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Reflex control of human locomotion: Existence, features and functions of common interneuronal system induced by multiple sensory inputs in humans

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Abstract Neural output from the locomotor system for each arm and leg influences the spinal motoneuronal pools directly and indirectly through interneuronal (IN) reflex networks. This review article mainly describes the recent findings concerning the existence, features and functions of common IN systems on spinal reflex pathways induced by multisensory inputs during human locomotion. In particular, we focus on regulation of polysynaptic cutaneous reflex pathways assessed by spatial facilitation. Furthermore, we provide evidence for activation of common presynaptic inhibitory INs that integrate locomotor-related commands and antagonist group Ia inputs. The experimental results are discussed in light of recent advances in motor control in humans and other animals with implications for locomotor rehabilitation.

Keywords : locomotion, reflex control, interneuronal network, common pathway, cutaneous afferents, humans

Introduction

Recent understanding of human movement control indicates that the neuronal coordination for the fore- and hindlimbs observed in quadrupedal locomotor systems in other animals is conserved in that for arms and legs during human bipedal locomotion^{1,2)}. This coordination may be mediated by interaction of locomotor generator outputs regulating rhythmic arm and leg movement, voluntary commands and locomotor-related afferent feedback²⁻⁸⁾. One methodology for assessing this coordination and understanding spinal neural mechanisms is to measure the modulation of segmental reflexes during rhythmic movement⁹⁻¹¹⁾.

Robert E. Burke¹²⁾ stated that “an understanding of the operation of the spinal cord, and motor control, in general, must involve an understanding of the spinal interneurons organization”. Burke and colleagues have produced excellent work in this context during cat locomotion using intracellular recordings¹²⁾. In human locomotion, however, comparatively less is known about the functions and features of putative interneuron (IN) organization in the spinal cord during human locomotion.

Described and developed in the decerebrate cat prepa-

ration by Anders Lundberg and his colleagues in the 1960s^{9,13)}, the “spatial facilitation” technique was an influential tool for exploring the organization of the spinal IN system. This technique consists of simultaneous two stimuli arising from different sources to assess if these afferents converge on the same IN in the spinal cord^{13,14)}. Although the results need to be interpreted with considerable sensitivity and caution in human experiments¹⁵⁾, this is also an important technique to explore these IN networks.

Here, recent findings concerning the features and functions of common IN systems on the spinal reflex pathways induced by multisensory inputs during human locomotion will be described. In particular, we focus on assessing polysynaptic cutaneous reflex pathways using spatial facilitation. Finally, the implications for locomotor rehabilitation after neurological injury such as spinal cord injury (SCI) will be discussed.

Reflexes as neural probes for revealing spinal locomotor systems

In contrast to reduced animal preparation such as the lamprey and cat, where direct intracellular recordings can be taken, we have to rely on indirect methods to assess the contributions of the spinal IN network and locomotion.

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tor circuits in humans. It has been shown already that somatosensory afferent feedback contributes to the modulation of central pattern generator (CPG) outputs in both quadrupedal animals and humans^{9,16,17}. Thus, modulation of somatosensory reflex pathways can be used to infer the activity of CPG.

Reversal of reflex signs in leg and arm muscles following stimulation of cutaneous nerves (*i.e.*, cutaneous reflex) suggest CPG activity in both decerebrated cats and intact humans^{2,9,18,19}. Furthermore, monosynaptic spinal reflex (*i.e.*, H-reflex) amplitudes in lower and upper limbs are strongly modulated during locomotion²⁰⁻²². Thus, spinal reflexes are powerful tools that are useful as neural probes to reveal characteristics of the locomotor control system in the human spinal cord.

Neuronal basis of cutaneous reflex modulation during human locomotion

In feline locomotion, cutaneous afferents from the foot have powerful effects on the locomotor cycle with direct connections onto the CPG system^{2,12}. Based on these reduced animal data, the modulation of human cutaneous reflexes has been extensively studied^{2,23-25}. Below we describe the features, origins and modulation patterns of cutaneous reflexes during human locomotion.

1. Features of cutaneous reflex components and their origins

Cutaneous reflexes in the lower and upper limb muscles can be elicited by non-noxious electrical stimulation to cutaneous nerves innervating various regions of the foot and hand. Cutaneous reflexes in human subjects have multiple peaks (facilitation) or valleys (suppression) observed in the rectified and averaged EMG signal. These consist of early (~40-80 ms after stimulation, ELR), middle (~80-120 ms, MLR) and long (~120-180 ms, LLR) latency responses. As for the origins of ELR and MLR reflex pathways, it is suggested that they are mediated by polysynaptic pathways within the spinal cord². LLR reflex would be conveyed not only via the spinal cord, but also via supraspinal regions including the brainstem and motor cortex.

a) Early latency reflex (ELR): The ELR typically has a small amplitude, and the short-latency suggests mainly a spinal cord locus^{26,27}. Thus, the ELR can have an advantage when focusing on the neural mechanisms in the spinal cord under different experimental conditions. Evidence for the spinal origin of ELR includes the fact that in infants lacking a fully myelinated corticospinal tract and associated descending supraspinal control, only the ELR is observed^{28,29}. During maturation and development of neural connectivity and motor function in conjunction with accumulating motor experiences, the ELR becomes less prominent²⁹. In contrast, the long-latency response

becomes more prominent with age, implying that supraspinal regulatory mechanisms contribute to cutaneous reflexes²⁸. Although often small in amplitude, clear ELR can be elicited in adults and they are strongly modulated depending on motor tasks. For instance, facilitation of the ELR occurs during unstable standing²⁶. During the locomotor tasks of walking and arm cycling, ELR is modulated in a phase-dependent manner²⁷ in leg and arm muscles³⁰. Thus, ELR can be regarded as a useful neural probe for observing excitability changes in polysynaptic spinal pathways across various motor tasks including locomotion.

b) Middle latency reflex (MLR): The MLR is a major component of the cutaneous response in humans, and can be elicited in both arm and leg muscles by non-noxious electrical stimulation (see Fig. 1A). The MLR in humans has been an important bridge from observations of cat locomotion²⁷. MLR can be readily observed in the surface EMG signal during static and dynamic locomotor tasks in human subjects. The sign of the MLR (suppressive or facilitatory) is modulated by the locomotor phase, motor tasks, muscle of interest, intensity of electrical stimulation and stimulation sites². After SCI and stroke, MLR were observed following distal tibial nerve stimulation during walking³¹⁻³³. In decerebrate cats, the P2 response (analogous of MLR in humans) behaves similarly³⁴, adding additional evidence that spinal cord mechanisms are the main contributors for modulation of the MLR during locomotion.

c) Long latency reflex (LLR): The LLR is generally thought to encompass neural networks arising from the spinal cord, brainstem, and cortical regions³⁵⁻³⁸. In cats, while walking, the LLR is prominent in knee extensor muscles like the quadriceps³⁹. Interestingly, this is similar to observations in humans during simultaneous arm and leg (ARM&LEG) cycling^{39,40}. Although the LLR is an integrated response mediated by several different levels of organization, it is reliably evoked after SCI^{31,41}. Thus, “subcortical pathways” contribute to the LLR and the spinal cord can be a likely candidate. Subcortical contributions to the LLR is also supported by findings that excitation of the LLR is partly preserved after decerebrate or spinal preparation in cats and monkeys⁴²⁻⁴⁴.

Additionally, the LLR is dramatically amplified during intravenous administration of the noradrenergic precursor L-DOPA in the decerebrate cat⁴⁵⁻⁴⁸. In these preparations, stimulation of flexor reflex afferents (FRA; including cutaneous afferents) elicited ipsilateral flexor activation and contralateral extensor activation^{48,49}. These reflex patterns of LLR in SCI patients are similar to the responses in the acute spinal cat with DOPA⁵⁰. This suggests that single train stimulation of FRA can trigger alternating activity in flexor and extensor muscles during human locomotion. Recently, Selionov et al.⁵¹ demonstrated that tonic

cutaneous nerve stimulation generated air-stepping in the suspended leg in intact human subjects. These results suggest a rationale for using enhanced sensory feedback to access and amplify activity in spinal locomotor networks in human subjects.

2. Phase-dependency during locomotion

During locomotion, each reflex component is modulated depending on the phase of the walking cycle in both cats and humans. This phase-dependency is thought to be regulated by premotoneuronal mechanisms which may be under the control of the spinal CPG system. CPG activity has been suggested to modulate both reflex amplitude and sign during locomotor phases, and from static to locomotor tasks^{2,23,24}. The pattern of such reflex reversal depends on the combinations of nerves stimulated, muscles recorded and locomotor phase, which is consistent with functional demands of locomotion^{25,32,52}.

3. Task-dependency

Cutaneous reflexes are typically of larger amplitudes during locomotion as compared to static contraction, regardless of background EMG activity. Such task dependency can also include a switch in the sign of the reflex from facilitation to suppression during movement (task-dependent reflex reversal)^{53,54}. As for amplitude modulation, much work has been conducted comparing different modes of locomotion (e.g. walking, running, backward walking, reduced locomotion, etc.), movement tasks (e.g. co-contraction vs. isolated contraction)⁵⁵, and looseness of ankle⁵⁶ and shoulder⁵⁷.

4. Location-specificity

Location-specificity of cutaneous reflex amplitudes

occurs in leg muscles during walking and leg cycling following the stimulation of cutaneous nerves in the foot and hand (*i.e.*, nerve- or location- specificity)^{32,53,55,58-61}. The anatomical innervation area of the nerve stimulated or location of skin surface are important factors for determining the features of the cutaneous reflex⁵⁸. It is likely that different modalities, afferent fiber type of receptors and synaptic connectivity between afferent fibers and responsible INs account for the location-specificity. Functionally, Zehr and colleagues have suggested that cutaneous reflexes serve to stabilize human gait against external perturbations produced by an uneven terrain or obstacle contact on the area of leg or foot which can be innervated by the stimulated nerve [*e.g.*, distal tibial (TIB; sole), superficial peroneal (SP; foot dorsum), sural (SUR; lateral margin) nerves] during walking^{32,53,55,58-61}.

Interestingly, within the area of the foot sole innervated by distal TIB and SUR nerves, there is a clear location-specificity (*e.g.*, forefoot medial, forefoot lateral and heel regions) of cutaneous reflexes^{55,60,61}. Cutaneous reflexes evoked by non-noxious stimulation of discrete foot sole regions produce topographically organized reflex patterns in ankle muscles while performing static motor tasks. The organization of lower limb muscles is somewhat similar to that of cats reported by Hongo et al.⁶² where they applied mechanical pressure to paw pads (digital or central pads) in the cat. Recently, we found that such intrinsic topographical organization was preserved during walking in humans, and those actions are shown to produce a kind of guided tuning -“sensory steering”- of foot motion that accommodates to the perturbations mimicked by electrical stimulation⁶³.

Taken in sum, modulations of reflexes following non-noxious electrical stimulation of cutaneous nerves during

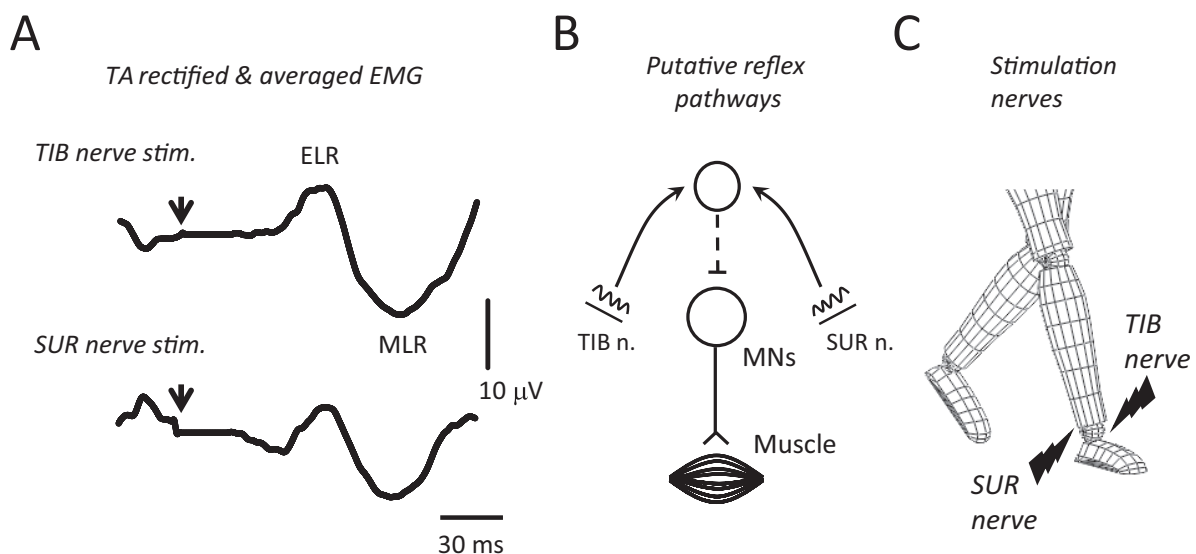


Fig. 1 Typical recordings of the cutaneous reflexes in tibialis anterior (TA) muscle following stimulation of distal tibial (TIB) and sural (SUR) nerves (A) obtained from a single subject. Note that the background EMG levels are equivalent, but the reflex components (facilitatory ELR and suppressive MLR) and their latencies are nearly the same between TIB and SUR nerve stimulation. Schematic illustration of putative reflex pathways (B) and stimulation nerves location on foot (C).

locomotion can be characterized as having: (1) phase-dependency; (2) task-dependency; and, (3) location-specificity. Functionally, the outputs from cutaneous reflex circuitry play a key role in avoiding obstacles and updating trajectories of limb motion during bipedal walking^{32,52,63,64}.

Some common features of cutaneous reflexes

Given the primary role of cutaneous afferents as extero-receptors needing to provide precise location information of inputs on the skin, it is not surprising that location-specificity appears to tightly link the functional role of cutaneous reflexes during locomotion. Despite this there are some “common features” produced regardless of nerve activated, suggesting the possibility of “shared reflex pathways” to the same muscles and motoneuronal pools^{2,65,66}. While this needs to be further elucidated in the future, there are some definitive features commonly evoked.

1. Similarity of reflex signs between nerves stimulated

As shown in Fig. 1A, the stimulation of either SUR or TIB nerves (also see Fig. 1C) commonly produces cu-

taneous reflexes with multiple and clearly differentiated components in the tibialis anterior (TA) muscle. Note that when applying electrical stimulation to two different cutaneous nerves while maintaining the same background EMG level in the TA, the pattern of reflex components (facilitatory ELR and suppressive MLR) and their latencies are almost the same for both TIB and SUR nerve stimulation (Fig. 1A). It may be that each nerve stimulation gives rise to the activation of separate reflex pathways that produce at the same latency facilitatory ELR and suppressive MLR (Fig. 1B). Alternatively and more likely, it is possible that the two different nerve stimulations activate reflex pathways, which are composed of common INs.

2. Similarity of pattern of phase-dependent modulation of reflex amplitudes during locomotion

Fig. 2A shows reflexes in the TA following stimulation of different cutaneous nerves (TIB, SP, and SUR nerves) innervating specific foot regions (foot sole, dorsum, and lateral margin, respectively) observed during treadmill walking by Van Wezel et al.⁵⁹. The overall patterns of phase-dependent modulation of MLR in TA look very similar. Other studies suggest similar findings (see Zehr

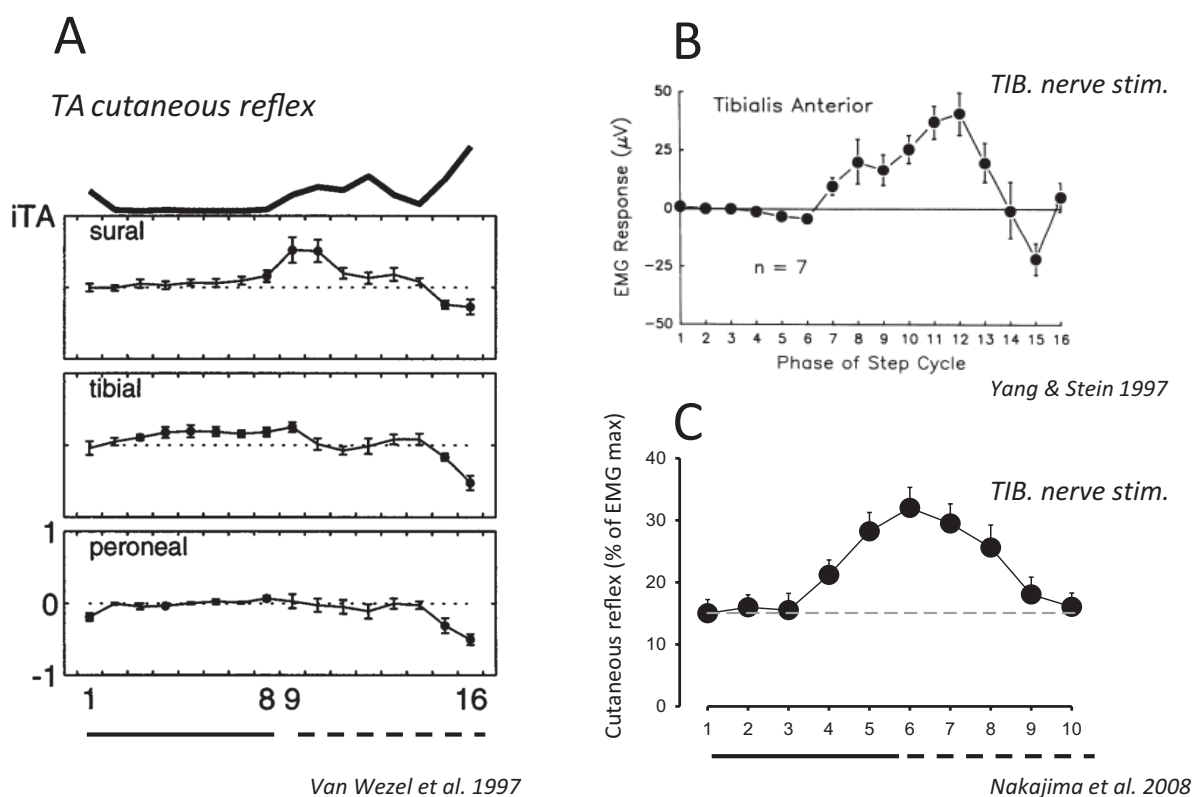


Fig. 2 Modulation of the cutaneous reflexes in tibialis anterior (TA) muscle during treadmill stepping. A: modulation of middle latency reflex (MLR) amplitudes following either sural, distal tibial and superficial peroneal nerves stimulation during walking adopted from Van Wezel et al. *Journal of Neuroscience*, 1997, 63: 3804-3814. B and C: modulation of MLR following tibial nerve stimulation during normal stepping (B) adopted from Yang & Stein, *Journal of Neurophysiology*, 1990, 63: 1109-1117 and passive stepping (B) adopted from Nakajima et al., *European Journal of Neuroscience*, 2008, 27: 1566-1576. Patterns of phase-dependent modulation of MLR in TA are very similar across different foot nerves stimulation. iTA: ipsilateral tibialis anterior muscle.

and Duysens²⁾ [show Fig. 3 with this]). For example, the TIB nerve-induced TA reflex during walking reported by Yang and Stein²⁴⁾ (Fig. 2B), Nakajima et al.³⁾ (Fig. 2C) and SUR nerve-induced reflex in Van Wezel et al.,⁵⁹⁾ (Fig. 2A, upper panel) show this. These observations of similar phase-dependent modulations of cutaneous reflexes in TA muscle suggest regulation by common locomotor centers and movement-related sensory feedback.

Based on the findings above, it would be reasonable to speculate that shared reflex pathways that accept sensory inputs from multiple nerves are activated during locomotion. However, the final amplitude of any cutaneous reflex is the cumulative total output arising from both “common” and “private” reflex pathways. The characteristics of this output can be evaluated with spatial facilitation following simultaneous multiple nerve stimulation¹³⁾.

A presumed common IN system during human locomotion as revealed by spatial facilitation

1. Background

The elegant concept of spatial facilitation was initially described and developed by Anders Lundberg and his col-

leagues to elucidate convergence of multiple inputs onto a single MN back in the 1960s⁹⁾. Since that time, spatial facilitation has been widely utilized to explore common characteristics of neuronal systems receiving and integrating disparate inputs in the polysynaptic pathways (*e.g.*, cortico-motoneuronal tracts and somatosensory reflex pathways) in humans and other animals^{13,14,47)}. In reduced animal experiments, the spatial facilitation technique has been used to reveal the existence of INs interposed in a specific neural pathway and convergence from different fiber systems onto common INs by using intracellular recordings from MN^{13,14,47)}. Although the results need to be carefully interpreted¹⁵⁾, spatial facilitation can also be used as an important tool in human subjects by using surface EMG, evoked potentials or single motor unit recordings.

2. Methodology

Spatial facilitation allows for elucidation of IN circuits in humans by means of the peri-stimulus time histogram (PSTH) of single MUs⁶⁷⁾, the motor evoked potentials by transcranial magnetic stimulation⁶⁸⁾, H-reflex amplitudes⁶⁹⁻⁷¹⁾ and ongoing EMG activities with tonic volun-

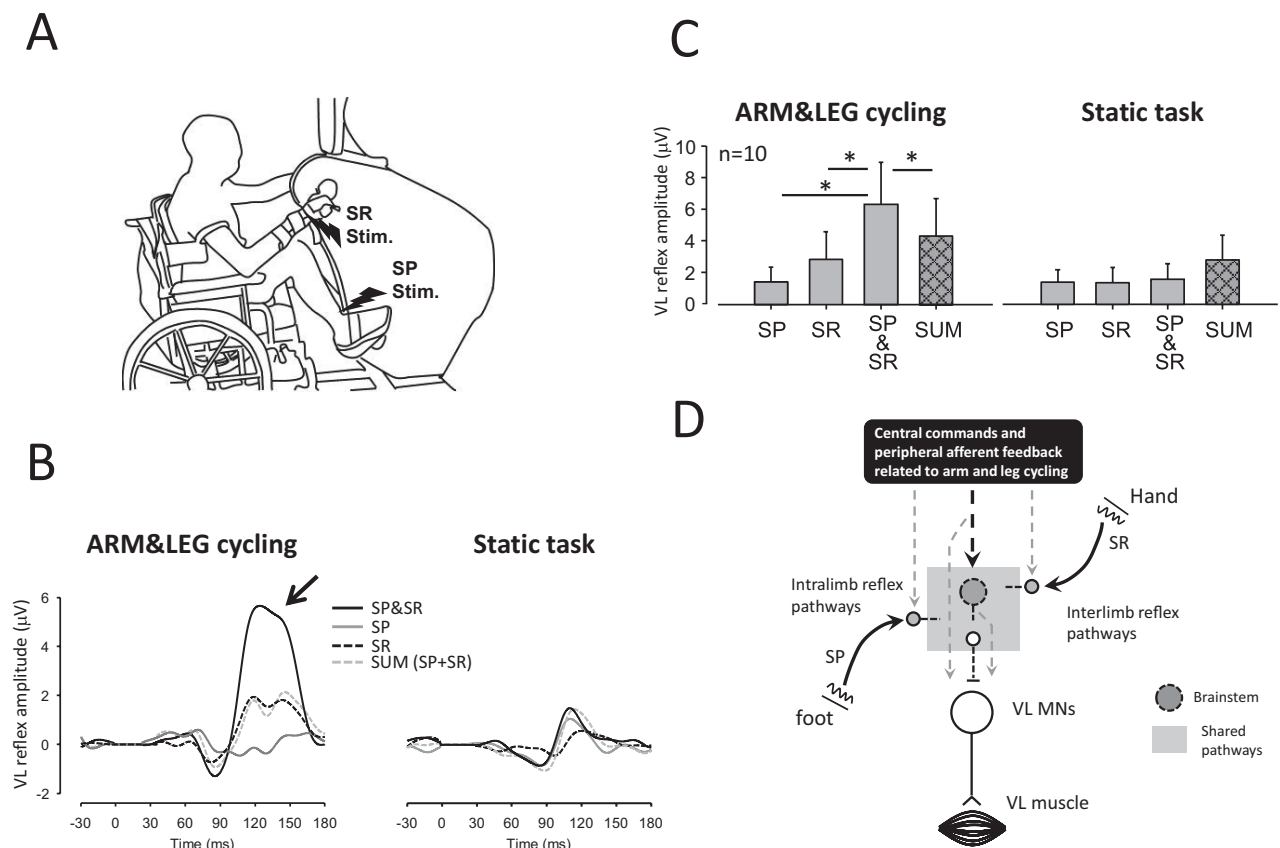


Fig. 3 Convergence of reflex pathways from multiple hand and foot nerve stimulation during ARM&LEG cycling adapted from Nakajima et al. *BMC Neuroscience*, 2013, 14: 28. A: Schematic illustration of the experimental set-up. B: rectified and averaged EMG responses following hand nerve (dashed black traces, superficial radial (SR) n.), foot nerve (dark gray traces, superficial peroneal (SP) n.) and simultaneous hand and foot nerves (black traces) stimulation during ARM&LEG cycling (left panel) and static condition (right panel). C: grand mean amplitudes of long latency reflex (LLR) after stimulation of SR, SP, and simultaneous stimulation of both nerves during ARM&LEG cycling (left panel) and static condition (right panel). D: Schematic diagram outlining a possible neurological framework for integration in cutaneous pathways from the hand and foot during locomotion.

tary contraction^{40,66}). In this approach, the intensity of the stimuli needs to be carefully adjusted such that separate stimulations coming from two disparate sources do not produce excitatory postsynaptic potentials (EPSPs) on their own. In this situation, almost all INs are subthreshold in response to each isolated stimulation channel. If combined stimulation of two different subthreshold source inputs generates EPSPs in the MN or overt modulation of the surface EMG, we can infer that an IN must receive convergent excitatory input from the two sources tested within a polysynaptic pathway^{14,15}.

If common INs are present, the amplitudes following combined stimulation will be larger than that of the algebraic sum of the two potentials induced by separate stimulation. The algebraic summation is the estimated value of the linear summation produced by the integrating function of the IN with projections to the MN produced by putative “private pathways” activated by separated stimulation¹⁴. Thus, the subtracted value obtained from the combined stimulation to that from the algebraic summation of separate stimulation can be determined as the effect of spatial facilitation on the presumed IN system¹⁴.

3. Evidence for common IN systems activated by cutaneous afferents

Using spatial facilitation in a feline model, Labella & McCrea⁷²) reported that cutaneous afferents from two different nerves converged onto common spinal interneurons to produce excitation and inhibition in functionally related groups of MNs. Also, we found convergence effects of foot cutaneous nerve stimulation on PSTH of MUs in leg muscles during static tasks⁷³). Interestingly, the results from this experiment showed that the probability of spatial facilitation was ~60%. These results suggest the likely existence of common interneurons within polysynaptic cutaneous reflex pathways from multiple nerves in humans.

“Reduced locomotion” model in humans: exploring neural circuits by regulating interactions of arm and leg movement

During rhythmic arm, leg or ARM&LEG movement, the amplitude modulation of the cutaneous reflexes in a limb muscle is greater when moving the test limb itself than when moving the other remote limbs^{74,75}). These findings imply that the amplitude modulation of cutaneous reflexes, during rhythmic movement, show a strong weighting according to limb activity. This suggests that when examining the effect from remote limb rhythmic movement on cutaneous reflexes in a given muscle, the remote effects could be easily “swamped” by the movement of the test limb during arm and leg movement. To effectively avoid this effect and to examine the effect of remote limb movement on the cutaneous reflexes in a given limb, “reduced locomotion” was recently developed

as an advanced protocol. We have used three-limb (both arms and one leg) or two-limb (arms or legs) movement tasks as a form of “reduced locomotion”^{7,76}). This paradigm allows control reflex excitability in the test limb while it stays stationary, and effectively extracts more subtle effects arising from remote limbs⁷⁶). In addition, we can investigate the contribution of the number of moving limbs on reflex expression. Thus, these paradigms are useful tools for revealing detailed evidence concerning the organization and integration of the locomotor system across all four limbs in humans.

Convergence onto common IN systems from multiple cutaneous nerves revealed during “reduced locomotion” in humans

Although neural output from the CPG systems for each arm and leg projects directly to each MN pool and indirectly through IN reflex networks, it has been less clearly understood whether these outputs modulate the excitability of common reflex pathways during locomotion. Recent findings concerning the effect of spatial facilitation on the putative common interneurons system during human “reduced locomotion” are described below^{40,65}.

1. Multiple inputs from hand and foot

Fig. 3 shows evidence for convergence during locomotion of reflex pathways from multiple nerves innervating the hand and foot⁴⁰). While subjects performed ARM&LEG cycling (Fig. 3A), 3 cutaneous nerve stimulation conditions were assessed: 1) SR, 2) SP, and 3) combined stimulation (SR&SP). Fig. 3B illustrates the cutaneous reflexes in the vastus lateralis (VL) during ARM&LEG cycling (left panel) and during static contraction (right panel) for the 3 different stimuli (SR, SP, and combined SR&SP). For reference, the simple algebraic summation of the reflex traces of both SR and SP is shown as “SUM”. In all stimulus paradigms, we can see clear MLR and LLR, though the main response of interest is LLR. It is notable that the amplitude of LLR following the combined SR&SP (black sweep; note arrow head) was significantly larger than those following a single SR, SP or algebraic summation of either SR and SP (See also Fig. 3C, left panel). In contrast, no such exponential increase in LLR can be seen during static contraction (see Fig 3B and 3C, right panel). These findings suggest that ARM&LEG cycling activates common IN reflex pathways (Fig. 3D, gray square), which would receive inputs from SR and SP and produce excitation to VL MNs. This common neural system appears to be activated only during locomotor movement. Although further study is needed, the activity of this common neural system appears to relate directly to locomotor drive from presumed midbrain, cerebellar, and CPG system in the spinal cord (Fig. 3D).

2. Multiple inputs from different nerves of foot

To further characterize the locomotor-related common neural system in humans, we stimulated the TIB and SUR nerves to elicit cutaneous reflexes in TA during reduced locomotion of ARM&LEG movement (bilateral arms and left leg movement, see Fig. 4A)⁶⁵. In addition, combined TIB&SUR stimulation was given to confirm the common neural system.

Fig. 4B shows typical recordings of EMG activities from ipsilateral (left) and contralateral (right) anterior deltoid (AD), VL, medial gastrocnemius (MG) and TA muscles during ARM&LEG movement for a single subject. EMG activities of the AD, VL, MG, and TA on the contralateral side and ipsilateral AD were rhythmically modulated during the task. In contrast, EMG activity of the ipsilateral TA (“test” limb) remained constant. Also, activities of other ipsilateral leg muscles (VL and MG)

were relatively inactive.

As shown in Fig. 4C and D, the amplitude of the facilitatory ELR following combined TIB&SUR was significantly larger than that following separate SUR and TIB stimulation and that of the algebraic summation of both. The exponential increase in the ELR amplitude following combined TIB&SUR stimulation is most easily explained by activity in a common neural system, which integrates disparate cutaneous inputs and projects to TA MNs during locomotor movement.

To investigate whether the number of moving limbs modulates facilitation of ELR following simultaneous stimulation, data were compared across the ARM&LEG, ARM, and LEG tasks (Fig. 5). As a result, the facilitation of ELR seen during combined nerve stimulation was smaller while performing ARM and LEG compared to the ARM&LEG task (Fig. 5B and C). Interestingly,

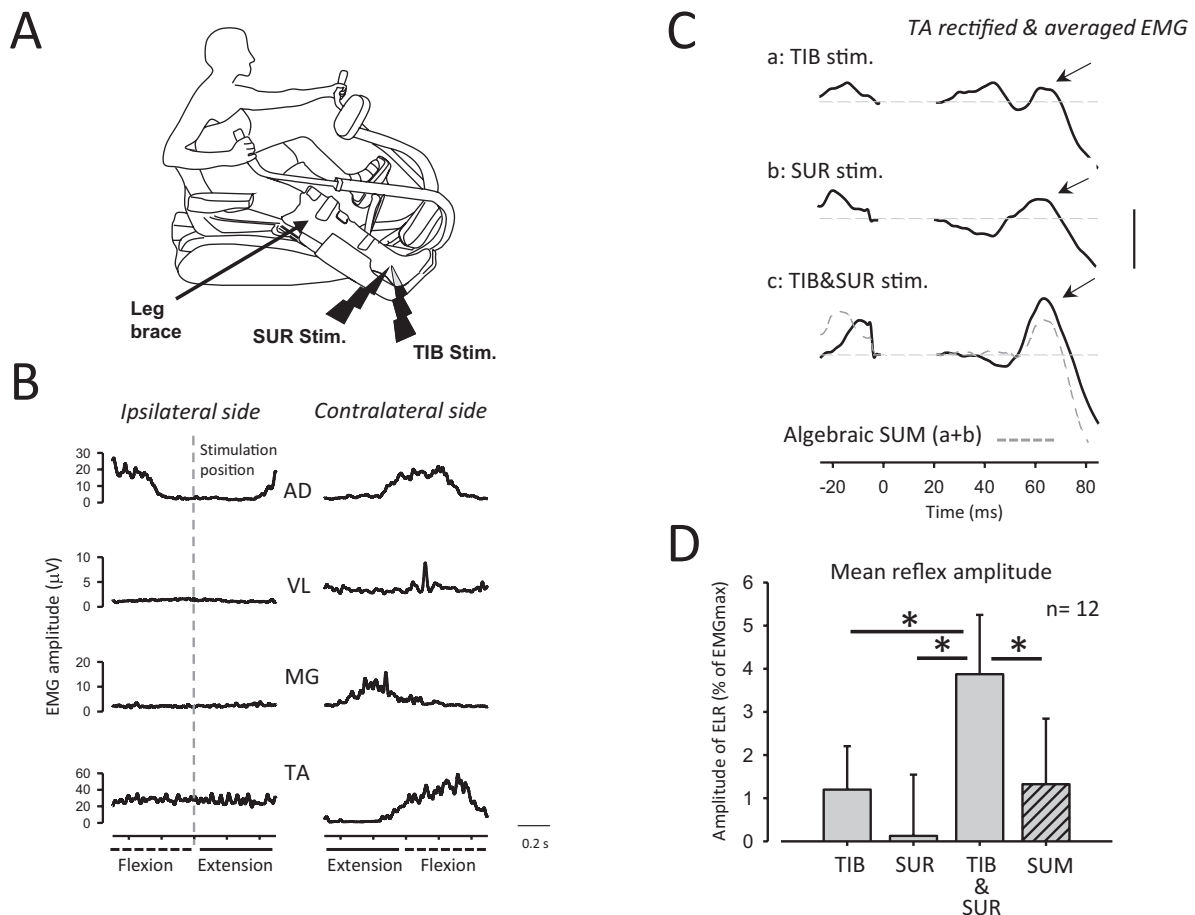


Fig. 4 Evidence showing convergence of reflex pathways from tibial (TIB) and sural (SUR) nerve stimulation during reduced ARM&LEG task in which the tested limb (right leg) was stationary, adapted from Nakajima et al. *PLoS One*, 2014, 9: e104910. A: Schematic illustration of experimental set-up. B: Typical recordings of ongoing EMG activities in AD, VL, MG, TA muscles during the reduced ARM&LEG movement for a single subject. Gray vertical line: the time of the stimulation of ipsilateral side. Dashed and thick horizontal lines: flexion and extension phase of the movement, respectively. C: Full-wave rectified and averaged EMG in TA muscle following the combined stimulation of sural and tibial nerves (TIB&SUR, third trace), SUR alone (second trace) and TIB alone (first trace) obtained from a single subject. Dashed gray trace: the simple mathematical summation of EMG traces for individual TIB and SUR nerves stimulation (Algebraic SUM). D: Grand means (± SD) of the magnitudes of early-latency reflex responses (45-80 ms after stimulation) following the combined stimulation of SUR and TIB nerves, SUR alone and TIB alone obtained from 12 subjects. Hatched gray bar: the simple mathematical summation of reflex amplitude for individual nerves (SUM) stimulation. * $p < 0.001$. Calibration bar = 10 mV.

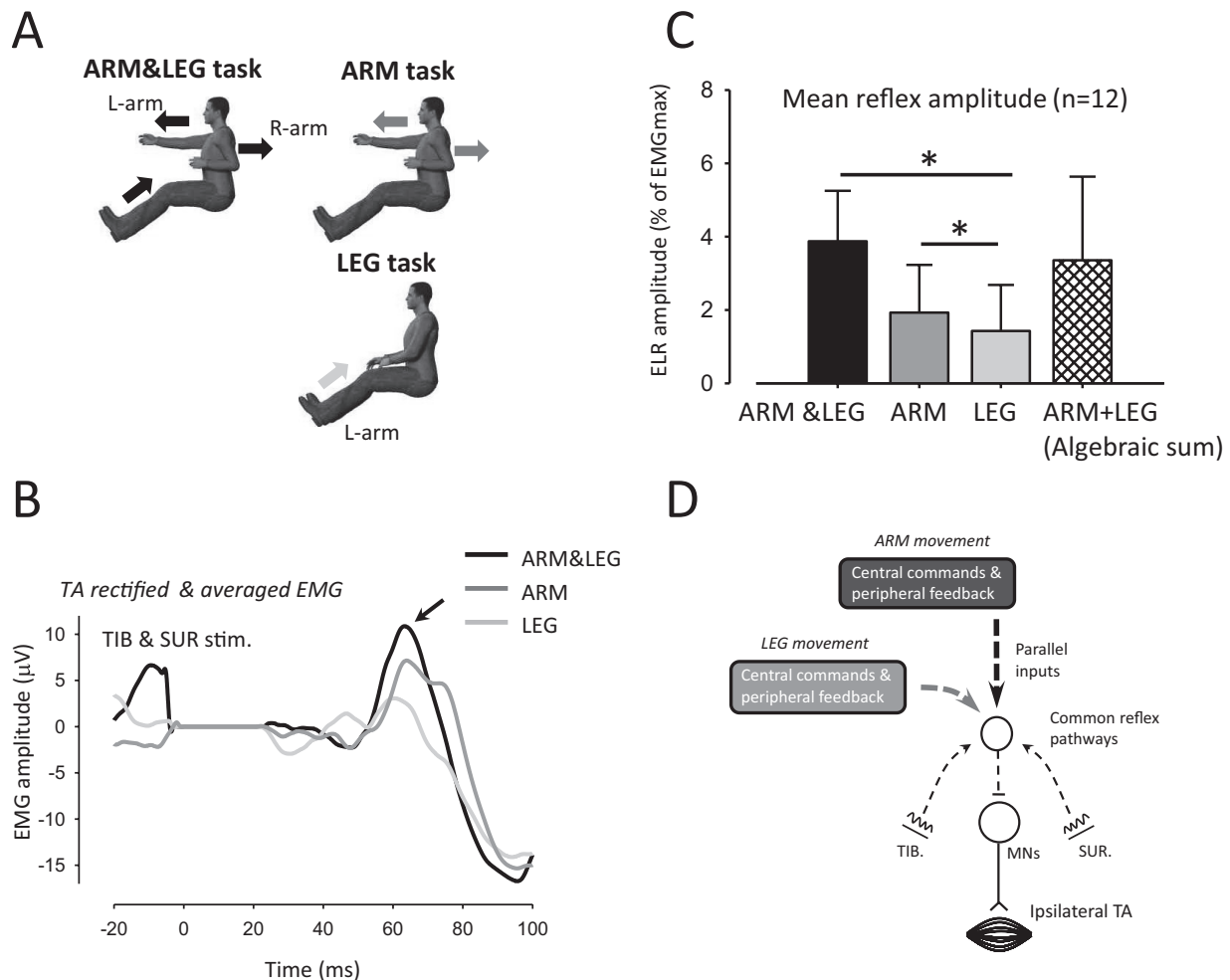


Fig. 5 Effect of number of moving limbs on early-latency reflex (ELR) following combined tibial (TIB) and sural (SUR) nerve stimulation (TIB&SUR) adapted from Nakajima et al. *PLoS One*, 2014, 9: e104910. **A:** Experimental tasks for remote rhythmic movements: bilateral arm and contralateral movement (upper left panel, ARM&LEG), bilateral arm movement (upper right panel, ARM) and contralateral leg movement (lower right panel, LEG) **B:** Full-wave rectified and averaged EMG in TA muscle following TIB&SUR stimulation during ARM&LEG (black trace), ARM (dark gray trace) and LEG (light gray trace) movement. **C:** Grand means (\pm SD) of the magnitudes of early-latency reflex responses (45-80 ms after stimulation) following simultaneous combined stimulation of SUR and TIB nerves during ARM&LEG (black bar), ARM (dark gray bar) and LEG (light gray bar) movement obtained from 12 subjects. Hatched gray bar: mathematical summation of reflex amplitude for individual tasks (ARM+LEG) stimulation. **D:** Schematic diagram outlining a possible neurological framework for integration in common cutaneous pathways from the ARM and LEG movements during locomotion. * $p < 0.001$

there was no significant difference between the reflexes of ARM&LEG and mathematical summation of ARM + LEG in the separate tasks (Fig. 5C).

To delineate possible neural mechanisms contributing to our findings, we suggest the schema in Fig. 5D. In our study, the observation of non-linear ELR facilitation following combined SUR and TIB nerve stimulation infers the existence of putative common IN pathways. Thus, the simplest explanation may be that individual inputs arising from active limbs during LEG and ARM movement converged onto “common” IN pathways during ARM&LEG movement (see squares of gray and black). The excitability of these unique common reflex pathways may perform a “weighting function” that is strongly affected by the number of moving limbs. In other words, they receive extensive input from the number of moving limbs and in-

tegrate sensory information from various limbs, descending inputs from the higher motor center, CPG systems and peripheral sensory inputs, all of which are seminal for retaining smooth locomotion. Although we cannot deny other neural mechanisms, these explanations are the simplest and most reasonable interpretations based on our observations.

Convergence onto common presynaptic inhibitory IN regulating group Ia afferent transmission during locomotion

Presynaptic inhibition (PSI) is known to play a crucial role in regulating the efficacy of synaptic transmission to a target neuron by controlling neurotransmitter release from the presynaptic terminals⁷⁷. This neural mechanism

regulates the excitability of the monosynaptic reflex arc from group Ia afferents to MNs without any changes in postsynaptic membrane potential^{15,77}, and is a major control mechanism of vertebrate locomotion^{10,78,79}. Recently, we reported evidence for the convergence of somatosensory inputs (*i.e.*, agonist Ia and cutaneous afferent input) and locomotor commands on presumed PSI INs using controlled conditioning-test (C-T) stimulation paradigms as described below.

Since the 1970s, it has been known that presynaptic inhibition of Ia afferent transmission to alpha MNs in the pathway for the H-reflex arc could be investigated in humans by using conditioning-test (C-T) stimulation paradigms^{80,81}. D1 inhibition, which was reported by Mizuno et al. (1970) with the H-reflex method, may be the first demonstration of PSI in humans. More recently, we found evidence for convergence onto putative PSI INs in the human cervical cord from antagonist Ia inputs and locomotor commands by measuring the effect of subthreshold somatosensory conditioning stimulation on flexor carpi radialis (FCR) H-reflex amplitudes during leg cycling⁶⁶. Suzuki et al.⁸² used a similar approach to demonstrate that presynaptic modulation of the soleus H-reflex amplitude arose following conditioning stimulation of cutaneous nerves in the contralateral leg during walking.

1. Contribution of presynaptic inhibition assessed with H-reflex modulation during remote rhythmic movements

Neuronal transmission from group Ia afferents to alpha MNs in the lumbar spinal cord has been investigated with stationary legs during rhythmic arm movement. Under such circumstances, the amplitude of the H-reflex in the soleus muscle is modulated in humans^{5,76,83-87}. Interestingly, rhythmic leg movement (see Fig. 6A) also leads to a modulation of H-reflex amplitude in forearm muscles^{4,6}. These results suggest that the CPG system is activated by locomotor commands to regulate flexor and extensor muscle activity. Afferent feedback strongly modulates the excitability of H-reflex pathways in remote muscles^{1,2}. As for these neural mechanisms, Zehr and co-workers suggested that a change in excitability of presynaptic inhibitory interneurons modulating transmission between Ia afferent terminals and alpha MNs (Ia PSI) is a major control mechanism associated with H-reflex modulation during rhythmic movement of the remote limbs⁵.

2. Interaction between somatosensory inputs and leg cycling on the modulation of forearm H-reflex amplitudes

Recently, we showed that INs mediating PSI at the group Ia afferent terminals in the cervical spinal cord were regulated by CPG activity during “reduced locomotion”.

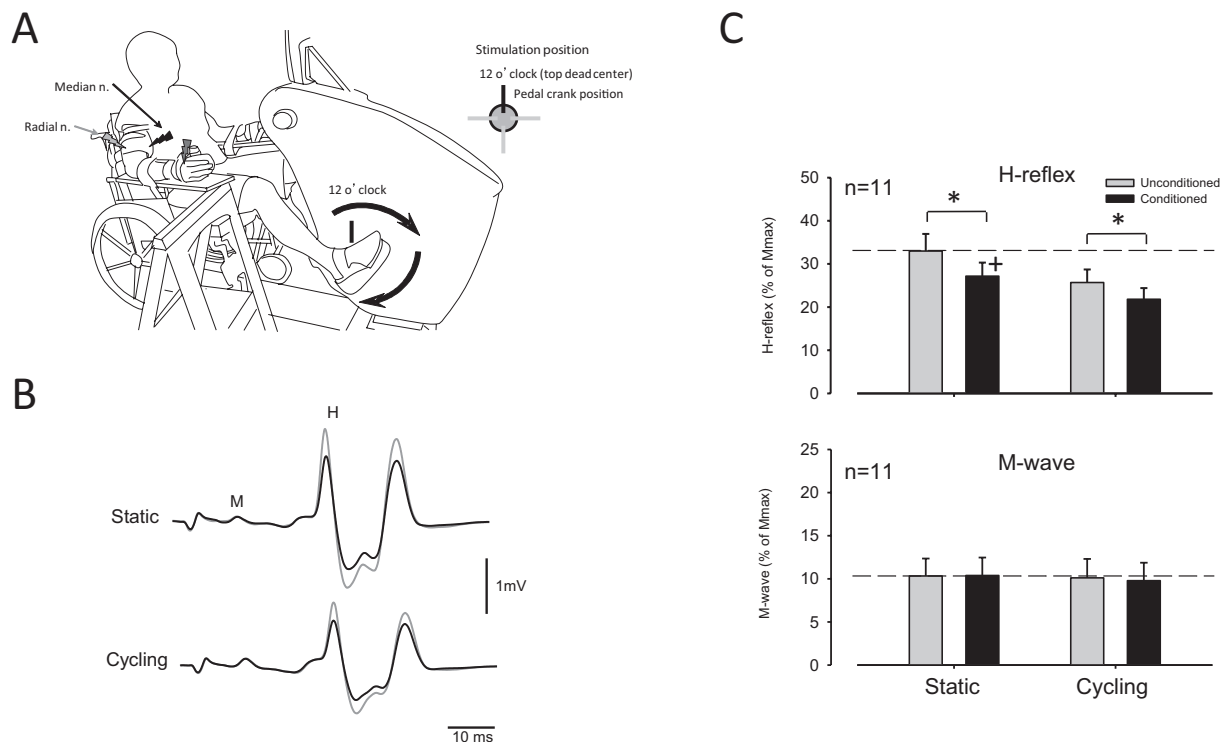


Fig. 6 Effect of conditioning the *flexor carpi radialis* H-reflex with radial nerve stimulation during leg cycling and static activation adapted from Nakajima et al. *PLoS One*, 2013, 8: e76313. A: Experimental tasks for remote rhythmic movements (*i.e.*, leg cycling). B: Typical averaged recordings of conditioned (black lines) and unconditioned (gray lines) H-reflex waveforms during static (upper traces) and cycling (lower traces) tasks obtained from a single subject. C: Grand means and SEM of magnitudes of the H-reflex (upper panel) and M-wave (bottom panel) during conditioned (black bars) and unconditioned (gray bars) trials in leg cycling and static condition. * $p < 0.01$ significantly different from the unconditioned values for each task. + $p < 0.01$ significantly different from the unconditioned static value.

tion” in humans (Fig. 6A). Fig. 6B depicts representative recordings of FCR H-reflex amplitudes from a single subject conditioned by radial nerve stimulation [1 x motor threshold (MT), C-T interval= 20 ms]. Suppression of the H-reflex amplitude induced by radial nerve stimulation can be seen clearly during the static condition. During leg cycling, the FCR H-reflex amplitude was reduced, compared with that during the static task, and the amount of suppression was enhanced by radial nerve conditioning stimulation as shown in Fig. 6C (upper panel).

Following stimulation of the radial nerve at MT, suppression of the FCR H-reflex amplitude occurs within a C-T interval of ~5-40 ms⁸⁸. This is well in line with the documented range of C-T intervals for Ia PSI in the FCR H-reflex pathway (*i.e.*, D1 inhibition). Berardelli et al.⁸⁸ demonstrated that stimulating the radial nerve with a C-T interval of ~20 ms elicited prominent suppression of the H-reflex amplitude in FCR muscle⁸¹. In the recent study during leg cycling, the suppression of the H-reflex amplitude induced by PSI associated with the CPG system interacted with radial nerve-induced PSI. Thus, we suggest that locomotor commands for leg cycling and afferent volleys from somatosensory conditioning stimulation converge and are integrated on common PSI interneurons modulating transmission between Ia afferent terminals and alpha MNs in the H-reflex pathway^{5,81,88}. FCR ongoing EMG following MT stimulation of the radial nerve was suppressed and had a latency that corresponded with the H-reflex evoked with a C-T interval of 20 ms (Fig. 7A). Thus, it is possible that FCR H-reflex modulation was induced not only by presynaptic mechanisms, but also by postsynaptic effects. In cats, it has been reported that the effect of relatively short C-T interval conditioning stimulation on the monosynaptic reflex gives rise to both presynaptic and postsynaptic effects^{77,89-91}.

3. Evidence for presynaptic modulation of the FCR H-reflex amplitude during locomotion: possible shared presynaptic pathway?

Fig. 7B depicts the effects of subthreshold radial nerve conditioning on FCR H-reflex amplitudes during static contraction and leg cycling obtained from a single subject. Radial nerve stimulation at 0.6 x MT did not affect the ongoing rectified and averaged EMG (see Fig. 7C), and thus did not contribute postsynaptic modulation. There were also no conditioning effects at 0.6 x MT on the H-reflex amplitude in the static condition (Fig. 7B, upper traces, and Fig. 7D). During leg cycling, however, the H-reflex amplitudes were significantly reduced by this weak (subthreshold for postsynaptic effects) conditioning stimulus (Fig. 7B, lower traces, and Fig. 7D, upper panel). The simplest interpretation is that since postsynaptic effects coming from conditioning volleys were relatively weak on the modulation of the H-reflex amplitude during leg cycling^{77,91}, it was assumed that PSI plays a major role in reducing the FCR H-reflex amplitude, and INs-

mediating PSI were facilitated by the CPG system during leg cycling.

An interesting finding is that the H-reflex modulation induced by weak conditioning stimulation was only observed during the leg cycling task, and not during static activation. A schematic representation of the possible circuitry is shown in Fig. 7E. While in a stationary condition, it is likely that the weak conditioning volleys (thin broken lines) do not reach the threshold for activation of the Ia PSI pathway through the presumed PSI INs (large gray circle). Also, the conditioning stimulation does not produce any reflex effect on the ongoing FCR EMG, showing that the postsynaptic effect due to the conditioning stimulation does not come into effect (see Figs. 7C and 7D). Thus, the locomotor drive plays a key role in controlling presumed presynaptic modulation of Ia terminals, suggesting that the leg cycling-related inputs and conditioning volleys converged onto shared premotoneuronal Ia PSI pathways during leg cycling (see the square with dashed line in Fig. 7E). During fictive locomotion in a cat, it has been suggested that afferent and locomotor inputs converge onto shared PSI pathways⁹². These findings suggest that there are parallel neural mechanisms of PSI regulation for interlimb locomotor control across species.

By using a similar method, Suzuki et al.⁸² demonstrated that presynaptic modulation of H-reflexes in the soleus muscle occurred by conditioning stimulation of cutaneous nerves in the contralateral leg during walking. This stimulation did not produce reflexes in the ongoing ipsilateral soleus EMG, although the H-reflex amplitudes were significantly suppressed. Thus, it is also likely that locomotor commands and contralateral somatosensory afferents converge onto PSI interneurons during bipedal walking.

Common core neuronal element from multiple sensory and locomotor inputs

Previous reports discussed in this brief review postulate the existence of a shared common pathway that integrates multiple sensory inputs including the CPG system. Fig. 8 illustrates a tentative schematic framework incorporating our findings so far. To recap, observations of non-linear reflex facilitation (*i.e.*, spatial facilitation) following combined nerve stimulation [*e.g.*, reflex pathways I (gray upward arrows) and II (black upward arrows)] infers the existence of putative converging IN pathways, “common core neuronal element (filled black circle)”. Interestingly, the convergences onto common INs from multiple nerve stimulation were only elicited during locomotor tasks. Thus, the activity of these common INs appears directly related to locomotor activity (dark gray circle). As a result, these outputs (down arrows of black) are sent onto MN pool (gray square) and presynaptic Ia terminals within the monosynaptic reflex. We could detect them in amplitude modulation of reflex responses in several limb

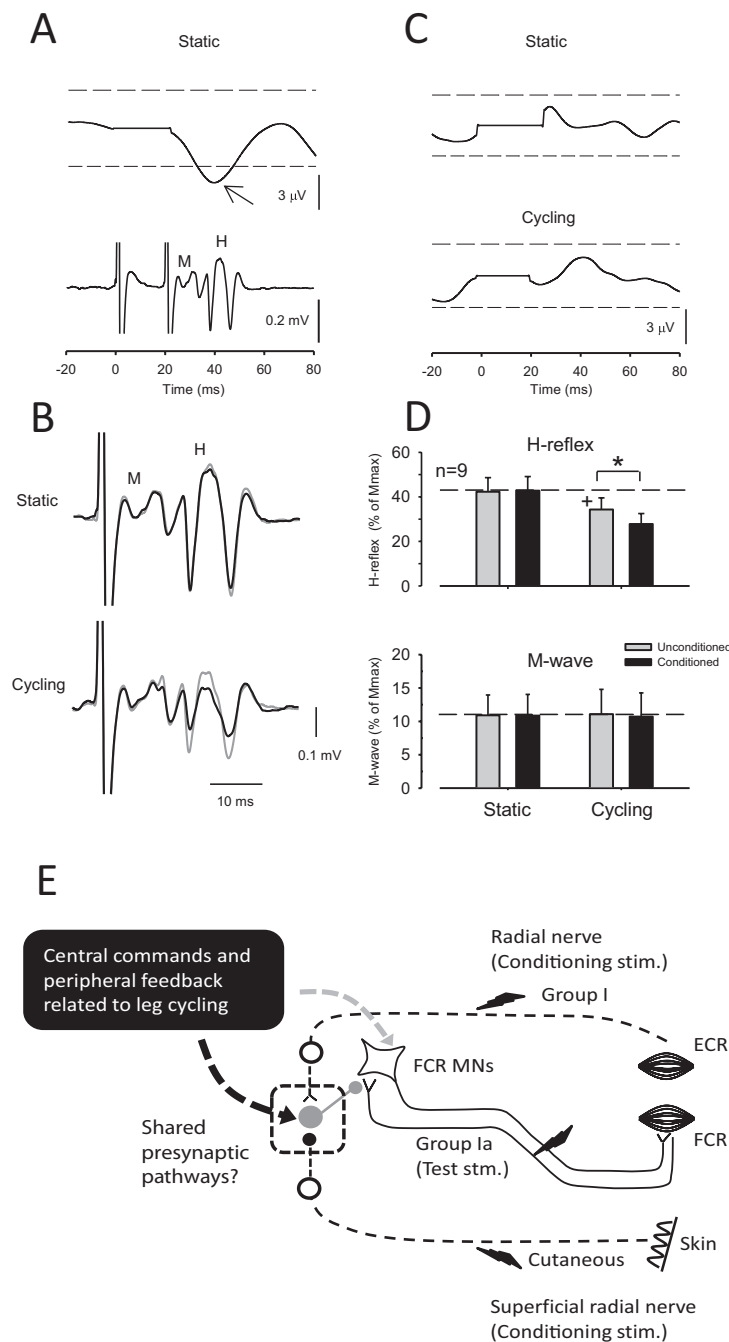


Fig. 7 Effects of subthreshold radial nerve conditioning on FCR H-reflex amplitudes during static task and leg cycling from Nakajima et al. *PLoS One*, 2013, 8: e76313. **A:** Rectified and averaged *flexor carpi radialis* (FCR) EMG (upper trace) and H-reflex waveforms (lower trace) following radial nerve stimulation [$1.0 \times$ motor threshold (MT)] obtained from a single subject. Time zero on the x-axis is at onset of conditioning stimulation. Please note that the EMG reflex responses had latencies that corresponded with the H-reflex during the conditioning-test interval. Horizontal arrows show analysis range for assessing ongoing FCR EMG. The arrow shows the suppressive response in the rectified EMG. **B:** Conditioning effect of weak radial nerve stimulation ($0.6 \times$ MT) on FCR H-reflex amplitude during static activation (upper traces) and leg cycling (bottom traces). **C:** EMG responses following weak radial nerve stimulation ($0.6 \times$ MT) during static and cycling tasks. Non-significant EMG responses were within 2 standard deviations (SD) of the pre-stimulus EMG levels. Broken lines in each panel represent a 2 SD band around the mean pre-stimulus EMG. Note that the stimulus artifact was replaced by the mean of the pre stimulus EMG. Data in Figs. 7A, B, and C were obtained from the same subject. **(D)** Grand means (\pm SEM) of H-reflex amplitudes (upper panel), M-waves (lower panel) in the FCR muscle during radial nerve conditioning obtained from 9 subjects. * $p < 0.01$ significantly different from the unconditioned values for each task. + $p < 0.01$ significantly different from the unconditioned static value. **E:** Schematic diagram outlining a possible neurological framework for integration in PSI pathways from the radial and cutaneous nerve and central commands during locomotion.

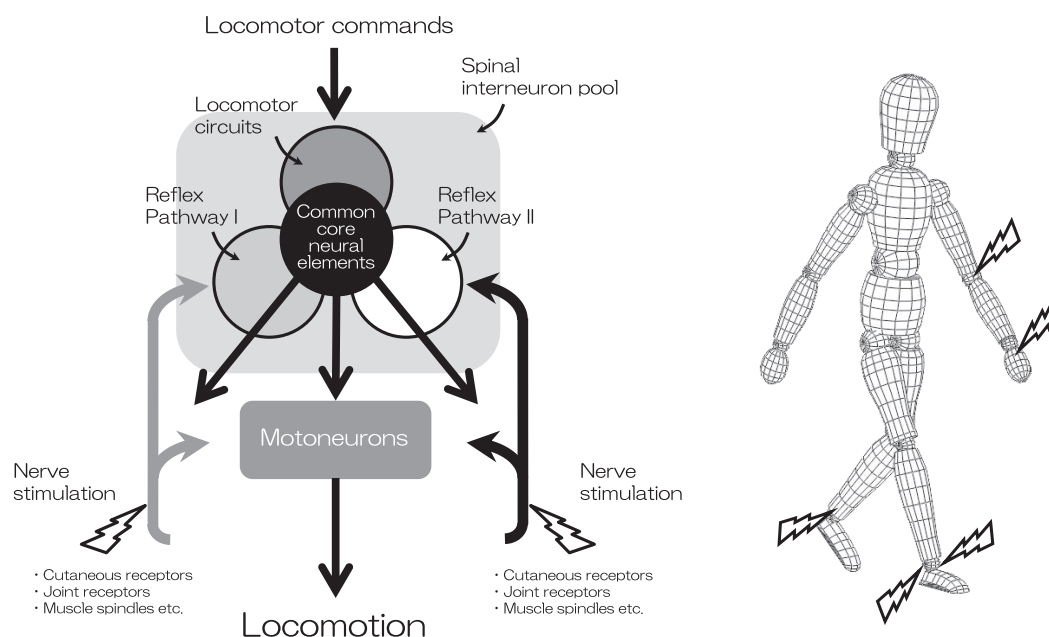


Fig. 8 Schematic illustration of a possible neural framework for integration system for cutaneous pathways from various sensory nerves during locomotion. In our study, observations of non-linear reflex facilitation following combined various nerves stimulation [e.g., Reflex pathway I (gray upward arrows) and II (black upward arrows)] infers the existence of these putative converging interneuronal pathways. The activity of these common interneurons appears directly related to locomotor activity (red circle, yellow downward arrow). These outputs (black downward arrows) are sent onto motoneuron pool (gray square) and presynaptic Ia terminals. This concept containing shared interneurons, “common core neural elements (filled black circle)” could be beneficial to enhance rehabilitation outcome. We propose this scheme as a new strategy for recovery of walking abilities using arm and leg movement and sensory modulation from the hands and feet.

muscles. Although the functional importance of these neural mechanisms remains unclear at this time, they play an important role in controlling posture, limb motion itself and corrective reaction to obstacles in preventing tripping and stumbling.

Translational implication for walking rehabilitation

Sensory information strongly modulates motor output of CPGs in the spinal cord as described above^{12,16,19,93,94}. After stroke and SCI, it has been suggested that these circuits need to be strongly activated for effective rehabilitation and regaining walking ability⁹⁵⁻⁹⁸.

As a translational implication for rehabilitation, we suggest that stimulation of multiple nerves (black and gray upward arrows in Fig. 8) during rhythmic arm and/or leg movement may be beneficial to improve accessibility of IN circuits that interconnect with the locomotor system in the human spinal cord⁹⁹ (see Fig. 8). This concept with a common core neural element (filled black circle in Fig. 8) could be used to accelerate the development of novel rehabilitative interventions for recovering walking ability using arm and leg movements and sensory information from the hands and feet.

Concluding remarks

Neural output from the locomotor system for each arm

and leg influences the spinal motoneuronal pools directly and indirectly through IN reflex networks. This review article mainly describes recent findings concerning the features of common IN systems intercalated in the spinal reflex pathways induced by multisensory inputs during human locomotion. Generally, multimodal convergence on spinal INs themselves has been reported voluminously by Sir John C. Eccles, Anders Lundberg and their colleagues using intracellular recording of single MN in acute spinal cats since the 1960s^{47,100}. To the best of our knowledge, however, little has been elucidated about the behaviors and functions of common INs integrating multisensory inputs during actual movement tasks in behaving humans. Recently, it was reported that these putative INs accessing multiple sensory nerves interact with locomotor systems^{40,65,66}. Thus, this concept of using multiple nerve stimulation has an advantage for improving access to INs that interconnect with locomotor regions after neural trauma. However, it is needed to be substantiated to what extent these tools can improve walking ability in conjunction with enhancement of locomotor activity after repetitive multiple nerve stimulation. This experiment needs to be further explored in the future.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this article.

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