J Neurophysiol 120: 53–77, 2018.
First published March 14, 2018; doi:10.1152/jn.00554.2017.

REVIEW | *Central Pattern Generators*

Sherlock Holmes and the curious case of the human locomotor central pattern generator

Taryn Klarner[1,2,3] and E. Paul Zehr[1,2,3,4]

[1]*Rehabilitation Neuroscience Laboratory, University of Victoria, Victoria, British Columbia, Canada;* [2]*Human Discovery Science, International Collaboration on Repair Discoveries, Vancouver, British Columbia, Canada;* [3]*Centre for Biomedical Research, University of Victoria, Victoria, British Columbia, Canada; and* [4]*Division of Medical Sciences, University of Victoria, British Columbia, Canada*

Submitted 25 July 2017; accepted in final form 11 March 2018

Klarner T, Zehr EP. Sherlock Holmes and the curious case of the human locomotor central pattern generator. *J Neurophysiol* 120: 53–77, 2018. First published March 14, 2018; doi:10.1152/jn.00554.2017.—Evidence first described in reduced animal models over 100 years ago led to deductions about the control of locomotion through spinal locomotor central pattern-generating (CPG) networks. These discoveries in nature were contemporaneous with another form of deductive reasoning found in popular culture, that of Arthur Conan Doyle's detective, Sherlock Holmes. Because the invasive methods used in reduced nonhuman animal preparations are not amenable to study in humans, we are left instead with deducing from other measures and observations. Using the deductive reasoning approach of Sherlock Holmes as a metaphor for framing research into human CPGs, we speculate and weigh the evidence that should be observable in humans based on knowledge from other species. This review summarizes indirect inference to assess "observable evidence" of pattern-generating activity that leads to the logical deduction of CPG contributions to arm and leg activity during locomotion in humans. The question of where a CPG may be housed in the human nervous system remains incompletely resolved at this time. Ongoing understanding, elaboration, and application of functioning locomotor CPGs in humans is important for gait rehabilitation strategies in those with neurological injuries.

INTRODUCTION AND BRIEF BACKGROUND ON CENTRAL PATTERN GENERATORS IN OTHER ANIMALS

> "The scientist, if he is to be more than a plodding gatherer of bits of information, needs to exercise an active imagination. The scientists of the past whom we now recognize as great are those who were gifted with transcendental imaginative powers, and the part played by the imaginative faculty of his daily life is as least as important for the scientist as it is for the worker in any other field—much more important than for most. A good scientist thinks logically and accurately when conditions call for logical and accurate thinking—but so does any other good worker when he has a sufficient number of well-founded facts to serve as the basis for the accurate, logical induction of generalizations and the subsequent deduction of consequences." (Pauling 1943).

> "Data! Data! Data!" he cried impatiently. "I can't make bricks without clay."
>
> "The Adventure of the Copper Beaches" in *The Adventures of Sherlock Holmes* (Sir Arthur Conan Doyle, 1892)

INTRODUCTION

Central pattern generators (CPGs) for walking are neuronal networks that produce rhythmic activation of muscles that control the limbs. There is a wealth of data to support the existence of spinal locomotor CPGs in other animals but very little direct evidence for CPGs in humans. In reduced animal models, direct recordings can be taken, giving indisputable evidence for the structure and function of CPGs in generating rhythmic movements. In humans, the experimental techniques needed to definitively confirm parallel observations are invasive and thus not feasible or ethical to perform. Therefore, we must rely on indirect evidence and inference—the process of logical deduction—to assess the contributions of CPGs in rhythmic human movements. The exact locations of the CPG networks, how many there may be, and how they are coordinated remains beyond the scope that our methodologies can reveal. Thus, in this review, we use the term CPG as an umbrella term encompassing one or many distributed CPG networks.

Address for reprint requests and other correspondence: E. P. Zehr, Rehabilitation Neuroscience Laboratory, PO Box 3010 STN CSC, University of Victoria, Victoria, BC, Canada V8W 3P1 (e-mail: pzehr@uvic.ca).

Over a century ago, Sir Charles S. Sherrington (1857–1952) discovered that rhythmic movements could be evoked by connections intrinsic to the spinal cord (Sherrington 1906). In decerebrate cats and dogs with full cervical transections, electrical and mechanical stimulation of the skin elicited repetitive, stereotyped, and automatic hip and knee movements that produced rudimentary stepping. Sherrington noted that the rhythm of the response was highly modifiable by peripheral feedback. As stimulus intensity increased, movement amplitude and the number of cycles increased, whereas onset latency decreased. From these observations, it was clear that the spinal cord was capable of producing a rhythm; however, Sherrington originally concluded that locomotor-like movements were of peripheral origin. He thought that the crossed extension reflex, involving ipsilateral flexion and contralateral extension, could be responsible, where one movement would elicit the next successive movement (Sherrington 1910).

Thomas Graham Brown (1882–1965), another pioneer in the field and a student of Sherrington's, made related observations of rhythmic movement using decerebrate cats with thoracic spinal cord transection. Unlike Sherrington's models, these animals were also deafferented by cutting the afferent nerves from the hindlimb muscles. With the animals under general anesthesia and lying on one side, tonic electrical and mechanical stimulation caused stepping movements in the hindlimbs. Brown recorded bursting in alternating pairs of antagonist muscles in the hindlimbs that occurred not only without higher level input from the brain, but without sensory input. From this observation, it was clear that something intrinsic to the spinal cord was responsible for generating patterned locomotor activity (Brown 1911). Thus Brown extended Sherrington's original observations to state that locomotor rhythms are not of peripheral origin but that a "mechanism confined to the lumbar part of the spinal cord is sufficient to determine in the hindlimbs an act of progression" (Brown 1911, p. 308).

From this, Brown (1911) proposed and developed the widely accepted "half-centre model." This model describes the essential structural design of a CPG and how it oscillates to produce the basic rhythm and pattern for stepping. Although this model has not been definitively demonstrated in all vertebrates, it is certainly a popular and useful model to describe how CPGs are structured. In the model, each half-center consists of two groups of spinal neurons that individually have no rhythmogenic ability. Activity in the first group of neurons (e.g., extensor half-center) sends commands to motoneurons to excite extensor muscles while simultaneously inhibiting the reciprocal group of neurons in the flexor half-center. Brown proposed that due to some "fatigue" mechanism, the firing in the active extensor half-center slowed, releasing the opposing flexor half-center from inhibition, and then the flexor half-center would predominate for a new phase of activity such that the pattern continues. It is important to note that Brown was not able to directly measure the activity from interneurons involved in his CPG model. Instead, he used logical deduction to lead to the conclusion that mechanisms intrinsic to the mammalian spinal cord were contributing to the locomotor pattern.

These early observations of Sherrington and Brown at the beginning of the 20th century opened a new line of research and altered thinking about the spinal cord and its intrinsic capacity for producing movement (Brown 1914). Despite this, there was a long pause in research, and decades passed before this work was investigated further. It was not until the 1960s and onward that the foundational work would be supported and extended. It was with the advent of new technologies that the cellular and neural mechanisms involved in CPG activity could be uncovered. For example, the development and application of intracellular recordings in the 1960s provided the first evidence to support Brown's idea of half-center activity. By electrically stimulating high-threshold cutaneous and muscle afferents (so-called "flexor reflex afferents"), short sequences of alternating rhythmic activity in flexor and extensor motoneurons were recorded (Jankowska et al. 1967). This revealed the ways in which spinal CPGs could serve as the basic building blocks of the circuitry required for locomotion.

Since the 1980s, various molecular, genetic, pharmacological, and imaging studies have been conducted to understand and determine the localization and organization of the cellular and neural substrates for the locomotor CPG (Grillner 1975; Kiehn and Butt 2003; Kiehn and Kjaerulff 1998). Electrophysiological recordings have revealed neuronal activity and cellular components all the way down to the level of a single spinal neuron (Ayers et al. 1983). To explain how an ensemble of spinal cells can elicit rhythmic motor patterns in the absence of supraspinal control or external feedback, many researchers have relied on simpler vertebrate species (particularly the lamprey) to model locomotion (Grillner et al. 1998a, 1998b). The lamprey makes a good model because its nervous system has a simple structure with very few neurons, making measurement somewhat easier (Grillner 2006). In addition, because the excised spinal cord can survive for days, direct cellular measurements can be taken while motion is produced indicative of a CPG (Grillner 2006). To understand the cellular basis of rhythmic motor and locomotor patterns, studies have been conducted on the sea slug, leech, cockroach, stick insect, and a variety of crustaceans (Büschges et al. 2008; Friesen and Kristan 2007; Hooper and DiCaprio 2004; Hughes and Wiersma 1960). In addition, experiments in in vitro isolated neonatal rat and mouse preparations and in transected adult rat and mouse models led to substantial advances in cellular target identification of the receptors and channels associated with locomotor rhythm generation and modulation (reviewed in Guertin 2013). Other observations further refined Brown's half-center CPG model by revealing an asymmetrical dominance in half-center activation (Duysens and Pearson 1976; Duysens 1977; Duysens et al. 2013). In most cases, and certainly when neuromodulators are used to induce locomotor-like activity in the isolated spinal cord, there is a bias toward a flexor dominance (Hägglund et al. 2013).

In this review, we frame the quest to identify CPG activity in human locomotor activity as a mystery requiring powers of logical deduction based on indirect evidence. As suggested above, early observations of neural mechanisms underlying motor control of walking began in the late 19th century, spurred by the work of Sir Charles Sherrington. We turn to 19th century popular culture and the deductive reasoning approach of the first of the great superheroes—the detective Sherlock Holmes.

Perhaps it is fitting that the approach of a fictional character like Sherlock Holmes is used to discuss a biomedical research problem. The inspiration for the reasoning approach of Sherlock Holmes in the writing of Sir Arthur Conan Doyle was

significantly influenced by a real-life physician and medical lecturer, Dr. Joseph Bell at the University of Edinburgh. During his own medical training, Doyle was impressed by Bell's "method of deducing the history and circumstances of his patients."

Finding supporting evidence to solve a perplexing puzzle was routinely described as "elementary" for Sherlock Holmes in the writings of Doyle. Borrowing the reasoning approach of Sherlock Holmes, we attempt to frame the mystery of human locomotor CPGs in terms of evidence, clues, and deductive conclusions. Indeed, the weight of reasoning and deduction has a long history in science, as described by Galileo Galilei (1564–1642): "...the authority of a thousand is not worth the humble reasoning of a single individual."

KEY "CLUES" SYMPTOMATIC OF HUMAN CPG ACTIVITY DERIVED FROM EVIDENCE IN REDUCED ANIMAL PREPARATIONS

> "Your case is an exceedingly remarkable one, and I shall be happy to look into it."
>
> "The Red-Headed League" (1891)

By studying and understanding simpler systems for the structure and function of CPGs, we can build up to understanding walking control in humans. In the style of Sherlock Holmes, using observations from other animal preparations as background allows speculation and hypothesis about what should be observable if CPGs are activated to control rhythmic human movement. Evidence and observations from humans based on hypotheses derived from studies in other animals will be used to assess the concept of CPG contributions to locomotion in humans.

Experimental data obtained from other animals reveal a very intricate and detailed model for locomotion. From these experiments, several key observations support the structure and function of locomotor CPGs. Below is a summary of the most important findings to support and describe spinal CPGs:

1) The isolated spinal cord can produce rhythmic motor output;
2) Sensory feedback is modulated by phase, task, and context to reinforce, modify, and sculpt rhythmic motor output to environmental conditions during locomotion;
3) Overlapping neuronal networks are recruited for different rhythmic tasks;
4) Locomotor circuitry are distributed along the spinal cord with cervical and lumbar enlargements regulating forelimb and hindlimb control respectively, which are connected by propriospinal pathways; and
5) Locomotor retraining induces recovery of walking ability.

QUESTIONING AND EXAMINING THE "CASE EVIDENCE" FOR CPGS IN HUMAN LOCOMOTION

> "He possesses two out of the three qualities necessary for the ideal detective. He has the power of observation and that of deduction. He is only wanting in knowledge."
>
> *The Sign of the Four* (1890)

In neurologically intact humans, the same experimental procedures used in reduced animal preparations are typically too invasive to be applied. Instead, we must rely on extrapolation of observations from the animal models of locomotion to humans based on the assumption that there are fundamental similarities in common principles of motor control across vertebrates and invertebrates (Duysens and Van De Crommert 1998; Pearson 1993; Zehr et al. 2016). This approach hearkens to the "principle of parsimony" commonly attributed as "Occam's Razor." William of Ockham (1287–1347) is said to have argued that whenever multiple hypotheses must be considered, we should always choose the one with the fewest and simplest set of assumptions. This relates to the underlying principle Doyle was getting at when he had Sherlock Holmes say "Once you eliminate the impossible, whatever remains, no matter how improbable, must be the truth."

Moving forward, we operate on the simple assumption that locomotor control in nature will be recapitulated in a similar but adapted form in all species, including humans. Thus evidence obtained from one species should be observable in another species. In view of the very extensive evidence for locomotor CPGs in other animals, it would be very surprising if there was a complete lack of a CPG network in humans, and no evidence has been presented to support this (Duysens and Van De Crommert 1998; MacKay-Lyons 2002). It will be shown below that there are indeed striking similarities between other reduced animal preparations and humans with respect to the neural control of locomotion. From the key observations listed above that support and describe CPGs made from reduced animal preparations, predictions can be formed on the structure and function of CPGs in humans.

1) Some Evidence That the Isolated Spinal Cord Can Produce Rhythmic Motor Output

> "The game is afoot!"
>
> "The Adventure of the Abbey Grange" (1904)

An observation from other species to evaluate in humans is that the spinal cord can produce rhythmic activity without modulation from the brain or sensory feedback. From reduced animal studies, it has been found that CPG networks are housed within the spinal cord and, in isolation, can produce the basic patterned motor outputs required for locomotion. Definitive evidence of a spinal CPG in humans would require the demonstration of locomotor-like rhythmic movements in an isolated spinal cord with no descending input and no feedback from the periphery. Such evidence in the human spinal cord is not fully available; however, some indirect observations of rhythmic activity support the suggestion of spinal and supraspinal integration in CPGs subserving human locomotion: for example, from studying stepping responses in those with spinal cord injury, from observations of air-stepping in healthy participants, an indirect observation of sleep-related rhythmic leg movement, and in walking in human infants. These examples all have one thing in common: descending input from supraspinal centers is limited because the spinal cord is functionally isolated from the brain. These examples are some of the best evidence for CPG activity in humans.

Clues from those with spinal cord injury.

> "It is more than possible; it is probable."
>
> "Silver Blaze" in *The Memoirs of Sherlock Holmes* (1893)

Perhaps the best examples of CPG-mediated locomotion in humans come from studying rhythmic movement in those with spinal cord injury (SCI) (Bussel et al. 1988; Calancie et al. 1994; Dietz et al. 1994a, 1998; Dimitrijevic et al. 1998; Harkema et al. 1997). This is because in this paradigm we can better assess the role of the spinal cord during reduced supraspinal regulation (Dietz et al. 1998). Following SCI, spinal circuitry below the lesion site does not become silent, but rather continues to maintain active and functional neuronal properties, although in a modified manner (de Leon et al. 2001; Edgerton et al. 2001). Although not the first observation, a case study of a patient with a clinically complete cervical SCI provides compelling evidence for a spinal CPG. Rhythmic, symmetrical, and bilateral myoclonic movements of the trunk and lower limbs, resulting in hip and knee flexion-extension at ~0.6 Hz, were recorded when the participant was placed over a treadmill (Bussel et al. 1988). This observation demonstrated that in humans, rhythmic activity could be generated within the spinal cord, without supraspinal inputs (Bussel et al. 1988). However, stimulation applied below the level of the transection, for example, by twisting the toes, could induce, slow, or interrupt the rhythmic activity (Bussel et al. 1988). Conversely, peripheral stimulation above the level of the spinal transection did not modify the myoclonus. Electrical stimulation of flexor reflex afferents from the sural nerve also affected rhythmic activity. During extensor activation, stimulation of flexor reflex afferents induced a flexion reflex that induced alternating flexor and extensor bursting activity that could be sustained for several cycles (Bussel et al. 1988). Similar activation of a spinal CPG by flexor reflex afferents was observed in cats (Duysens and Stein 1978; Jankowska et al. 1967; Pearson 1995; Seki and Yamaguchi 1997).

Other evidence comes from a patient with an incomplete injury of the cervical spinal cord (Calancie et al. 1994). Although this person had no ability to generate voluntary lower leg muscle activity, involuntary lower extremity stepping-like movements were expressed spontaneously when the patient was lying in a supine position. The movements were rhythmic with "forceful and patterned" bursts of alternating activity recorded from muscles of both legs. Peripheral feedback modified the rhythm such that movements increased with dorsiflexion of the toes and were abolished by the patient flexing the hips to 90°, rolling over, sitting up, or being moved to a standing posture (Calancie et al. 1994). However, due to the incompleteness of the lesion, this observation solicited further substantiation in patients with a complete SCI.

This evidence from incomplete SCI is supported by the presence of myoclonic rhythmic movements in six patients with complete SCI (Calancie 2006) and spontaneous motor rhythms of the legs, resembling bipedal stepping, in another patient with complete spinal cord transection (Nadeau et al. 2010). It must be noted, however, that the observation of spontaneous activity occurs more often in those with an incomplete compared with complete SCI (Harkema 2008), suggesting a strong modulatory role for supraspinal input.

Clues for CPG activity in humans have been provided by observations of rhythmic, locomotor-like movement of the lower limbs in complete SCI patients following epidural electrical stimulation of the spinal cord (Dimitrijevic et al. 1998). Tonic stimulation below the level of the injury (near L1–L3) triggered phasic bursts of rhythmic output in motoneurons for the legs. Increased stimulation amplitude resulted in increased electromyography (EMG) amplitudes and an increased frequency of rhythmic activity (Dimitrijevic et al. 1998) in a manner reminiscent of Sherrington's early observations in the cat. This is evidence that a human spinal cord, with minimal or absent supraspinal input, can generate rhythmic movements. However, there is still the presence of modulatory sensory feedback. To address this, in subsequent studies it was shown that epidural stimulation could produce rhythmic EMG activities even when the legs were stationary and thus producing minimal step-related sensory feedback (Minassian et al. 2004). Although sensory feedback has an influence on many features of the spinal rhythm, it seems that it is not required to produce the elementary CPG activity even in humans.

A final compelling observation that argues in favor of CPG regulation taken from SCI participants is that leg muscle activity recorded during walking far exceeds in amplitude the maximum that can be achieved during a voluntary contraction (Dietz 2003; Morawietz and Moffat 2013). This important observation supports the notion that locomotor EMG is centrally driven by something more than direct output from descending supraspinal commands.

Clues from restless leg syndromes.

"Circumstantial evidence is a very tricky thing..."

"The Boscombe Valley Mystery" in *The Adventures of Sherlock Holmes* (1891)

Another human model where supraspinal regulation of spinal cord activity is functionally diminished is found in restless leg syndromes. These syndromes can be found in those with SCI, multiple sclerosis, sleep disruptions, and other neurological disorders (Guertin 2013). Coming on either spontaneously or during sleep, restless leg syndrome presents as rhythmic flexion and extension of the toe, ankle, knee, and hip (Clardy and Connor 2010). This clue provides evidence of a CPG because patterned rhythmic movement can still be observed despite reduced descending supraspinal regulation. In the case of those sleeping, restless leg syndromes could arise from a transient interruption in descending inhibition where spinal CPGs for locomotion are activated (Coleman et al. 1980; Chervin et al. 2003). In any case, periodic leg movements of rhythmic activity may be associated with abnormal and involuntary activation of CPG networks.

Clues from passive air-stepping.

"You have brought detection as near an exact science as it will ever be brought in this world."

A Study in Scarlet (1887)

Under normal conditions, it is difficult to investigate CPG functioning because of the interfering interactions of feedback from the ongoing task of body weight and balance control. A way to activate and reveal rhythm generation via CPG circuits in conditions not affected by these extraneous factors is by using an air-stepping paradigm in a reduced gravity situation (Gerasimenko et al. 2010; Gurfinkel et al. 1998; Selionov et al. 2009; Sylos-Labini et al. 2014a). In this paradigm, with one leg horizontally suspended and with subjects instructed to relax and not to intervene with the induced movement, vibration of

a muscle of the suspended leg can elicit cyclical hip and knee movements in both legs (Gurfinkel et al. 1998). Rhythmic EMG activity is reciprocally organized in the muscles around the hip joint with movement restricted to the hip and knee. The ankle joint is only involved if minimal loading forces are applied to the foot (Gurfinkel et al. 1998). Interlimb connections were revealed when it was also shown that cervical transcutaneous stimulation with vibration of the cervical spinal cord significantly facilitated involuntary activation of the lumbosacral locomotor-related neuronal circuitry, producing leg movements (Gorodnichev et al. 2012). The constant inflow of proprioceptive afferents, due to the vibration, is thought to have initiated and sustained activation of the spinal pattern generation circuitry (Solopova et al. 2015). One possible route for these trigger signals is through intrinsic spinal pathways mediated by presumed propriospinal interneurons linking cervical to lumbosacral regions in humans (Nathan et al. 1996).

Although rhythmic air-stepping activity evoked by vibration is not strong enough for body support and propulsion, it does support the view that the basic rhythm underlying locomotion can be generated involuntarily in humans (Gerasimenko et al. 2010; Gurfinkel et al. 1998; Selionov et al. 2009; Solopova et al. 2015; Sylos-Labini et al. 2014a). Reduced gravity also offers unique opportunities for altered locomotor conditions for gait rehabilitation while still activating pattern-generating networks (Sylos-Labini et al. 2014b).

Clues from infant walking.

> "Altogether it cannot be doubted that sensational developments will follow."
>
> "The Adventure of the Norwood Builder" in *The Return of Sherlock Holmes* (1903)

Indirect evidence for a locomotor CPG also comes from studies of the automatic stepping response in human infants. Providing physical support for an infant (who is unable to walk and bear weight on its own) suspended over a treadmill can allow elicitation of rhythmic stepping movements (Yang et al. 1998). This observation supports the notion of spinally driven locomotor movements, because descending regulatory pathways involving the cerebellum and motor cortex are not fully mature in a human infant (Khater-Boidin and Duron 1991; Yang et al. 2004). Stepping movements have also been observed in anencephalic infants, further intimating the existence of CPG locomotor control centers below the level of the brain stem (Forssberg 1992). In addition, ultrasound recordings have revealed in utero images of human fetuses producing alternating primitive, steplike coordinated movement long before brain development (Ianniruberto and Tajani 1981; Kozuma et al. 1997). These data support the notion that the onset of voluntary stepping precedes development and full myelination of descending pathways from the brain, and thus that the infant stepping response is mediated by a spinal CPG mechanism.

Stepping movements in human infants are modulated by movement-related sensory feedback. Limb loading is a powerful signal for regulating the stepping pattern (Pang and Yang 2000; Yang et al. 1998). Manually adding limb load during the stance phase of gait by pushing down on the hips prolonged the stance phase (Pang and Yang 2000), whereas unloading the limb was an important cue for the transition into swing phase for forward, backward, and sideways walking (Pang and Yang 2000, 2001, 2002). Infants showed well-organized and location-specific reflex responses to mechanical disturbances during forward, backward, and sideways walking (Lamb and Yang 2000; Pang and Yang 2000, 2001). These results are consistent with the concept that sensory feedback can access and entrain CPGs subserving multiple modes of locomotion, as is found in spinalized cats.

Recordings of leg muscle activity during stepping in neonates, toddlers, preschoolers, and adults revealed that two basic patterns of stepping are retained through development (Dominici et al. 2011). The observation of a conservation of neural patterning across development is also seen in other species, including the rat, cat, macaque, and guineafowl (Dominici et al. 2011). As rudimentary movements adapt and coalesce during development, there is a conservation of locomotor patterning apparent across species. This observation supports the notion that a common ancestral neural network for central locomotor control may exist (Dominici et al. 2011).

Summary of the evidence for rhythmic motor output from the "isolated" human spinal cord. Stepping responses in those with SCI, observations of air-stepping in healthy participants, indirect observation of sleep related rhythmic leg movement, and walking in human infants provide clues for a spinal locomotor CPG in humans. A spinal mechanism is presumed because descending input from supraspinal centers is functionally diminished. These clues are some of the strongest evidence for a spinal CPG in humans. It must be noted, however, that peripheral feedback and supraspinal inputs can never be totally removed in these models. Thus, compared with other animals, there is a more distributed "address" for where locomotor elements "live" in the human nervous system.

2) Some Evidence That Sensory Feedback is Modulated During Human Locomotion

> "There is nothing more deceptive than an obvious fact."
>
> "The Boscombe Valley Mystery" in *The Adventures of Sherlock Holmes* (1892)

Although the functionally isolated spinal cord possesses impressive capacity to generate rhythmic output via CPG networks, afferent signals are a critical part of the adaptive motor control system. The timing information and reflex corrections derived from sensory feedback are essential for effective locomotion and adaptation to the environment (Grillner and Zangger 1984). Very early on, the importance of sensory feedback in the control of locomotion was acknowledged for its "regulative" role, rather than a "causative" role (Brown 1911, 1914). When Brown demonstrated that central oscillating mechanisms generated the basic stepping pattern, he also acknowledged the role of sensory input in shaping this output, commenting "there can be no question of its importance nor its suitability to augment the central mechanism" (Brown 1911, p. 318).

There is ample evidence that CPGs require sensory feedback to modulate and adapt their rhythmic output appropriately. Indeed, if step cycle durations and muscle patterns were fixed centrally and immutable, it would be impossible to adapt to changes in the external environment and we would be constrained to locomote on flat planes. To achieve effective locomotion, afferent feedback acts directly on the CPG and

contributes to the modulation of its output (Duysens and Van De Crommert 1998; Van de Crommert et al. 1998). In addition, afferent feedback is also relayed to motoneurons via various reflex pathways, and these pathways themselves are under the control of the CPG (Burke et al. 2001; Zehr et al. 2004a; Zehr 2005). This way, the CPG ensures that reflex activations are facilitated at appropriate times in the step cycle and suppressed when not appropriate (phase-dependent modulation; Duysens and Van De Crommert 1998).

From evidence in other animals, sensory feedback from load, muscle stretch, and tactile cutaneous receptors provides information required by the CPG circuitry to generate functional and adaptive locomotion. Electrical stimulation at intensities that preferentially activate afferent axons from these so-called proprioceptive sensory receptors reveal they have the ability to directly access, entrain, and reset CPG output. Sensory feedback has a role in acting directly on the CPG to initiate and facilitate phase transitions in rhythmic movements (Conway et al. 1987; Duysens and Pearson 1980). For example, activating hip flexor (sartorius muscle) afferents with electrical stimulation modulated CPG activity by resetting the locomotor rhythm from flexion to extension and caused generation of flexor bursts in contralateral leg flexor muscles in the cat (Perreault et al. 1995). Flexor reflex afferents can access deeply into CPG networks to reset the step cycle to a new flexion (Jankowska et al. 1967; Schomburg et al. 1998). It must be noted, however, that in these animals with reduced descending control, sensory feedback from a single input pathway is sufficient to affect CPG activity. In intact animals, manipulation of just a single type of sensory feedback is not sufficient to modulate and reset rhythmic activity (Duysens and Stein 1978; Whelan and Pearson 1997).

Related observations are found also in human experiments where transient changes in afferent activity do increase muscle activity. However, an attempt to activate load sensory feedback during the stance phase by adding a substantial weight at the center of mass was insufficient to significantly change the stance duration of the step cycle (Stephens and Yang 1999). Therefore, it is unclear to what extent CPGs and sensory feedback are integrated in the control of rhythmic motor timing in humans. There are no studies in humans, as there are in cats, that directly evaluate the exact contribution of sensory feedback to CPG output. However, indirect methodologies allow observations to be made in an intact nervous system to evaluate how the CPG regulates afferent feedback during rhythmic movement (Burke 1999; Zehr 2005). Although patterning is not accessible directly, the effects of reflexes as indexes of CPG-related modulation are. Reflexes arising because of activation of afferent projections from receptors in skin and muscle have been studied widely and support the role of locomotor CPGs in the neural control of rhythmic human movement.

Examining reflex activity and modulation during rhythmic movement provides clues that indicate CPG regulation. Reflexes, measured as changes in muscle activity, are the response to electrical or mechanical stimulation of a sensory pathway. This approximates the input-output properties of neural control where stimulation of a given sensory input and a record of the pattern of modulation of motor output during movement are compared. This approach has been used to great effect in the quadrupedal locomotor system (Burke et al. 2001) and is also effectively used in humans (Zehr and Duysens 2004; Zehr et al. 2004a). Examining the modulation of reflexes during rhythmic movement, as an indirect indicator of CPG regulation of afferent input, provides more data from which clues for CPGs in humans have been gleaned.

Clues from task- and phase-dependent modulation of reflex amplitudes.

> "It is a capital mistake to theorize before one has data. Insensibly one begins to twist facts to suit theories, instead of theories to suit facts."
>
> "A Scandal in Bohemia" in *The Adventures of Sherlock Holmes* (1892)

The presence of task- and phase-dependent modulation has been used to infer the activity of CPGs in humans. Task- and phase-dependent modulation of reflexes means that efficacy of sensory input varies depending on the timing within a behavior in which it occurs (Duysens et al. 1992; Van Wezel et al. 1997; Yang and Stein 1990; Zehr et al. 1997; Zehr and Stein 1999). An example of task-dependent modulation is depicted in Fig. 1. H-reflexes are progressively inhibited across different tasks from standing to walking to running (Stein and Capaday 1988). H-reflexes examined during walking also show phase-dependent modulation (Brooke et al. 1997; Zehr and Stein 1999). Over the course of the gait cycle, there is phasic modulation of the magnitude of the H-reflex and of the stretch reflex (the mechanical analog of the H-reflex). At the late stance phase, the reflexes in the soleus are facilitated, likely due to an increase in excitability via facilitation along Ia reflex pathways (Yang and Whelan 1993). Functionally, this assists in maintaining an upright position where the reflex is largest in stance phase when balance is required and smallest in the swing phase when free movement is required and when a reflex activation of soleus would counteract the flexion at the ankle (Capaday and Stein 1986; Verschueren et al. 2002).

Task- and phase-dependent modulation is also observed for modulation of cutaneous reflexes. In the cat, activation of sensory afferents of cutaneous receptors from the foot, with either direct skin stimulation or electrical stimulation of the nerves, causes a dramatic effect on the locomotor cycle. With

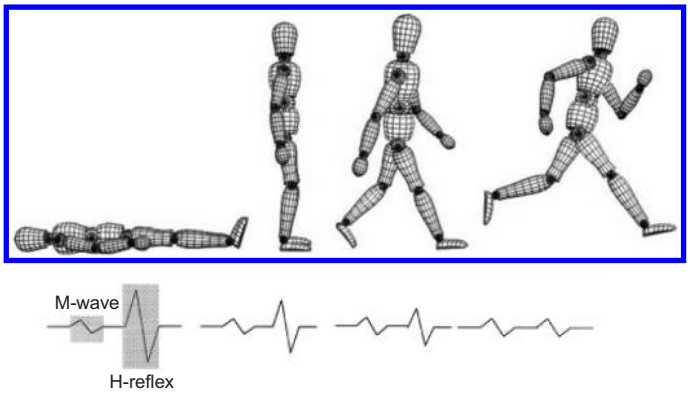

Fig. 1. Attenuation of reflexes under different behaviors. The cartoon subject depicted in the *top* row is shown performing 4 different motor tasks. Results show a corresponding decrease in H-reflex amplitude. Note that the M wave is held constant and that the M wave and H-reflex amplitude would be normalized to the maximal M wave for each condition across motor tasks to ensure stimulus constancy and proper comparison. [Adapted from Zehr (2002).]

stimulation of both the pad of the foot (Duysens and Pearson 1976) and dorsum of the foot (Forssberg et al. 1975), and in fictive locomotion of decerebrate-paralyzed cats (Guertin et al. 1995) or decerebrate cats with transected spinal cords (LaBella et al. 1992), cutaneous stimulation during the stance phase evoked prolongation of extension to delay the foot leaving the ground. Observations from these different spinal cat models confirm that cutaneous feedback pathways make direct connections with spinal cord networks by accessing excitation of the extensor half-center and promoting increased extensor activity (Pearson 2004).

In humans, the same observations of phase-dependent modulation of cutaneous feedback are confirmed. In some cases, modulation is so powerful that a reflex can completely reverse in sign. Such a phase-dependent reflex reversal is highlighted in the tibialis anterior, where in the same muscle, the sign of the reflex reverses from excitation in the early swing phase to inhibition at the stance transition (see Fig. 2) (Duysens et al. 1992; Haridas and Zehr 2003; Yang and Stein 1990; Zehr et al. 1997).

Phase dependency is a symptomatic outcome of CPG output that serves a functional role tuned to locomotor conditions, allowing smooth progression. This keeps walking safe by incorporating afferent information at appropriate times in the walking cycle. For example, as part of the "stumble corrective response" during walking, activation of the top of the swing foot (by a physical perturbation or by electrical activation of cutaneous nerves) causes a reduction in dorsiflexion, allowing the foot to move past the perturbation and not disturb locomotor progression. However, if the same input to the foot in stance yielded similar neural coordination, the person would collapse. Thus, depending on the phase, the same sensory input is transformed by CPG activity to produce functionally relevant outcomes. Control of sensory input is so finely tuned and regulated that even among functional synergists (e.g., soleus, lateral gastrocnemius, and medial gastrocnemius), the size of a reflex can vary throughout the step cycle and can reverse in sign (see Fig. 3) (Zehr et al. 1997).

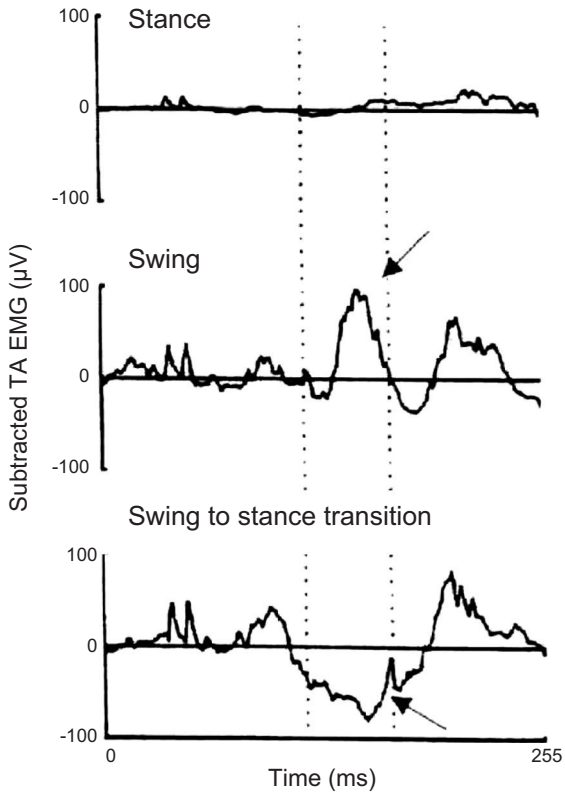

Fig. 2. Phase-dependent modulation and reversal of cutaneous reflex during locomotion in the tibialis anterior (TA). The electromyography (EMG) traces are from TA muscle and are the reflexes to tibial nerve stimulation once the background locomotor-related EMG has been subtracted. An arrow marks the excitatory reflex during swing, which becomes an inhibitory one at the swing-to-stance transitions. [Adapted from Yang and Stein (1990) and reprinted from Zehr and Stein (1999).]

Clues from mechanistic study of phase-dependent reflex modulation.

> "...the problem was already one of interest, but my observations soon made me realize that it was in truth much more extraordinary than would at first sight appear."
>
> "The Adventure of the Crooked Man" (1893)

There has been much speculation as to how phase-dependent modulation occurs during rhythmic motor tasks. Sensory feedback itself could be involved in modulating other movement-related feedback from muscle or joint receptors (Drew and Rossignol 1987; Misiaszek et al. 1998). The same inputs that generate reflex output could alter presynaptic inhibition to change the gain from muscle spindle group Ia and II and Golgi tendon organ Ib pathways. However, phase-dependent modulation is present in the hindlimb (Quevedo et al. 2005b) and forelimb of the cat (Hishinuma and Yamaguchi 1989), examined by intracellular analysis of reflex pathways underlying the stumble corrective reflex during fictive locomotion, when movement is completely absent (Andersson et al. 1978; Schomburg and Behrends 1978). The observation of phase-dependent reflex modulation in the fictive preparation means reflex modulation must be ascribed, at least in part, to spinal CPG regulation (Andersson et al. 1978; LaBella et al. 1992). Convergence of information from locomotor CPGs onto segmental interneurons within feedback pathways has been proposed as the source of the observed reflex modulation (Seki and Yamaguchi 1997). Thus, along with presynaptic inhibition, the CPG modulates the amplitude of primary afferent depolarizations in afferent reflex pathways (Gossard and Rossignol 1990).

Thus CPGs are likely responsible for regulating and balancing the overall strength of excitatory and inhibitory connections in the spinal cord that allow sensory information to be incorporated (Abraham and Loeb 1985; Andersson et al. 1978; Dietz 2002; Dietz et al. 2001; Duysens and Van De Crommert 1998; Duysens et al. 1990, 1992; Forssberg 1979; Komiyama et al. 2000; Quevedo et al. 2005a; Van Wezel et al. 1997; Yang and Stein 1990; Zehr and Duysens 2004; Zehr et al. 2004b). With intracellular recording, spinal interneurons in spinal cord circuits can be observed to participate in reflex modulation (Bui et al. 2016; Quevedo et al. 2005a). In humans there are several characteristics that reveal a central control mechanism in modulating sensory feedback for task- and phase-dependent modulation. These characteristics include that reflex modulation is independent of changes in background EMG, only occurs with active rhythmic but not passive movement, and is not influenced by feedback in other sensory pathways.

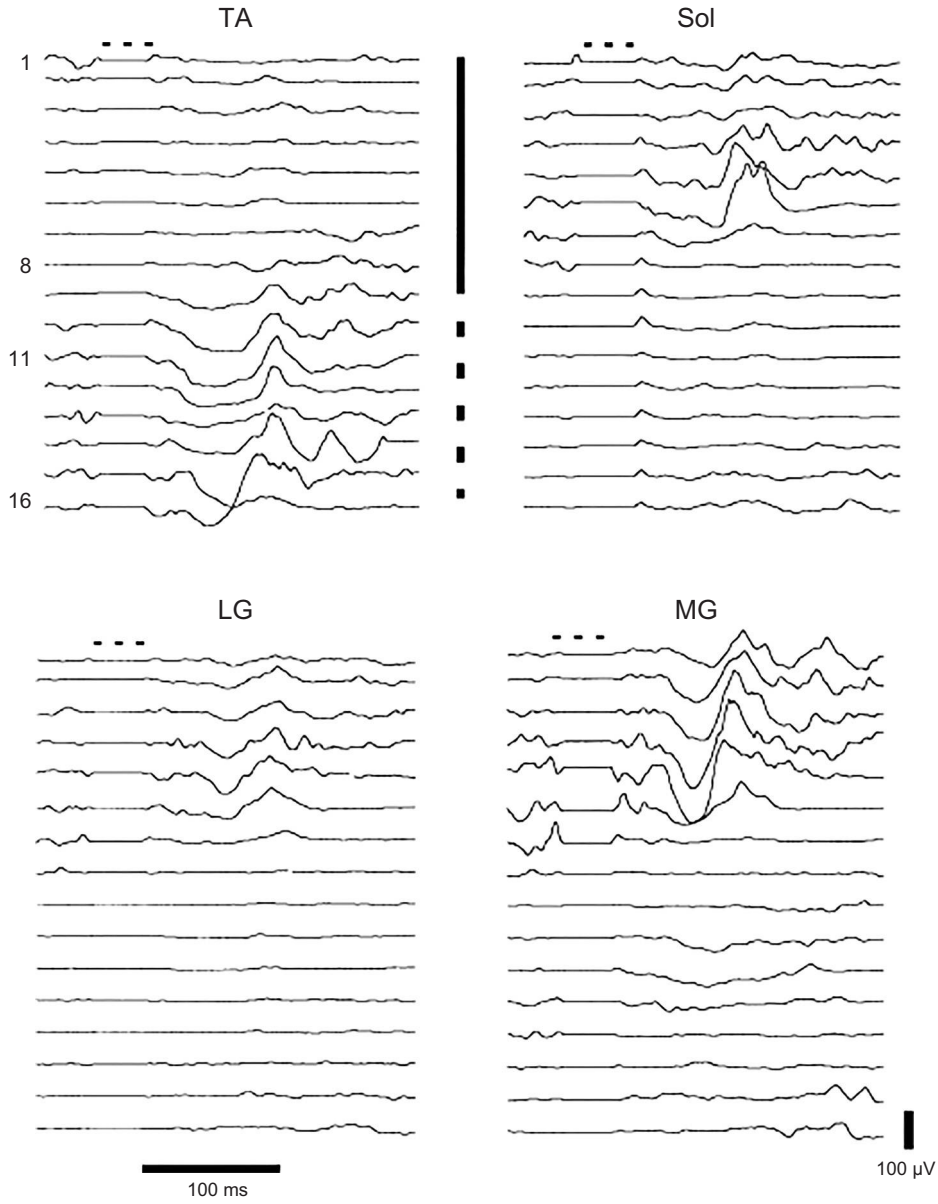

Fig. 3. Subtracted electromyograms (EMGs) of tibialis anterior (TA; *top left*), soleus (Sol; *top right*), lateral gastrocnemius (LG; *bottom left*), and medial gastrocnemius (MG; *bottom right*) muscles after superficial peroneal (SP) nerve stimulation for 1 representative subject. Throughout, the stimulus artifact has been suppressed and replaced by a flat line, atop which has been placed a thick dashed line. Each trace runs from 50 ms before stimulation to 250 ms after stimulation. Note phase-dependent reflex reversals in functional synergists. [Adapted from Zehr et al. (1997).]

In static tasks, there is a strong linear relationship between reflex and background muscle activity, whereas during walking, reflexes are relatively uncorrelated and do not follow background activation (Haridas and Zehr 2003; Van Wezel et al. 1997; Yang and Stein 1990; Zehr et al. 1997). Such observations suggest that modulation occurs at a premotoneuronal level (Duysens and Tax 1994; Matthews 1986). An example is shown in Fig. 4 where kinematics of knee movement were matched to locomotor amplitudes during treadmill walking (Zehr et al. 2007a). Cutaneous reflexes evoked in knee extensor muscle vastus lateralis were tightly correlated with background EMG level during voluntary knee extension but completely dissociated during walking.

In the case of muscle afferent pathways, an increased reflex attenuation during tasks implies a premotoneuronal mechanism, because the response is independent of locomotor EMG (Stein and Capaday 1988). Most likely, it is presynaptic inhibition of Ia afferent transmission from CPGs as a mechanism for inhibition of the same pathway, because presynaptic inhibition is a major mechanism influencing spinal cord excitability during interlimb locomotor activity (Capaday and Stein 1986; Crenna and Frigo 1987; Zehr 2006).

There is more evidence that spinal CPGs are responsible for task- and phase-dependent modulation of sensory feedback during locomotion. When a CPG for rhythmic movement is not active, as in passive movements, phase-dependent modulation is absent (Brooke et al. 1999; Carroll et al. 2005). This suggests that modulation is not the result of movement-related afferent feedback, associated with the passive movement, but is driven by a central mechanism. This was confirmed with the observation that there was no effect on cutaneous reflex modulation when muscle spindle sensory receptors were activated from quadriceps muscles with patellar taps (Brooke et al. 1999). A central mechanism, such as CPG networks, is predicted to be responsible for phase-dependent modulation because reflex modulation does not occur with passive movement, nor does the interaction of other reflex pathways affect modulation (Brooke et al. 1999).

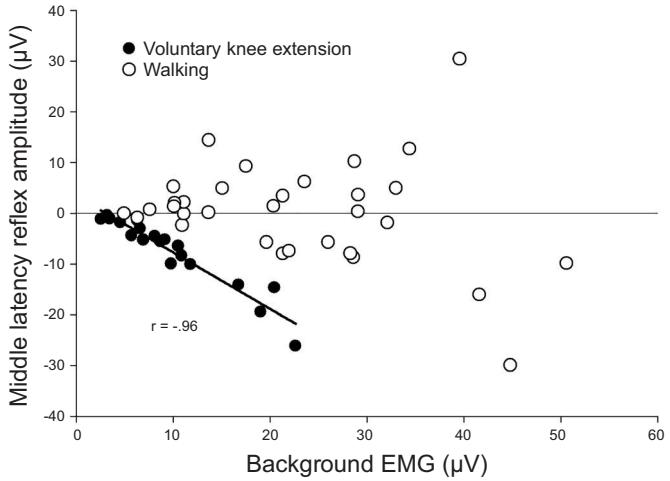

Fig. 4. Strong correlation between reflex amplitude during voluntary knee extension is absent during walking due to the modulation of presumed central pattern generator activity. EMG, electromyography. [Adapted from Zehr et al. (2007a).]

The way in which CPG neurons transform cutaneous input changes as a function of the locomotor cycle. The fact that cutaneous feedback during walking can cause a flexor response during the swing phase, and an extensor response during the stance phase, in the same muscle suggests that parallel excitatory and inhibitory cutaneous pathways could exist between cutaneous receptors and motoneuron pools (Yang and Stein 1990). Indeed, the existence of parallel excitatory and inhibitory pathways to motoneurons was revealed by analysis with poststimulus time histograms (PSTH) of single motor units from the tibialis anterior during walking (De Serres et al. 1995). With posterior tibial nerve stimulation, PSTH showed that the same motor unit was excited during swing and inhibited during the transition from swing to stance. The opening and closing of these parallel pathways depends on the phase of the rhythmic cycle where CPGs act to govern the overall strength of the excitatory and inhibitory connections in these parallel pathways (Duysens et al. 1992; Yang and Stein 1990).

Summary of the evidence from task- and phase-dependent modulation of reflex amplitudes. The importance of the CPG is its ability not only to generate repetitive cycles but also to receive, interpret, and predict the appropriate action at each part of the step cycle. This is made possible by constant input from peripheral sources to update and sculpt CPG output. In other animals, this relationship can be directly shown, but in humans, examining task- and phase-dependent modulation of reflexes during rhythmic movement provides an indirect indicator of the relationship between CPG regulation and afferent input. In humans, these observations provide some of the main data on which the concept of spinal CPGs has been built. There are several characteristics that reveal a central control mechanism in modulating sensory feedback. These characteristics include the facts that reflexes are modulated according to the task- and phase- of movement, that reflexes are independent of changes in background EMG, that modulation only occurs with voluntary movement and not passive movement, and that modulation is not influenced by feedback in other sensory pathways. Together, these observations are evidence that a spinal CPG is responsible for the fine-tuning of sensory feedback during rhythmic movement.

3) Some Evidence for Similar Neuronal Networks Recruited into Different Rhythmic Human Motor Tasks

"You know my methods. Apply them!"

The Hound of the Baskervilles (1902)

In cats, the pattern-generating circuits for different rhythmic functions overlap with shared networks to produce the behaviors they generate. Functional temporal reversals during backward locomotion provide evidence of the adaptability of pattern generators in the control of locomotion. In the cat, backward walking is produced by a phase shift in activation of unit burst generators controlling flexion and extension of knee and hip muscles (Buford and Smith 1993). If shared circuitry for various rhythmic movements is also within the human spinal cord, it should be observed as a characteristic of human reflex modulation. Indeed, reflex modulation, as well as joint power, limb kinematics, and EMG activity in some muscles, is essentially reversed in time during backward walking (Duysens et al. 1996; Thorstensson 1986; Winter et al. 1989). Cutaneous reflexes are thought to be regulated by an equivalent neural CPG mechanism, because responses are phase-reversed in lower leg muscles such as tibialis anterior (Duysens et al. 1996).

Reflex modulation in pedaling (Brooke et al. 1997; Brown and Kukulka 1993) is similar to that in walking (Yang and Stein 1990), suggesting that related neural circuitry may be operational in both tasks (Ting et al. 1999). Similar to observations in walking, forward and backward arm cycling are also regulated by an equivalent neural mechanism, where at similar phases in the movement cycle, responses of corresponding sign and amplitude were seen regardless of movement direction (Zehr and Hundza 2005). This extended also to leg cycling, where a simple reversal in reflex patterning suggests that forward and backward leg cycling are regulated by a similar neural mechanism (Zehr et al. 2009a). In a further example, in human infants, different directions of walking are ascribed to flexible use of common locomotor spinal circuits (Lamb and Yang 2000).

Comparable coordination patterns between activities involving all four limbs moving simultaneously and rhythmically also exist. For example, during walking, creeping, and swimming, responses that are suggestive of similar CPG output in all activities have been shown (Wannier et al. 2001). Commonalities in cutaneous reflex amplitudes in arm and leg muscles were also seen across level walking, incline walking, and stair climbing (Lamont and Zehr 2006). In other quadrupedal tasks, reflexes were modulated in a similar way across walking, arm and leg cycling, and arm-assisted recumbent stepping, where similar phase-dependent modulation was observed despite differences in movement kinematics (Zehr et al. 2007a). This led to the conceptualization of relatively equivalent partitioning of the locomotor cycle across different tasks (see Fig. 5). In the damaged nervous system with descending disruptions after stroke, common neural patterning from conserved subcortical regulation persisted (Klarner et al. 2014b). This was evidenced by a similarity in reflex modulation between different rhythmic tasks (see Fig. 6). These findings imply that networks for arm and leg coordination could reside in subcortical areas, because damage to the brain following stroke still expressed common neural regulation (Klarner et al. 2014b).

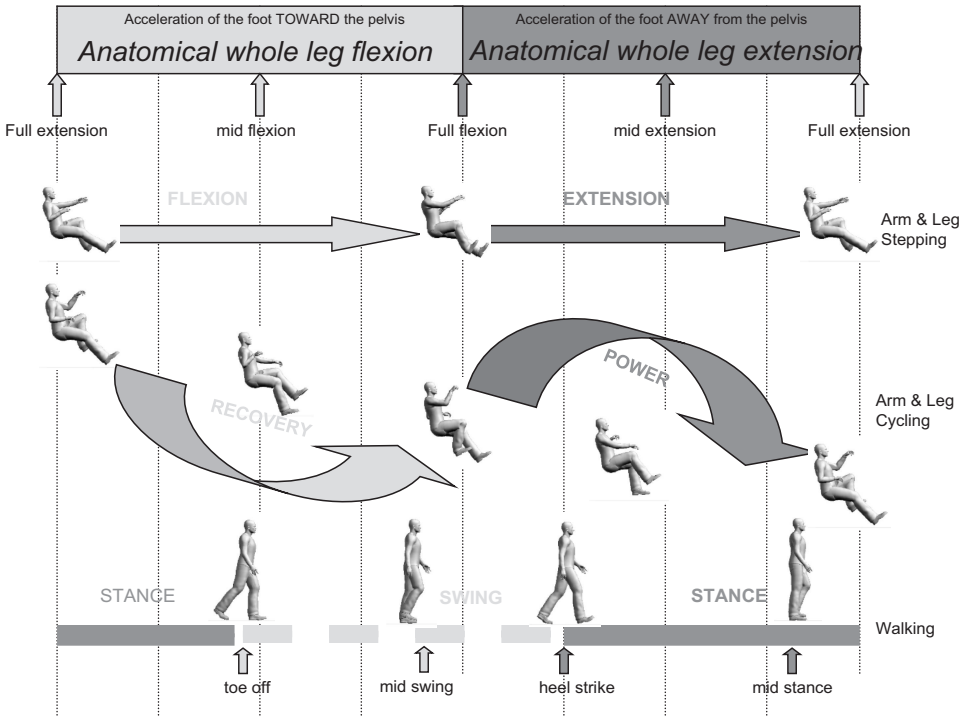

Fig. 5. Comparison of different human locomotor behaviors involving all 4 limbs. [Adapted from Zehr et al. (2007a).]

Summary of the evidence across different rhythmic locomotor behaviors. The "common core hypothesis" (Zehr 2005) describes the concept that neural control, evidenced by examining similarities in reflex modulation, is conserved across rhythmic arm and leg movements for different tasks such as cycling, walking, stepping, and arm and leg cycling and can be activated for different directions of action. That is, a flexible central mechanism is likely responsible for regulating various types of rhythmic movement in a similar oscillatory fashion with a common core of subcortical elements expressing neural activity to produce the basic pattern of arm and leg movement (Klarner et al. 2014b; Zehr 2005; Zehr et al. 2007a). The ability of a muscle to contribute to more than one function, with the expression of each under neural modulation, gives the control scheme flexibility and thus the capability to execute a variety of tasks (Ting et al. 1999).

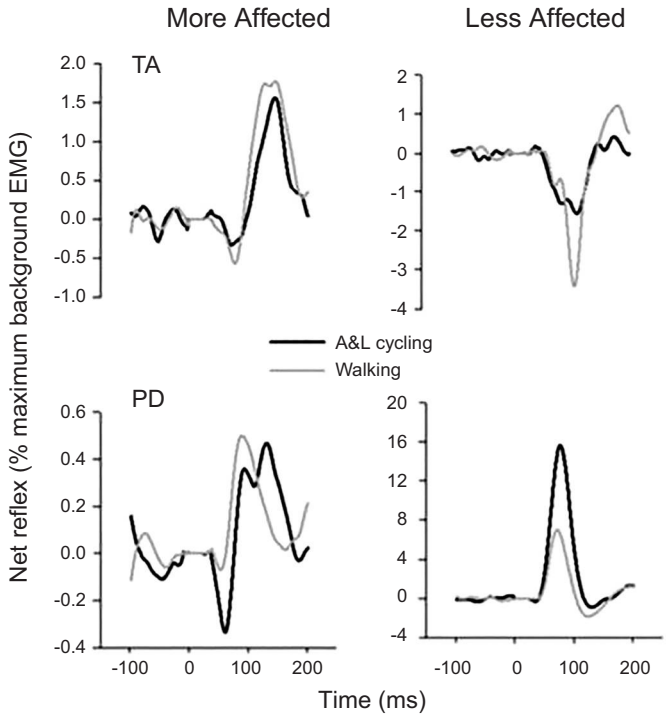

Fig. 6. Ensemble grand-average subtracted reflex traces from all phases and all subjects for arm and leg (A&L) cycling and walking. Note that there is a similar pattern of cutaneous reflex modulation across tasks. Despite some changes in amplitudes, the general pattern is conserved. EMG, electromyography; TA, tibialis anterior; PD, posterior deltoid. [Adapted from Klarner et al. (2014b).]

4) Some Evidence of Distributed Locomotor Networks and Interlimb Connectivity in Human Locomotion

> "I make a point of never having any prejudices, and of following docilely where fact may lead me."
>
> "The Reigate Squires" in *The Memoirs of Sherlock Holmes* (1893)

As outlined above, EMG and reflex studies support the role of locomotor CPGs in the neural control of rhythmic human movement. In other animals, CPG networks are distributed along the spinal cord for functional integration between the forelimbs and hindlimbs. Given the potential for evolutionary conservation, we presume that in humans, CPG networks can be found in the cervical spinal cord and produce rhythmic activity for arm swing. We would predict that, reminiscent of what is demonstrated in quadruped locomotor studies, CPGs for all limbs are interconnected in the central nervous system.

Clues from rhythmic arm activity.

> "When one tries to rise above Nature one is liable to fall below it."
>
> "The Adventure of the Creeping Man" in *The Case Book of Sherlock Holmes* (1927)

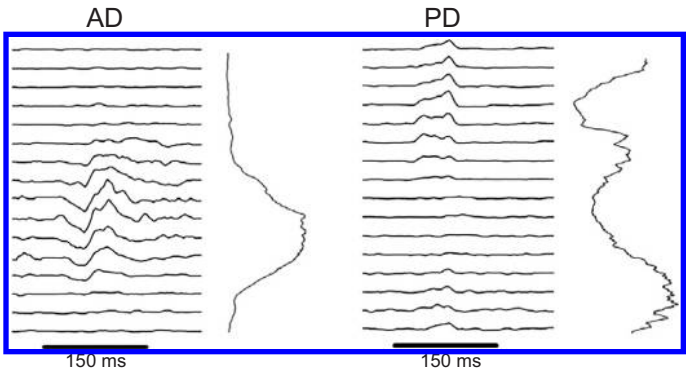

Fig. 7. Phase-dependent modulation of cutaneous reflexes in arm muscles anterior deltoid (AD) and poster deltoid (PD) from stimulation to the superficial radial nerve during arm cycling. Cutaneous reflexes are modulated across the movement cycle (from *top* to *bottom*). [Adapted from Zehr et al. (2012).]

The first evidence to consider is whether the arms show features of CPGs, similar to what exists for forelimbs in quadrupeds. We will see below that cervical CPG activity does regulate arm swing, and in a similar way to how lumbar spinal circuits are believed to regulate rhythmic leg movement. One limitation to the extrapolation from cats to humans is that bipeds and quadrupeds use different modes to provide propulsion during locomotion. As humans, we can walk without moving our arms, and there is no obvious reason why humans need to move their arms when they walk, yet rhythmic movements coordinated with the legs naturally emerge during walking (Ford et al. 2007; Meyns et al. 2013; Umberger 2008).

Rhythmic arm movements have been compared with a pendular motion, although arm swing is not a passive action (Ferris et al. 2006). Arm swing enhances stability by generating a horizontal torque at the upper trunk that may counteract pelvis rotation and leg progression to minimize angular momentum (Li et al. 2001; Park 2008; Umberger 2008). Arm swing movements are also affected by the legs, by forces being transferred to the arms between trunk and shoulder ligaments and muscles during walking (Pontzer et al. 2009). Indeed, it has long been believed that the natural arm movement during walking is not just a simple pendular movement resulting from leg motion, but instead is neurally integrated into movement (Elftman 1939).

Similarities between the control of legs and arms have been observed by examining coordination and electromyographic activity. Coordination patterns between the upper extremities are similar to those of the lower extremities in human bipedal locomotion, common with those of quadrupedal locomotion (Van Emmerik et al. 1998). As for EMG activity, in general, arm muscle activity is out of phase and reciprocating, as with that of the leg muscles, but with slightly more coactivation (Zehr and Kido 2001; Zehr et al. 2003b). In addition, within-arm EMG activation patterns are coordinated with contralateral arm muscles (Zehr and Kido 2001) and with EMG activation in the legs (Zehr et al. 2003b).

Also as in the legs, task- and phase-dependent reflex modulation, of both cutaneous and H-reflex pathways, is seen during rhythmic arm movement (Zehr and Chua 2000; Zehr and Kido 2001; Zehr et al. 2003a). For example, cutaneous reflexes evoked with stimulation to the median, ulnar, or radial nerve were of differing amplitude and sign during arm cycling compared with static contractions at matched positions in the cycle (see Fig. 7) (Zehr and Kido 2001). Cutaneous reflex reversal can be seen in some arm muscles, in which reflexes may be excitatory during static contraction but inhibitory during arm cycling. There is also extensive task- and phase-dependent modulation of cutaneous reflexes in arm muscles during the natural arm swing of walking compared with static contractions in matched positions (Zehr et al. 2003b).

Muscle afferent reflexes in arm muscles also showed task- and phase-dependent modulation. In the forearm muscle flexor carpi radialis (FCR), H-reflexes evoked during arm cycling were phase modulated during rhythmic movement, independent from background EMG modulation, and modulation was not observed during static contractions at matched positions (see Fig. 8) (Zehr et al. 2003a). During movement, forearm reflexes were strongly inhibited compared with the amplitude expressed during static contraction (Zehr et al. 2003a). Indicating the interactive influence of afferent feedback on this reflex pathway, H-reflex amplitudes were suppressed with both active and passive movement (Zehr et al. 2003a) as seen in the legs (Brooke et al. 1997).

Phase- and task-dependent reflex modulation of reflex amplitude in the arms, characteristic of CPG regulation, suggests equivalent neural control mechanism for the arms and legs during rhythmic movement (Balter and Zehr 2007; Dietz 2002; Dietz et al. 2001; Zehr and Duysens 2004; Zehr and Kido 2001; Zehr et al. 2003b, 2004a, 2007c). Supporting a central locus of control for rhythmic arm movement, as seen in the legs (Brooke et al. 1999), cutaneous reflexes are not phase modulated during passive arm cycling (Carroll et

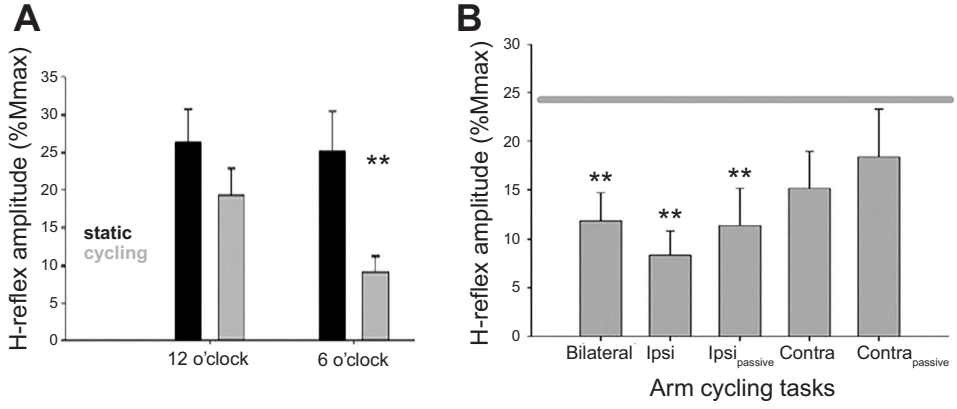

Fig. 8. Modulation of the forearm flexor H reflex by arm movement. Modulation of forearm H reflexes during arm cycling (*A*; light gray bars) but not during static contraction (*A*; black bars) and during different arm cycling tasks (*B*; gray bars) including bilateral arm cycling, active movement of the ipsilateral (Ipsi) or contralateral (Contra) arm, or with the ipsilateral ($Ipsi_{passive}$) or contralateral ($Contra_{passive}$) arm passive. There were no differences in M-wave amplitudes or flexor carpi radialis electromyography levels (not plotted). Values are means ± SE. $^{**}P < 0.01$, significant differences between static and cycling conditions. [Adapted from Zehr et al. 2003a).]

al. 2006). These observations support the hypothesis that rhythmic arm movements are partly regulated by CPGs, just as for the leg (Dietz 2002; Dietz et al. 2001; Jackson 1983; Zehr and Duysens 2004). During static contractions, reflex amplitudes are highly correlated with background muscle activity, whereas during rhythmic tasks, this relationship is weak or absent, and indeed, reflex amplitudes in the arms are modulated in a manner that is independent of background EMG activity (Zehr and Kido 2001; Zehr et al. 2003a, 2003b). These results highlight the different patterns of reflex modulation between static contractions and rhythmic arm movement, reflecting the differences in their neural control. These observations also suggest premotoneuronal gating of afferent feedback by spinal rhythm-generating circuits in the arms, as described for the legs (Dietz 2002; Dietz et al. 2001; Zehr et al. 2004a).

Other evidence supporting CPG contributions to rhythmic arm movements comes from measuring the size of motor-evoked potentials in response to transcranial magnetic stimulation (TMS) during rhythmic arm movement (Carroll et al. 2006). It was found that motor-evoked potentials were reduced in size compared with those recorded with tonic, voluntary contraction (Carroll et al. 2006). This suggests a reduction in the corticospinal influence during rhythmic compared with voluntary arm movement. Thus, despite highly developed corticospinal projections to the human upper limb, subcortical regions likely contribute to the control of rhythmic arm movements. Indeed, spinal motoneuron excitability, as assessed using TMS-induced motor-evoked potentials from the biceps brachii, was increased in arm cycling, showed task and phase dependency, and was modified by cycling cadence (Forman et al. 2014, 2015).

A difference between neural regulation of rhythmic human upper and lower limb movement is the degree of coupling between the limbs. Bilateral coupling between the arms compared with that between the two legs is not as strong, perhaps because of their different functional roles during bipedal walking. For the legs, reflex modulation on the ipsilateral side is dependent on contralateral active or passive leg movement where a general suppressive effect was recorded in the ipsilateral leg (Cheng et al. 1998; Collins et al. 1993). In addition, contralateral reflexes follow the movement phase of the contralateral leg, not the stimulated one (Duysens et al. 1990; Tax et al. 1995). For the arms, modulation for both cutaneous and H-reflexes on the ipsilateral side is not dependent on contralateral active or passive rhythmic arm movement (Carroll et al. 2005; Delwaide et al. 1988; Zehr et al. 2003b). Instead, reflex modulation in the arm is more dependent on the activity state of the limb in which the reflex is evoked (Carroll et al. 2005; Hundza and Zehr 2006). These findings suggest that although coupling is strong between the CPGs for each leg, the CPGs for each arm seem to be less involved in gating crossed responses (Carroll et al. 2005). Comparatively stronger coupling between legs is likely explained by differences in the functional roles of the arms vs. the legs in human bipedal walking. Although the arms can be free to act independently, it is essential to have strong leg coordination to maintain dynamic upright posture.

Clues from interlimb reflex coordination between the arms and legs.

> "There is nothing more stimulating than a case where everything goes against you."
>
> *The Hound of the Baskervilles* (1902)

Evidence suggests CPGs contribute to coordination of rhythmic arm and leg movements, but to support interlimb coordination, significant connection between lumbar and cervical spinal cord CPGs actuating individual limbs is required (Swinnen and Duysens 2005). Indeed, during rhythmic arm and leg movements, arm activity contributes to the neural excitation of leg muscles, indicating neural coupling between upper and lower limbs in humans reminiscent of what is found in quadrupeds (Zehr et al. 2009b, 2016). In the following, as above, evidence will be presented from human studies to show that the arms and legs are neurologically connected. The basic idea of all the experiments presented below is to detect coupling between the arms and legs of bipeds based on indirect evidence for interlimb locomotor linkages.

Clues for the existence of interlimb connections regulating rhythmic activity of all limbs in humans will be presented across several categories of experimental evidence. Through observations of maintained coupling by changes in arm and leg mechanical interactions and evidence of a widespread network of reflexes in leg or arm muscles, there is strong support for pathways linking muscles in the arms and legs. Effects of remote rhythmic movement on motor output and reflex excitability in the opposite set of limbs also demonstrate interlimb coordination in humans. We will review different modes of evidence that probe interlimb connections for the arms and legs through spinal CPGs in humans.

> "Education never ends, Watson. It is a series of lessons with the greatest for the last."
>
> "The Adventure of the Red Circle" in *His Last Bow* (1911)

A way to probe for neural interactions between the arms and legs during rhythmic movement is to study somatosensory linkages in the form of interlimb reflexes (Burke et al. 1991; Zehr et al. 2004a). For instance, interlimb coupling in humans has previously been demonstrated by evoking reflexes in one limb and observing the extent to which the movement of another limb modulates reflex expression (Massaad et al. 2014; Mezzarane et al. 2011; Zehr et al. 2003b). A possible route for these interlimb coordination signals is through intrinsic spinal pathways, made up of propriospinal interneurons, linking cervical and lumbosacral regions. There is some direct evidence in humans with supraspinal lesions and spinal cord transections (Nathan et al. 1996). Pathways connecting spinal cord segments are suggested from studying those with SCI (Calancie et al. 1996). The location of the injury in the 15 subjects studied was at the cervical level, sparing the propriospinal pathways linking the cervical and lumbar enlargements in the spinal cord. With stimulation of cutaneous (distal tibial) and muscle afferent (tibial and median) nerves, widespread responses in all limbs were evoked, identified with single motor unit recordings. Discharge of motor units was also evoked with light touch of the feet and individual hair movements (Calancie et al. 1996). Interlimb reflex properties were similar for both SCI

and control groups for radial nerve stimulation at the elbow, suggesting that the neural circuitry underlying these reflexes does not develop as a result of SCI (Butler et al. 2016).

In humans with intact nervous systems, there is also indirect evidence to suggest efficacy of these interlimb pathways. It was initially shown that with noxious, high-intensity stimulation of tactile afferents in nerves from the hand (median) and foot (sural), distant motor nuclei undergo excitability changes (Delwaide et al. 1981). A reciprocal pattern of facilitation and suppression for the flexor and extensor reflexes in arm muscles emerged with sural nerve stimulation, suggesting a coordinated and functional interlimb linkage (Delwaide and Crenna 1984). A connection between the arms and legs was also found in human subjects where descending lumbosacral cord potentials were recorded intrathecally after stimulation of the median nerve at the elbow (Sarica and Ertekin 1985).

Examining cutaneous reflexes during static and rhythmic movement has revealed a widespread interlimb network. There is an extensive distribution of reflexes across many muscles in both the arms and the legs, irrespective of which limb is directly stimulated (Haridas and Zehr 2003; Zehr and Duysens 2004; Zehr et al. 2001). In humans in seated positions, strong, early latency interlimb cutaneous reflexes were documented in all limbs following stimulation to either the foot or the hand (see Fig. 9) (Zehr et al. 2001). Responses were recorded from multiple ipsilateral and contralateral muscles, particularly from those that cross the ankle, wrist, and shoulder joints. These connections provide a means for the direct relay of sensory information through the nervous system that could be used to increase coordination between the arms and legs for balance and movement.

During walking, phase-dependently modulated interlimb reflexes in leg muscles were observed after wrist stimulation (superficial radial nerve) and in arm muscles after ankle stimulation (superficial peroneal nerve) (Haridas and Zehr 2003). Compensatory responses at the ankle were reversed (see Fig. 10), where stimulation at the foot caused ankle plantarflexion, and stimulation at the hand caused dorsiflexion (Haridas and Zehr 2003). Connections between the arms and legs have also been identified during other arm and leg movements, including leg cycling (Sasada et al. 2010). Responses to superficial radial nerve stimulation in the arms were evaluated, and it was found that cutaneous reflexes in arm muscles were modulated by leg cycling and further amplified with increased leg cycling frequency (Sasada et al. 2010).

Afferent signals related to specific arm movement are crucial signals to modify leg muscle activity through linked CPGs. Phase-dependent responses found in muscles of all four limbs during rhythmic movement are modulated in a way suggestive of coupling between segmental spinal networks (Duysens et al.

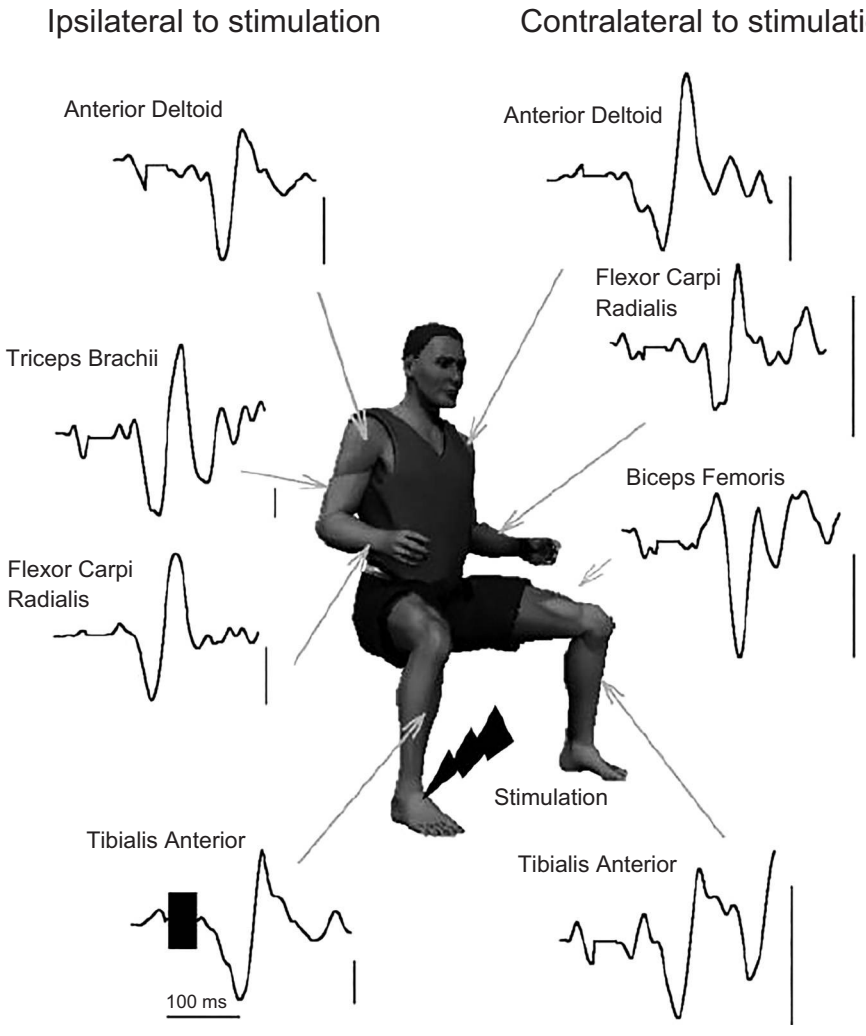

Fig. 9. Interlimb responses to superficial peroneal nerve stimulation. Shown are the mean electromyographic responses ($n = 50$ sweeps) from different single subjects. Responses are shown for muscles ipsilateral (*left* side) and contralateral (*right* side) to the site of stimulation. In each trace the stimulus artifact has been blanked during the interval shown by the solid black rectangle for ipsilateral tibialis anterior. Arrows indicate the approximate anatomical location for each muscle. Individual calibration bars represent 20% maximum voluntary contraction for each muscle shown. Note that different scales are used to highlight the reflexes for each muscle because reflex amplitudes were of different sizes across muscles, and thus the size of the calibration bar is different in each graph. [Adapted from Zehr et al. (2001).]

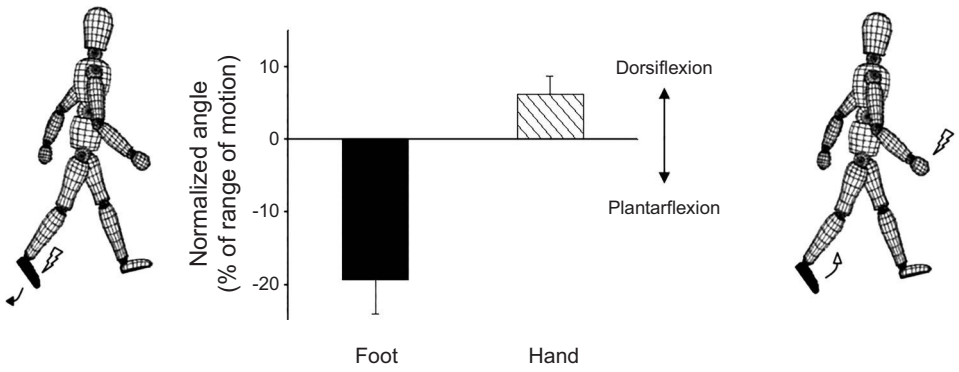

Fig. 10. Summary of the kinematic changes at the ankle with superficial peroneal nerve stimulation at the stance-swing transition for both the ipsilateral (*left*) and contralateral (*right*) sides. Solid foot represents the foot in which the response to stimulus occurred. Jagged arrow indicates site of stimulation; solid arrow indicates plantar flexion; open arrow indicates dorsiflexion. Note the changes in ankle kinematics with different sites of stimulation. [Adapted from Haridas and Zehr (2003).]

1992, 1996; Haridas and Zehr 2003; Yang and Stein 1990; Zehr et al. 2003b). For example, rhythmic arm movement significantly contributed to reflex expression in the legs (Balter and Zehr 2007). The largest effect was observed during the power phase of arm and leg cycling, which is at a comparable time to heel strike in walking. The contribution from the arm at this point could be explained by a reliance on multisensory integration to ensure limb placement and safe walking.

Clues from mechanical changes in interlimb coordination.

> "The authorities are excellent at amassing facts, though they do not always use them to advantage."
>
> "The Adventure of the Naval Treaty" in *The Memoirs of Sherlock Holmes* (1893)

Arm swing is coordinated with the legs, and the frequency of the relationship depends on walking speed (Craik et al. 1976; Donker et al. 2002). At most walking speeds (normal walking, jogging, running), this pattern consists of a 1:1 frequency ratio with out-of-phase arm swing where each arm is paired with its contralateral leg and synchronized with stride frequency. Even across quadrupedal tasks such as walking, creeping, and swimming, arm and leg movements remain frequency-locked with a fixed relationship (Wannier et al. 2001). The characteristics of this coordination correspond to the observation that coordination is indicative of intrinsic spinal interconnections between the upper and lower spinal CPGs that are engaged in the locomotor function (Wannier et al. 2001).

To further reveal changes in interlimb coordination due to changes in interlimb kinetics, weights were added to the wrist or ankle (Donker et al. 2002). Adding mass to the wrist during walking resulted in increased muscle activity in both arms and a decrease in the movement amplitude in only the loaded limb but did nothing to change leg kinematics or cadence. Conversely, adding load to the ankle produced increased muscle activity and movement amplitude in both arms (Donker and Beek 2002; Donker et al. 2002). These results indicate that during walking, the loading of one of the limbs induces a general reorganization, involving all participating bodily segments, presumably to maintain balance while providing rhythm constancy. Alterations in coupling patterns between upper and lower extremities are also shown with changes in walking speed and implicate interaction among CPGs. Decreasing walking velocity to relatively slow speeds at approximately $<0.7–0.8$ m/s causes both arms to swing minimally and in phase at twice the ipsilateral step frequency (producing a 2:1 frequency ratio) (Donker et al. 2001; Ford et al. 2007; Wagenaar and van Emmerik 2000), resulting in a change in interlimb coordination between the arms and the legs. As humans change walking speed, the nervous system adapts muscle activation patterns to modify arm swing to the appropriate frequency (Collins et al. 1993).

Coordination of arm and leg movements during human locomotion has also been evaluated by examining the effects of small leg perturbations during gait on leg and arm EMG activity (Dietz et al. 2001). During walking with split-belt treadmill accelerations or decelerations or with stimulation of the distal tibial nerve, responses were observed in arm muscles that were small or absent during standing, largest when the perturbation was applied to the stance phase, and correlated to compensatory responses in the ankle dorsiflexor tibialis anterior muscle (Dietz et al. 2001). These observations show that there is a task-dependent, flexible neuronal coupling between lower and upper limb muscles as a residual function of quadrupedal locomotion (Dietz et al. 1994b, 2001). Also, by using a split-belt paradigm and applying four different combinations of left and right speed ratios, upper and lower limb coordination was revealed. Increasing the right-side belt speed caused increased amplitude in the right limb and decreased amplitude in the left limb but increased amplitude in both upper limbs (MacLellan et al. 2013) These observations show that CPGs for the upper and lower limb regulate full body movement to maintain the rhythmic locomotor pattern.

Further support for a ascending bias in locomotor coupling was found when deliberate changes in leg cycling cadence led to modified arm cycling cadence, but voluntary changes in arm cycling cadence did not affect the legs (Sakamoto et al. 2007). This was evaluated by using a combined arm and leg cycling task where arm and leg ergometers were mechanically independent.

In addition to changes in frequency coupling and kinematic amplitudes as a result of altering interlimb coordination, changes in EMG amplitudes also emerge. Active arm movement during arm and leg recumbent stepping significantly increased involuntary activation of the leg muscles (Ferris et al. 2006; Huang and Ferris 2004). This observation was only seen when the arms were active and disappeared when the legs were externally driven. The effect of changing arm movement frequency on interlimb coupling and leg activation was also examined during recumbent stepping (Kao and Ferris 2005). Fast upper limb movement facilitated neuromuscular recruitment of lower limb muscles (Kao and Ferris 2005), likely via spinal interlimb connections from propriospinal neural circuitry (Dietz 2002; Kao and Ferris 2005).

In a final paradigm revealing interlimb connections, when participants were laid horizontally on their side with each leg suspended in an unloading exoskeleton, locomotor-like leg movements were evoked by rhythmic arm movements, reminiscent of Graham Brown's early work (Sylos-Labini et al. 2014a). Leg movements were accompanied by EMG activity in proximal leg muscles, which were modulated over each movement cycle and displayed similar timing as in normal locomotion (Sylos-Labini et al. 2014a). In particular, movement at the shoulder increased activity of hip muscles and amplitude of hip and knee joint movements, whereas and movement of the forearms and wrists had a similar facilitating effect but with a stronger influence on distal segments (Selionov et al. 2016).

Clues from remote modulation of spinal cord excitability.

> "Never trust to general impressions, my boy, but concentrate yourself upon details."

"A Case of Identity" in *The Adventures of Sherlock Holmes* (1891)

Determining the specific locus mediating interlimb coordination is difficult because of the concurrent and interfering effects of rhythmic arm and leg activity. Interlimb reflex effects could result from afferent signals arising from the rhythmic movement (Haridas and Zehr 2003). To mitigate these effects, interlimb coordination has been examined by evaluating the remote effects of rhythmic movement on stationary limbs (Frigon et al. 2004). An interaction between upper limb posture and reflex transmission in the lower limb was first identified by changes in upper limb posture altering stretch reflexes in soleus, quadriceps, and biceps femoris muscles (Delwaide et al. 1977). In addition, passive flexion and extension movements at the elbow facilitated soleus H-reflex amplitudes (Hiraoka and Nagata 1999), and conversely, arm swing movements reduced soleus H-reflex amplitudes (Hiraoka 2001).

An observation of interlimb effects has also been made by systematically examining the effects of remote movement on H-reflex excitability (Frigon et al. 2004). In this paradigm, subjects performed rhythmic arm cycling while soleus H-reflexes were evoked and recorded (see Fig. 11). During arm cycling, soleus H-reflexes were significantly reduced compared with amplitudes evoked when no arm movement was performed (Frigon et al. 2004). These results provided evidence of the existence of neuronal coupling between the arms and the legs (de Ruiter et al. 2010; Dietz 2002; Dragert and Zehr 2009; Frigon et al. 2004; Hundza and Zehr 2009; Hundza et al. 2012; Loadman and Zehr 2007; Mezzarane et al. 2011; Zehr et al. 2007c). The effect of arm cycling on soleus H-reflex excitability is independent from background EMG; therefore, a spinal process is presumed where suppression comes from increased segmental Ia presynaptic inhibition from arm CPG circuits (Frigon et al. 2004).

Subsequent studies were conducted to further evaluate and characterize this observation of modulation of soleus H-reflex amplitude induced by rhythmic arm cycling. It was found that there was phase-dependent modulation of suppression that displayed a bell-shaped modulation curve (de Ruiter et al. 2010). It also was found that soleus H-reflexes were suppressed for all arm, trunk, or leg movements, but a distinct and marked reflex modulation occurred during locomotor-like anti-phase arm swing and was maximally suppressed at a moment when the heel strike would occur (Massaad et al. 2014). Changes in arm range of motion during cycling, resulting in muscle length changes, did not alter soleus H-reflex suppression (Loadman and Zehr 2007), and an inhibitory effect was only observed with active, rhythmic arm cycling and was not apparent during passive, externally driven arm movement (Hundza et al. 2012). By varying arm cycling frequency from 0.3 to 2 Hz, a threshold of ~0.8 Hz for the interlimb modulation was discovered (Hundza and Zehr 2009). This was interpreted as a threshold frequency for effective activation of CPG elements for rhythmic arm movement that are then signaled to the lumbar spinal cord. It is worth pointing out that this frequency of 0.8 Hz is very close to the intrinsic cycle frequencies for many locomotor systems. Increased frequency of upper limb movement also enhanced the modulatory effect of arm cycling on soleus H-reflex excitability (Hundza and Zehr 2009). There was no additional effect of varying arm cycling load or by adding vibration to the arm muscles (Hundza et al. 2012). After stroke, partial preservation of the descending modulatory effects of rhythmic arm cycling on lumbosacral spinal cord excitability can be seen where arm cycling modulates the soleus H-reflex (Barzi and Zehr 2008) and stretch reflex (Mezzarane et al. 2014).

In the reverse experiment, it was shown that leg cycling also leads to suppression of H-reflexes in stationary arm muscles, including the FCR (Zehr et al. 2007c). However, the temporal resolution (i.e., number of phases analyzed) needed to detect phase-dependent modulation was lacking. In walking, when 16 phases of movement were analyzed, phase-dependent modulation of H-reflexes in FCR was evident (Domingo et al. 2014). To highlight the importance of movement-related

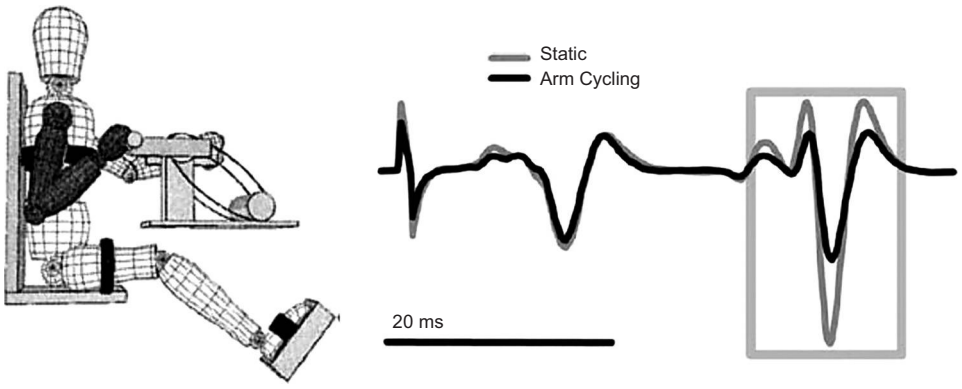

Fig. 11. Inhibition of soleus H-reflex amplitude by arm cycling. Amplitudes during cycling (black line) and during static trials (gray line) are shown for a single subject. The gray rectangle indicates the H reflex. Control data are taken during static contraction at the same position sampled during arm cycling. [Adapted from Frigon et al. (2004).]

feedback in modifying interlimb coordination, as opposed to load-related feedback, FCR H-reflex amplitudes were studied during robotic-assisted stepping with and without body weight support (Nakajima et al. 2011). Reflexes in the forearm muscles were suppressed with stepping, and suppression was seen at all phases of stepping, irrespective of whether stepping was unloaded or body weight support was provided (Nakajima et al. 2011).

With the use of this interlimb paradigm, observations to support the idea that the interlimb mechanics underlying arm and leg coupling are preferentially expressed during rhythmic tasks came from studying subthreshold segmental Ia presynaptic inhibition conditioning (Nakajima et al. 2013). Conditioning the H-reflex with superficial radial nerve stimulation removes the suppression effect of leg cycling, and radial nerve stimulation amplifies suppression. When conditioning stimulation intensity was reduced so that there was no postsynaptic effect, it was shown that conditioning reemerged only during the rhythmic locomotor behavior (Nakajima et al. 2013). Together, these results suggest that it is a central motor command, likely from the spinal cord, as the main source of regulation.

Summary of the evidence of distributed CPG elements and interlimb connectivity. Indirect observation from human studies supports the observation that CPG networks are distributed in cervical and lumbar spinal cord areas and are interconnected for functional interlimb locomotor integration. In the arms, as in the legs, observations of rhythmic muscle activity and task- and phase-dependent modulation of reflexes suggest that regulation is from CPGs. Between the arms and legs, there is a measurable functional neural coupling during rhythmic movement. This is shown by flexible interactions between lower and upper limb muscles from mechanical changes in interlimb coordination, the presence of task- and phase-dependent interlimb reflex modulation, and modulatory effects of remote rhythmic activity on local reflex excitability. Overall, these data suggest that interlimb coordination is apparent and contributes to the control of human locomotion.

Interlimb coordination likely arises from distributed locomotor network interactions between the cervical and lumbar CPGs. Some of this coordination clearly arises also from descending supraspinal commands along with these interactions; however, many of the observations found in neurologically intact participants are mirrored in participants with SCI and stroke with diminished descending influences. In addition, reflex effects, recorded at latencies shorter than what can be influenced by descending supraspinal commands, implicate the contribution of lower level structures such as spinal cord networks.

5) Some evidence that locomotor retraining induces recovery of walking ability

> "I have seldom known a case which at first sight presented a more singular problem."
>
> "The Adventure of the Devil's Foot" (1910)

As detailed above, evidence suggests that, like other animals, we humans have access to locomotor pattern generating networks that are capable of coordinating the basic walking pattern. It also appears that at least some of the neural networks responsible for producing rhythmic movement are housed within the spinal cord. We have seen that in other animals with task-specific therapy, such circuits are amenable to retraining and plastic adaptation. A major translational implication of this observation is that the evidence of related observations should be seen in humans.

From studies in other animals after spinal cord transection, evidence shows the remaining spinal pathways can be trained by using treadmill walking to facilitate positive use-dependent plasticity corresponding to enhanced recovery of walking (Barbeau and Rossignol 1987). In cats with complete spinal cord transection at T12–L1 between the forelimbs and hindlimbs, hindlimb stepping recovered after 3–4 weeks of intense daily treadmill training. Initially after the injury, cats demonstrated a poorly organized hindlimb stepping pattern, but after training, they demonstrated a "near-normal" pattern. EMG recordings from hindlimb muscles in trained spinal cats are generally similar to those from intact cats and many of the normal muscle and skin reflex responses are apparent. Furthermore, by the end of training, the cats were able to adjust the locomotor cycle to adapt to varying treadmill speeds (Barbeau and Rossignol 1987), which suggests functional recovery.

Clues from interlimb neural coupling after stroke and spinal cord injury.

> "Those are the facts of the case, Doctor, and if they are of any use to your collection, I am sure that they are very heartily at your service."
>
> "The Adventure of The Gloria Scott" (1893)

In humans with neurotrauma, remaining neural networks are strengthened with training proposed to enable activation of spinal cord circuitry that restores normal CPG function and corresponding locomotor activity (Dobkin 2004; Langhorne et al. 2009). Caveats remain, however, about the extent to which pathways mediating arm and leg movement remain accessible after neurological damage such as SCI and stroke.

Data on interlimb responses obtained in persons with cervical SCI and stroke suggest that pathways mediating arm and leg interactions are conserved and remain accessible after neurological damage (Calancie 1991; Calancie et al. 1996; Wirz et al. 2001; Zehr and Loadman 2012; Zehr et al. 1998, 2009b). In chronic stroke, partial preservation of rhythmic patterning of arm muscle activation and neural control of spinal cord excitability during arm cycling persists in both the more and the less affected arms but is somewhat "blunted" (Zehr et al. 2012). The simplest explanation is that presumed pattern generator contributions to rhythmic human arm movement remain accessible after injury. The observation of bigger impairment of discrete reaching than of rhythmic actions after stroke also supports subcortical contributions (Leconte et al. 2016). Interlimb coupling is also partially preserved after stroke (Zehr et al. 2007b). Bilateral (but weaker on the more affected side) modulation of soleus H-reflex amplitudes during arm cycling was also evident after stroke. Subsequent experiments assessing stretch reflexes in chronic stroke participants produced bidirectional reflex modulation induced by arm cycling (Mezzarane et al. 2014). Interlimb reflex coupling is also maintained after stroke (Zehr and Loadman 2012), as deduced from cutaneous stimulation in the more affected arm or leg during walking (see Fig. 12).

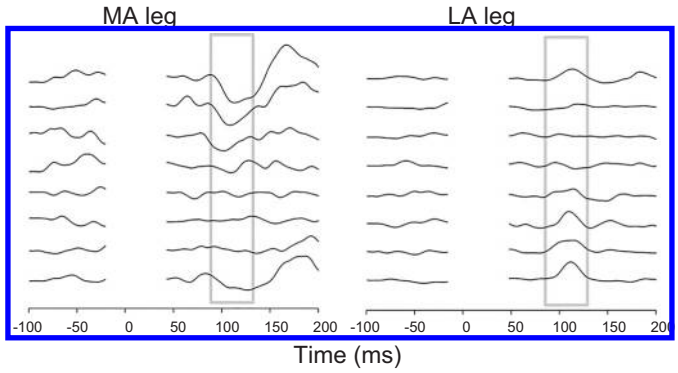

Fig. 12. Single-subject example of cutaneous interlimb reflexes evoked by superficial radial nerve stimulation in the biceps femoris muscle of the more affected (MA) and less affected (LA) leg of a stroke participant. The gray rectangle highlights the middle latency response. [Adapted from Zehr and Loadman (2012).]

Thus the evidence suggests that after neurotrauma, neural pathways remain open and accessible. If the pathways are preserved after neurological injury, perhaps they are amenable to training-induced plasticity from locomotor rehabilitation exercise.

Clues from locomotor retraining interventions in humans with neurological injury.

"I can discover facts, Watson, but I cannot change them."

"The Problem of Thor Bridge" (1922)

For other animals, step training is made possible by placing the animal over a treadmill. The ability to step with training is replicated in humans with body weight-supported treadmill training therapy (Duncan et al. 2011; Moseley et al. 2003; Senthilvelkumar et al. 2015). For this therapy, participants practice walking on a motorized treadmill with a harness system providing body weight support, and stepping movements are achieved with the help of robotic interfaces or therapists.

In humans with clinically complete SCI, there is evidence that treadmill training can improve some aspects of walking. After training in patients who were otherwise unable to voluntarily produce muscle activation, some locomotor activity with rhythmic leg muscle activation patterns could be elicited (Dietz et al. 1995, 1998; Maegele et al. 2002). Even individuals with clinically motor complete paralysis demonstrated modulated activity of distal leg muscles during assisted stepping with body weight support (Dietz 2002; Harkema et al. 1997). As training progressed, the levels of applied body weight support significantly decreased (Dietz et al. 1995) and activity in leg extensor muscles significant increased (Wirz et al. 2001). These improvements are thought to be a consequence of a reactivation of neural circuits located at the spinal level (Van de Crommert et al. 1998). Taken together, these findings support the idea that the stepping ability of clinically complete SCI subjects can improve in response to step training. However, in all of these cases, some weight support assistance was provided, and patients did not recover enough for independent walking.

Results from this therapy, where training leads to improved walking for those with neurological injury, remain positive (Dietz et al. 1998; Dobkin 2004; Duncan et al. 2011; Edgerton et al. 2001; Field-Fote 2001; Moseley et al. 2003). Yet, body weight-supported treadmill training does not fully exploit the neuronal and mechanical linkages between the arms and legs that are vital in normal human walking (Dietz and Michel 2009; Ferris et al. 2006; Klimstra et al. 2009; Zehr et al. 2009b). Normal walking involves arm movement, which we assume is regulated by spinal CPG networks that are functionally integrated with those for the legs. With body weight-supported treadmill training, the arms are typically used for postural support on parallel bars or hand rails to help bear weight from the legs (Behrman and Harkema 2000). With current therapies, the lack of involvement with the arms not only adds to the neural limitations that are already present due to the pathology, but impaired arm function may actually inhibit rhythmic stepping of the legs (Behrman and Harkema 2000). To optimize the benefits of task-dependent rehabilitation, given that the arms are linked to the legs during locomotion, it has been suggested that rehabilitation include arm movements (Behrman and Harkema 2000; Dietz 2002; Ferris et al. 2006; Klimstra et al. 2009; Zehr et al. 2009b, 2016).

Indeed, several studies have found benefits of incorporating arm movements in gait rehabilitation. In subjects with incomplete cervical SCI, when arm activity is incorporated with locomotor-like arm and leg movements, leg muscle activity is facilitated (Kawashima et al. 2008). Gait symmetry and a more normal presentation of EMG were also apparent in patients with spastic paresis when arm swings were incorporated with body weight-supported treadmill training (Visintin and Barbeau 1994). Compared directly with a paradigm that focuses on leg training alone, FES-assisted arm and leg cycling nearly doubles the improvements in overground walking capacity following SCI (Zhou et al., in press). Thus activation of cervicolumbar networks, compared with lumbar networks alone, is critical to enhancing the benefits of rehabilitation.

This strategy is also effective in people with stroke where, after arm and leg cycling training (meant to activate similar cervicolumbar neural networks as walking), plasticity (Klarner et al. 2016a) and improved neurological integrity and locomotor ability (Klarner et al. 2016b) were obtained. In this paradigm, participants with chronic stroke performed 30 min of arm and leg cycling training (at a frequency of ~0.9 Hz) 3 times a week for 5 wk (Klarner et al. 2014a).

The extent to which rhythmic arm training by itself activates interlimb CPG networks for locomotion was also recently assessed by studying chronic stroke participants before and after 5 wk of arm cycling training (Kaupp et al. 2018). Strength, assessed bilaterally via maximal voluntary isometric contractions in the legs and hands, was improved for grip and plantarflexion on the more affected side following arm cycling training. Muscle activation during arm cycling was also enhanced, and a "normalization" of cutaneous reflex modulation was observed. There was also enhanced activity in the dorsiflexor muscles on the more affected side during the swing phase of walking, and interlimb coupling was shown to be increased as assessed by modulation of soleus stretch reflex amplitudes during arm cycling after training. Improvement in clinical evaluations also resulted, showing improved walking ability and balance. These results are most easily explained by training-induced changes in CPG function and interlimb connectivity and underscore the need for arm training in the

functional rehabilitation of walking after neurotrauma. At least some of this improvement was directly related to rhythmic activation of the arms, because arm cycling training alone produced similar improvements in walking capacity (Kaupp et al. 2018).

As well as maximization of the contribution of arm activity to the recovery of activity in the leg muscles, another part of the nervous system to maximize is the contribution of sensory feedback. Rehabilitation procedures for SCI patients should not only look to active locomotor CPGs from both the arms and the legs but also maximize phase-appropriate sensory signals. For example, the use of periodic stimulation to ankle muscle load afferents or stimulation to hip flexor stretch receptors could usefully entrain CPG function (Duysens and Pearson 1998).

Because training improvements after stroke or incomplete SCI in humans are partially correlated with increased corticospinal drive to muscles and/or increased activity in cortical areas (Dobkin 2004; Dobkin et al. 2004; Winchester et al. 2005), the engagement of supraspinal motor areas may also be beneficial for gait recovery (van den Brand et al. 2012). There are several ways to mimic supraspinal initiation of locomotion experimentally. For example, transcutaneous electrical stimulation of the spinal cord can be used as a noninvasive tool for activation of locomotor circuitry in humans (Gorodnichev et al. 2012). Indirect activation can also be achieved with peripheral muscle vibration, where steplike behavior is generated in those with SCI (Field-Fote et al. 2012). The addition of neuromodulators can also be used to boost lumbar CPG activation and bipedal stepping expression (Guertin 2013). Although the majority of this research is on animals, there is some evidence to suggest that the pharmacological activation of locomotor CPGs may improve function and walking speed in severely impaired individuals with SCI (Domingo et al. 2012). In this example, clonidine and cyproheptadine were administered. Interestingly the same or similar derivates of these pharmacological agents can be used to reactivate CPGs in other animals as well as in humans. The fact that the same chemical can be used to activate spinal cord circuitry points to a conservation of nervous system control across species.

Determining the exact localization of CPG elements in the human spinal cord will prove useful in the development of novel approaches for rehabilitation. With information on the exact location of a CPG, more directed therapies, such as intraspinal stimulation or epidural drug delivery, could be usefully applied to fully maximize spinal cord excitability. If we can make more definite conclusions about CPG location and the mechanisms involved in interlimb communication, more targeted approaches can be invented.

Summary of the evidence that locomotor retraining improves walking integrity consistent with CPG adaptations. The neural control of walking is not completely similar between humans and other quadrupeds, and although walking improvements are seen with locomotor training, they are not as profound as those found in quadrupeds like the cat (Barbeau and Rossignol 1987; Lovely et al. 1986) and nonhuman primates (Eidelberg et al. 1981; Fedirchuk et al. 1998). Differences in locomotor recovery between humans and other animals suggest that adult human locomotion is certainly under more supraspinal regulation and control than that found in other animals (reviewed in Capaday 2002; Nielsen 2003; Yang and Gorassini 2006). Although this is the case, humans do benefit from exercise therapy, and to fully maximize recovery, rehabilitation programs should incorporate rhythmic arm movements. As a means of further bolstering activity, all parts of the nervous system should be activated. Including contributions from appropriately timed sensory feedback signals or adding electrical, mechanical, or chemical stimulation to nervous system function may help to further amplify the effects of rehabilitation.

SUMMARY OF THE "CLUES" AND EVIDENCE IN THE CASE FOR HUMAN LOCOMOTOR CENTRAL PATTERN GENERATOR

> "...but none the less you must come round to my view, for otherwise I shall keep on piling fact upon fact on you, until your reason breaks down under them and acknowledges me to be right."
>
> "The Red-Headed League" in *The Adventures of Sherlock Holmes* (1892)

In this review we used a deductive reasoning approach, made popular by the fictional character Sherlock Holmes, to present and assess indirect evidence for CPG networks in humans. Below is a summary of the "clues" and evidence for key observations of human locomotor CPGs.

1) Some Evidence for a Spinal CPG Address in Humans

Observations of spontaneous rhythmic movements in the legs, particularly from those with complete SCI, provide compelling evidence for the contributions of spinal networks to CPG activity regulating locomotion in humans. Other evidence for a spinal CPG comes from observations of air-stepping in healthy participants, an indirect observation of sleep-related rhythmic leg movement, and study of the stepping response in human infants.

However, sensory feedback below the level of the injury is still intact and cannot be discounted in modifying the locomotor rhythm. On this basis, the observation in animals that the spinal cord in isolation can produce rhythmic activity via a CPG is not fully supported in bipedal humans.

It is apparent that the human spinal cord is much more reliant on supraspinal control for the expression of locomotor activities compared with other quadrupedal animals (Barthélemy et al. 2011; Beloozerova et al. 2013; Capaday 2002; Nielsen 2003; Petersen et al. 2012; Yang and Gorassini 2006). This is not surprising given the mechanical differences in quadrupedal vs. bipedal gait.

Therefore, because of an increased reliance on supraspinal control during walking, it is concluded that the CPG network in humans is much more distributed throughout the central nervous system compared with that in other animals. More definite evidence is needed to fully determine the anatomical and functional delineations and hierarchies of the locomotor CPG.

2) Some Evidence That Sensory Feedback is Modulated During Human Locomotion

Although CPGs can function without sensory input, peripheral feedback signals gained during locomotor movements are strong modulators capable of altering the activity of CPG networks, exposing their flexibility and adaptability. In other animal studies, direct connections between sensory feedback

and CPG activity have been shown where feedback entrains and modifies rhythmic CPG activity.

In humans, indirect methodologies for examining the modulation of reflexes during rhythmic movement are used as an indicator of CPG regulation of afferent input. Reflexes, arising because of activation of afferent projections from receptors in skin and muscle, have been studied widely and support the role of locomotor CPGs in the neural control of rhythmic human movement. CPG activity allows for flexible transmission of sensory feedback during gait where signals are controlled and modulated by the motor task and phase of transmission. In this way the relationship between sensory feedback and CPG networks goes both ways: sensory feedback during rhythmic movement modulates CPG output, and the state of the CPG gates the expression of sensory feedback. Thus afferent information from the periphery (i.e., the limbs) influences the central pattern, and, conversely, the CPG selects appropriate afferent information according to the external requirement (Dietz 2003). In addition to this, part of the reflex modulation could be influenced by changes in descending supraspinal input (Duysens et al. 2004).

Nevertheless, changes in modulation of the expression of sensory reflexes certainly point to a central mechanism gating inputs and outputs during rhythmic movement. This was seen as an observation that phase-dependent modulation is only apparent with voluntary movement and not passive, is independent from background EMG, is not influenced by feedback in other sensory pathways, and is evident after supraspinal damage. These clues provide the main data on which the concept of spinal CPGs in humans has been built. Sensory feedback allows for CPG output to not simply be a stereotyped pattern of flexor and extensor activity, but to have usefulness in a wide variety of situations where feedback provides the cues required to make CPGs respond in behaviorally appropriate ways. Therefore, as in cats, humans possess a CPG for locomotion that is capable not only of rhythmic pattern generation but also remarkable sensory feedback-induced modulation and adaptation.

3) Some Evidence for Similar Neuronal Networks Recruited into Different Rhythmic Human Motor Tasks

In other animals it has been shown that the circuits producing pattern generation are the same across different functional tasks. If shared circuitry for various rhythmic movements are also within the human spinal cord, it should be observed as a characteristic of human reflex modulation. Indeed, as in other animals, in humans it has been demonstrated that there is a conservation of neural control in movements of different directions and in different full body rhythmic tasks. This observation is supported in neurologically intact participants and in those with stroke. In the latter model, the existence of common neural patterning across rhythmic tasks implies a central processing, because stroke does not seem to significantly affect common neural regulation. Thus the observation of similar neuronal networks recruited into different rhythmic tasks as seen in other animals is also supported in humans.

4) Some Evidence of Cervical and Lumbar Locomotor Networks and Interlimb Connectivity in Human Locomotion

Direct intracellular measurements have revealed that the CPG network in quadrupeds are distributed in the cervical and lumbar sections of the spinal cord, leading to a hypothesis that a cervicolumbar network should exist for humans too. Indeed, indirect observation from human studies supports that CPG networks are distributed in cervical and lumbar spinal cord areas and are interconnected for functional interlimb integration. Rhythmic forelimb movements are controlled by cervical spinal CPGs, as evidenced during fictive locomotion in cat. In humans, observations of rhythmic muscle activity and task-and phase-dependent modulation of reflexes suggests that the control of rhythmic arm movements, as in cat forelimbs, are from spinal CPGs. Also, there is evidence that control of rhythmic arm movements is similar to that of rhythmic leg movements; however, coupling between the arms is not as strong as that between the legs.

Despite the functional differences in usage of the upper limbs in humans compared with the cat, data suggest that interlimb coordination is apparent and contributes to the control of human locomotion. Between the arms and legs there is also a measurable functional neural coupling during rhythmic movement as shown by flexible interactions between lower and upper limb muscles from mechanical changes in interlimb coordination, the presence of task- and phase-dependent interlimb reflex modulation, and modulatory effects of remote rhythmic activity on local reflex excitability. Therefore, the clues suggest that similarly to other animals, humans also possess a distributed locomotor network and interlimb connectivity as a result of interconnected cervical and lumbar CPG networks.

5) Some Evidence That Locomotor Retraining Induces Recovery of Walking Ability

The translational implications of identifying that, indeed, a human CPG likely exists, and at least part of the circuity is contained within the spinal cord, mean that more targeted approaches to therapy can be planned. Activating these networks with locomotor training for those with stroke or SCI does lead to plastic adaptation as in other animals where some

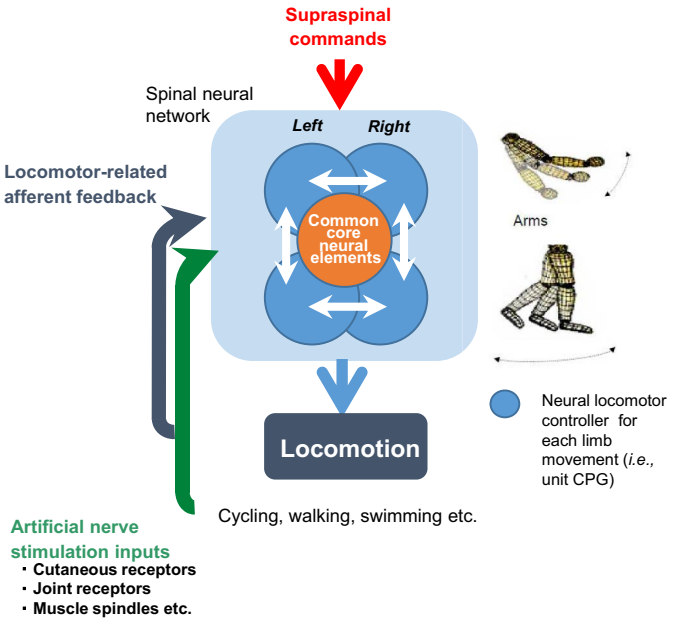

Fig. 13. Cartoon schematic indicating idealized interrelationships between supraspinal regulation, central pattern generator (CPG) patterning and reflex control, and afferent feedback. [Adapted from Zehr et al. (2016).]

parts of walking function are recovered. Maximizing the inherent functioning of the spinal cord and nervous system with the involvement of all four limbs, and with enhanced involvement of supraspinal areas, is most effective in promoting recovery of walking in humans.

In humans, the evidence suggests pathways mediating arm and leg movement remain accessible after neurological damage such as SCI and stroke. However, even with training, for humans with a complete SCI or even for those with anatomical sparing, the recovery of walking is not fully possible. This is in contrast to findings of locomotor recovery in other animals, although for these animals, only those with complete or severe training respond well to training, and a treadmill or harness must be provided. Observed differences in the success of locomotor training between other quadrupedal animals and humans may suggest a more distributed network requiring supraspinal regulation of spinal cord excitability.

To fully maximize the benefits of training, evidence also supports the inclusion of methods to bolster neural activity. For example, the addition of rhythmic arm activity as a regular part of locomotor rehabilitation after neurotrauma may facilitate stepping and may be an important component needed to harness interlimb neural coupling (de Kam et al. 2013; Ferris et al. 2006; Kawashima et al. 2008; Zehr et al. 2009b). In addition, it is also apparent that the engagement of supraspinal motor areas may be beneficial for gait recovery. CPG activity can be further boosted with the addition of neuromodulators that act on spinal cord interneurons to amplify activity.

OVERALL CASE CONCLUSION

> "I am a practical man, Mr. Holmes, and when I have got my evidence I come to my conclusions..."
>
> Scotland Yard's Inspector G. Lestrade in "The Cardboard Box" (1893)

Although direct evidence from animal models supports the notion that CPGs are involved in the control of locomotion, there is only indirect evidence in humans. In summary, all the evidential clues point to CPG activity that is shaped by afferent feedback and integrated to regulate all four limbs during locomotion in humans (see Fig. 13). This conclusion comes from evaluating the indirect evidence available in humans. Clues from observations of rhythmic movements in the legs of those with reduced supraspinal input provide the best evidence for a locomotor CPG in humans. A major difference from other animals lies in trying to deduce precisely where the CPG lives in the human nervous system. From studying stepping responses, especially in those with SCI, it can be concluded that at least part of the circuitry controlling rhythmic movement is contained within the spinal cord. However, given the balance demands required for human walking, there is a higher reliance on intact supraspinal input. Clues to support the role of locomotor CPGs in the neural control of rhythmic human movement also come from studying reflexes and their modulation during rhythmic movement. As in other animals, there are also clues to support an overlapping interlimb CPG network that controls rhythmic movements for both the arms and the legs.

Despite the fact that all the clues for a human locomotor CPG are indirect, there is still much evidence to suggest that the general operational principles for the control of rhythmic movement found in other animals extend as well to humans. We conclude that, indeed, rhythmic movements receive large contributions from neuronal central pattern generators, as found in other animals. Questions still remain on the exact locations of the CPG networks, how many there may be, and how they are coordinated across all limbs for rhythmic human locomotion.

Perhaps the most important translational implication of this conclusion is that locomotor recovery after neurological injury with task-specific training of the remaining networks should be possible in humans as it is in other animals. Indeed, improvements in walking are observed with different types of locomotor training. To further improve walking recovery, more direct information is needed on the structure and function of the human CPG. This information is critical to the novel design of targeted therapies for locomotor enhancement and recovery.

> "It was my duty to bring the facts to light, and there I must leave it..."
>
> "The Adventure of Shoscombe Old Place" (1927)

ACKNOWLEDGMENTS

We thank the participants who gave time and effort during experimental testing and training sessions in the original research summarized.

GRANTS

This project was supported by a Natural Sciences and Engineering Research Council of Canada Discovery grant (to E. P. Zehr).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

T.K. and E.P.Z. conceived and designed research; T.K. and E.P.Z. prepared figures; T.K. drafted manuscript; T.K. and E.P.Z. edited and revised manuscript; T.K. and E.P.Z. approved final version of manuscript.

REFERENCES

Abraham LD, Loeb GE. The distal hindlimb musculature of the cat. *Exp Brain Res* 58: 580–593, 1985. doi:10.1007/BF00235874.

Andersson O, Forssberg H, Grillner S, Lindquist M. Phasic gain control of the transmission in cutaneous reflex pathways to motoneurones during 'fictive' locomotion. *Brain Res* 149: 503–507, 1978. doi:10.1016/0006-8993(78)90493-6.

Ayers J, Carpenter GA, Currie S, Kinch J. Which behavior does the lamprey central motor program mediate? *Science* 221: 1312–1314, 1983. doi:10.1126/science.6137060.

Balter JE, Zehr EP. Neural coupling between the arms and legs during rhythmic locomotor-like cycling movement. *J Neurophysiol* 97: 1809–1818, 2007. doi:10.1152/jn.01038.2006.

Barbeau H, Rossignol S. Recovery of locomotion after chronic spinalization in the adult cat. *Brain Res* 412: 84–95, 1987. doi:10.1016/0006-8993(87)91442-9.

Barthélemy D, Grey MJ, Nielsen JB, Bouyer L. Involvement of the corticospinal tract in the control of human gait. *Prog Brain Res* 192: 181–197, 2011. doi:10.1016/B978-0-444-53355-5.00012-9.

Barzi Y, Zehr EP. Rhythmic arm cycling suppresses hyperactive soleus H-reflex amplitude after stroke. *Clin Neurophysiol* 119: 1443–1452, 2008. doi:10.1016/j.clinph.2008.02.016.

Behrman AL, Harkema SJ. Locomotor training after human spinal cord injury: a series of case studies. *Phys Ther* 80: 688–700, 2000.

Beloozerova IN, Stout EE, Sirota MG. Distinct thalamo-cortical controls for shoulder, elbow, and wrist during locomotion. *Front Comput Neurosci* 7: 62, 2013. doi:10.3389/fncom.2013.00062.

Brooke JD, Cheng J, Collins DF, McIlroy WE, Misiaszek JE, Staines WR. Sensori-sensory afferent conditioning with leg movement: gain control in spinal reflex and ascending paths. *Prog Neurobiol* 51: 393–421, 1997. doi:10.1016/S0301-0082(96)00061-5.

Brooke JD, McIlroy WE, Staines WR, Angerilli PA, Peritore GF. Cutaneous reflexes of the human leg during passive movement. *J Physiol* 518: 619–628, 1999. doi:10.1111/j.1469-7793.1999.0619p.x.

Brown DA, Kukulka CG. Human flexor reflex modulation during cycling. *J Neurophysiol* 69: 1212–1224, 1993. doi:10.1152/jn.1993.69.4.1212.

Brown TG. The intrinsic factors in the act of progression in the mammal. *Proc R Soc Lond B Biol Sci* 84: 308–319, 1911. doi:10.1098/rspb.1911.0077.

Brown TG. On the nature of the fundamental activity of the nervous centres; together with an analysis of the conditioning of rhythmic activity in progression, and a theory of the evolution of function in the nervous system. *J Physiol* 48: 18–46, 1914. doi:10.1113/jphysiol.1914.sp001646.

Buford JA, Smith JL. Adaptive control for backward quadrupedal walking. III. Stumbling corrective reactions and cutaneous reflex sensitivity. *J Neurophysiol* 70: 1102–1114, 1993. doi:10.1152/jn.1993.70.3.1102.

Bui TV, Stifani N, Akay T, Brownstone RM. Spinal microcircuits comprising dI3 interneurons are necessary for motor functional recovery following spinal cord transection. *eLife* 5: e21715, 2016. doi:10.7554/eLife.21715.

Burke D, Dickson HG, Skuse NF. Task-dependent changes in the responses to low-threshold cutaneous afferent volleys in the human lower limb. *J Physiol* 432: 445–458, 1991. doi:10.1113/jphysiol.1991.sp018393.

Burke RE. The use of state-dependent modulation of spinal reflexes as a tool to investigate the organization of spinal interneurons. *Exp Brain Res* 128: 263–277, 1999. doi:10.1007/s002210050847.

Burke RE, Degtyarenko AM, Simon ES. Patterns of locomotor drive to motoneurons and last-order interneurons: clues to the structure of the CPG. *J Neurophysiol* 86: 447–462, 2001. doi:10.1152/jn.2001.86.1.447.

Büschges A, Akay T, Gabriel JP, Schmidt J. Organizing network action for locomotion: insights from studying insect walking. *Brain Res Brain Res Rev* 57: 162–171, 2008. doi:10.1016/j.brainresrev.2007.06.028.

Bussel B, Roby-Brami A, Azouvi P, Biraben A, Yakovleff A, Held JP. Myoclonus in a patient with spinal cord transection. Possible involvement of the spinal stepping generator. *Brain* 111: 1235–1245, 1988.

Butler JE, Godfrey S, Thomas CK. Interlimb reflexes induced by electrical stimulation of cutaneous nerves after spinal cord injury. *PLoS One* 11: e0153063, 2016. doi:10.1371/journal.pone.0153063.

Calancie B. Interlimb reflexes following cervical spinal cord injury in man. *Exp Brain Res* 85: 458–469, 1991. doi:10.1007/BF00229423.

Calancie B. Spinal myoclonus after spinal cord injury. *J Spinal Cord Med* 29: 413–424, 2006. doi:10.1080/10790268.2006.11753891.

Calancie B, Lutton S, Broton JG. Central nervous system plasticity after spinal cord injury in man: interlimb reflexes and the influence of cutaneous stimulation. *Electroencephalogr Clin Neurophysiol* 101: 304–315, 1996. doi:10.1016/0924-980X(96)95194-2.

Calancie B, Needham-Shropshire B, Jacobs P, Willer K, Zych G, Green BA. Involuntary stepping after chronic spinal cord injury. Evidence for a central rhythm generator for locomotion in man. *Brain* 117: 1143–1159, 1994.

Capaday C. The special nature of human walking and its neural control. *Trends Neurosci* 25: 370–376, 2002. doi:10.1016/S0166-2236(02)02173-2.

Capaday C, Stein RB. Amplitude modulation of the soleus H-reflex in the human during walking and standing. *J Neurosci* 6: 1308–1313, 1986. doi:10.1523/JNEUROSCI.06-05-01308.1986.

Carroll TJ, Baldwin ERL, Collins DF, Zehr EP. Corticospinal excitability is lower during rhythmic arm movement than during tonic contraction. *J Neurophysiol* 95: 914–921, 2006. doi:10.1152/jn.00684.2005.

Carroll TJ, Zehr EP, Collins DF. Modulation of cutaneous reflexes in human upper limb muscles during arm cycling is independent of activity in the contralateral arm. *Exp Brain Res* 161: 133–144, 2005. doi:10.1007/s00221-004-2050-7.

Cheng J, Brooke JD, Misiaszek JE, Staines WR. Crossed inhibition of the soleus H reflex during passive pedalling movement. *Brain Res* 779: 280–284, 1998. doi:10.1016/S0006-8993(97)01168-2.

Chervin RD, Consens FB, Kutluay E. Alternating leg muscle activation during sleep and arousals: a new sleep-related motor phenomenon? *Mov Disord* 18: 551–559, 2003. doi:10.1002/mds.10397.

Clardy SL, Connor JR. Restless leg syndrome. In: *Encyclopedia of Neuroscience*, edited by Squire LR. Oxford, UK: Academic, 2009, p. 131–135.

Coleman RM, Pollak CP, Weitzman ED. Periodic movements in sleep (nocturnal myoclonus): relation to sleep disorders. *Ann Neurol* 8: 416–421, 1980. doi:10.1002/ana.410080413.

Collins DF, McIlroy WE, Brooke JD. Contralateral inhibition of soleus H reflexes with different velocities of passive movement of the opposite leg. *Brain Res* 603: 96–101, 1993. doi:10.1016/0006-8993(93)91303-A.

Conway BA, Hultborn H, Kiehn O. Proprioceptive input resets central locomotor rhythm in the spinal cat. *Exp Brain Res* 68: 643–656, 1987. doi:10.1007/BF00249807.

Craik R, Herman R, Finley F. Human solutions for locomotion. II. Interlimb coordination. In: *Neural Control of Locomotion. Advances in Behavioral Biology*, edited by Herman RM, Grillner S, Stein PS, Stuart DG. Boston, MA: Springer, 1976, vol. 18, p. 51–64.

Crenna P, Frigo C. Excitability of the soleus H-reflex arc during walking and stepping in man. *Exp Brain Res* 66: 49–60, 1987. doi:10.1007/BF00236201.

de Kam D, Rijken H, Manintveld T, Nienhuis B, Dietz V, Duysens J. Arm movements can increase leg muscle activity during submaximal recumbent stepping in neurologically intact individuals. *J Appl Physiol (1985)* 115: 34–42, 2013. doi:10.1152/japplphysiol.00510.2012.

de Leon RD, Roy RR, Edgerton VR. Is the recovery of stepping following spinal cord injury mediated by modifying existing neural pathways or by generating new pathways? A perspective. *Phys Ther* 81: 1904–1911, 2001.

de Ruiter GC, Hundza SR, Zehr EP. Phase-dependent modulation of soleus H-reflex amplitude induced by rhythmic arm cycling. *Neurosci Lett* 475: 7–11, 2010. doi:10.1016/j.neulet.2010.03.025.

De Serres SJ, Yang JF, Patrick SK. Mechanism for reflex reversal during walking in human tibialis anterior muscle revealed by single motor unit recording. *J Physiol* 488: 249–258, 1995. doi:10.1113/jphysiol.1995.sp020963.

Delwaide PJ, Crenna P. Cutaneous nerve stimulation and motoneuronal excitability. II: Evidence for non-segmental influences. *J Neurol Neurosurg Psychiatry* 47: 190–196, 1984. doi:10.1136/jnnp.47.2.190.

Delwaide PJ, Crenna P, Fleron MH. Cutaneous nerve stimulation and motoneuronal excitability: I, soleus and tibialis anterior excitability after ipsilateral and contralateral sural nerve stimulation. *J Neurol Neurosurg Psychiatry* 44: 699–707, 1981. doi:10.1136/jnnp.44.8.699.

Delwaide PJ, Figiel C, Richelle C. Effects of postural changes of the upper limb on reflex transmission in the lower limb. Cervicolumbar reflex interactions in man. *J Neurol Neurosurg Psychiatry* 40: 616–621, 1977. doi:10.1136/jnnp.40.6.616.

Delwaide PJ, Sabatino M, Pepin JL, La Grutta V. Reinforcement of reciprocal inhibition by contralateral movements in man. *Exp Neurol* 99: 10–16, 1988. doi:10.1016/0014-4886(88)90122-7.

Dietz V, Wirz M, Colombo G, Curt A. Locomotor capacity and recovery of spinal cord function in paraplegic patients: a clinical and electrophysiological evaluation. *Electroencephalogr Clin Neurophysiol* 109: 140–153, 1998.

Dietz V. Do human bipeds use quadrupedal coordination? *Trends Neurosci* 25: 462–467, 2002. doi:10.1016/S0166-2236(02)02229-4.

Dietz V. Spinal cord pattern generators for locomotion. *Clin Neurophysiol* 114: 1379–1389, 2003. doi:10.1016/S1388-2457(03)00120-2.

Dietz V, Colombo G, Jensen L. Locomotor activity in spinal man. *Lancet* 344: 1260–1263, 1994a. doi:10.1016/S0140-6736(94)90751-X.

Dietz V, Colombo G, Jensen L, Baumgartner L. Locomotor capacity of spinal cord in paraplegic patients. *Ann Neurol* 37: 574–582, 1995. doi:10.1002/ana.410370506.

Dietz V, Fouad K, Bastiaanse CM. Neuronal coordination of arm and leg movements during human locomotion. *Eur J Neurosci* 14: 1906–1914, 2001. doi:10.1046/j.0953-816x.2001.01813.x.

Dietz V, Michel J. Human bipeds use quadrupedal coordination during locomotion. *Ann N Y Acad Sci* 1164: 97–103, 2009. doi:10.1111/j.1749-6632.2008.03710.x.

Dietz V, Zijlstra W, Duysens J. Human neuronal interlimb coordination during split-belt locomotion. *Exp Brain Res* 101: 513–520, 1994b. doi:10.1007/BF00227344.

Dimitrijevic MR, Gerasimenko Y, Pinter MM. Evidence for a spinal central pattern generator in humans. *Ann N Y Acad Sci* 860: 360–376, 1998.

Dobkin BH. Strategies for stroke rehabilitation. *Lancet Neurol* 3: 528–536, 2004. doi:10.1016/S1474-4422(04)00851-8.

Dobkin BH, Firestine A, West M, Saremi K, Woods R. Ankle dorsiflexion as an fMRI paradigm to assay motor control for walking during rehabilitation. *Neuroimage* 23: 370–381, 2004. doi:10.1016/j.neuroimage.2004.06.008.

Domingo A, Al-Yahya AA, Asiri Y, Eng JJ, Lam T; Spinal Cord Injury Rehabilitation Evidence Research Team. A systematic review of the effects of pharmacological agents on walking function in people with spinal cord injury. *J Neurotrauma* 29: 865–879, 2012. doi:10.1089/neu.2011.2052.

Domingo A, Klimstra M, Nakajima T, Lam T, Hundza SR. Walking phase modulates H-reflex amplitude in flexor carpi radialis. *J Mot Behav* 46: 49–57, 2014. doi:10.1080/00222895.2013.854731.

Dominici N, Ivanenko Y, Cappellini G, D'Avella A, Mondì V, Cicchese M, Fabiano A, Silei T, Di Paolo A, Giannini C, Poppele R, Lacquaniti F. Locomotor primitives in newborn babies and their development. *Science* 334: 997–999, 2011. doi:10.1126/science.1210617.

Donker SF, Beek PJ. Interlimb coordination in prosthetic walking: effects of asymmetry and walking velocity. *Acta Psychol (Amst)* 110: 265–288, 2002. doi:10.1016/S0001-6918(02)00037-9.

Donker SF, Beek PJ, Wagenaar RC, Mulder T. Coordination between arm and leg movements during locomotion. *J Mot Behav* 33: 86–102, 2001. doi:10.1080/00222890109601905.

Donker SF, Mulder T, Nienhuis B, Duysens J. Adaptations in arm movements for added mass to wrist or ankle during walking. *Exp Brain Res* 146: 26–31, 2002. doi:10.1007/s00221-002-1145-2.

Dragert K, Zehr EP. Rhythmic arm cycling modulates Hoffmann reflex excitability differentially in the ankle flexor and extensor muscles. *Neurosci Lett* 450: 235–238, 2009. doi:10.1016/j.neulet.2008.11.034.

Drew T, Rossignol S. A kinematic and electromyographic study of cutaneous reflexes evoked from the forelimb of unrestrained walking cats. *J Neurophysiol* 57: 1160–1184, 1987. doi:10.1152/jn.1987.57.4.1160.

Duncan PW, Sullivan KJ, Behrman AL, Azen SP, Wu SS, Nadeau SE, Dobkin BH, Rose DK, Tilson JK, Cen S, Hayden SK; LEAPS Investigative Team. Body-weight-supported treadmill rehabilitation after stroke. *N Engl J Med* 364: 2026–2036, 2011. doi:10.1056/NEJMoa1010790.

Duysens J. Reflex control of locomotion as revealed by stimulation of cutaneous afferents in spontaneously walking premammillary cats. *J Neurophysiol* 40: 737–751, 1977. doi:10.1152/jn.1977.40.4.737.

Duysens J, Bastiaanse CM, Smits-Engelsman BC, Dietz V. Gait acts as a gate for reflexes from the foot. *Can J Physiol Pharmacol* 82: 715–722, 2004. doi:10.1139/y04-071.

Duysens J, De Groote F, Jonkers I. The flexion synergy, mother of all synergies and father of new models of gait. *Front Comput Neurosci* 7: 14, 2013. doi:10.3389/fncom.2013.00014.

Duysens J, Pearson KG. The role of cutaneous afferents from the distal hindlimb in the regulation of the step cycle of thalamic cats. *Exp Brain Res* 24: 245–255, 1976. doi:10.1007/BF00235013.

Duysens J, Pearson KG. Inhibition of flexor burst generation by loading ankle extensor muscles in walking cats. *Brain Res* 187: 321–332, 1980. doi:10.1016/0006-8993(80)90206-1.

Duysens J, Pearson KG. From cat to man: basic aspects of locomotion relevant to motor rehabilitation of SCI. *NeuroRehabilitation* 10: 107–118, 1998. doi:10.1016/S1053-8135(97)00050-4.

Duysens J, Stein RB. Reflexes induced by nerve stimulation in walking cats with implanted cuff electrodes. *Exp Brain Res* 32: 213–224, 1978. doi:10.1007/BF00239728.

Duysens J, Tax AA, Murrer L, Dietz V. Backward and forward walking use different patterns of phase-dependent modulation of cutaneous reflexes in humans. *J Neurophysiol* 76: 301–310, 1996. doi:10.1152/jn.1996.76.1.301.

Duysens J, Tax AA, Trippel M, Dietz V. Phase-dependent reversal of reflexly induced movements during human gait. *Exp Brain Res* 90: 404–414, 1992. doi:10.1007/BF00227255.

Duysens J, Tax T. Interlimb reflexes during gait in cat and human. In: *Interlimb Coordination: Neural, Dynamical, and Cognitive Constraints*, edited by Swinnen SP, Massion J, Heuer H, Casaer P. San Diego, CA: Academic, 1994, p. 97–126.

Duysens J, Trippel M, Horstmann GA, Dietz V. Gating and reversal of reflexes in ankle muscles during human walking. *Exp Brain Res* 82: 351–358, 1990. doi:10.1007/BF00231254.

Duysens J, Van de Crommert HW. Neural control of locomotion; Part 1: the central pattern generator from cats to humans. *Gait Posture* 7: 131–141, 1998. doi:10.1016/S0966-6362(97)00042-8.

Edgerton VR, de Leon RD, Harkema SJ, Hodgson JA, London N, Reinkensmeyer DJ, Roy RR, Talmadge RJ, Tillakaratne NJ, Timoszyk W, Tobin A. Retraining the injured spinal cord. *J Physiol* 533: 15–22, 2001. doi:10.1111/j.1469-7793.2001.0015b.x.

Eidelberg E, Walden JG, Nguyen LH. Locomotor control in macaque monkeys. *Brain* 104: 647–663, 1981. doi:10.1093/brain/104.4.647-a.

Elftman H. The function of arms in walking. *Hum Biol* 11: 529–535, 1939.

Fedirchuk B, Nielsen J, Petersen N, Hultborn H. Pharmacologically evoked fictive motor patterns in the acutely spinalized marmoset monkey (*Callithrix jacchus*). *Exp Brain Res* 122: 351–361, 1998. doi:10.1007/s002210050523.

Ferris DP, Huang HJ, Kao PC. Moving the arms to activate the legs. *Exerc Sport Sci Rev* 34: 113–120, 2006. doi:10.1249/00003677-200607000-00005.

Field-Fote E, Ness LL, Ionno M. Vibration elicits involuntary, step-like behavior in individuals with spinal cord injury. *Neurorehabil Neural Repair* 26: 861–869, 2012. doi:10.1177/1545968311433603.

Field-Fote EC. Combined use of body weight support, functional electric stimulation, and treadmill training to improve walking ability in individuals with chronic incomplete spinal cord injury. *Arch Phys Med Rehabil* 82: 818–824, 2001. doi:10.1053/apmr.2001.23752.

Ford MP, Wagenaar RC, Newell KM. Arm constraint and walking in healthy adults. *Gait Posture* 26: 135–141, 2007. doi:10.1016/j.gaitpost.2006.08.008.

Forman D, Raj A, Button DC, Power KE. Corticospinal excitability of the biceps brachii is higher during arm cycling than an intensity-matched tonic contraction. *J Neurophysiol* 112: 1142–1151, 2014. doi:10.1152/jn.00210.2014.

Forman DA, Philpott DTG, Button DC, Power KE. Cadence-dependent changes in corticospinal excitability of the biceps brachii during arm cycling. *J Neurophysiol* 114: 2285–2294, 2015. doi:10.1152/jn.00418.2015.

Forssberg H. Stumbling corrective reaction: a phase-dependent compensatory reaction during locomotion. *J Neurophysiol* 42: 936–953, 1979. doi:10.1152/jn.1979.42.4.936.

Forssberg H. Evolution of plantigrade gait: is there a neuronal correlate? *Dev Med Child Neurol* 34: 920–925, 1992. doi:10.1111/j.1469-8749.1992.tb11391.x.

Forssberg H, Grillner S, Rossignol S. Phase dependent reflex reversal during walking in chronic spinal cats. *Brain Res* 85: 103–107, 1975. doi:10.1016/0006-8993(75)91013-6.

Friesen WO, Kristan WB. Leech locomotion: swimming, crawling, and decisions. *Curr Opin Neurobiol* 17: 704–711, 2007. doi:10.1016/j.conb.2008.01.006.

Frigon A, Collins DF, Zehr EP. Effect of rhythmic arm movement on reflexes in the legs: modulation of soleus H-reflexes and somatosensory conditioning. *J Neurophysiol* 91: 1516–1523, 2004. doi:10.1152/jn.00695.2003.

Gerasimenko Y, Gorodnichev R, Machueva E, Pivovarova E, Semyenov D, Savochin A, Roy RR, Edgerton VR. Novel and direct access to the human locomotor spinal circuitry. *J Neurosci* 30: 3700–3708, 2010. doi:10.1523/JNEUROSCI.4751-09.2010.

Gorodnichev RM, Pivovarova EA, Pukhov A, Moiseev SA, Savokhin AA, Moshonkina TR, Shcherbakova NA, Kilimnik VA, Selionov VA, Kozlovskaia IB, Edgerton VR, Gerasimenko IP. [Transcutaneous electrical stimulation of the spinal cord: non-invasive tool for activation of locomotor circuitry in human]. *Fiziol Cheloveka* 38: 46–56, 2012.

Gossard JP, Rossignol S. Phase-dependent modulation of dorsal root potentials evoked by peripheral nerve stimulation during fictive locomotion in the cat. *Brain Res* 537: 1–13, 1990.

Grillner S. Locomotion in vertebrates: central mechanisms and reflex interaction. *Physiol Rev* 55: 247–304, 1975. doi:10.1152/physrev.1975.55.2.247.

Grillner S. Neuronal networks in motion from ion channels to behaviour. *An R Acad Nac Med (Madr)* 123: 297–298, 2006.

Grillner S, Ekeberg Ö, El Manira A, Lansner A, Parker D, Tegnér J, Wallén P. Intrinsic function of a neuronal network—a vertebrate central pattern generator. *Brain Res Brain Res Rev* 26: 184–197, 1998a.

Grillner S, Parker D, El Manira A. Vertebrate locomotion—a lamprey perspective. *Ann N Y Acad Sci* 860: 1–18, 1998b.

Grillner S, Zangger P. The effect of dorsal root transection on the efferent motor pattern in the cat's hindlimb during locomotion. *Acta Physiol Scand* 120: 393–405, 1984. doi:10.1111/j.1748-1716.1984.tb07400.x.

Guertin P, Angel MJ, Perreault MC, McCrea DA. Ankle extensor group I afferents excite extensors throughout the hindlimb during fictive locomotion in the cat. *J Physiol* 487: 197–209, 1995. doi:10.1113/jphysiol.1995.sp020871.

Guertin PA. Central pattern generator for locomotion: anatomical, physiological, and pathophysiological considerations. *Front Neurol* 3: 183, 2013. doi:10.3389/fneur.2012.00183.

Gurfinkel VS, Levik YS, Kazennikov OV, Selionov VA. Locomotor-like movements evoked by leg muscle vibration in humans. *Eur J Neurosci* 10: 1608–1612, 1998. doi:10.1046/j.1460-9568.1998.00179.x.

Hägglund M, Dougherty KJ, Borgius L, Itohara S, Iwasato T, Kiehn O. Optogenetic dissection reveals multiple rhythmogenic modules underlying locomotion. *Proc Natl Acad Sci USA* 110: 11589–11594, 2013. doi:10.1073/pnas.1304365110.

Haridas C, Zehr EP. Coordinated interlimb compensatory responses to electrical stimulation of cutaneous nerves in the hand and foot during walking. *J Neurophysiol* 90: 2850–2861, 2003. doi:10.1152/jn.00531.2003.

Harkema SJ. Plasticity of interneuronal networks of the functionally isolated human spinal cord. *Brain Res Brain Res Rev* 57: 255–264, 2008. doi:10.1016/j.brainresrev.2007.07.012.

Harkema SJ, Hurley SL, Patel UK, Requejo PS, Dobkin BH, Edgerton VR. Human lumbosacral spinal cord interprets loading during stepping. *J Neurophysiol* 77: 797–811, 1997. doi:10.1152/jn.1997.77.2.797.

Hiraoka K. Phase-dependent modulation of the soleus H-reflex during rhythmical arm swing in humans. *Electromyogr Clin Neurophysiol* 41: 43–47, 2001.

Hiraoka K, Nagata A. Modulation of the soleus H reflex with different velocities of passive movement of the arm. *Electromyogr Clin Neurophysiol* 39: 21–26, 1999.

Hishinuma M, Yamaguchi T. Modulation of reflex responses during fictive locomotion in the forelimb of the cat. *Brain Res* 482: 184–188, 1989. doi:10.1016/0006-8993(89)90559-3.

Hooper SL, DiCaprio RA. Crustacean motor pattern generator networks. *Neurosignals* 13: 50–69, 2004. doi:10.1159/000076158.

Huang HJ, Ferris DP. Neural coupling between upper and lower limbs during recumbent stepping. *J Appl Physiol (1985)* 97: 1299–1308, 2004. doi:10.1152/japplphysiol.01350.2003.

Hughes GM, Wiersma CA. The co-ordination of swimmeret movements in the crayfish, *Procambarus clarkii* (Girard). *J Exp Biol* 37: 657, 1960.

Hundza SR, de Ruiter GC, Klimstra M, Zehr EP. Effect of afferent feedback and central motor commands on soleus H-reflex suppression during arm cycling. *J Neurophysiol* 108: 3049–3058, 2012. doi:10.1152/jn.00485.2011.

Hundza SR, Zehr EP. Cutaneous reflexes during rhythmic arm cycling are insensitive to asymmetrical changes in crank length. *Exp Brain Res* 168: 165–177, 2006. doi:10.1007/s00221-005-0089-8.

Hundza SR, Zehr EP. Suppression of soleus H-reflex amplitude is graded with frequency of rhythmic arm cycling. *Exp Brain Res* 193: 297–306, 2009. doi:10.1007/s00221-008-1625-0.

Ianniruberto A, Tajani E. Ultrasonographic study of fetal movements. *Semin Perinatol* 5: 175–181, 1981.

Jackson KM. Why the upper limbs move during human walking. *J Theor Biol* 105: 311–315, 1983. doi:10.1016/S0022-5193(83)80010-1.

Jankowska E, Jukes MG, Lund S, Lundberg A. The effect of DOPA on the spinal cord. 6. Half-centre organization of interneurones transmitting effects from the flexor reflex afferents. *Acta Physiol Scand* 70: 389–402, 1967. doi:10.1111/j.1748-1716.1967.tb03637.x.

Kao PC, Ferris DP. The effect of movement frequency on interlimb coupling during recumbent stepping. *Mot Contr* 9: 144–163, 2005. doi:10.1123/mcj.9.2.144.

Kaupp C, Pearcey G, Klarner T, Sun Y, Cullen H, Barss T, Zehr EP. Rhythmic arm cycling training improves walking and neurophysiological integrity in chronic stroke: the arms can give legs a helping hand in rehabilitation. *J Neurophysiol* 119: 1095–1112, 2018. doi:10.1152/jn.00570.2017.

Kawashima N, Nozaki D, Abe MO, Nakazawa K. Shaping appropriate locomotive motor output through interlimb neural pathway within spinal cord in humans. *J Neurophysiol* 99: 2946–2955, 2008. doi:10.1152/jn.00020.2008.

Khater-Boidin J, Duron B. Postnatal development of descending motor pathways studied in man by percutaneous stimulation of the motor cortex and the spinal cord. *Int J Dev Neurosci* 9: 15–26, 1991. doi:10.1016/0736-5748(91)90068-W.

Kiehn O, Butt SJB. Physiological, anatomical and genetic identification of CPG neurons in the developing mammalian spinal cord. *Prog Neurobiol* 70: 347–361, 2003. doi:10.1016/S0301-0082(03)00091-1.

Kiehn O, Kjaerulff O. Distribution of central pattern generators for rhythmic motor outputs in the spinal cord of limbed vertebrates. *Ann N Y Acad Sci* 860: 110–129, 1998. doi:10.1111/j.1749-6632.1998.tb09043.x.

Klarner T, Barss TS, Sun Y, Kaupp C, Loadman PM, Zehr EP. Exploiting interlimb arm and leg connections for walking rehabilitation: a training intervention in stroke. *Neural Plast* 2016: 1517968, 2016b. doi:10.1155/2016/1517968.

Klarner T, Barss T, Sun Y, Kaupp C, Beattie S, Zehr EP. Reliability of multiple baseline measures for locomotor retraining after stroke. In: *Replace, Repair, Restore, Relieve–Bridging Clinical and Engineering Solutions in Neurorehabilitation*, Biosystems & Biorobotics, edited by Jensen W, Andersen OK, Akay M. Cham, Switzerland: Springer, 2014a, vol. 7, p. 479–486.

Klarner T, Barss TS, Sun Y, Kaupp C, Loadman PM, Zehr EP. Long-term plasticity in reflex excitability induced by five weeks of arm and leg cycling training after stroke. *Brain Sci* 6: E54, 2016a. doi:10.3390/brainsci6040054.

Klarner T, Barss TS, Sun Y, Kaupp C, Zehr EP. Preservation of common rhythmic locomotor control despite weakened supraspinal regulation after stroke. *Front Integr Neurosci* 8: 95, 2014b. doi:10.3389/fnint.2014.00095.

Klimstra MD, Thomas E, Stoloff RH, Ferris DP, Zehr EP. Neuromechanical considerations for incorporating rhythmic arm movement in the rehabilitation of walking. *Chaos* 19: 026102, 2009. doi:10.1063/1.3147404.

Komiyama T, Zehr EP, Stein RB. Absence of nerve specificity in human cutaneous reflexes during standing. *Exp Brain Res* 133: 267–272, 2000. doi:10.1007/s002210000411.

Kozuma S, Okai T, Nemoto A, Kagawa H, Sakai M, Nishina H, Taketani Y. Developmental sequence of human fetal body movements in the second half of pregnancy. *Am J Perinatol* 14: 165–169, 1997. doi:10.1055/s-2007-994120.

LaBella LA, Niechaj A, Rossignol S. Low-threshold, short-latency cutaneous reflexes during fictive locomotion in the "semi-chronic" spinal cat. *Exp Brain Res* 91: 236–248, 1992. doi:10.1007/BF00231657.

Lamb T, Yang JF. Could different directions of infant stepping be controlled by the same locomotor central pattern generator? *J Neurophysiol* 83: 2814–2824, 2000. doi:10.1152/jn.2000.83.5.2814.

Lamont EV, Zehr EP. Task-specific modulation of cutaneous reflexes expressed at functionally relevant gait cycle phases during level and incline walking and stair climbing. *Exp Brain Res* 173: 185–192, 2006. doi:10.1007/s00221-006-0586-4.

Langhorne P, Coupar F, Pollock A. Motor recovery after stroke: a systematic review. *Lancet Neurol* 8: 741–754, 2009. doi:10.1016/S1474-4422(09)70150-4.

Leconte P, Orban de Xivry JJ, Stoquart G, Lejeune T, Ronsse R. Rhythmic arm movements are less affected than discrete ones after a stroke. *Exp Brain Res* 234: 1403–1417, 2016. doi:10.1007/s00221-015-4543-y.

Li Y, Wang W, Crompton RH, Gunther MM. Free vertical moments and transverse forces in human walking and their role in relation to arm-swing. *J Exp Biol* 204: 47–58, 2001.

Loadman PM, Zehr EP. Rhythmic arm cycling produces a non-specific signal that suppresses Soleus H-reflex amplitude in stationary legs. *Exp Brain Res* 179: 199–208, 2007. doi:10.1007/s00221-006-0782-2.

Lovely RG, Gregor RJ, Roy RR, Edgerton VR. Effects of training on the recovery of full-weight-bearing stepping in the adult spinal cat. *Exp Neurol* 92: 421–435, 1986. doi:10.1016/0014-4886(86)90094-4.

MacKay-Lyons M. Central pattern generation of locomotion: a review of the evidence. *Phys Ther* 82: 69–83, 2002. doi:10.1093/ptj/82.1.69.

MacLellan MJ, Qaderdan K, Koehestanie P, Duysens J, McFadyen BJ. Arm movements during split-belt walking reveal predominant patterns of interlimb coupling. *Hum Mov Sci* 32: 79–90, 2013. doi:10.1016/j.humov.2012.08.001.

Maegele M, Müller S, Wernig A, Edgerton VR, Harkema SJ. Recruitment of spinal motor pools during voluntary movements versus stepping after human spinal cord injury. *J Neurotrauma* 19: 1217–1229, 2002. doi:10.1089/08977150260338010.

Massaad F, Levin O, Meyns P, Drijkoningen D, Swinnen SP, Duysens J. Arm sway holds sway: locomotor-like modulation of leg reflexes when arms swing in alternation. *Neuroscience* 258: 34–46, 2014. doi:10.1016/j.neuroscience.2013.10.007.

Matthews PB. Observations on the automatic compensation of reflex gain on varying the pre-existing level of motor discharge in man. *J Physiol* 374: 73–90, 1986. doi:10.1113/jphysiol.1986.sp016066.

Meyns P, Bruijn SM, Duysens J. The how and why of arm swing during human walking. *Gait Posture* 38: 555–562, 2013. doi:10.1016/j.gaitpost.2013.02.006.

Mezzarane RA, Klimstra M, Lewis A, Hundza SR, Zehr EP. Interlimb coupling from the arms to legs is differentially specified for populations of motor units comprising the compound H-reflex during "reduced" human locomotion. *Exp Brain Res* 208: 157–168, 2011. doi:10.1007/s00221-010-2467-0.

Mezzarane RA, Nakajima T, Zehr EP. After stroke bidirectional modulation of soleus stretch reflex amplitude emerges during rhythmic arm cycling. *Front Hum Neurosci* 8: 136, 2014. doi:10.3389/fnhum.2014.00136.

Minassian K, Jilge B, Rattay F, Pinter MM, Binder H, Gerstenbrand F, Dimitrijevic MR. Stepping-like movements in humans with complete spinal cord injury induced by epidural stimulation of the lumbar cord: electromyographic study of compound muscle action potentials. *Spinal Cord* 42: 401–416, 2004. doi:10.1038/sj.sc.3101615.

Misiaszek JE, Cheng J, Brooke JD, Staines WR. Movement-induced modulation of soleus H reflexes with altered length of biarticular muscles. *Brain Res* 795: 25–36, 1998. doi:10.1016/S0006-8993(98)00246-7.

Morawietz C, Moffat F. Effects of locomotor training after incomplete spinal cord injury: a systematic review. *Arch Phys Med Rehabil* 94: 2297–2308, 2013. doi:10.1016/j.apmr.2013.06.023.

Moseley AM, Stark A, Cameron ID, Pollock A. Treadmill training and body weight support for walking after stroke. *Stroke* 34: 3006, 2003. doi:10.1161/01.STR.0000102415.43108.66.

Nadeau S, Jacquemin G, Fournier C, Lamarre Y, Rossignol S. Spontaneous motor rhythms of the back and legs in a patient with a complete spinal cord transection. *Neurorehabil Neural Repair* 24: 377–383, 2010. doi:10.1177/1545968309349945.

Nakajima T, Kitamura T, Kamibayashi K, Komiyama T, Zehr EP, Hundza SR, Nakazawa K. Robotic-assisted stepping modulates monosynaptic reflexes in forearm muscles in the human. *J Neurophysiol* 106: 1679–1687, 2011. doi:10.1152/jn.01049.2010.

Nakajima T, Mezzarane RA, Klarner T, Barss TS, Hundza SR, Komiyama T, Zehr EP. Neural mechanisms influencing interlimb coordination during locomotion in humans: presynaptic modulation of forearm H-reflexes during leg cycling. *PLoS One* 8: e76313, 2013. doi:10.1371/journal.pone.0076313.

Nathan PW, Smith M, Deacon P. Vestibulospinal, reticulospinal and descending propriospinal nerve fibres in man. *Brain* 119: 1809–1833, 1996. doi:10.1093/brain/119.6.1809.

Nielsen JB. How we walk: central control of muscle activity during human walking. *Neuroscientist* 9: 195–204, 2003. doi:10.1177/1073858403009003012.

Pang MY, Yang JF. The initiation of the swing phase in human infant stepping: importance of hip position and leg loading. *J Physiol* 528: 389–404, 2000. doi:10.1111/j.1469-7793.2000.00389.x.

Pang MY, Yang JF. Interlimb co-ordination in human infant stepping. *J Physiol* 533: 617–625, 2001. doi:10.1111/j.1469-7793.2001.0617a.x.

Pang MY, Yang JF. Sensory gating for the initiation of the swing phase in different directions of human infant stepping. *J Neurosci* 22: 5734–5740, 2002. doi:10.1523/JNEUROSCI.22-13-05734.2002.

Park J. Synthesis of natural arm swing motion in human bipedal walking. *J Biomech* 41: 1417–1426, 2008. doi:10.1016/j.jbiomech.2008.02.031.

Pauling L. Imagination in science. *Tomorrow* 3: 38–39, 1943.

Pearson KG. Common principles of motor control in vertebrates and invertebrates. *Annu Rev Neurosci* 16: 265–297, 1993. doi:10.1146/annurev.ne.16.030193.001405.

Pearson KG. Proprioceptive regulation of locomotion. *Curr Opin Neurobiol* 5: 786–791, 1995. doi:10.1016/0959-4388(95)80107-3.

Pearson KG. Generating the walking gait: role of sensory feedback. *Prog Brain Res* 143: 123–129, 2004. doi:10.1016/S0079-6123(03)43012-4.

Perreault MC, Angel MJ, Guertin P, McCrea DA. Effects of stimulation of hindlimb flexor group II afferents during fictive locomotion in the cat. *J Physiol* 487: 211–220, 1995.

Petersen TH, Willerslev-Olsen M, Conway BA, Nielsen JB. The motor cortex drives the muscles during walking in human subjects. *J Physiol* 590: 2443–2452, 2012. doi:10.1113/jphysiol.2012.227397.

Pontzer H, Holloway JH 4th, Raichlen DA, Lieberman DE. Control and function of arm swing in human walking and running. *J Exp Biol* 212: 523–534, 2009. doi:10.1242/jeb.024927.

Quevedo J, Stecina K, Gosgnach S, McCrea DA. Stumbling corrective reaction during fictive locomotion in the cat. *J Neurophysiol* 94: 2045–2052, 2005a. doi:10.1152/jn.00175.2005.

Quevedo J, Stecina K, McCrea DA. Intracellular analysis of reflex pathways underlying the stumbling corrective reaction during fictive locomotion in the cat. *J Neurophysiol* 94: 2053–2062, 2005b. doi:10.1152/jn.00176.2005.

Sakamoto M, Tazoe T, Nakajima T, Endoh T, Shiozawa S, Komiyama T. Voluntary changes in leg cadence modulate arm cadence during simultaneous arm and leg cycling. *Exp Brain Res* 176: 188–192, 2007. doi:10.1007/s00221-006-0742-x.

Sarica Y, Ertekin C. Descending lumbosacral cord potentials (DLCP) evoked by stimulation of the median nerve. *Brain Res* 325: 299–301, 1985. doi:10.1016/0006-8993(85)90327-0.

Sasada S, Tazoe T, Nakajima T, Zehr EP, Komiyama T. Effects of leg pedaling on early latency cutaneous reflexes in upper limb muscles. *J Neurophysiol* 104: 210–217, 2010. doi:10.1152/jn.00774.2009.

Schomburg ED, Behrends HB. Phasic control of the transmission in the excitatory and inhibitory reflex pathways from cutaneous afferents to alpha-motoneurones during fictive locomotion in cats. *Neurosci Lett* 8: 277–282, 1978. doi:10.1016/0304-3940(78)90136-2.

Schomburg ED, Petersen N, Barajon I, Hultborn H. Flexor reflex afferents reset the step cycle during fictive locomotion in the cat. *Exp Brain Res* 122: 339–350, 1998. doi:10.1007/s002210050522.

Seki K, Yamaguchi T. Cutaneous reflex activity of the cat forelimb during fictive locomotion. *Brain Res* 753: 56–62, 1997. doi:10.1016/S0006-8993(96)01486-2.

Selionov VA, Ivanenko YP, Solopova IA, Gurfinkel VS. Tonic central and sensory stimuli facilitate involuntary air-stepping in humans. *J Neurophysiol* 101: 2847–2858, 2009. doi:10.1152/jn.90895.2008.

Selionov VA, Solopova I, Zhvansky DS. [The activation of interlimb interactions increases the motor output in legs in healthy subjects under the conditions of arm and leg unloading]. *Fiziol Cheloveka* 42: 43–53, 2016. doi:10.1134/S0362119716010151.

Senthilvelkumar T, Magimairaj H, Fletcher J, Tharion G, George J. Comparison of body weight-supported treadmill training versus body weight-supported overground training in people with incomplete tetraplegia: a pilot randomized trial. *Clin Rehabil* 29: 42–49, 2015. doi:10.1177/0269215514538068.

Sherrington CS. Observations on the scratch-reflex in the spinal dog. *J Physiol* 34: 1–50, 1906. doi:10.1113/jphysiol.1906.sp001139.

Sherrington CS. Flexion-reflex of the limb, crossed extension-reflex, and reflex stepping and standing. *J Physiol* 40: 28–121, 1910. doi:10.1113/jphysiol.1910.sp001362.

Solopova IA, Selionov VA, Sylos-Labini F, Gurfinkel VS, Lacquaniti F, Ivanenko YP. Tapping into rhythm generation circuitry in humans during simulated weightlessness conditions. *Front Syst Neurosci* 9: 14, 2015. doi:10.3389/fnsys.2015.00014.

Stein RB, Capaday C. The modulation of human reflexes during functional motor tasks. *Trends Neurosci* 11: 328–332, 1988. doi:10.1016/0166-2236(88)90097-5.

Stephens MJ, Yang JF. Loading during the stance phase of walking in humans increases the extensor EMG amplitude but does not change the duration of the step cycle. *Exp Brain Res* 124: 363–370, 1999. doi:10.1007/s002210050633.

Swinnen S, Duysens J. *Neuro-Behavioral Determinants of Interlimb Coordination: A Multidisciplinary Approach*. New York: Springer, 2005.

Sylos-Labini F, Ivanenko YP, Maclellan MJ, Cappellini G, Poppele RE, Lacquaniti F. Locomotor-like leg movements evoked by rhythmic arm movements in humans. *PLoS One* 9: e90775, 2014a. doi:10.1371/journal.pone.0090775.

Sylos-Labini F, Lacquaniti F, Ivanenko YP. Human locomotion under reduced gravity conditions: biomechanical and neurophysiological considerations. *BioMed Res Int* 2014: 547242, 2014b. doi:10.1155/2014/547242.

Tax AA, Van Wezel BM, Dietz V. Bipedal reflex coordination to tactile stimulation of the sural nerve during human running. *J Neurophysiol* 73: 1947–1964, 1995. doi:10.1152/jn.1995.73.5.1947.

Thorstensson A. How is the normal locomotor program modified to produce backward walking? *Exp Brain Res* 61: 664–668, 1986. doi:10.1007/BF00237595.

Ting LH, Kautz SA, Brown DA, Zajac FE. Phase reversal of biomechanical functions and muscle activity in backward pedaling. *J Neurophysiol* 81: 544–551, 1999. doi:10.1152/jn.1999.81.2.544.

Umberger BR. Effects of suppressing arm swing on kinematics, kinetics, and energetics of human walking. *J Biomech* 41: 2575–2580, 2008. doi:10.1016/j.jbiomech.2008.05.024.

Van de Crommert HW, Mulder T, Duysens J. Neural control of locomotion: sensory control of the central pattern generator and its relation to treadmill training. *Gait Posture* 7: 251–263, 1998. doi:10.1016/S0966-6362(98)00010-1.

van den Brand R, Heutschi J, Barraud Q, DiGiovanna J, Bartholdi K, Huerlimann M, Friedli L, Vollenweider I, Moraud EM, Duis S, Dominici N, Micera S, Musienko P, Courtine G. Restoring voluntary control of locomotion after paralyzing spinal cord injury. *Science* 336: 1182–1185, 2012. doi:10.1126/science.1217416.

Van Emmerik RE, Wagenaar RC, Van Wegen EE. Interlimb coupling patterns in human locomotion: are we bipeds or quadrupeds? *Ann N Y Acad Sci* 860: 539–542, 1998. doi:10.1111/j.1749-6632.1998.tb09098.x.

Van Wezel BM, Ottenhoff FA, Duysens J. Dynamic control of location-specific information in tactile cutaneous reflexes from the foot during human walking. *J Neurosci* 17: 3804–3814, 1997. doi:10.1523/JNEUROSCI.17-10-03804.1997.

Verschueren SM, Swinnen SP, Desloovere K, Duysens J. Effects of tendon vibration on the spatiotemporal characteristics of human locomotion. *Exp Brain Res* 143: 231–239, 2002. doi:10.1007/s00221-001-0987-3.

Visintin M, Barbeau H. The effects of parallel bars, body weight support and speed on the modulation of the locomotor pattern of spastic paretic gait. A preliminary communication. *Paraplegia* 32: 540–553, 1994.

Wagenaar RC, van Emmerik RE. Resonant frequencies of arms and legs identify different walking patterns. *J Biomech* 33: 853–861, 2000. doi:10.1016/S0021-9290(00)00020-8.

Wannier T, Bastiaanse C, Colombo G, Dietz V. Arm to leg coordination in humans during walking, creeping and swimming activities. *Exp Brain Res* 141: 375–379, 2001. doi:10.1007/s002210100875.

Whelan PJ, Pearson KG. Plasticity in reflex pathways controlling stepping in the cat. *J Neurophysiol* 78: 1643–1650, 1997. doi:10.1152/jn.1997.78.3.1643.

Winchester P, McColl R, Querry R, Foreman N, Mosby J, Tansey K, Williamson J. Changes in supraspinal activation patterns following robotic locomotor therapy in motor-incomplete spinal cord injury. *Neurorehabil Neural Repair* 19: 313–324, 2005. doi:10.1177/1545968305281515.

Winter DA, Pluck N, Yang JF. Backward walking: a simple reversal of forward walking? *J Mot Behav* 21: 291–305, 1989. doi:10.1080/00222895.1989.10735483.

Wirz M, Colombo G, Dietz V. Long term effects of locomotor training in spinal humans. *J Neurol Neurosurg Psychiatry* 71: 93–96, 2001. doi:10.1136/jnnp.71.1.93.

Yang JF, Gorassini M. Spinal and brain control of human walking: implications for retraining of walking. *Neuroscientist* 12: 379–389, 2006. doi:10.1177/1073858406292151.

Yang JF, Lam T, Pang MYC, Lamont E, Musselman K, Seinen E. Infant stepping: a window to the behaviour of the human pattern generator for walking. *Can J Physiol Pharmacol* 82: 662–674, 2004. doi:10.1139/y04-070.

Yang JF, Stein RB. Phase-dependent reflex reversal in human leg muscles during walking. *J Neurophysiol* 63: 1109–1117, 1990. doi:10.1152/jn.1990.63.5.1109.

Yang JF, Stephens MJ, Vishram R. Infant stepping: a method to study the sensory control of human walking. *J Physiol* 507: 927–937, 1998. doi:10.1111/j.1469-7793.1998.927bs.x.

Yang JF, Whelan PJ. Neural mechanisms that contribute to cyclical modulation of the soleus H-reflex in walking in humans. *Exp Brain Res* 95: 547–556, 1993. doi:10.1007/BF00227148.

Zehr EP. Considerations for use of the Hoffmann reflex in exercise studies. *Eur J Appl Physiol* 86: 455–468, 2002. doi:10.1007/s00421-002-0577-5.

Zehr EP. Neural control of rhythmic human movement: the common core hypothesis. *Exerc Sport Sci Rev* 33: 54–60, 2005.

Zehr EP. Training-induced adaptive plasticity in human somatosensory reflex pathways. *J Appl Physiol* 101: 1783–1794, 2006. doi:10.1152/japplphysiol.00540.2006.

Zehr EP, Balter JE, Ferris DP, Hundza SR, Loadman PM, Stoloff RH. Neural regulation of rhythmic arm and leg movement is conserved across human locomotor tasks. *J Physiol* 582: 209–227, 2007a. doi:10.1113/jphysiol.2007.133843.

Zehr EP, Barss TS, Dragert K, Frigon A, Vasudevan EV, Haridas C, Hundza S, Kaupp C, Klarner T, Klimstra M, Komiyama T, Loadman PM, Mezzarane RA, Nakajima T, Pearcey GE, Sun Y. Neuromechanical interactions between the limbs during human locomotion: an evolutionary perspective with translation to rehabilitation. *Exp Brain Res* 234: 3059–3081, 2016. doi:10.1007/s00221-016-4715-4.

Zehr EP, Carroll TJ, Chua R, Collins DF, Frigon A, Haridas C, Hundza SR, Thompson AK. Possible contributions of CPG activity to the control of rhythmic human arm movement. *Can J Physiol Pharmacol* 82: 556–568, 2004a. doi:10.1139/y04-056.

Zehr EP, Chua R. Modulation of human cutaneous reflexes during rhythmic cyclical arm movement. *Exp Brain Res* 135: 241–250, 2000. doi:10.1007/s002210000515.

Zehr EP, Collins DF, Chua R. Human interlimb reflexes evoked by electrical stimulation of cutaneous nerves innervating the hand and foot. *Exp Brain Res* 140: 495–504, 2001. doi:10.1007/s002210100857.

Zehr EP, Collins DF, Frigon A, Hoogenboom N. Neural control of rhythmic human arm movement: phase dependence and task modulation of Hoffmann reflexes in forearm muscles. *J Neurophysiol* 89: 12–21, 2003a. doi:10.1152/jn.00416.2002.

Zehr EP, Duysens J. Regulation of arm and leg movement during human locomotion. *Neuroscientist* 10: 347–361, 2004. doi:10.1177/1073858404264680.

Zehr EP, Frigon A, Hoogenboom N, Collins DF. Facilitation of soleus H-reflex amplitude evoked by cutaneous nerve stimulation at the wrist is not suppressed by rhythmic arm movement. *Exp Brain Res* 159: 382–388, 2004b. doi:10.1007/s00221-004-2092-x.

Zehr EP, Fujita K, Stein RB. Reflexes from the superficial peroneal nerve during walking in stroke subjects. *J Neurophysiol* 79: 848–858, 1998. doi:10.1152/jn.1998.79.2.848.

Zehr EP, Haridas C. Modulation of cutaneous reflexes in arm muscles during walking: further evidence of similar control mechanisms for rhythmic human arm and leg movements. *Exp Brain Res* 149: 260–266, 2003b. doi:10.1007/s00221-003-1377-9.

Zehr EP, Hundza SR, Balter JE, Loadman PM. Context-dependent modulation of cutaneous reflex amplitudes during forward and backward leg cycling. *Mot Contr* 13: 368–386, 2009a. doi:10.1123/mcj.13.4.368.

Zehr EP, Hundza SR, Vasudevan EV. The quadrupedal nature of human bipedal locomotion. *Exerc Sport Sci Rev* 37: 102–108, 2009b. doi:10.1097/JES.0b013e31819c2ed6.

Zehr EP, Hundza SRS. Forward and backward arm cycling are regulated by equivalent neural mechanisms. *J Neurophysiol* 93: 633–640, 2005. doi:10.1152/jn.00525.2004.

Zehr EP, Kido A. Neural control of rhythmic, cyclical human arm movement: task dependency, nerve specificity and phase modulation of cutaneous reflexes. *J Physiol* 537: 1033–1045, 2001. doi:10.1113/jphysiol.2001.012878.

Zehr EP, Klimstra M, Dragert K, Barzi Y, Bowden MG, Javan B, Phadke C. Enhancement of arm and leg locomotor coupling with augmented cutaneous feedback from the hand. *J Neurophysiol* 98: 1810–1814, 2007b. doi:10.1152/jn.00562.2007.

Zehr EP, Klimstra M, Johnson EA, Carroll TJ. Rhythmic leg cycling modulates forearm muscle H-reflex amplitude and corticospinal tract excitability. *Neurosci Lett* 419: 10–14, 2007c. doi:10.1016/j.neulet.2007.03.045.

Zehr EP, Komiyama T, Stein RB. Cutaneous reflexes during human gait: electromyographic and kinematic responses to electrical stimulation. *J Neurophysiol* 77: 3311–3325, 1997. doi:10.1152/jn.1997.77.6.3311.

Zehr EP, Loadman PM. Persistence of locomotor-related interlimb reflex networks during walking after stroke. *Clin Neurophysiol* 123: 796–807, 2012. doi:10.1016/j.clinph.2011.07.049.

Zehr EP, Loadman PM, Hundza SR. Neural control of rhythmic arm cycling after stroke. *J Neurophysiol* 108: 891–905, 2012. doi:10.1152/jn.01152.2011.

Zehr EP, Stein RB. What functions do reflexes serve during human locomotion? *Prog Neurobiol* 58: 185–205, 1999. doi:10.1016/S0301-0082(98)00081-1.

Zhou R, Alvarado L, Ogilvie R, Chong S, Shaw O, Mushahwar V. Non-gait specific intervention for the rehabilitation of walking after sci: role of the arms. *J Neurophysiol* 119: 2194–2211, 2018. doi:10.1152/jn.00569.2017.