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Synaptic Linkages Between Corticomotoneuronal Cells Affecting Forelimb Muscles in Behaving Primates

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Smith WS, Fetz EE. Synaptic linkages between corticomotoneuronal cells affecting forelimb muscles in behaving primates. *J Neurophysiol* 102: 1040–1048, 2009. First published June 10, 2009; doi:10.1152/jn.91052.2008. To elucidate the cortical circuitry controlling primate forelimb muscles we investigated the synaptic interactions between neighboring motor cortex cells that had postspike output effects in target muscles. In monkeys generating isometric ramp-and-hold wrist torques, pairs of cortical cells were recorded simultaneously with independent electrodes and corticomotoneuronal ("CM") cells were identified by their postspike effects on target forelimb muscles in spike-triggered averages (SpTAs) of electromyographs (EMGs). The response patterns of the cells were determined in response-aligned averages and their synaptic interactions were identified by cross-correlograms of action potentials. The possibility that synchronized firing between cortical cells could mediate spike-correlated effects in the SpTA of EMG was examined in several ways. Sixty-two pairs consisted of one CM cell and a non-CM cell; 15 of these had correlogram peaks of the same magnitude as that of other pairs, but the synchrony peaks did not mediate any postspike effect from the non-CM cell. Twelve pairs of simultaneously recorded CM cells were cross-correlated. Half had features (usually synchrony peaks) in their cross-correlograms and the cells of these pairs also shared some target muscles in common. The other half had flat correlograms and, in most of these pairs, the CM cells affected different muscles. The latter group included pairs of CM cells that facilitated synergistic muscles. These results indicate that common synaptic input specifically affects CM cells that have overlapping muscle fields. Reconstruction of the cortical locations of CM cells affecting 12 different muscles showed a wide and overlapping distribution of cortical colonies of forelimb muscles.

INTRODUCTION

The functional organization of cortical connections between precentral corticomotoneuronal (CM) cells and motoneurons has been elucidated by intracellular recording of CM excitatory postsynaptic potentials (Jankowska et al. 1975; Phillips and Porter 1964; Porter and Lemon 1993), by anatomic tracing of CM terminals (Shinoda et al. 1981), and by measuring the postspike effects of CM cells in behaving monkeys (Buys et al. 1986; Davidson et al. 2007; Fetz and Cheney 1980; Griffin et al. 2008; Jackson et al. 2003; Kasser and Cheney 1985; Schieber and Rivlis 2005; Smith 1989; Smith and Fetz 2009). These studies indicate that single CM cells typically send divergent excitatory connections to motoneurons of multiple muscles and, in some cases, exert reciprocal inhibitory effects on antagonists of their facilitated target muscles. The next step

in understanding the functional hierarchy of these cells concerns the way that CM cells are controlled by their synaptic inputs in motor cortex. When two CM cells are coactivated during a movement in which their target muscles are synergistically activated, they may be driven by common presynaptic inputs or by separate coactivated inputs. These two possibilities can be experimentally distinguished by determining whether the action potentials of coactivated CM cells show evidence of synchrony.

Simultaneously recorded pairs of CM cells can show evidence of synchronous firing during alternating wrist movements (Cheney and Fetz 1985; Smith and Fetz 1989) and during a precision grip task (Jackson et al. 2003). Examining the degree of synchronization in a specific correlation window, Jackson et al. (2003) found positive synchrony between CM cells with similar muscle fields and negative correlations between cells with opposing effects in the same muscles. We here document parameters of these correlations for 12 pairs of CM cells with forearm target muscles, recorded during alternating isometric wrist torques and 62 pairs that included one CM cell. We found that all CM pairs that project to one or more common muscles receive a form of common synaptic input, whereas pairs with nonoverlapping muscle fields appear to be driven by independent inputs. We also document the cortical locations of CM cells facilitating 12 specific forelimb muscles. These data are combined with previous results (Smith and Fetz 2009) into a model of functional synaptic connections within primate precentral cortex.

METHODS

Experimental techniques for this study were largely the same as previously described (Smith and Fetz 2009). Cells were classified as pyramidal tract (PT) or nonpyramidal tract (NPT) neurons, depending on whether they could be activated antidromically by stimulating the medullary pyramids. In addition, CM cells were identified by compiling spike-triggered averages (SpTAs) of rectified forelimb electromyographic (EMG) activity from the second of two *Macaca mulatta* monkeys (Fetz and Cheney 1980). Multiple flexor and extensor muscles of the right forelimb were routinely implanted for bipolar recordings using multistranded, Teflon-insulated, stainless steel wire (Bioflex, Cooner Wire). The six flexor muscles included flexor digitorum sublimis (FDS), flexor digitorum profundus (FDP), flexor carpi radialis (FCR), flexor carpi ulnaris (FCU), pronator teres (PT), and palmaris longus (PL). Six of the following extensor muscles were implanted: extensor digitorum communis (EDC), extensor digitorum 4 and 5 (ED4,5), extensor digitorum 2 and 3 (ED2,3), extensor carpi radialis longus (ECR), extensor carpi ulnaris (ECU), abductor pollicis longus (APL), extensor pollicis longus (EPL), and supinator (SUP). EMG signals were tested for cross talk for each implant and every

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muscle combination, as described elsewhere (Fetz and Cheney 1980). EMG recordings were considered independent if EMG-triggered averages of all other EMGs were flat or if features that were found did not exceed 15% of baseline mean. When a CM cell was observed to produce postspike facilitation (PSpF) in two EMGs exhibiting cross talk, the average exhibiting smaller PSpF was rejected and not taken as evidence for independent PSpF in that muscle.

Many of the recorded neurons were within the anterior bank of the central sulcus, making it desirable to derive topographic maps of CM cell and horseradish peroxidase (HRP)–labeled neurons from histological sections. To represent these locations more accurately, the precentral cortex and portions of postcentral cortex were "unfolded" by projecting relevant locations to layer V, then mapping the layer V contour to a plane. A custom program translated each cell locus (both recorded cell location and the location of HRP-labeled cells) to the nearest point on the layer V contour. A line integral from this projection point along layer V to a reference point was calculated. The reference point was defined as the intersection of a vertical plane parallel to the central sulcus and normal to the layer V contour. The cell location was then mapped to a rectangular x/y location on the projection plane; the x coordinate was the line integral and the y coordinate was the slice's parasagittal location. Three histological reference points were also projected: the location of the area 3a/4 junction, the point of maximum curvature of the convexity, and the depth of the central sulcus. These boundaries were mapped to the projection plane and connected by lines (see Figs. 6–8).

RESULTS

Correlations between CM and non-CM cells

Sixty-two pairs of motor cortex cells consisted of one CM cell and either a PT neuron (22 pairs) or an NPT cell (40 pairs). Most of these pairs (76%) showed no features in their cross-

correlation histograms (CCHs)—a larger proportion of uncorrelated pairs than that in any other group. Fifteen of these pairs showed evidence of synchrony in the form of a central peak in the CCH. The mean area of these peaks ($A_N = 0.052 \pm 0.037$) was essentially the same as that of all the cortical pairs ($A_N = 0.053 \pm 0.041$). In none of these 15 cases was the synchrony peak sufficient to mediate postspike effects from the non-CM cell. An example of a CM–PT neuron pair is illustrated in Fig. 6 of the companion paper (Smith and Fetz 2009). Despite a relatively large central CCH peak ($A_N = 0.11$) the PT neuron showed no PSpF in any of the five muscles facilitated by the CM cell. Figure 1 illustrates an example of a CM–NPT cell pair with a lagged central peak ($A_N = 0.06$). The NPT cell covaried with the CM cell, firing at a much higher rate. The CM cell facilitated three target muscles (*bottom left*), but the NPT cell showed insignificant postspike effects, even for an exceptionally large number of triggers.

Cross-correlation of CM cell pairs

Twelve pairs of CM cells were recorded simultaneously for a sufficient duration to characterize their muscle fields and perform cross-correlation analysis of their spike trains. Examples of such paired recordings are shown in Figs. 2–4. Figure 2 shows two CM cells that facilitated flexor muscles. Cell 103-2 facilitated FDS and FDP, whereas cell 104-3 facilitated FDS, FDP, and FCU. Both cells fired phasically at the onset of flexion and less so at the onset of extension torques. Cross-correlation of their spike trains revealed a significant central peak, with $A_N = 0.06$. Both cells were recorded on the convexity of the precentral gyrus,
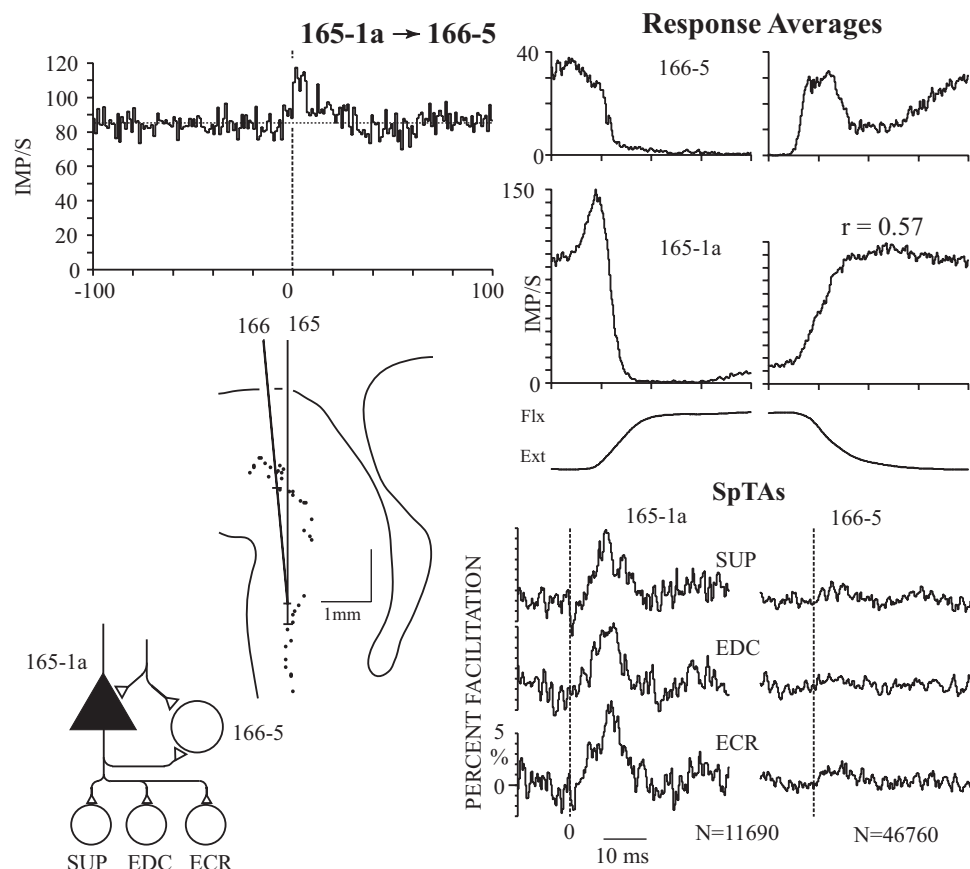

FIG. 1. Synaptic interactions and force relation of coactivated CM and NPT neurons. *Top left*: the cross-correlation histogram of units 165-1a and 166-5. *Top right*: response averages for ramp-and-hold wrist torques. $r = 0.57$ measures the covariation of cell firing. SpTAs (*bottom right*) show clear PSpF in SUP, EDC, and ECR for the CM cell (165-1a). (*N* indicates the number of sweeps in the SpTA.) Cortical location of cell pair is shown in *middle left*; dots represent antidromically labeled corticospinal cells. Diagram at *bottom left* represents the simplest synaptic circuit producing lagged and central peak. CCH, cross-correlation histogram; CM, corticomotoneuronal; ECR, extensor carpi radialis longus; EDC, extensor digitorum communis; NPT, nonpyramidal tract; PSpF, postspike facilitation; SpTA, spike-triggered average; SUP, supinator.
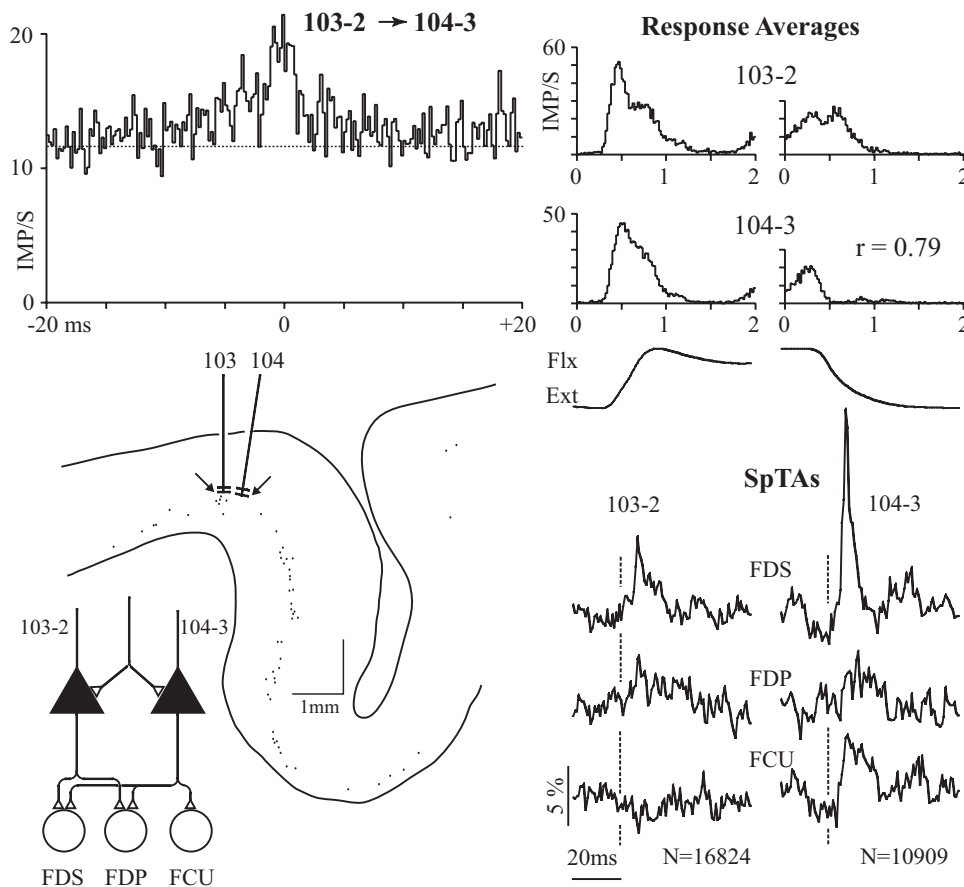
FIG. 2. Interactions and force relation of 2 synergist CM cells during active wrist torques. The CCH of units 103-2 and 104-3 is shown in the *top left*. Response averages (*top right*) show firing frequency for ramp-and-hold wrist torques. $r = 0.79$ gives a measure of the covariation of cell firing. SpTAs for 3 flexor muscles show clear PSpF in FDS and FDP for unit 103-2 (*left column*) and in FDS, FDP, and FCU for unit 104-3 (*right column*). (Ordinate is scaled in percentage facilitation above baseline.) *Bottom left*: the location of recorded cells in independent electrodes from the precentral convexity. The diagram illustrates the simplest circuitry mediating effects: both CM cells receive common synaptic input and project to overlapping muscle fields. FCU, flexor carpi ulnaris; FDP, flexor digitorum profundus; FDS, flexor digitorum sublimis.

with independent electrodes. Although many spikes in these two CM cells were correlated, several lines of evidence indicate that the synchrony between them is not sufficient to explain the PSpF from one cell as mediated by correlation with the other. First, the FCU muscle was facilitated only by 104-3 but not by 103-2. Second, for the large PSpFs in FDS, convolving the correlogram peak with the PSpF from either cell could not replicate the sharp PSpF from the other cell (Smith and Fetz 1989). However, at sufficiently high gain, the convolution did match the early rise, attributed to synchrony. These CM cells also showed sharp postspike cross-correlation peaks with a single motor unit in FDS (Fig. 20 in Fetz et al. 1991), which were too sharp to be mediated by the broad correlogram peak between the cells. Third, selective SpTAs that eliminated the above-baseline spikes in the other cell still produced PSpF with the same shape (Smith and Fetz 1989). Four other CM pairs were recorded with central peaks in their correlograms; all had at least one muscle in common in their muscle fields (Fig. 4).

Six additional pairs of CM cells showed no overlap in their muscle fields. The example in Fig. 3 shows that unit 144-4 fired phasically prior to flexion of the wrist and facilitated the supinator muscle, whereas unit 143-3, recorded on an adjacent electrode, fired tonically with extension and facilitated EDC. The cross-correlogram between the units is flat, consistent with the absence of any detectable synaptic interaction. Five other CM pairs with flat correlograms were recorded simultaneously (Fig. 5).

The relationships between cross-correlograms and muscle fields are shown for all 12 CM pairs in Figs. 4 and 5. In Fig. 4,

five CM pairs exhibit significant central correlogram peaks and in all pairs the muscle fields of the two CM cells have a least one muscle in common. The cell pair whose correlogram shows a central trough, also shown in Fig. 4, facilitated antagonist muscles. Figure 5 shows the six CM pairs with flat correlograms and their corresponding muscle fields; in none of these did both cells facilitate a common muscle. However, in two of these six cases the cells in the pair produced opposite effects on the same muscle. Together, these results suggest that common synaptic drive may be directed preferentially to CM cells that have common target muscles. In addition, reciprocal common input may be directed to CM cells facilitating antagonists.

Cortical location of CM cells and cortical representation of facilitated muscles

To elucidate the anatomic distribution in motor cortex of CM cells facilitating particular muscles, their location was mapped from histological sections. The entire sample of 39 CM cells was projected to layer V and the cortex unfolded as described in METHODS (Fig. 6). The locations of corticospinal cells, labeled from a wheatgerm agglutinin (WGA)–HRP injection into the contralateral cervical cord, are shown by dots. The labeled population is denser in the anterior bank of the central sulcus (43 cells/mm^2) than anterior to the convexity (21 cells/mm^2) and in area 3 (19 cells/mm^2). Corticospinal cells in any of these regions were absent 2 mm more lateral to the area reconstructed in Fig. 6, which corresponded to regions where

Response Averages

143-3 → 144-4

143-3

144-4

r= 0.13

Flx

Ext

SpTAs

143-3   144-4

EDC

SUP

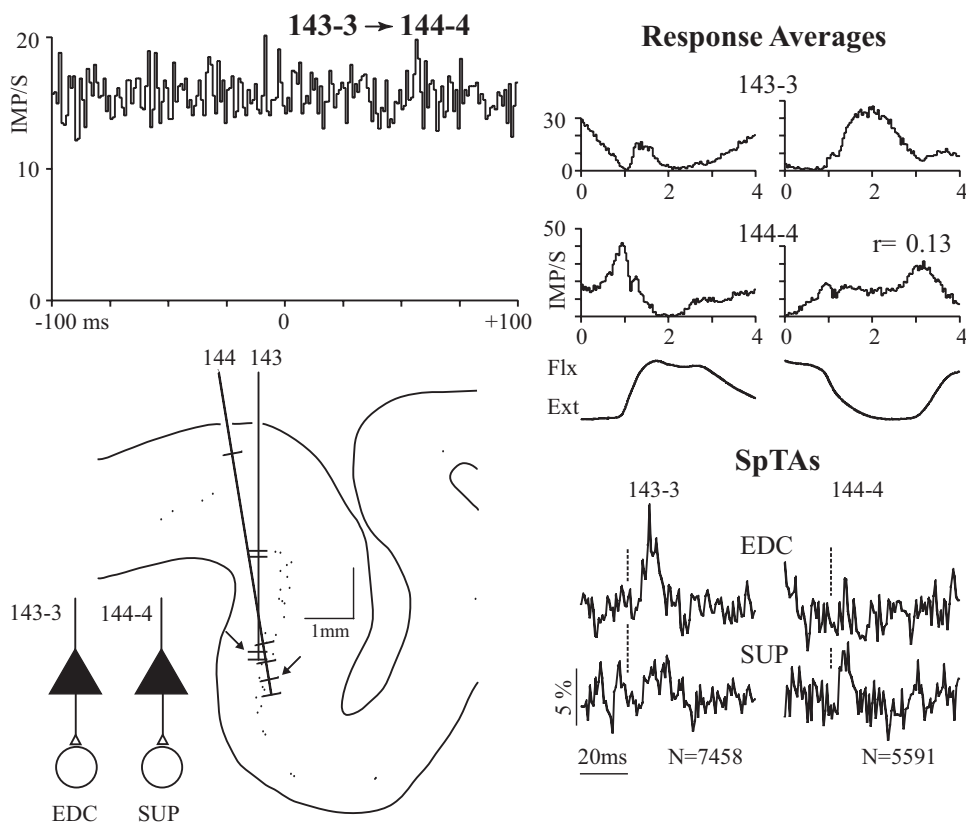5 %

20ms   N=7458   N=5591

FIG. 3. Absence of any feature in the cross-correlogram of 2 CM cells with non-overlapping muscle fields and low covariation. Illustration conventions are the same as described in the caption of Fig. 2. Both cells were recorded deep in the precentral bank.

144 143

143-3   144-4

EDC   SUP

1mm

microstimulation evoked jaw movements and receptive fields were found on the contralateral face.

All CM cells were recorded within area 4 (solid icons in Fig. 6). CM cells that facilitated flexor muscles (circles) clustered in a crescent-shaped region anterolaterally, with the highest den-sity on the lateral convexity. Extensor cells (triangles) were more evenly distributed, but had a higher density posterome-dially. Two CM cells that cofacilitated flexor and extensor muscles were located in the convexity (squares) and another was located deep in the bank near the high extensor density.
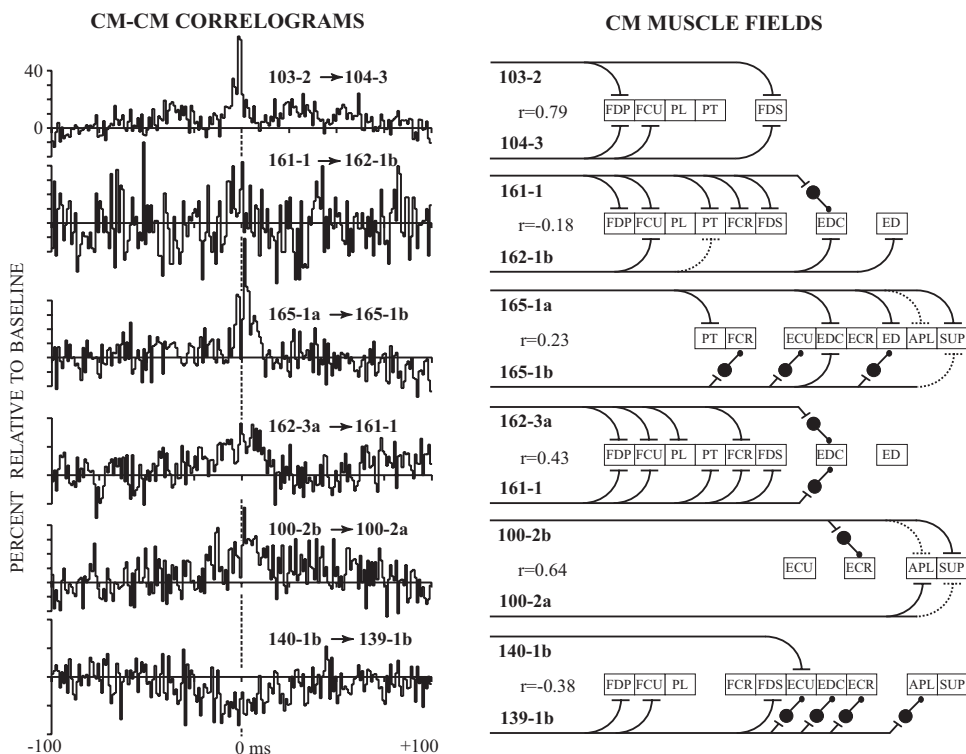
CM-CM CORRELOGRAMS

103-2 → 104-3

161-1 → 162-1b

165-1a → 165-1b

162-3a → 161-1

100-2b → 100-2a

140-1b → 139-1b

PERCENT RELATIVE TO BASELINE

-100   0 ms   +100

CM MUSCLE FIELDS

103-2
r=0.79
104-3
FDP FCU PL PT   FDS

161-1
r=-0.18
162-1b
FDP FCU PL PT FCR FDS   EDC   ED

165-1a
r=0.23
165-1b
PT FCR   ECU EDC ECR ED APL SUP

162-3a
r=0.43
161-1
FDP FCU PL PT FCR FDS   EDC   ED

100-2b
r=0.64
100-2a
ECU   ECR   APL SUP

140-1b
r=-0.38
139-1b
FDP FCU PL   FCR FDS ECU EDC ECR   APL SUP

FIG. 4. Correlograms for all pairs of CM cells with significant features. The cross-correlogram for each cell pair is shown at *left*, scaled in percentage above baseline. Drawings at *right* indicate the CM cells' muscle fields. The reference and target cell projections are on the *top* and *bottom*, respectively. The *r* values give the response similarity of the pair during ramp-and-hold wrist torques. A square in the muscle column indicates the muscle was recorded and SpTAs were compiled. A flat terminal projection implies PSpF and a link via a darkened interneuron indicates PSpS. The dashed terminals represent synchrony effects, whose perispike latency was too early to be mediated directly.

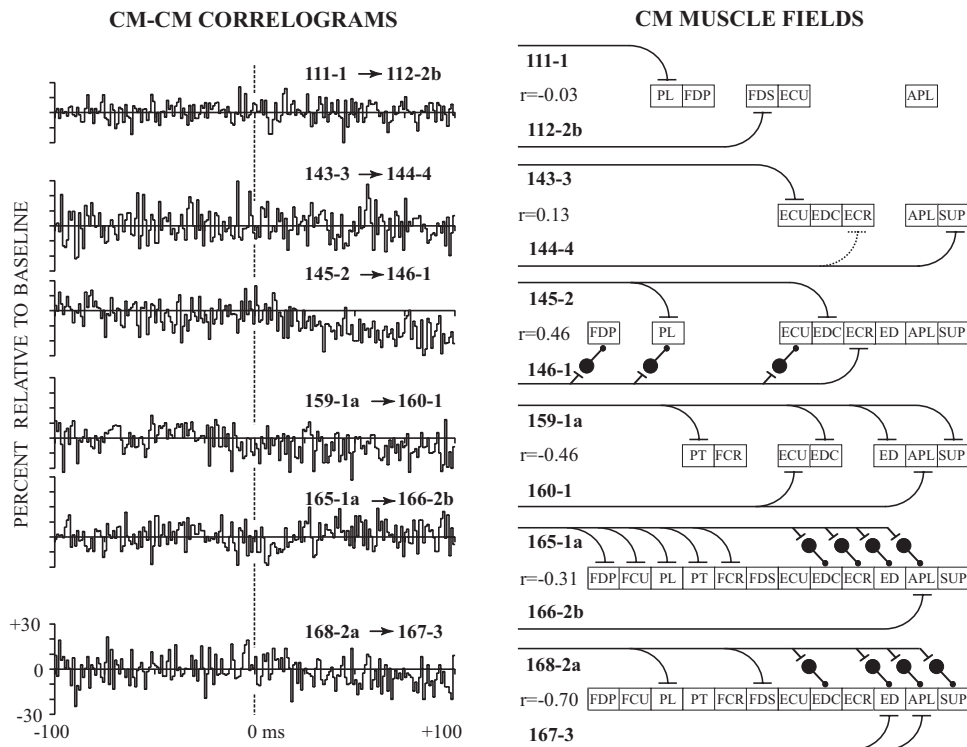## CM-CM CORRELOGRAMS

CM MUSCLE FIELDS

FIG. 5. Correlograms and muscle fields from CM cell pairs with featureless correlograms. Illustration conventions are the same as in Fig. 4. These pairs had no facilitated target muscles in common, although 2 pairs had reciprocal effects on common muscles.

This inhomogeneous distribution of flexor and extensor cells is a result of a clustered representation of the facilitated muscles, as shown in Figs. 7 and 8. Figure 7 shows the locations of CM cells facilitating each of the six flexor muscles. Squares represent CM cells that facilitated the identified muscle and dots indicate the locations where SpTAs were performed for that muscle, but showed no PSpF. CM colonies of the muscles FDP, FCU, FDS, FCR, and PL had similar cortical distributions, whereas CM cells of muscle PT were more evenly distributed. The absence of cells facilitating flexor muscles in the posteromedial region may be due to the rarity with which flexor muscles were studied in this location. The colonies of cells facilitating extensor muscles were more widely distributed than flexors (Fig. 8). Only EDC and ECU formed a

localized cluster compared with the cortical representations of extensors of the thumb and SUP. The higher density of extensor CM cells in the posteromedial region is due mostly to the punctate representation of muscle EDC.

DISCUSSION

Synchronization between CM cells and postspike facilitation

The primary defining characteristic of CM cells is postspike facilitation, which identifies a correlational linkage to muscles. Whether this correlational linkage is produced by anatomic corticomotoneuronal connections depends on the mechanisms mediating PSpF. In addition to a primary correlational linkage
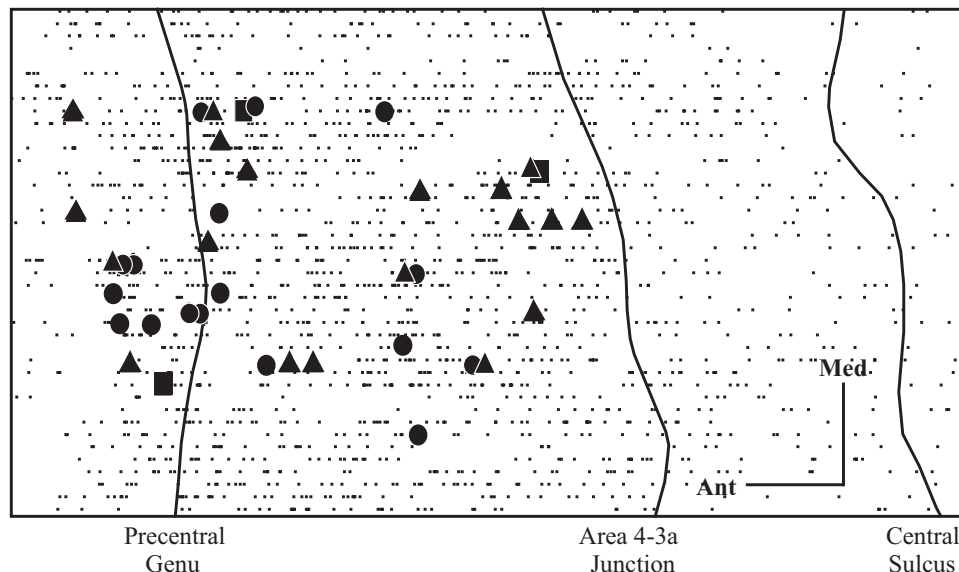

FIG. 6. Cortical locations of all CM and corticospinal cells with precentral gyrus unfolded. The central dividing line represents the transition between area 4 (*left*, anterior) and area 3a (*right*, posterior). The *left line* indicates the convexity (point of maximum curvature) and the *right line* represents the depth of the central sulcus. The bank of area 4 lies between the convexity and the area 4–3a border. Dots represent corticospinal cells labeled by wheatgerm agglutinin–horseradish peroxidase. All CM cells were recorded within area 4. Flexor CM cells (circles) and extensor CM cells (triangles) overlapped spatially. Squares indicate CM cells cofacilitating flexors and extensors. Scale bar = 1 mm.
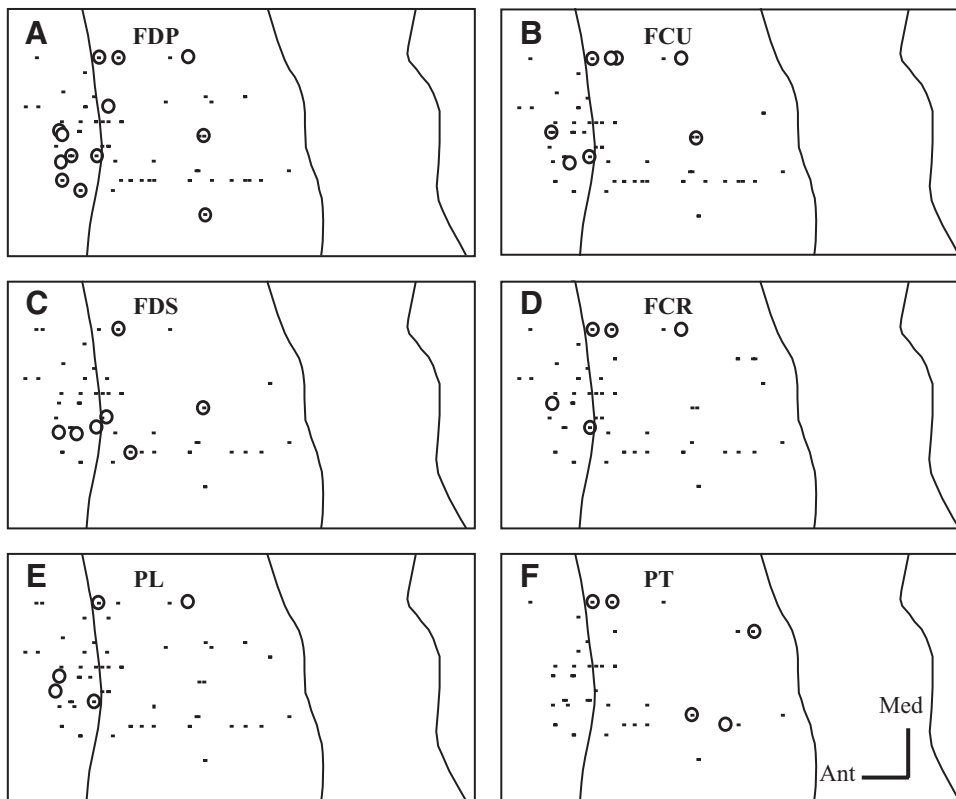
FIG. 7. Location of CM cells facilitating specific flexor muscles, shown on unfolded precentral cortex; dots indicate sites where SpTAs were compiled but found to have insignificant features. Dividing lines are as indicated in Fig. 6. Muscles FDP, FCU, FDS, FCR, PL, and PT are shown in panels *A–F* respectively. All flexor muscles with the exception of PT had representation in the anterolateral area corresponding to the high-density of flexor CM cells shown in Fig. 6. Scale bar is 1 mm for all panels. FCR, flexor carpi radialis; PL, palmaris longus; PT, pronator teres.

via monosynaptic connections to motoneurons, CM cells may have secondary linkages via polysynaptic serial connections or via synchrony with anatomic CM cells (Fetz and Cheney 1980; Jackson et al. 2003; Schieber and Rivlis 2005). Thus a fundamental question concerning its underlying mechanisms is the

degree to which PSpF from one cell may actually be mediated by synchronous firing with another cell that does have anatomic projections. Synchrony here refers to cross-correlational evidence for common synaptic input, not covariation of activity. Our evidence indicates that normal synchrony between
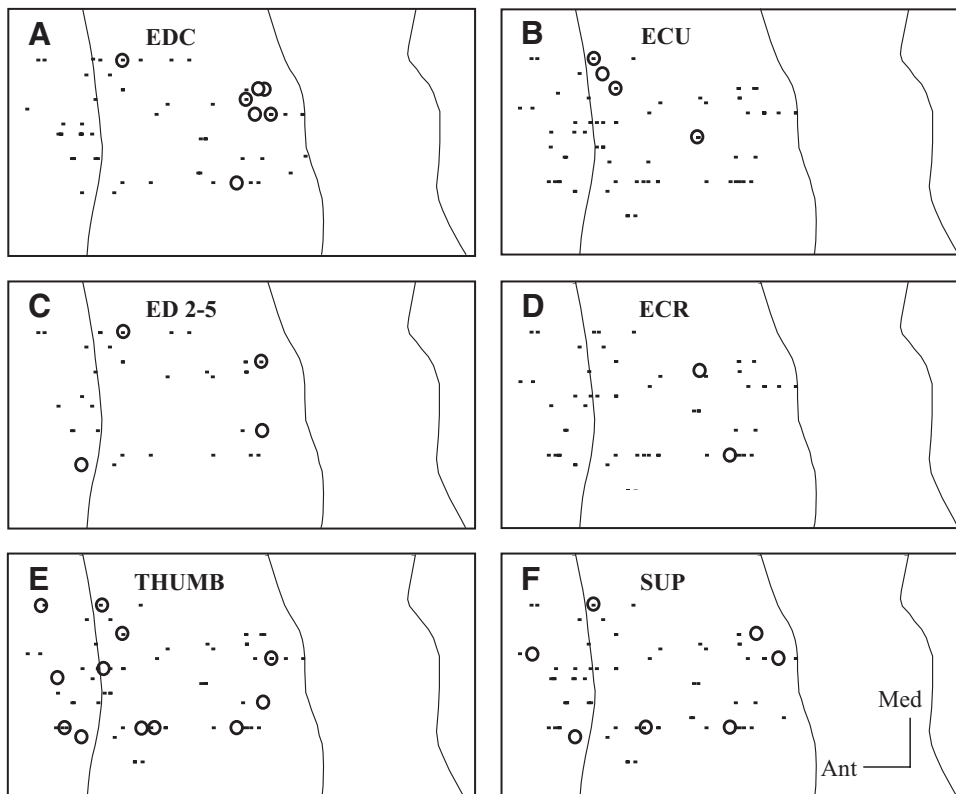

FIG. 8. Location of CM cells facilitating extensor muscles and the thumb, shown on unfolded precentral cortex. Muscles EDC, ECU, ED2–5 (combined ED2–3 and ED4–5), ECR, thumb (combined APL and EPB), and SUP are shown in *A–F*, respectively. Scale bar: 1 mm for all panels. APL, abductor pollicis longus; ECU, extensor carpi ulnaris; ED2–5, extensor digitorum 2 to 5; EPB, extensor pollicis brevis.

cortical cells is insufficient to mediate a significant spurious effect, in agreement with similar observations from the work of others (Jackson et al. 2003; Porter and Lemon 1993). Motor cortical neurons can be clearly synchronized with CM cells but yet exhibit no postspike effects themselves (see also Fig. 4.21 in Porter and Lemon 1993). Moreover, the synchrony between CM cells with partially overlapping muscle fields indicates that some muscles can exhibit PSpF from one cell but not from the synchronized cell.

In contrast to these empirical findings, a simulation study (Baker and Lemon 1998) has indicated that a sufficiently strong synchronizing mechanism may mediate a postspike correlational linkage without a direct corticomotoneuronal synaptic connection. This model calculated the PSpF produced by triggering from a non-CM cell that was synchronized with all of the CM cells (10–30) of a muscle via a single common input cell. It is relevant to note that the assumed single input would produce a stronger synchronizing effect than would be obtained if the pairwise cross-correlogram features were created by separate common inputs. Such a single common input cell that also contacts the non-CM cell (as in the model), would elevate the firing probability of all CM cells simultaneously with the non-CM cell. On the other hand, if the cells are synchronized by independent pairwise common inputs, these different input neurons would be firing at distributed times relative to spikes from the non-CM cell, producing dispersed contributions and a much smaller synchrony peak in the SpTA from the non-CM cell. Physiological evidence for single common input cells that contact all the CM cells of a muscle remains to be found. Indeed this seems unlikely, given the partial overlap of muscle fields and the many cases of non-CM cells synchronized with CM cells.

This simulation led to a proposed criterion for distinguishing whether PSpF was produced by synchrony effects in SpTAs from a non-CM cell or by direct monosynaptic connections from a CM cell. A model CM cell that was not synchronized with any others produced a relatively sharp PSpF; thus a possible distinguishing criterion was the half-width at half-maximum (HWHM) of the PSpF, which exceeded 7 ms for the synchrony mechanism. For model CM cells that were synchronized with others, this distinction was less clear-cut. As documented here and in Jackson et al. (2003), CM cells of the same muscle do tend to be synchronized, suggesting that this HWHM criterion should be interpreted with caution. As the authors acknowledged, their width criterion may reject direct postspike effects, which are likely to appear on top of synchrony effects (e.g., Fig. 2). Moreover, even pure direct effects could generate dispersed PSpFs. A relevant physiological analysis separated the factors that contribute to the poststimulus facilitation (PStF) of EMG produced by single cortical microstimuli. Recording single motor units in forearm muscles, Palmer and Fetz (1985) found that the width of the PStF in the EMG could be accounted for in roughly equal measure by *1*) the width of the poststimulus histogram of motor unit firing (mean: 1.8 ms), *2*) the width of the single muscle unit potential (an additional 2.2 ms), and *3*) the contributions of other motor units with different conduction times (another 2.4 ms). Thus for single microstimuli (which were unsynchronized with other sources of descending effects) the width of PStF was influenced significantly by temporal dispersion of motor unit potentials. For SpTAs from CM cells, cross-correlation results

indicate that a fourth factor would be the synchronization of CM cells of a muscle. Given the high risk of rejecting real effects (false negatives) we did not apply the HWHM criterion to our CM cells.

Synaptic organization of CM cells

Studies of CM cell pairs have elucidated the way that the synaptic coordination between CM cells is related to their muscle fields. Previous evidence that CM cells with similar muscle fields were interconnected came from cross-correlation of such cells (Cheney and Fetz 1985; Jackson et al. 2003; Smith 1989) and from the observation that microstimuli near CM cells evoked poststimulus effects with a profile that matched the profile of postspike effects from the CM cells, but were several times larger (Cheney and Fetz 1985). In our study, half of the 12 pairs of CM cells recorded had significant correlogram features and half did not. None of the uncorrelated pairs had CM cells that facilitated common muscles, although their target muscles could include synergists. In the 6 pairs with correlogram features, 5 pairs were synchronized with common input and the CM cells in these pairs facilitated some target muscles in common. The sixth pair had a central trough in the correlogram and the cells facilitated antagonist muscles. This suggests that CM cells with overlapping targets receive common synaptic inputs and that pairs that facilitate antagonist muscles may receive opposing effects by common pathways, in agreement with the findings of Jackson et al. (2003).

These results suggest a resolution of an apparent paradox concerning divergent connections of CM cells to muscles. CM cells are thought to be responsible, in part, for the relatively isolated finger movements unique to higher primates (Porter and Lemon 1993; Schieber and Rivlis 2005). This would seem incompatible with the divergence of individual CM cells—the smallest direct cortical output unit—to multiple muscles. This connection scheme would appear to preclude access to individual muscles by the regions that drive motor cortex. However, selective common input to those CM cells that converge to common targets could support such precise control. Since other forelimb muscles will share fewer common CM cells among this activated population, the muscles in this "subliminal fringe" could remain subthreshold. Such an anatomic substrate, i.e., the presence of neurons that provide common input to all CM cells that contain a particular muscle in their field, represents a "labeled line" that could be used toward selectively activating particular muscles.

Previous evidence that neighboring CM cells may have identical or overlapping muscle fields suggested a clustered organization of CM cells (Cheney and Fetz 1985). This was further supported by the resemblance between the muscle field of a recorded CM cell and the PStF produced by single-pulse intracortical microstimulation (S-ICMS) applied at the site of recording. In all cases the muscle profile was identical for stimulus-evoked facilitation and spike-produced facilitation, although the stimulus evoked a larger effect. However, S-ICMS evokes activity of cells and passing axons with similar thresholds (Jankowska et al. 1975); given that CM cells with overlapping muscle fields receive common input, it seems likely that these stimuli activated many CM cells via such common afferents. Intracortical fibers that project to CM cells facilitating particular muscles would provide a pathway for S-ICMS to affect distant

CM cells with similar projections. For example, in Fig. 8 stimuli at any cortical site found to facilitate EDC may evoke discharges from all other cortical sites affecting EDC.

Cortical distribution of CM cells

Our reconstruction of the cortical location of CM cells with correlational linkages to particular muscles indicates that most of them were recorded in the precentral bank (Figs. 7 and 8). CM cells affecting different forelimb muscles were largely intermingled. These observations are consistent with previous maps of CM cells (Griffin et al. 2008; Porter and Lemon 1993) and with anatomic evidence from retrograde tracer methods (Rathelot and Strick 2006, 2009). Reconstructing the locations of CM cells labeled by transynaptic retrograde transport from forearm muscles injected with rabies virus, the latter authors found the somas primarily in the depth of the bank and largely intermingled. Their study and ours both mapped the colonies associated with EDC. Our distribution of CM cells facilitating EDC (Fig. 8*A*) is entirely consistent with the anatomic location of cells retrogradely labeled from this muscle (Fig. 3 of Rathelot and Strick 2006).

Summary of synaptic connections to CM cells

Figure 9 schematically summarizes the types of synaptic connections to CM cells that would mediate the correlations seen in this and other studies (Jackson et al. 2003). We found that common synaptic input was preferentially distributed to CM cells that facilitated common target muscles, as shown by the common afferent to two flexor CM cells (#1 and #2) with overlapping muscle fields. Also, antagonist CM cells (*right column*) are shown to be coordinated by reciprocal common input mediated by inhibitory linkages in cortex. The network of common synaptic inputs can be viewed as a "labeled line" to activate individual, corticomotoneuronally innervated muscles. One flexor CM cell (#1) is also shown to produce postspike suppression in an extensor motoneuron through the Ia inhibitory interneuron in the spinal cord. In addition to activating CM cells that are synergists, input fibers may also produce disynaptic inhibition on CM cell antagonists. The cortical inhibitory neurons responsible for such inhibition were recorded rarely, probably due to the bias against recording small neurons with closed dendrites. Nevertheless, the observation that γ-aminobutyric acid blockade with bicuculline may convert motor cortex neurons with unidirectional response patterns to bidirectional patterns (Matsumura et al. 1991) shows that intracortical inhibitory interneurons play a significant role in coordinating cortical neurons.

This and other cross-correlation studies of neocortical neurons found that common input is the most commonly observed synaptic interaction between cortical cells (reviewed in Fetz et al. 1991). In motor cortex one function of this input would be to selectively facilitate a single target muscle or group of target muscles that provide a behaviorally relevant motor synergy. Thus activations of individual distal muscles would be controlled by specific input connectivity as well as the specificity of the influences of individual CM cells. The remarkable absence of common inputs to CM cells with nonoverlapping muscle fields, even when neighboring CM cells facilitate synergists, suggests that the synaptic drives to such cells operate in parallel. Such parallel input to synergists would preserve the specificity of the effects of individual CM cells.
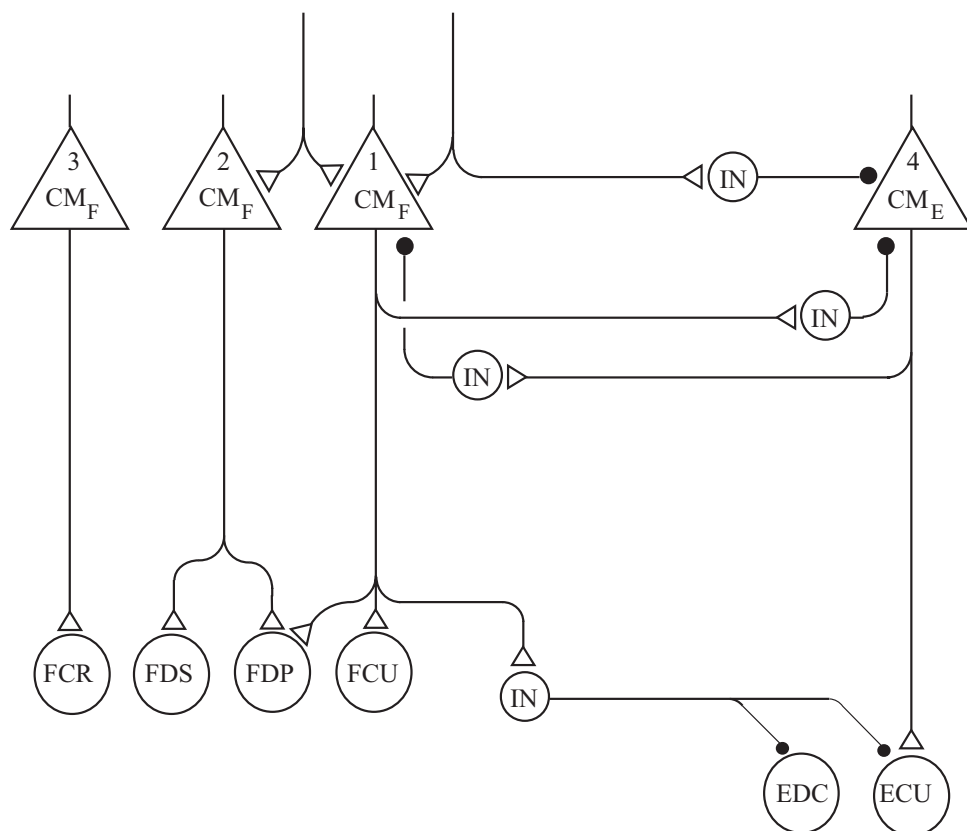

FIG. 9. Schematic representation of synaptic interactions between CM cells projecting to synergistic and antagonistic muscle groups. Motoneurons of 4 flexor and 2 extensor muscles are shown below, each receiving excitatory inputs from precentral CM cells. An inhibitory spinal interneuron is shown to mediate disynaptic inhibition from a CM cell to extensor motoneurons. Although other synaptic interactions are likely to be present, we have shown the simplest circuitry summarizing our data.

This study has documented CM cell activity during a single task: a ramp-and-hold movement that has also been used to document many other classes of premotor neurons (e.g., Fetz et al. 2002); other studies have shown that the postspike effects from CM cells are modulated during different motor synergies (Bennett and Lemon 1996; Davidson et al. 2007; McKiernan et al. 2000). An interesting question for further investigation concerns the task-dependent modulation of inputs that synchronize the relevant CM cells.

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