Functions of mammalian spinal interneurons during movement

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The major recent advances in understanding the role of spinal neurons in generating movement include new information about the modulation of classic reflex pathways during fictive locomotion and in response to pharmacological probes. The possibility of understanding movements in terms of spinal representations of a basic set of movement primitives has been extended by the analysis of normal reflexes. Recordings of the activity of cervical interneurons in behaving monkeys has elucidated their contribution to generating voluntary movement and revealed their involvement in movement preparation.

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Abbreviations

C	cervical
CM	corticomotoneuronal
CPG	central pattern generator
EMG	electromyogram
EPSP	excitatory postsynaptic potential
FFP	force field primitive
IN	interneuron
NMDA	*N*-methyl-D-aspartate
PAD	primary afferent depolarization
PN	propriospinal neuron
PreM	premotor
STA	spike-triggered average

Introduction

In recent years, our understanding of spinal cord circuits has advanced significantly on multiple fronts, providing new information about the functional organization of spinal interneurons (INs) and their contribution to movement. These advances involve different but complementary approaches to defining the basic operational building blocks of spinal circuitry. Classically, spinal cord INs have been extensively categorized in relation to reflex responses evoked by stimulation of receptors, nerves and descending pathways [1,2]. These reflex pathways can be envisioned to form a set of basic circuits that are modulated by descending commands during normal voluntary movements. In this scenario, the possible functions of different classes of INs in natural movements have been inferred from their responses to peripheral and descending inputs documented in immobile preparations, and from their role in fictive locomotion. An extension of this classic reflex approach defines the basic functional units in terms of central pattern generators (CPGs), whose operation has been analyzed in fictively or actually moving animals. This second approach characterizes INs in terms of their activity during rhythmic behaviors and their participation in, or connections with, the CPG; this field has been well summarized in other reviews [3–5]. Again, other types of voluntary movement are seen to involve recruitment of these same INs in different patterns. A third approach defines the fundamental spinal modules in terms of the limb movements evoked by intraspinal stimulation [6–8]. A basic set of stimulus-evoked ‘movement primitives’ has been proposed to generate the larger range of voluntary movements by appropriate summation. Finally, a fourth approach analyses INs in terms of their contribution to activation of muscles during voluntary movement [9,10]: in this scheme, the functional organization involves hierarchical sets of INs and supraspinal neurons defined in terms of their correlational linkage with agonist motoneurons, with each neuron contributing in proportion to its activity. Here, we review recent advances in these approaches as they pertain to understanding the role of spinal INs in generating movements in vertebrates. Finally, we address the issue of integrating the information obtained using these different approaches.

Reflex organization of spinal cord circuitry

The classic approach of analyzing reflex circuits has generated a wealth of fundamental information, as summarized in comprehensive reviews [1,2] and recent symposia [11,12]. The basic functional modules are reflexes evoked from muscle, cutaneous and joint afferents, mediated by various classes of INs such as the Ia inhibitory neuron, which mediates reciprocal inhibition associated with the Ia stretch reflex. Recent studies have investigated the modulation of basic reflex circuits during fictive movement and their modification by neuromodulators. The reflex framework has also been useful for investigating long-term plasticity following adaptation to nerve section [13] (see the review by S Rossignol, pp 708–716, this issue).

The basic reflex circuits revealed in acute preparations are found to be highly variable in gain and polarity under conditions of fictive or actual movement [14•,15–18]. As a recent example, Burke and colleagues analyzed state-dependent transmission through polysynaptic pathways from low-threshold cutaneous and muscle afferents to hindlimb flexor and extensor motoneurons during fictive locomotion and scratching in decerebrate cats [16,19]. Postsynaptic potentials evoked from cutaneous afferents were enhanced during the flexor phase of fictive locomotion but these cutaneous reflexes were depressed during all phases of fictive scratching. Disynaptic group I post-synaptic potentials were also modulated during both fictive movements, albeit differently for locomotion and scratching (Figure 1).

Many recent studies have focused on the role of monoamines and other [20•,21] neuromodulators in mediating changes in the excitability of sensory and motor

Figure 1

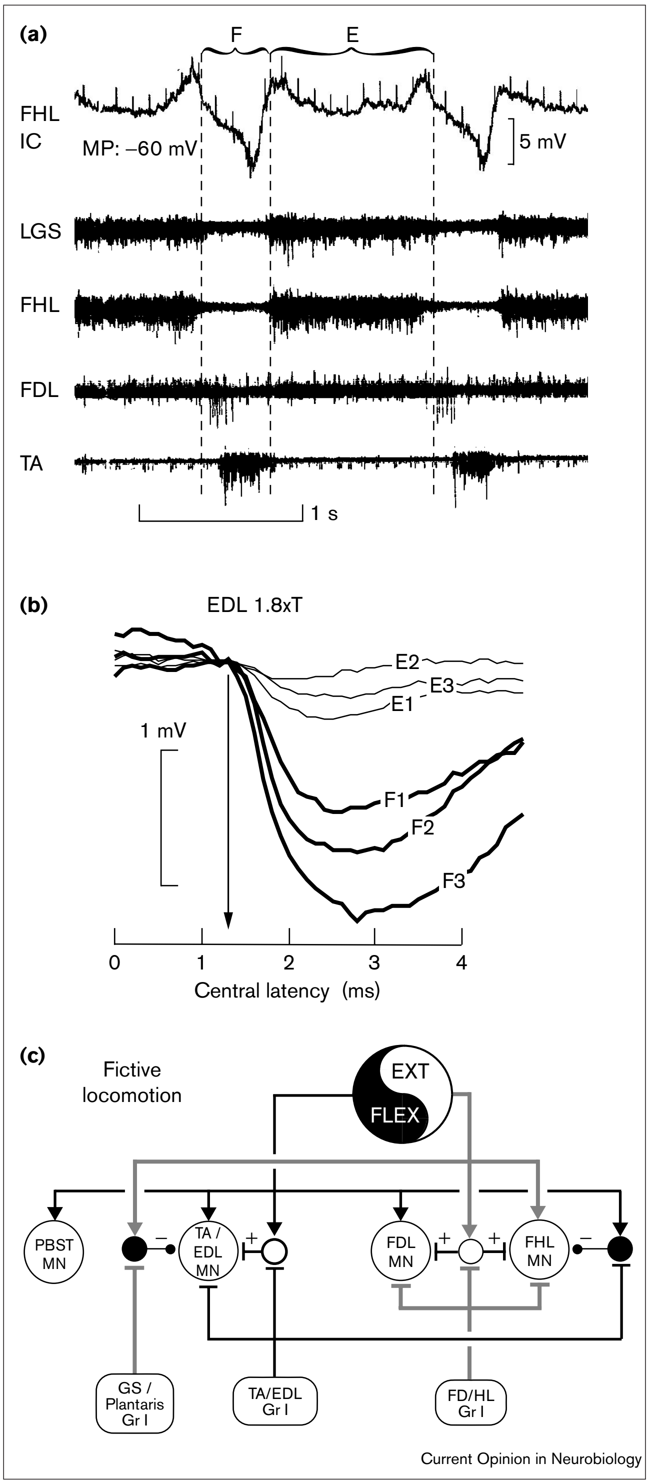

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Figure 1 legend

Modulation of reflexes during fictive locomotion in the cat. **(a)** Records during fictive locomotion, identifying flexor (F) and extensor (E) phases. From top: intracellular recording from flexor hallucis longus motoneuron (FHL IC) and electroneurograms from muscle nerves (LGS, lateral gastrocnemius-soleus; FDL, flexor digitorum longus; TA, tibialis anterior). **(b)** Averaged disynaptic Ia inhibitory postsynaptic potentials (IPSPs) evoked during different parts of the step cycle by stimulating extensor digitorum longus nerve (EDL) at 1.8 times threshold (T). Note increase in IPSPs during flexion despite hyperpolarization shown in (a). **(c)** Schematic diagram of reflex circuits from hindlimb muscle afferents, showing types of modulation from CPG during flexor and extensor components of fictive locomotion. Large circles are motoneurons (MN); small circles are INs; filled boutons represent inhibitory connections. (PBST, posterior biceps-semitendinosis; Gr I, group I muscle afferents) [16].

pathways in the spinal cord. Monoaminergic actions on motor pathways continue to be demonstrated with morphological [22,23] and behavioral [24] evidence. Studies have suggested that descending monoaminergic pathways are important for maintained motor output, especially in tonic hindlimb muscles [24–26], and perhaps for the selection of specific spinal reflex patterns [27]. For example, in the isolated neonatal rat cord, NMDA-induced locomotor activity deteriorates over time, but a coordinated, rhythmic motor pattern can be “rescued” by bath-applied noradrenaline [25]. Jankowska and colleagues have extended their studies on the modulation by monoamines of transmission in muscle spindle, tendon organ, and cutaneous afferent pathways [28••,29,30]. Their results, using iontophoretic application of drugs to identified neurons in spinal reflex pathways or ascending tract cells, show that serotonin and noradrenaline have facilitatory or suppressive effects, depending on both the type of afferent and the IN involved. In addition, serotonin and noradrenaline have similar effects on some INs, but opposite effects on others.

During voluntary movements, the INs of these reflex pathways are driven by descending supraspinal commands. A class of IN of particular interest for the cortical control of forelimb movements is the upper cervical (C) propriospinal neuron (PN). In the cat, a disynaptic excitatory pathway from motor cortex to motoneurons through C3–C4 PNs has been implicated in mediating cortical control of target-reaching movements [31]. Lemon has argued that in the evolution toward higher primates, the relative importance of direct corticomotoneuronal projections increased, while that of the propriospinal pathway weakened [32]. This suggestion is supported by the low proportion of upper limb motoneurons with disynaptic excitatory postsynaptic potentials (EPSPs) in response to electrical stimulation of the contralateral pyramidal tract in the macaque [33], and the larger proportion in the squirrel monkey [34], whose finger movements are less advanced than the macaque’s. Challenging this view, Alstermark and colleagues recently reported that the C3–C4 system also exists in macaques, but is under stronger inhibitory control than in the cat or squirrel monkey [35]; intravenous strychnine uncovered disynaptic pyramidal EPSPs in forelimb motoneurons that were not evident prior to administration of the glycine blocker. The existence of disynaptic corticospinal excitation in man is supported by evidence from studies of the H-reflex (monosynaptic activation of motoneurons by electrical stimulation of muscle nerve) combined with transcranial magnetic stimulation of the motor cortex [36,37], although the segmental location of the excitatory premotor neurons remains debatable.

The reflex responses evoked by afferent volleys appear not only in motor output, but also include depolarization of primary afferent fibers, which can evoke dorsal root reflexes [38•] and affects subsequent sensory input through presynaptic inhibition. The underlying mechanisms have been recently reviewed [38•,39••,40] and the reader is referred to these excellent reviews for further details.

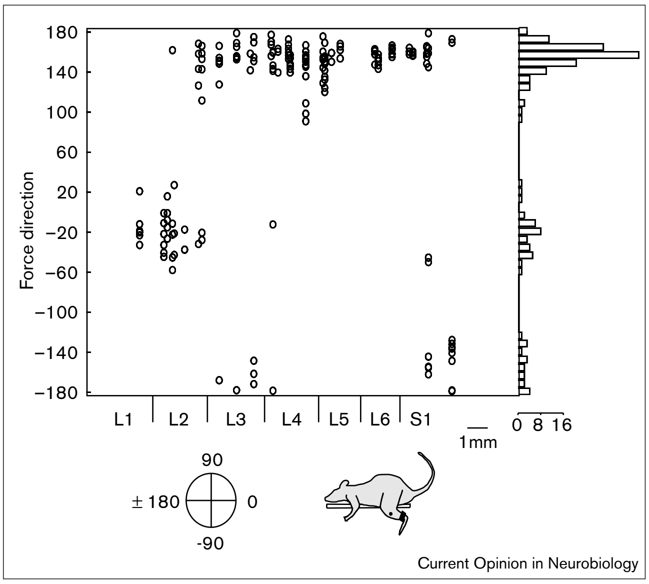
Modular organization of spinal cord revealed by stimulation

A drastically different approach to investigating the organization of spinal circuitry, introduced by Bizzi and colleagues [6,8], bypasses the detailed functional and anatomical analysis of the INs comprising spinal circuitry and uses a movement-based framework to study spinal cord organization. Using repetitive intra-spinal stimulation in frogs whose ankles were anchored in different locations in the workspace, they mapped the isometric force field generated by stimulus trains delivered at different spinal sites [8]. A small number of stereotypical force fields were found consistently across different frogs, leading the authors to suggest the existence of corresponding spinal centers controlling "movement primitives". Furthermore, simultaneous stimulation at two spinal sites resulted in a field that resembled the linear sum of the two fields produced by stimulating each site separately, leading to the suggestion that different movements could be linear combinations of a small number of movement primitives [41,42].

Having taken great pains to elucidate the intricate details of intertwined reflex pathways, many classical neurophysiologists greeted the direct electrical stimulation of these circuits with some concern. To address the concern that repetitive electrical stimulation produces widespread activation of functionally diverse cells and passing fibers, Bizzi and colleagues used focal intra-spinal injection of NMDA to more selectively activate dendrites and somata of local INs [42]. NMDA injection evoked responses at 30% of the sites from which electrical stimulation was effective, and the responses were usually in the same direction. In addition to sites that elicited tonic activation of muscles, NMDA produced rhythmic activation at many other neighboring sites. Regions that generated rhythmic muscle activation were usually in close proximity to sites that generated a tonic response in the same direction as that expressed during some phases of the rhythmic response. The authors suggested that tonic responses are the building blocks of the CPG and that this CPG has a patchy structure.

To investigate the applicability of these findings to mammals, Tresch and Bizzi repeated the stimulation experiment in the rat [43]. They found that a smaller repertoire of responses was obtained in the rat compared to the frog, and that the elicited response was usually a limb withdrawal movement towards the body (Figure 2). The optimal depth for evoking a response was more dorsal than in the frog. Surprisingly, stimulation in the intermediate zone (where most of the motor-related interneuronal system resides) was practically ineffective.

Figure 2



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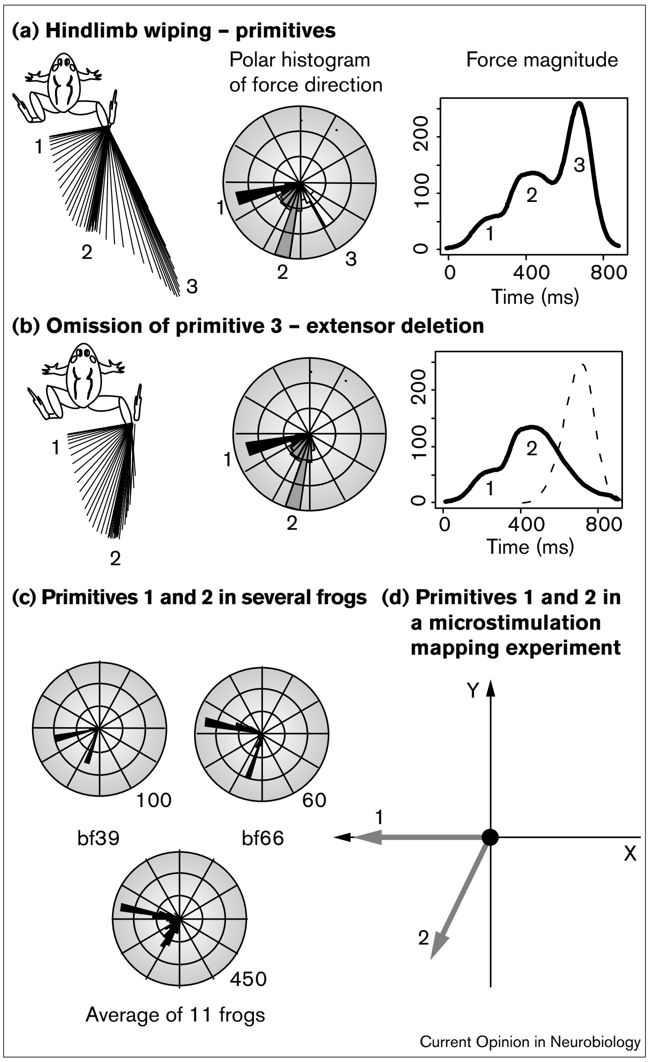
Forces evoked by intraspinal stimulation in the rat. Stimulation at different segmental levels (abscissa) evokes two major directions of movements (ordinate): flexion withdrawal (upper points) and extension (middle set) [43]. L, lumbar; S, sacral.

To address the concern that electrical stimulation evokes artificial movements, the modular organization of the spinal cord was developed further in terms of a natural reflex movement, the wipe reflex [8,44,45••]. Giszter and colleagues showed that the wipe reflex in spinal frogs can be construed as the appropriate time-varying summation of the force field primitives (FFPs) found with electrical stimulation [8]. Figure 3 shows the correspondence between the directions of torque components of the wipe response and torques evoked by intraspinal electrical stimulation. The observation that a specific component of the wipe was spontaneously deleted in some trials further argues for modular organization. The modulation of the wipe reflex in response to an encountered obstacle could also be explained as a single stimulus-evoked FFP superimposed on those FFPs comprising the wipe reflex [45••].

Irrespective of the existence of spinal modules controlling movement primitives, the fact that intraspinal stimulation elicits specific types of stereotyped motor responses provides a potential therapeutic tool for aiding people with impairment or loss of descending control of spinal activity [46,47•]. A small set of intraspinally evoked movements and their linear summation could simplify the requirements for control parameters, as compared with stimulating single muscles individually to generate appropriate movements. Prochazka and colleagues showed that

Figure 3



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Movement primitives underlying frog hindlimb wiping reflexes. Force production under isometric conditions at a single limb position is examined in hindlimb wiping in a spinal frog. This frog spontaneously omitted a phase of wiping in some trials. **(a)** Complete wiping pattern. **(b)** Pattern in trials in which the knee extensor component was deleted. Force vectors over time are plotted in reference to the frog and drawn anchored at the ankle (left). Forces tend to develop and dwell in three specific directions in (a), and in two directions in (b), in which phase 3 is omitted. Polar histograms (center) show direction of force-magnitude peak in each phase. Plots of torque magnitude (right) and the vector difference (dotted line) suggest that the difference corresponds to a missing primitive; moreover, the loss of the third force-direction occurs independently of the other elements of the pattern (cf. [45••]). **(c)** Polar histograms from two other frogs (bf39, bf66) and average polar histogram from combined data of 11 frogs. Numbers give number of samples represented by outer circles. **(d)** Force response direction vectors elicited by microstimulation in an extensive spinal cord mapping (direction vectors extracted using K-means analysis). Directions of electrically evoked primitives correspond to those of primitives 1 and 2 of the wiping response (SF Giszter, WJ Kargo, unpublished observations).

intraspinal microwires implanted in an otherwise intact cat provided a secure and reliable method for motor stimulation [47•]. The evoked responses typically involved coordinated movements about a joint, and in some cases were sufficient to support the cat's hindquarters. These results have implications for neural prostheses: intraspinal stimulation could be used to generate appropriate forces to maintain posture or facilitate locomotion, or to 'amplify' impaired commands for voluntary movement in patients with reduced muscle tone.

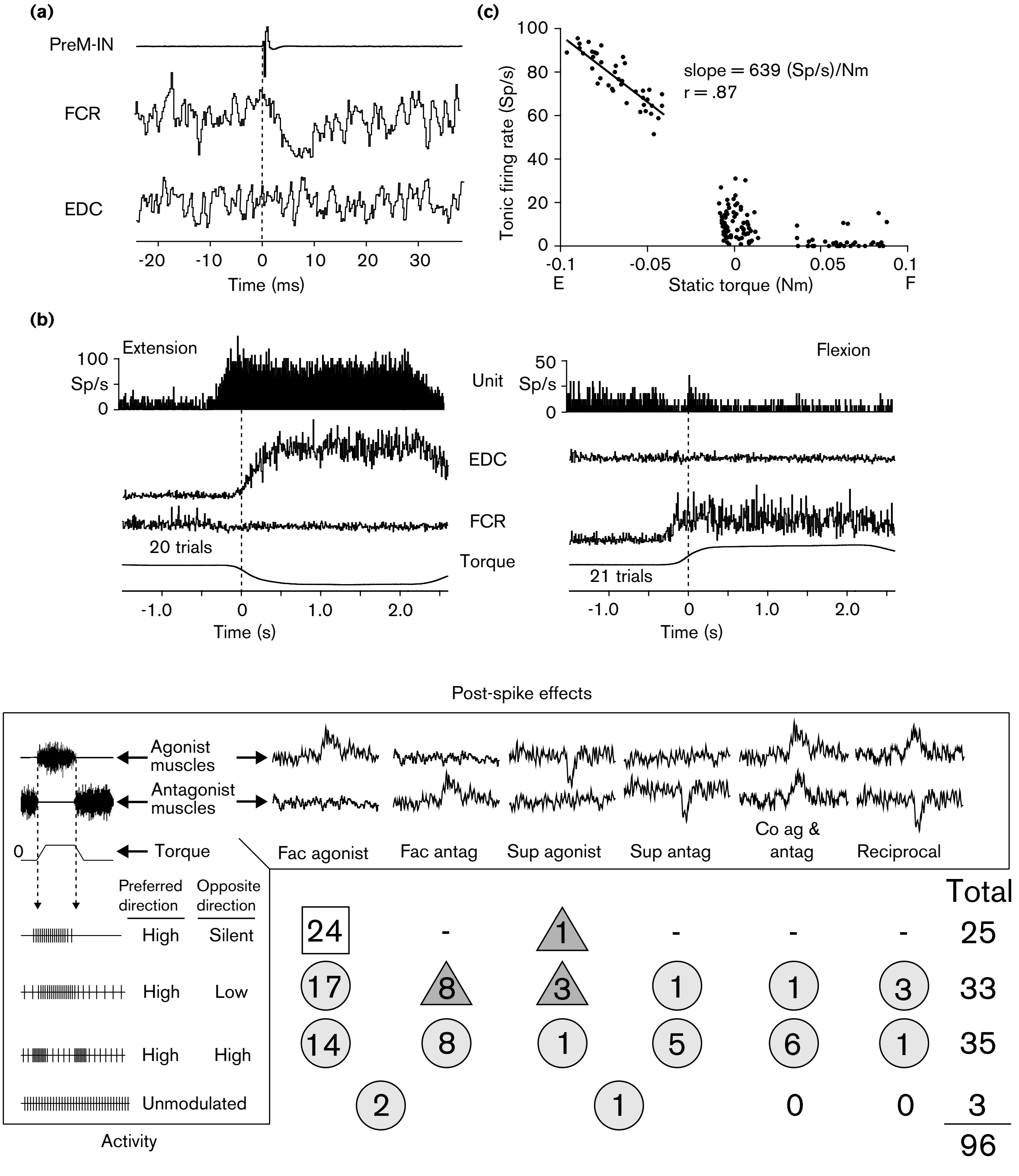
Organization of interneurons generating voluntary movement

A direct approach to understanding the function of spinal INs in normal voluntary movement has become available with the application of chronic unit recording techniques in spinal cord of behaving monkeys [9,10,48]. The contribution of cervical INs to controlling forearm muscles during a step-tracking task was investigated by documenting their activity in monkeys generating flexion–extension torques about the wrist. A striking finding was the high level of activity in many INs: most spinal INs (77%) exhibited some activity during both flexion and extension as well as at rest, in contrast to the strictly unidirectional activity of motoneurons, corticomotoneuronal (CM) cells [49] and spindle afferents [48]. Task-related INs increased their activity more strongly in one of these two directions; the response patterns in their preferred direction were typically tonic or phasic–tonic, and their activity was an increasing function of the active torque generated.

In addition to revealing IN activity during normal behavior, these studies allowed identification of the correlational linkages to muscles by spike-triggered averages (STAs) of electromyographic (EMG) activity. Reflex studies have extensively documented the inputs to INs evoked from afferent and descending pathways; in contrast, in these behavioral studies, STAs reveal the output connections to motoneurons of multiple forelimb muscles. STAs detected significant features in agonist and antagonist muscle activity for many task-related spinal neurons. Interneurons that produced post-spike facilitation or suppression of EMG at appropriate latencies were identified as premotor INs (PreM-INs). STA features were predominantly facilitatory (85%) and occurred twice as often in flexor as in extensor muscles. Figure 4 shows an example of an inhibitory PreM-IN that produced post-spike suppression of flexor muscles. This IN increased its activity during active extension, with a rate that was an increasing function of torque. These are the characteristics expected of the reciprocal Ia inhibitory interneuron, which would suppress antagonist muscles in proportion to agonist activity. This example illustrates the advantage of combining information about the normal firing rate and the output effects in inferring functional contribution to muscle control. The relationships between movement modulation and the postspike effects for many PreM-INs are summarized in Figure 4. The post-spike effects were generally synergistic with the response pattern of the PreM-IN.

To contrast the role of motor cortex and spinal cord in controlling movements and muscles, it is interesting to

Figure 4



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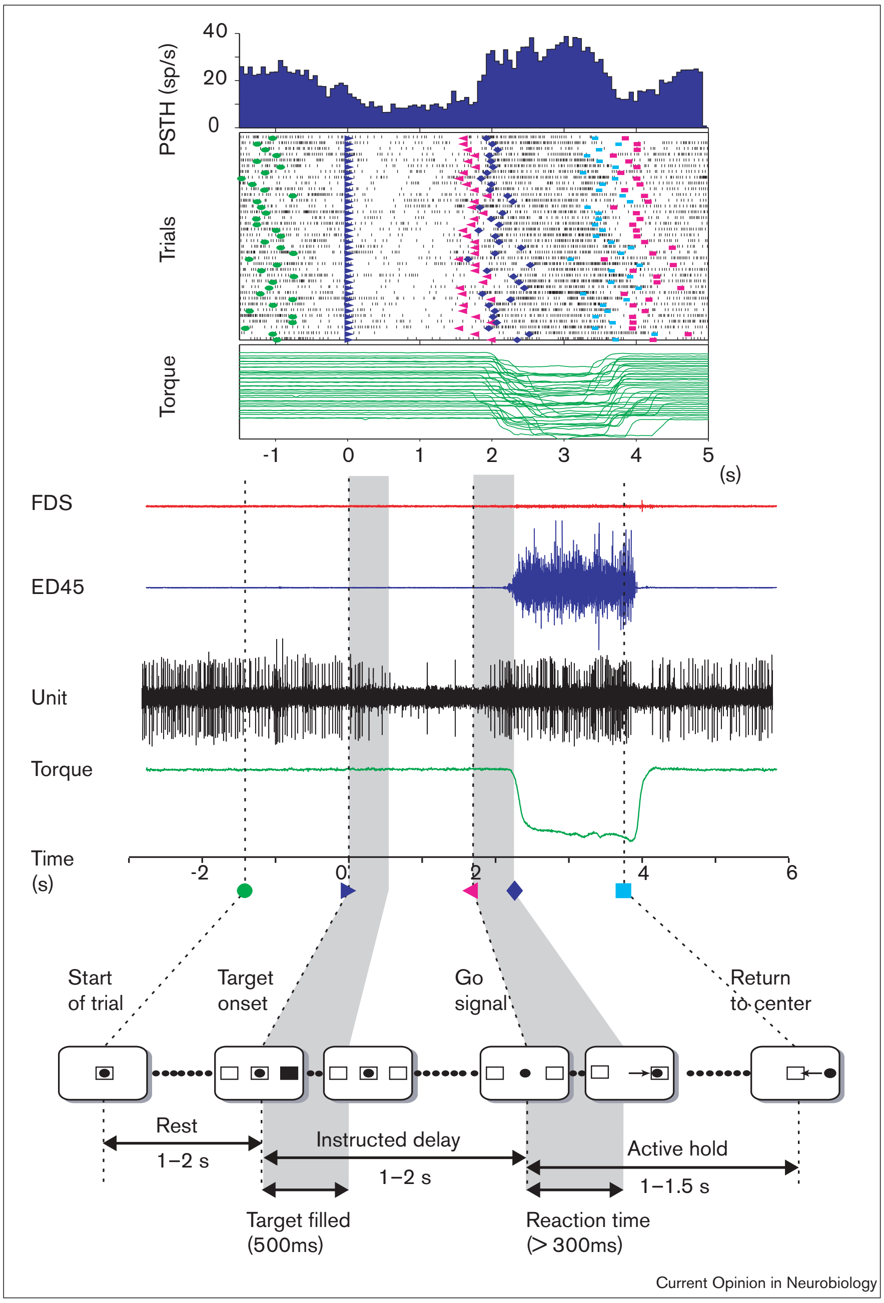
Activity and output effects of spinal INs in behaving monkeys. **(a)** Illustrates an inhibitory IN that produced post-spike suppression of EMG in flexor carpi radialis (FCR) muscle and no effect in extensor digitorum communis (EDC) in spike-triggered averages. **(b)** Response averages show the increased tonic activity of this IN during extension (left) and lower tonic activity during flexion (right). **(c)** Activity of IN during static hold was an increasing function of extensor force [10]. This behavior is consistent with that expected for Ia INs mediating the classic reciprocal inhibitory reflex [1]. Bottom: Summary of the relations between post-spike effects (columns) and movement modulation of PreM-INs during wrist movement (rows). Agonist muscles are those activated in the IN's preferred direction. Columns indicate whether IN produced post-spike facilitation (fac) or suppression (sup) or cofacilitated both groups (co). Numbers in symbols give number of INs, with totals on the right. The symbols indicate functional relationships that are entirely consistent (square), partially consistent (circle) or inconsistent (triangle) [9].

Figure 5



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Activity of spinal IN inhibited during an instructed delay period. At the bottom is a schema of the behavioral components of the task. Filled circle represents a cursor whose position is controlled by the monkey; squares represent targets. The instructed delay begins with a transient visual cue (right target is filled for 500 ms) and ends with a go signal (extinguishing of center hold target). Middle traces illustrate activity of flexor digitorum sublimis (FDS) and extensor digitorum 4 and 5 (ED45) muscles and IN, and isometric torque. The top part of the figure shows responses during successive extension trials, aligned on cue onset (at time 0). From bottom up, traces of torque trajectories, rasters of IN responses in successive trials and peristimulus histogram (PSTH) of IN firing rate [50••].

compare the properties of spinal PreM-INs and CM cells, documented under similar experimental conditions. The muscle fields of PreM-INs were smaller than those of supraspinal PreM cells in cortex and red nucleus [49], and rarely involved reciprocal inhibitory effects on antagonist muscles. This suggests that single CM cells more often represent synergistic groups of muscles, whereas PreM-INs are organized to target specific muscles. In contrast to the bidirectional activity of PreM-INs (and rubromotoneuronal cells), CM cells fire either during flexion or extension, not both. Thus, CM cells are more strictly recruited for particular movements, whereas PreM-INs are more widely activated and operate through superimposed excitation and inhibition of motoneurons.

Interneuronal participation in preparation for voluntary movement

The ability to record activity of spinal INs in awake behaving animals provides an opportunity to investigate whether INs participate in behavioral functions other than sensory or motor processing. The first direct indication that this is the case comes from recordings in monkeys trained to perform an instructed delay task [50••]. Neurons in many cortical areas show preparatory activity during an instructed delay period between the presentation of a cue that indicates the appropriate movement and a subsequent 'go' signal for execution. Similarly, many spinal INs modulate their activity during the instructed delay period. Figure 5 illustrates an IN that was inhibited during the instructed delay and increased its activity during generation of active torque. Such suppression during the delay was characteristic of two thirds of the INs with delay period modulation. For other INs the delay period activity changed in the same direction (increase or decrease) as the subsequent movement-related activity, suggesting a subthreshold shift in the direction required for the active response. The overt expression of this shift may be prevented by a global superimposed suppression of the spinal INs.

This set-related activity indicates that spinal circuitry is involved, with cortex, in the earliest stages of movement preparation. An intriguing question for future investigation is whether spinal INs will be shown to be involved in other 'higher' functions [51]. This seems plausible, given the extensive interconnections between cortical and spinal levels. For example, subjects instructed to imagine pressing a foot pedal showed enhanced spinal reflexes to the involved soleus muscle [52]. The electrically evoked H-reflex was bilaterally enhanced, while the tendon reflex increased specifically for the appropriate side. Recent evidence shows that the representation of observed movements seen in cortical mirror neurons [53] also has effects at the spinal level: in subjects passively watching the performance of a grasping movement, the H-reflex in the agonist muscle was modulated (L Fadiga, personal communication). These H-reflex experiments showed changes in motoneuron excitability, but similar effects would be expected in INs. If these and other 'cognitive' representations previously documented in cerebral cortex are found to involve spinal INs, our ideas about spinal cord function will be significantly expanded.

Concluding comments

Finally, can these different approaches to understanding the spinal cord ever be integrated? Each approach is clearly investigating the same system but producing different reports, like the blind men sampling the elephant. Unlike this analogy, however, a synthesis will involve more than simply combining the different observations because each approach deals with different states of the elephant, from tranquilized to performing. Spinal reflexes are strongly modulated during movement, rendering the usefulness of the reflex concept as either debatable [54] or exploitable [14•]. Obviously, one way to synthesize these different approaches would be to examine the same cells under each of the appropriate conditions. For example, identifying the INs recorded in behaving monkeys in terms of particular reflex circuits (e.g. the IN in Figure 4) would involve testing with appropriate electrical stimuli; unfortunately, high intensity nerve stimulation is incompatible with maintaining cooperative monkeys. Another challenge is to integrate the framework of movement primitives, which involves special methodologies; one question is how these concepts would be applied to interpreting neural activity during voluntary movements (but see [45••]).

Another strategy that could help bridge the gaps between these approaches, but has been largely neglected in spinal cord research, is neural network modeling. Several notable starts to modeling spinal circuits have been made [55,56] and these efforts could be developed much further. The experimental results generated by the many studies of spinal cord INs provide a rich database for deriving neural networks that could simulate different functional states using the same circuit elements.

Update

Y Aoyagi, VK Mushahwar, RB Stein and A Prochazka have found that the directions of hindlimb movements evoked by intraspinal stimulation in the cat lumbar cord resemble those evoked by muscle and nerve stimulation, and suggest that the preferred movement vectors could reflect biomechanical groupings rather than spinal primitives (personal communication). Moreover, the movement vectors evoked from a given intraspinal site could change when the state of the cat changed from anesthetized to decerebrate to spinal. Movement vectors were also a function of stimulus intensity.

Acknowledgements

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A readable and authoritative review of the modulation of hindlimb reflexes during fictive locomotion and scratching, drawing largely on the experimental results of [16] and [19]. The reflexes evoked by cutaneous and muscle afferents are usually modulated in a direction that is synergistic with the motoneurons' activity during the movement phases, but a surprising difference appeared between the modulation of certain last-order INs during fictive scratching as compared to locomotion.

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In addition to the monoamines, numerous neuropeptides are now known to act as neuromodulators in the spinal cord. Using a preparation consisting of the isolated lamprey spinal cord with the tail fin attached, this study examines the behavioral consequences of neuropeptide modulation of sensory circuitry, previously described at the cellular and synaptic levels. Neuromodulatory effects were limited to sensory neurons by isolating the caudal segments and tail fin from the remainder of the spinal cord with Vaseline barriers. Substance P and bombesin facilitated synaptic inputs to rostral motoneurons evoked by electrical stimulation of the skin of the tail fin, whereas neuropeptide Y and baclofen reduced the strength of these inputs.

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Now in press

The personal communication from L Fadiga is now in press:

Baldissera F, Cavallari P, Craighero L, Fadiga L: **Modulation of spinal excitability during observation of hand actions in humans.** *Eur J Neurosci* 2001, **13**:in press.