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*Current Pharmaceutical Design*, 2017, *23*, 1-11 1

REVIEW ARTICLE

# Tonic and Rhythmic Spinal Activity Underlying Locomotion

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ARTICLE HISTORY

Received: November 2, 2016
Accepted: January 20, 2017

*DOI: 10.2174/1381612823666170125 152246*

**Abstract:** In recent years, many researches put significant efforts into understanding and assessing the functional state of the spinal locomotor circuits in humans. Various techniques have been developed to stimulate the spinal cord circuitries, which may include both diffuse and quite specific tuning effects. Overall, the findings indicate that tonic and rhythmic spinal activity control are not separate phenomena but are closely integrated to properly initiate and sustain stepping. The spinal cord does not simply transmit information to and from the brain. Its physiologic state determines reflex, postural and locomotor control and, therefore, may affect the recovery of the locomotor function in individuals with spinal cord and brain injuries. This review summarizes studies that examine the rhythmogenesis capacity of cervical and lumbosacral neuronal circuitries in humans and its importance in developing central pattern generator-modulating therapies.

**Keywords:** Central pattern generator, spinal cord, rhythmogenesis, muscle tone, neuromodulators, sensory input, Kohnstamm phenomenon, electromagnetic stimulation, locomotion.

## 1. INTRODUCTION

Rising interest in the improvement of gait control in injured populations is pushing a greater number of researchers towards innovative approaches that help understanding the functional state of the spinal cord for performing locomotor movements in both human and animals [1-5]. It is generally accepted that the inherent capacity for generating rhythmic movements is largely provided by collections of neurons (termed *central pattern generators*, CPG) localized in the spinal cord [6]. Normally CPGs are inactive and become engaged by neurons with command function [7]. However, the origin of this central command is not fully clear and the specific contribution of different descending systems in initiation of stepping is not completely known [6,8]. While the bulk of research on the neural control of locomotion is dedicated to rhythmic spinal cord activity and its modulation by the sensory input and by the supraspinal structures, the importance of the functional state of the spinal network becomes increasingly evident [9]. The same interneurons and motoneurons can be involved in a wide range of movements, from simple reflex and postural adjustments to more complex phasic and rhythmic movements, such as locomotion and voluntary movements [1,10]. Because of this redundancy in the control domain, in order to specifically trigger CPG commands, neurons with command functions should fire under a properly prepared physiological state of the spinal network. It is also worth noting that most synapses are inhibitory (see, for instance, [11]) and contribute to maintain network stability, select/activate neurons of a particular elementary spinal network and avoid an excessive motor reaction [12]. In addition, there are various neuromodulators involved in the control of locomotion ([8,13]) that affect the physiological state and plasticity of the spinal locomotor circuitry [5].

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The spinal cord is not a simple relay structure for communication between central and peripheral structures [1], a reduced form of body schema may also exist in the spinal cord [14,15]. For instance, it has been demonstrated that the spinal cord of the frog [16,17] and of the cat [18] is capable of performing transformations that map information from sensory coordinates to motor coordinates and encode a global representation of limb mechanics. This structure is flexible and able to correct kinematic errors in limb coordination through practice in rats [19]. As a general rule, a remarkable percentage of new synapses in the central nervous system are formed every day while others die (*e.g.*, [20]). To our knowledge, the fraction of synapses renewed daily in the spinal cord was not systematically studied, however, it is reasonable to suggest that the turnover occurs, reflecting a common property (synaptic plasticity) of neuronal networks. For instance, a degeneration of spinal networks and synapses occurs after a spinal cord injury (SCI). Therefore, to maintain appropriate neuronal activity below the lesion level, many studies emphasized the importance of early locomotor training after injury [21,22]. Furthermore, the major part of the spinal circuity is constituted by interneurons. Thus, it is important to maintain a proper physiological state of the spinal networks. One way to control the automaticity of the spinal cord and generate rhythmic locomotor output is to provide its tonic activation.

Historically, Goltz and Freusberg [23] in the 19th century were likely the first to show the link between excitatory state of the spinal circuitry and rhythmic locomotor activity. They reported spontaneous stepping-like hindlimb movements in the spinal cord-transected dog prior to voiding the distended bladder and their disappearance after voiding. Thus, a tonic excitatory state of the spinal network can be a sufficient stimulus for the transition of these circuits from an inhibited to an active state producing rhythmic output.

The tonic excitatory input is an integral part of many CPG models previously developed to explain the functioning of spinal

 

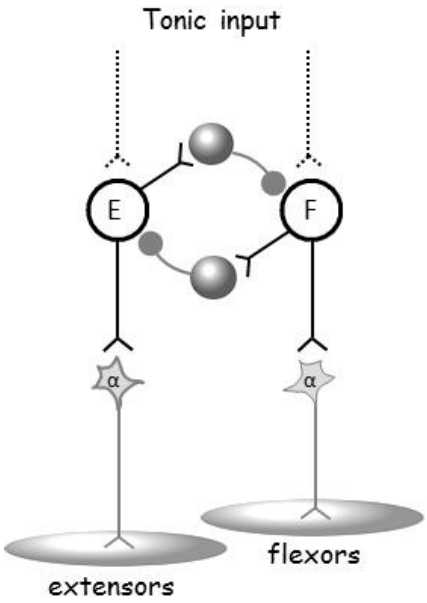


**Fig. (1).** Classical simplistic version of the Graham Brown's [24] half-center model. A tonic input is transformed into a rhythmic output. α - alpha motoneurons; E and F - extensor and flexor half centers, respectively; open endings - excitatory connections; small filled circles - inhibitory connections. Half-centers interconnected together may form a structure of spinal oscillatory networks [25-28].

pathways for reciprocal motoneuron activation. Early classical studies by the Scottish physiologist Thomas Graham Brown [24] suggested the existence of half-center central pattern generators (CPGs) controlling rhythmic muscle activity [30,31]. Figure **1** illustrates an influential scheme of the half-center model with the extensor half-center shown on the left (E) and the flexor half-center on the right (F). Control relies on a self-regulating mutually inhibitory loop. For example, flexor half-center activity inhibits extensor half-center activity and the other way around. When activated, 'E' group neurons simultaneously send motor commands to extensor motoneurons and inhibitory signals to the reciprocal 'F' group neurons, thus preventing flexor excitation (Fig. **1**). Following a period of 'depression' (*e.g.* post-inhibitory rebound) of the extensor half-center, there would be a new phase of predominant activity from the flexor half-center. This is a simplest version of the Graham Brown's half-center model that is often used for illustration of the basic operational principles of rhythmic movement control [26, 29, 32].

Various models of the spinal pattern generators including a half-center component have been put forward [29,33]. Half-centers interconnected together may form an assembly of spinal oscillatory networks [25-28], resulting in a sequential alternating activity of several groups of flexor and extensor muscles. Current data in animals tend to exclude a simple half-center organization [34]: for instance, flexor-related or extensor-related networks are able to burst without reciprocal activity. It has been suggested that such flexible network composition of multiple flexor and extensor rhythm-generating modules may be beneficial [34]. Also, some studies point to a dominant role of flexor circuits and an asymmetric organization of pattern-generating circuits and sensory feedback [35-38]. It is important to note that the tonic input signal in this scheme is transformed into a rhythmic output (Fig. **1**). Other models (*e.g.*, the ring model, the Miller and Scott model, the unit burst generator, the flexor burst generator model, etc., reviewed in [29]) also assume the important role of tonic excitatory input for activation of CPG. More recently, several additional layers of complexity have also been proposed by McCrea and Rybak [27] for the organization of mammalian spinal locomotor circuitry.

The spinal neural controllers may generate a relatively complex rhythmic pattern that is muscle- and context-dependent. In addition, basic patterned commands directed to the leg muscles and spinal locomotor output in humans demonstrate functional reorganization during development [39-41]. We will not discuss a detailed description of the structure and activity patterns of various skeletal muscles participating in the control of locomotion and refer to other reviews (*e.g.*, see companion paper of Sylos-Labini and colleagues about muscle coordination in human locomotion). The main focus of this review is placed on the rhythmogenesis of the spinal cord and on the role of the tonic input in its activation. The organization of the spinal pattern generation network has been extensively studied in animal locomotion [6] though our knowledge about such organization in the human spinal cord remain very limited [9,42-44]. While we refer to some literature on the CPG functioning in animals, our review will mainly focus on tonic and rhythmic spinal activity in humans, both for the lower and upper limbs. These findings have also important clinical implications.

## 2. MUSCLE TONE AND LOCOMOTION

The control of posture and locomotion are inherently interrelated. Postural tone is an unconscious muscle tension distributed along the entire body and originated from diverse supraspinal structures, including the reticular formation, vestibular nuclei, cerebellum, and mesodiencephalic nuclei [45]. Circuitry within these structures can exhibit sustained, long-lasting activity, which may provide a prolonged excitation or inhibition of executive motor systems. Both postural orientation [46-49] and gait characteristics are substantially influenced even by small alterations in the level of tonic muscle activity [40,50]. Below we provide important examples of an interrelation between static muscle postural tone and locomotion.

The central nervous system is able to combine mobility with stability and the nature of interactions between posture and movement is a long-standing problem in movement neuroscience. This important relationship was best described by Sherrington more than a century ago [51] - 'posture follows movement like a shadow'. Traditionally, tonus is linked to the activity level of muscle, and evaluated by the extent of the muscle resistance to stretch. This widely accepted emphasis on the stretch reflex as the means to explain and quantify tonus seems somewhat restricted, however [52]. For instance, muscle tone and muscle responses to changes in its length during rest may also be characterized by the presence of shortening reactions and/or by postural adjustments of other 'remote' muscles not being primarily stretched [53-55]. Therefore, Bernstein's [56] interpretation of muscle tone seems more meaningful. He viewed tonus as *the degree of readiness for movement*, and related to movement as a state is related to an action, or as a precondition is related to an effect.

It has been also argued that the ability to perform a movement and simultaneously avoid an excessive motor reaction is achieved by the combined use of two types of central commands: one may subserve an appropriate 'state' or 'readiness' of the spinal circuitry, and the other be more directly related to movement control ("*lock with two keys*" hypothesis [52]). Probably, in the control of movements the readiness command is associated with both diffuse and quite specific tuning effects (see also [12,57,58]). In the context of this review, it is important to emphasize that the state of the spinal circuitry, including significant reflex modulation [59,60], is not 'invariant' (as in the case of a simple relay for information transmitted to and from the brain) but necessitates task-dependent tuning. Its excitation level is specifically related to the elaboration of both postural and locomotor automatisms.

Over a century ago, in 1915, Beritoff [61] demonstrated that a rhythmic limb stepping reflex in chronically decerebrated animals

could be elicited by peripheral stimulation as long as the extensor tonus was appropriate. The level of rigidity in these animals exhibited spontaneous fluctuations: if the level of muscle rigidity was too low or too high, reflex rhythmic limb movements were not observed. Therefore, postural and rhythmic pattern generation circuits cooperate while controlling locomotion. Almost 70 years later, Mori and colleagues [62] provided convincing evidence of crucial importance of muscular tone for gait. They showed that brainstem evoked locomotion in the cat must be preceded by an increase in postural muscle tone. These findings clearly demonstrated that postural control and locomotor control are not separate phenomena [50]. Finally, a certain level of pharmacological or sensory stimulation may generate locomotor movements when the limbs are placed on the moving treadmill belt and exert a certain level of postural and load-related sensory activity, while this stimulation is not sufficient to induce locomotor movements of suspended hindlimbs [9].

Pre-existing postural automatisms can also be influenced by muscle tone. For instance, tonic neck reflexes are typically not visible or are very weak in healthy adults under normal conditions [63]. However, there are situations in which neck influences in humans become prominent if there is increased tonic readiness: *i.e.*, in newborns, in adults after extensive cortical lesions, during the early stage of narcosis, during fatigue, etc. [64-68]. Considering that complex postural mechanisms participate in the maintenance of equilibrium and upright body orientation during locomotion, the state of the muscle tone may affect its various characteristics and control circuits. For instance, it may affect not only the 'steady-state' locomotor patterns (*e.g.*, frequently observed abnormal toe-walking in children with cerebral palsy due to enhanced extensor tone) but also specific correcting muscle synergies or postural responses incorporated into the basic locomotor program, walking along a curved path [69] and gait asymmetries.

## 3. TONIC ACTIVATION OF THE SPINAL CORD

In this section, we will review various findings related to non-specific activation of the spinal circuitry that can facilitate the manifestation of locomotor automatisms (rhythmogenesis) in humans. They corroborate earlier observations that a simple tonic stimulation applied to the mesencephalic locomotor region in the decerebrate cat can induce stepping at different speeds depending on the stimulation intensity [70], but they also extend this type of control to the lumbosacral spinal cord level attributable to its tonic excitability [4,71].

### 3.1. Tonic sensory input

Proprioceptive sensory input has various functions in the control of gait: it controls the timing of major gait cycle phase transitions, may mediate error signals in the control of limb coordination and contributes to the pre-programmed motoneuronal drive [59,72]. It is also worth noting that descending central motor commands and the input from peripheral sensory afferents are integrated at the level of common spinal interneurons [60]. Another key feature of the interneuronal networks is a semi-random distribution of inputs and a wide variety of possible interactions within and between different populations of neurons [1,10,34]. Consequently, along with the control of the timing of the gait cycle phases and of the degree of muscle activity, sensory input has access to the functional state of the spinal cord and may generate coordinated locomotor responses [4,71,73]. For instance, in the decerebrate cat, electrical stimulation of the dorsal roots may induce stepping movements [73].

A variety of sensory stimulation techniques have been explored for eliciting or facilitating rhythmic limb movements in humans: continuous vibration (40-60 Hz, ~1 mm amplitude) of one or several muscles [4], electrical stimulation of the superficial sural, tibial or peroneal nerves (60 Hz, 0.3 ms pulses, 2-3 mA) [74] and applying an additional load to the foot sole [74,75]. Muscle vibration elicits a powerful stimulation of predominantly Ia muscle spindle afferents (and other afferents as well, though to a lesser extent, [76]), while peripheral peroneal, tibial or sural nerves contain cutaneous afferents from specific innervation areas at the foot [77]. Stimulation of peripheral receptors and nerves either mechanically or electrically augments the afferent flow, which is spread to several segments of the spinal cord, and their enhanced excitability level may in turn result in CPG activation and the appearance of locomotor-like responses. Furthermore, tonic peripheral stimulation may cause plateau potentials in the spinal neurons giving rise to involuntary muscle forces or facilitating motoneuron activation [78].

To diminish interference with maintaining body weight and balance control, stepping movements can be eased under conditions of the lack of gravity influences and minimized external resistance, *i.e.*, during air-stepping. A facilitatory effect of simulated weightlessness on rhythmogenesis has been demonstrated in both quadrupedal animals [79] and humans [71,74,80], and, in general, air-stepping promises to be an important paradigm for investigating rhythmogenesis in both human and animals, developing central pattern generator-modulating therapies and pharmacological studies [79,81-83].

Figure **2A** illustrates an example of cyclic movements of the suspended legs elicited by continuous electrical stimulation of the sural nerve [74]. The subject was asked to relax and not to intervene with movements that might be induced by peripheral stimuli. Moreover, when the subject performed mental arithmetic (counting backward) to minimize attention to leg movements, their oscillations were typically similar or even increased [74,84], making it unlikely that they were attributable to voluntary drive. Typically, the amplitude and the frequency of rhythmic movements increased monotonically for several cycles following the onset of stimulation then reached a relatively constant level and could be sustained provided that the stimulation continued. The amplitudes of hip and knee joint oscillations were about 20-70° (Fig. **2A**), while movements in the ankle joint were minute if any during involuntary air-stepping. The pattern of interjoint coordination was similar to that when the subject was asked to perform voluntary air-stepping [4]. The stepping movements could be evoked by stimulation of various muscles of the leg or peripheral nerves [74].

The lack of involvement of the ankle joint in involuntary air-stepping (Fig. **2A**) is consistent with the idea of the predominant ('pacemaker') role of the upper lumbar pattern generator, whereas the sacral generator may constitute a subordinator oscillator that adapts to foot loading and depends on foot-support interactions [81,85]. Indeed, load-related sensory activity (Golgi tendon organs, muscle spindles, cutaneous receptors, mechanoreceptors in the foot arch) significantly contributes to motoneuronal drive of the distal extensors during locomotion [72,86], also in individuals with clinically motor complete paralysis [87]. In the absence of this sensory input, both extensor muscle activity and accurate control of foot trajectory are missing unless minimal interaction with the support surface during air-stepping is provided [74,88].

In sum, even though the functional tonic sensory stimulation touches upon only a small part of the total peripheral sensory nerve fibers (as compared, for instance, to the direct electrical stimulation of the dorsal roots), still it may noticeably contribute to the excitation level of the spinal cord circuitry and evoke involuntary rhythmic leg movements.

### 3.2. Postcontraction Activity (Kohnstamm Phenomenon)

Given the conceptual framework for the role of the tonic input (Fig. **1**) and powerful connections from tonogenic brain structures onto the spinal cord [45], it may not be so surprising that the state of the CPG circuitry can be affected by central tonic influences. Among approaches that change the excitatory level of spinal motoneurons one can use remote muscle activation (*e.g.*, Jendrassik

maneuver) or postcontraction facilitation of muscle activity (Kohnstamm phenomenon). Such central tonic facilitatory influences may elicit or assist rhythmogenesis and lower limb oscillations in humans [74]. The Jendrassik maneuver (voluntary isometric contraction of extensors of both arms against each other) has been previously used to facilitate leg muscle reflexes [89] and rhythmic movements [74] though per se it does not evoke rhythmic stepping. Voluntary arm contractions (Jendrassik maneuver) are less efficient for inducing stepping responses since they act primarily on the cervical enlargement of the spinal cord. A particularly interesting effect related to the appearance of tonic involuntary leg muscle activity of presumably subcortical origin is the Kohnstamm phenomenon that we consider here.

The classic Kohnstamm phenomenon consists of the appearance of involuntary postcontraction muscle activity after the cessation of a long-lasting (tens of seconds) strong isometric effort [90]. This involuntary muscle activity is also accompanied by a strong feeling of "lightness". It provides an interesting experimental model for modifying temporarily an excitatory state of neuronal circuits that can last for more than half a minute [55].

In static conditions, involuntary postcontraction activity is often observed in the muscles being activated during the voluntary effort (*i.e.*, in the preconditioned muscles). However, in conditions of unrestricted leg movements and reduced external resistance (air-stepping), it may induce the transition of the CPG circuits to the active state. We used one of its variations by asking participants to exert a strong isometric effort in the anterior-posterior direction for 30 s of one leg against another one [74]. It is worth noting that the direction of the isometric contraction differed between limbs (flexor for one limb, extensor for the other). Immediately after the termination of the voluntary effort the research assistant released both legs allowing the manifestation of involuntary responses in leg muscles and/or leg movement. Figure **2B** illustrates an example of the observed alternating leg movements due to the postcontraction aftereffect in one subject. Typically, leg oscillations started within a few seconds after the cessation of voluntary muscle activity, the amplitude and frequency of leg motion first augmented, reached a steady-state level and then diminished. Contrary to application of the tonic sensory input, when cyclic movements persisted as long as sensory stimulation continued (see the previous section 3.1), in the case of the postcontraction after effect the duration of cyclic movements normally did not exceed 20-40 s (*e.g.*, Fig. **2B**), corresponding to a limited interval for manifestation of the Kohnstamm phenomenon [91].

The Kohnstamm generator is assumed to reflect a property of the central "tonogenic" neuronal structures to maintain long-lasting activation states though the opinions about the exact physiological mechanisms remain controversial (for review see [91,92]. Even though the "residual" sensory activity after the cessation of voluntary effort may take place [93,94], purely peripheral factors such as thixotropic properties of muscle proprioceptors [94,95] can unlikely explain continuous rhythmic movements since the aftereffect would be expected to disappear after one or two cycling leg movements during air-stepping (as thixotropy of both extrafusal and intrafusal muscle fibers substantially declines following muscle lengthening or shortening, [96]). Furthermore, there are other arguments in sup-

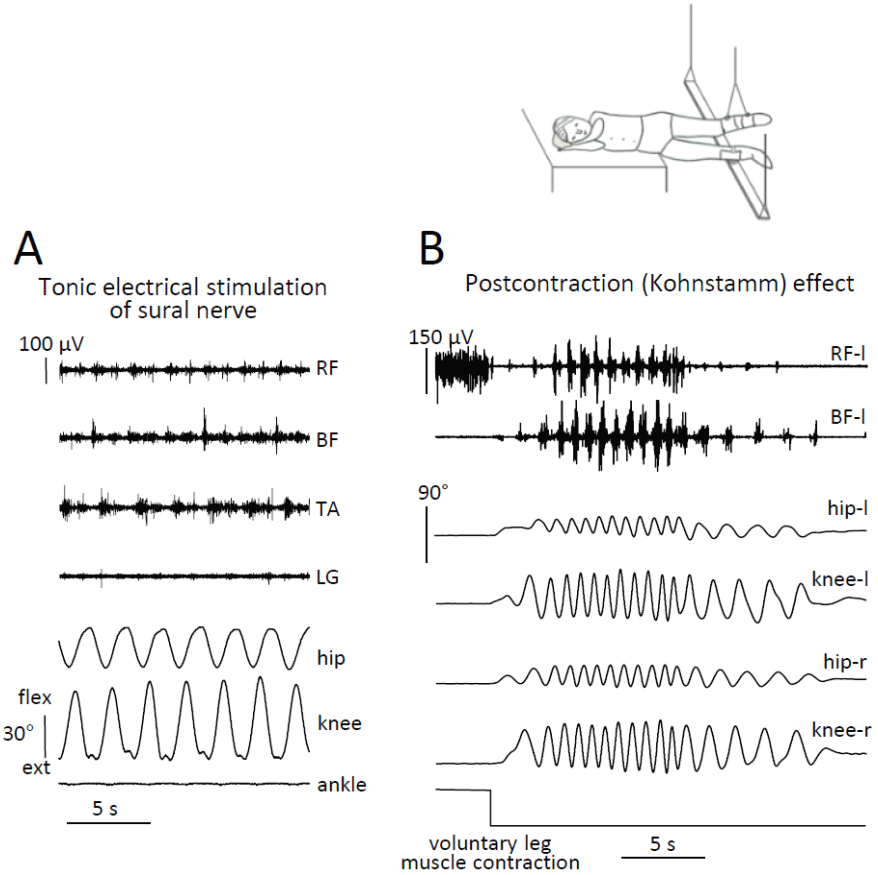


**Fig. (2).** Eliciting involuntary rhythmic leg movements in simulated weightlessness conditions (adapted from [74]). A - example of cyclic leg movements induced by electrical stimulation of the sural nerve. Note the lack of motion in the ankle joint. B - example of Kohnstamm-evoked lower limb air-stepping: appearance of involuntary alternating leg movements following long-lasting (~30 s) isometric voluntary leg muscle contraction (left leg exerted an effort in the forward direction and the right leg backward). LG - lateral gastrocnemius, TA - tibialis anterior, BF - biceps femoris,, RF - rectus femoris, l - left, r - right.

port of the central origin of the Kohnstamm phenomenon: the delayed (~1 s) onset of EMG activity after passive stretching [91], the ability to trigger or switch involuntary motor aftereffects to not-preconditioned muscles (*e.g.*, antagonists or even remote muscles) depending on postural conditions [55,93], or to evoke an involuntary arm lift when imagining the voluntary effort [91]. It has even been argued that the Kohnstamm command may also originate upstream of the motor cortex, since the silent period in EMG activity is present during both involuntary (Kohnstamm-evoked) and voluntary muscle contraction in response to transcranial magnetic stimulation of the human motor cortex. [92]. The neurophysiological substrates may comprise spinal circuitry (interneurons and motoneurons), increased input from peripheral sensory nerves and supraspinal structures [55,69,92,93].

Whatever the exact mechanism, it is important to note that long-lasting central motor commands underlie the Kohnstamm phenomenon [92], and this has been used for changing the state of the neuromuscular system and the locomotor circuitry [4,74]. In the clinical practice these maneuvers may represent a tool to probe the state and the responsiveness of CPG circuitry to its tonic activation in individual subjects [81].

### 3.3. Electromagnetic Stimulation of the Spinal Cord

In animals, intraspinal or epidural electrical stimulation applied to the spinal neural networks has been extensively used to assess their functional organization and can result in both locomotor and postural improvements after a complete spinal cord transection in animals (*e.g.*, [97-100]). In humans, the techniques for modulation of the physiological state of the spinal circuitry may include both non-invasive and invasive electromagnetic stimulation. The non-invasive methods involve direct stimulation of the spinal cord using electromagnetic [71] or transcutaneous electrical stimulation [101-103]. In the former case, electromagnetic spinal cord stimulation is provided by the magnetic impulses using a coil placed over the lower thoracic (T11-T12 or T12-L1) or upper lumbar (L1-L2 or L2-L3) vertebrae [71], while in the latter case, transcutaneous electrical stimulation of the spinal cord is delivered using pairs or array of electrodes placed midline or laterally on the skin at the T11-L1 spinous processes [101-103]. The invasive techniques include epidural electrical stimulation of the spinal cord. In this case, the researchers use an implanted array of electrodes directly placed over the back portion of the upper lumbar - lower thoracic spinal cord, typically below a paralyzing injury of individuals with spinal cord lesion [9,104,105].

Current understanding of the neuronal substrates is that electromagnetic spinal cord stimulation primarily activates large-to-medium-diameter sensory fibers within the dorsal roots and then trans-synaptically interneuronal circuits targeting the lumbar spinal cord [106]. It may activate CPG circuitry and initiate locomotor responses more robustly than by stimulation of peripheral afferent fibers (see section 3.1) since it can stimulate the larger number of sensory fibers. Using appropriate stimulation parameters (amplitude and/or frequency modulation), one may trigger or facilitate both postural and locomotor responses in leg muscles in humans [104,105,107]. Using multi-site spinal cord stimulation and modifying the exact location of the stimulating electrodes or their temporal activation sequence, one may alter the relative amplitude and phase of oscillations in different lower limb joints [104,108], in line with the idea that there might be individual relatively autonomous CPGs for each joint or each limb [25]. It is also worth noting that the more direct spinal cord stimulation, as opposed to peripheral tonic sensory stimulation (see section 3.1), often induces movements in the ankle joint during air-stepping [71], likely because posterior roots' stimulation comprises load-related afferents to a greater extent. Nevertheless, even though the cite of stimulation has an effect on the motor output, one should keep in mind that it is still dispersed and involves trans-synaptically various reflex pathways and interneuronal structures, which participate in a wide range of possible movements.

Tonic stimulation alone may lead to the production of rhythmic activity. Normally, 'tonic' is associated with non-patterned prolonged stimulation with unlimited parameters. However, the type of tonic stimulation and its parameters are also important. Indeed, electrical stimulation of the lumbar spinal cord may evoke a wide spectrum of motor reactions, from short-latency responses in muscles to bilaterally alternating flexor-extensor activity [104]. For example, at high frequencies of stimulation, the frequency of locomotor-like stepping responses in paraplegic patients was independent of the stimulus frequency and rhythmic movements were continuing for a number of cycles after the cessation of stimulation, whereas at lower frequencies of stimulation (3-12 imp/s), the "reflexogenic stepping" could be coupled to the stimulus frequency and ended with the end of stimulation [101]. Altering spinal cord excitability may also help regaining voluntary movement and stand training in sensory incomplete spinal cord injury individuals [107].

It should also be noted that not all (neurologically intact or spinal cord injured) participants exhibit involuntary limb oscillations in response to tonic stimulation of the spinal cord. As stressed by Sten Grillner [7], "if CPGs invariably produced rigidly fixed action patterns, animals would behave like automata - stereotypic robots or soldiers in a parade." As a matter of fact, CPG functioning and output depend on diverse modulatory influences and display also a great amount of individual adjustments (to specific anthropometric data, style of walking, gender differences, etc.), providing a large flexibility in the control of movements. Involuntary CPG activity is not easily demonstrated in fully conscious subjects, thereby explaining why some of the evidence was not seen for all participants [71,74]. The degree to which diffuse tonic input can imitate the 'locomotor' state of the spinal cord requires further investigations given the impact of various modulatory influences and the multiple function of the same spinal interneurons. Nevertheless, it is remarkable that various types of tonic stimulation may elicit or facilitate rhythmic activity in both neurologically intact or spinal cord injury individuals.

Spinal cord stimulation has been used for a long time for testing and regaining motor function in spinal cord injury, and such studies accumulated evidence for CPG circuits residing in the spinal cord of humans [101,105,106]. Current research aims at advancing our understanding of the spinal control of limb movements in humans, searching for optimal spatiotemporal parameters of stimulation in both monopolar and bipolar configurations, optimal stimulation of circuits belonging to both postural and locomotor lumbosacral networks and using a multi-electrode array technology for multi-site spinal cord stimulation [108].

Thus, the usage of spinal cord stimulation for investigating and modulating the state of the spinal circuitry is not limited only to the basic research but has also significant clinical implications for regaining motor control even after a severe spinal cord injury and also in combination with other pharmacological interventions, step-synchronized load-related sensory stimulation and locomotor training [5].

### 3.4. Neuromodulators

The neurotransmitters and neuromodulators involved in the regulation of locomotor neuronal networks comprise various (tens) neurochemicals, including 5-hydroxytryptamine, N-methyl-D-aspartate, dopamine, noradrenaline and cholinergic agonists. Different descending command pathways are associated with different transmitters, as well as their action and duration differ. We refer to other reviews for a detailed description of numerous examples of pharmacological manipulations using the isolated neonatal spinal cord as an experimental model to study the efferent patterns during fictive locomotion or under *in vivo* conditions ([8,9], see also companion papers of Guertin and Radhakrishna and colleagues).

The neurotransmitters that support interlimb coordination may differ. For instance, contrary to the hindlimb facilitation mechanisms in the cat, the forelimb facilitatory effect on hindlimb stepping is attributed to non-5-HT receptor-dependent pathways [109]. The exact neurotransmitter systems and pathways mediating forelimb-facilitated stepping of the hindlimbs are not identified yet. Cholinergic systems seem to contribute to the coordination and rhythmic coupling of limb movements since blocking cholinergic transmission disrupts the coordination between the cervical and lumbar spinal cord rhythmic activity [110]. Noradrenergic [111], glutamatergic [112], GABAergic, or glycinergic [113] neurotransmitter systems may also support interlimb coordination.

Regarding the topic of our review, it is important to note that the level of excitability of the sensorimotor circuitry can be induced pharmacologically. Modulating the excitation level via glutamatergic, noradrenergic, dopaminergic, and serotonergic neurons can facilitate locomotor movements or may well initiate rhythmic activity in isolated spinal cord preparations [8].

The neurotransmitter systems that mediate spinal locomotion undoubtedly involve multiple neurotransmitter systems and, in particular, serotonergic receptors play an essential role [8]. The descending serotonergic pathways in the rostral compartments of the lumbar spinal cord seem to act on neurons involved in the rhythm-generating function while caudal compartments are consistent with their influence on the recruitment of motoneurons [114]. The above-described effects and posteffects of tonic stimulation (see sections 3.1-3.3) are related to modification of the physiological state of the spinal neuronal circuitry, which can comprise the action of neuromodulators. For instance, in addition to the contribution of peripheral and central networks to the Kohnstamm phenomenon (Fig. **2B**), prolonged excitation of spinal motor circuits after a long-lasting voluntary effort may be mediated by serotonin through a long-lasting modulation of plateau properties at the cellular level [115]. Serotonin is known to have a critical role in shaping the locomotor pattern.

Pharmacological modulation of the state-dependency of neuronal circuits represents a promising approach for enabling locomotion. When the researcher attempts to neuromodulate the physiological state of the spinal circuitry by means of epidural electrical stimulation or pharmacological treatment of the spinal cord aimed at performing central pattern generator-modulating therapies [13], he/she should bear in mind their diffuse nature and a potential effect on various elementary interneuronal spinal networks [10]. Future research will focus on how these treatments can tune the physiological state of the spinal cord to activate the CPG circuitry and to respond appropriately to proprioceptive input and provide the control of both posture and locomotion [9].

## 4. CERVICAL AND LUMBOSACRAL HUMAN SPINAL CORD TONIC ACTIVATION

An interesting aspect of human bipedal gait is that humans use elements of quadrupedal neuronal limb control related to both preservation of evolutionary-adopted ancestral neural CPG circuitry of animal gait [116] and biomechanical benefits of arm-trunk-leg coordination [117,118]. For instance, despite the fact that human walking is bipedal, step-synchronized activity in both proximal and distal muscles is often present in many natural locomotor-related tasks - walking, running, swimming, rowing, cycling, climbing, crawling, skiing, obstacle avoidance, etc. The idea of quadrupedal coordination in human locomotion is also supported by modulation of cross-limb reflexes and sharing many features with hind- and forelimb coordination in mammals, though the coupling between the limbs is weaker in humans.

In animals, the cervical and lumbosacral segments of the spinal cord contain CPG circuitries that coordinate the locomotor movements of the forelimbs and hindlimbs, respectively. Both ascending and descending connections between lumbosacral and cervical pattern generating oscillators have been characterized in quadrupedal animals. In humans, the major support for the neural coupling between the lower and upper limbs comes from the modulation of cross-limb reflexes. However, the occurrence of upper limb muscle activity during bipedal walking and phase-specific interlimb reflex modulation may not imply that the cervical enlargement *per se* possesses an ability of rhythmogenesis, since normally its functioning might be driven or at least complemented by lumbosacral CPG activity. Still, it is reasonable to suggest that the cervical spinal cord may possess an ability of sustaining rhythmic activity also in humans, considering automatism of rhythmic upper limb movements in locomotor-related activities in adults (walking, running, swimming, rowing, cycling, climbing, etc.) and developmental data in babies (infant crawling [119]).

It is problematic to study the putative cervical CPG in humans in isolation (especially by invasive methods). Nevertheless, one may explore various types of stimulation and investigate the conditions for inducing involuntary arm oscillations with reciprocal muscle activity, *e.g.*, by applying tonic sensory or central inputs. Recently, such stimulation has been explored in conditions of simulated weightlessness to investigate rhythmogenesis in the upper limbs in humans [84]. Both arms and legs were suspended in air that eliminated the effect of gravity on the limbs (Fig. **3A**, upper panel). Interestingly, stimulation using tonic sensory inputs or the Kohnstamm maneuver could elicit not only cyclic lower limb movements (when it was applied to the legs) but also arm oscillations (when it was applied to the upper limbs). In the latter case, cyclic arm movements could be observed either in isolation or together with lower limb oscillations [84]. Figure **3A** illustrates Kohnstamm-evoked cyclic arm oscillations in a gravity neutral position for ~30 s following the cessation of the preceding voluntary arm muscles' contraction.

It has also been demonstrated that, in animals, hindlimb stepping movements can be initiated by activating cervical CPG circuitry and by performing forelimb stepping [120-122]. Similar facilitatory effects can be observed in humans. Figure **3B** illustrates an example of involuntary cyclic leg movements induced during hand walking [80]. Furthermore, it has recently been demonstrated that transcutaneous electrical stimulation of the human cervical spinal cord *per se* does not evoke rhythmic leg movements but it may considerably facilitate involuntary leg movements evoked by other stimuli [108], as well as upper limb movements are able to potentiate muscle drive of the lower limbs during recumbent stepping [123]. Finally, even though it is often assumed that the contribution of the proximal arm muscles is major during normal bipedal human walking, the involvement of the distal arm muscles in cyclic movement production and coordination is also suggested considering their active participation in many locomotor-related tasks (crawling, running, skiing, and so on). For instance, rhythmic wrist flexion-extension movements potentiate lower limb air-stepping and the soleus H-reflex [124]. New insights into the role that the rhythmogenesis capacity of the cervical human spinal cord plays in neurological injuries may have various clinical implications to assist and improve the lower limb locomotor output in both paretic and nonparetic legs and for neurorehabilitation of the locomotor function in gait pathologies that disrupt inter-limb coupling [125].

## 5. DISTURBANCIES OF POSTURAL TONE AND RHYTHMOGENESIS OF THE SPINAL CIRCUITRY

Elucidating the neural mechanisms for locomotor control is a key to developing novel and more effective rehabilitation systems. The use of such techniques spans from diffuse spinal cord stimulations [2,74,104,105,107] to more addressed effects (*e.g.*, by modulating specific spinal cord reflexes [126]). There are methods available now which allow one to obtain information of the neural circuitries involved in locomotion (reflex studies, transcranial magnetic stimulation, EEG-EMG coherence, etc.) and their impairment

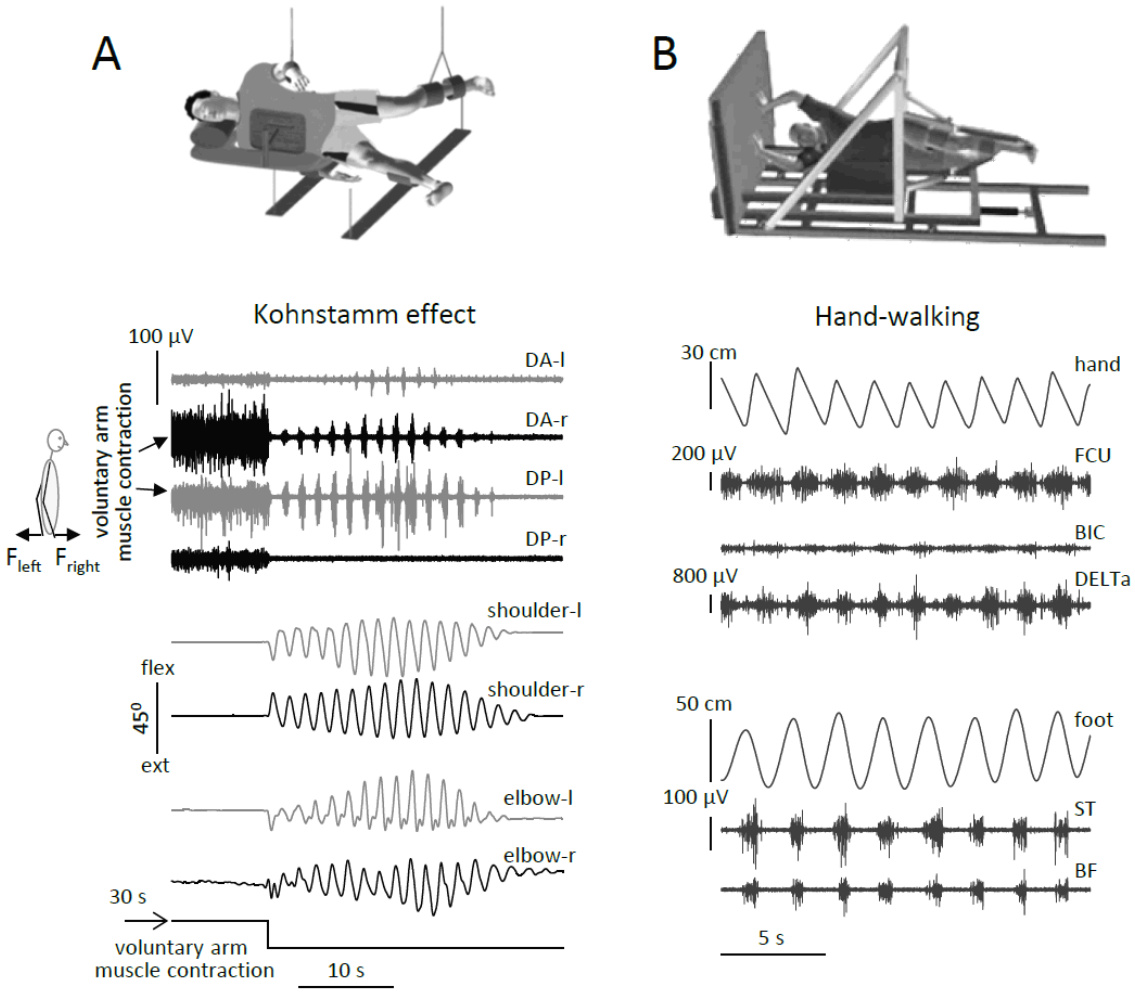


**Fig. (3).** Eliciting involuntary upper and lower limb stepping-like movements under conditions of simulated weightlessness (suspended limbs). A - example of involuntary (Kohnstamm-evoked) alternating cycling upper limb movements following the termination of long-lasting (30 s) isometric voluntary effort (right limb applied the force forward and left limb backward - see left drawing). Both arms and legs were suspended in air that eliminated the effect of gravity on the limbs. Involuntary rhythmic movements could be observed for ~30-40 s following the cessation of voluntary muscle contraction (adapted from [84]). B - example of involuntary cyclic lower limb movements during hand walking (adapted from [80]). Legs were suspended using a low-friction exoskeleton. Anterior-posterior motion of the (left) hand and foot is shown. Note slightly different rhythm (frequency) of arm and leg oscillations. DP - posterior deltoid, DA (and DELTa) - anterior deltoid, BF - biceps femoris, ST - semitendinosus, BIC - biceps brachii, FCU - flexor carpi ulnaris, l, left, r, right.

in various populations of patients. While such techniques allow to probe the excitatory state or conductivity of specific pathways, they rarely consider an integrative view on the complexity of postural and locomotor control.

The physiological state of the spinal cord and interactions of CPG circuitry with other elementary spinal networks may be significantly affected by impairments in postural tone. An increased muscle tone may have both positive (*e.g.*, for interpreting afferent inputs during stepping in complete spinal cord injury patients [87,127]) and negative (*e.g.*, tremor, spasticity, rigidity, etc.) impacts on motor behavior. The spinal cord also comprises various circuits for the postural reflexes, originating from the somatosensory inputs from the limb mechanoreceptors [128-131]. In intact animals, these reflexes may be modulated due to both tonic and phasic supraspinal drive [132]. The remarkable findings of the British neurologist James Purdon Martin (described in his well-known book "The Basal Ganglia and Posture" [49]) provide excellent examples of disturbances to postural tone in humans and their consequences on the ability to perform movements. As we argue in this review, an appropriate postural tone is an integral part of the control of locomotion. As an example, stimulating internal globi pallidi (by means of a chronic electrode implantation) in Parkinson disease (PD) patients results in quasi-parallel changes of the upper trunk orientation and gait performance, suggesting that the basal-ganglia circuitry may provide an appropriate tuning and common framework for the control of posture and movement [133].

If the rhythmogenesis spinal cord capacity is compromised by disease, the supraspinal control may interfere with the normal functioning of the spinal circuitry or it may be involved to a larger extent to cope with impaired sensorimotor neuromodulation at the spinal cord level. For instance, in patients with Parkinson's disease, tonic central and sensory influences had little effect on leg movement rhythmogenesis, contrary to eliciting involuntary stepping-like responses in healthy individuals [134]. These findings point to the impaired tonic state of the CPG circuitry in PD. This complex disease is primarily associated with a loss of dopaminergic neurons in the substantia nigra, but it involves several regions of the central nervous system including the spinal cord. A recent study on direct electrical stimulation of the spinal cord [135] supports the observed failure to evoke involuntary rhythmic leg oscillations in PD in a

gravity neutral position [134]. In contrast to effective CPG activation and gait improvement in individuals after spinal cord lesions [9,101], the epidural electrical stimulation of the dorsal columns failed to restore locomotion in PD patients [135]. All these observations are consistent with the idea of impaired CPG access by central and sensory activations in patients with PD, in addition to impairments in supraspinal regions. These findings also corroborate previous observations on impairments in muscle tone [54,136] and sensory feedback [137-140], suggesting that the physiological state of the spinal network is indeed affected in PD.

A disruption of the habitual distribution of postural tone may even have direct consequences on the bipedal human gait. For instance, cases of human quadrupedalism, first reported by Muybridge [141], documented 'quadrupedal humans' walking on all four limbs. It is important to note though that many individuals with disorders of posture (*e.g*., who have camptocormia [40]) are capable of upright standing and upright walking, if they consciously concentrate on standing upright, though the preferred unconscious posture and gait are quadrupedal. Thus, those locomotor disturbances are associated largely with an automatic (rather than voluntary) regime of the control of posture and gait. Indeed, human quadrupedalism is a behavior that may be caused by adaptive processes triggered by disorders in postural tone [40]. Therefore, it is important to get further insights into how postural tone is generated and controlled.

## CONCLUSION

Overall, the large body of evidence supports the notion that tonic and rhythmic spinal activity control are not separate phenomena but are closely integrated. The concepts of 'readiness for movement' [56], or the 'lock with two keys' hypothesis [52], or neuromodulation of the 'physiological state' of the spinal circuitry [9], all emphasize an important role of tonic influences to maintain network stability and to activate central pattern generation circuitry for performing automatic stepping movements. Furthermore, a facilitatory effect of simulated weightlessness has its potential for promoting movement rhythmogenesis and evaluating the state of the central pattern generator circuits in injured populations [81, 108].

Nevertheless, caution is required when generalizing the effects to other conditions or comparing the rules for eliciting involuntarily (pharmacologically or by means of sensory stimulation) and centrally initiated stepping movements. First, the motor cortex plays a more important role in human locomotion than in animals [142,143]. Second, the spinal reflexes in the two cases can be differentially affected. For instance, the amplitude of motor evoked potentials in response to transcranial magnetic stimulation of the motor cortex and the soleus H-reflex is substantially smaller during involuntary stepping responses [83]. Greater responsiveness of the spinal cord during voluntary stepping [83] supports the idea of active engagement of supraspinal motor areas for promoting locomotor movements and developing CPG-modulating treatments [2]. Novel pharmacological and neuromodulator stimulations are being developed to restore lumbosacral circuit function in humans and primates [5,13,144] with the hope that a part of the applied stimuli is targeted at the central pattern generator circuitry. In fact, how these pharmacological interventions or tonic central and peripheral stimulation procedures imitate the intrinsic locomotor state of the spinal cord represents a fascinating avenue for future research and a clinical translational pathway.

## LIST OF ABBREVIATIONS

CPG = central pattern generator

PD = Parkinson disease

SCI = spinal cord injury

## CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

## ACKNOWLEDGEMENTS

The authors gratefully acknowledge funding by the Italian Ministry of Health (IRCCS Ricerca corrente), Italian Space Agency (COREA grant 2013-084-R.0), grants #15-04-02825 and 16-29-08181 of the Russian Foundation of Basic Research, and Horizon 2020 Robotics Program (ICT-23-2014 under Grant Agreement 644727-CogIMon). The authors also thank Dr. Vittorio Caggiano for the comments on some points discussed in this article.

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