

Review

Roles of primate spinal interneurons in preparation and execution of voluntary hand movement

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Abstract

To study the contribution of primate cervical interneurons (INs) to preparation and execution of normal voluntary hand movement we investigated their *activity* and *correlational linkages* to muscles in monkeys performing tracking tasks. During ramp-and-hold flexion–extension torques about the wrist most task-related spinal INs exhibited some activity during both flexion and extension, in unexpected contrast to the strictly unidirectional activity of corticomotoneuronal (CM) cells and motoneurons. Most INs increased their activity more in one of these two directions; response patterns in their preferred direction were typically tonic or phasic-tonic. Spike-triggered averages of EMG detected significant features in muscle activity for many task-related INs. Premotor INs (PreM-INs) were identified by post-spike facilitation or suppression with appropriate onset latencies after the trigger spike. Muscle fields of PreM-INs were smaller than those of supraspinal PreM cells in cortex and red nucleus, and rarely involved reciprocal effects on antagonist muscles. To investigate the relation of spinal INs to a repertoire of *different muscle synergies*, activity of INs was recorded from a macaque performing a multidirectional wrist task. The monkey generated isometric torques in flexion/extension, radial/ulnar deviation, pronation/supination, and executed a power grip that co-contracted wrist flexor and extensor muscles. Many INs showing task-modulated activity had preferred directions in this multidirectional space, typically with broadly tuned activation. The role of spinal INs in *preparation* for voluntary movement was revealed in monkeys performing instructed delay tasks. During the delay between a transient visual cue and a go signal a third of the tested INs showed significant delay modulation (SDM) of firing rate relative to the pre-cue rate. The SDM responses often differed from the INs' responses during the subsequent active torque period. In a monkey instructed by either visual or proprioceptive cues the delay period activity for many INs was similar in visual and perturbation trials, although other INs exhibited different SDM for visually and proprioceptively cued trials. These results suggest that spinal INs are involved, with cortex, in the earliest stages of movement preparation. The *sensory input* to INs could be identified in transient responses to the torque pulse, which showed two predominant patterns, consistent with inputs from cutaneous or proprioceptive receptors. We also investigated the *task-dependent modulation* of neural responses to peripheral input in a monkey performing wrist flexion/extension movements in a visually cued instructed delay task. Monosynaptic responses evoked by electrical stimulation of the superficial radial nerve through a cuff electrode were suppressed or abolished during the dynamic movement phase. Since task-related activity of the INs increased at the same time, the suppression was mediated by presynaptic rather than postsynaptic inhibition. These observations indicate that under normal behavioral conditions many spinal INs have response properties comparable to those previously documented for cortical neurons in behaving animals.

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1. Introduction

A cross-section of the spinal cord reveals a compact version of the entire nervous system. Sensory input from peripheral receptors arriving via afferent fibers dominates responses of dorsal horn neurons, while the motor output is generated by motoneurons in the ventral horn. Between input and output the intermediate layers of the spinal cord embody complex networks that mediate variable sensorimotor associations. Similarly, different areas of cerebral cortex are specialized for sensory, motor and associational processing. Extensive experiments on the task-related activities of cortical neurons in trained monkeys reveal a rich capacity for coding behavioral variables, including the generation of forces required to move limbs in multiple directions, cue-dependent preparation for delayed movements, as well as innumerable higher-order 'cognitive' variables. In contrast, spinal cord interneurons have been studied almost entirely in anesthetized, spinal or decerebrate animals, typically in relation to their sensory input and their possible role in mediating motor reflexes (for reviews see Refs. [2,12,20]). As a result, cerebral cortex is commonly considered to be the place where higher-order sensorimotor computations and cognitive functions are processed, while spinal cord deals with 'lower-order' peripheral processing. However, spinal interneurons are heavily interconnected with cerebral cortex through numerous ascending and descending pathways. The possibility that these connections could involve spinal interneurons in some of the same behavioral roles as cortical neurons has remained largely unexplored. To test these possibilities requires examining the properties of spinal interneurons in awake animals under appropriate behavioral conditions. We here review some recent observations indicating that spinal interneurons are involved in the preparation and execution of voluntary movements in ways that both resemble and contrast with cortical neurons.

2. Role of INs in execution of voluntary movement

While classical studies have revealed much about the inputs to spinal INs from afferent and descending pathways, little is known about two properties that are essential to understanding the role of INs in voluntary movements, namely their response patterns during normal limb movements and their output effects on the agonist muscles. These two properties together provide significant information about how spinal neurons normally contribute to generation of muscle activity. To elucidate the role of segmental neurons in voluntary hand movement, we used movable tungsten microelectrodes to record the activity of INs in the C6-T1 spinal segments in macaques while they performed isometric flexion and extension torques about the wrist [36]. In the step-tracking task the monkeys acquired and maintained flexion and extension torque targets, either in an alternating fashion or interspersed with a zero-torque hold. Electromyographic (EMG) activity from multiple wrist and digit flexor and extensor muscles was recorded with multi-stranded wires implanted trans- or subcutaneously.

Spike-triggered averages (STAs) of full-wave rectified EMG activity were computed to detect correlational linkages with muscles. Interneurons that produced a significant change in averaged EMG activity beginning at a post-spike latency of ≥ 3.5 ms (calculated from the minimal latency of post-stimulus effects evoked by single-pulse microstimuli delivered through the spinal recording electrode) were classified as premotor interneurons (PreM-INs; not to be confused with last-order INs that have identified monosynaptic connections to motoneurons [19,20,45]). Most PreM-INs produced either post-spike facilitation or post-spike suppression of EMG. The cell's muscle field was defined as the set of muscles exhibiting post-spike effects (after elimination of potentially redundant muscle recordings via electrical cross-talk). Some STAs showed changes in the level of averaged EMG activity that started

before or near the trigger point. These early changes could be due only to synchronous activity in other PreM units that fired before the triggering neuron and were termed synchrony effects.

Fig. 1 shows the response averages and STAs for an excitatory PreM-IN, estimated to reside in the intermediate zone of the caudal C8 segment. This PreM-IN discharged tonically during static torques in both directions, with a higher rate during flexion, as shown by the response average (left). This neuron produced post-spike facilitation (PSF) in both the pronator teres (PT) and flexor carpi ulnaris (FCU) muscle (middle). A schematic of the most direct mediating circuit shows how post-spike effects on a target motor unit are related to conduction times and firing probability (right). Of the PreM-INs, 82% showed PSF of target muscles, either in isolation (as in Fig. 1) or superimposed on synchrony facilitation [36].

Fig. 2 shows a PreM-IN in segment C6 whose activity increased during active extension (Fig. 2B). The firing rate during the static hold increased in proportion to the extension torque (Fig. 2C). This IN had no post-spike effect on any extensor muscles, but produced post-spike suppression of a flexor (Fig. 2A). Such properties could be expected of Ia inhibitory interneurons, whose firing would suppress antagonist muscle activity in proportion to agonist activity [2,15,20,21,34]. This example illustrates the advantage of combining information about the output effect on muscles with firing rate for inferring the functional contribution to movement.

Post-spike and synchrony effects of INs were about twice as common in flexor muscles as in extensors. The number of muscles affected by PreM-INs was relatively

restricted. Two-thirds of the PreM-INs had post-spike effects in only one of the recorded muscles; the rest had larger muscle fields. The PreM-INs with divergent post-spike effects in more than one muscle typically affected either flexor or extensor muscles, but not both.

2.1. Response patterns of spinal interneurons

The effect of a PreM-IN on its target muscles would have the polarity of its post-spike effects and be proportional to its instantaneous firing rate. Most of the PreM-INs showed tonic or phasic-tonic activity associated with the ramp-and-hold torque trajectory in their preferred direction. Fig. 3 summarizes the responses of four classes of spinal neurons: PreM-INs, INs with synchrony effects in STAs (Sy-IN), INs with no effects in STAs (U-IN) and motoneurons (MN). Interestingly, the relative proportions of response patterns were generally similar among the three groups of interneurons, indicating no clear preferential patterns for those with functional linkages to muscles. The table also summarizes the firing patterns of other PreM cells in their preferred direction, namely corticomotoneuronal (CM) and rubromotoneuronal (RM) cells and dorsal root ganglion afferents with post-spike effects (DRG). All populations included phasic, tonic and phasic-tonic cells, in varying proportions. The tonic component of these responses was generally an increasing function of active torque in all groups tested.

While the neural populations showed similarities in the types of response patterns in the cells' preferred directions, they differed in the degree to which they were active in the non-preferred direction. CM cells, afferent PreM fibers and

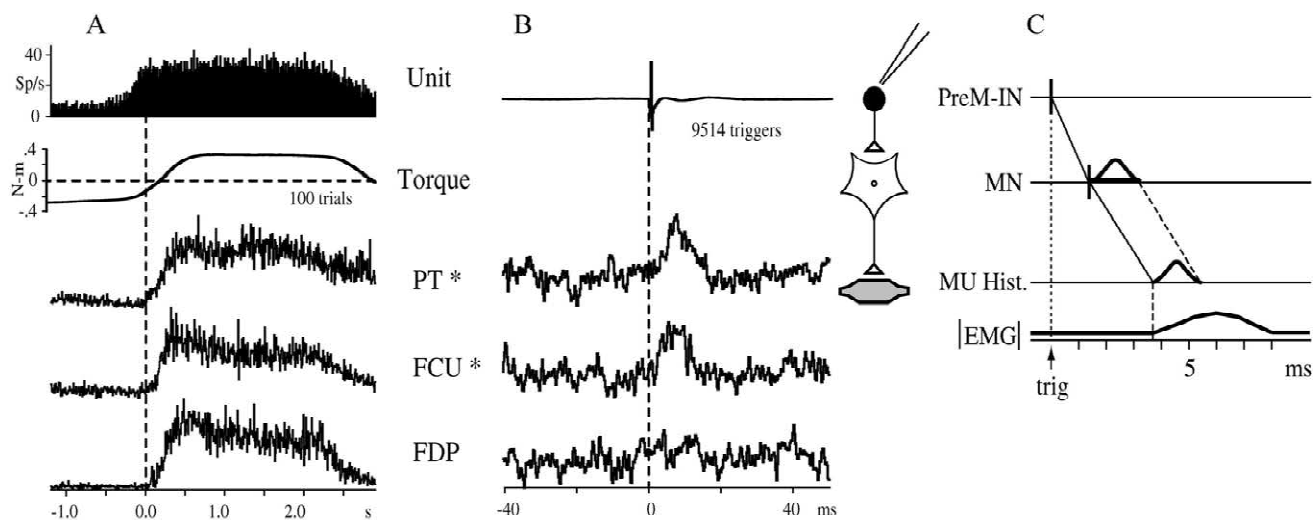


Fig. 1. Response averages and STAs of a facilitatory PreM-IN located in caudal C8. (A) The average activity of the neuron during flexion torques is shown above the average torque trajectory (positive torque is flexion, negative torque is extension) and average responses of three independently recorded co-active muscles. This neuron exhibited tonic firing during static torques in both directions, with higher rates for flexion. (B) The STAs show the triggering action potential (top) and average of rectified EMG in the three muscles. Two muscles (asterisks) had significant post-spike effects. (C) Diagram of monosynaptic circuit from PreM-IN and post-spike firing probabilities of a fast motoneuron (MN) and its peripheral motor unit (MU); |EMG| represents increase in average rectified EMG, called post-spike facilitation. (From Ref. [36])

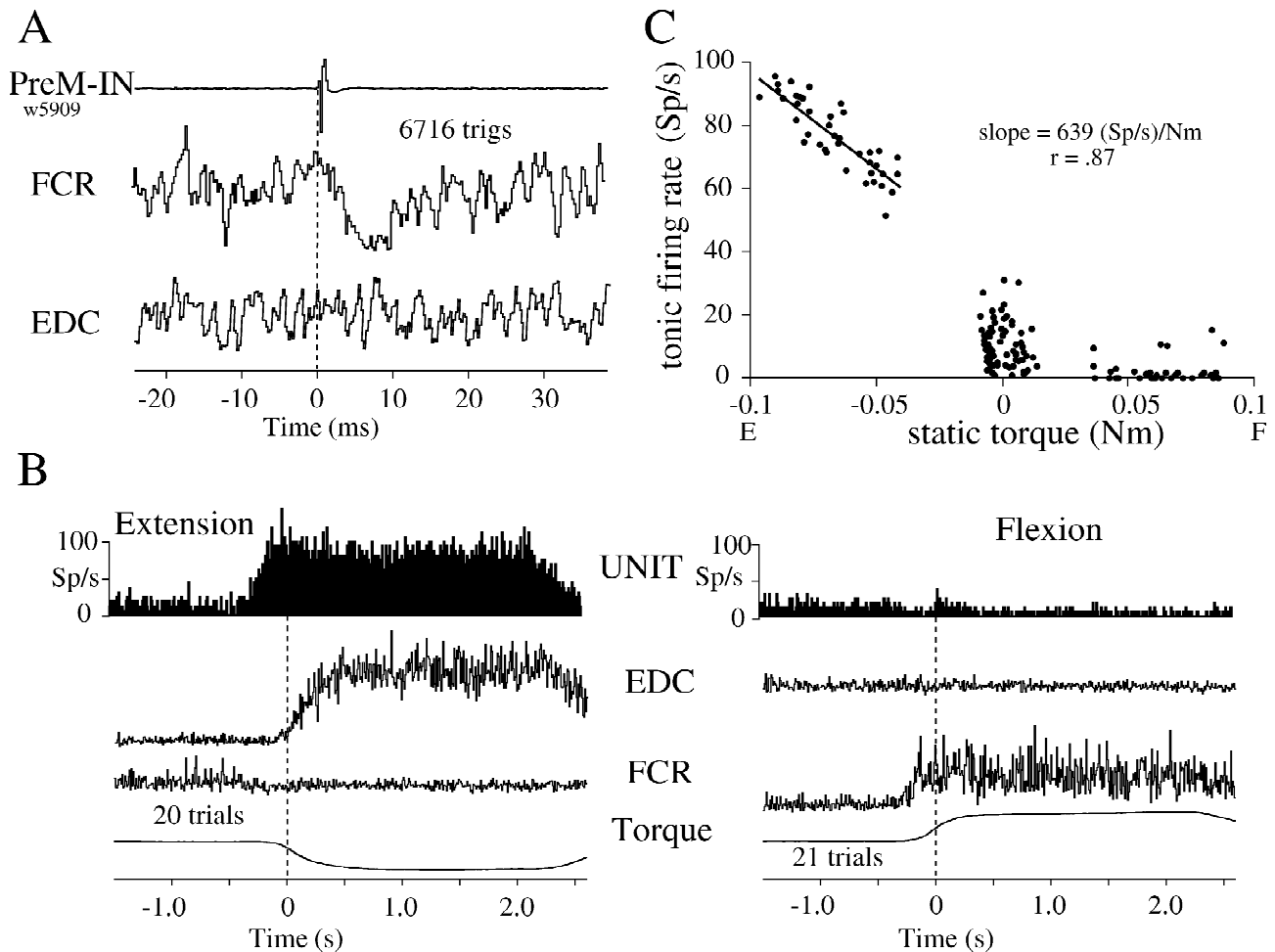


Fig. 2. Inhibitory PreM-IN that produced post-spike suppression of EMG in flexor carpi radialis (FCR) and no effect in extensor muscles (e.g. EDC, shown) in STAs (A). (B) Response averages show increased activity of IN during extension (left), and low level of activity during flexion (right). (C) Firing rate of IN during static hold was an increasing function of extensor torque. (From Ref. [27])

motor units were strictly unidirectionally active, firing for either flexion or extension, not both. In contrast, three quarters of the INs were activated in both movement directions, as well as at rest. Most task-related INs were more active during movements in their preferred direction, but also exhibited some activity during movement in the opposite direction. In that sense, most INs resembled RM cells, all of which were bidirectionally active.

A basic functional question concerns the relationship between the post-spike output effects of a PreM-IN and its response patterns relative to its target muscles. These relations are tabulated in Fig. 4, which shows the types of post-spike effects in 'agonist' muscles, activated in the cell's preferred direction, and in the 'antagonist' muscles. For some PreM-INs this relationship was totally congruent: the post-spike effects and activation patterns are functionally completely consistent with simple reciprocal control of flexion/extension movements. In Fig. 4 this would be the 24 PreM-INs that facilitated agonist muscles and fired only when these muscles were active (indicated by the square). All the other PreM-INs had more complex

relations: they showed some degree of incongruent activity, in which the post-spike effect would seem counterproductive. The circled numbers indicate INs that had post-spike effects that were partially consistent with their activation, for example, those that facilitated agonist muscles, but were also active during antagonist muscle activity (Fig. 1). The cells denoted by triangles had paradoxical relations. For example, some inhibitory INs were recruited with the muscles whose activity they inhibited, a pattern expected for Renshaw cells. A few PreM-INs had a steady discharge rate that was not modulated during alternating flexion and extension torques, similar to the previously discovered unmodulated RM cells [28,29].

2.2. Contrasting contributions of cortical and spinal PreM neurons to voluntary movement

The differences in the response properties and projection patterns of CM cells and PreM-INs suggest corresponding

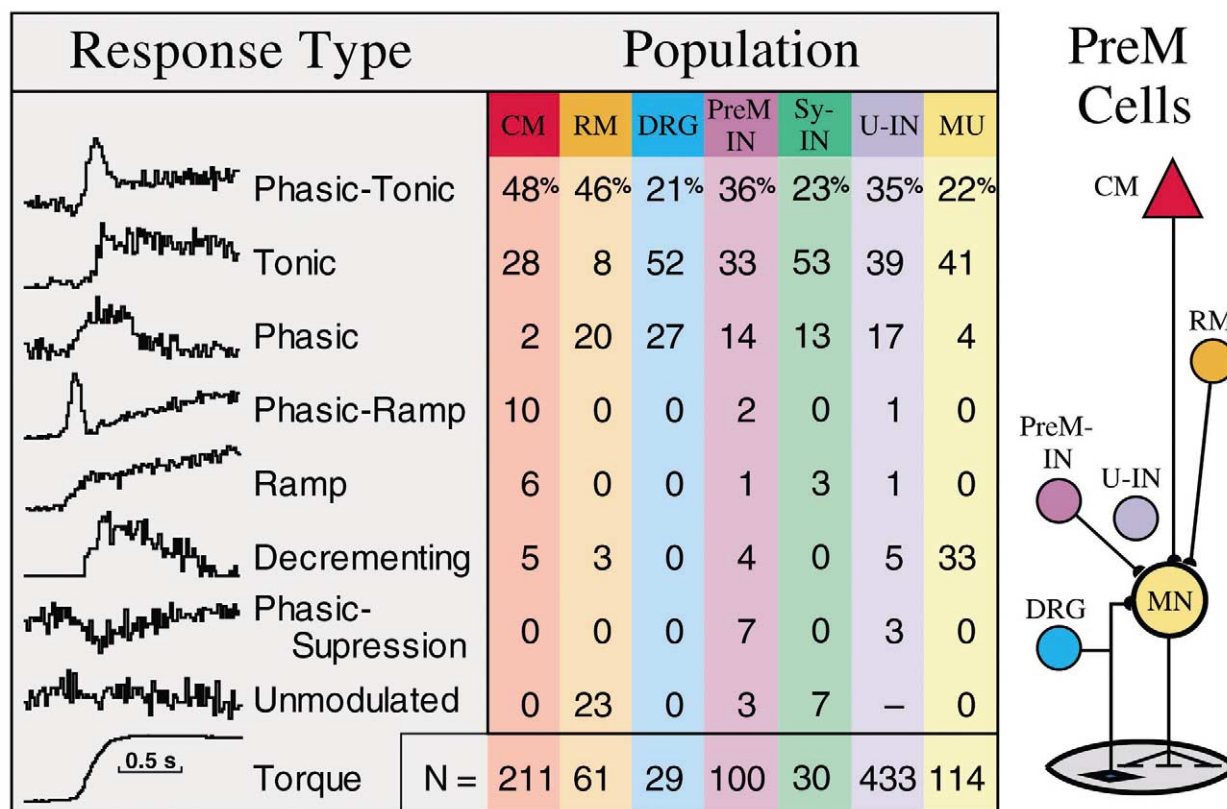


Fig. 3. Summary of response patterns in the preferred direction for different populations of neurons during generation of flexion and extension torques at the wrist. Examples of each pattern are illustrated on the left, and schematic of populations on the right. Proportions are given for corticomotoneuronal (CM) [7,8] and rubromotoneuronal cells (RM) [29], premotor afferents in dorsal root ganglia (DRG) [14], spinal premotor interneurons (PreM-IN), spinal unidentified interneurons (U-IN), spinal interneurons with synchrony effects (Sy-IN) and motoneurons (MU; combined data from motor units [35] and motoneurons [27]). Unmodulated U-INS are not included because their proportion could be made arbitrarily large.

differences in their contributions to reciprocal wrist movements. The muscle fields of CM cells were larger, and more often involved reciprocal inhibition of antagonists of the facilitated target muscles [6,11,23,26], indicating that CM cell activity tends to produce a coordinated activation of muscle groups. In contrast, PreM-INS tend to facilitate or suppress single or small sets of synergistic muscles. On the other hand, the activation of CM cells was more specific: CM cells fired with flexion or extension, but not both, whereas most spinal INs were bidirectionally active. This suggests that CM cells are activated under relatively particular movement conditions, while spinal PreM-INS are recruited more generally, with excitatory and inhibitory INs largely coactivated. Thus CM cells represent more explicitly a pattern of coordinated muscle activity, while spinal INs tend to be more ubiquitously active during a variety of movements, including those in which their post-spike effects would be inappropriate. Seen from the point of view of single motoneurons, the segmental INs provide continuously superimposed excitatory and inhibitory synaptic input, although the relative balance shifts in accordance with the need to activate or suppress the motoneuron during a movement. In contrast, the direct corticospinal input from CM cells is more strictly synergis-

tic with the current role of the motoneuron in voluntary movement.

3. Responses of INs during multidirectional hand movements

One-dimensional alternating wrist movements are fine for answering questions about the coding of dynamic movements and static forces, but they cannot address neural mechanisms controlling multidirectional movements. For example, a basic question about PreM cells that have divergent effects on two muscles that are synergistic in one movement is whether and how these cells are activated when their target muscles become antagonists. To investigate the relation of spinal INs to a repertoire of movements involving *different muscle synergies*, the activity of C7–C8 INs was recorded from a macaque performing a multidirectional target tracking task. This monkey generated isometric torques in flexion/extension (FE), radial/ulnar deviation (RU) and pronation/supination (PS), and executed a power grip (G) that co-contracted wrist flexor and extensor muscles. These forces controlled the location, orientation and size of a square

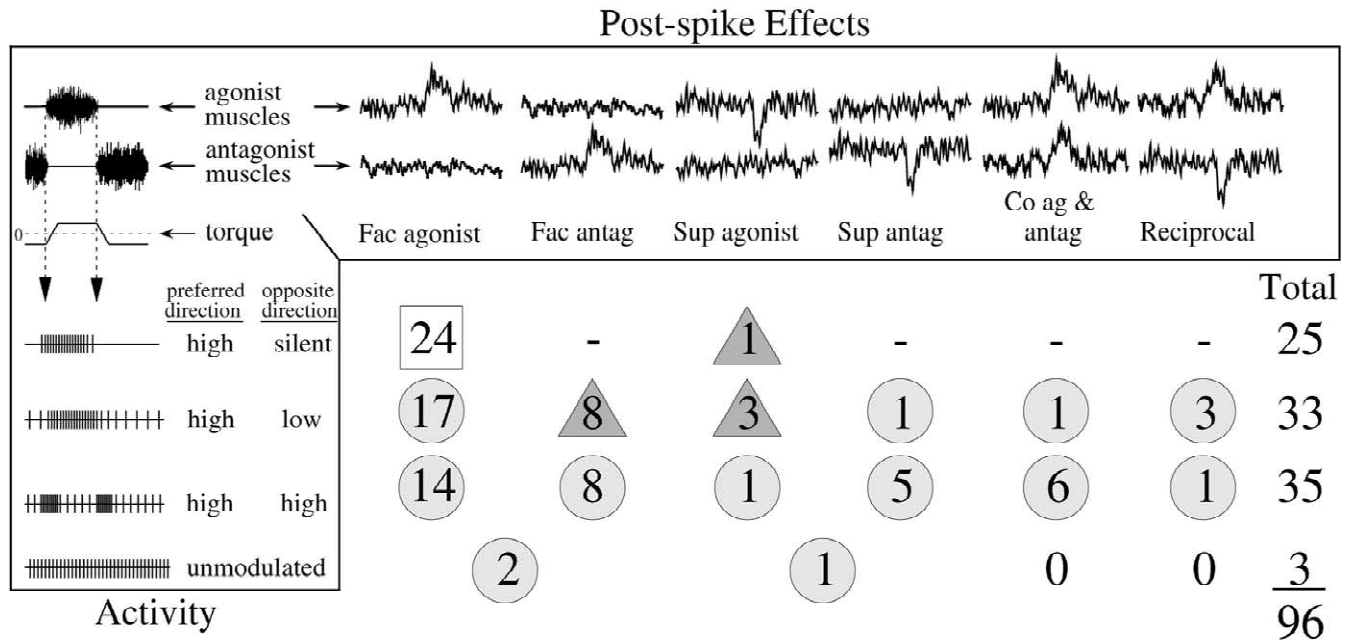


Fig. 4. Relation between movement modulation and post-spike effects of PreM-INs. The neuron's 'agonist' muscles are those active in the cell's preferred direction (the torque direction for which the neuron has the largest increase in activity). Columns indicate numbers of INs that produced post-spike facilitation (Fac), suppression (Sup), or cofacilitation (Co) effects in muscles (dashes denote effects undetectable by spike-triggered averaging; agonist and antagonist muscles are undefined for unmodulated neurons). Symbols indicate whether the relation between response pattern and post-spike effects are entirely consistent (square), partially consistent (circle) or inconsistent (triangle). (From Ref. [36])

cursor, which the monkey matched to a target box. Fig. 5 illustrates the responses of a cervical IN as the monkey exerted torques in these different directions. To document spatial tuning, the change in average firing rate during the static torque period relative to rest was defined as the response magnitude for each direction. Of the INs showing task-modulated activity ($n=27$), about half had preferred directions in the FE-RU space, with cosine-tuned activation, and another quarter were broadly tuned for FE-RU. Preferred directions were distributed throughout the FE-RU space, but significantly more vectors had radial than ulnar components. Most INs with FE-RU responses were also modulated strongly during PS and/or G. The tuning of the INs tended to be broader than the tuning of forearm muscle EMG and almost all INs were active in the absence of wrist EMG. Few INs were inhibited for FE-RU or PS directions opposite their preferred directions. In fact, many INs exhibited increased firing for both preferred and non-preferred torques relative to rest. These results suggest that INs share some properties of spatial tuning with motor cortical neurons related to movements of the arm [16] (Schwartz et al., 1988) and the wrist [22]. However, the tuning of wrist-related cortical cells under our repertoire of responses remains to be further documented.

Unlike previous studies of directional tuning of cortical neurons whose projections were unknown, spike-triggered averages could identify the target muscles of PreM cells. One of the INs was a PreM-IN, which facilitated a single target muscle, flexor carpi radialis (Fig. 5). The tuning

curve of this IN in FE-RU space overlapped the narrower curve of its target muscle, although their preferred directions differed by 45° . It will be interesting to compare the tuning curves of additional excitatory as well as inhibitory PreM-INs with those of their target muscles.

4. Involvement of INs in motor preparation

To document the role of spinal INs in *preparation* for voluntary movement we trained monkeys to perform instructed delay tasks [37,38]. Two monkeys performed isometric wrist flexion or extension after a visually cued delay period. The components of the delay task and the responses of a modulated IN are illustrated in Fig. 6. During such delay periods between a transient cue instructing the correct target and a subsequent go signal many cortical neurons have been shown to change their activity as the monkey prepares for the upcoming movement [1,24,43,44,49]. Of all the tested INs about one third showed modulation of firing rate during the delay period following the visual cue, relative to the pre-cue rate. These changes occurred in the absence of any somatosensory input or motor output. The significant delay modulations (SDM) often differed from the INs' responses during the subsequent active torque period and were not accompanied by any EMG activity (Fig. 6). Delay modulations occurring during correct trials were usually absent in trials in which the monkey made directional errors. Many INs with

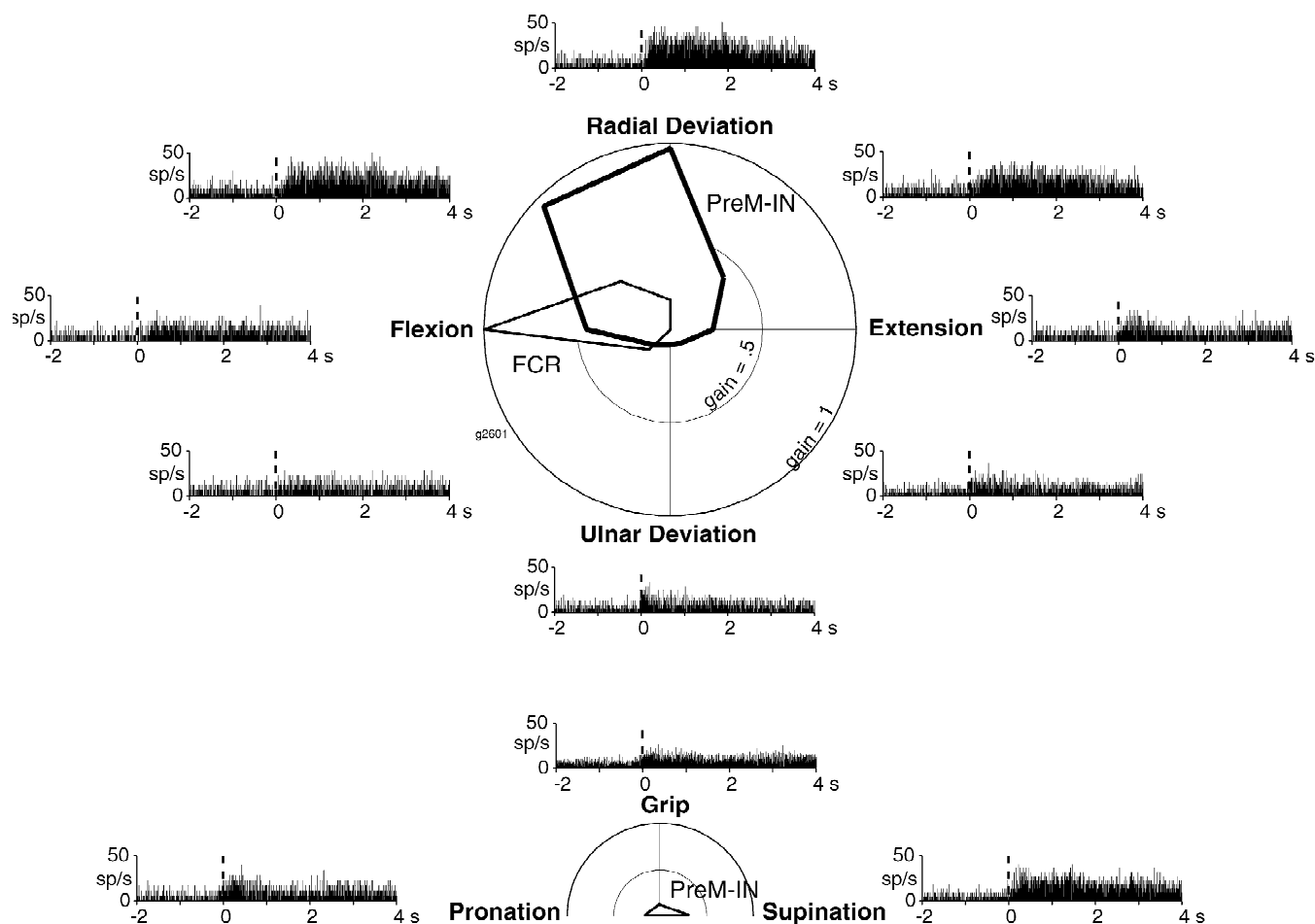


Fig. 5. Spatial tuning of activity of an excitatory PreM-IN and its facilitated target muscle (FCR) for multidirectional wrist movements. Polar plots give normalized response gains of the IN (labelled PreM-IN) and target muscle EMG (FCR) for different directions of torque generated about the wrist. Response gain was computed as the difference between the mean firing rate of rectified EMG level during the last second of the static hold in target and the baseline period at rest (zero torque), divided by the baseline value. Upper plots show response gain for combinations of flexion–extension and radial–ulnar deviation. Lower plot shows gains for pronation, supination and power grip. Response gains of IN and FCR were normalized separately to their maximum values (radial deviation for IN and flexion for FCR). Histograms show average firing rate of IN for ramp-and-hold torques in the corresponding directions, aligned on movement onset (time=0).

SDM showed changes in firing during the delay period with the same polarity (increase or decrease) as the cell's activity during the active hold period. This is consistent with a subthreshold preparation for the subsequent movement, involving priming of INs in the direction they must fire during movement execution. However this was not the case for the majority of INs. Two-thirds of all INs modulated during movement had no SDM, and a few INs showed changes specifically in the delay period, but not during movement. Of the INs that showed changes in both, firing rates during the delay and torque periods were modulated with the opposite polarity for 39% of INs with SDM. About two-thirds of the SDM were inhibitory, suggesting a global suppression of spinal activity during the delay, preventing the overt expression of the movement.

To test the dependence of SDM on cue modality, a third monkey was instructed by transient visual or propriocep-

tive cues to perform delayed wrist movements against an elastic load. The proprioceptive cue was a brief wrist perturbation whose direction and amplitude indicated the target of the subsequent movement. Excluding any brief response to the perturbation, the delay period activity for many INs was similar in visual and perturbation trials, consistent with motor preparation that is independent of the cue modality. Fig. 7 illustrates the responses of such a cervical IN that showed an increase in delay period activity for both flexion and extension, as well as for both types of instruction cues. This IN also fired phasically with active movements in either direction. Some INs exhibited different SDM in the visual trials and the perturbation trials; this may be due to different descending commands or differences in sustained peripheral inputs triggered by the proprioceptive cue. Cue-dependent preparatory activity has also been observed in premotor cortical areas [25,49] and in somatosensory cortex [33].

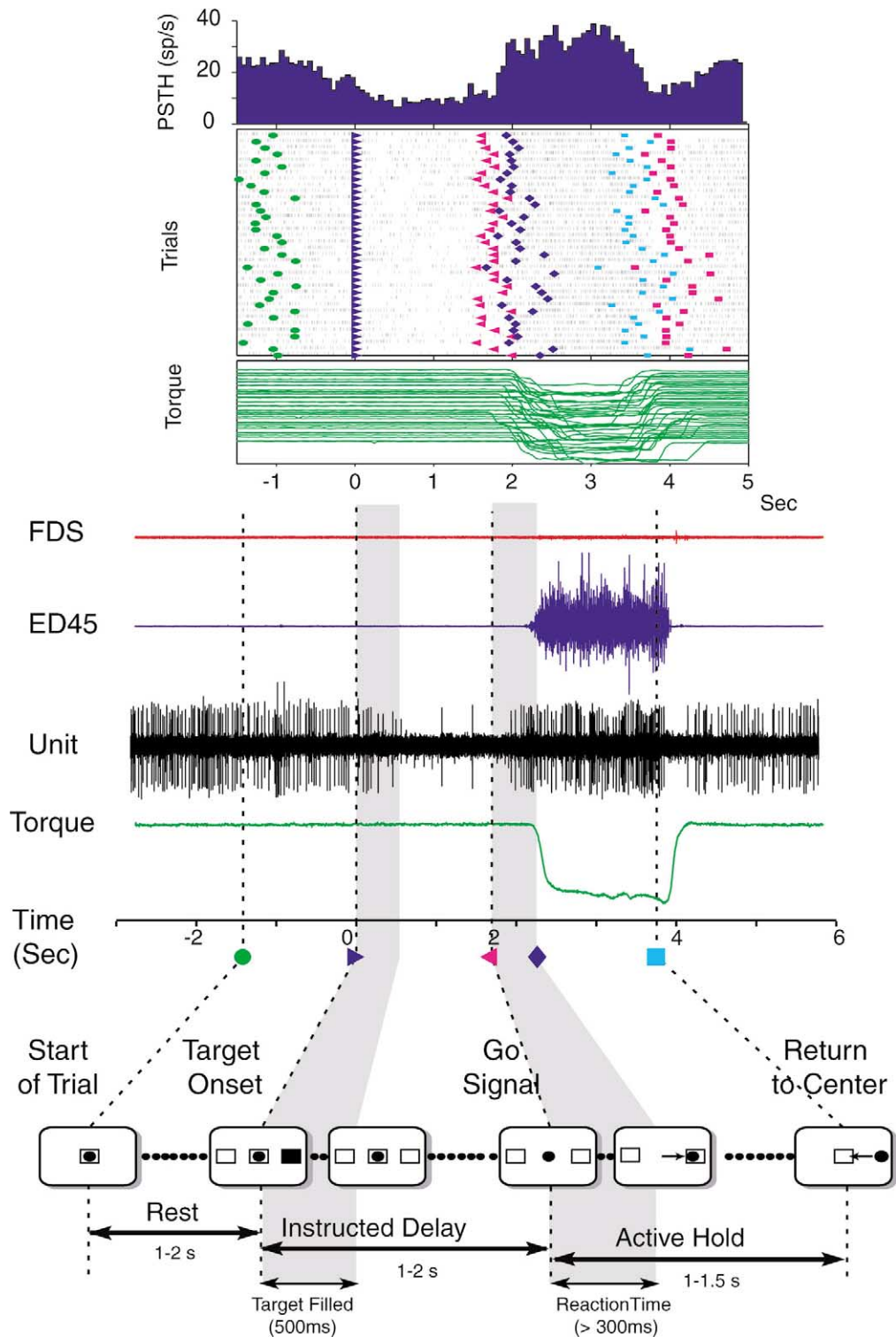


Fig. 6. Activity of spinal IN during instructed delay task. Components of the behavioral task are schematically illustrated at bottom. Filled circle represents a cursor whose position is controlled by the monkey's wrist torque; squares represent targets. The instructed delay period begins with a transient visual cue (right target filled for 500 ms) and ends with a go signal (extinguishing of center hold target). Middle traces show activity of flexor digitorum sublimis (FDS) and extensor digitorum 4 and 5 (ED45) muscles and the IN, and isometric torque about the wrist. Top section shows responses during successive extension trials, aligned on cue onset (at time 0). From top down, peristimulus histogram (PSTH) of IN firing rate, rasters of IN spikes in successive trials, and torque trajectories. (Adapted from Ref. [38])

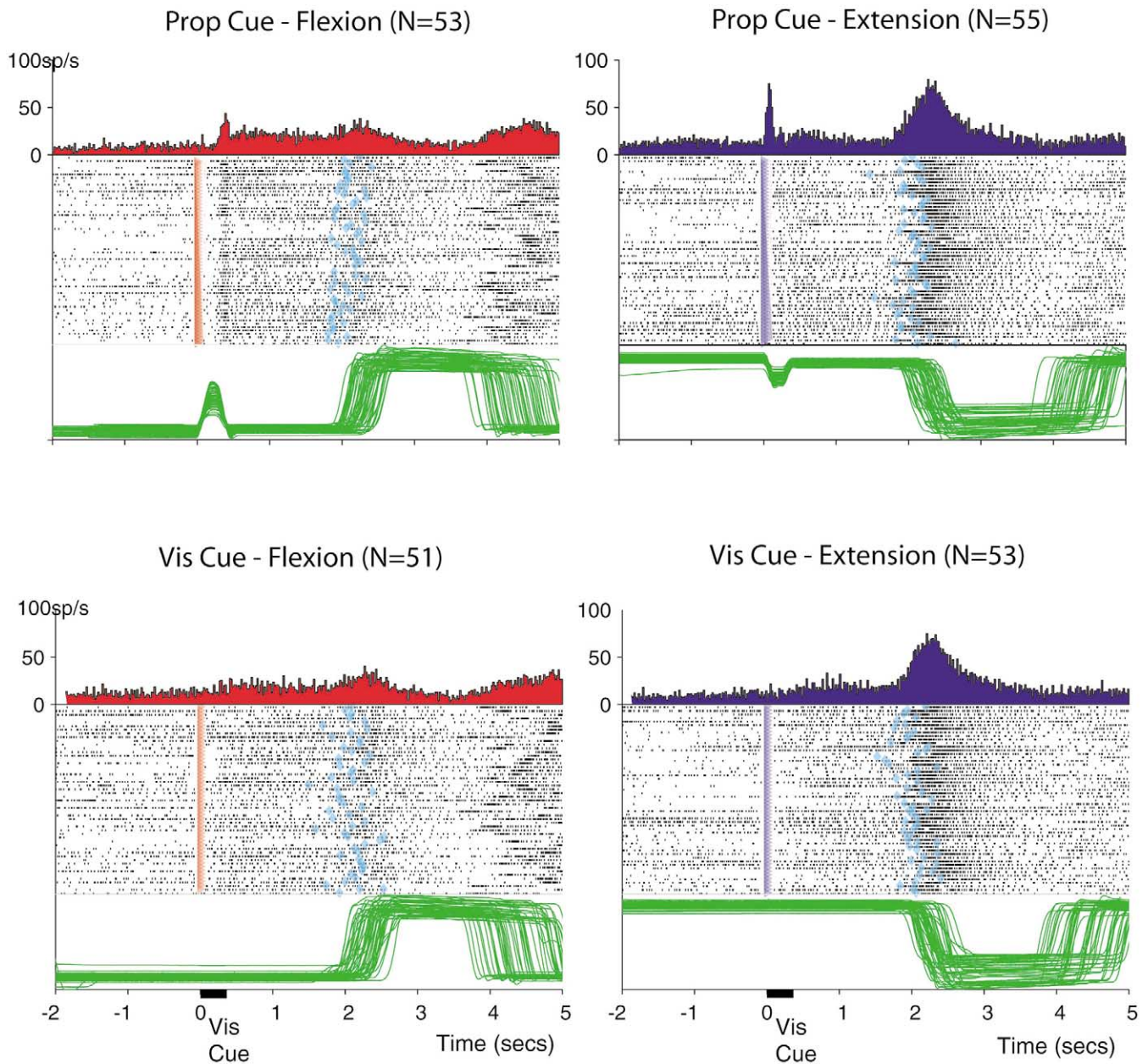


Fig. 7. Spinal IN that showed increases in activity during the instructed delay period for both proprioceptive cues (top) and visual cues (bottom). This increased SDM occurred for both flexion trials (left) and extension trials (right). This unit also responded briefly to the extension component of the perturbation. Each quadrant shows, from top down: histogram of IN firing rate aligned on cue onset, rasters of IN spikes in successive trials, and superimposed traces of torque trajectories. Rasters also indicate time of cue (red or blue triangles) and time of go signal (blue diamonds).

These results suggest that spinal INs are involved, with cortex, in the earliest stages of movement preparation instructed by various cue modalities. The instructed delay period activity at segmental levels resembles that documented in motor cortical areas, indicating a widely distributed network for movement preparation, mediated by descending and ascending pathways between cortex and spinal cord.

5. Sensory input to spinal INs

The above studies documented the response properties and output effects of segmental interneurons during voluntary motor responses but could not identify these INs according to criteria traditionally used in acute experiments. This is due in part to practical difficulties in removing the arm and hand from the manipulandum and

testing responses to passive natural stimulation while continuing to maintain unit isolation. Our ability to evoke reflex responses in awake monkeys was also limited by the need to avoid aversive stimuli. Nevertheless, the perturbations used for instructional cues often evoked characteristic

short-latency sensory responses in many INs that revealed two major groups of INs (Fig. 8) [39]. Some INs gave bidirectional excitatory responses at the onset and offset of the perturbation pulses, consistent with cutaneous inputs (Fig. 8A). These INs often fired transiently and bidirection-

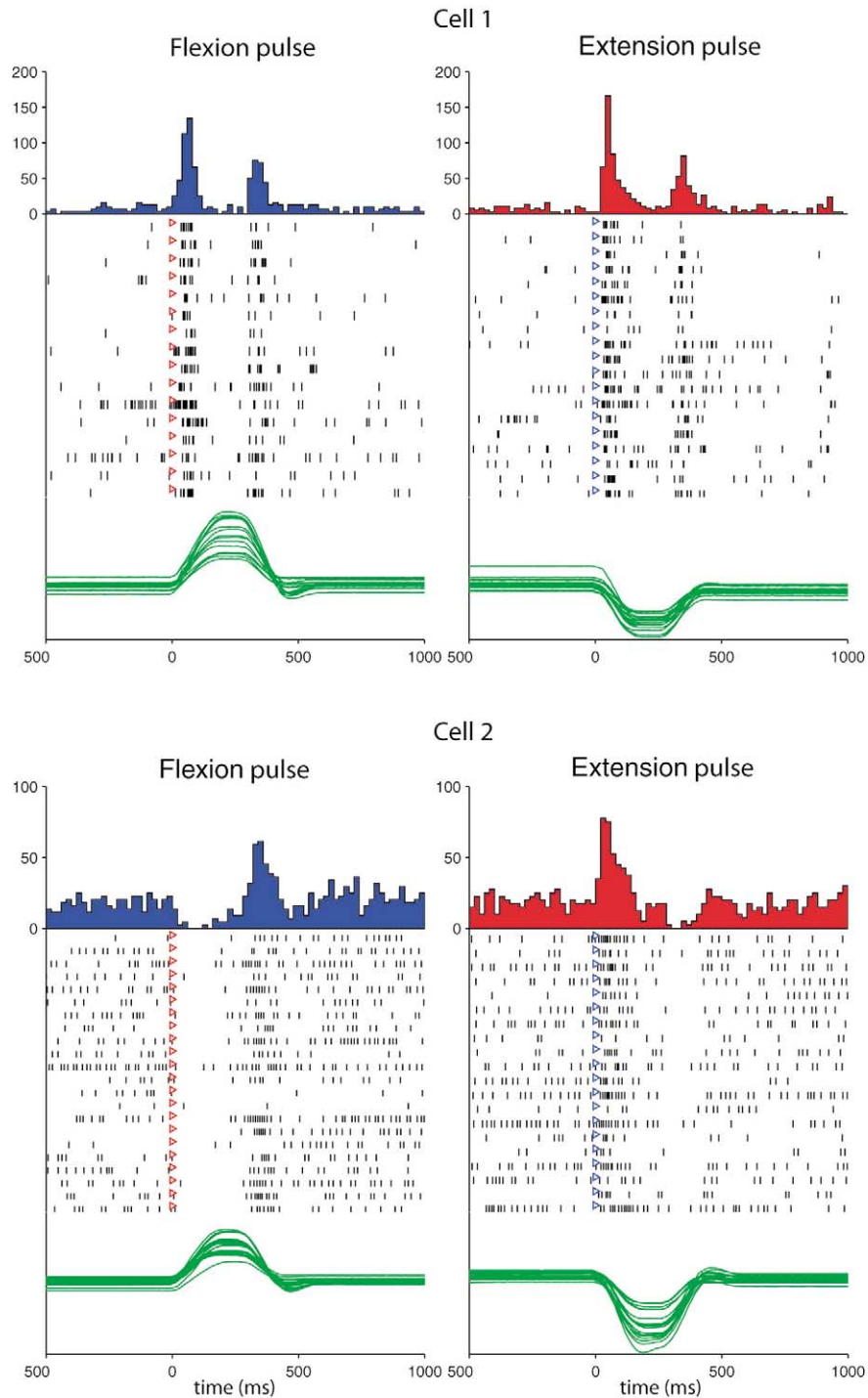


Fig. 8. Sensory responses of two spinal INs to brief perturbations of wrist. (Top) Cell 1 responded with bursts at both onset and offset of both flexion perturbations (left) and extension perturbations (right). (Bottom) Cell 2 showed biphasic responses, i.e. suppression with flexion component and excitation with extension component of both flexion and extension pulses. These represent the two largest classes of torque pulse responses, possibly corresponding to INs with cutaneous input (top) and proprioceptive input (bottom). Displays show, from top to bottom, peristimulus response histogram, rasters of unit responses in successive trials (triangle is pulse onset), and superimposed torque pulses, with flexion up.

ally with active movements, a pattern also seen in the responses of somatosensory cortex cells with identified cutaneous fields [42]. Other INs exhibited biphasic responses to the perturbation pulses, being activated by the flexion component and inhibited by the extension component, or vice versa (Fig. 8B). Such biphasic responses are consistent with proprioceptive input from muscle or joint receptors, and were characteristic of cortical neurons that responded to passive joint movement [13,42]. These INs tended to more often exhibit sustained activity during the active hold in their preferred direction, and to show SDM. Their preferred direction during active movements was usually opposite to the direction of the effective passive stimulus, a relationship commonly seen in motor cortex as well [13,31].

6. Modulation of sensory input during movement

Although electrical stimulation of peripheral nerves at high intensity (up to seven times threshold) is precluded in awake monkeys, they readily tolerate low intensity electri-

cal stimulation of nerves [5,9]. This allowed us to investigate the *task-dependent modulation* of neural responses to peripheral input. In a monkey performing wrist flexion/extension movements in a visually cued instructed delay task, responses were evoked by electrical stimulation of the cutaneous superficial radial (SR) nerve through a cuff electrode ($2.6 \pm 1.5 \times$ threshold for an afferent volley). SR stimulation produced excitatory responses in many INs, sometimes at monosynaptic latencies from the afferent cord dorsum volley (<1.5 ms). Post-stimulus histograms were compiled separately for different phases of the task, such as the intertrial rest, instructed delay, dynamic movement and active hold periods. These revealed that the SR-evoked responses were typically suppressed or abolished during the dynamic phase of active movement (Fig. 9). Monosynaptic excitation from the SR was suppressed at the same time that task-related activity of many INs increased, indicating that the suppression was mediated by presynaptic rather than postsynaptic inhibition. The amplitudes of monosynaptic field potentials were also reduced during the dynamic movement period. Preliminary evidence from antidromic volleys in the nerve cuff evoked

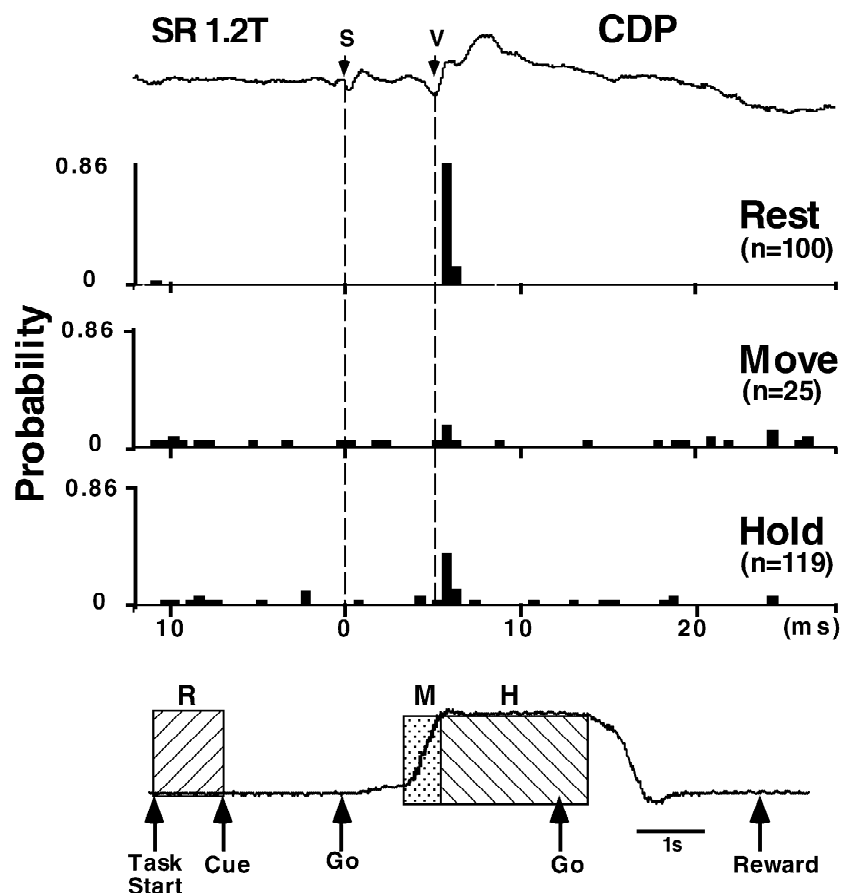


Fig. 9. Modulation of monosynaptic response of IN to electrical stimulation of superficial radial nerve during performance of instructed delay task. Histograms show responses to electrical stimulation of nerve cuff compiled during task periods schematized at bottom: rest prior to cue (R), dynamic active movement (M) and static hold (H). Top trace shows cord dorsum potential (CDP), indicating time of stimulus (S) and afferent volley (V). Short latency of histogram peak after afferent volley indicates a monosynaptic response. Response is reduced during Move and Hold. Probability gives spikes per stimulus per bin.

by intraspinal stimulation suggests that the excitability of SR afferents increased transiently during the dynamic movement, consistent with primary afferent depolarization [46]. Altogether, these results indicate that presynaptic inhibition of cutaneous input increases significantly during the dynamic phase of active movement.

7. Behavioral functions of spinal INs

The observations reviewed here suggest that under normal behavioral conditions many spinal INs have response properties similar to those previously documented for cortical neurons in behaving animals. The similarities and differences can be summarized as follows.

Cortical and spinal PreM neurons exhibit similar response patterns during ramp-and-hold wrist movements, and the activity of both groups is an increasing function of muscle force. However, they exhibit interesting differences in the representation of movements and muscles. The CM cells represent functional muscle synergies more distinctly than spinal INs: they produce post-spike effects in larger muscle groups, including post-spike suppression of antagonists of their facilitated target muscles, and they fire more specifically during particular movements. In contrast, spinal PreM-INs affect one or a few specific muscles, and are broadly activated over a wider range of movements.

The spatial tuning of cortical neurons related to reaching [16,41] and wrist movements [22] is also characteristic of spinal INs related to multidirectional hand movements. However, many spinal INs appear to have broader tuning curves, showing activity in all directions as well as specialized changes with additional response dimensions like co-contraction during grip. The first direct comparison of spatial tuning in a PreM-IN and its target muscle (Fig. 5) shows partial overlap in their tuning curves.

The preparatory activity during instructed delay periods documented in cortical neurons appears also in spinal INs. Cortical studies have emphasized increased delay period activity, while we found many INs with inhibitory delay activity. Assuming that this difference is real rather than a sampling effect, the difference would suggest a general descending inhibition of spinal circuits during the delay period, which would tend to suppress the expression of movement. This would be consistent with evidence that premotor cortex exerts inhibitory influences on motor activity [4,30].

Clearly, recordings in the spinal cord of behaving animals will provide rich opportunities to investigate additional behavioral functions of segmental interneurons beyond processing peripheral sensory information and motor commands. Indeed attention and task relevance have been shown to modulate sensory responses in lumbar cord of awake rats [47] and trigeminal neurons of behaving monkeys [17]. An intriguing question is whether spinal INs will be shown to be involved in other higher-order

‘cognitive’ functions represented in cortical areas projecting to spinal levels [10,18,32]. For example, the ‘approach’ responses to objects moving toward the body have been seen in motor cortical neurons [48], including an identified pyramidal tract neuron [13]. Also, the responses of cortical ‘mirror’ neurons to observed movements performed by others [40] can also have effects at spinal levels: in human subjects passively watching the performance of grasping movements the H-reflex in the agonist muscles was suppressed [3]. If motoneurons can exhibit such changes in excitability to observed movements, one can anticipate similar effects in INs. If these and other ‘cognitive’ representations previously documented in cortical areas are found to involve spinal INs, our ideas about spinal cord functions and the extent of distributed representations will be considerably expanded.

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References

- [1] G.E. Alexander, M.D. Crutcher, Preparation for movement: neural representations of intended direction in three motor areas of the monkey, *J. Neurophysiol.* 64 (1990) 133–150.
- [2] F. Baldissera, H. Hultborn, M. Illert, Integration in spinal neuronal systems in: J.M. Brookhart, V.B. Mountcastle (Eds.), *Handbook of Physiology. The Nervous System, Vol. II, American Physiological Society, Bethesda, MD, 1981, pp. 509–595, Sect. 1.*
- [3] F. Baldissera, P. Cavallari, L. Craighero, L. Fadiga, Modulation of spinal excitability during observation of hand actions in humans, *Eur. J. Neurosci.* 13 (2001) 190–194.
- [4] C. Baumgartner, I. Podreka, A. Olbrich, K. Novak, W. Serles, S. Aull, G. Almer, S. Lurger, U. Pietrzyk, D. Prayer, G. Lindinger, Epileptic negative myoclonus: an EEG-single-photon emission CT study indicating involvement of premotor cortex, *Neurology* 46 (1996) 753–758.
- [5] M.A. Bromberg, E.E. Fetz, Responses of single units in cervical spinal cord of alert monkeys, *Exp. Neurol.* 55 (1977) 469–482.
- [6] E.J. Buys, R.N. Lemon, G.W.H. Mantel, R.B. Muir, Selective facilitation of different hand muscles by single corticospinal neurons in the conscious monkey, *J. Physiol. (Lond.)* 381 (1986) 529–549.
- [7] P.D. Cheney, E.E. Fetz, Functional classes of primate corticomotoneuronal cells and their relation to active force, *J. Neurophysiol.* 44 (1980) 773–791.
- [8] P.D. Cheney, E.E. Fetz, K. Mewes, Neural mechanisms underlying corticospinal and rubrospinal control of limb movements, *Prog. Brain Res.* 87 (1991) 213–252.
- [9] K.R. Courtney, E.E. Fetz, Unit responses recorded from cervical spinal cord of awake monkey, *Brain Res.* 53 (1973) 445–450.
- [10] R.P. Dum, P.L. Strick, The origin of corticospinal projections from the premotor areas in the frontal lobe, *J. Neurosci.* 11 (1991) 667–689.

- [11] E.E. Fetz, P.D. Cheney, Postspike facilitation of forelimb muscle activity by primate corticomotoneuronal cells, *J. Neurophysiol.* 44 (1980) 751–772.
- [12] E.E. Fetz, S.I. Perlmutter, Y. Prut, Functions of mammalian spinal interneurons during movement, *Curr. Opin. Neurobiol.* 10 (2000) 699–707.
- [13] E.E. Fetz, D.V. Finocchio, M.A. Baker, M.J. Soso, Sensory and motor responses of precentral cortex cells during comparable passive and active joint movements, *J. Neurophysiol.* 43 (1980) 1070–1089.
- [14] D. Flament, P.A. Fortier, E.E. Fetz, Response patterns and post-spike effects of peripheral afferents in dorsal root ganglia of behaving monkeys, *J. Neurophysiol.* 67 (1992) 875–889.
- [15] N. Fritz, M. Illert, S. Motte, P. Reeh, P. Saggau, Pattern of monosynaptic Ia connections in the cat forelimb, *J. Physiol. (Lond.)* 419 (1989) 321–352.
- [16] A.P. Georgopoulos, J.F. Kalaska, R. Caminiti, J.T. Massey, On the relations between the direction of two-dimensional arm movements and cell discharge in primate motor cortex, *J. Neurosci.* 2 (1982) 1527–1537.
- [17] R.L. Hayes, R. Dubner, D.S. Hoffman, Neuronal activity in medullary dorsal horn of awake monkeys trained in a thermal discrimination task. II. Behavioral modulation of responses to thermal and mechanical stimuli, *J. Neurophysiol.* 46 (1981) 428–443.
- [18] S.Q. He, R.P. Dum, P.L. Strick, Topographic organization of corticospinal projections from the frontal lobe: motor areas on the lateral surface of the hemisphere, *J. Neurosci.* 13 (1993) 952–980.
- [19] T. Hongo, S. Kitazawa, Y. Ohki, M.C. Xi, Functional identification of last-order interneurons of skin reflex pathways in the cat forelimb segments, *Brain Res.* 505 (1989) 167–170.
- [20] E. Jankowska, Interneuronal relay in spinal pathways from proprioceptors, *Prog. Neurobiol.* 38 (1992) 335–378.
- [21] E. Jankowska, W.J. Roberts, Synaptic actions of single interneurons mediating reciprocal Ia inhibition of motoneurons, *J. Physiol. (Lond.)* 222 (1972) 623–642.
- [22] S. Kakei, D.S. Hoffman, P.L. Strick, Muscle and movement representations in the primary motor cortex, *Science* 285 (1999) 2136–2139.
- [23] R.J. Kasser, P.D. Cheney, Characteristics of corticomotoneuronal postspike facilitation and reciprocal suppression of EMG activity in the monkey, *J. Neurophysiol.* 53 (1985) 959–978.
- [24] K. Kurata, Premotor cortex of monkeys: set- and movement-related activity reflecting amplitude and direction of wrist movements, *J. Neurophysiol.* 69 (1993) 187–200.
- [25] K. Kurata, J. Tanji, Contrasting neuronal activity in supplementary and precentral motor cortex of monkeys. II. Responses to movement triggering versus non-triggering sensory signals, *J. Neurophysiol.* 53 (1985) 142–152.
- [26] R.N. Lemon, G.W. Mantel, R.B. Muir, Corticospinal facilitation of hand muscles during voluntary movement in the conscious monkey, *J. Physiol. (Lond.)* 381 (1986) 497–527.
- [27] M. Maier, S. Perlmutter, E.E. Fetz, Response patterns and force relations of monkey spinal interneurons during active wrist movement, *J. Neurophysiol.* 80 (1998) 2495–2513.
- [28] K. Mewes, P.D. Cheney, Facilitation and suppression of wrist and digit muscles from single rubromotoneuronal cells in the awake monkey, *J. Neurophysiol.* 66 (1991) 1965–1977.
- [29] K. Mewes, P.D. Cheney, Primate rubromotoneuronal cells: parametric relations and contribution to wrist movement, *J. Neurophysiol.* 72 (1994) 14–30.
- [30] L. Moll, H.G. Kuypers, Premotor cortical ablations in monkeys: contralateral changes in visually guided reaching behavior, *Science* 198 (1977) 317–319.
- [31] J.T. Murphy, H.C. Kwan, W.A. MacKay, Y.C. Wong, Spatial organization of precentral cortex in awake primates. III. Input–output coupling, *J. Neurophysiol.* 41 (1978) 1132–1139.
- [32] E.A. Murray, J.D. Coulter, Organization of corticospinal neurons in the monkey, *J. Comp. Neurol.* 195 (1981) 339–365.
- [33] R.J. Nelson, V.D. Douglas, Changes in premovement activity in primary somatosensory cortex differ when monkeys make hand movements in response to visual versus vibratory cues, *Brain Res.* 484 (1989) 43–56.
- [34] J. Nielsen, Y. Kagamihara, The regulation of disynaptic reciprocal Ia inhibition during co-contraction of antagonistic muscles in man, *J. Physiol. (Lond.)* 456 (1992) 373–391.
- [35] S.S. Palmer, E.E. Fetz, Discharge properties of primate forearm motor units during isometric muscle activity, *J. Neurophysiol.* 54 (1985) 1178–1193.
- [36] S. Perlmutter, M. Maier, E.E. Fetz, Activity and output linkages of spinal premotor interneurons during voluntary wrist movements in the monkey, *J. Neurophysiol.* 80 (1998) 2475–2494.
- [37] S.I. Perlmutter, Y. Prut, Transformation of descending commands into muscle activity by spinal interneurons in behaving primates, in: T.C. Cope (Ed.), *Motor Neurobiology of the Spinal Cord*, CRC Press, Boca Raton, FL, 2001, pp. 193–213.
- [38] Y. Prut, E.E. Fetz, Primate spinal interneurons show pre-movement instructed delay activity, *Nature* 401 (1999) 590–594.
- [39] Y. Prut, S.I. Perlmutter, E.E. Fetz, Distributed processing in the motor system: spinal cord perspective, *Prog. Brain Res.* 130 (2001) 267–278.
- [40] G. Rizzolatti, L. Fadiga, V. Gallese, L. Fogassi, Premotor cortex and the recognition of motor actions, *Cogn. Brain Res.* 111 (1966) 246–252.
- [41] A.B. Schwartz, R.E. Kettner, A.P. Georgopoulos, Primate motor cortex and free arm movements to visual targets in three dimensional space. I. Relations between single cell discharge and direction of movement, *J. Neurosci.* 8 (1988) 2913–2927.
- [42] M.J. Soso, E.E. Fetz, Responses of identified cells in postcentral cortex of awake monkeys during comparable active and passive joint movements, *J. Neurophysiol.* 43 (1980) 1090–1110.
- [43] J. Tanji, E.V. Evars, Anticipatory activity of motor cortex neurons in relation to direction of an intended movement, *J. Neurophysiol.* 39 (1976) 1062–1068.
- [44] J. Tanji, K. Taniguchi, T.J. Saga, Supplementary motor area: neuronal response to motor instructions, *J. Neurophysiol.* 43 (1980) 60–68.
- [45] Y. Terakado, T. Yamaguchi, Last-order interneurons controlling activity of elbow flexor motoneurons during forelimb fictive locomotion in the cat, *Neurosci. Lett.* 111 (1990) 292–296.
- [46] P.D. Wall, Excitability changes on afferent fiber terminations and their relation to slow potentials, *J. Physiol. (Lond.)* 142 (1958) 1–21.
- [47] P.D. Wall, J. Freeman, D. Major, Dorsal horn cells in spinal and freely moving rats, *Exp. Neurol.* 19 (1967) 512–529.
- [48] T.M. Wannier, M.A. Maier, M.C. Hepp-Reymond, Responses of motor cortex neurons to visual stimulation in the alert monkey, *Neurosci. Lett.* 98 (1989) 63–68.
- [49] M. Weinrich, S.P. Wise, The premotor cortex of the monkey, *J. Neurosci.* 2 (1982) 1329–1345.