. Although evidence for columnar organization in primary sensory cortical areas is very clear, comparable evidence for columns in motor cortex is lacking. There can be no doubt that the basic architecture of motor cortex is radial in its orientation. The thalamocortical and association fibers supplying afferent inputs to motor cortex are radially oriented as are the apical dendrites of pyramidal tract neurons themselves (Phillips and Porter, 1977). Asanuma and Rosen (1972) presented evidence for a columnar organization of input-output modules in motor cortex. In experiments combining microstimulation and unit recording in tranquilized monkeys, they found that sites evoking the same movement, for example, abduction of the thumb, tended to be aligned as columns within the cortex. Moreover, the sensory receptive fields of neurons in a column typically included the joint or skin region moved by stimulation at that site. Based on these results, a columnar organization of tightly organized input-output processing modules was proposed. However, Lemon and Porter (1976) failed to find evidence of a precise segregation of sensory inputs to cortical cells of a single output zone in awake monkeys, meticulously trained to allow passive manipulation of the limbs. Of 18 pairs of neighboring neurons (within 500 μm of each other), 11 pairs showed closely related afferent input zones but the remainder had widely disparate sensory inputs. Existing evidence concerning the columnar organization of motor output zones is also complicated by the fact the "columns" thus far studied have been largely in the bank of the precentral gyrus making vertical penetration through the full length of a single column difficult. Furthermore, conclusions about the size and distribution of motor cortical columns have been based on relatively few observations. Also, evoked movements rather than a more sensitive measure of muscle activation, such as EMG activity, has been used to identify motor output effects. It seems clear that much additional work is needed to place columnar organization in motor cortex on a firm footing.

Functional aggregates of CM and RM cells

Although strong evidence for columnar organization of cells in motor cortex is lacking, evidence favoring the existence of functional aggregates or assemblies of CM cells in lamina V of motor cortex is compelling. Large injections of HRP in the spinal cord have shown that corticospinal neurons are not uniformly distributed in lamina V of motor cortex but rather are organized as aggregates or

clusters consisting of 4–20 cells occupying a 0.5–1.0 mm diameter area (Coulter et al., 1976; Jones and Wise, 1977; Murray and Coulter, 1981). Clustering of corticospinal neurons has also been suggested based on antidromic activation of pyramidal tract neurons (Humphrey and Rietz, 1976; Kwan et al., 1978). Fig. 13 illustrates corticospinal cell clustering from an experiment in which all or nearly all the corticospinal neurons were labelled with HRP (Jones and Wise, 1977). This reconstruction shows the distribution of corticospinal neurons both in sagittal sections and viewing the surface of the cortex as a flattened sheet. Aggregation of corticospinal neurons in area 4 and adjacent cortical areas is clear from sagittal sections. Reconstruction of the distribution of these neurons across the entire territory of area 4 and SI viewed as a flattened sheet shows that the corticospinal cell aggregates tend to form strips oriented medio-laterally. Individual strips give off

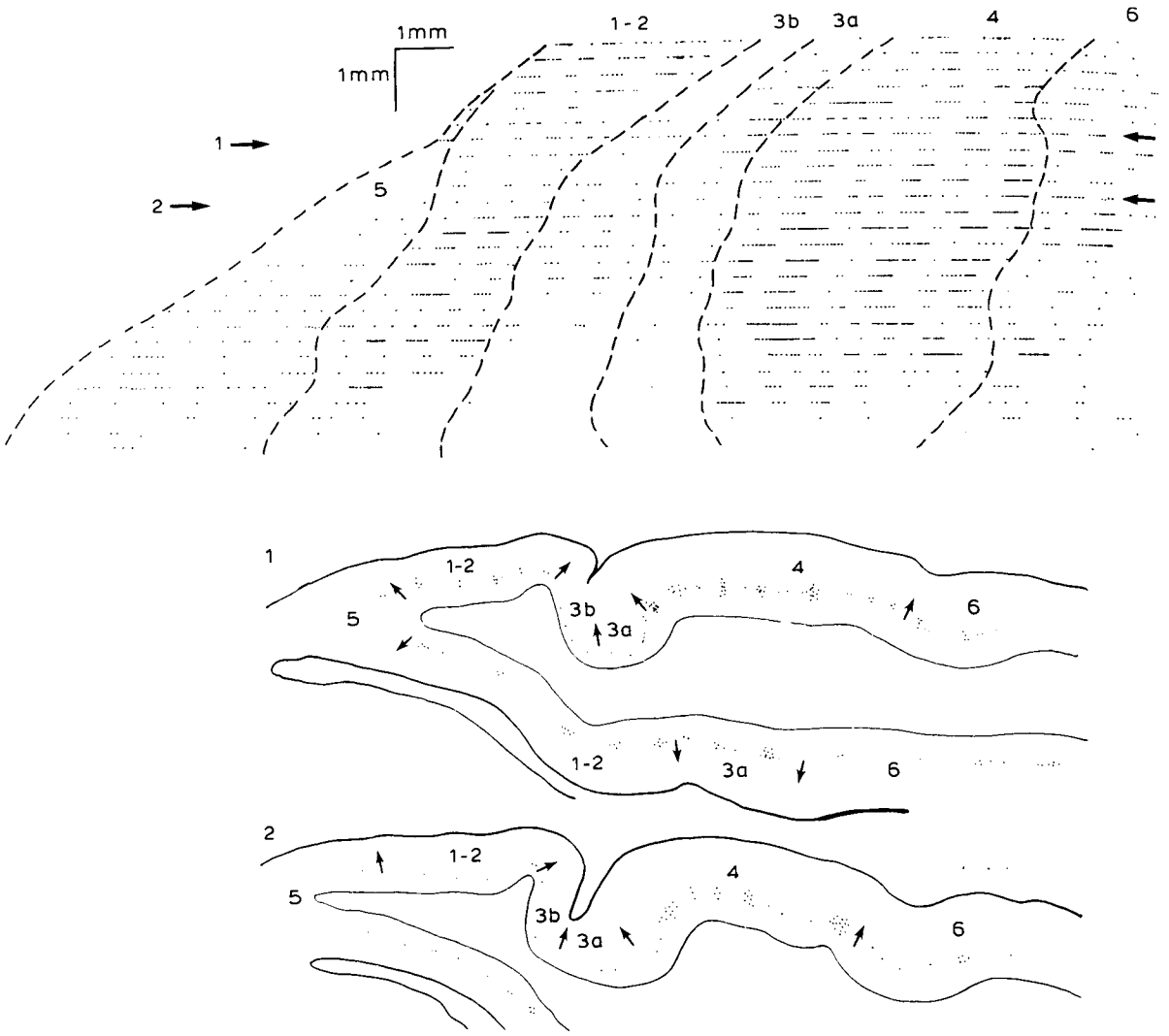

Fig. 13. Distribution of HRP labelled corticospinal neurons in cerebral cortex of monkey. Distribution is shown for cross sections and for the flattened cortex. Arrows indicate levels of cross sections. Note that corticospinal neurons occur as clusters and that the clusters tend to form medio-laterally oriented strips. (From Jones and Wise, 1977)

branches that merge with adjacent strips.

Although the functional significance of the strips is unknown, clusters of corticospinal cells may represent fundamental modules of output from motor cortex. If these clusters are to be viewed as unit modules of output organization, it must be shown that the cells of a cluster share common functional properties. What may be the common functional property of neurons belonging to a cluster? Recent evidence comparing the postspike and poststimulus effects obtained at CM cell sites suggests that the common property shared by neighboring CM cells (probably cells of the same cluster) is the distribution of output terminations to motoneurons. Cheney and Fetz (1985) found that the pattern of poststimulus facilitation across a set of six extensor or flexor muscles closely matched the pattern of postspike facilitation obtained from a single CM cell recorded at the same site. Stimuli were applied through the microelectrode at the recording sites of CM cells under the same behavioral conditions that were used to compute spike-triggered averages (Fig. 14). To avoid spread of effects by temporal summation, stimuli were delivered at a rate of 15 Hz or less. Because this intracranial microstimulation method reveals the effects of a single stimulus, it is referred to as stimulus-triggered averaging or S-ICMS. The results from one CM cell site are illustrated in Fig. 15. In this example, FCU was the only muscle facilitated by the CM cell. Stimulus-triggered averages at 8, 10 and 20 μA revealed poststimulus facilitation (PStF) restricted to FCU, strengthening the conclusion that PSpF was mediated by the recorded CM cell. Although exhibiting a similar distribution, PStF was much greater in magnitude than PSpF. In Fig. 15, the magnitude of effects in FCU at 8 μA appear similar to that of PSpF. However, PStF is actually much greater in magnitude because it was obtained with only 500 trigger pulses compared to 10,000 spikes for PSpF. Because the signal-to-noise ratio increases as the square root of the number of trigger events, the PStF at 8 μA is actually about five times greater than PSpF. Whereas PSpF reflects the output effects of a single cell, PStF reflects the output ef-

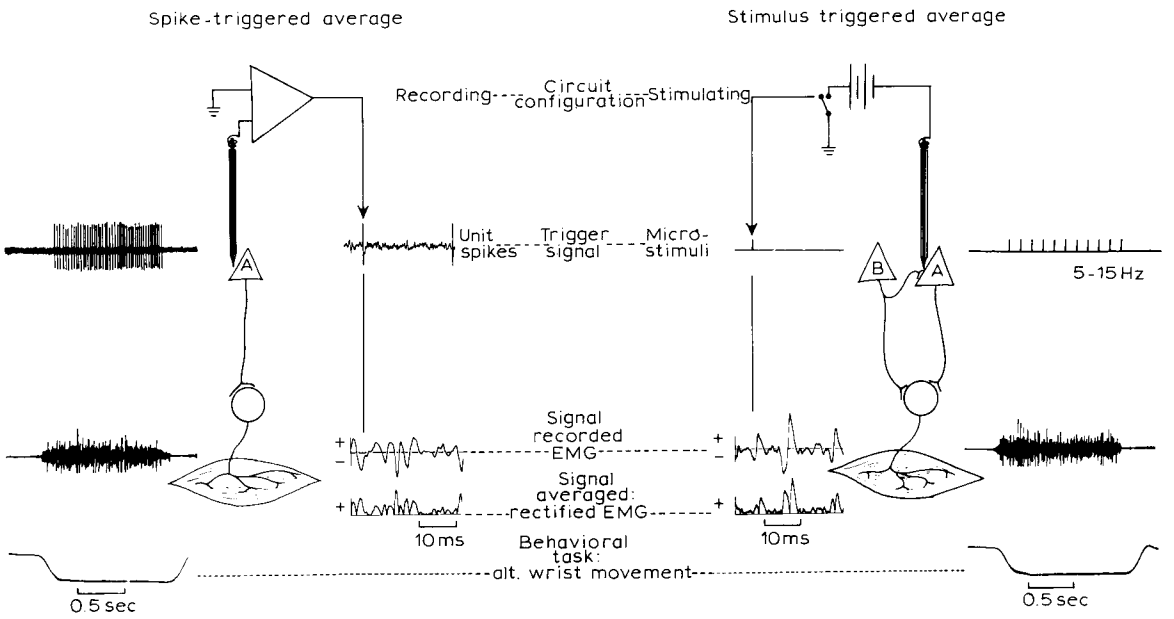

Fig. 14. Comparison of spike and stimulus-triggered averaging methods. For stimulus-triggered averaging, microstimuli are applied at a low rate (15 Hz or less) and under the same behavioral conditions used for computing the spike-triggered averages. (From Cheney and Fetz, 1985)

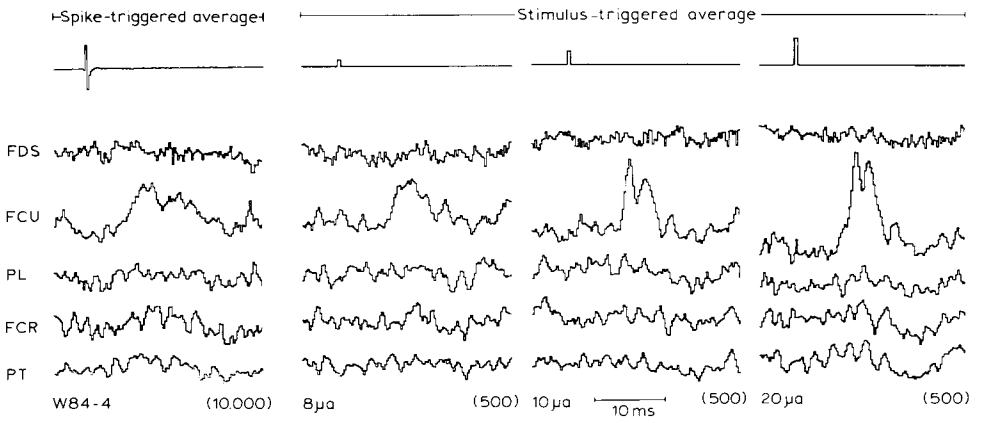

Fig. 15. Postspike facilitation (PSpF) of an individual flexor muscle (FCU) from a CM cell. Poststimulus facilitation (PStF) from microstimuli applied to the recording site during wrist flexion. Note that the pattern of PStF matches the pattern of PSpF but is greater in magnitude. Number of trigger events in parentheses. (From Cheney and Fetz, 1985)

fects of the population of cells excited by the stimulus. The strength of poststimulus effects at 5 – 10 μA was generally 2 – 20 times greater than postspike effects confirming the involvement of many CM cells. The fact that PStF involved many CM cells but had the same basic profile across synergist muscles as PSpF from the single CM cell at the same site indicates that neighboring cells activated by the stimulus have similar patterns of synaptic connections with motoneurons.

The similarity in target muscle fields of neighboring CM cells was confirmed by computing spike-triggered averages from cells located within the same track and separated by 0.6 mm or less. Results for a pair of simultaneously recorded cells are illustrated in Fig. 16. Both CM cells facilitate ECU and ED4,5 most strongly. Weaker PSpF is present in EDC and ECR and the weakest effect was in ED2,3. Stimulation at 10 μA produced a pattern of PStF closely matching the pattern of PSpF, except that the magnitude of PStF was much greater than that of PSpF. Eight pairs of neighboring cells were tested and all showed a high degree of similarity in their muscle fields. Therefore, just as neighboring sensory neurons in various parts of primary sensory cortex share common receptive fields, CM cells in lamina V of motor cortex share common muscle fields.

If the muscle fields of neighboring CM cells are similar, a related issue is whether their discharge patterns in relation to active movement are also similar. In sensory cortex, the response properties of cells in the same column are usually similar; for example, all the cells might be rapidly adapting or slowly adapting; in the visual system, orientation of an effective light stimulus might be the same for all cells of a column. In motor cortex, the details of functional properties are not necessarily similar for neighboring CM cells that presumably belong to the same cluster. Functional similarity does not seem to extend beyond the fact that neighboring CM cells are related to movements of the same joint. For example, Fig. 16 shows that both of the CM cells of this simultaneously recorded pair were coactivated with wrist extension but the pattern of discharge was dissimilar. One cell of the pair had a pure tonic pattern of discharge in relation to ramp-and-hold wrist movement while the other had a clear phasic-tonic pattern. The significance of this difference is strengthened by the fact that the qualitative pattern of discharge seems to be a rather robust feature of CM cell discharge. For example, Cheney and Fetz (1985) found that the pattern for a particular cell was the same under both isometric and auxotonic (same torque but with wrist movement) conditions. The discharge of

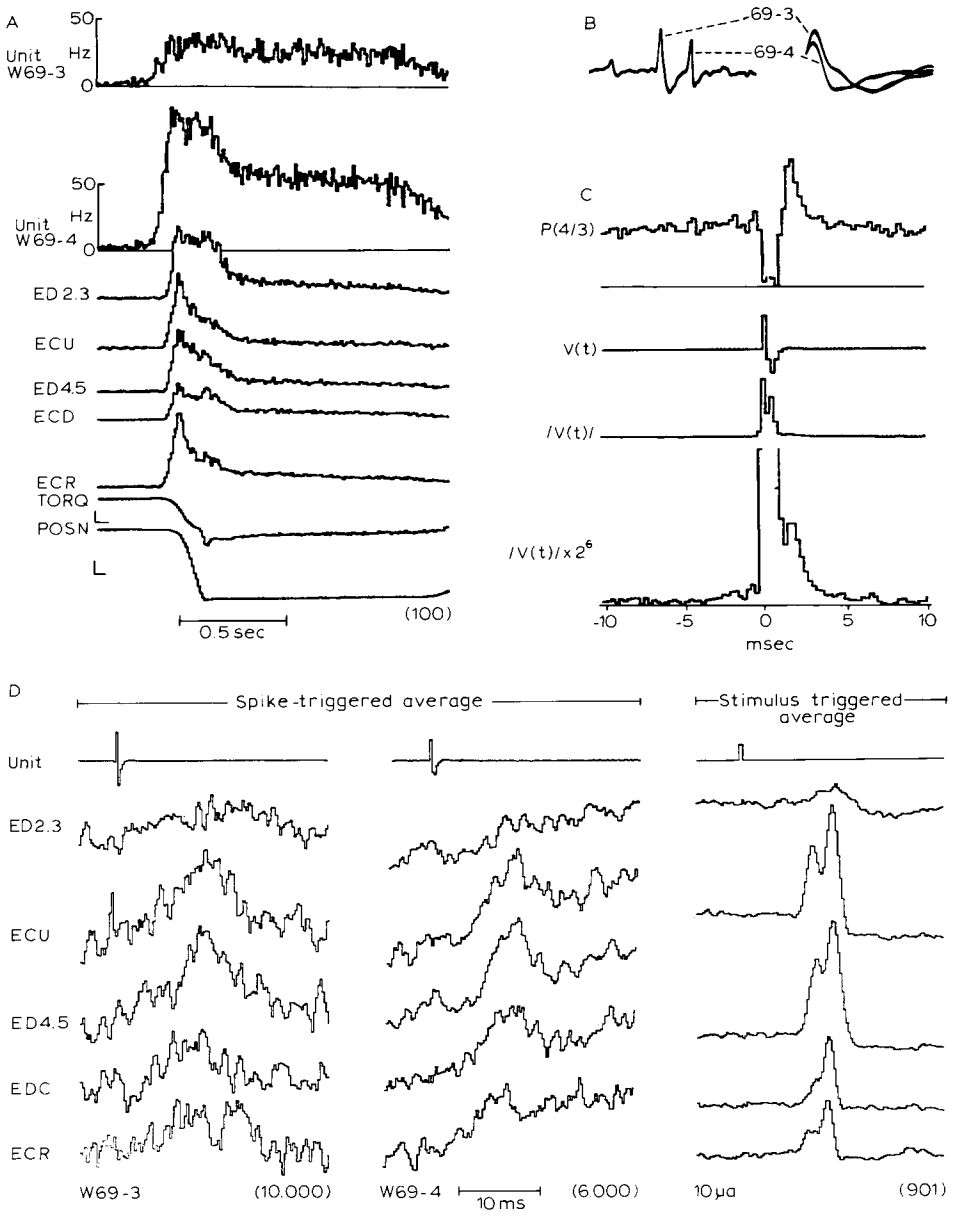

Fig. 16. Active movement relations and output effects for a pair of neighboring CM cells simultaneously recorded through the same microelectrode. (A). Discharge pattern of the two CM cells during ramp and hold wrist extension. (B). Spike waveforms of each CM cell. (C). Cross-correlogram (P4/3) of cell W69-4 with reference to the spike discharge of W69-3 at zero time. Correlogram is zero for period when spikes occur simultaneously and discrimination of separate waveforms fails. V(t) and channel below it are averages of the unrectified and rectified spike recordings respectively triggered from the spikes of cell W69-3. Lower channel is rectified average expanded. Both the correlogram and the average of rectified spike activity show peaks at about 2 ms suggesting that cell W69-4 received excitatory collateral synaptic input from cell W69-3. (D). Spike-triggered averages from each CM cell and a 10 μA stimulus-triggered average computed at the same cortical site. Note the high degree of similarity in the pattern of PSpF from each cell and the pattern of PStF. In additional tests, synchronized spikes in (C) were eliminated as triggers and a similar pattern of PSpF was observed from each cell. (Modified from Cheney and Fetz, 1985)

motor cortex cells recorded at the same site may also be related to opposite directions of movement at a joint. However, examples of neighboring CM cells with opposing target muscles have not been found.

Fig. 17 illustrates the output organization postulated by Cheney and Fetz (1985) for motor cortex. The basic module of output is a cluster of CM cells in layer V. The feature shared in common by each cell of a cluster is the muscle field. The similarity in synaptic output from different CM cells of a cluster seems to extend beyond the cell's simple muscle field. The fact that the relative magnitude of PSpF across different target muscles is similar for different cells in a cluster suggests not only that the target muscles are the same but also that the relative strength of synaptic input to target motoneuron pools is also similar. The muscle fields of different clusters involve different muscles; some facilitate a single motoneuron pool (A) but most facilitate different combinations of synergist motoneuron pools (for example, B and F). The most common output patterns for CM cells are pure facilitation, in which the cell has no effect on antagonist muscles (clusters A and C), and reciprocal, in which the cells of a cluster not only facilitate agonist muscles but simultaneously suppress antagonists, probably through spinal inhibitory interneurons (B and E).

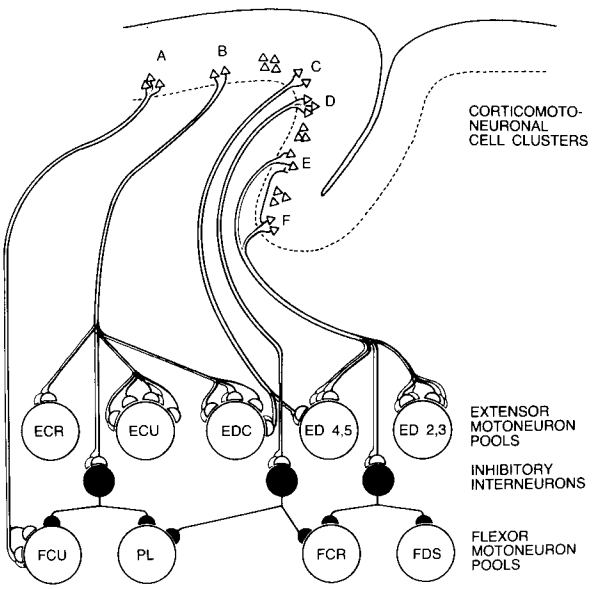

Fig. 17. Model of motor cortex output organization based on findings from spike and stimulus-triggered averaging. CM cells occur as clusters or aggregates in which each cell of the aggregate has a similar pattern of terminations with motoneurons. (From Cheney and Fetz, 1985)

Mewes et al. (1987) studied rubrospinal output organization using the same approach of comparing the pattern of poststimulus effects with the pattern of postspike effects. Although clustering of magnocellular red nucleus cells is not clear anatomically, at most RM cell sites stimulus-triggered averaging yielded results similar to those for CM cell sites (Fig. 18). However, overall the match between the pattern of PSpF and PStF at RM cell sites was less consistent than at CM cell sites. Flexor RM cell sites yielded the poorest match because stimulation always produced the strongest facilitation in extensor muscles. These results suggest that the output from red nucleus consists of functional modules in which neighboring RM cells have similar patterns of synaptic connections with motoneurons. However, the number of cells in a module (output zone) is smaller than in motor cortex and the modules show more overlap and/or less muscle field homogeneity. Greater stimulation of axons of passage might also be a factor contributing to a larger number of mismatches between the profile of PSpF and PStF across muscles at RM cell sites than at CM cell sites. The existence of actual clusters of RM cells separated by space lacking RM cells seems doubtful. However, the basic principle of organization presented here could apply just as well to neighboring cells and does not depend on the existence of actual anatomical cell clusters separated by boundary regions lacking neurons.

Discharge patterns of premotor descending neurons in relation to wrist movements

The discharge patterns of CM and RM cells in relation to a standard ramp and hold trajectory of wrist torque fall into specific categories as il-

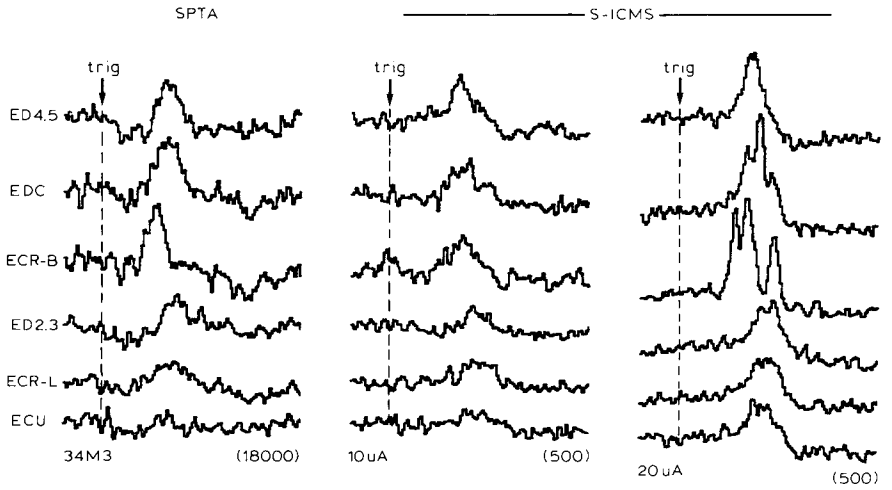

Fig. 18. Spike and stimulus-triggered averages from an RM cell site. Note the similarity between the pattern of PSpF and PStF. (Mewes and Cheney, unpublished observations)

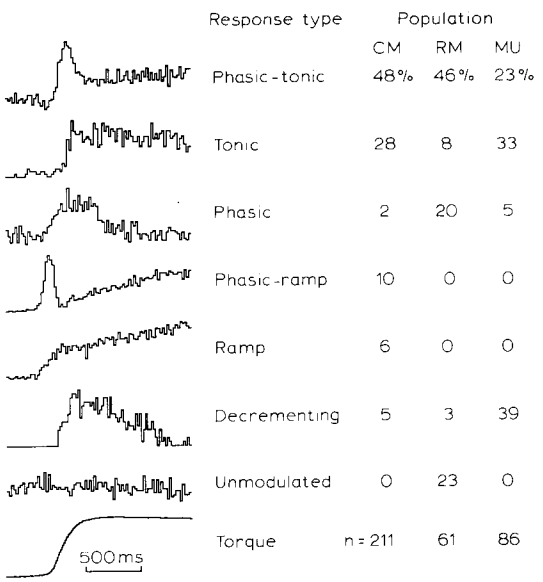

Fig. 19. Response patterns of CM cells, RM cells and motor units in relation to ramp-and-hold wrist movements against moderate loads. Table gives percent of each response type in each population. (From Fetz et al., 1989.)

lustrated in Fig. 19. For comparison, the patterns exhibited by single motor units are also shown (Palmer and Fetz, 1985a). The most common pattern of discharge for premotor cells was phasic-tonic; about half of all CM and RM cells were of this type. The CM population contained a large fraction of pure tonic cells but few pure phasic cells, whereas the RM population contained a large fraction of pure phasic cells but few pure tonic cells. This is consistent with the observations of others emphasizing the phasic nature of red nucleus discharge and its involvement with the phasic aspects of movement (Ghez and Kubota, 1977; Ghez and Vicaro, 1978; Gibson et al., 1985a,b; Kohlerman et al., 1982). Nevertheless, the presence of a tonic component of discharge for most RM cells is clear (Cheney and Mewes, 1986; Cheney et al., 1988). Surprisingly, a significant fraction (23%) of the RM cell population showed no modulation of discharge in relation to wrist movements despite the presence of strong PSpF of forearm muscles directly involved in the task. These cells show gradual increases in background firing rate associated with the transition from a resting state to task performance. This activity would raise the background level of motoneuronal excitability without actually contributing to the modulation of muscle activity that generates a particular movement. It is possible that these cells might be clearly modulated in relation to some other task involving the forearm muscles. However, some unmodulated RM cells remained

unmodulated when tested in relation to a much different task involving a visually guided arm movement terminating in precision grip of a food morsel. Therefore, under normal conditions, a significant fraction of the RM cell population seems to be unmodulated in relation to specific movement parameters.

Like CM cells, the majority of motor units were either phasic-tonic or tonic (Fig. 19). However, unlike either CM or RM cells, a large fraction of motor units showed a gradually decrementing discharge during the hold phase of the task when wrist torque was either constant or decreasing at a slower rate than cell discharge.

Encoding of specific movement parameters by premotor descending neurons

Identification of homogeneous premotor cell populations

One of the challenges facing neuroscientists studying the properties of brain descending systems is understanding the significance of the discharge of single neurons in functional terms. For example, what aspect of motor output or movement is encoded in the discharge of single premotor descending neurons and what do these neurons contribute to the movement? These types of questions were first directly addressed by Evarts (1968) in a study of pyramidal tract neuron discharge in relation to wrist movements against different external loads. Based on the finding that the discharge of pyramidal tract neurons preceded the onset of movement and that firing rate was graded in relation to the external load against which the monkey worked, Evarts proposed that these neurons initiate the movement and encode the force of movement. Since Evarts' original work, some reports have confirmed encoding of static force by motor cortex cells while others have emphasized that motor cortex cells are better related to movement kinematics (direction, velocity) rather than movement dynamics (force, rate of change of force, torque) (Schmidt et al., 1975; Georgopoulos et al., 1983). However, it must be recognized that motor cortex contains a wide variety of cell types with different inputs and different target structures. Different categories of neurons may encode different types of information and it becomes essential to identify the target structures of recorded neurons.

Clear delineation in an awake animal of the movement parameters encoded in premotor cell output requires demonstration that a particular cell influences motoneurons and is causally involved in the movement. The presence of PSpF in spike-triggered averages of rectified EMG activity provides confirmation of a cell's linkage to motoneurons independent of its discharge pattern. Identifying premotor neurons in this way has provided some definitive answers to questions concerning parameters of movement encoded in the discharge from motor cortex and red nucleus.

Encoding of static torque

Over a large range, the tonic activity of both CM and RM cells is linearly related to the static wrist torque to which the cell's target muscles contribute. An example of a torque-encoding RM cell is illustrated in Fig. 20. Spike-triggered averages show that this RM cell is reciprocally organized and facilitates multiple extensor muscles while suppressing multiple flexor muscles. The relation between tonic firing rate and static torque for this cell is linear with a slope of 139 Hz/Nm (Fig. 21A). Of 61 RM cells studied in relation to static torque, 54% showed a load dependent tonic discharge compared to 99% (209 of 211 tested) of CM cells. The slope of the relationship between firing rate and static torque is referred to as the rate-torque slope and provides a measure of the sensitivity with which the cell encodes wrist torque. Representative relationships for the CM and RM cells and motor units are represented in Fig. 22. Although both CM and RM cells encode the torque of movement, the mean rate-torque slope for CM cells was 3 – 4 times that of RM cells (Table III). CM cells, therefore, encode static torque with greater resolution than RM cells. Another consistent finding, evident from the plots in Fig. 22, is that the rate-torque slopes of cells facilitating extensor muscles

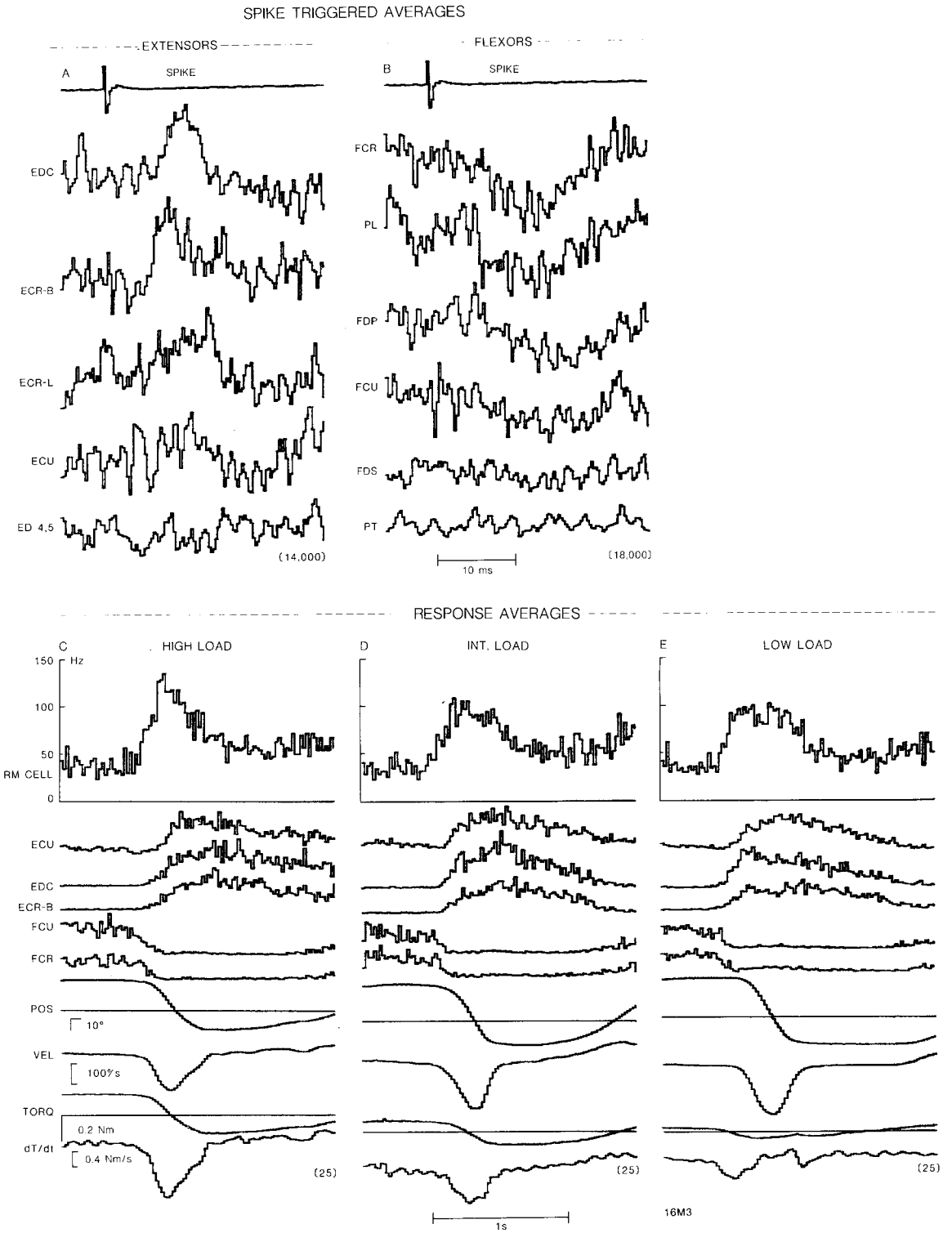

Fig. 20. Responses of an RM cell in relation to three different external load levels. Spike-triggered averages (top) show that the cell was reciprocally organized and facilitated extensor muscles while suppressing flexor muscles. (From Cheney et al., 1988)

are greater than those of cells facilitating flexor muscles. This difference was present in both the CM and RM cell data but its explanation is unclear. It does not appear to result from a peripheral factor, such as a greater mechanical advantage of flexor muscles compared to extensors because a similar difference was not present in the data for motor units recorded under the same conditions.

Encoding of static torque by CM and RM cells has also been confirmed under isometric conditions where wrist torque can be clearly and unambiguously dissociated from position. In all cases, rate-torque relationships determined under isometric conditions were similar to those for auxotonic conditions in which movements away from a zero position were opposed by a spring-like load (Cheney and Fetz, 1980; Cheney and Mewes, 1986). In conclusion, encoding of static force is a consistent property of nearly all CM and RM cells with a tonic discharge in relation to movement.

Relation to phasic parameters of movement

Many CM and RM cells exhibit a clear phasic component of discharge at movement onset, either alone or in combination with a tonic component. The phasic component of discharge is measured as the peak or mean discharge rate associated with the phasic burst minus the tonic discharge rate occurring during the static hold phase of the task. In general, correlations between discharge rate and movement velocity or rate of torque change are more mixed and variable across cells than relations to static torque. This could be due in part to greater difficulty in accurately measuring the relevant variables and examining an adequate range of the parameter of interest, but it is also clear that premotor cells simply show more variability in the extent and nature of encoding of phasic features of

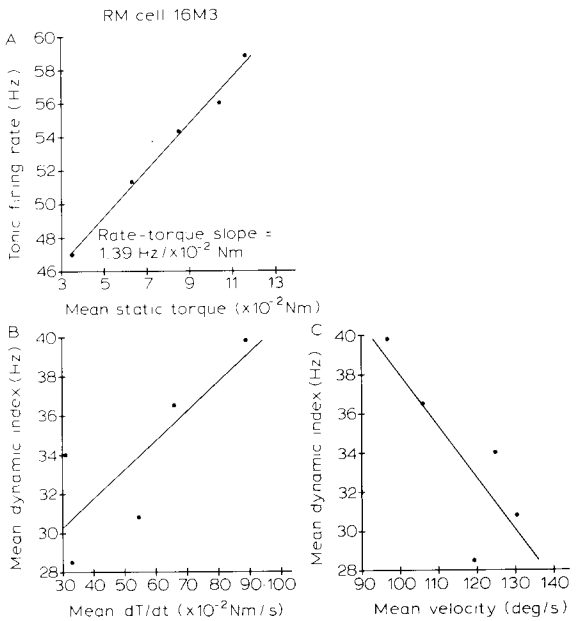

Fig. 21. Relations between discharge rate and movement parameters for the cell illustrated in Fig. 20. (A). Tonic firing rate measured during the hold phase of the task (0.25 – 0.5 s after the peak of movement) versus static torque. (B and C). Plots of the cell's phasic activity measured as dynamic index against movement velocity and mean dT/dt. Dynamic index was calculated by subtracting tonic activity from the phasic discharge during movement. (From Cheney et al., 1988)

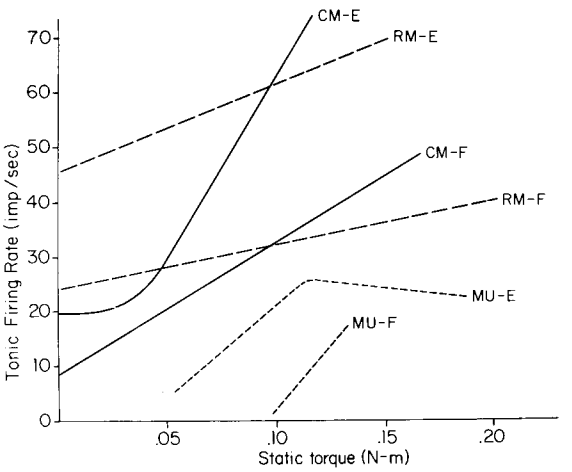

Fig. 22. Relationships between firing rate and static torque for typical CM cells, RM cells and motor units. Extensor and flexor units are plotted separately. Note that the mean rate-torque slopes for the CM cells are greater than for the RM cells. Supraspinal premotor cells are active at the lowest force levels, while motor units are recruited at increasing forces. (From Fetz et al., 1989)

TABLE III

Functional properties of CM and RM cells

Discharge properties for active movement	CM	RM
Onset relative to target muscle	−54 ms	−89 ms
	*(−71, −63,	+5, +101)
Tonic component of activity		
% of tonic cells with relation to static torque	100%	100%
Rate-torque slope		
Extension	480 Hz/Nm	159 Hz/Nm
	(140 − 800)	(39 − 342)
Flexion	250 Hz/Nm	61 Hz/Nm
	(60 − 500)	(28 − 99)
Phasic component of activity		
Number cells tested	16	32
Relation to dT/dt	50%	34%
Relation to velocity	?	31%
Unrelated	50%	34%

* Mean onset times for phasic-tonic, phasic-ramp, tonic, and ramp CM cells respectively.
CM cell data from Cheney and Fetz (1980); RM cell data from work of Mewes and Cheney.

movement than the static features of movement. Evarts (1968) concluded that just as the tonic discharge of PTNs was related to static force, so the phasic discharge of many PTNs was related to the rate of change of force. Other studies since have confirmed this relation for motor cortex cells (Smith et al., 1975) and for red nucleus cells (Ghez and Vicaro, 1978). Cheney and Fetz (1980) reported that the phasic discharge of about half of CM cells was related to the rate of change of torque (dT/dt) and that the phasic discharge was the same for similar torque trajectories under both auxotonic or isometric conditions, confirming that the key parameter encoded was dT/dt not velocity. However, CM cell relations to velocity have not been specifically investigated.

Ghez and Vicaro (1978) emphasized the phasic nature of discharge of magnocellular red nucleus neurons in the cat studied in relation to a forelimb isometric task and concluded that the discharge encoded the rate of change of force. More recently, Gibson et al. (1985a,b) and Houk et al. (1988) found that the discharge of many magnocellular red nucleus neurons in the monkey was highly correlated with movement velocity. Cheney and Mewes (1986; also see Cheney et al., 1988) found that the phasic discharge of about a third of RM cells was best related to movement velocity. Correlation coefficients were greater for velocity than dT/dt and the phasic component of discharge was diminished under isometric conditions. However, the phasic discharge of another third of RM cells was best related to dT/dt and the remaining third were not significantly correlated with either velocity or dT/dt (Table III).

Fig. 21 shows plots of phasic activity measured as dynamic index for the RM cell illustrated in Fig. 20. Dynamic index was calculated by subtracting the tonic discharge rate measured during the hold period of the task from the mean firing rate of the phasic component of discharge. The magnitude of the phasic discharge of this cell was positively correlated with the rate of torque change in the extension direction – the direction of the cell's target muscles. Because this monkey's movements slowed somewhat as external load and dT/dt increased, velocity and dT/dt were inversely related. Consequently, the cell's phasic discharge was also inversely related to movement velocity in the extension direction. A primary relation to dT/dt was further confirmed under isometric conditions, for which movement velocity was zero.

Significant correlations with specific movement parameters can be established for RM cells suggesting encoding of these parameters by the central motor program. However, the varied nature of the best parameter – velocity in some cases, dT/dt in others and neither in still others – coupled with a large trial by trial variability raise the question of whether any of these parameters can actually be said to be encoded by RM cell discharge. Certainly any one cell makes a relatively small contribution to torque and the sum of a population of cells is likely to show a much better correlation than in-

dividual cells. Nevertheless, if velocity or dT/dt were the actual primary parameter encoded by the motor program, tighter, more uniform correlations might be expected. It is possible that some other motor parameter, such as average EMG activity in the cell's target muscles, might correlate better with the movement related phasic modulation of premotor cells.

Encoding of movement vectors by populations of motor cortex cells

Humphrey et al. (1970) first showed that correlations between cortical cell discharge rate and force or rate of change of force can be improved by considering coding in a population of cells rather than any individual cell. Clearly, all movements involve thousands of premotor cells and, although the precision with which any given cell specifies a parameter of movement may show substantial variance, the sum total of the entire population of premotor neurons involved in the movement specifies key parameters with little variance. More recently, Georgopoulos and colleagues examined the encoding of arm movement direction by populations of motor cortex neurons (Georgopoulos et al., 1983). Monkeys were trained to move a handle to each of eight targets in two dimensional space. The discharge of motor cortex neurons in relation to each direction was measured and plotted as shown in Fig. 23 for one neuron. This neuron, like most others in motor cortex, shows broad tuning of discharge with movement direction but with a best direction, for which discharge is greatest, in this case for movements at 135 degrees. A cell's directional tuning curve represents its contribution to movement in different directions of two dimensional space. The contribution of a cell to movement in a particular direction can be plotted as a vector whose length is the change in cell discharge rate for that movement direction and whose direction is the cell's preferred movement direction. The movement vectors for 241 motor cortex neurons recorded in relation to movement in eight different directions (same task as Fig. 23) are illustrated in Fig. 24. The vectorial sum of the whole population is illustrated by the dotted line. Note the high degree of congruence between the direction of the vectorial sum of the population and the actual movement direction indicated by the arrows in the center of the figure. This data demonstrates how functions exhibited by a neuronal population can match a parameter such as movement direction.

It should be pointed out that the rationale

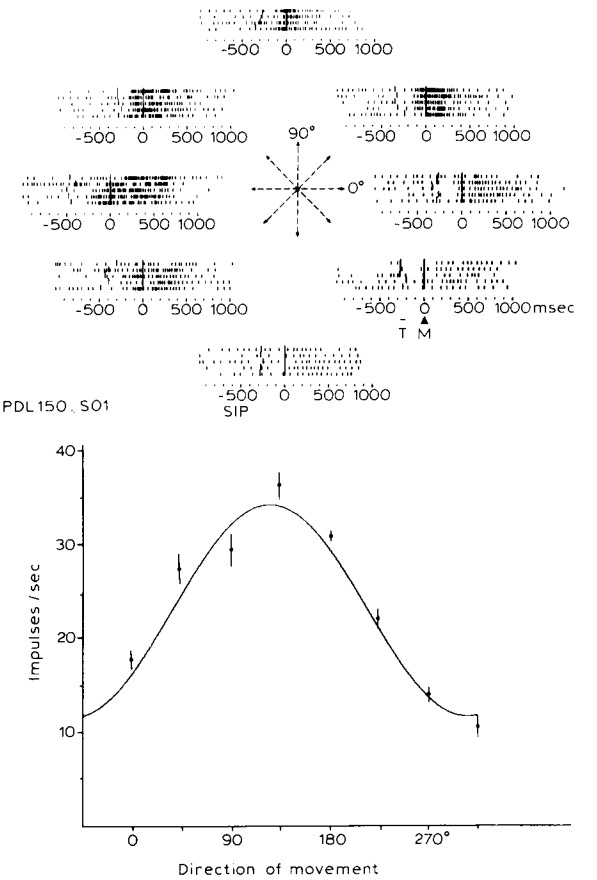

Fig. 23. Discharge of a motor cortex cell in relation to eight different directions of arm movement in a two dimensional plane. Movement started from a center point surrounded by the targets. *Top:* dot rasters of trials. *Bottom:* average rate throughout movement as a function of movement direction. This cell is typical of many motor cortex cells in showing broad tuning around a single best direction. (From Georgopoulos et al., 1983)

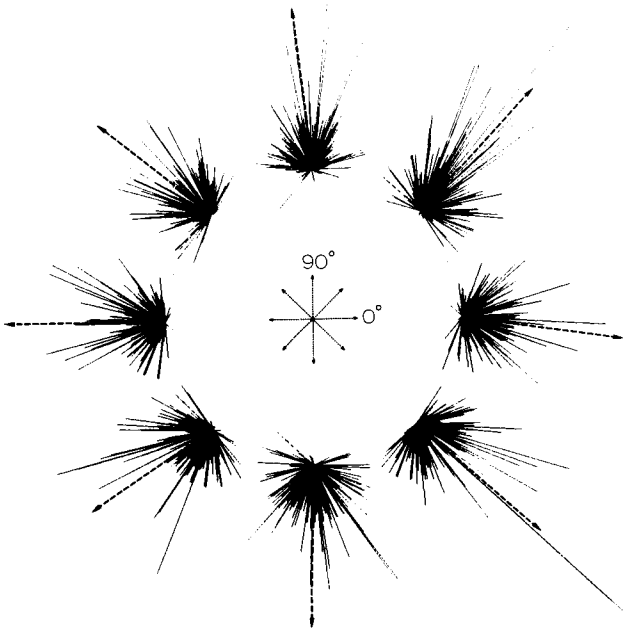

Fig. 24. Representation of the directional tuning of motor cortex cells recorded in experiments such as illustrated in Fig. 23. Discharge of each cell for each movement direction is plotted as a vector whose length is equal to the discharge rate for movements to the target in that direction and whose orientation indicates the direction for which the cell's discharge was strongest. The vector contributions of each cell to the movement were summed to yield a population vector (broken arrow). Note the high degree of conformity between the population vector and the direction of the actual movement. (From Georgopoulos et al., 1983)

underlying calculation of neuronal population vectors differs fundamentally from the approach of Humphrey et al. (1970) in that, for vector calculation, the aim of examining a population of neurons is not to reduce unwanted variability. Rather the broad directional tuning of any particular cell is a consistent property stemming from a similar broad tuning of the cell's target muscles. It is only by considering the net contribution of a population of such broadly tuned cells involved in a particular movement that the direction of movement is unambiguously matched. This type of analysis might also be applied to other movement parameters, such as force direction, with similar results (Georgopoulos et al., 1983). Kalaska et al. (1989) recently confirmed this suggestion. They applied vectorial analysis to a population of motor cortex neurons using the same task for which the data in Figs. 23 and 24 were collected but with the addition of external loads to assist or oppose movement toward each of the targets. Fig. 25 summarizes the neuronal discharge vectors for all cells recorded in the absence of external loads (A) and with external loads (B). In A, the position of each cluster of vectors relative to the center point represents the direction of movement for that cluster; in B the position of the cluster relative to the center point represents the direction the external load pulled the pendulum away from the center starting point. External loads that pulled the pendulum in each of the 8 target directions were applied for active movements in each direction. The movement direction vectors (A) are calculated and plotted in the same way as in Fig. 24. In (B), the activity of each cell is represented by a vector oriented along the axis of its preferred movement direction measured in the control block (A). The length of the vector in (B) was determined by the

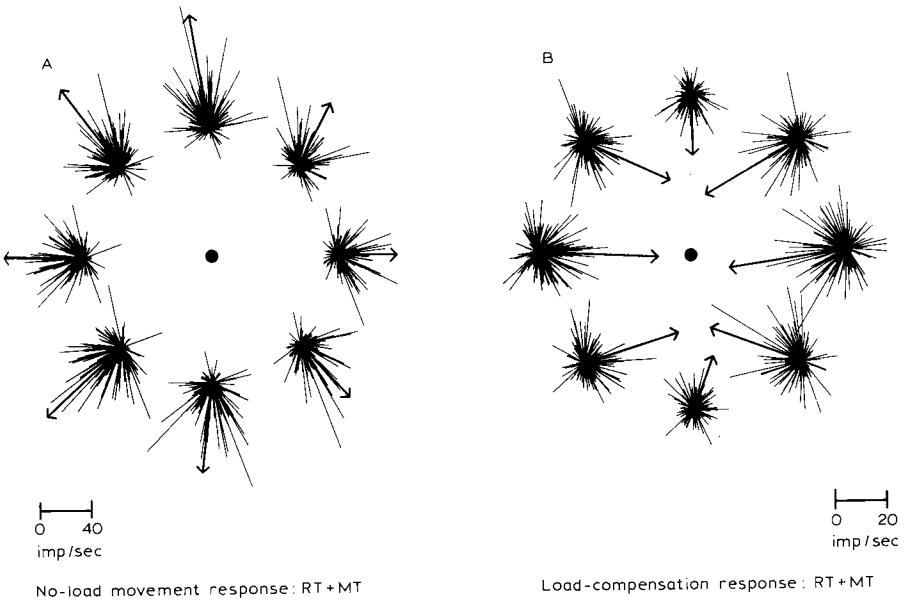

Fig. 25. Vectors representing the discharge of motor cortex neurons in relation to movement direction and load direction. Monkeys moved a handle to target positions surrounding a centrally located starting position (center filled circle). In (A) the position of each cluster of vectors relative to the center point represents the direction of movement for that cluster; in (B) the position of the cluster relative to the center point represents the direction the external load pulled the pendulum away from the center starting point. External loads that pulled the pendulum in each of the target directions were then applied for each of the 8 directions of active movement. For any movement direction, external load could reduce the magnitude of the movement vector to near zero (for loads assisting movement) or substantially increase it (for loads opposing movement). See text for further description. (From Kalaska et al., 1989)

load related change in activity of the cell, relative to the activity during the control block. Increases in discharge rate relative to the rate for the same movement direction during the control block were represented as vectors pointing towards the cell's preferred movement direction; decreases in discharge rate caused by the load were represented as vectors pointing opposite the cell's preferred movement direction. Each vector cluster represents the change in discharge of the sample population caused by one direction of load. Note that for each outwardly oriented load direction, the vector sum of the motor cortex population discharge (heavy arrows) is oriented inward, appropriate to compensate for the externally applied load. In other words, loads opposing movement in a particular direction strongly activated cells for which that was the preferred movement direction, whereas loads assisting movement in that direction greatly reduced cell activity. Most cells (95%) showed significant variations in tonic discharge associated with external loads. However, some cells showed clear modulation with movement direction, but were not influenced by loads, confirming earlier work of Thach (1978). Most of the cells were probably pyramidal neurons in layer V based on their large spike amplitudes and location at intermediate cortical depths. Preliminary findings reported by Kalaska, as part of the same study, suggest that the majority of cells in more superficial layers of motor cortex encode movement direction; that is, these cells are insensitive to external load. For example, microstimulation threshold was negatively correlated with an index of cell sensitivity to load. Based on these early findings, it is tempting to speculate that a transfor-

mation from representation of kinematics (intended direction and velocity of movement) to dynamics (joint torques required to produce the intended movement) occurs within motor cortex. In any case, the discharge of most motor cortex cells sampled from deep layers in this task was dependent on the load against which the monkey worked and the force generated by the agonist muscles. These findings are consistent with previous studies showing that motor cortex cells, and particularly CM cells, encode force or torque parameters of movement (Evarts, 1968; Cheney and Fetz, 1980).

Georgopoulos et al. (1984) found that the preferred movement direction of motor cortex cells tends to be columnarly organized in a way that may correlate with the cluster organization of CM cells described in an earlier section. CM cells probably exhibit preferred movement directions reflecting the cell's weighted facilitation of a particular combination of target muscles (Georgopoulos, 1988). The discharge of cells in more superficial layers of the same cortical column might also exhibit similar preferred movement directions but with a primary relation to movement direction rather than muscle activation parameters.

Task specific discharge of descending premotor neurons

By their facilitation of target muscles, individual CM and RM cells can be considered to represent muscle fields, in some cases individual muscles but more frequently combinations of muscles. The activity of motoneurons is rigidly coupled to the activity of the muscle fibers they innervate, and is predictable based on the principle of orderly recruitment. One can ask whether the functional activity of premotor cells is similarly linked to the activity of their target muscles? As discussed in previous sections, consistent coactivation of premotor cells with their target muscles is commonly observed; however, dissociation of premotor cell discharge and target muscle activity has been demonstrated under a variety of conditions, emphasizing the task specific nature of the discharge of some premotor neurons. Dissociation in this case is defined as coactivation under some conditions but absence of coactivation or reciprocal activation under other conditions, despite the presence of clear postspike effects in the cell's target muscles. Conditions under which dissociation has been observed for CM cells include: 1) power grip (Cheney et al., 1985), 2) precision grip (Muir and Lemon, 1983), 3) ballistic movements (Cheney and Fetz, 1980). Fig. 26 compares the discharge of a CM cell under two different task conditions, both of which were associated with strong consistent coactivation of the cell's target muscles (Cheney et al., 1985). One task was alternating wrist movement, which required reciprocal activation of wrist flexor and extensor muscles. The second was a power grip task, which involved squeezing a pair of nylon bars and required coactivation of wrist flexors and extensors to stabilize the wrist. Fig. 26 shows that the cell's activity was strongly engaged for wrist extension – the direction of its target muscles. However, during power grip cell activity was actually reduced despite equally strong activation of the cell's target muscles. Task specificity such as this might be understood in terms of the cell's output effects on muscle activity. The spike-triggered averages (top) show that this cell facilitated multiple wrist extensors and suppressed a wrist flexor. These effects were confirmed in stimulus-triggered averages computed at the same site. The functional uncoupling of the activity of this CM cell and its target muscles may be related to the fact that the cell reciprocally suppressed the flexor muscles. Because this suppression would interfere with the cocontraction of flexors and extensors needed for power grip, the central motor program for cocontraction may exclude reciprocally organized cells.

A similar dissociation was reported by Muir and Lemon (1983) for CM cells facilitating intrinsic hand muscles. They found that CM cells were preferentially active in relation to precision grip, but were relatively inactive during power grip despite the fact that power grip involved greater

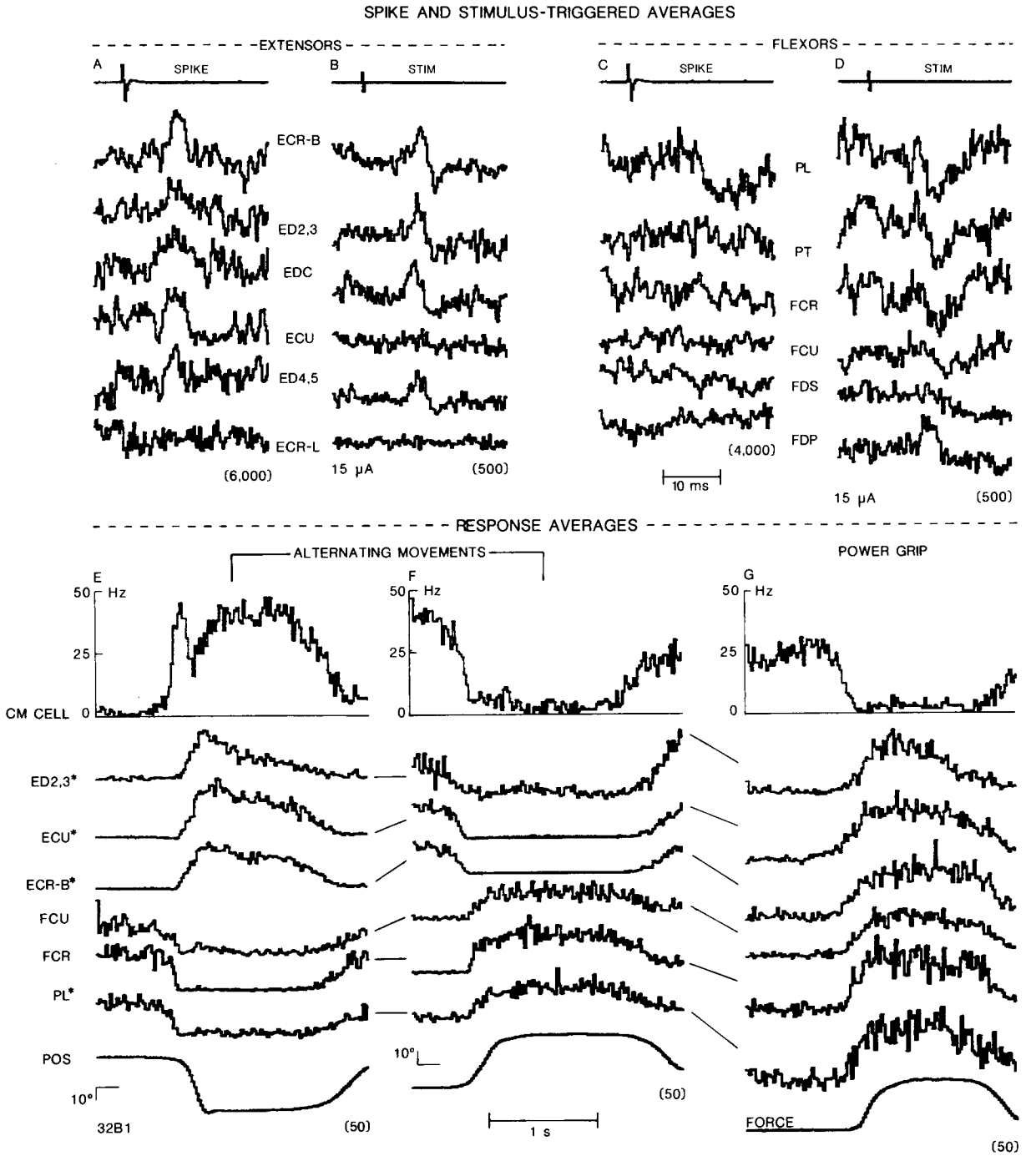

Fig. 26. Active movement discharge of a CM cell during alternating wrist movements and power grip. Spike-triggered averages show that this is a reciprocally organized cell which facilitated extensors and suppressed a flexor-PL. These effects were confirmed in stimulus-triggered averages computed at the same cortical site. Note that cell discharge shuts off during power grip despite strong activation of the cell's target muscles. (From Cheney et al., 1985)

activation of the cell's target muscles (Fig. 27).

Still another example of functional uncoupling of the activity of a premotor cell and its target muscles was reported by Cheney and Fetz (1980). CM cells were highly active during accurate, controlled wrist movements to 10 degree targets but nearly inactive during ballistic, uncontrolled movements that more strongly activated the cell's target muscles.

In all these instances, a muscle representation can be identified for each cell. PSpFs computed under different task conditions might differ somewhat in absolute magnitude and occasionally a muscle would show PSpF in one task but not the other. Nevertheless, the clearest PSpFs typically were present in both task conditions and the relative magnitude of PSpF was usually similar. Therefore, over short periods of time the muscle field seems relatively fixed, reflecting "hard wired" neural connections. Functional activation of the premotor cell, on the other hand, is subject to much greater short term flexibility. Cell activation shows a task specificity that, in some cases, may be related to the functional role of the cell's suppressed target muscles, but in other cases, seems to depend on factors beyond simple circuitry, such as the accuracy of a movement or its position along a scale from least to most automatic.

Relative contribution of CM and RM cells to movement

Much of the functional organization of different descending systems is revealed in the response properties and correlational linkages of their individual premotor neurons. However, comparisons of the relative contribution of different descending systems to movement requires that the effects of individual neurons on muscle activity be synthesized as an estimate of the population effect. Quantitative information about the magnitude of synaptic effects from single premotor neurons and the distribution of these effects, coupled with knowledge of the number of neurons converging on a typical motoneuron, enables estimates of the contribution of each descending system to movement. The relative contribution of particular systems may differ for different categories of movement and for movements at different joints. For example, it is likely that reticulospinal and vestibulospinal neurons make a greater contribution to movements at proximal joints during locomotion than the corticospinal and rubrospinal

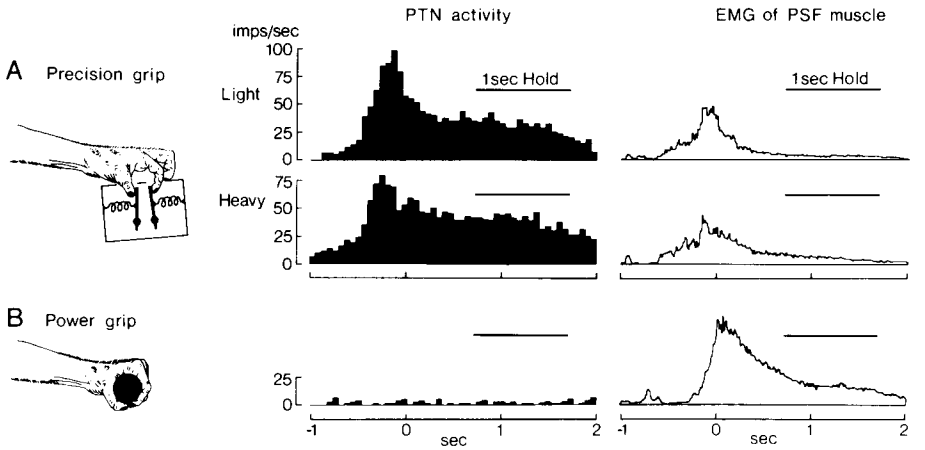

Fig. 27. Active movement discharge of a CM cell during precision grip and power grip. EMG activity of the cell's target muscle is also shown. Note that the cell discharges intensely for precision grip but is unrelated to power grip despite stronger activation of its target muscles. (From Muir and Lemon, 1983)

systems. On the other hand, skilled movements of the hand rely more heavily on the corticospinal and rubrospinal systems. Sufficient quantitative information now exists on the synaptic effects and firing patterns of individual CM and RM cells during wrist movements to begin to estimate their relative contribution to motoneuron activity.

Fetz et al. (1989) estimated the net contribution of corticospinal and rubrospinal colonies to motoneuron firing rate during the hold period of a ramp-and-hold movement. The static component of movement was chosen to avoid the complications associated with the many unknown variables that come into play during transitions between flexion to extension. The contribution of CM and RM cell populations to the firing of an average target motoneuron was estimated from:

1. The increment in firing of a motoneuron associated with a premotoneuronal EPSP of a particular amplitude. Cope et al. (1987) found that the unitary EPSPs from single muscle spindle Ia afferents produced above chance discharge of target motoneurons that was proportional to EPSP amplitude (Fig. 2). Although derived from muscle spindle Ia afferent data, this relation may also hold for other inputs to the motoneuron.
2. The number of CM or RM cells converging on a single motoneuron, that is, the size of the CM or RM colony.
3. The firing rates of CM and RM cells during the hold phase of the task.

These factors can be expressed by the following relationship:

$$(1)\ df_m \cong 0.0001*h*n*f$$

where df_m is the increment in motoneuron firing rate, 0.0001 is the constant that provides the transformation from EPSP amplitude to motoneuron firing (a 100 μV EPSP evokes 1 spike for every 100 occurrences), h is the mean amplitude of the EPSP for a particular input, n is the number of neurons converging onto the motoneuron and f is the mean firing rate of the presynaptic neurons. The number of CM or RM cells converging on a single motoneuron is difficult to estimate as is the size of the individual EPSPs from these neurons. However, the product of h and n is the maximal EPSP which has been measured in anesthetized preparations. Measurements of the maximal CM-EPSP range from 1 to 3 mv (Clough et al., 1968; Phillips and Porter, 1977; Shapovalov et al., 1971; Fritz et al., 1985). Shapovalov found that RM-EPSPs in macaque monkeys averaged 0.6 mv. Using an intermediate magnitude of 2 mv for CM cells in expression (1) above and a measured extensor CM cell mean firing rate of about 62 Hz for holding against an intermediate extension load of 0.1 Nm (Fig. 22) yields a motoneuron firing rate increment of 12.4 Hz attributable to the CM input. Similarly, a maximal RM-EPSP of 0.6 and a measured mean extensor RM cell firing rate of 60 Hz at 0.1 Nm yields a motoneuron firing rate increment of 3.6 Hz. The sum of these is 16 Hz which is about 75% of the mean firing rate of extensor motor units at 0.1 Nm. The contribution of the CM system is about three times greater than that of the RM system.

Conclusion

The technique of spike-triggered averaging of EMG activity in awake monkeys is yielding new information at the level of individual premotor neurons concerning the sign, strength and distribution of synaptic effects from descending systems to spinal motoneurons. This data complements and extends that derived from intracellular and monosynaptic reflex conditioning studies in anesthetized animals. More importantly, the technique can be applied in awake animals, enabling not only identification of motor output cells within the brain but also correlations between a cell's synaptic influences and its functional relations to movement. Spike-triggered averaging of EMG activity has provided new insights concerning the organization and function of the rubrospinal and corticospinal systems in primates and future applications of the method can be ex-

pected to further elucidate the role of different premotor neurons in movement.

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Abbreviations

CM – corticomotoneuronal
CNS – central nervous system
dT/dt – rate of change of torque
EMG – electromyogram
EPSP – excitatory postsynaptic potential
HRP – horseradish peroxidase
IPSP – inhibitory postsynaptic potential
PSpF – postspike facilitation
PSpS – postspike suppression
PStF – poststimulus facilitation
PStS – poststimulus suppression
PTN – pyramidal tract neuron
RIFMs – relatively independent finger movements
RM – rubromotoneuronal
S-ICMS – single pulse intra-cranial microstimulation
SpTA – spike triggered average
StTA – stimulus triggered average

Muscles:

ED 2,3 – extensor digitorum two and three
ED 4,5 – extensor digitorum four and five
EDC – extensor digitorum communis
ECU – extensor carpi ulnaris
ECR-B – extensor carpi radialis brevis
ECR-L – extensor carpi radialis longus
FDS – flexor digitorum sublimis
FDP – flexor digitorum profundus
FCU – flexor carpi ulnaris
PL – palmaris longus
FCR – flexor carpi radialis
PT – pronator teres

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