CHAPTER 17

Distributed processing in the motor system: spinal cord perspective

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Background

The motor system has long been thought to operate in a serial mode of processing (Thach, 1978; Kurata, 1993). In this mode, information regarding motor action evolves sequentially through a series of motor stations, with each successive station translating the arriving information into a set of instructions that progressively contain more motor-related information. Ultimately, the neural information is transformed into muscle action by the segmental spinal circuitry. However, there is abundant evidence, both anatomical and physiological, that conflicts with this notion, leading to the conclusion that the system incorporates parallel processing as well as serial processing (Alexander et al., 1990; Alexander and Crutcher, 1990). The relative extent to which the system employs each of these modes of operation is not yet known. In this paper we will summarize some of the evidence supporting parallel processing in the motor system during generation of voluntary arm movements, and will estimate the role of synchronous firing in such information processing.

Parallel descending information

The anatomy of descending pathways to the spinal cord (Kuypers, 1981) shows that cortical motor cen-

ters control motoneurons (MNs) through three layers (Fig. 1).
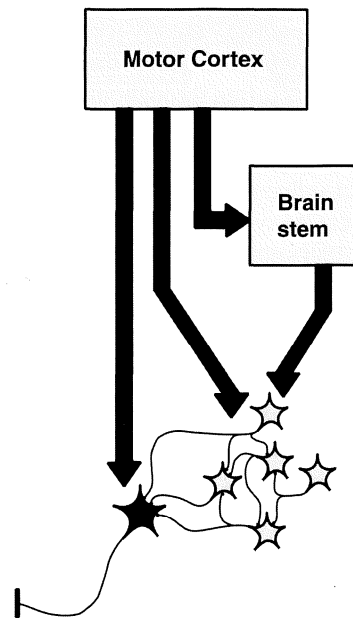

Fig. 1. Schematic illustration of cortical control of MNs. Three main routes are available: CM control originating from layer V cortical cells in primary and non-primary motor areas synapse on MNs (black filled cell); corticospinal control originates from sensory and motor cortices and terminates on spinal INs (gray filled cells), which in turn make synaptic contacts with MNs; cortico-reticulo-spinal pathway affects MNs through a polysynaptic route, including a synapse in the reticular formation and a synapse on spinal INs.

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The first is the corticomotoneuronal (CM) control mediated through *direct* synapses of cortical neurons on MNs. CM axons arise from layer V pyramidal cells located in primary and non-primary motor cortical areas (Murray and Coulter, 1981; Toyoshima and Sakai, 1982; Dum and Strick, 1991; Porter and Lemon, 1993). It has been shown that a single corticospinal axon can contact most, or even all, MNs of a given pool, as well as multiple pools (Lawrence et al., 1985; Shinoda et al., 1986). The second layer of control is the indirect corticospinal pathway; cortical axons contact spinal interneurons (INs), which project mono- or polysynaptically to MNs. These contacts can span up to several segments (Kuypers, 1981) and their specific termination zone is dependent on the area of origin (Martin, 1996). The third layer of control is indirectly mediated through brain stem nuclei (Moll and Kuypers, 1977; Kuypers, 1981). This cortico-reticulo-spinal pathway mostly terminates on long propriospinal INs, which distribute their axons to multiple spinal segments (often throughout the length of the cord). The latter two levels of supraspinal control affect MNs indirectly through segmental INs. Although this indirect influence may seem weak compared with the direct CM synapses, it can have a powerful impact given that spinal INs provide more than 90% of the input to MNs (Porter and Lemon, 1993). It has been estimated that each MN receives input from several thousand segmental INs (Alstermark and Kummel, 1990). The relative numbers of MNs (several thousand) and INs (few hundred thousand) in each segment (Binder, 1989) suggest a high degree of convergence of IN input on MNs. The supraspinal information arriving to the spinal cord through these various routes is diverse, containing both motor, premotor and sensory information (Murray and Coulter, 1981; Toyoshima and Sakai, 1982; Dum and Strick, 1996). Our experiments were designed to evaluate the impact of the indirect corticospinal route on the segmental spinal network during voluntary movement.

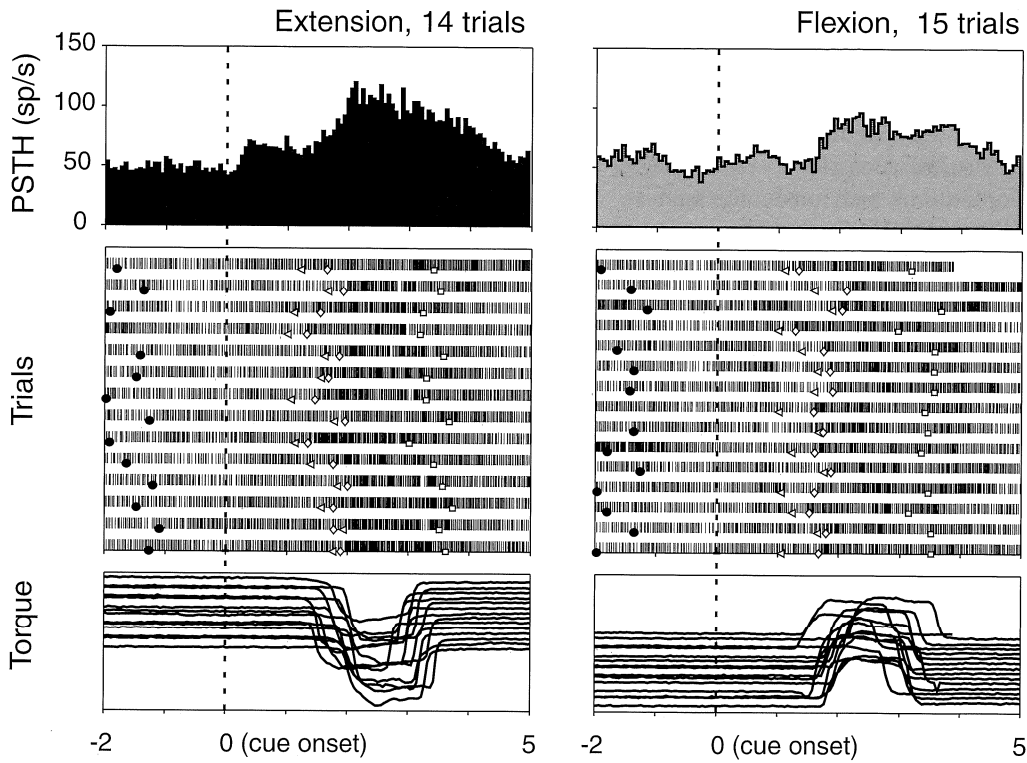## Motor preparatory activity

In addition to the anatomy of the motor system, which provides the structural foundation for parallel processing of information, the physiology is also in agreement with this parallel mode of operation. Existence of pre-movement activity was documented for many supraspinal structures in a task that included an instructed delay period, namely a time period between a cue onset and a trigger 'go' cue (Tanji and Evarts, 1976; Thach, 1978; Kubota and Hamada, 1979; Weinrich and Wise, 1982; Wise et al., 1986; Georgopoulos et al., 1989; Riehle and Requin, 1989). Alexander and Crutcher (1990) observed that the onset time of this preparatory activity greatly overlapped across motor centers regardless of the large difference in their 'synaptic distance' from the effectors (i.e., muscles). Since preparatory activity was considered to be a reflection of motor planning of forthcoming movement, it was suggested that the motor plan is generated in a distributed manner throughout the supraspinal motor system. This notion provided major support to the idea that information in the motor system is processed in parallel.
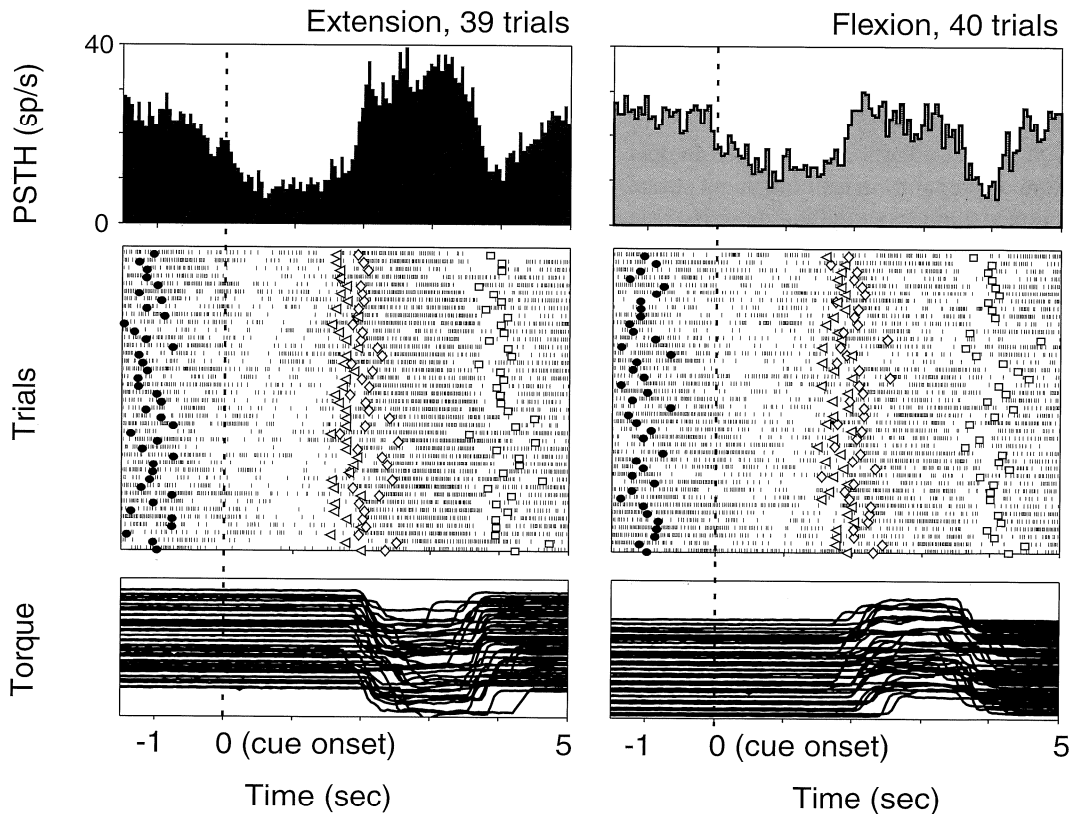
Spinal preparation for movement

To date, the participation of the spinal cord in preparation for movement has been estimated only indirectly. Modulations of monosynaptic reflex pathways (Requin et al., 1977; Bonnet and Requin, 1982; Brunia et al., 1982; Komiyama and Tanaka, 1990) were considered to reflect cortically mediated presynaptic inhibition, which modifies sensory inflow and motoneuuronal excitability in preparation for the ensuing movement. Recently, we have shown (Prut and Fetz, 1999) that in primates performing a flexion/extension wrist task with an instructed delay period, many spinal INs exhibit specific pre-movement delay period modulation of firing rate (Fig. 2A

Fig. 2. Examples of spinal INs exhibiting pre-movement preparatory activity. (A) Spinal IN with an excitatory rate modulation during pre-extension period. Extension (left, black histogram) and flexion (right, gray histogram) trials are plotted separately. For each set of trials, the torque traces (bottom chart), the raster plot (middle chart) and the peri-stimulus-time histogram (PSTH, top chart) are plotted. All trials and events are aligned on cue onset (time zero). In each trial, the event before cue onset is the start of the trial. The events after cue onset are the 'go' signal (triangles), movement onset (diamonds), and movement offset (squares). (B) Spinal IN with inhibitory preparatory activity. (From Prut and Fetz, 1999.)

A. F1303ee, Cell 1

Extension, 14 trials

Flexion, 15 trials

-2   0 (cue onset)   5   -2   0 (cue onset)   5

B. F3905ee, Cell 1

Extension, 39 trials

Flexion, 40 trials

-1   0 (cue onset)   5   -1   0 (cue onset)   5

Time (sec)   Time (sec)

and B). This preparatory activity was found in more than 30% of the recorded cells. The distribution of onset times for spinal preparatory activity had an average of 220 ms (median of 190 ms) and greatly overlapped the onset time previously reported by Alexander and Crutcher (1990) for cortical cells. However, it should be recognized that our measuring technique differed from that employed by others, and this may have contributed methodological differences in the estimated onset times. The preparatory rate modulation that was found in spinal INs was often inhibitory, and in reverse polarity compared with the subsequent movement response of the cell (Fig. 3). Often, the preparatory activity that was found in correct trials was absent when the monkey made an erroneous movement response to the cue. This further indicates that spinal preparatory activity reflects a correct cue-to-response match, as opposed to being cue-related or purely motor-related activity. The existence of rate modulation during the delay period may not be surprising given the extensive input to the spinal cord from sensory and motor areas that exhibit such activity.

Spinal preparatory activity may not only reflect supraspinal processes. It may also take an active part in gating or modulating sensory information arriving from the periphery, which will subsequently be transmitted to supraspinal centers to continuously update the motor plan (Evarts and Granit, 1976; Tanji and Evarts, 1976; Evarts et al., 1984). In this scenario, as soon as preparation for movement starts, activity reverberates throughout the motor system via anatomical parallel loops.

Synchronization within spinal and supraspinal circuitry

In view of the broad and diverse impact of descending pathways on spinal activity and the high degree of convergence of input from segmental INs upon MNs, what is the mechanism by which descending inputs arriving to the cord select a specific motor pattern? In part this input affects spinal circuitry through a direct excitatory drive. Indeed, interrupting descending pathways results in muscle weakness, which presumably reflects the loss of the excitatory drive (Rymer, 1993). An additional mechanism through which supraspinal drive can shape
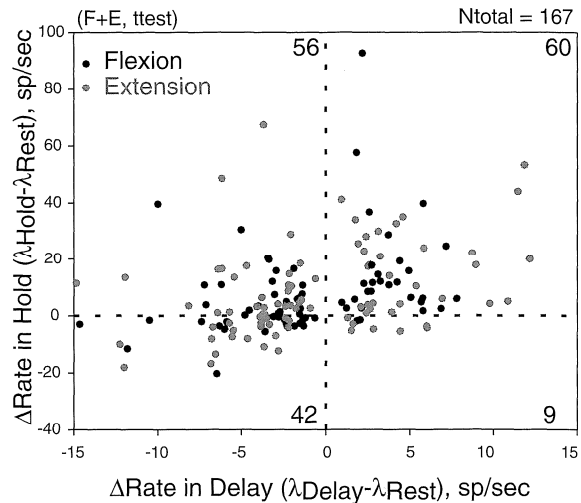

Fig. 3. Relations between polarity of movement response and polarity of delay-period response. Each point represents a case of significant delay modulation in either flexion (black) or extension (gray) trials. Each cell contributes either one or two points. X-axis value is the averaged rate modulation during the delay period relative to the rate during the rest period. Y-axis value is the averaged rate modulation during the subsequent active hold period (when the monkey is actively generating either flexion- or extension-directed torque) relative to the rate during the rest period. The upper-right and lower-left quadrants represent cases of congruency in the polarity of the delay-period activity and hold-period activity (excitation or inhibition in both periods relative to rest). These two quadrants contain 102/167 (61%) of the cases (number of points in each quadrant shown in corners). The upper-left and lower-right quadrants represent cases of reverse polarity between delay- and hold-period activity (excitation/inhibition or inhibition/excitation, respectively, relative to rest). These two quadrants contain 65/167 (39%) of the cases. Of 167 cases plotted, 98 (59%) have inhibitory delay-period modulation (the left two quadrants of the graph). (From Prut and Fetz, 1999.)

spinal activity and control muscle recruitment is by modifying the *temporal properties* of the firing of these neurons.

Synchronized firing was shown for both motor cortical cells (Smith and Fetz, 1989; Vaadia et al., 1995; Hatsopoulos et al., 1998; Grammont and Riehle, 1999; Maynard et al., 1999) and motor units (MUs) (Datta and Stephens, 1990; Nordstrom et al., 1992; De Luca et al., 1993; Schmied et al., 1993). Many have suggested that the synchronized firing of MUs is the result of cortical input (Baker et al., 1988; Farmer et al., 1993; Schmied et al., 1994; Smith et al., 1999) and is most likely gener-

ated by branching of CM fibers within MN pools and across pools of similar muscles (Datta et al., 1991). It seems remarkable that branches emerging from single cells could have such a prominent impact on the firing of two MNs. In fact other factors may play a role in the observed synchronization. The first factor is synchronization among CM cells. Two synchronized CM cells, projecting to different MUs, may entrain those MUs to fire synchronously without direct branching input from either CM cell to both MUs.

A second factor that may contribute to correlation in firing among MUs is synchronization among spinal INs. In our study we recorded activity of spinal INs from three behaving monkeys performing wrist flexion and extension movements. Recordings were made from either single or a pair of electrodes. EMG activity was simultaneously recorded from up to 14 forearm muscles. Online and offline spike-sorting techniques were used to separate multiple waveforms from a single electrode. Spike-triggered averages were compiled for each neuron to determine functional connectivity between cells and muscles.

Firing properties of spinal INs

We first studied the firing properties of single spinal INs (Fig. 4). In many cases, the autocorrelation of spinal INs (Fig. 4A) and MNs (Fig. 4B) had periodic features, reflecting a tendency to fire with regular interspike intervals (ISI). The extent of regularity in firing was quantified by the coefficient of variation (CV) of the ISI. The mean CV values for INs during rest and hold periods (Fig. 4C) were 0.72 and 0.65, respectively; MNs exhibited the highest level of regularity (~0.35). In contrast, the CV of cortical neurons tends to be higher, above 1 (Lee et al., 1998; Shadlen and Newsome, 1998). A value of 0.8 is a lower bound for cortical regularity (Stevens and Zador, 1998). It is clear that spinal circuitry expresses a much higher level of regular firing than cortical cells. For comparison, primary afferent inputs to spinal INs fire more regularly than INs (Matthews and Stein, 1969; Nordh et al., 1983). However, when the fusimotor drive to the muscle spindle is severed, the firing of primary afferents becomes even more regular (Matthews and Stein,

1969). This observation led to the assumption that the supraspinal input, which affects the γ-system, is the source for the increase in variability of primary afferents. Similar supraspinal inputs on spinal INs may act to increase their variability in firing as well.

Correlation in firing among spinal INs

We have found that neighboring spinal INs are more likely to exhibit similar response properties than are neurons located far apart. Such similarity in response patterns can be the result of a common drive. This type of common drive also was considered as a source for a rapid correlation in firing (on the order of a few tens of milliseconds) between cortical neurons (Abeles, 1982). Fig. 5 shows an example of two spinal INs with a significant correlation in their firing. The results of this study are summarized in Table 1.

Correlations were measured between pairs of spinal INs recorded by single or neighboring electrodes. The duration of the computed correlation was ±100 ms. Only cases where at least 200 spikes from each of the units (i.e., the trigger unit and the reference unit) were available were considered. For each pair of units three correlograms were compiled: during rest, during flexion-hold, and during extension-hold (periods in which the monkey actively maintained the cursor within the target on the screen). Of the 438 neuronal pairs for which correlation was computed in at least one behavioral mode, 255 were pairs of units recorded from the same electrode and 183 were pairs recorded from two different electrodes. Of all the histograms, 49 (11%) had a peak in at least one behavioral mode. The frequencies of correlation as a function of behavioral mode and distance between cells are listed in Table 1.

As shown in Fig. 5, in some cases the correlations were dynamic, changing in strength or existence depending on the behavioral mode. We counted the number of cases in which correlation exhibited such dynamic features for those pairs whose correlation was computed in more than one behavioral mode (385 pairs). Only 212 pairs provided sufficient data to compute correlation in three behavioral modes, 173 pairs in two modes, and 53 pairs in one mode only. Of these, 42 pairs had a peak in at least one behavioral mode. Table 2 summarizes the tendency

REST **HOLD FLX** **HOLD EXT**
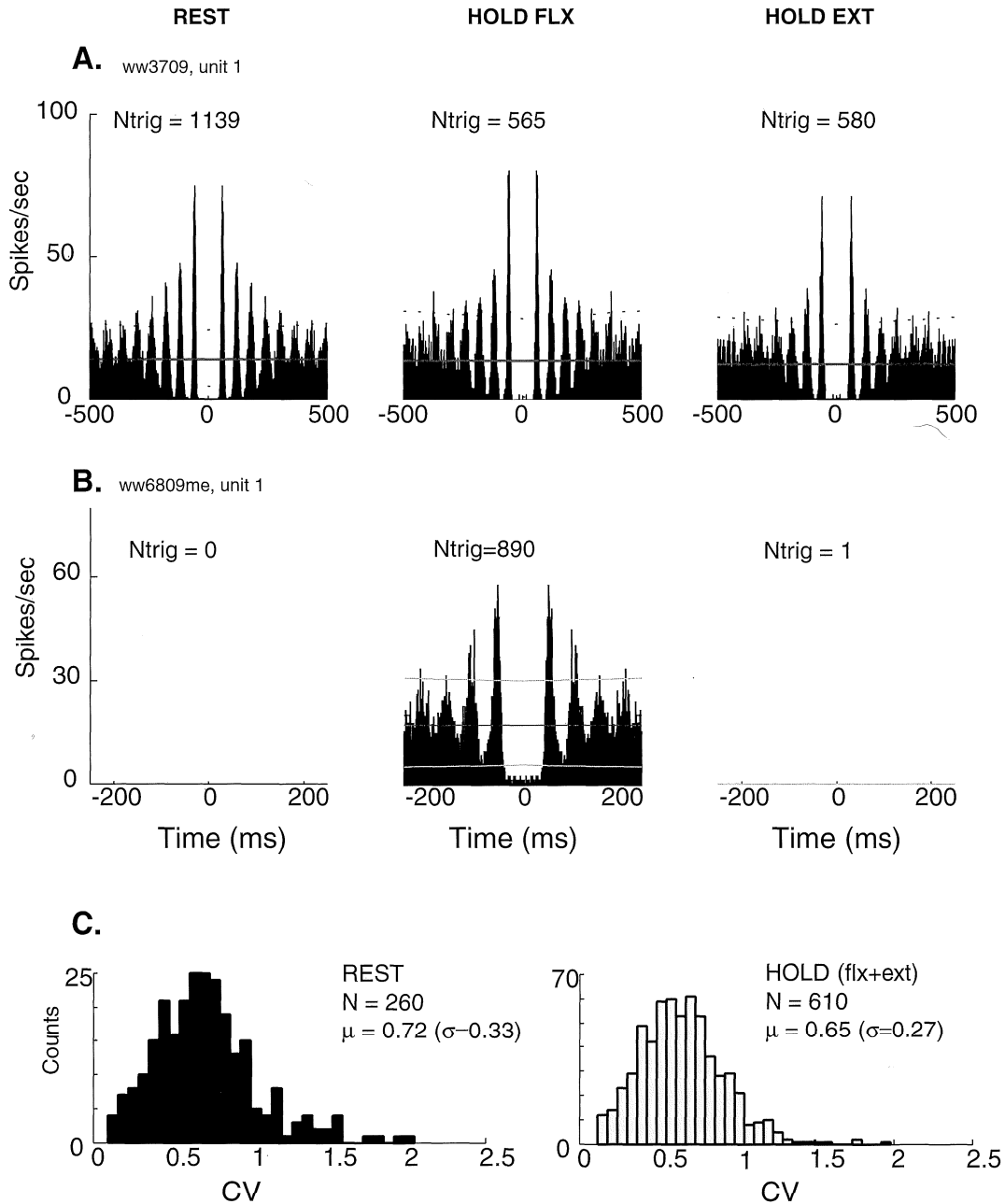
A. ww3709, unit 1

Fig. 4. Firing properties of single spinal INs. (A) Autocorrelation of a spinal IN computed for data collected during rest (left histogram), flexion-hold (middle histogram) and extension-hold (right histogram). The number of triggers is given for each histogram. (B) The same as A but for a spinal MN that is inactive during rest and extension periods. (C) Distribution of CV values computed during rest (left, black) and hold period (right, gray) for the whole population of spinal neurons. The total number of cases, the average value and the standard deviation are given for each histogram.

REST   HOLD EXT   HOLD FLX

A. F3002a, 5*6

Ntr=519 Nrf = 421   Ntr=745 Nrf = 527   Ntr=807 Nrf = 651
Ttime = 14112   Ttime = 6516   Ttime = 9494

B. F3205: 4*5

Ntr=2496 Nrf = 1792   Ntr=1536 Nrf = 1491   Ntr=1772 Nrf = 1281
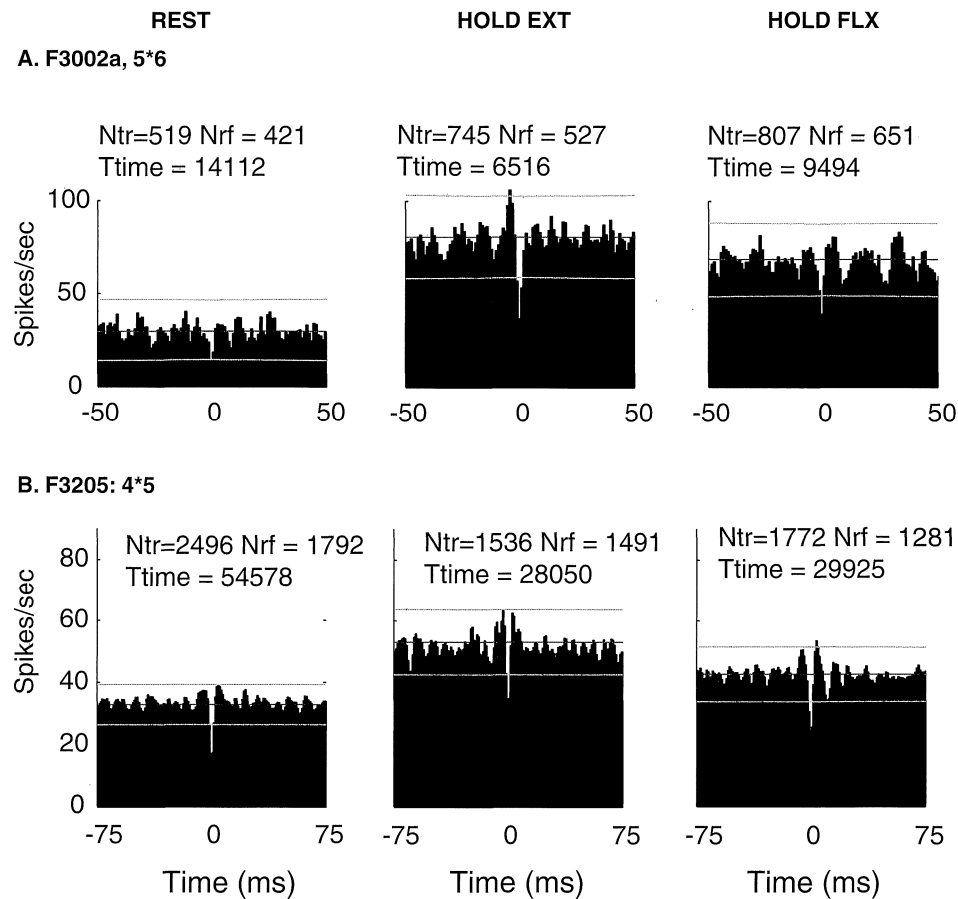Ttime = 54578   Ttime = 28050   Ttime = 29925

Fig. 5. Two examples of cross-correlograms computed for pairs of spinal INs. (A) Correlograms computed during rest (left histogram), extension-hold (middle histogram) and flexion-hold (right histogram). A significant peak in the correlogram exists during extension-hold. The horizontal lines show the average rate of the target unit (middle line) and the 99% confidence interval (upper and lower lines). The central dip is the result of the fact that the two cells were recorded by the same electrode. (B) The same as A but for a different pair of units. In this case, a peak of different extent can be seen in all three behavioral modes, while it crosses the lines of significance during flexion-hold only.

TABLE 1

Frequency of synchronization among spinal INs

$N^1 = 49/438$	Rest	Hold flexion	Hold extension
Cross-correlogram peaks	22	28	18
NS [2] correlograms	250	227	239
% Peaks	9	12	8
Peaks at distance [3] = 0	19	26	17
NS correlogram at distance = 0	123	118	132
% Peaks	15	22	13

[1] Number of pairs with a significant peak in at least one behavioral mode over the total number of pairs.
[2] Non-significant.
[3] Distance = 0 refers to cells recorded by a single electrode.

TABLE 2

Modulation of synchronization across behavioral modes

Computed correlograms [1]	Type [2]	N	%
3 modes	3 peaks	4	10
	2 peak + 1 NS	6	14
	1 peak + 2 NS	16	38
2 modes [3]	2 peaks	5	12
	1 peak + 1 NS	11	26
Total		42	100
Dynamic/constant [4]		33/42	79

NS = non-significant.

[1] Number of behavioral modes (out of 3) at which correlograms were computed.

[2] Type of observed correlograms, namely either flat (NS) or with a significant peak.

[3] Two modes were found for pairs for which there were not enough data in one mode to compute a correlogram. In a few cases the correlogram had a clear peak, which was either insignificant or was based on low number of triggers or reference spikes (<200). These correlograms were excluded.

[4] Ratio between pairs for which synchronization was modified according to the behavioral mode and pairs with a constant synchronization.

of correlogram to change in different behavioral modes.

The majority of correlograms were sensitive to the behavioral mode. Therefore the existence of correlated activity reflects not only the hardwired input arriving to these cells (which is constant throughout the trial), but also the behavioral epoch. Also, correlated firing seemed to be more frequent during flexion-hold periods than during rest and extension-hold periods (Table 1). Additional differences between the properties of INs during flexion and extension were previously reported from our lab (Perlmutter et al., 1998). Accordingly, functional linkages between cells and muscles are observed more frequently in spike-triggered averages of flexor than of extensor muscles. It therefore may be that part of the observed effect of INs firing on muscle activity could be explained by a synchrony in firing among spinal INs. The increased tendency for correlated firing during flexion may increase both the frequency and the potency of the observed effects on flexor muscles, making them more common.

However, it is important to note that the observed synchronizations between spinal INs occurred over a short time scale (often not more then a few mil-

liseconds), and their peak area, which corresponds to their strength, was often small.

Discussion

Our study of spinal activity during preparation for movement further supports the idea of distributed, parallel processing in the motor system. The spinal manifestation of pre-movement delay period activity suggests that spinal circuitry is involved already in early stages of movement preparation. The role of this activity and its source remains unknown. It was previously suggested (Moll and Kuypers, 1977; Baumgartner et al., 1996) that the premotor cortex has a predominantly inhibitory effect on spinal activity. Premotor cortex cells exhibit very robust preparatory activity (Weinrich and Wise, 1982; Wise, 1985; Wise et al., 1986; Kurata, 1993) and therefore these cells could be the source of inhibition of INs during the preparatory period. Further study will be required to test this hypothesis.

Existence of synchrony between spinal INs

The second question that we addressed in our study is the way the diverse information arriving to the spinal cord is processed by spinal INs. We found that spinal INs tend to fire in a very regular manner. This finding is in contrast with the data provided for cortical cells (including M1), which fire in a highly *irregular* manner (Smith, 1989; Softky and Koch, 1993; Lee et al., 1998; Shadlen and Newsome, 1998; Stevens and Zador, 1998). Furthermore, spinal circuitry also differs from motor cortical neurons in the extent of correlation in firing. Despite the fact that nearby spinal INs have similar response properties, only a small fraction of them were correlated in their firing, and these correlations were brief and weak. For M1 neurons, the estimated numbers of correlated cells ranged between 20% and 35% (Smith, 1989; Fetz et al., 1991; Hatsopoulos et al., 1998; Lee et al., 1998), while in the spinal cord the total number of correlated cells was about 11%. The two results (higher regularity and lower correlation) are in agreement with other findings demonstrating the inverse relations between these two factors for γ-motoneurons (Davey and Ellaway, 1984). A possible reason for the relative low number of correlated

pairs found among spinal INs may reside in a specific connectivity scheme, in which cells of the same type are connected, regardless of their anatomical distance. However, it has been shown that the pattern of input arriving to INs is in some cases random (Harrison and Jankowska, 1985), so that local branches of a given fiber will synapse on INs in their vicinity regardless of the specific origin of this fiber. Also we have found a tendency of correlated activity to occur among neighboring cells (those that were recorded by the same electrode). This suggests that neighboring INs are more likely to share their input (as opposed to a case where cell identity rather than its location determines its input), and therefore the low frequency of correlated activity found in our study is not due to the bias in recording mostly neighboring cells. Also, the impact of distance on cortical correlation seems to be less pronounced (Smith, 1989; Vaadia et al., 1995; Maynard et al., 1999) than in the cord. These facts are all in agreement with a tendency for asynchronous firing among INs compared with cortical neurons.

Functional role of spinal synchrony

Several observations suggest that spinal synchrony has a functional context. The first finding is that spinal synchrony was modulated by the behavioral mode. The majority of correlated pairs were correlated only in some but not all the behavioral epochs. This result is similar to the dynamic correlations of firing that were found in the prefrontal cortex (Vaadia et al., 1995) and the 'information capacity' reported for M1 synchronization (Hatsopoulos et al., 1998; Maynard et al., 1999). Given the firing properties of spinal INs, with their highly regular firing, and the lower number of correlations in the cord compared with the number of correlations in M1, spinal synchronization may be induced by converging inputs arriving to the cord, rather than intrinsic computational processes taking place within spinal circuitry. Accordingly, the behavioral modulation of spinal synchronization is the result of modulations among corticospinal inputs.

The second finding that suggests a functional role for the correlation between spinal INs is the consistency between the tendency of spinal cells to have a functional linkage with flexors muscles (Perlmutter

et al., 1998) and the excess of correlation during active flexion. Regardless of the source of the synchronization, such activity can enhance the impact of a single cell upon its target muscle. This is particularly important for cells that have an oligosynaptic linkage to MNs, whose efficacy tends to be relatively weak. On the other hand, the limited extent of the correlation may help to limit the muscle fields of spinal INs compared with the larger muscle fields of CM cells (Perlmutter et al., 1998). Accordingly, spinal synchronization may sharpen the broad input to spinal neurons, as the existence or absence of synchronization within a group of INs may respectively amplify or attenuate the impact of arriving inputs.

The contribution of spinal correlation to MU synchronization is still unclear. Although IN synchronization is comparable to MU synchronization in duration (Datta and Stephens, 1990; Schmied et al., 1994) and task dependency (Bremner et al., 1991) the two events differ in their frequency. The number of synchronized MU pairs found within a muscle and across muscles is about 60–90% (Datta and Stephens, 1990; Bremner et al., 1991). On the other hand, there is a large convergence in the spinal cord where hundred of thousands of INs project to several thousands of MNs. Such a convergence pattern may amplify the limited correlation found between INs. However, a direct test is required to estimate the role of spinal INs in MU synchronization.

Summary and conclusions

Recordings of spinal INs during a flexion/extension wrist task with an instructed delay period have shown directly that many spinal neurons modulate their rate during the preparatory period soon after a visual cue. The onset time and the relation between the delay period activity of spinal INs and the ensuing movement response suggest that this type of activity is not simply related to the forthcoming motor action, but rather reflects a correct match between the visual cue and the motor response. The existence of such activity further supports the notion that the motor system operates in a parallel mode of processing, so that even during early stages of motor processing multiple centers are activated regardless of their anatomical distance from muscles.

The firing properties of spinal INs during the performance of the task seem to differ from the comparable properties of motor cortical cells. Spinal INs fire in a highly regular manner — their CV is substantially lower than the observed CV of cortical cells. Also, although neighboring cells tend to have similar response properties, the frequency of significant correlation is lower than for cortical cells and the anatomical extent of the correlation seems to be narrower.

The similarity and differences between cortical and spinal cells in terms of response and firing properties suggests that while both type of cells are active in parallel throughout the behavioral phases of the motor task, each may operate in a different mode of information processing.

Abbreviations

INs	spinal interneurons
CM	corticomotoneuronal
MU	motor units
MN	motoneurons
M1	primary motor cortex

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References

Abeles, M. (1982) *Local Cortical Circuits — An Electrophysiological Study*. Springer, Berlin.

Alexander, G.E. and Crutcher, M.D. (1990) Preparation for movement: neural representations of intended direction in three motor areas of the monkey. *J. Neurophysiol.*, 64: 133–150.

Alexander, G.E., Crutcher, M.D. and DeLong, M.R. (1990) Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, 'prefrontal' and 'limbic' functions. *Prog. Brain Res.*, 85: 119–146.

Alstermark, B. and Kummel, H. (1990) Transneuronal transport of wheat germ agglutinin conjugated horseradish peroxidase into last order spinal interneurones projecting to acromio- and spinodeltoideus motoneurones in the cat. 2. Differential labelling of interneurones depending on movement type. *Exp. Brain Res.*, 80: 96–103.

Baker, J.R., Bremner, F.D., Cole, J.D. and Stephens, J.A. (1988) Short-term synchronization of intrinsic hand muscle motor units in 'Deafferented' man. *J. Physiol.*, 396: 155.

Baumgartner, C., Podreka, I., Olbrich, A., Novak, K., Serles, W., Aull, S., Almer, G., Lurger, S., Pietrzyk, U., Prayer, D. and Lindinger, G. (1996) Epileptic negative myoclonus: An EEG-single-photon emission CT study indicating involvement of premotor cortex. *Neurology*, 46: 753–758.

Binder, M.D. (1989) Peripheral motor control: spinal reflex actions of muscle, Joint and cutaneous recetors. In: H.D. Patton, A.M. Scher, A.F. Fuchs, R. Steiner and B. Hille (Eds.), *Textbook of Physiology, Vol. 1*. W.B. Saunders, Philadelphia, PA, pp. 522–548.

Bonnet, M. and Requin, J. (1982) Long loop and spinal reflexes in man during preparation for intended directional hand movements. *J. Neurosci.*, 2: 90–96.

Bremner, F.D., Baker, J.R. and Stephens, J.A. (1991) Effect of task on the degree of synchronization of intrinsic hand muscle motor units in man. *J. Neurophysiol.*, 66: 2072–2083.

Brunia, C.H., Scheirs, J.G. and Haagh, S.A. (1982) Changes of Achilles tendon reflex amplitudes during a fixed foreperiod of four seconds. *Psychophysiology*, 19: 63–70.

Datta, A.K. and Stephens, J.A. (1990) Synchronization of motor unit activity during voluntary contraction in man. *J. Physiol. (Lond.)*, 422: 397–419.

Datta, A.K., Farmer, S.F. and Stephens, J.A. (1991) Central nervous pathways underlying synchronization of human motor unit firing studied during voluntary contractions. *J. Physiol. (Lond.)*, 432: 401–425.

Davey, N.J. and Ellaway, P.H. (1984) Patterns of discharge of γ-motoneurons and their tendency to synchronized firing. *Neurosci. Lett. Suppl.*, 18: S267.

De Luca, C.J., Roy, A.M. and Erim, Z. (1993) Synchronization of motor-unit firings in several human muscles. *J. Neurophysiol.*, 70: 2010–2023.

Dum, R.P. and Strick, P.L. (1991) The origin of corticospinal projections from the premotor areas in the frontal lobe. *J. Neurosci.*, 11: 667–689.

Dum, R.P. and Strick, P.L. (1996) Spinal cord terminations of the medial wall motor areas in macaque monkeys. *J. Neurosci.*, 16: 6513–6525.

Evarts, E.V. and Granit, R. (1976) Relations of reflexes and intended movements. *Prog. Brain Res.*, 44: 1–14.

Evarts, E.V., Shinoda, Y. and Wise, S.P. (1984) *Neurophysiological Approaches to Higher Brain Functions*. Wiley, New York.

Farmer, S.F., Swash, M., Ingram, D.A. and Stephens, J.A. (1993) Changes in motor unit synchronization following central nervous lesions in man. *J. Physiol. (Lond.)*, 463: 83–105.

Fetz, E.E., Toyama, K. and Smith, W. (1991) Synaptic interactions between cortical neurons. In: A. Peters and E.G. Jones (Eds.), *Cerebral Cortex, Vol. 9*. Plenum, New York, 1–47.

Georgopoulos, A.P., Crutcher, M.D. and Schwartz, A.B. (1989) Cognitive spatial-motor processes. 3. Motor cortical prediction of movement direction during an instructed delay period. *Exp. Brain Res.*, 75: 183–194.

Grammont, F. and Riehle, A. (1999) Precise spike synchro-

nization in monkey motor cortex involved in preparation for movement. *Exp. Brain Res.*, 128: 118–122.

Harrison, P.J. and Jankowska, E. (1985) Organization of input to the interneurones mediating group I non-reciprocal inhibition of motoneurones in the cat. *J. Physiol. (Lond.)*, 361: 403–418.

Hatsopoulos, N.G., Ojakangas, C.L., Paninski, L. and Donoghue, J.P. (1998) Information about movement direction obtained from synchronous activity of motor cortical neurons. *Proc. Natl. Acad. Sci. USA*, 95: 15706–15711.

Komiyama, T. and Tanaka, R. (1990) The differences in human spinal motoneuron excitability during the foreperiod of a motor task. *Exp. Brain Res.*, 79: 357–364.

Kubota, K. and Hamada, I. (1979) Preparatory activity of monkey pyramidal tract neurons related to quick movement onset during visual tracking performance. *Brain Res.*, 168: 435–439.

Kurata, K. (1993) Premotor cortex of monkeys: set- and movement-related activity reflecting amplitude and direction of wrist movements. *J. Neurophysiol.*, 69: 187–200.

Kuypers, H.G.J.M. (1981) Anatomy of the descending pathways. In: J.M. Brookhart and V.B. Mountcastle (Eds.), *The Nervous System, Vol. II*. American Physiological Society, Bethesda, MD, pp. 597–666.

Lawrence, D.G., Porter, R. and Redman, S.J. (1985) Corticomotoneuronal synapses in the monkey: light microscopic localization upon motoneurons of intrinsic muscles of the hand. *J. Comp. Neurol.*, 232: 499–510.

Lee, D., Port, N.L., Kruse, W. and Georgopoulos, A.P. (1998) Variability and correlated noise in the discharge of neurons in motor and parietal areas of the primate cortex. *J. Neurosci.*, 18: 1161–1170.

Martin, J.H. (1996) Differential spinal projections from the forelimb areas of the rostral and caudal subregions of primary motor cortex in the cat. *Exp. Brain Res.*, 108: 191–205.

Matthews, P.B. and Stein, R.B. (1969) The regularity of primary and secondary muscle spindle afferent discharges. *J. Physiol. (Lond.)*, 202: 59–82.

Maynard, E.M., Hatsopoulos, N.G., Ojakangas, C.L., Acuna, B.D., Sanes, J.N., Normann, R.A. and Donoghue, J.P. (1999) Neuronal interactions improve cortical population coding of movement direction. *J. Neurosci.*, 19: 8083–8093.

Moll, L. and Kuypers, H.G. (1977) Premotor cortical ablations in monkeys: contralateral changes in visually guided reaching behavior. *Science*, 198: 317–319.

Murray, E.A. and Coulter, J.D. (1981) Organization of corticospinal neurons in the monkey. *J. Comp. Neurol.*, 195: 339–365.

Nordh, E., Hulliger, M. and Vallbo, A.B. (1983) The variability of inter-spike intervals of human spindle afferents in relaxed muscles. *Brain Res.*, 271: 89–99.

Nordstrom, M.A., Fuglevand, A.J. and Enoka, R.M. (1992) Estimating the strength of common input to human motoneurons from the cross-correlogram. *J. Physiol.*, 453: 547–574.

Perlmutter, S.I., Maier, M.A. and Fetz, E.E. (1998) Activity of spinal interneurons and their effects on forearm muscles during voluntary wrist movements in the monkey. *J. Neurophysiol.*, 80: 2475–2494.

Porter, R. and Lemon, R.N. (1993) *Corticospinal Function and Voluntary Movement*. Clarendon Press, Oxford.

Prut, Y. and Fetz, E.E. (1999) Primate spinal interneurons show pre-movement instructed delay activity. *Nature*, 401: 590–594.

Requin, J., Bonnet, M., Semjen, A. (1977) Is there a specificity in the supraspinal control of motor structures during preparation? In: S. Dornic (Ed.), *Attention and Performance, Vol. VI*. Lawrence Erlbaum, Hillsdale, NJ, pp. 139–147.

Riehle, A. and Requin, J. (1989) Monkey primary motor and premotor cortex: single-cell activity related to prior information about direction and extent of an intended movement. *J. Neurophysiol.*, 61: 534–549.

Rymer, W.Z. (1993) Spinal cord injury: physiology and transplantation. *Adv. Neurol.*, 59: 157–162.

Schmied, A., Ivarsson, C. and Fetz, E.E. (1993) Short-term synchronization of motor units in human extensor digitorum communis muscle: relation to contractile properties and voluntary control. *Exp. Brain Res.*, 97: 159–172.

Schmied, A., Vedel, J.P. and Pagni, S. (1994) Human spinal lateralization assessed from motoneurone synchronization: dependence on handedness and motor unit type. *J. Physiol. (Lond.)*, 480: 369–387.

Shadlen, M.N. and Newsome, W.T. (1998) The variable discharge of cortical neurons: implications for connectivity, computation, and information coding. *J. Neurosci.*, 18: 3870–3896.

Shinoda, Y., Yamaguchi, T. and Futami, T. (1986) Multiple axon collaterals of single corticospinal axons in the cat spinal cord. *J. Neurophysiol.*, 55: 425–448.

Smith, H.C., Davey, N.J., Savic, G., Maskill, D.W., Ellaway, P.H. and Frankel, H.L. (1999) Motor unit discharge characteristics during voluntary contraction in patients with incomplete spinal cord injury. *Exp. Physiol.*, 84: 1151–1160.

Smith, W.S. (1989) *Synaptic interactions between identified motor cortex neurons in the active primate*. Ph.D. Thesis, Department of Physiology and Biophysics, University of Washington, Seattle, WA.

Smith, W.S. and Fetz, E.E. (1989) Effects of synchrony between primate corticomotoneuronal cells on post-spike facilitation of muscles and motor units. *Neurosci. Lett.*, 96: 76–81.

Softky, W.R. and Koch, C. (1993) The highly irregular firing of cortical cells is inconsistent with temporal integration of random EPSPs. *J. Neurosci.*, 13: 334–350.

Stevens, C.F. and Zador, A.M. (1998) Input synchrony and the irregular firing of cortical neurons. *Nat. Neurosci.*, 1: 210–217.

Tanji, J. and Evarts, E.V. (1976) Anticipatory activity of motor cortex neurons in relation to direction of an intended movement. *J. Neurophysiol.*, 39: 1062–1068.

Thach, W.T. (1978) Correlation of neural discharge with pattern and force of muscular activity, joint position, and direction of intended next movement in motor cortex and cerebellum. *J. Neurophysiol.*, 41: 654–676.

Toyoshima, K. and Sakai, H. (1982) Exact cortical extent of the origin of the corticospinal tract (CST) and the quantitative contribution to the CST in different cytoarchitectonic areas. A study with horseradish peroxidase in the monkey. *J. Hirnforsch.*, 23: 257–269.

Vaadia, E., Haalman, I., Abeles, M., Bergman, H., Prut, Y.,

Slovin, H. and Aertsen, A. (1995) Dynamics of neuronal interactions in monkey cortex in relation to behavioural events. *Nature*, 373: 515–518.

Weinrich, M. and Wise, S.P. (1982) The premotor cortex of the monkey. *J. Neurosci.*, 2: 1329–1345.

Wise, S.P. (1985) The primate premotor cortex fifty years after Fulton. *Behav. Brain Res.*, 18: 79–88.

Wise, S.P., Weinrich, M. and Mauritz, K.H. (1986) Movement-related activity in the premotor cortex of rhesus macaques. *Prog. Brain Res.*, 64: 117–131.