Response Patterns and Force Relations of Monkey Spinal Interneurons During Active Wrist Movement

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Maier, Marc A., Steve I. Perlmutter, and Eberhard E. Fetz. Response patterns and force relations of monkey spinal interneurons during active wrist movement. *J. Neurophysiol.* 80: 2495–2513, 1998. The activity of C_6–T_1 spinal cord neurons was recorded in three macaques while they generated isometric wrist flexion and extension torques in visually guided step-tracking tasks. Electromyographic activity (EMG) was recorded in ≤12 independent forearm muscles. Spike-triggered averages (STAs) of rectified and unrectified EMG were used to classify neurons into four groups. *Motoneurons* (MNs) had a clear postspike motor unit signature in the unrectified STA of one muscle. *Premotor interneurons* (PreM-INs) had postspike effects in at least one muscle, with onset latencies of ≥3.5 ms from the trigger. *Synchrony interneurons* (Sy-INs) were non-PreM-Ins that had spike-related features with latencies <3.5 ms in at least one muscle. *Unidentified interneurons* (U-INs) showed no features in any of the STAs. A total of 572 task-related spinal neurons were studied; 29 cells were MNs, 97 PreM-INs, 32 Sy-INs, and 414 U-INs. MNs were activated predominantly in a tonic fashion during the ramp-and-hold torques and were active in one direction only. The most common response pattern for interneurons, irrespective of their class, was phasic-tonic activity, followed by purely tonic and purely phasic activity. Most interneurons (77%) were bidirectionally active in both flexion and extension. For all classes of interneurons, units with phasic response components tended to be activated first, before torque onset, followed by tonic units. The onset times of PreM-INs relative to onsets of their target muscles were distributed broadly, with a mean of −25 ± 128 (SD) ms. For most neurons with tonic response components (all MNs, 71% of PreM-INs, 67% of Sy-INs, and 84% of U-INs), activity during the hold period was correlated significantly with the magnitude of static torque exerted by the monkey. The rate-torque regressions generally had positive slopes with higher mean slopes for extension than for flexion. The phasic response components were correlated significantly with rate of change of torque for a smaller percentage of tested PreM-Ins (50%), Sy-INs (83%), and U-INs (77%). In contrast to other premotor neurons [corticomotoneuronal (CM), rubromotoneuronal (RM), and dorsal root ganglion (DRG) afferents] previously characterized under similar conditions, a larger proportion of the spinal PreM-INs were activated after onset of their target muscles, probably reflecting a larger proportion of PreM-INs driven by peripheral input. The rate-torque slopes of PreM-INs tended to be less steep than those of CM and RM cells. Unlike the CM and DRG PreM afferents, which were activated unidirectionally, most spinal PreM-INs showed bidirectional activity, like RM cells.

INTRODUCTION

A quantitative picture of the neural inputs driving primate forearm motoneurons during voluntary movement must include synaptic inputs from several groups of last-order neurons. In behaving animals, such premotor cells can be identified by postspike effects (PSEs) in spike-triggered averages (STAs) of muscle activity. This technique has elucidated the projections and response properties of premotor cells in primary motor cortex [corticomotoneuronal (CM) cells (Fetz and Cheney 1980; Lemon et al. 1986)], red nucleus [rubromotoneuronal (RM) cells (Cheney et al. 1988; Mewes and Cheney 1991)], and peripheral afferents in dorsal root ganglia (DRG cells) (Flament et al. 1992). Segmental spinal interneurons provide another major source of direct input to motoneurons. Specifically, spinal premotor interneurons (PreM-INs), i.e., those producing PSEs on motoneurons, play a major role in shaping motoneuron discharge. These neurons receive convergent projections from various descending tract neurons, including cortico-, rubro- and reticulo-spinal fibers, as well as from cutaneous and proprioceptive afferent fibers. In the companion paper (Perlmutter et al. 1998), we described the output properties of PreM-INs identified by STAs of forearm muscle activity. In this paper, we quantify the task-related responses of PreM-INs and other intraspinal neurons during voluntary wrist movement.

Spinal interneurons have been studied most extensively in the lumbo-sacral segments of anesthetized cats. They have been classified physiologically according to their peripheral input and anatomically according to their locations in Rexed's laminae (reviews: Baldissera et al. 1981; Jankowska 1992). Identified interneurons such as Ia-inhibitory interneurons, Ib interneurons, Renshaw cells, flexor reflex afferent interneurons, and others have been characterized during segmental reflexes and fictive locomotion, from which their roles in voluntary movement have been inferred indirectly. For example, Ia-inhibitory interneurons may be responsible primarily for inhibiting motoneurons in reciprocal movements. The Ib-interneurons, with a broader pattern of divergence, may be responsible for wider motor synergies across muscles acting at different joints. Recurrent inhibition via Renshaw cells may have a role in coactivating antagonist muscles. These hypotheses emphasize the need for direct physiological evidence regarding the role of spinal interneurons during voluntary limb movements.

The extent to which the properties of interneurons in the feline lumbo-sacral cord resemble those of interneurons in the primate cervical cord is another open question. Some data reveal clear differences between lumbo-sacral and cervical circuitry. For example, connections from Ia-afferents (Fritz et al. 1989) and Renshaw cells (Horner et al. 1991) to motoneurons may be organized differently in the forelimb segments than in hindlimb segments in the cat (Hamm et

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al. 1987; Thomas and Wilson 1967). This also seems to be the case in monkeys (Flament et al. 1992) and humans (Aymard et al. 1995; Chalmers and Bawa 1997; Day et al. 1984; Pierrot-Deseilligny 1989).

Some information on cervical PreM-INs is available for cats. The location and input-output properties of some neurons of the forelimb skin reflex pathway have been characterized (Hongo et al. 1989a,b; Kitazawa et al. 1993). The rhythmic activity of last-order interneurons controlling the activity of elbow motoneurons during fictive locomotion also has been described (Ichikawa et al. 1991; Terakado and Yamaguchi 1990). Less is known about PreM-INs in monkeys. Earlier accounts of cervical interneuronal activity during voluntary movement are relatively anecdotal and do not identify PreM-INs (Bromberg and Fetz 1977; Courtney and Fetz 1973).

In this paper, we document the responses of spinal cord neurons during behaviorally controlled voluntary wrist movement. Interneurons were classified according to their correlational linkages with active muscles. Their contribution to the generation of active torque about the wrist was elucidated by their discharge patterns. As described for PreM-INs (Perlmutter et al. 1998), most spinal interneurons exhibit a significant level of activation with both flexion and extension. By analyzing whether and how this activity covaries with muscle force, we could further resolve the parametric relation between firing rate and torque and the functional relations between interneurons and voluntary movements.

METHODS

In three male macaques (2 *Macaca nemestrina* and 1 *M. mulatta*), we recorded the activity of single C_6–T_1 interneurons extracellularly with glass-coated tungsten microelectrodes. The surgery for implanting the recording chamber, the experimental setup, the behavioral paradigm, and the procedures for recording electromyographic activity (EMG) and for identifying PreM-INs are described in the companion paper (Perlmutter et al. 1998). Briefly, a unilateral laminectomy of vertebrae C_5–T_1 was performed with the animals under halothane or isoflurane anesthesia and a recording chamber was implanted. The implant remained securely fixed to the vertebrae for ≤6 mo. During recording, the monkey was seated in a primate chair with its head and upper back restrained. Unit activity and EMG from wrist and digit flexor and extensor muscles (see Perlmutter et al. 1998 for muscle abbreviations) were recorded and interneurons were classified on the basis of STAs of rectified EMG as described below.

Behavioral paradigm

The monkeys were trained to produce isometric ramp-and-hold flexion or extension torques of the wrist after step changes in a visual target. One animal, *monkey W*, was trained in the center-out task and the other two monkeys, *B* and *R*, in the alternating task (Perlmutter et al. 1998). In the center-out task, a trial always began from a relaxed wrist position (center position) and required sustained active flexion or extension at one of three different torque levels—0.04, 0.07, or 0.1 Newton-meters (Nm), ±0.02 Nm—followed by a release back to the center position. Hold times varied randomly between 1.5 and 2.0 s for flexion and extension targets and between 1.0 and 4.0 s for the center position. In the alternating task, used previously in studies of wrist-related CM cells (Fetz and Cheney 1980), RM cells (Mewes and Cheney 1991), and peripheral afferents (Flament et al. 1992), the monkeys switched from active extension directly to active flexion without an intervening neutral hold. For this task, we occasionally tested the monkeys with different torque levels. Although the center-out and alternating tasks are identical under steady-state conditions, the center-out task offers the advantage of a clearer comparison between active and passive states, is more sensitive for detecting bidirectionally modulated activity, and can identify transient OFF responses at the release of active torque.

Force was measured by a calibrated strain gauge transducer with a sensitivity of 0.26 mV/Nm. Torque was computed as the product of force times the length of the radial arm from the attachment point.

Unit identification

Units were grouped into four classes according to features in their STAs (cf. Perlmutter et al. 1998). *Motoneurons* (MNs) had a large ''motor unit'' signature in the STA of unrectified EMG in a single muscle. *Premotor interneurons* (PreM-INs) had a PSE with an onset latency of ≥3.5 ms in the STA of rectified EMG for at least one muscle. PreM-INs with at least one PSE with a latency of <4.5 ms were classified as last-order interneurons. STA features with onsets earlier than 3.5 ms after the trigger spike were classified as early spike-related effects that could not be due to a synaptic connection from the trigger cell to MNs. Interneurons with STAs that exhibited an early effect but no PSEs were classified as *synchrony interneurons* (Sy-INs). *Unidentified interneurons* (U-INs) showed no spike-related modulations of EMG in any of the sampled muscles. Neurons were classified as PreM-INs, Sy-INs, and U-INs only if ≥2,000 triggers were available to compute STAs.

Response patterns

To identify the response patterns of spinal neurons during the ramp-and-hold task, we compiled averages separately for flexion and extension trials. In the center-out task, trials were aligned at onset of the torque ramps; in the alternating task, trials were aligned on the point of torque reversal (i.e., 0 torque at the transition from flexion to extension or vice versa). Unit histograms and torque trajectories were averaged separately for each of the six target levels for the center-out task and also across all flexion or extension trials. Response averages were compiled off-line with a binwidth of 80 ms per channel. Figures show torque in the flexion and extension directions as positive and negative deflections, respectively.

A unit was said to modulate its activity if the response was significantly above or below baseline activity (*t*-test, $P < 0.001$). In the center-out task, baseline was defined as the activity during the last second of the center hold period; in the alternating task, baseline was defined as the activity during the static hold period for the opposite torque. Response patterns were classified as tonic, phasic, phasic-tonic, decrementing, or ramp according to the summed response average of all flexion or all extension trials. Phasic peaks or troughs had to differ significantly from tonic components or baseline activity (*t*-test, $P < 0.001$). For each unit, a preferred direction, i.e., flexion or extension, was defined as the direction with the strongest increase in discharge. No preferred direction was assigned for 24 units whose only modulation was decreasing activity, relative to baseline, in one or both directions.

Onset estimation

Criteria for defining the onset of activity in response averages were formulated empirically on representative data and then applied consistently to all trials. In the center-out task, torque onset for each successful trial was calculated as the first bin in which

the rate of change of torque was >0.8 Nm/s (smaller values were in the noise level during steady torque production) and torque rose continuously afterwards.

Unit onset was determined as the first of three bins, of five consecutive bins, that had counts >2 SD above baseline activity. EMG onset was determined as the first of four bins, of five consecutive bins, that had counts >2 SD above baseline activity. Occasionally, these criteria were applied to 1 SD for units or EMGs with weak modulation. Statistical differences were determined with Student's *t*-test or analysis of variance (ANOVA) with post hoc Scheffe tests.

Relation to movement parameters

The relation between neuronal firing rate and torque was assessed from trial-by-trial data. For units with a *tonic response* component (i.e., a constant firing rate during the static hold), mean instantaneous firing rate (spikes/s) and mean torque (Nm) were calculated in the last second of the hold period of each trial (Fig. 1). A scatter plot of tonic firing rate versus static torque was displayed for all trials and linear Pearson correlation coefficients were calculated separately for flexion and extension. Torque sensitivity was measured by the *rate-torque slope*, i.e., the slope of the linear regression line in spikes/s/Nm. Rate-torque slopes were calculated for neurons that were recorded in ≥10 trials. Averages of correlation coefficients (using Fisher's *z* transformation) and slopes were calculated for different neuronal groups.

For units with a *phasic response* component, i.e., a transient increase in firing rate during the dynamic torque transition, the peak firing rate (spikes/s), peak rate of change of torque (Nm/s), and the time interval between them were calculated for each trial. Peak firing rate was determined from the four consecutive interspike intervals with the shortest average interval. Peak rate of change of torque (dT/dt) was calculated as the maximum of the first derivative of torque (max dT/dt, Fig. 1). These data were displayed in scatter plots of peak firing rate versus peak dT/dt for all trials, and linear correlation and regression coefficients were computed as described above.

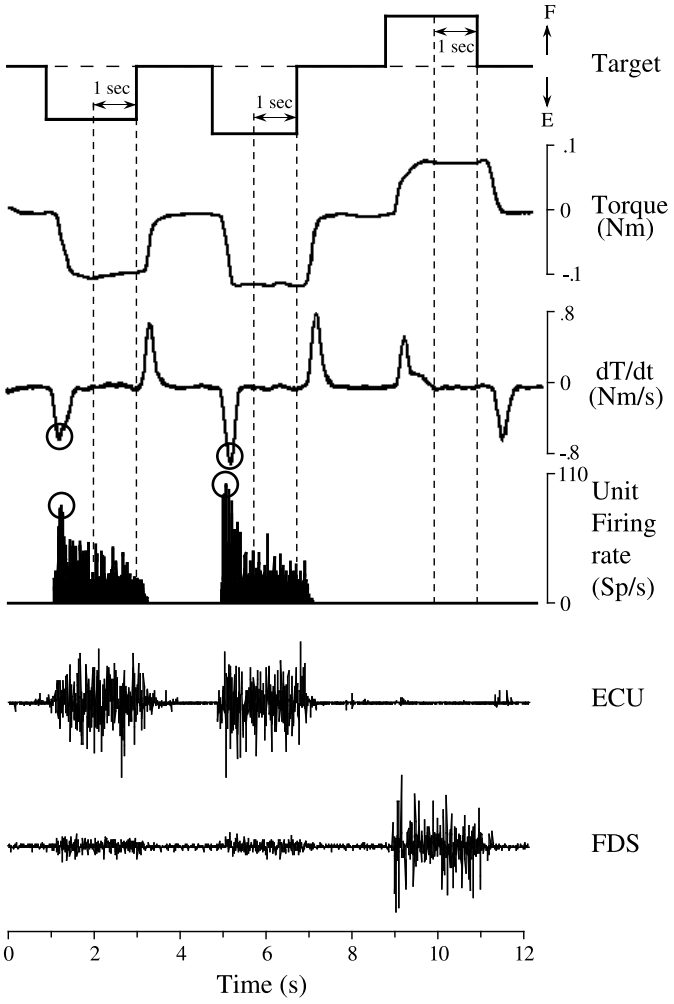


FIG. 1. Recordings of 3 trials of the step-tracking task. *Top* to *bottom*: *1*: target position. Shown are 2 extension trials of different amplitudes followed by a flexion trial. *2*: isometric wrist torque. Monkey followed the target and produced 2 static extension torques of different amplitudes followed by a flexion torque. *3*: rate of torque change (dT/dt). Monkey usually scaled its torque change according to the target torque required. *4*: unit activity of a spinal interneuron processed by a frequency meter that provided a continuous signal proportional to the instantaneous frequency. *5*: electromyogram (EMG) of a representative wrist extensor muscle (extensor carpi ulnaris). *6*: EMG of a representative wrist flexor muscle (flexor digitorum superficialis). For parametric analysis: static torque and tonic firing rate were averaged trial-by-trial in the last second of the hold period (arrows). Peak firing rate and peak dT/dt are indicated by circles.

RESULTS

Database

Data were collected for 572 task-related spinal neurons: 409 from *monkey W*, 141 from *monkey B*, and 22 from *monkey R*. STAs of at least three flexor and three extensor muscles were obtained for these units.

Figure 1 illustrates raw data for three trials of the center-out step-tracking task, two in extension and one in flexion. In response to the higher target level for the second extension trial (*top*), the monkey generated a higher static torque and larger rate of change of torque (dT/dt). The spinal interneuron fired during extension with a phasic-tonic pattern and was silent in flexion and in the center position. The EMGs of a flexor and an extensor muscle show that only the agonists were activated during torque production and that the center position was reached and maintained by muscle relaxation.

Identification of neurons

The 572 task-related neurons identified on the basis of STA features comprised 29 MNs, 97 PreM-INs, 32 Sy-INs, and 414 U-INs. Typical examples are shown in Figs. 2–5, which illustrate the criteria used to classify the spinal neurons. Eighteen of the PreM-INs were classified as last-order interneurons (see METHODS). The properties of these last-order interneurons were not significantly different from those of other PreM-INs for all neuronal characteristics described in this report. Therefore, last-order interneurons are not considered separately for the remainder of this paper.

Figure 2 (*top*) shows the STAs and response averages of a putative *MN*. MNs exhibited a motor-unit ''signature'' in the STA of unrectified EMG in a single muscle. The motor-unit signature was characterized by a high signal-to-noise ratio and usually showed a clear PSE after a small number of triggers. This signature had a relatively short duration with a sharp rise and fall. The PSE onset latency

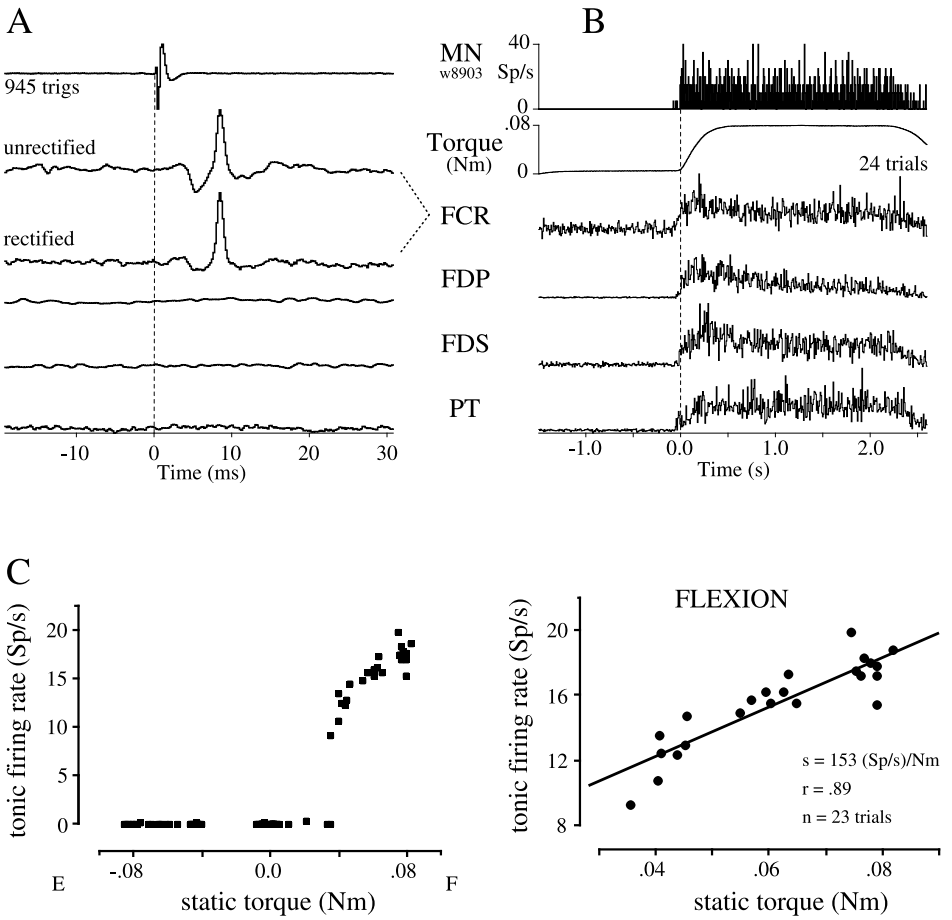


FIG. 2. Properties of a putative FCR motoneuron. *A*: spike-triggered averages (STAs) of, from *top*, triggering action potential and EMG for coactive flexor muscles. FCR shows a clear ''motor-unit'' action potential in the unrectified STA. Stippled vertical line at *time 0*: onset of trigger spike. Number of trigger spikes for STAs is given *below top trace*. *B*: response histogram of the motoneuron (MN), showing tonic flexor-related activity, isometric torque, and rectified EMG of coactive muscles. Number of averaged trials given *below* torque trace. Positive torques indicate flexion. Stippled line at *time 0*: torque onset. *C*: scatter diagrams for tonic firing rate vs. static torque. *Left*: ''whole-task'' plot showing the static activity in extension (E), center position (near-zero torque) and flexion (F). *Right*: scatter plot for the flexion direction with regression line. s, rate-torque slope of the regression; *r*, correlation coefficient; *n*, number of data points, i.e., trials, used for the regression. This FCR MN is shut off in extension and center position and has a threshold of ~0.04 Nm flexion torque.

of the unit shown in Fig. 2 was 4.2 ms after the trigger spike. Putative MNs had firing frequencies in the range characteristic of motor units (steady firing rates of 7–40 spikes/s) and were inactive when the parent muscle was inactive (i.e., during hold in the center position and during antagonist contractions). The putative flexor carpi radialis (FCR) MN shown in Fig. 2 exhibited tonic activity during flexion and was silent during extension. In contrast to the onset of many interneurons, the onset of MN activity always occurred with or after onset of the parent muscle activity. All MNs had finite recruitment thresholds in their preferred directions.

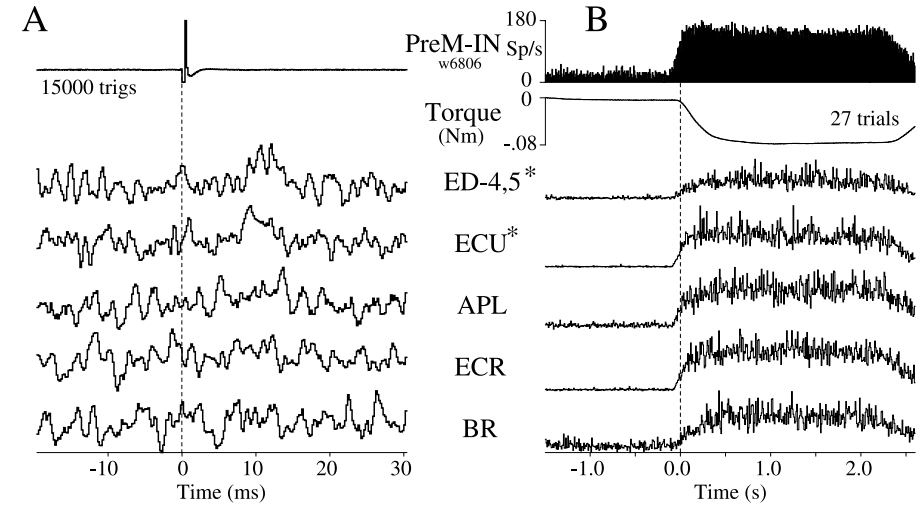
The properties of an *excitatory PreM-IN* are illustrated in Fig. 3. The STA of a PreM-IN showed postspike facilitation or suppression of rectified EMG from one or several muscles with onset latencies of ≥3.5 ms (Perlmutter et al. 1998). The PreM-IN shown in Fig. 3 produced postspike facilitations in extensor digitorum-4,5 (ED-4,5) and extensor carpi ulnaris (ECU) at onset latencies of 8–9 ms. This excitatory PreM-IN had a high tonic firing rate during extension and a slow resting discharge during the center hold (both properties distinguished this neuron from a MN).

Figure 4 shows an *inhibitory PreM-IN* that produced postspike suppression in a flexor muscle, flexor carpi radialis (FCR), at a latency of 3.9 ms. This PreM-IN was most strongly and tonically modulated for extension torques, but showed enough activity during flexion to compile STAs revealing suppression of its target muscle.

Neurons with STAs that exhibited spike-related features that all began <3.5 ms after the trigger were classified as Sy-INs (Figs. 7 and 8 in Perlmutter et al. 1998). U-INs showed no spike-related features in any of the tested muscles in STAs of ≥2,000 sweeps. Figure 5 illustrates an *U-IN* that had a resting discharge in the center position and increased its activity in both the flexion and extension directions. The STAs of flexor and extensor muscles (not shown) exhibited no spike-related fluctuation.

Response patterns

For the center-out task, spinal neurons were classified according to the modulation of their firing rates during flexion and extension with respect to any activity in the center hold position. The direction that corresponded to the strongest increase in firing rate was called the unit's *preferred direction*. Spinal neurons showed a variety of response patterns in relation to the ramp-and-hold torques. The proportion of the response patterns seen in the preferred direction for each cell type is summarized in Table 1 and Fig. 13. Patterns of increased activity were classified as tonic (t+, e.g., Figs. 2 and 3), phasic (p+, Figs. 9 and 11), phasic-tonic (p + t+, Fig. 10), decrementing (decr, Fig. 8 of Perlmutter et al. 1998), ramp (monotonically increasing activity during static torque), and phasic-ramp (p + ramp). For the center-out task, it was also possible to identify a decrease of activity relative to any resting discharge in the



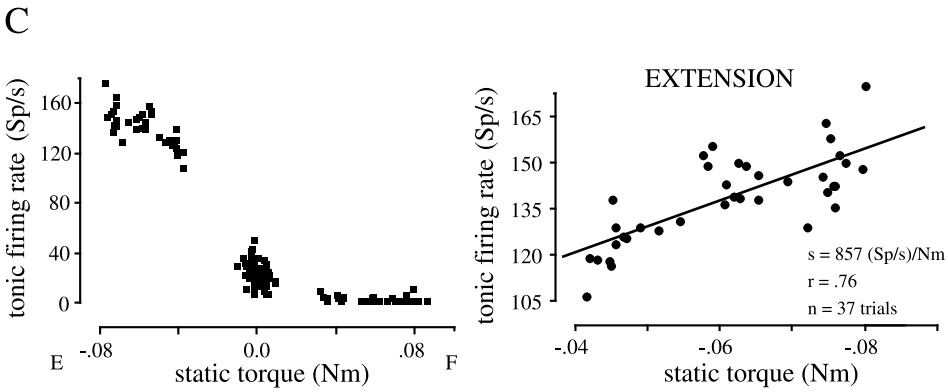


FIG. 3. *A*: STA of an excitatory premotor interneuron (PreM-IN) recorded in C_7. This unit produced postspike facilitation in 2 extensor muscles (*) with onset latencies of 8.9 and 8.4 ms. *B*: response average of neuron and muscles. Negative torque indicates extension. Unit was activated tonically during extension (onset at −72 ms), had resting activity in the center position, and shut off in flexion (not shown). *C*: activity in extension (*right*) is correlated highly with torque (plot inverted around the vertical axis).

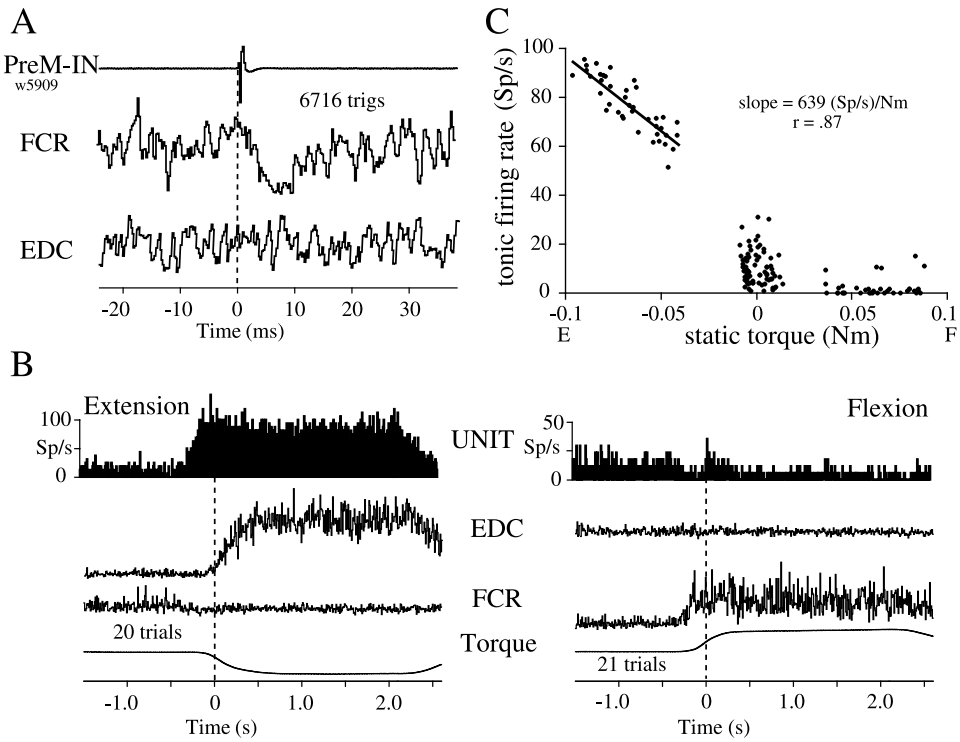


FIG. 4. STA and response average of an inhibitory PreM-IN recorded in caudal C_6. *A*: STA shows postspike suppression in FCR; no effects were seen in other simultaneously recorded, independent muscles (5 other flexors and 6 extensors). *B*: response average of neuron and muscles during flexion and extension responses. *C*: rate-torque relations.

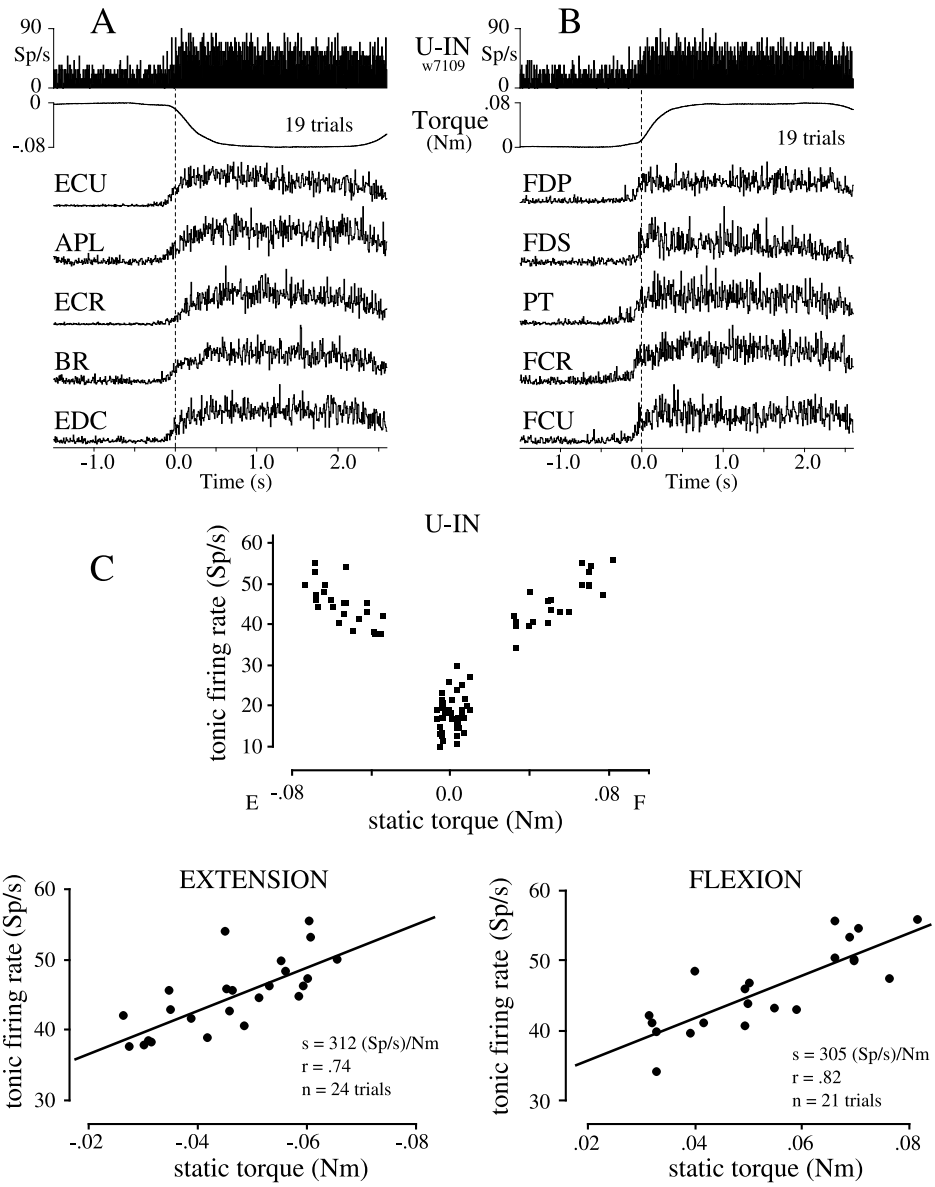


FIG. 5. *A* and *B*: response averages of a bidirectionally and tonically activated unidentified interneuron (U-IN) recorded in C_7. Onset latency was 0 ms for both extension and flexion. This unit had no postspike effects (PSEs) in any of the recorded EMGs after 2,000 trigger spikes. *C*: static flexion and extension activity show high correlations to torque with similar slopes.

center position; thus in this task inhibitory response patterns could be classified as tonic (t−, Fig. 9*B*), phasic (p−), and phasic-tonic (p−t−). These inhibitory patterns usually occurred in the nonpreferred direction. A few ''mixed'' units had an increasing and decreasing component in a single direction. For the alternating task, the cell's increased activity was judged relative to that in the opposite direction, which precluded identification of tonic suppressed activity (t−). Thus in the alternating task, the only inhibitory response pattern that could be classified was phasic (p−). A few neurons exhibited only inhibitory response patterns, and no preferred direction was assigned (Table 1).

The most common response patterns in each cell type were tonic and phasic-tonic discharge (Table 1). Pure tonic discharge, which parallels the torque trajectory, was characteristic of 66% of MNs and 36% of interneurons. The phasic-tonic pattern, which includes a phasic burst of activity during the change of torque, was seen more often for interneurons (35%) than for motoneurons (17%). In addition to these predominant patterns, there were some less frequent variations, as shown in Table 1.

The center-out task revealed that 8% of the interneurons exhibited a phasic burst or suppression of activity during the release of torque, i.e., when the monkey relaxed the agonist muscles to return to the zero-torque center position (Table 2). Figure 6 shows an example of such a ''release'' unit. There was no antagonist muscle activity during the transient phase of release, and no MN showed this kind of activity. All release units also exhibited some kind of modulation during dynamic increases of torque.

In the alternating task, phasic increases in activity during release could be confounded with increased discharge prior to torque increases in the opposite direction. The prevalence of this confound could be evaluated in the center-out task. In fact, most release units (39/46 = 85%) that fired a burst at the end of torque in one direction also showed increased activity for active torque in the opposite direction (5/8 PreM-INs, 1/2 Sy-INs, and 33/36 U-INs).

TABLE 1. *Type and numbers of response patterns in alternating and center-out tasks in the preferred direction*

	MN				PreM-IN				Sy-IN				U-IN			
	Alternating		Center-Out		Alternating		Center-Out		Alternating		Center-Out		Alternating		Center-Out	
Type	*n*	Percent	*n*	Percent	*n*	Percent	*n*	Percent	*n*	Percent	*n*	Percent	*n*	Percent	*n*	Percent
p+t+	2	29	3	14	11	25	26	46	1	10	6	25	25	24	121	39
t+	3	43	16	72	16	36	16	28	5	50	11	46	38	36	107	35
p+	—		—		7	16	2	4	2	20	3	13	28	26	40	13
decr	1	14	3	14	3	7	1	2	—		—		7	6	14	5
(p+)ramp	—		—		—		3	5	1	10	—		—		3	1
mixed+−	—		—		1	2	6	1 1	—		—		1	1	9	3
No pref. dir.	—		—		3	7	2	4	—		2	8	3	3	14	5
Nonclassified*	1	14	—		3	7	—		1	10	2	8	4	4	—	
Total	7		22		44		56		10		24		106		308	
Grand Total		29				100				34				414		

Percentages in terms of task-modulated units sampled. p+t+, phasic-tonic increase in activity; t+, tonic increase in activity; p+, phasic increase in activity; decr, decrementing activity; (p+)ramp, ramp activity with or without preceding phasic burst; MN, motoneurons; PreM-IN, premotor interneurons; Sy-IN and U-IN, synchrony and unidentified interneurons. * Two Sy-INs (1 in alternating task, 1 in center-out task) and 3 PreM-INs had activity that was not modulated with the task; these cells are described in the companion paper (Perlmutter et al. 1998) and are not discussed further in this paper. For other nonclassified cells, insufficient data were recorded on tape to classify response patterns.

Directionality

The activity of neurons in their nonpreferred direction further differentiates their directional tuning (Table 2). For each unit, the activity in the nonpreferred direction was classified as being absent, unmodulated relative to baseline activity, or ''similar'' to or the ''inverse'' of the activity in the preferred direction. Units were classified as ''similar'' if they showed increased activity with both flexion and extension and ''inverse'' if their activity increased in one direction and decreased in the other.

All of the MNs exhibited *unidirectional activity* (i.e., activity in only 1 direction), but only 23% of the interneurons were unidirectional. The majority of interneurons (77%) were *bidirectionally active*, i.e., discharged in some form during flexion and extension, with similar proportions for both variations of the task. Almost half of the interneurons (46%) were *bidirectionally modulated*, showing task-modulated activity in the nonpreferred direction with either a similar or inverse response pattern. These included 175 interneurons with bidirectional increases in activity (32% of interneurons) and 67 interneurons with increased discharge for one direction and decreased discharge (relative to baseline) for the other (12%). Increasing responses in the nonpreferred direction had phasic or phasic-tonic patterns more often than responses in the preferred direction. Among these units, about half showed identical response patterns for both directions (15 of 30 PreM-INs, 8 of 14 Sy-INs, and 65 of 128 U-INs). The proportion of bidirectionally modulated interneurons was greater in the center-out task (55%) than in the alternating task (30%), due in part to the fact that a decreasing tonic response is undefinable in the alternating task. Remarkably, there were no clear differences between these proportions for PreM-INs, Sy-INs, and U-INs. PSEs of PreM-INs with bidirectional increases in activity did not preferentially affect muscles with bidirectional activity (e.g., brachioradialis) nor were the magnitude and latency of these PSEs significantly different from those of other PSEs.

Bidirectional release activity was also common. Responses during release from both flexion and extension tar-

TABLE 2. *Directionality (response in nonpreferred direction) and release activity*

	MN				PreM-IN				Sy-IN				U-IN			
	Alternating		Center-Out		Alternating		Center-Out		Alternating		Center-Out		Alternating		Center-Out	
	n	Percent	*n*	Percent	*n*	Percent	*n*	Percent	*n*	Percent	*n*	Percent	*n*	Percent	*n*	Percent
Activity in non-preferred direction																
No activity	7	100	22	100	12	30	14	25	3	33	4	17	12	11	72	23
Unmodulated	—		—		17	41	4	7	3	33	2	9	55	52	64	21
Similar to p.d.	—		—		7	17	23	41	3	33	11	48	24	22	107	35
Inverse to p.d.	—		—		2	5	11	20	—		3	13	7	7	44	14
No p.d.	—		—		3	7	2	4	—		2	9	3	3	14	5
Nonclassified	—		—		—		2	4	—		1	4	5	5	7	2
Total	7		22		41		56		9		23		106		308	
Units with release activity							8	14			2	9			36	12

Percentages in terms of task-modulated units sampled. p.d., preferred direction. Nonclassified: as in Table 1 or mixed response patterns prevented classification.

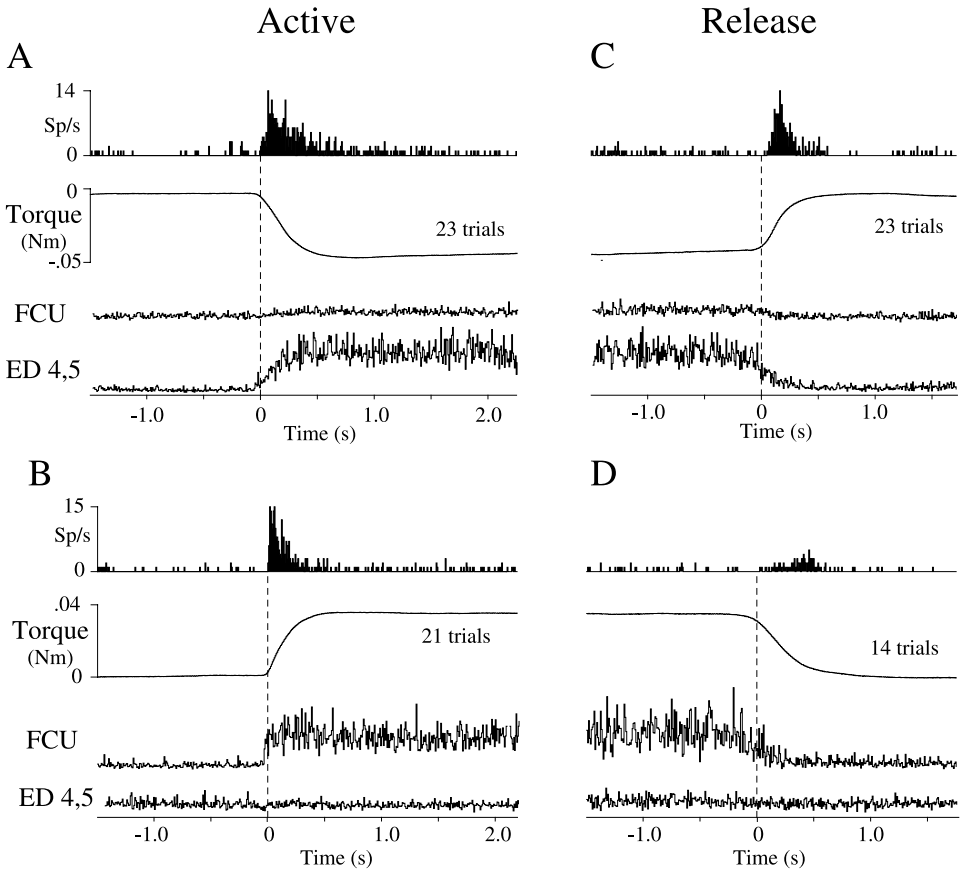


FIG. 6. Response averages of an interneuron with release activity. Traces are, from *top*, unit histogram, averaged torque, averaged EMGs of agonist, and antagonist muscles. Responses are shown for active extension (*A*), active flexion (*B*), release from extension (*C*), and release from flexion (*D*).

gets were seen for 6/8 PreM-INs, 0/2 Sy-INs, and 17/36 U-INs with release activity. Most of these cells also had bidirectional responses during active torque production.

Onset latency

Onset time indicates the possible source of a neuron's initial activation—central versus peripheral. Figure 7 summarizes the onset times of muscle and interneuronal activity with respect to torque onset for the center-out task and with respect to torque reversal for the alternating task. Muscles with primary action of wrist or digit flexion or extension (i.e., carpi and digitorum muscles) were activated earlier and exhibited smaller variations than muscles without primary actions [brachioradialis (BR), abductor pollicis longus (APL), palmaris longus (PL), pronator teres (PT)]. Similar tendencies were found in the alternating task, although the precise order of onsets was different. Muscle onsets appeared to be earlier in the alternating task than in the center-out task, but this is largely attributable to the different reference points for the measurements. Although the absolute values of the onset latencies for the two tasks cannot be compared, their relative orders are directly comparable.

The onset times of PreM-INs, Sy-INs, and U-INs were distributed broadly. There was no significant statistical difference between them nor between flexor and extensor units (ANOVA). In general the range of onset times was at least twice as large for interneurons as for muscles.

When grouped according to firing patterns, the interneurons showed some differences in mean onset latencies (Table 3). In both tasks, PreM-INs, Sy-INs, and U-INs with excitatory phasic components (p+&) tended to change activity earlier than excitatory tonic units. Comparisons between the PreM-INs and the U-INs revealed no significant differences.

Because the PreM-INs contribute directly to motoneuron excitability, it is particularly interesting to compare their onset latencies relative to the onset of their target muscles (Fig. 8). For the center-out task, the activity of PreM-INs started, on average, 11 ± 84 (SD) ms before the onset of activity in the target muscle (83 unit-muscle pairs). For the alternating task, the mean onset of PreM-INs was 46 ± 172 ms before that of their target muscles (58 pairs). The difference between the two tasks was not significant (*t*-test, $P > 0.2$). The combined onset latency was −25 ± 128 ms (86 PreM-INs). For most of the PreM-IN-target muscle pairs (86/141 = 61%) the PreM-IN began firing before its target muscle. The rank order of onset times relative to target muscle onset for PreM-IN with different response patterns was similar to that relative to torque. In the center-out task, units with phasic components had an earlier onset than those with tonic components. Interestingly, the excitatory PreM-INs had significantly earlier onset times (−34 ± 119 ms; 74 cells) relative to their facilitated target muscles than the inhibitory PreM-INs relative to their suppressed target muscles (+51 ± 156 ms; 12 cells; difference $P < 0.02$).

Relation to static torque

To quantify the firing rate of interneurons and MNs as a function of torque, we required *monkey W* to generate three

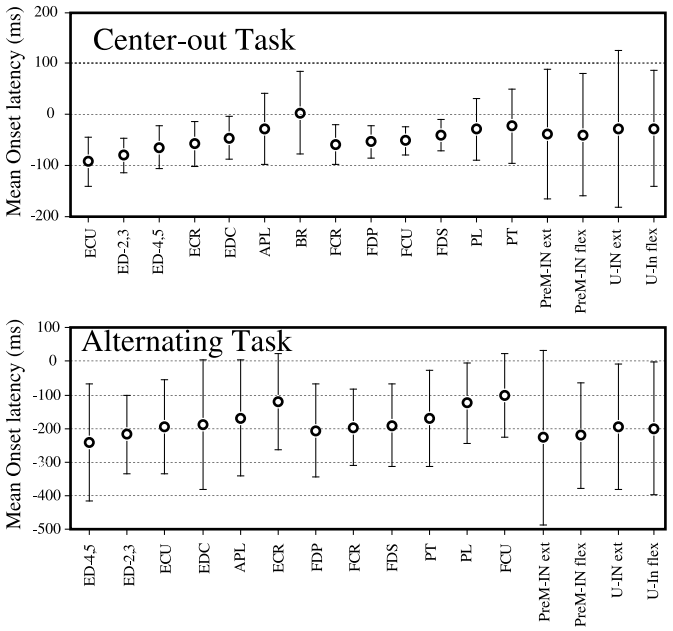


FIG. 7. Mean onset latencies of extensor and flexor EMGs with respect to torque onset for the center-out task and with respect to torque reversal for the alternating task. Negative latencies indicate onset before torque onset or torque reversal. Error bars are standard deviations. Muscles ordered according to increasing mean onset latency. Muscles with primary action of wrist or digit flexion or extension were activated earlier and had smaller variations than other muscles. Onset latencies of extensor and flexor PreM-INs and U-INs shown to *right* of muscle onsets. Larger variations for the alternating task are due to the alignment of response averages on torque reversal, which was more variable than torque onset from trial to trial. Mean onset times for the center-out task (with similar values in flexion and extension) were −28 ms for U-INs and −38 ms for PreM-INs (SD ~ 130 ms). The mean onset time of MNs was −27 for extensor and −5 ms for flexor MNs (SD ~ 43 ms). For the alternating task, mean latencies were −190 ms for U-INs and −230 ms for PreM-INs (SD ~ 250 ms) with little difference between flexion and extension.

different levels of static torque in each direction in the center-out task. The relation between tonic firing rate and static torque was tested for 13 MNs, 50 PreM-INs, 15 Sy-INs, and 182 U-INs in *monkey W* that had a tonic component in their firing pattern. In addition, nine PreM-INs and six U-INs were tested at different static torque levels in the alternating task. Scatter plots of tonic firing rate versus static torque are illustrated for a MN, an excitatory, and an inhibitory PreM-IN and a U-IN in Figs. 2–5. The points in the scatter plots represent the mean static activity during a 1-s period of steady torque in single trials, and the plots combine values for extension, center position, and flexion. A regression line and associated statistics are included in the expanded scatter plots for active torque of either flexion or extension (excluding the center hold).

The FCR MN illustrated in Fig. 2 was silent in the center position and in extension. Recruitment threshold was reached at flexion torques of ~0.04 Nm, where the activity jumped to ~10 spikes/s. Firing rate increased with increasing flexion torque, reaching ~20 spikes/s at 0.08 Nm. The high correlation coefficient of 0.89 confirms a close linear relation between firing rate and torque with a rate-torque slope of 153 spikes/s/Nm.

The functional significance of the torque relation of a PreM-IN is related to the polarity of its PSE. The PreM-IN shown in Fig. 3 facilitated ED-4,5 and ECU and exhibited strong modulation with extension, a resting discharge in the center position, and no activity during flexion. The tonic firing rate showed a clear positive correlation with extension torque, with a rate-torque slope of 857 spikes/s/Nm. The interneuron's output effect on extensor muscles, together with a strong correlation between firing rate and static extension torque, was functionally consistent with producing graded input to extensor MNs. The inhibitory PreM-IN shown in Fig. 4 also fired during extension but produced postspike suppression in FCR. Its activity increased in proportion to extension torque, suggesting that increasing muscle activity in one direction is associated with increasing suppression of antagonist muscles.

The U-IN shown in Fig. 5*C* also had a strong task-related activity and was modulated with torque in both flexion and extension directions. The firing rate showed clear linear relations with increasing torque in both directions, with almost symmetrical slopes of 305 and 312 spikes/s/Nm.

Although the activity of most units showed a positive correlation with torque, the activity of some was correlated negatively with torque. An example of a PreM-IN that facilitated three flexor muscles [PL, flexor carpi ulnaris (FCU), and FCR] is shown in Fig. 9. This neuron was activated phasically during flexion, but its firing rate for maintained

TABLE 3. *Mean onset latency in milliseconds with respect to torque onset (center-out task) and torque reversal (alternating task)*

Type	MN	PreM-IN	Sy-IN	U-IN
Center-out task				
t+	−21.0 ± 46 (16)	−44.7 ± 51* (17)	−4.3 ± 126 (13)	−13.3 ± 120* (126)
p+&	−40.0 ± 14 (3)	−53.1 ± 88* (62)	−91.5 ± 120 (16)	−57.9 ± 80* (258)
decr	26.7 ± 12 (3)	— —	— —	1.6 ± 100 (15)
t−&/supr	— —	120.4 ± 300† (10)	56.0 ± 221 (8)	74.4 ± 241† (69)
p−&	— —	−62.4 ± 20 (5)	— —	−164.4 ± 174* (9)
Alternating task				
t+	−336.0 ± 227 (3)	−186.8 ± 194 (17)	−36 ± 367 (4)	−149.7 ± 224 (35)
p+&	−40.0 ± 56 (2)	−273.7 ± 221 (21)	−354.7 ± 121 (6)	−241.2 ± 234 (74)
decr	— —	−394.7 ± 142 (3)	— —	−323.3 ± 151 (7)
p−&	— —	−168.0 ± 237 (5)	— —	−196.6 ± 241 (14)

Values are means ± SD. *n* values are in parentheses. t+, tonic increase in activity; p+&, phasic increase in activity with or without other response components; decr, decrementing activity; t−&/supr, tonic decreasing or suppressed activity with or without other response components; p−&, phasic decrease in activity with or without other response components. * Significantly different from † among same group and task (analysis of variance, $P < 0.05$).

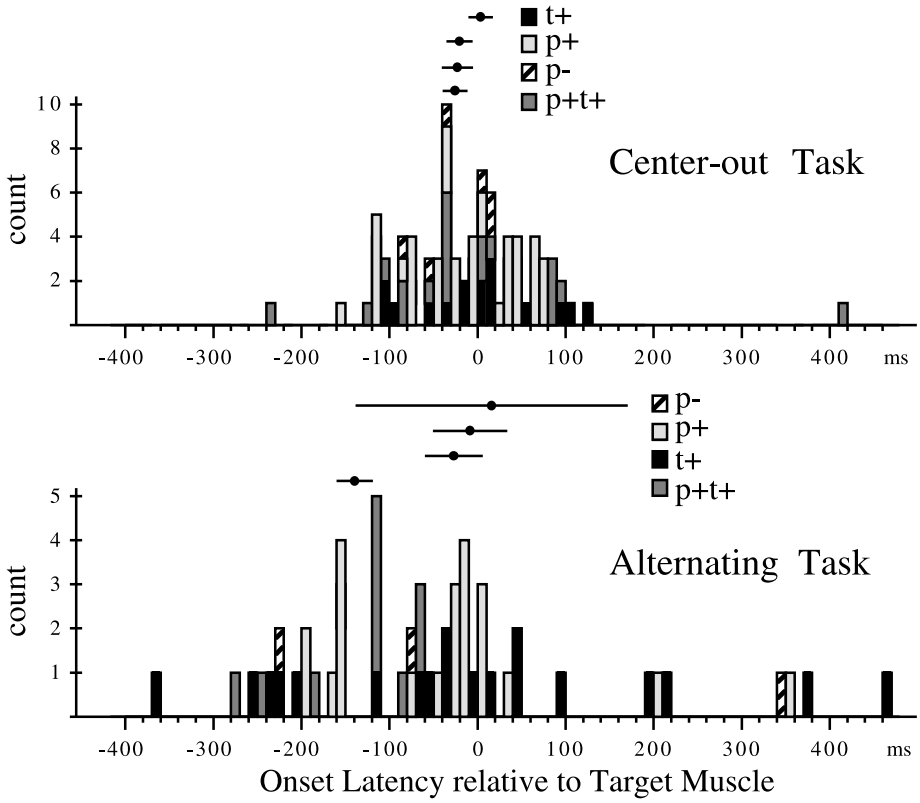


FIG. 8. Histograms of onset times of activity for PreM-INs relative to target muscle onset. Response types of PreM-INs are indicated separately by shading. ●, mean ± SE of onset times for PreM-INs separated into groups by response pattern. Decrementing and ramp patterns included in t+. *A*: PreM-INs sampled in the center-out task. Mean onset time is −11 ms (n = 83 cell-muscle pairs). *B*: PreM-INs sampled in the alternating task. Mean onset time is −46 ms (n = 58 cell-muscle pairs).

flexion torques did not increase over its relatively high firing level in the center hold. During extension, the activity decreased monotonically (Fig. 9*B*). The regression shows a negative slope (−600 spikes/s/Nm), indicating the gradual decrease of activity with increases in extension torque until the unit was silenced at the highest torques. Given the relatively high resting discharge of this flexor PreM-IN, it makes functional sense to suppress its activity during extension. Interestingly, its activity dropped in a graded manner. Seven PreM-INs of this type were recorded and five had the same pattern: negative correlation with torque produced by the antagonists of the facilitated muscles. Only one of these also had a significant positive correlation to torque produced by the facilitated muscles.

A significant correlation with static torque ($P < 0.05$) was found for the activity of all the MNs, 71% of the PreM-INs, 67% of the Sy-INs, and 84% of the U-INs (of those with a sustained response component). Activity in the neutral hold was excluded from the calculation of these correlations. Table 4 shows the mean values of the correlations and rate-torque slopes for the four populations separately for flexion and extension responses and for neurons with facilitatory and suppressive features in STAs. Not surprisingly, the MNs showed the closest correlations with torque (mean r = 0.84). The mean correlation coefficients of PreM-INs, Sy-INs, and U-INs were lower and resembled each other. The average extension rate-torque slopes of PreM-INs and U-INs were similar and higher than those of MNs and Sy-INs. However, these means were not significantly different (ANOVA, $P > 0.73$). For flexion, the mean rate-torque slopes of PreM-INs, Sy-INs, and U-INs were similar to each other and higher than those of MNs. Again, these differences were not statistically significant (ANOVA, $P > 0.75$). Generally, for all four groups of spinal units with positive correlation to torque the average rate-torque slope was higher for extension (overall mean: 322 spikes/s/Nm) than for flexion (mean: 257 spikes/s/Nm, ANOVA, $F = 6.3$, $P < 0.013$). Among the units with negative correlations to torque were seven PreM-INs and 13 U-INs. The negative extension and flexion slopes were similar for the U-INs.

Relation to dynamic torque

Many spinal neurons also showed phasic activity associated with the dynamic transition to new levels of active torque. The peak rate of change of torque during individual trials varied as the monkeys produced different levels of static torque; higher static levels were acquired with higher rates of change (Fig. 1). The relation between peak firing rate and peak dT/dt was investigated in *monkey W* for 34 PreM-INs, 6 Sy-INs, and 65 U-INs with a phasic response component. A phasic-tonic PreM-IN that facilitated a single flexor muscle, flexor digitorum superficialis (FDS), is shown in Fig. 10*A*. The scatter plot of peak firing rate versus peak dT/dt indicates a significant covariation of the phasic response component with dT/dt, with a slope of 228 (spikes/s)/(Nm/s) (Fig. 10*B*, *left*). In addition, the tonic firing rate of this PreM-IN was well correlated with static flexion torque (Fig. 10*B*, *right*). A purely phasic, bidirectional response of a U-IN is shown in Fig. 11. Peak firing rate was related to the rate of torque change in both extension and flexion, with similar slopes of 249 and 289 (spikes/s)/(Nm/s) (Fig. 11*B*).

The average dynamic torque sensitivities for the three populations are summarized in Table 5. Of the tested inter-

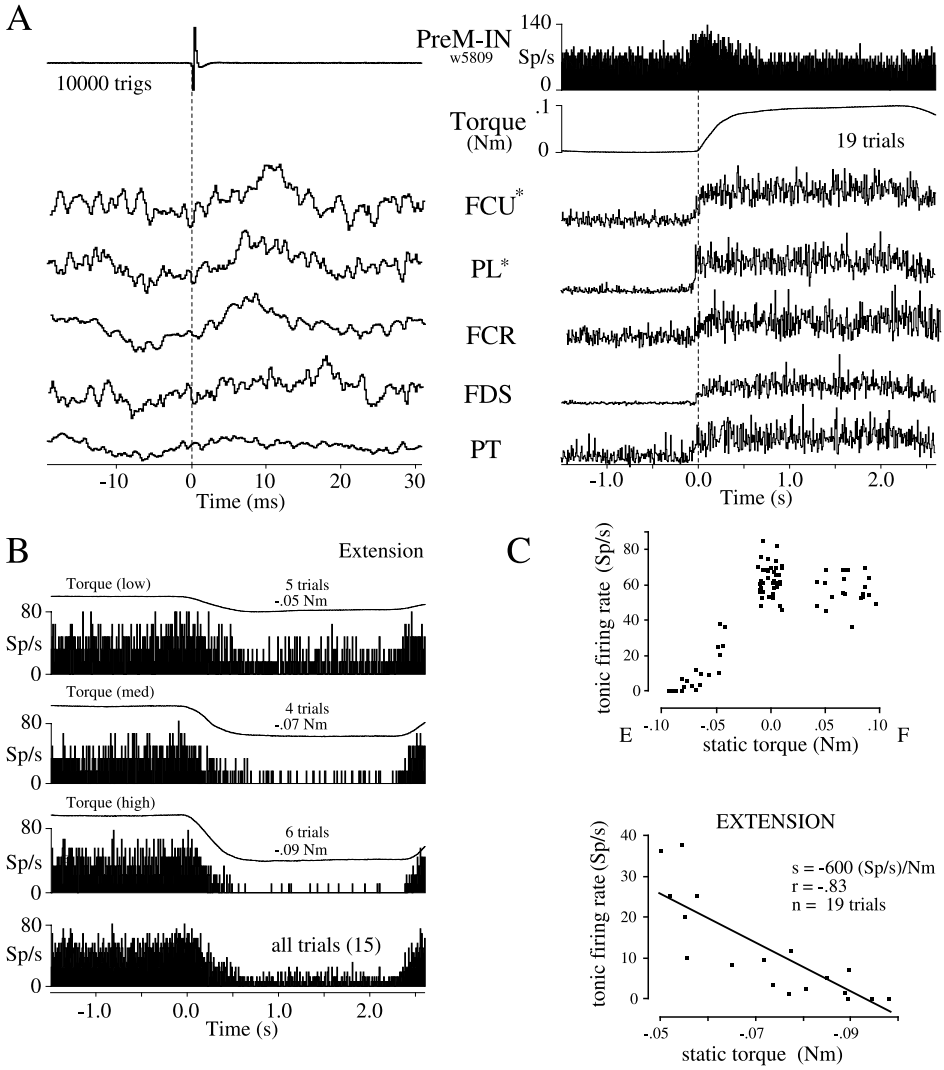


FIG. 9. STAs and responses of a PreM-IN recorded in C_6. *A*: STAs show a facilitation of 2 flexor muscles [palmaris longus (PL), flexor carpi ulnaris (FCU); *] and synchronous facilitation in FCR. Response average shows a phasic task modulation during flexion (onset: −88 ms). *B*: responses for extension averaged separately for (*top* to *bottom*) low, medium, high, and combined torque levels; neuron becomes silent at higher torque levels. *C*: whole-task scatter plot shows decreasing activity during extension and unmodulated tonic activity during flexion. Significant negative correlation and slope between firing rate and extension torque shown in the *bottom scatter plot*.

neurons (with phasic activity), the majority showed significant relations to peak dT/dt (50% of the PreM-INs, 83% of the Sy-INs, and 77% of the U-INs). The mean correlation coefficients between peak firing rate and peak dT/dt were similar among the interneuron groups. For each group, the average slope between peak firing rate and peak dT/dt was higher for extension than for flexion. These differences between extension and flexion, as well as differences between the groups, were not, however, statistically significant (ANOVA, $P > 0.5$). Nevertheless, these trends in dynamic sensi-

TABLE 4. *Mean correlations and slopes between tonic firing rate and static torque*

	MN	PreM-IN	Sy-IN	U-IN
Units	13	34	10	145
Positive r	0.84 ± 0.27	0.66 ± 0.28	0.65 ± 0.17	0.70 ± 0.27
Slope				
Extension	253 ± 104 (8)	PSF: 342 ± 300 (21) PSS: 344 ± 292 (3)	SF: 244 ± 118 (4) SS: 314 ± 213 (2)	328 ± 231 (91)
Flexion	194 ± 75 (5)	PSF: 271 ± 151 (15) PSS: 91 ± 67 (3)	SF: 252 ± 88 (6) SS: 245 (1)	268 ± 159 (78)
Units	0	7	0	13
Negative r	—	−0.63 ± 0.23	—	−0.66 ± 0.20
Slope				
Extension	— —	PSF: −325 ± 196 (4)	— —	−185 ± 81 (6)
Flexion	— —	PSS: −187 ± 27 (3)	— —	−206 ± 95 (8)

Values are means ± SD. *n* values are in parentheses. Slopes are in spikes/s/Nm. PSF, neurons with postspike facilitation; PSS, neurons with pure postspike suppression; SF, neurons with early facilitation; SS, neurons with pure early suppression.

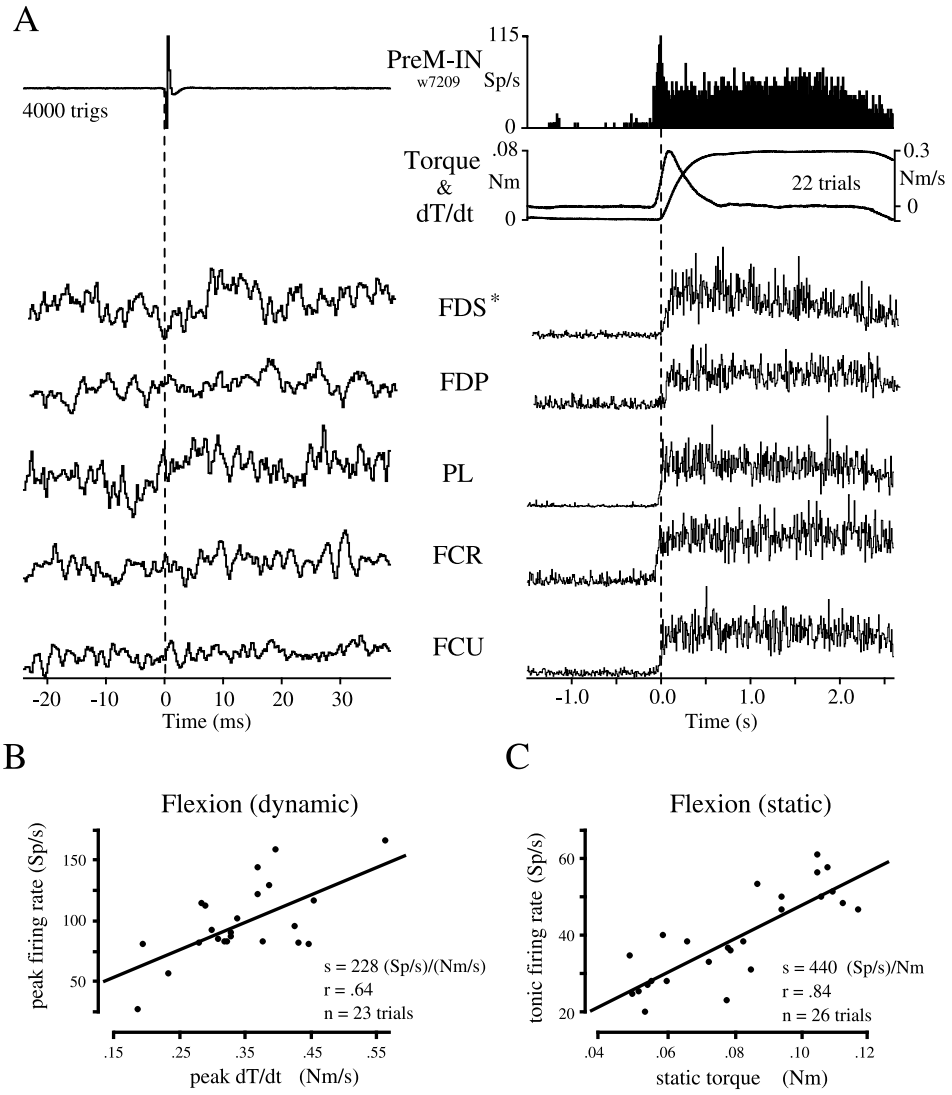


FIG. 10. Spinal PreM-IN with phasic response component. *A*: STA and response averages show facilitation of a single flexor muscle [flexor digitorum superficialis (FDS); *] and phasic-tonic activity during flexion. *B*: scatter plot of peak firing rate vs. peak d*T*/d*t* in flexion. *C*: scatter plot of tonic firing rate vs. static torque in flexion.

tivity are qualitatively similar to those found for the static relation between firing rate and torque.

On average, peak firing rate occurred after peak d*T*/d*t* for all three groups of interneurons, with an overall average latency of 62 ms (Table 5). However, the majority of PreM-INs (11/17) had peak firing rates occurring before peak torque change. In contrast, peak firing rate occurred after peak torque change for most U-INs (34/56).

Relation between PSEs and static torque correlation

Figure 12 tabulates all the spinal neurons in terms of the parametric relation between tonic firing rate and static torque, in both their preferred and nonpreferred directions, represented as a continuum on a single axis (as done implicitly in the abscissa of the rate-torque figures). Neurons are classified by the slopes (positive, negative, or flat) of these relations (diagrams on *left* of figure) rather than by response pattern. For example, *group 8* of Fig. 12 includes neurons that had increased, tonic activity for one direction of torque, but for which firing rate was independent of the magnitude of the torque.

The largest proportion of each neuronal type exhibited positive torque correlation in the preferred direction, and no significant correlation in the nonpreferred direction (*group 1*). The most obvious examples are MNs, which all increased their activity unidirectionally. In addition, several other neurons had unidirectional parametric torque relations (*groups 2–4*) and a few showed reciprocal correlations (*group 5*). Thus the neurons in *groups 1–5* showed monotonic changes in rate across the extended torque range. These monotonically modulated cells can be understood broadly as being organized to contribute to movement in a given direction. In contrast, a significant proportion of each interneuron type showed bidirectional positive torque relations, increasing their rates in both the preferred and nonpreferred directions (*group 6*). These could contribute parametrically to movement in both directions. Finally, a large group of bidirectionally activated neurons (included in *group 8*) showed no significant parametric changes with static torque in either direction. Although active, they were not involved in controlling the torque levels in either direction.

PreM-INs are tabulated separately in Fig. 12, according to their PSEs on agonist muscles (defined as the muscles

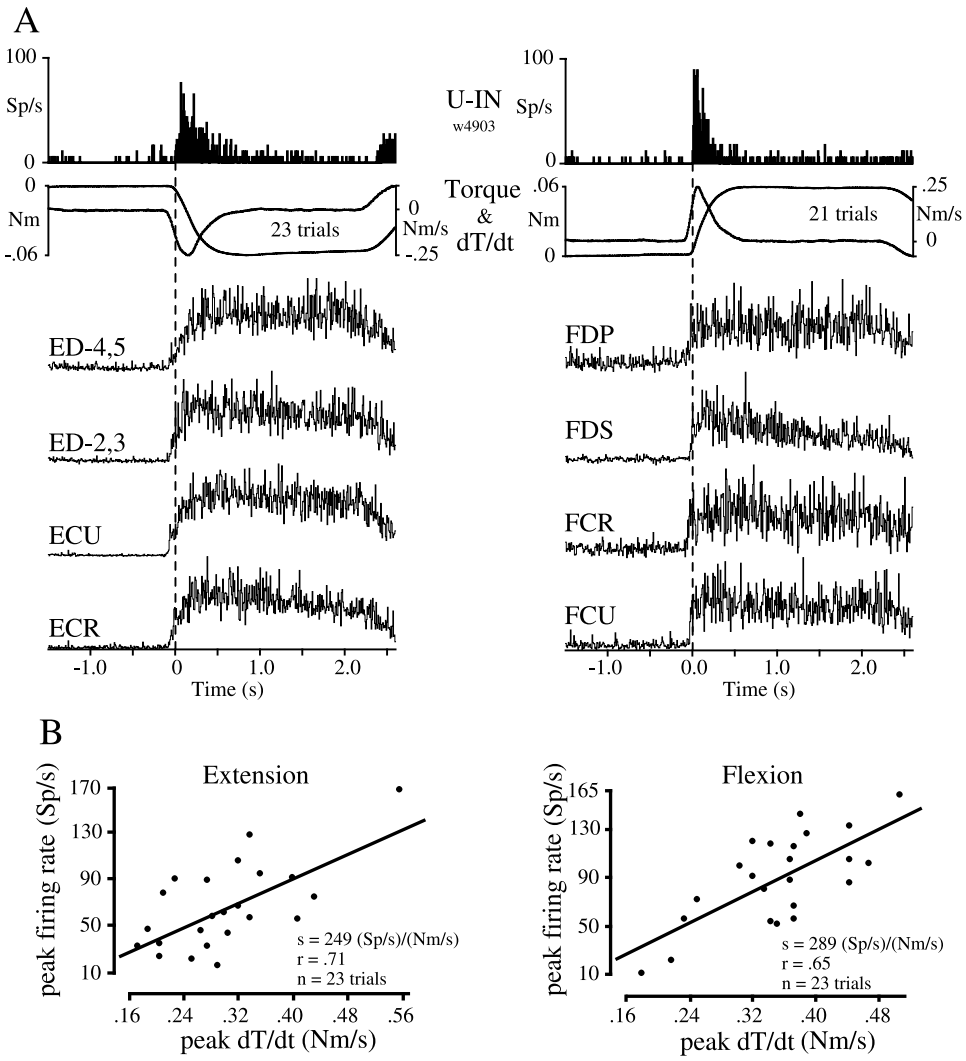


FIG. 11. U-IN with bidirectional phasic activity recorded in C_6. No significant PSEs were detected in 11 independent, simultaneously recorded muscles. *A*: response averages show onset at 0 ms for flexion and extension. *B*: scatter plots show clear correlations of peak firing rate to rate of change in torque for both extension and flexion.

active in the cell's preferred direction) and on antagonist muscles. Extending the previous analysis of the relation between cell activity and PSEs (Fig. 12 of Perlmutter et al. 1998), Fig. 12 shows the correspondence between the static rate-torque slopes and the PSEs. Combining these two properties provides a functional description of how PreM-INs control the graded activity of wrist muscles during ramp-and-hold movements. Most of the PreM-INs tested (42/59 = 71%) had firing rates that were correlated significantly with static torque. Three kinds of PreM-INs can be distinguished. Those with ''matched'' relations between parametric properties and PSEs were consistent with reciprocal control of the flexion/extension continuum. Indeed, 40% of the PreM-INs tested (24/59) had a matched relation. They all were modulated monotonically over the extended torque continuum and had a variety of functionally consistent PSEs. Among those, five different patterns could be distinguished (indicated by squares in Fig. 12). For the most common pattern, firing rate increased in proportion to torque in the ON direction of facilitated muscles and was uncorrelated with opposite torques (*group 1*, Fac agonist). Cells with ''mixed'' relations had parametric behavior that was only partially consistent with reciprocal activation of agonist and antagonist muscles (numbers shown in circles). These cells included neurons that had positive rate-torque slopes in the ON direction of facilitated muscles but also were correlated with torque in the opposite direction, when these muscles were silent. A few PreM-INs had purely counterintuitive or ''incongruent'' relations (numbers shown in triangles); for example, the

TABLE 5. *Mean correlations and slopes between peak firing rate and torque change*

	PreM-IN	Sy-IN	U-IN
Units	17	5	50
Positive r	0.52 ± 0.14	0.45 ± 0.09	0.54 ± 0.14
Slope			
Extension	PSF: 144 ± 87 (6) PSS: 320 ± 24 (2)	SF: 91 ± 29 (3) SS: 169 (1)	171 ± 161 (26)
Flexion	PSF: 88 ± 65 (8) PSS: 160 (1)	SF: 49 ± 27 (3) SS: —	132 ± 139 (30)
P.−p. latency	60 ± 219 (17)	46 ± 112 (7)	65 ± 109 (56)

Values are means ± SD, *n* values in parentheses. Slopes expressed in (spikes/s)/(Nm/s). PSF, neurons with postspike facilitation; PSS, neurons with pure postspike suppression; SF, neurons with early facilitation; SS, neurons with pure early suppression; P.-p., peak-to-peak.

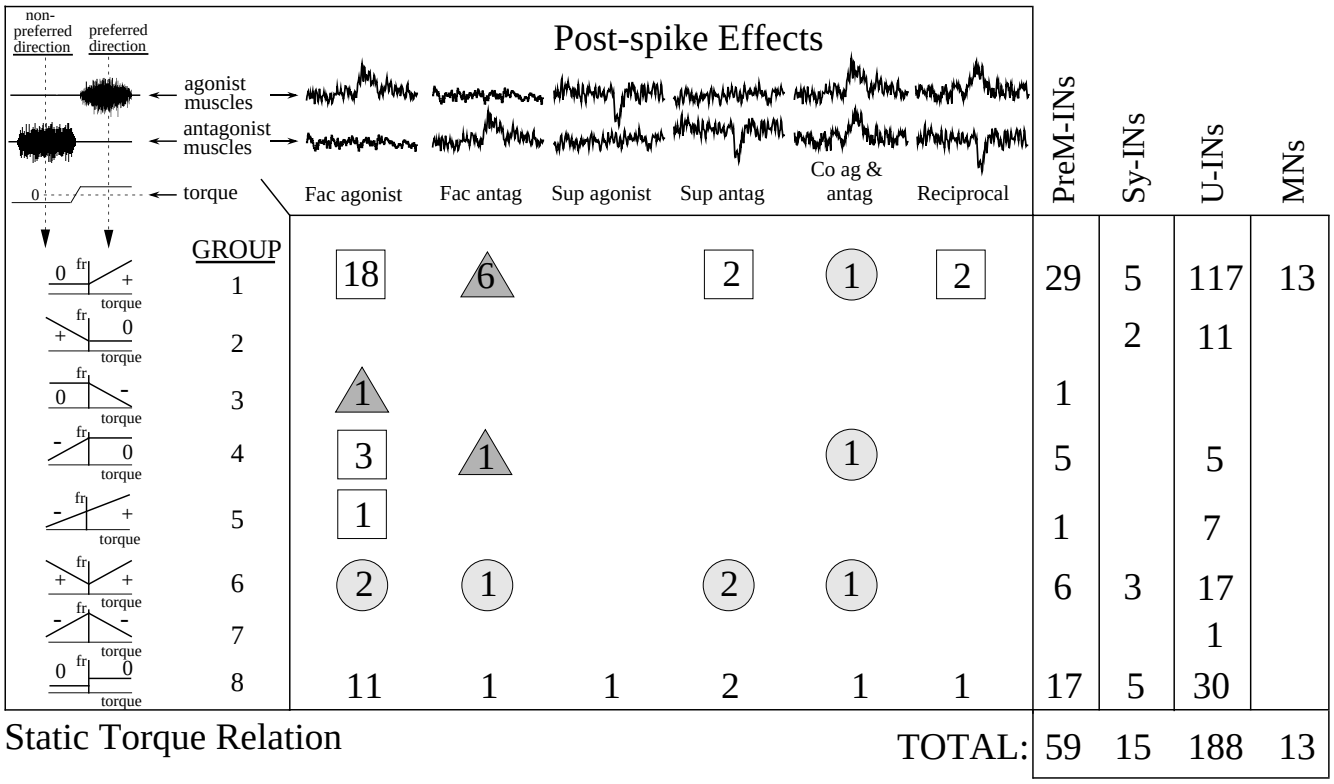


FIG. 12. Rate-torque relationships in preferred and nonpreferred directions for different groups of spinal neurons. PreM-INs are tabulated separately according to their PSEs on agonist and antagonist muscles. Preferred direction was defined on the basis of highest phasic as well as tonic activity, so some neurons could show parametric increases of static firing rates in the nonpreferred direction (e.g., *group 2*). For this figure only, neurons for which the only task-related modulation was a decrease in activity for 1 direction of torque (''no preferred dir'' in Table 1) were assigned a preferred direction opposite that in which the firing rate decreased. Slope of parametric rate-torque relation is schematically indicated on *left*. Note that these slopes do not indicate response patterns; for example, 0 slope could represent unmodulated activity during the static hold period, modulated activity with no significant relation to static torque level, or no activity at all. For *groups 2* and *3*, continuity at 0 torque level shown in diagrams is schematic only (firing rate-torque relationships for 7/14 of these neurons were not continuous at transition between flexion and extension torques). Squares represent matched properties between PSE and static torque relation (see text for details), circles and triangles represent mixed and incongruent relations, respectively.

firing rates of six neurons increased parametrically with torques for which facilitated target muscles were inhibited.

Although Sy-INs do not generate output effects directly, they are linked synaptically with premotor cells that do, so their torque relations also have functional implications. All Sy-INs with early facilitatory effects in STAs showed matched relations between their PSEs and their static torque-firing rate correlations. Of the 10 Sy-INs associated with facilitation of coactive muscles, 6 had positive correlations to torque produced by those muscles and 4 had no static torque-firing rate correlation. Sy-INs with early suppressive effects had primarily incongruent relations.

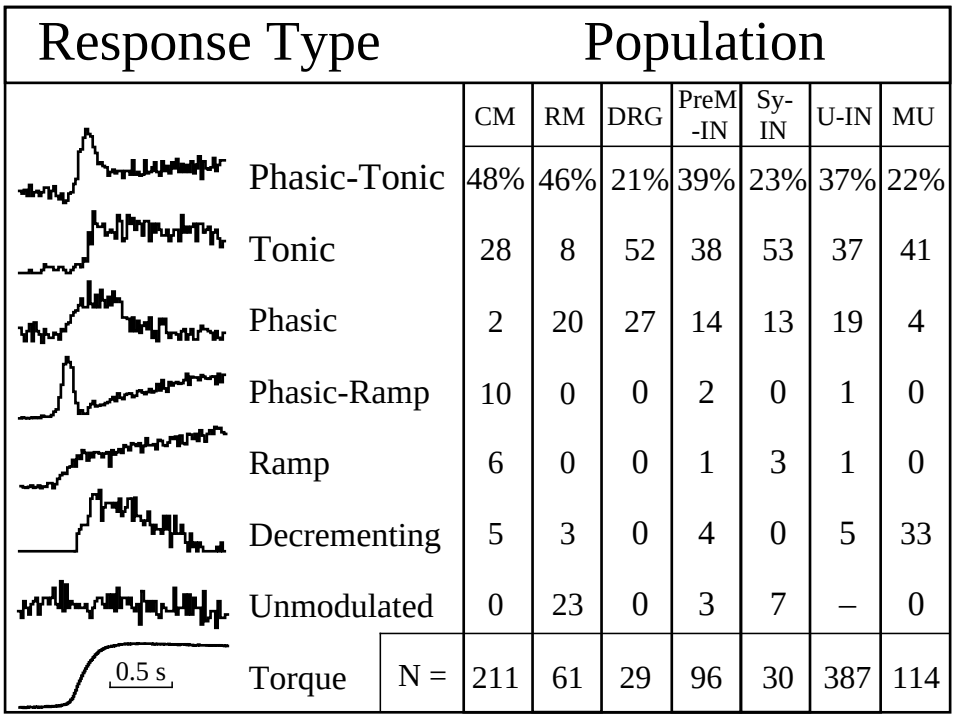
Interestingly, all three types of INs showed essentially similar distributions with regard to the extended rate-torque relationships. For all types, the most common group was unidirectional monotonic increase in the preferred direction (*group 1*, representing 55% of the total), followed by bidirectional unmodulated (*group 8;* 19%) and bidirectional increase (*group 6,* 10%).

DISCUSSION

Identification of spinal neurons

Ideally, it would be desirable to identify the spinal interneurons described here in terms of the ''classical'' cell types characterized in acute experiments. Determining such correspondence is complicated by the different identification criteria used in chronic and acute experiments. Spike-triggered averaging of EMG permits the classification of spinal neurons into MNs, PreM-INs with PSEs in forearm muscles, Sy-INs associated with early, ''synchrony'' effects in muscles, and U-INs with no spike-related modulation of muscle activity. This classification is based strictly on the *output* effects associated with the recorded neuron. In contrast, the classical identification of spinal interneurons in anesthetized animals (e.g., Ia-inhibitory interneuron) is based largely on the profile of synaptic *input* activating the interneurons. In addition, we could characterize the response patterns and force relations of neurons during normal voluntary activity. This basic difference in criteria represents a fundamental dichotomy between the classification schemes used classically and in the present study.

One could hope that the anatomic location of our interneurons might help in correlating them with the classical groups. Unfortunately, our interneurons seemed to be distributed widely among Rexed's laminae, in part due to the limited accuracy of reconstruction procedures. Moreover, the classical groups also show widely overlapping distributions, fur-



	CM	RM	DRG	PreM-IN	Sy-IN	U-IN	MU
Phasic-Tonic	48%	46%	21%	39%	23%	37%	22%
Tonic	28	8	52	38	53	37	41
Phasic	2	20	27	14	13	19	4
Phasic-Ramp	10	0	0	2	0	1	0
Ramp	6	0	0	1	3	1	0
Decrementing	5	3	0	4	0	5	33
Unmodulated	0	23	0	3	7	–	0
N =	211	61	29	96	30	387	114

FIG. 13. Summary of response patterns in the preferred direction for different populations of neurons during generation of flexion and extension torques at the wrist. Examples of each pattern are illustrated on *left*. Proportions are given for corticomotoneuronal (CM) (Fetz et al. 1989) and rubromotoneuronal cells (RM) (Fetz et al. 1989), premotor afferents in dorsal root ganglia (DRG) (Flament et al. 1992), spinal premotor interneurons (PreM-IN), spinal unidentified interneurons (U-IN), spinal interneurons with synchrony effects (Sy-IN), and motoneurons (MU). Latter combines motor unit data from Palmer and Fetz (1985) with putative motoneurons from present study. In contrast to Table 1, which includes inhibitory patterns identifiable only in the center-out task, this figure summarizes patterns identifiable in the alternating task used in previous studies. Unmodulated U-INs are not included because they were not studied systematically and their proportion could be made arbitrarily large.

ther vitiating any attempts to cross-identify interneuron types on the basis of anatomic location.

Although our classification of interneurons provides little insight into their possible participation in the classical spinal reflexes, it does provide more direct functional evidence regarding their role in voluntary movement. The PreM-INs represent interneurons with causal linkages to MNs, probably either mono- or disynaptic. Although the Sy-INs had no causal output effects, they are synchronized with other PreM cells, and their properties resemble those of PreM-INs and MNs more closely than those of U-INs. Of course, the different categories should be interpreted with caution because there are several reasons why some U-INs and Sy-INs may be unidentified PreM-INs. Only some of the forearm muscles could be monitored, and even the recorded EMGs probably sampled a subset of the motor units in the monitored muscles. Moreover some of the unidirectional interneurons might have had undetected connections to muscles that were inactive when the unit was active. Irrespective of these qualifications, the properties of identified PreM-INs do provide significant information about the output effects and activity of premotor interneurons and their target muscles during normal voluntary movements.

Response patterns

The units' response patterns during ramp-and-hold torque trajectories consist of two major components: the phasic activity that occurs during dynamic changes in torque and the sustained discharge during maintained static torque. The sustained activity was tonic in most cases but also could be increasing or decrementing. The firing patterns in the preferred direction for different cell groups, including other PreM populations, are shown in Fig. 13. This tabulation combines our MNs with motor units recorded in forearm muscles under similar conditions (Palmer and Fetz 1985). The previous motor unit sample included a larger proportion of decrementing patterns, probably due to the higher torque levels examined in that study.

In contrast to MNs, interneurons showed a greater variety of response patterns, and a larger proportion of these patterns had a phasic component. Response patterns of PreM-INs and Sy-INs were remarkably similar to the proportions seen in U-INs, suggesting that the activity of premotor interneurons did not differ significantly from that of the larger population of INs.

The center-out task allowed identification of some new response patterns, such as ''suppressed'' discharge during active production of torque, measured relative to a resting discharge during the relaxed center hold. Many decreasing patterns resembled mirror images of phasic-tonic, tonic, and phasic types (Table 1). Furthermore, the center-out task revealed that some units had release activity, i.e., transient activity during cessation of active torque, usually accompanied by phasic modulation at onset of active torque. Release activity was observed in all three classes of interneurons but never in MNs or in the EMGs.

In this one-dimensional movement task, >90% of the task-related units had a preferred direction, defined as the direction associated with the strongest increase in firing. However, most interneurons were also active in the nonpreferred direction, and for many this activity was also task-modulated. Bidirectional activation also has been observed for last-order cervical interneurons during both the flexor and extensor phases of the fictive locomotor step cycle (Ichikawa et al. 1991). This indicates that although muscles are activated reciprocally during flexion-extension movements, spinal neurons involved in these movements are not strictly partitioned into separate flexion and extension groups. The flexion-extension dimension may be represented centrally as

a movement continuum, with interneurons having overlapping domains of activity in these two opposing directions.

Relation to static torque and rate of change of torque

The PreM cells, which have output effects on their target muscles, contribute causally to generating active force in proportion to their activity. For this reason, their firing rate as a function of active torque is a salient issue. Earlier studies in monkeys have investigated force coding of neurons in motor cortex (reviewed by Evarts 1981; Hepp-Reymond 1988), cerebellum (Smith and Bourbonnais 1981; Thach 1978), basal ganglia (Allum et al. 1983; Mink and Thach 1991a,b), and thalamus (Anner-Baratti et al. 1986). Similar analyses have been done for CM cells (Cheney and Fetz 1980; Maier et al. 1993) and RM cells (Cheney et al. 1988; Mewes and Cheney 1994). In this study, we found that most PreM-INs with tonic response components showed a significant parametric relation to static torque. The mean rate-torque slope (i.e., the sensitivity, or gain, of this relation) tended to be higher for PreM-INs, Sy-INs, and U-INs than for MNs. Generally, mean extension slopes were higher than flexion slopes.

The sensitivity of MNs should be similar to that measured for motor units under comparable conditions. Palmer and Fetz (1985) found mean values of 260 and 410 spikes/s/Nm, respectively, for extension and flexion motor units. Mean values were similar for our extension MNs but not for the flexion MNs. This discrepancy is probably due to the restricted samples in both studies.

Most of the tested interneurons with phasic increasing components showed clear correlations between peak phasic activity and rate of change of torque (dT/dt). As found for static torques, all three populations showed a trend for higher sensitivity in extension than in flexion.

Output effects versus torque relation

To understand the contribution of PreM-INs to movement, we must interpret their response patterns in the context of their output projections. In the companion paper we described the various relations between the PSEs and activity patterns of PreM-INs (Perlmutter et al. 1998). In the present study, we extended this analysis to the parametric change in firing rate with static torque in the context of both torque directions. We observed a variety of parametric rate changes (Fig. 12), consisting of different combinations of increasing, decreasing, or unchanged activity with torques in the preferred and nonpreferred directions. In considering the flexion-extension axis as a continuum, we broaden the concept of the ''strict'' reciprocal organization and suggest that the cells' relation to increasing torque in the preferred direction could be seen as a continuation of its relation to decreasing torque in the nonpreferred direction.

Most cells exhibited a monotonic change in rate over this extended torque range, usually with a transition at the origin (*groups 1–5* in Fig. 12). The most common monotonic behavior for each population was increased activity with torque in the preferred direction and no change with torque in the opposite direction (*group 1*). The other groups with monotonic changes seem different, but all five can be seen as special cases of a sigmoidal relation between firing rate and torque, as exhibited by MNs. MN firing rates are zero below their recruitment threshold, then increase with torque over a restricted range and saturate at the upper end, as illustrated for forelimb motor units studied in a similar task (Palmer and Fetz 1985). The behavior of most monotonic interneurons can be viewed as components of a similar sigmoidal behavior, with the nonlinear transitions occurring at different points of the extended torque range. Most (n = 26) of the PreM-INs with monotonic increases toward the preferred direction produced functionally consistent PSEs, i.e., facilitation of agonist muscles and/or suppression of antagonists (squares in Fig. 12). Because the increase of firing rate with torque produces a proportional facilitation or suppression of target muscles, PreM-INs with these properties can be regarded as being causally involved in generating and regulating active force.

Other PreM-INs showed an apparent incongruity between the correlation with torque and their PSEs. Relatively few of the monotonic PreM-INs (n = 8, triangles) showed the inverse relation between extended rate-torque slope and PSEs. The nonmonotonically modulated cells of *group 6*, which showed parametric increases in both directions, also do not make simple functional sense in a task with alternating sets of activated muscles. Although some muscles with only secondary flexion/extension action were bidirectionally active, they were not facilitated preferentially by incongruent PreM-INs. One could make functional sense of these units by considering several points. First, all the incongruent PreM-INs were activated bidirectionally, which indicates that they facilitated their target muscles whether they were producing torque or not. However, the seemingly inappropriate excitation is countered by simultaneous inhibition. Such inhibition of MNs is provided exclusively by interneurons, including the inhibitory PreM-INs identified by postspike suppression. Moreover, in other behavioral situations, such as grasping, the wrist needs to be stabilized in all of its degrees of freedom. Neurons related to the acts of stiffening the wrist or radial/ulnar deviation could have incongruent relations between their PSE and response in the flexion-extension task. Alternatively, seemingly incongruent facilitatory PSEs may not generate inappropriate excitation of motoneurons if they are mediated by an intervening interneuron that is inactive when the muscle is inactive.

Comparison with supraspinal and afferent PreM cells

It is interesting to compare the properties of spinal PreM-INs with those of other populations of neurons previously tested under similar conditions, i.e., in the alternating task. The majority of *response patterns* of PreM-INs also have been seen in supraspinal and afferent premotor cells (Fig. 13). The most prominent among those were phasic-tonic, followed by tonic and phasic patterns, which also were common in the CM, RM, and DRG populations (Cheney and Fetz 1980; Flament et al. 1992; Mewes and Cheney 1994).

Functionally it is useful to consider these neuronal response patterns in terms of the activity during the dynamic transition in torque and during the sustained, static hold. The phasic activity during dynamic torque change is initiated by central commands and reflects the neural mechanisms that

alter the balance of muscle activity. In contrast, the sustained activity during the static hold represents a combination of central and peripheral drive, which maintains a steady level of muscle activity. Phasic modulations during changes in torque were significantly more prevalent in spinal interneurons (58%) than in motor units (26%). Supraspinal PreM cells also showed a greater proportion of phasic modulation (CM, 60%; RM, 66%). The fact that strong phasic input from these PreM cells did not generate more phasic responses in their target MNs may reflect the need for this early synaptic drive to bring MNs to firing level and overcome any remaining inhibitory inputs from the antagonist response. The prevalence of sustained activity during the static hold also differed for each population. While virtually all MNs and CM cells had sustained activity, the proportion was slightly less among spinal PreM-INs (86%), U-INs (81%), PreM afferents (73%), and RM cells (80%).

Whether the sustained activity is a *parametric function* of the level of static torque exerted is a further indication of functional involvement. Of the tested PreM-INs, 71% had activity that was correlated significantly with static torque compared with 100% of CM cells and 70% of RM cells (Cheney and Fetz 1980; Mewes and Cheney 1994). Rate-torque slopes tended to be higher for extension than for flexion in all three PreM populations. However, PreM-INs seem to be less sensitive than CM cells but more sensitive than RM cells (e.g., extension mean slopes: CM, 480 spikes/s/Nm; PreM-IN, 342 spikes/s/Nm; RM, 160 spikes/s/Nm; MN, 253 spikes/s/Nm).

Negative correlations between firing rate and wrist torque in the step tracking task have not been described so far for CM or RM cells. Thach (1978) showed that some motor cortical neurons exhibit parametrically decreasing activity in the nonpreferred direction. Some spinal PreM-INs displayed significant negative correlations to static torque, usually to static torque produced by antagonists of their facilitated muscles. These units thus shut off their facilitation when torque was generated in the nonfacilitated direction and did so in a linearly graded fashion. In contrast, some CM cells had negative correlations to force produced in the precision grip and facilitated force-producing muscles (Maier et al. 1993).

Interestingly, the populations differed significantly in their tendency to exhibit *bidirectional activity*. Including unmodulated activity, about three-fourths of the PreM-INs showed some activity in both flexion and extension. Such bidirectional activity was seen for all RM cells, but none of the CM cells and relatively few DRG PreM afferents. Thus the unidirectional activity of the CM and DRG afferents resembles that of their target muscles, whereas the bidirectional activity of INs and RM cells is related more broadly to movement.

The wide distributions of PreM *onset times* relative to target muscle onset may reflect functional divisions within the population: those with earlier onset may be driven by networks initiating movements (feedforward), and those with later onsets may be involved in controlling movement via sensory feedback. Two-thirds of PreM-INs and DRG premotor neurons were activated before EMG onset in target muscles (Flament et al. 1992). Among CM and RM cells a larger proportion was activated before target onset (71 and 94%), indicating that more of the supraspinal PreM units may be involved in movement initiation (Cheney and Fetz 1980; Mewes and Cheney 1994). This trend also is reflected in the mean lead onset times relative to target muscles. The average onsets of segmental neurons in the alternating task [46 ms for PreM-INs and 51 ms for PreM DRG afferents (Flament et al. 1992)] were later than the mean onset of supraspinal CM and RM cells [82 and 88 ms, respectively (Cheney and Fetz 1980; Mewes and Cheney 1994)].

Among each of the four PreM populations, phasic units tended to be activated first, followed by tonic units. The PreM-INs that were activated after EMG onset, such as the majority of inhibitory PreM-INs, might include cells primarily driven by peripheral input from cutaneous and proprioceptive receptors activated after EMG onset. In contrast, the PreM-INs activated before EMG onset could be driven by supraspinal sources (including branches of CM and RM cells) as well as by fusimotor-activated spindle afferents (Baldissera et al. 1981). The mean onset times suggest a successive recruitment order, with supraspinal PreM cells tending to be activated first, followed by afferent PreM cells, and, finally, spinal PreM-INs. However, the large dispersion in each of these distributions produces considerable overlap of onset times; this could be interpreted as a network of PreM units primarily activated in parallel, with some units preceding and others following muscle onset.

Functional conclusions

These results suggest that spinal interneurons and CM cells differ from each other in their relations to alternating flexion-extension wrist movements. Whereas almost all CM cells fired unidirectionally, with either flexion or extension, but not both, most of the INs were bidirectionally active. This reflects a sharper representation of opposing movement direction in the premotor cortical output neurons than the broader, overlapping representation in spinal neurons. Indeed, some spinal neurons increased their activity with torque in both directions, a property never seen in any supraspinal CM or RM cells. The bidirectional activity of excitatory PreM-INs has a counterproductive component—i.e., the activity that occurs when their facilitated target muscles must be inactivated. Clearly these inappropriate excitatory effects are gated out or overridden by simultaneous inhibition from inhibitory interneurons. This coactivation of excitatory and inhibitory PreM-INs in the spinal cord differs from the reciprocal activation of excitatory CM cells in the cortex.

Another difference between cortex and spinal cord involves the organization of the muscle fields. CM cells generally have larger excitatory muscle fields and often exert reciprocal inhibition on antagonists of their facilitated target muscles. In contrast, spinal PreM-INs have smaller muscle fields that are either excitatory or inhibitory but not both (Perlmutter et al. 1998). The more specific projections of spinal INs, combined with their broader activation, indicate that spinal circuits tend to operate more in terms of separate but simultaneously activated excitatory and inhibitory influences, whereas cortical output cells are organized more in terms of muscle synergies generating movement.

In the present task, the multifunctional wrist has been restricted to a 1 degree-of-freedom joint working in a reciprocal fashion. It seems likely that PreM-INs could have a

variety of preferred directions for two-dimensional wrist movements that would include radial-ulnar deviations. In this case, the ''preferred directions'' in our one-dimensional task would represent projections of these two-dimensional vectors on the flexion-extension axis. Wrist-related cells may turn out to exhibit broad tuning in two dimensions, like the cosine functions documented for proximal shoulder movements (Georgopoulos et al. 1982, 1988; Kalaska et al. 1989) and like many muscles acting at the wrist (Hoffman and Strick 1986). In this case, the bidirectional interneurons might be seen as having a sufficiently broad activation range to generate a component in the ''nonpreferred'' flexion-extension direction. In this context, the CM cells would appear to be relatively sharply tuned in their preferred direction, exhibiting no activity in the nonpreferred direction. It seems possible that non-CM cortical neurons with wrist-related activity may show more broadly tuned behavior, like shoulder-related cells; in fact some of these may be pyramidal tract neurons driving spinal interneurons. This issue can be elucidated by documenting the activity of cortical and spinal neurons and the action of their target muscles in relation to two-dimensional wrist movements.

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