

Tonic Central and Sensory Stimuli Facilitate Involuntary Air-Stepping in Humans

V. A. Selionov,¹ Y. P. Ivanenko,² I. A. Solopova,¹ and V. S. Gurfinkel³

¹Laboratory of Neurobiology of Motor Control, Institute for Information Transmission Problems, Russian Academy of Science, Moscow, Russia; ²Laboratory of Neuromotor Physiology, Istituti di Ricovero e Cura a Carattere Scientifico Fondazione Santa Lucia Roma, Rome, Italy; and ³Neurological Sciences Institute, Oregon Health and Science University, Beaverton, Oregon

Submitted 7 August 2008; accepted in final form 25 March 2009

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. First published April 1, 2009; doi:10.1152/jn.90895.2008. Air-stepping can be used as a model for investigating rhythmogenesis and its interaction with sensory input. Here we show that it is possible to entrain involuntary rhythmic movement patterns in healthy humans by using different kinds of stimulation techniques. The subjects lay on their sides with one or both legs suspended, allowing low-friction horizontal rotation of the limb joints. To evoke involuntary stepping of the suspended leg, either we used continuous muscle vibration, electrical stimulation of the superficial peroneal or sural nerves, the Jendrassik maneuver, or we exploited the postcontraction state of neuronal networks (Kohnstamm phenomenon). The common feature across all stimulations was that they were tonic. Air-stepping could be elicited by most techniques in about 50% of subjects and involved prominent movements at the hip and the knee joint (~40–70°). Typically, however, the ankle joint was not involved. Minimal loading forces (4–25 N) applied constantly to the sole (using a long elastic cord) induced noticeable (~5–20°) ankle-joint-angle movements. The aftereffect of a voluntary long-lasting (30-s) contraction in the leg muscles featured alternating rhythmic leg movements that lasted for about 20–40 s, corresponding roughly to a typical duration of the postcontraction activity in static conditions. The Jendrassik maneuver per se did not evoke air-stepping. Nevertheless, it significantly prolonged rhythmic leg movements initiated manually by an experimenter or by a short (5-s) period of muscle vibration. Air-stepping of one leg could be evoked in both forward and backward directions with frequent spontaneous transitions, whereas involuntary alternating two-legged movements were more stable (no transitions). The hypothetical role of tonic influences, contact forces, and bilateral coordination in rhythmogenesis is discussed. The results overall demonstrated that nonspecific tonic drive may cause air-stepping and the characteristics and stability of the evoked pattern depended on the sensory input.

INTRODUCTION

In vertebrates, rhythmic locomotor movements are produced by a brain stem–spinal central pattern generator (CPG) that is activated by descending command signals and sensory feedback (Grillner 1981). The capacity of neural circuits to generate rhythmic activity in the absence of peripheral and supraspinal inputs is a well-established notion in animal models (CueLLar et al. 2009; Feldman and Orlovsky 1975; Grillner and Zangger 1979; Pearson and Rossignol 1991; Rybak et al. 2006) and there is indirect evidence that CPGs may also be a feature of the human spinal cord (Calancie et al. 1994; Dietz 2003). It

may, in fact, represent the common core for various rhythmic movements in humans (Zehr 2005), even though the natural locomotor output is highly adaptable to specific conditions (Clarac et al. 2004; Ivanenko et al. 2008). Afferent information influences the central pattern and, conversely, the CPG selects the appropriate afferent information according to external requirements (Dietz 2003). The convergence of spinal reflex pathways and descending pathways on common spinal interneurons seems to play an integrative role.

Most CPGs are quiescent under resting condition and become recruited only by neurons with command function (Grillner 2006). Yet, the nature of this central command is unclear (Jordan et al. 2008). In particular, for the command to trigger the action, the physiological state of the spinal network needs to be properly prepared (Edgerton et al. 2008) since the same interneurons may contribute to a vast repertoire of motor actions (Hultborn 2001). Historically, Goltz and Freusberg (1874) were the first to report spontaneous air-stepping of the hindlimbs of the spinal dog before voiding the distended bladder, presumably due to some excitatory state of the spinal circuitry. After voiding, spontaneous rhythmic limb movements disappeared. In decerebrated animals exhibiting spontaneous fluctuations in their level of rigidity, rhythmic movements can be evoked by peripheral stimulation, providing there is an appropriate level of background extensor tonus and that the tonus is neither too low nor too high (Beritoff 1915). In addition, an increase in tonus precedes the initiation of locomotion (Mori et al. 1982). The state of the spinal network is thus of particular importance and it may require only a minimal sensory input (Goldberger 1988). In fact, the transition from rest to locomotion is characterized by a specific tuning of the spinal cord by descending activity, resulting in the so-called *locomotor state* of the spinal circuitry (Shik 1983).

The most convincing evidence for CPGs comes from fictive locomotion, which has no direct equivalent in humans (Dietz 2003). Nevertheless, pattern generation in humans is basically innate, suggesting that a spinal mechanism may coordinate rhythmic movements. Yang and colleagues (2004) used the primitive pattern of walking in babies as a model to study the CPG and its sensory control. The limitation of the infant model is that the state of functional maturity of many structures in the nervous system cannot be known with certainty. In adults, indirect evidence for a spinal pattern generator for locomotion has been suggested from recordings of locomotor activity induced in patients with complete paraplegia. In particular, afferent input from hip joints, in combination with that from

Address for reprint requests and other correspondence: Y. P. Ivanenko, Laboratory of Neuromotor Physiology, IRCCS Fondazione Santa Lucia, 306 via Ardeatina, 00179 Rome, Italy (E-mail: y.ivanenko@hsantalucia.it).

load receptors, is essential for the generation of locomotor activity in the isolated human spinal cord (Dietz et al. 2002).

Air-stepping represents an interesting example of alternating rhythmic leg movements in the absence of contact events and with minimal influence by gravity. It may be used as a unique and important model for investigating rhythmogenesis since its manifestation is largely facilitated by the absence of external resistance and it engages intact sensory inputs. We previously demonstrated that it is possible to elicit automatic air-stepping in healthy humans using continuous vibration of selected leg muscles (Gurfinkel et al. 1998). The observed cyclic movements featured reciprocal electromyographic (EMG) activity bursts in the flexor and extensor muscles of the hip and knee joints, although we did not record motion in the distal (ankle) joint. This behavior may reflect inherent relationships between oscillators in the major limb joints [e.g., individual CPGs operating at each joint (Grillner 1981) or separate upper lumbar and sacral sites of CPG circuitry (Cazalets and Bertrand 2000; Kremer and Lev-Tov 1997)]. If these kinematic oscillators are centrally linked, one might expect that the relative amplitudes of joint angular motion would resemble those of normal walking. If oscillators are relatively independent instead, one might expect different kinematic behavior. The air-stepping model may thus provide a tool to study the rhythmogenic properties of neuronal networks and the sensory control of CPGs in adult humans.

Here we explored various stimulation techniques for eliciting involuntary air-stepping and we examined whether the evoked motor patterns depended on the site of stimulation and/or application of loading forces. In particular, we examined whether nonspecific central and peripheral tonic activations might excite CPG circuitry in a manner that would be predicted if air-stepping is largely coordinated by subcortical CPGs. To elicit involuntary stepping of the suspended leg, we used continuous quadriceps (Q) muscle vibration, electrical stimulation (ES) of the superficial peroneal or sural nerves, the

Jendrassik maneuver, and the postcontraction state of neuronal networks (Kohnstamm phenomenon). The former three techniques rely primarily on peripheral sensory stimulation (Gurfinkel et al. 1998; Rossignol et al. 2006; Van Wezel et al. 1997; Zehr et al. 1997), whereas the latter two techniques involve central tonic facilitatory influences (Craske and Craske 1986; Delwaide and Toulouse 1981; Duclos et al. 2004; Ivanenko et al. 2006b). The common feature of all stimulations used in this study is that they are tonic. The results overall demonstrated that nonspecific tonic drive (both central and peripheral) might excite CPG circuitry in humans and the characteristics and stability of the evoked pattern depended on the sensory input.

METHODS

Subjects

Participants were 33 healthy volunteers [24 males, 9 females; ages between 23 and 58 yr (mean 43 ± 12 yr)]. Six of these subjects participated in the earlier work and were preselected again based on whether, in the previous study, air-stepping could be entrained using muscle vibration (Gurfinkel et al. 1998). None of the subjects had any known neurological or motor disorders. The experiments were performed according to the procedures of the Ethics Committee of the Institute for Information Transmission Problems and in conformity with the Declaration of Helsinki for experiments on humans. All subjects had given informed consent.

Experimental setup

The experimental setup in this study (Fig. 1) was similar to that described in detail in our previous study (Gurfinkel et al. 1998). To avoid the effects of gravity and external resistance, the subjects lay on their sides with the upper leg suspended to permit its unimpeded motion in the horizontal plane (Fig. 1A). The suspension system consisted of a two-segment exoskeleton (0.9 kg) with low-friction rotation (due to bearing junctions) at the hip and the knee joint. The axes of hip and knee joint were adjusted to be collinear with the axes

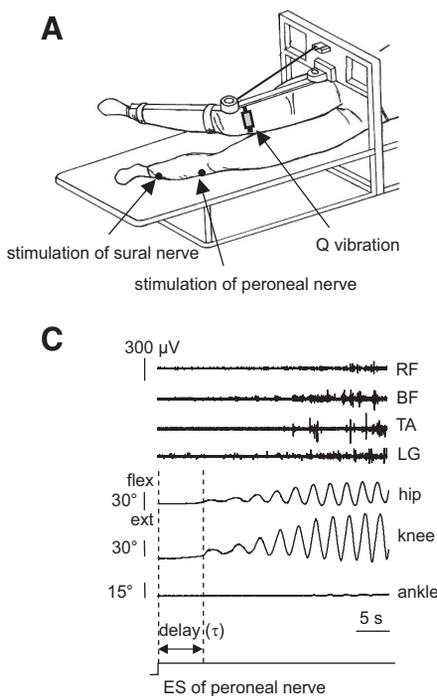


FIG. 1. Experimental setup. *A*: the subject laid on her/his left side on a couch with the upper leg suspended, using an exoskeleton such that movements were possible only in the horizontal plane. Bearings were used to provide low-friction rotations in the exoskeleton axes so that the only resistance to leg movements was due to the intrinsic passive and active properties of the musculoskeletal limb apparatus. Rotations in the 3 limb joints (hip, knee, and ankle) were recorded using potentiometers attached laterally to the suspended leg. The stepping movements were evoked either by low-intensity electrical stimulation of peroneal or sural nerves or by continuous vibration of the quadriceps muscle. *B*: 2-legged air-stepping system using a pendulum-like support (3-m ropes) of both legs in a high-ceilinged room. The shank segment of the left (lower) limb was placed on a long wooden stick (suspended to the ceiling using 2 vertical ropes) that permitted motion in the horizontal plane with minimal resistance (bearing was introduced between the shank and the stick). The right limb was suspended directly to the ceiling using a long rope. *C*: an example of evoked rhythmic movements of the suspended leg induced by electrical stimulation (ES) of peroneal nerve of the contralateral (left) leg. An upward deflection of the hip- and knee-joint-angle traces denotes flexion. Note a delay of about 5 s in the onset of rhythmic movements.

of hinges to exclude any limitation of mobility. The foot segment remained unrestrained in air so that there was also no resistance in the ankle joint motion.

In some experiments (see following text) we also used the two-legged suspension system that allowed a low-friction motion of both legs in the horizontal plane (Fig. 1B). Both legs were supported using long ropes attached to the ceiling (height, 4 m) so that they provided low-friction pendulum-like leg motion with a limited vertical motion component. The shank segment of the left (lower) limb was placed on a 2.5-m-long horizontal wooden stick that was suspended from the ceiling using two vertical ropes of 3-m length. The length of the horizontal stick was long for the lower leg not to interfere with the motion of the upper leg. A bearing junction was introduced between the shank and the stick, allowing free rotation of the shank relative to the stick around the vertical axis. The right limb was suspended directly from the ceiling using a long rope attached to the shank segment (Fig. 1B). The weight of the upper- and lower-limb suspension systems (0.9 and 1.5 kg, respectively) was much less than that of the limb so that it had minimal impact on the inertia of the system.

Subjects were instructed to relax and not intervene with movements that might be induced by stimulation. When lying down, each subject's relaxed, suspended leg assumed the equilibrium position with joint angles determined by the relative passive stiffness of agonist and antagonists and other soft tissues around joints. The hip angle in the initial position varied between 135 and 160° and the knee angle between 115 and 155° (180° refers to the hip and knee angles of the extended leg with the thigh and shank segments being parallel to the trunk). In the following text we describe the stimulation techniques used for eliciting automatic air-stepping and the experimental protocols.

Stimulation techniques

The following stimulation techniques and procedures were used:

1 Quadriceps muscle vibration (40–60 Hz, ~1-mm amplitude). Muscle vibration was produced by a small DC motor with an attached eccentric weight. The vibrator was fastened with a rubber belt over the quadriceps muscle at the right knee tendon, about 5 cm over the patella.

2 Electrical stimulation (ES) of the sural nerve (innervating the lateral aspect of the foot). The rationale of applying ES of the peripheral nerves was that somatosensory feedback from skin, muscles, and joints of the foot is essential in the normal execution of human gait and might have access to the pattern generation circuits. The bipolar stimulation electrodes ($2 \times 2 \text{ cm}^2$ and an interelectrode distance of 2 cm) were positioned over the sural nerve (approximately halfway between the lateral malleolus and the Achilles tendon), firmly pressed with adhesive straps. A custom-made constant-current stimulator provided the desired stimulation train. The nonnociceptive electrical stimulus consisted of repetitive trains of rectangular pulses (0.3-ms duration each, at 60 Hz). Before beginning the recordings, the perception threshold was determined psychophysically by gradually increasing the stimulus amplitude (Duysens et al. 1996). The stimulus intensity (range 2–3 mA for all subjects) was kept constant at twice

the perceptual threshold. Once the intensity value was set, it remained fixed throughout the session. Subjects who showed one-legged air-stepping during ipsilateral leg stimulation (Table 1) were also tested with contralateral (stationary) leg stimulation under the assumption that oscillator mechanisms may be shared, e.g., due to the presence of commissural interneurons (Kiehn 2006) and interlimb reflex coordination (Tax et al. 1995).

3 Electrical stimulation of the superficial peroneal nerve (innervating the foot dorsum and the peroneus muscles). The bipolar electrodes for the superficial peroneal nerve were placed on the anterior surface of the shank near the knee joint. The stimulus intensity was determined by gradually increasing and decreasing the current amplitude to be as close as possible to the motor threshold without exceeding it (i.e., without any visible ankle-joint movement). Once the intensity value was set, it remained fixed throughout the session. The same stimulating procedure was used as in the case of ES of the sural nerve. By stimulating different nerves we aimed to investigate whether the site of stimulation affected the evoked motor pattern (e.g., the amplitude of ankle-joint motion).

4 Jendrassik maneuver. The classical Jendrassik maneuver consists of simultaneous voluntary isometric contraction of the extensors of both arms against each other and is known to evoke the facilitation in the leg muscle reflexes (Delwaide and Toulouse 1981; Gregory et al. 2001). We used this procedure in 18 healthy individuals who showed prominent air-stepping in response to quadriceps muscle vibration and ES (Table 1). The Jendrassik maneuver was performed for 10–20 s. Since the Jendrassik maneuver did not induce air-stepping (see RESULTS) we also tested whether it would facilitate the effects induced by other means. To this end, we used a short (5-s) Q-muscle vibration of the right leg and passive limb perturbations performed by an experimenter. In the latter case, the experimenter performed one to two passive cyclic movements of the upper (right) leg imitating air-stepping. The cycle duration of evoked passive movements and the amplitude of hip and knee angle displacements were similar with and without the Jendrassik maneuver (1.8 ± 0.3 vs. 1.9 ± 0.3 s, 33 ± 8 vs. $32 \pm 10^\circ$, and 51 ± 15 vs. $48 \pm 18^\circ$, respectively). The other leg was left free to move.

5 Aftereffect of a strong long-lasting (~30 s) isometric muscle contraction (Kohnstamm phenomenon). In static conditions, the cessation of the voluntary effort may result in involuntary contraction of the preconditioned muscles (Kohnstamm 1915). In healthy humans, the postcontraction aftereffects emerge most clearly in proximal rather than in distal muscles (Gurfinkel et al. 1989). They are commonly thought to result from long-lasting changes (tens of seconds) in the excitatory state of the neuromuscular system (Duclos et al. 2004; Ivanenko et al. 2006b). However, the exact physiological mechanisms underlying this phenomenon have not yet been clearly identified, even though extensive literature exists (for a review see Craske and Craske 1986). Here we studied whether it may also induce a transition in the locomotor circuits from the inhibited to the active state. Subjects were positioned on their sides (Fig. 1B) with both legs in a neutral position with respect to the longitudinal axis of the trunk. They were asked to perform a strong (about half-maximal) isometric contraction of one leg against another in the horizontal plane. A research assistant

TABLE 1. Number of subjects tested and number of subjects who demonstrated involuntary air-stepping

	Q Muscle Vibration	Electrical Stimulation				Postcontraction	Jendrassik Maneuver
		Peroneal Nerve		Sural Nerve			
		Ipsi	Contra	Ipsi	Contra		
Number of subjects tested	33	33	19	33	18	18	18
Number of subjects who demonstrated air-stepping	21	19	13	18	12	16	17*

Asterisk (*) corresponds to the number of subjects with significantly prolonged rhythmic leg movements initiated manually by an experimenter (Jendrassik maneuver per se did not evoke air-stepping).

stabilized a distal part of the shank segments of both legs during voluntary exertion. The force was performed by the hip flexor and extensor muscles of both legs (one leg in the forward direction while another one in the backward direction), although the knee muscles were involved as well. Immediately after the cessation of the voluntary contraction the research assistant released both legs of the subject, thus allowing a manifestation of any unconstrained leg motion in the horizontal plane. The same 18 subjects that participated in *procedure 4* also participated in this experiment.

Protocols and experimental conditions

The first three stimulation techniques were applied both in one-legged (Fig. 1A) and in two-legged (Fig. 1B) suspension systems, whereas the latter two techniques were always tested using the two-legged suspension (Fig. 1B). At least 2- to 3-min periods of rest were taken between testing probes. Prior to recording, one to two sensory stimulation probes were delivered so that subjects could become familiar with the stimulus. Each experimental condition was repeated three times and about 1- to 3-min periods of rest were taken between testing probes. The duration of each recording was 1 min. The total duration of the experiment was about 2–3 h. The following experimental conditions were adapted in random order across subjects:

1 One-legged air-stepping (Fig. 1A). The other leg was lying motionlessly. The head was put on a pillow and the trunk and the arms were relaxed.

2 One-legged air-stepping with a small “loading” force (4 and 8 N) applied constantly to the center of the sole in the rostral direction along the longitudinal axis of the trunk using a long (5-m) elastic horizontal cord. The resting (nonstretched) length of the cord was about 2 m so that small changes in its length (~20–30 cm) during rhythmic movements evoked only small changes (<10%) in the applied elastic force. These forces (4 and 8 N) produced little shortening of the relaxed suspended leg (~2–12 cm), although larger forces could evoke significant changes in the initial limb configuration (>30 cm shortening for the 25 N force) and were not used in the standard protocol. We applied a larger force (25 N) for comparison to only six subjects. The actual loading in all limb joints during normal walking is not constant throughout the gait cycle and the moment arms may as well vary during air-stepping and thus our loading force was somewhat artificial. However, the rationale for this experiment was to investigate the effect of a small loading force applied constantly during air-stepping, under the assumption that even minimal surrogate contact forces may affect foot motion (Ivanenko et al. 2002).

3 One-legged air-stepping with an elastic band (10 cm wide) wrapped around the forefoot. This protocol was used as a control (to *protocol 2*) for a potential nonspecific effect of skin pressure on air-stepping. In contrast to *protocol 2*, this procedure did not evoke any resultant external loading force on the foot.

These conditions were recorded in all subjects ($n = 33$, Table 1). If they showed air-stepping, they were also tested in the two-legged suspension system (Fig. 1B) using continuous vibration and ES of the right leg only.

Finally, normal overground walking (one trial) was recorded to compare the amplitudes of angular motion and EMG activity with those of air-stepping. The subjects were asked to walk along an 8-m walkway at a natural speed. On average, the walking speed was 4.4 ± 0.9 km/h across all subjects.

In additional experiments (on a separate day), to minimize voluntary contributions, we also attempted to evoke one-legged air-stepping while the subjects were closely attending to another (cognitive) task and compared it with *normal* air-stepping performance (without cognitive task). To this end, mental arithmetic (counting down out loud by 7's; Glasauer et al. 2007) was performed while experiencing continuous Q vibration or ES of the peripheral nerves. We performed

these experiments in 10 healthy individuals who showed air-stepping in the previous experimental session. Three trials were recorded in each condition (total trials = 18).

Data recording

Recordings of EMG activity were obtained using surface bipolar electrodes (BAC Electronics, Rockville, MD) from four muscles of the suspended leg: rectus femoris (RF), biceps femoris (BF, long head), lateral gastrocnemius (LG), and tibialis anterior (TA). In the case of bilateral air-stepping, we recorded RF and BF activity in both legs. The skin was abraded and cleaned with alcohol. EMG activity was preamplified and filtered (bandwidth 20 Hz to 1 kHz). To monitor the onset and termination of the voluntary isometric contraction of the extensors of both arms against each other (Jendrassik maneuver), the activity of m. brachioradialis (BR) was recorded. The force of the elastic cord (4 or 8 N) applied to the sole was recorded by means of a strain gauge to characterize its variation across movement cycle. Angular movements in the three limb joints (hip, knee, and ankle) were recorded using potentiometers attached laterally to the suspended leg. In the case of bilateral air-stepping (Fig. 1B), potentiometers were attached to each joint of both legs. The kinematic and EMG data were sampled at 800 Hz and stored for subsequent analysis.

Data analysis

Cycle duration, amplitudes, and phase shifts of hip, knee, and ankle angular changes were assessed as the movement parameters averaged across eight cycles during the last 15–30 s of the trial. Since three trials were always recorded for each air-stepping condition, the data were also averaged across these trials and used for the subsequent statistical analysis. Raw EMG data were numerically rectified, low-pass-filtered with a zero-lag Butterworth filter with cutoff at 10 Hz, time-interpolated over a time base with 100 points for individual step cycles, and averaged. The cycle was defined using horizontal ankle motion reconstructed from the hip and knee joints and the lengths of the shank and thigh segments. Onset of the air-stepping cycle (and the stance and swing phases, accordingly) was determined as the timing when the ankle motion changed its direction. To characterize the phase of LG activity during application of the 25-N loading force we computed the timing of the main peak (see RESULTS). The phase shift between hip and knee movements was defined as an interval between maxima of knee and hip angle divided by the cycle duration. If the shift exceeded 0.5, unity was subtracted from its value, so that phase shifts were in the range of -0.5 to 0.5 . The negative phase shift means that hip movement leads over knee movement and vice versa. The onset of motion in the hip and knee joints was determined by visual inspection as the onset of prominent angular deviation prior to the first rhythmic cycle and was used as an estimation of latency in evoking cyclic movements (Fig. 1C).

Statistics

Descriptive statistics included means and SD of the mean. Paired t -test and ANOVA were used when appropriate to compare means. In particular, the following parameters were statistically assessed across conditions: amplitude of angular motion, mean EMG activity, the occurrence (number) of FW (forward) versus BW (backward) air-stepping movements, and the number of oscillations induced by 5-s Q vibration or by one to two passive cyclic movements with and without the Jendrassik maneuver. The level of statistical significance was set at 0.05.

RESULTS

Tonic peripheral stimulation

ONE-LEGGED AIR-STEPPING PRODUCED BY PERIPHERAL SENSORY STIMULATION. Experiments showed that, as in the case of muscle vibration (Gurfinkel et al. 1998), it was also possible to elicit rhythmic locomotor-like leg movements using ES of peripheral nerves. It is known that effects of muscle vibration are evident in only some subjects (Eklund and Hagbarth 1966; Gurfinkel et al. 1998). A similar observation was found in this study using both quadriceps muscle vibration and electrical nerve stimulation (Table 1). Out of 33 healthy persons tested, only about 60% of subjects (18–21 subjects) were sensitive to peripheral sensory stimulation and produced cyclic movements. Most subjects ($n = 18$) who showed rhythmic movements to muscle vibration also showed responses to ES (Table 1). A few subjects ($n = 3$) responded to only one or two types of sensory stimuli, although with relatively low (<10 – 15°) or nonstable amplitudes of angular oscillations. The remaining subjects ($n = 12$) did not show stepping movements to any of sensory stimuli. Strikingly, we were also able to evoke rhythmic movement of the suspended leg using ES of the contralateral limb, although in fewer subjects (Table 1). Moreover, the angular amplitude was comparable to that of the ipsilateral stimulation in these subjects ($P > 0.05$, paired t -test). These data with contralateral leg stimulation were used to illustrate the EMG activity during evoked rhythmic movements of the suspended leg because ipsilateral ES produced large artifacts in

EMG recordings. Instead, the kinematic data were analyzed for all subjects ($n = 18$) and all stimulation conditions.

An example of involuntary rhythmic movements is shown in Fig. 1C. The latency of the elicited cyclic movements varied significantly (5.4 ± 7.9 s across all subjects and conditions, range 1.5–26.5 s). Generally, cyclic movements increased monotonically for 2–10 cycles (Fig. 1C) until they reached a relatively constant amplitude of angular oscillations (coefficient of variation across 8 successive cycles was $7 \pm 3\%$ across all trials and subjects) that persisted throughout the stimulus application. We analyzed these oscillations for the last 8 cycles (during the last 15–30 s of the trial).

Figure 2A illustrates an example of overground walking at a natural speed and evoked air-stepping movements in the same subject. In most subjects, RF, TA, and LG showed very low activation levels, whereas rhythmic BF activity was more prominent. The mean EMG activity during air-stepping was significantly smaller than that during overground walking. The cycle duration was significantly longer (Fig. 2B), likely due to the absence of gravity influences on the pendulum behavior of the swinging limb (Mochon and McMahon 1980). The amplitude of the hip and knee angular movements was comparable during normal walking and air-stepping. However, the ankle joint motion was remarkably different (Fig. 2A). On average, the ankle joint (peak-to-peak) oscillations were $<2^\circ$ during involuntary air-stepping, whereas during overground stepping they were $25 \pm 8^\circ$ (Fig. 2C). The amplitudes of the hip, knee, and ankle joints during air-stepping did not depend signifi-

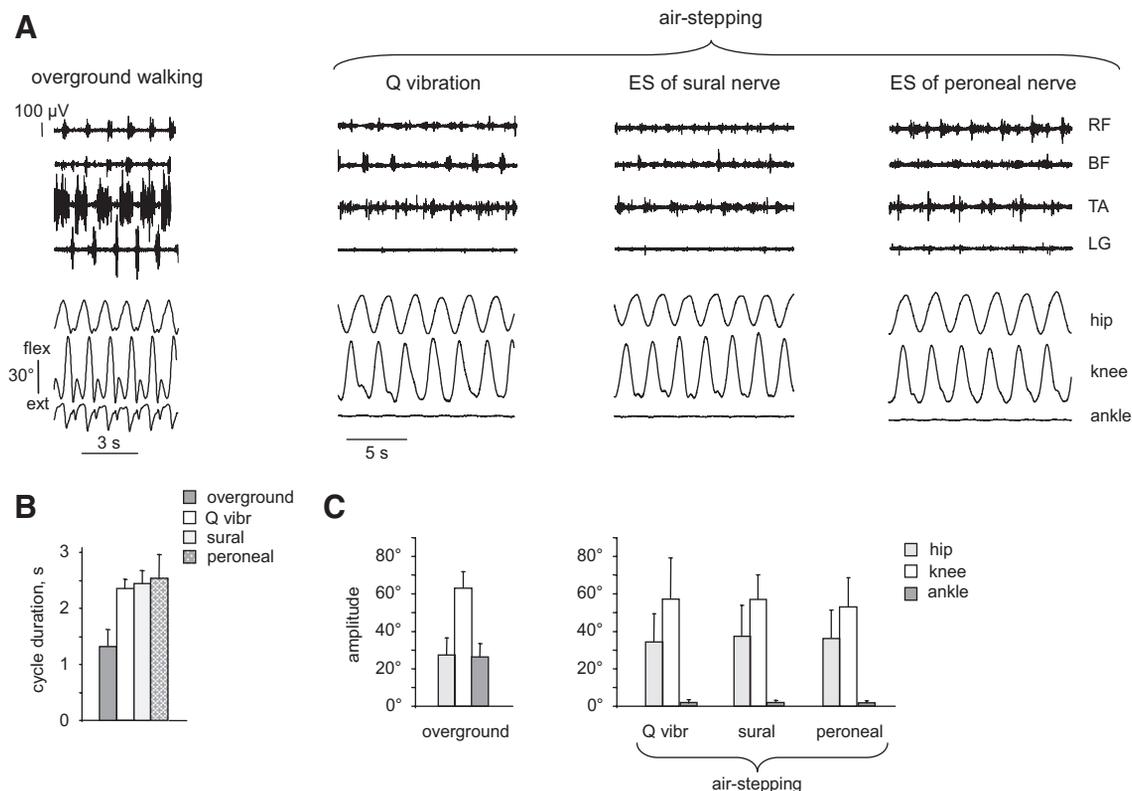


FIG. 2. Overground walking at a natural speed and involuntary air-stepping of the suspended leg. *A*: an example of electromyograms (EMGs) and angular movements in one representative subject are shown. Overground stepping was performed at 4.5 km/h. Rhythmic leg movements were evoked by muscle vibration and ES of sural and peroneal nerves. ES was applied to the contralateral leg. An upward deflection of traces denotes flexion in the hip and knee joint angles and dorsiflexion in the ankle joint. *B*: mean cycle duration (\pm SD) of stepping movements across all subjects and conditions. *C*: mean amplitude of joints angles across all subjects and stimulation conditions. Note a lack of involvement of the distal (ankle) joint in air-stepping.

cantly on the stimulation technique [3×3 ANOVA, joint \times stimulation, $F_{(2,51)} = 0.204$, $P = 0.82$].

EFFECT OF CONCURRENT COGNITIVE TASK. In 10 subjects we compared air-stepping with and without the concurrent cognitive task. Figure 3 illustrates the results. Concurrent mental arithmetic did not abolish the appearance of air-stepping in all tested subjects using all stimulation techniques and angular amplitudes were similar [ANOVA, $F_{(1,54)} = 1.87$, $P = 0.17$]. Moreover, the amplitude of hip and knee angular motion was even slightly larger (although not significantly), whereas the ankle joint motion was not involved in both cases (Fig. 3). We did not quantitatively assess their performance (counting down out loud by 7's); nevertheless, the experimenter did not notice any change in counting speed when they started to step.

EFFECT OF SMALL LOAD FORCES. A small load applied constantly to the foot during air-stepping (Fig. 4A) provoked significant (~ 5 – 15° , $7 \pm 8^\circ$ on average) ankle joint angle movements [3×3 ANOVA, force condition \times stimulation, $F_{(2,51)} = 26.31$, $P < 0.00001$ for the effect of force]. It is worth noting that even the smallest force (4 N) augmented ankle joint oscillations (Fig. 4B). Variations in the elastic force due to the lengthening of the elastic cord throughout the movement cycle were very small ($< 10\%$, Fig. 4A, bottom right). Moreover, the ankle joint movements were accompanied by activation of the distal shank muscles (Fig. 4A). A small force could also slightly increase the amplitude of the knee joint oscillations by about 5–15% on average [3×3 ANOVA, force condition \times stimulation, $F_{(2,51)} = 6.30$, $P = 0.003$ for the effect of force]. Hip joint oscillations also tended to increase but not significantly ($P > 0.05$).

This small force applied to the foot was accompanied by only limited increments in the EMG activity in the distal extensors (LG). For instance, mean LG activity was 16 ± 12 and $8 \pm 8 \mu\text{V}$ with and without the 8-N force, respectively (the data for all stimulation techniques were pooled together; an increment of mean activity was significantly different from zero, $P < 0.01$, one-tailed t -test), TA activity also tended to increase ($P = 0.04$), and activity of proximal muscles (RF and BF) did not show significant changes ($P > 0.1$). Application of small loading forces and a burstlike character of evoked muscle activity often resulted in higher-order harmonics of the ankle

joint modulations (Fig. 4A, right). To test this further, we applied a larger force (25 N) to six subjects (Fig. 4C). This noticeably shortened the relaxed leg in both cases by about 30 cm. However, as soon as the rhythmic movement was evoked by sensory stimulation (vibration or ES), their legs straightened and the evoked cyclic movements were accompanied by prominent oscillations in the ankle joint ($\sim 20^\circ$) and by a considerably increased activation of the TA and LG muscles (two- to threefold relative to the 8-N force). EMG activity of TA and LG was modulated throughout the cycle. The timing of the main peak of LG activity varied somewhat across subjects ($n = 6$); however, it occurred during “stance” (on average, at $31 \pm 17\%$ of cycle during forward stepping, whereas the relative stance duration was $56 \pm 3\%$). In sum, even small forces applied to the foot seemed to provoke prominent movements in the distal (ankle) joint.

This facilitatory effect of force seemed to be due to limb loading rather than to tactile stimulation of the foot. Indeed, when we applied pressure using an elastic band wrapped around the forefoot, it evoked only minute (if any) changes in the distal joint behavior (Fig. 4B, $P > 0.3$ for all stimulation techniques, paired t -test). The pressure on the forefoot was mostly tactile and essentially not transmitted to the limb, whereas with any loading force, no matter how minimal, there is some force transmission to the limb, which is likely sensed by the proprioceptive system. It is also worth noting that in the relaxed limb, in the absence of air-stepping, loading forces evoked limb shortening (by 2–12 cm for smaller forces and ~ 30 cm for the 25-N force). However, as soon as the rhythmic movement was evoked, the leg straightened so that the loading force was actively compensated across all limb joints during air-stepping.

BILATERAL VERSUS UNILATERAL AIR-STEPPING. Since an essential feature of natural human locomotion is represented by the alternating movements of the two legs, in another protocol we attempted to elicit rhythmic activity using the two-legged suspension system (Fig. 1B). An example of involuntary stepping evoked by quadriceps muscle vibration is shown in Fig. 5, A and B. Interestingly, unilateral application of the stimulus produced cyclic movements of both legs in all subjects. Movements of both legs were alternating and the amplitude of hip

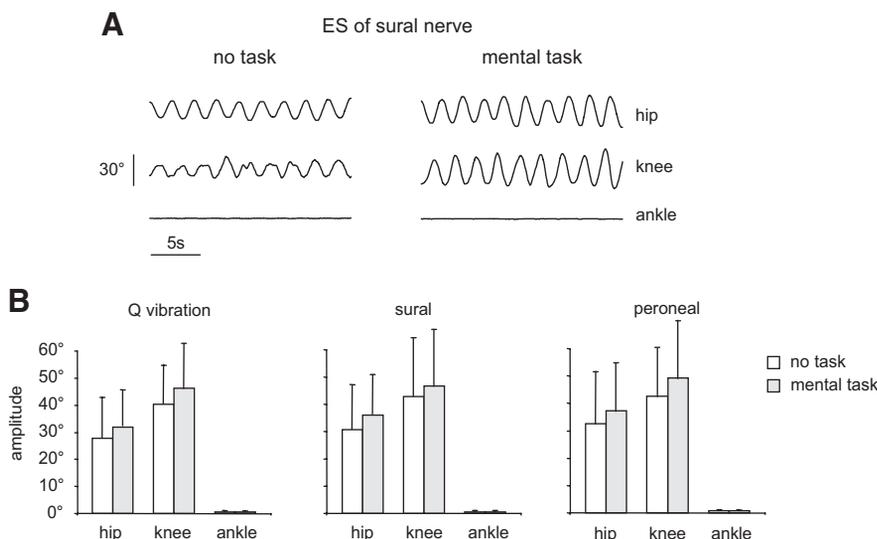


FIG. 3. Effect of the concurrent mental task. A: an example of one-legged air-stepping movements in response to ipsilateral ES of the sural nerve. B: mean amplitude (\pm SD) of joints angles across all subjects ($n = 10$) and stimulation conditions.

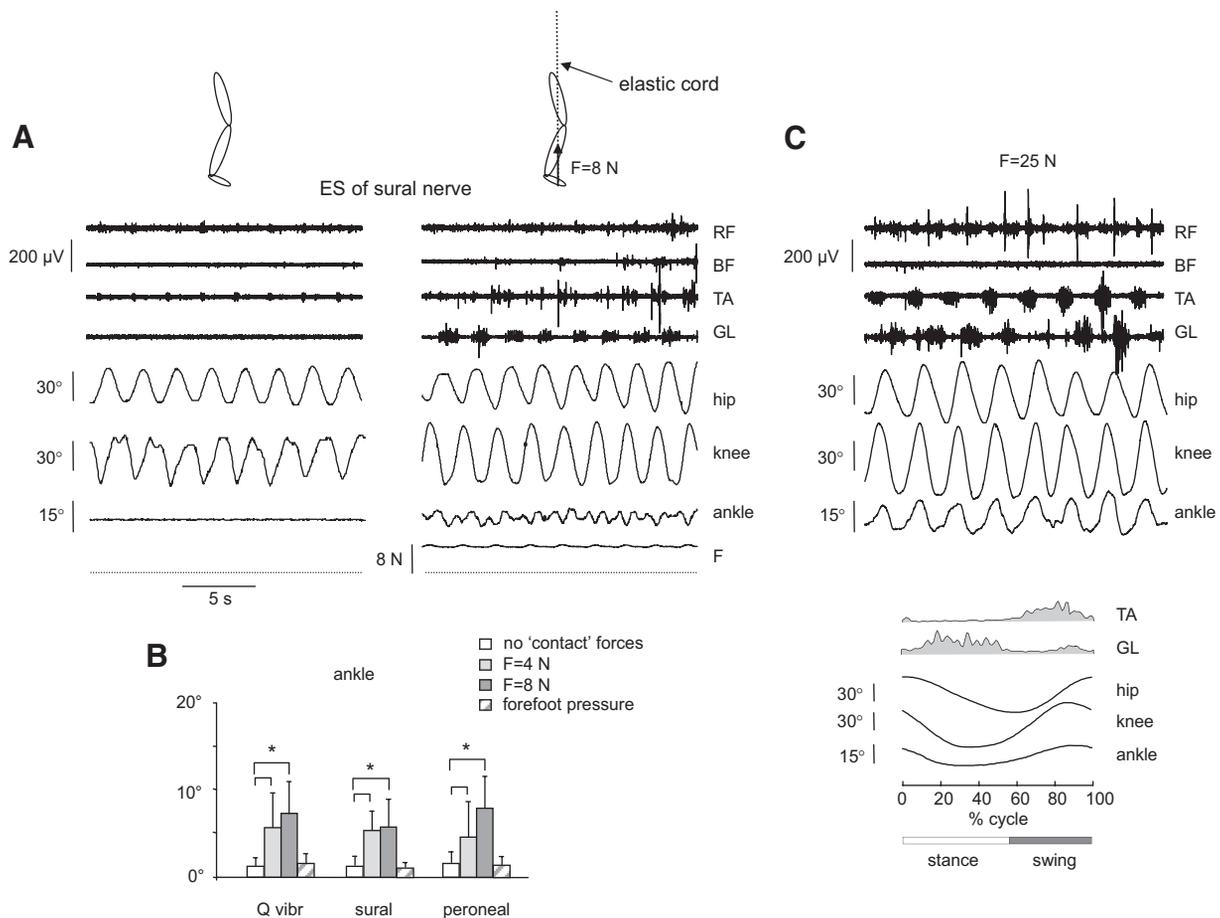


FIG. 4. Effect of small forces (4 and 8 N) applied constantly to the foot via a long elastic thread cord on the kinematics of involuntary leg movements. *A*: rhythmic movements evoked by continuous ES of the sural nerve of the contralateral leg in the absence (*left*) and presence (*right*) of small (8 N) force applied to the forefoot part of the foot in one representative subject. Eight consecutive cycles are shown for each condition. The force was applied approximately in the direction of the longitudinal axis of the body using a long elastic thread cord. The length of the thread cord was about 5 m so that fluctuations in its force due to the length changes were minimal ($<10\%$) during air-stepping. Note the appearance of noticeable oscillations in the ankle joint angle and activity in the distal muscles in the presence of small load force. *B*: mean amplitude of oscillations in the ankle joint across all subjects and stimulation conditions. The “forefoot pressure” condition corresponds to the condition when an elastic band (10 cm wide) was wrapped around the forefoot, thus producing only tactile stimulation (pressure), without any resultant foot loading. Asterisks denote significant differences with respect to the “no contact force” condition ($P < 0.05$). *C*: rhythmic movements evoked by continuous ES of the sural nerve of the contralateral leg at $F = 25$ N in one subject. Averaged angular movements and EMG activity patterns of the distal muscles are shown on the *bottom*.

and knee angular oscillations was basically identical in both legs (Fig. 5*B*). These amplitudes were comparable using all stimulation techniques and were slightly (but not significantly, $P > 0.15$) smaller than those during one-legged stepping, although the cycle duration was shorter ($P < 0.001$, paired t -test) (Table 2). The ankle joint was typically not involved (not shown) as in the case of one-legged air-stepping. We never observed in-phase leg movements or only motion in one (stimulated) leg in the two-legged suspension protocol.

Another essential feature of locomotor movements is the direction of stepping. Normally, humans walk forward, although automatic backward stepping can often be used in particular cases (for instance, when crossing the road and having seen a sudden red light or a car). For one-legged stepping, the vibration or ES could produce both forward and backward locomotion in most subjects.

The evoked rhythmic movements in the hip joint always occurred with phase shift with respect to the movement in the knee joint (Figs. 1*C*, 2*A*, 4*A*, and 5, *A* and *B*). When the knee extension preceded the hip extension, the movement was per-

ceived by the subject as the forward locomotion. If knee movement lagged behind hip movement, the extension of the hip took place with the flexed knee. In this case the subject described the movement as backward locomotion. Sometimes a spontaneous transition from forward to backward stepping or vice versa was observed during application of continuous sensory stimulus (Fig. 5*A*). Backward stepping was observed more frequently during quadriceps muscle vibration (in 41% of cases) than during ES of peroneal (17%) or sural (24%) nerves. However, whereas one-legged forward stepping occurred more often than backward ($P < 0.03$ for all sensory stimulations, paired t -test), both stepping directions and spontaneous transitions were observed during one-legged rhythmic movements using all stimulation techniques. We could not identify the factors influencing the moment of transition. In particular, the transition could occur both when the hip was flexed and when it was extended (Fig. 5*D*). The transition could be accompanied by transient stoppage at the knee joint (as in Fig. 5*A*) or at the hip joint.

In contrast, for two-legged stepping, we observed only forward stepping without spontaneous transitions (except for

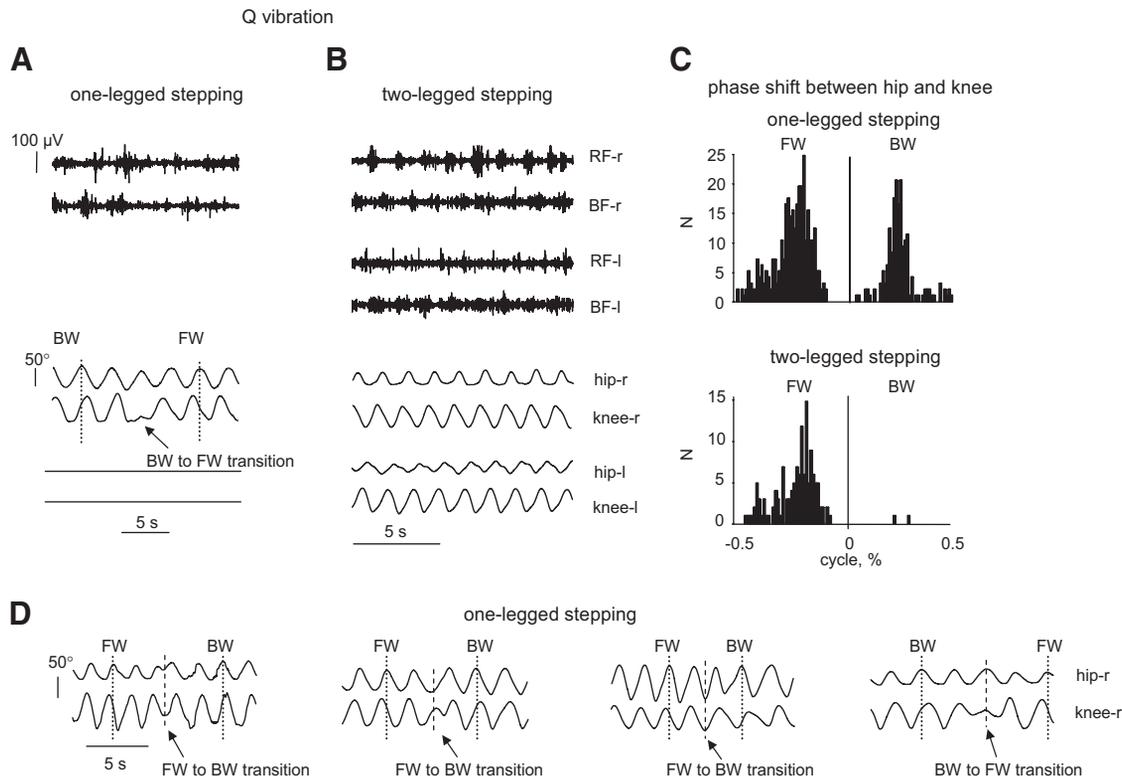


FIG. 5. One-legged vs. two-legged air-stepping evoked by quadriceps muscle vibration. *A*: an example of one-legged air-stepping. Note the transition from backward (BW) to forward (FW) stepping in the middle of the record. *B*: an example of 2-legged alternating leg movements. *C*: histogram of the phase shift between hip and knee joints across all subjects and probes. Note similar occurrence of forward and backward one-legged air-stepping and predominantly forward 2-legged stepping. *D*: examples of transitions from FW to BW stepping and vice versa in 4 subjects.

the two trials in one subject; Fig. 5*C*, bottom), using both muscle vibration (Fig. 5, *B* and *C*) and ES of the peripheral nerves (not shown). In sum, two-legged involuntary air-stepping consisted of alternating leg movements, was more “stable” (no transitions) than one-legged stepping, and was predominantly forward.

Tonic central influences

JENDRASSIK MANEUVER. In the previous sections we reported the characteristics of involuntary rhythmic movements evoked by peripheral sensory stimulation. In the two other protocols, we attempted to elicit rhythmic movements of both legs (Fig. 1*B*) using specific central tonic influences known to facilitate reflex activity in the legs (the Jendrassik maneuver; Delwaide and Toulouse 1981) and to evoke long-lasting tonic muscle contraction (the postcontraction Kohnstamm phenomenon;

TABLE 2. General characteristics of one-legged and two-legged involuntary air-stepping movements evoked by peripheral sensory stimulation

	Cycle Duration, s	Peak-to-Peak Amplitude, degrees		
		Hip	Knee	Ankle
One-legged stepping	2.3 ± 0.2	34.1 ± 17.3	54.2 ± 25.8	1.3 ± 0.8
Two-legged stepping	1.6 ± 0.4*	25.8 ± 16.8	43.3 ± 20.2	1.2 ± 0.8

Values are means ± SD. The data for all stimulation techniques were pooled together. Asterisk (*) indicates significant difference between one-legged and two-legged air-stepping.

Craske and Craske 1986; Duclos et al. 2004; Ivanenko et al. 2006b).

The Jendrassik maneuver per se did not evoke movements of the suspended legs nor did it evoke noticeable changes in EMG activity of the leg muscles (Fig. 6*A*). We tried to “provoke” rhythmic stepping by using a short (5-s) period of Q-muscle vibration. Short vibration per se could result in only one to two small oscillations that rapidly decayed after the cessation of the stimulus (Fig. 6*B*). However, the Jendrassik maneuver facilitated rhythmic stepping that considerably outlasted the vibratory stimulus (Fig. 6*C*). In 11 of 18 subjects, the number of oscillations during the 15-s period after the cessation of vibration was significantly larger with versus without Jendrassik (8.3 ± 1.2 vs. 3.4 ± 0.9 , respectively, $P < 0.0001$). In the remaining seven subjects, the duration of vibration (5 s) was not sufficient for eliciting involuntary air-stepping (in these subjects the latency for evoked air-stepping using muscle vibration was >7 s) and the Jendrassik maneuver did not show any effect.

We also tried to “provoke” rhythmic stepping in all subjects ($n = 18$, Table 1) by using one to two passive cyclic movements imposed by an experimenter. During passive movements, involuntary muscle contraction could sometimes occur (see BF in Fig. 7*A*, left), consistent with earlier observations (Andrews et al. 1973; Burke et al. 1978; Gurfinkel and Ivanenko 1987; Landau et al. 1966; Safronov 1970). If passive movements were performed when the subject was relaxed, oscillations decayed very quickly after the experimenter released the leg and the contralateral limb remained motionless. If passive movements were performed during the Jendrassik

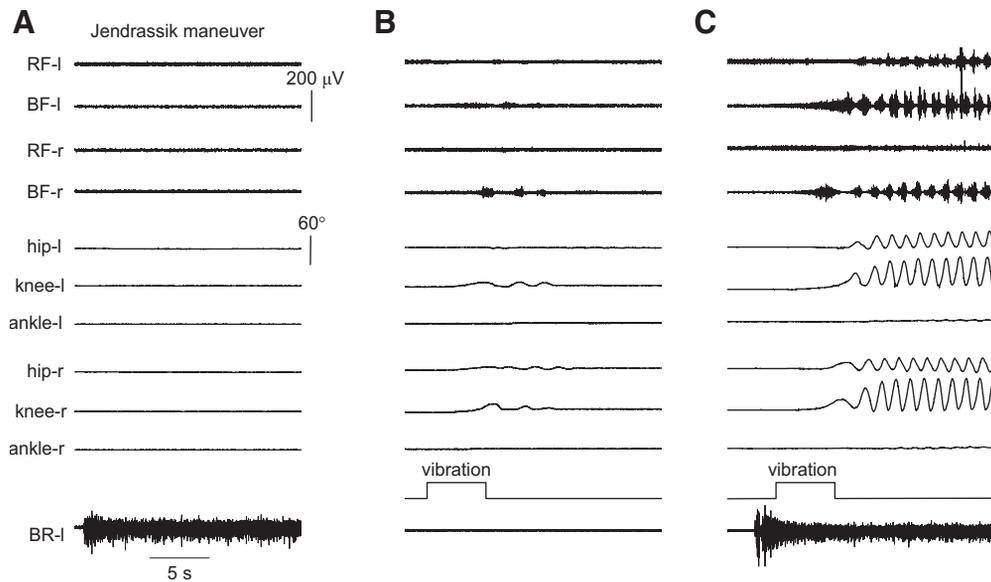


FIG. 6. An example of 2-legged movements during the Jendrassik maneuver (*A*), application of a short period of muscle vibration (*B*), and their combined action (*C*). The voluntary activity of the left brachioradialis muscle (BR-l) is shown on the *bottom* to indicate the timing of application of the Jendrassik maneuver. Note the absence of leg movements in *A*, their quick decay after the cessation of muscle vibration in *B*, and a prominent facilitation of air-stepping in *C*. Note also that Q muscle vibration was applied unilaterally (to the right leg) while involuntary air-stepping was evoked in both legs.

maneuver, involuntary oscillations continued after the experimenter released the leg (Fig. 7*A*). Moreover, these oscillations involved the contralateral limb as well, resulting in alternating rhythmic leg movements (Fig. 7, *A* and *B*). The number of oscillations during the 10-s period after the experimenter released the leg was significantly larger with versus without Jendrassik ($P < 0.00001$, Fig. 7*B*). Once the subject relaxed the arm muscles, leg oscillations decayed quickly. This pattern was observed in 13 of the 18 subjects tested. In 4 subjects oscillations decayed but significantly longer (for more than four cycles) than that without performing the Jendrassik maneuver (one to two cycles only). One subject did not show any significant increments in rhythmic leg responses. The frequency of alternating leg movements (Fig. 7*A*) was similar to that induced by peripheral sensory stimulation (Fig. 5*B*).

POSTCONTRACTION PHENOMENON. Another intriguing approach related to the role of tonic influences is the Kohnstamm phenomenon (Kohnstamm 1915), which consists in appearance of involuntary tonic activity and a particular sensation of “lightness” after the cessation of the long-lasting (30- to 40-s) isometric effort. Postactivation phenomena can therefore be used as a tool to study tonic influences (for a review see Craske and Craske 1986). We used one of its modifications by asking the subject to perform a strong isometric contraction of one leg against another one in the anterior–posterior direction for 30 s (see *METHODS*).

Immediately after the cessation of the voluntary contraction the research assistant released both legs of the subject, thus allowing the manifestation of any unconstrained leg motion in the horizontal plane. Figure 7*C* illustrates an example of the observed aftereffect in one representative subject. After the termination of the voluntary effort, almost all subjects (16 of 18, Table 1) showed involuntary alternating movements of both legs (always forward) with appropriate reciprocal activation of proximal leg muscles (Fig. 7*C*). Only one subject in one trial demonstrated in-phase movements of both legs at the

beginning, although in 3–4 s these in-phase oscillations transitioned to alternating leg movements. Even though the release could provide a small impulse to the leg, it could not account for the observed long-lasting stepping movements (Fig. 7*C*). In addition, the angular changes for the 2-s period following the cessation of the voluntary effort were very small in many cases ($<10^\circ$) and thus likely could not trigger the response. Typically, the movements started within a few seconds after the termination of the voluntary EMG activity; the frequency of leg oscillations first increased, reached a steady-state level, and then decreased with decreasing the amplitude of leg motion (Fig. 7, *C* and *D*). The duration of involuntary rhythmic movements varied across subjects from 5 to 60 s (~ 3 –30 cycles), corresponding roughly to a typical time course of involuntary muscle contraction for the Kohnstamm phenomenon reported in the literature (Craske and Craske 1986; Duclos et al. 2004; Ivanenko et al. 2006b). The maximal frequency and amplitude of the hip and knee joint movements occurred after 3–7 cycles. No ankle joint angle motion was typically observed ($<3^\circ$; not shown), as was the case during involuntary air-stepping in response to peripheral sensory stimulation (Fig. 2).

DISCUSSION

Involuntary air-stepping in the horizontal plane is likely to reveal some basic properties of the CPG. In this study we examined the effects of tonic excitability changes involving both peripheral and central mechanisms. We found that both types of excitability change were capable of producing involuntary rhythmic movements in one or both legs. An interesting feature of these findings was that tonic sensory stimulation did not produce tonic vibratory reflexes or static changes in the leg configuration.

Given that oscillator mechanisms are a major component of the motor systems of animals (Craske and Craske 1984; Grillner 1981), the tendency of the neuronal networks to generate rhythmic movements of the suspended leg is likely not so surprising. Air-stepping could be elicited by most techniques (Figs. 2 and 7),

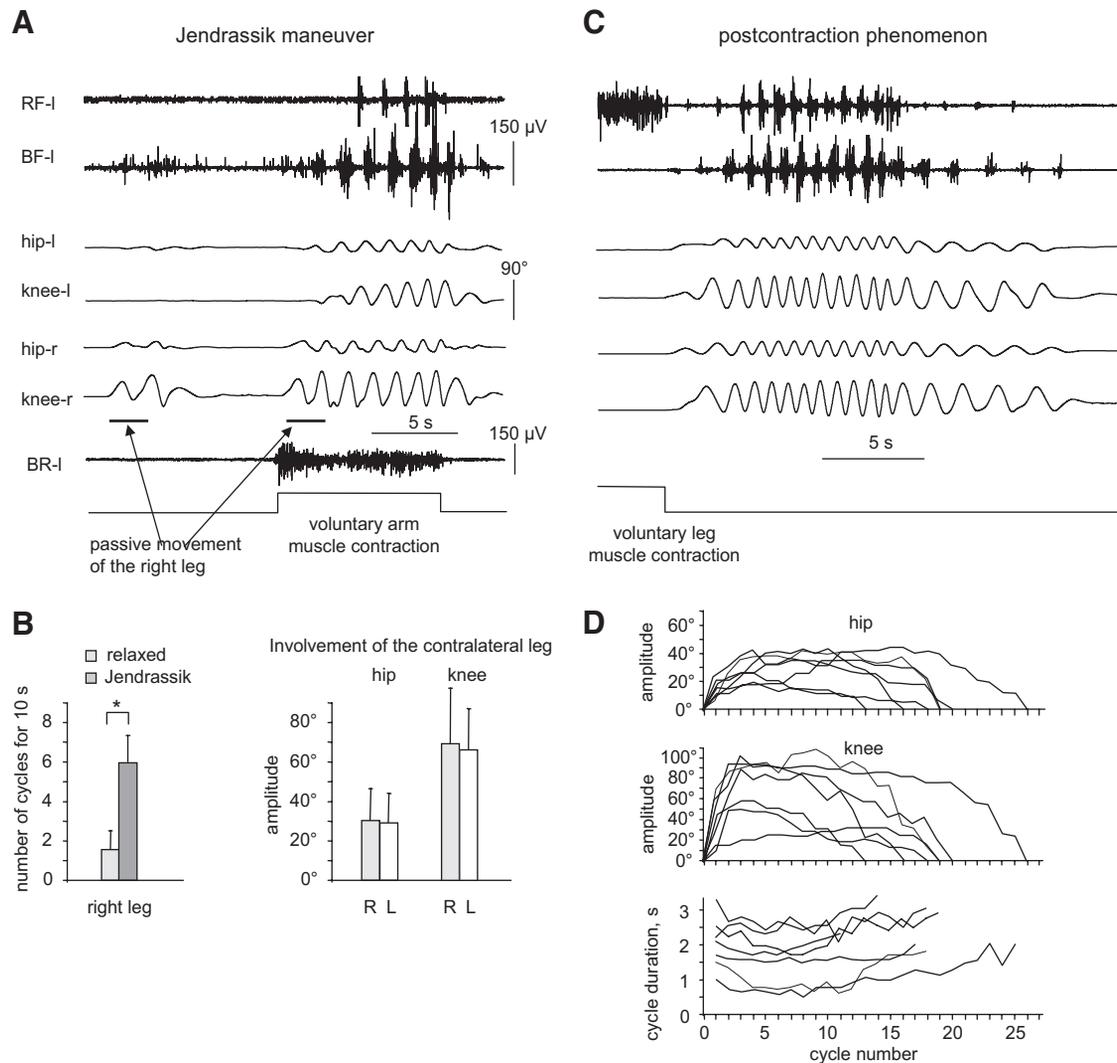


FIG. 7. Two-legged air-stepping evoked by tonic central influences. *A*: an example of involuntary rhythmic leg movements initiated manually by an experimenter. Passive movement of the right leg was initiated by an experimenter twice, during relaxed state and while the subject performed the Jendrassik maneuver. Note a quick decay of the right leg oscillations without voluntary arm contraction and sustained rhythmic movements during the Jendrassik maneuver. Also, note an involvement of the contralateral limb in the latter case. *B*: number of cycles (*left*) and maximal amplitude of hip and knee joint oscillations (*right*) for all subjects ($n = 17$, mean \pm SD) during the 10-s period. *C*: an example of involuntary alternating leg movements after long-lasting (30-s) voluntary contraction of leg muscles (left leg exerted the force in the forward direction and the right leg backward). Involuntary alternating leg movements were observed for the period of about 15 s after the termination of the voluntary effort. *D*: time course of the postcontraction effect on the amplitude and period of involuntary rhythmic leg movements in 7 subjects (the data for the left and right legs were averaged). Note a monotonic increment and subsequent decrement of the amplitude and frequency of leg motion.

consistent with a general notion that nonspecific activation of the lumbosacral enlargement may produce rhythmic leg movements (Calancie et al. 1994; Dickel et al. 1994; Grillner and Zangger 1979; Gurfinkel et al. 1998; Roaf and Sherrington 1910; Shapkova and Schomburg 2001) as long as dorsal root afferents are mostly intact (Goldberger 1988; Lavrov et al. 2008).

It is unlikely that air-stepping was attributable to voluntary drive because the instruction was to relax and because the appearance of self-sustained rhythmic movements was not abolished when the subjects were engaged in the mental task (Fig. 3). It is likely subcortical in origin, although our data cannot shed light on the exact contribution or tuning of the supraspinal structures. Whereas the rhythm generation for human locomotion is largely centered in the upper lumbar spinal cord (Minassian et al. 2007; Shapkova and Schomburg 2001) there is also growing speculation that the source of the rhythms may be distributed (Cuellar et al.

2009; Ivanenko et al. 2009; McLean et al. 2008; Molinari 2009). Our findings indicate that nonspecific tonic excitability may elicit or facilitate CPG activity.

The afferent signals due to vibration or ES may increase the excitability of several segments of the spinal cord (Gurfinkel et al. 1993; Roll et al. 1980), which may facilitate triggering of locomotor-like movements. In addition, percutaneous electrical stimulation may evoke involuntary forces arising from activation of plateau potentials in the spinal neurons (Collins et al. 2001). The major part of the proprioceptive input was nevertheless intact, thus allowing study of how it interacts with rhythmogenesis. In fact, the characteristics of involuntary air-stepping (the amplitude and frequency of hip and knee oscillations) resembled those observed during voluntary air-stepping in the same conditions (Gurfinkel et al. 1998). Aftereffect of a voluntary long-lasting contraction in the leg muscles featured

alternating rhythmic leg movements that lasted for about 20–40 s (Fig. 7C), corresponding roughly to a typical duration of the postcontraction activity (Duclos et al. 2004; Ivanenko et al. 2006b). Again, the characteristics of involuntary air-stepping were similar to the voluntary stepping in the same conditions. The difference in the effects of the last two techniques (the postcontraction phenomenon and the Jendrassik maneuver; Fig. 7) may point to the importance of tonic activation of the lumbosacral enlargement since voluntary arm contractions acted primarily on the cervical spinal cord and were not sufficient to evoke air-stepping unless the experimenter triggered them.

The mechanisms of step generation in humans do not necessarily duplicate the CPG organization known from animal studies (Capaday 2002; Ivanenko et al. 2006a; Winter 1989); nevertheless, the evoked cyclic movements share many of their characteristics. For instance, given the extensive evidence for the presence of commissural interneurons that could drive the contralateral locomotor circuitry (Kiehn 2006), oscillator mechanisms and tonic influences may not be limb specific. We found, for example, that treating one limb can have its output transferred to another limb (Fig. 7A), even if the treated limb is kept stationary (as in the case of ES; Fig. 2). Also, although each limb controller potentially has the ability to generate relatively autonomous rhythmic patterns (e.g., when walking on a treadmill with split belts; Choi and Bastian 2007; Forssberg et al. 1980; Yang et al. 2005), during natural conditions right and left sides are strongly coupled (Ivanenko et al. 2008; Orlovsky et al. 1999; Wannier et al. 2001). Further evidence of the importance of bilateral coupling is demonstrated by the findings that two-legged stepping was more stable, whereas one-legged stepping displayed frequent spontaneous transitions from forward to backward direction and vice versa (Fig. 5).

The present study revealed other essential features of the intrinsic rhythm generation in humans. Air-stepping involved prominent movements in the hip and knee joints, whereas the ankle joint was typically not involved unless minimal loading forces were applied to the foot (Fig. 4). The facilitatory effect of forces was accompanied by modulation of EMG activity (Fig. 4C), consistent with phase-dependent contribution of sensory activity to the preprogrammed motoneuronal drive of the distal muscles during human walking (Duysens et al. 2000; Sinkjaer et al. 2000). Although a combined action of several sensory inputs could not be ruled out, the effect was likely due to limb loading since foot pressure (Fig. 4B) as well as ES of the peripheral sural and peroneal nerves (innervating the lateral aspect of the foot and the foot dorsum, respectively) were not effective in engaging ankle motion. Whatever the exact sensory sources were, it is worth stressing that, in the absence of loading forces, the ankle joint motion was not observed for all stimulation techniques used in this study, making it a general property of rhythm production. Sensory feedback makes a substantial contribution to the activation of distal muscles during locomotion (Donelan and Pearson 2004). Therefore the sacral pattern generation circuitry (Cazalets and Bertrand 2000) could possibly be inactivated when the input from the support surface is lacking. It is also worth noting that the kinematics of walking during body weight unloading (Ivanenko et al. 2002) is similar across all body weight support levels (0–95%), although it does not involve ankle motion in most subjects when the body weight is fully supported (air-stepping). The present results strongly support this hypothesis and suggest that the upper lumbar pattern generator activity may constitute the

major oscillator “pacemaker,” whereas the sacral generator could play a subordinator role for adaptation to specific foot–support interactions.

In sum, the results highlight the importance of investigating the tonic “state” of the spinal circuits. Given that the spinal cord is not simply a relay structure for information transmitted to and from supraspinal systems (Collins et al. 2001; Hultborn 2001; Person 2004; Poppele and Bosco 2003), one may even argue that motor control systems make use of several types of command signals (Jordan et al. 2008): e.g., one for generating *tonic readiness* and the other for performing the movement. The reported phenomena (Figs. 2 and 7) are all consistent with nonspecific tonic excitation of the spinal networks that may facilitate activity in the CPG circuitry. Thus the rhythmic movements we evoked in air-stepping are most likely coordinated by spinal CPGs.

Since the air-stepping is free from many of the mechanical constraints of normal walking it may provide an effective model for studying how peripheral inputs influence CPG behavior in human adults. This could provide a valuable addition to our understanding of the role of sensory control of locomotion that has come from work in quadrupeds (Duysens and Pearson 1980) and human infants (Yang et al. 2004). Moreover, by activating the spinal CPG circuitry with minimal mechanical constraints, this technique might also find use in helping to retrain walking following stroke or spinal cord injury.

ACKNOWLEDGMENTS

We thank Dr. R. Poppele and Dr. G. Bosco for helpful comments.

GRANTS

This research was supported by Russian Foundation for Basic Research Grant 09-04-01183 and by Italian Space Agency/Disturbi del Controllo Motorio e Cardiorespiratorio grant.

REFERENCES

- Andrews, Neilson PD, Lance JW. Comparison of stretch reflexes and shortening reactions in activated normal subjects with those in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 36: 329–333, 1973.
- Beritoff JS. On the mode of originating of labyrinthine and cervical tonic reflexes and on their part in the reflex reactions of decerebrate preparation. *Q J Exp Physiol* 9: 199–229, 1915.
- Burke D, Hagbarth KE, Löfstedt L. Muscle spindle activity in man during shortening and lengthening contractions. *J Physiol* 277: 131–142, 1978.
- 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.
- Cazalets JR, Bertrand S. Coupling between lumbar and sacral motor networks in the neonatal rat spinal cord. *Eur J Neurosci* 12: 2993–3002, 2000.
- Choi JT, Bastian AJ. Adaptation reveals independent control networks for human walking. *Nat Neurosci* 10: 1055–1062, 2007.
- Clarac F, Brocard F, Vinay L. The maturation of locomotor networks. *Prog Brain Res* 143: 57–66, 2004.
- Collins DF, Burke D, Gandevia SC. Large involuntary forces consistent with plateau-like behavior of human motoneurons. *J Neurosci* 21: 4059–4065, 2001.
- Craske B, Craske JD. Oscillator mechanisms in the human motor system: investigating their properties using the aftercontraction effect. *J Mot Behav* 18: 117–145, 1986.
- Cuellar CA, Tapia JA, Juarez V, Quevedo J, Linares P, Martinez L, Manjarrez E. Propagation of sinusoidal electrical waves along the spinal cord during a fictive motor task. *J Neurosci* 29: 798–810, 2009.
- Delwaide PJ, Toulouse P. Facilitation of monosynaptic reflexes by voluntary contraction of muscle in remote part of the body. Mechanisms involved in Jendrassik maneuver. *Brain* 104: 701–709, 1981.
- Dickel MJ, Renfrow SD, Moore PT, Berry RB. Rapid eye movement sleep periodic leg movements in patients with spinal cord injury. *Sleep* 17: 733–738, 1994.

- Dietz V.** Spinal cord pattern generators for locomotion. *Clin Neurophysiol* 114: 1379–1389, 2003.
- Dietz V, Müller R, Colombo G.** Locomotor activity in spinal man: significance of afferent input from joint and load receptors. *Brain* 125: 2626–2634, 2002.
- Donelan JM, Pearson KG.** Contribution of sensory feedback to ongoing ankle extensor activity during the stance phase of walking. *Can J Physiol Pharmacol* 82: 589–598, 2004.
- Duclos C, Roll R, Kavounoudias A, Roll JP.** Long-lasting body leanings following neck muscle isometric contractions. *Exp Brain Res* 158: 58–66, 2004.
- Duysens J, Clarac F, Cruse H.** Load-regulating mechanisms in gait and posture: comparative aspects. *Physiol Rev* 80: 83–133, 2000.
- Duysens J, Pearson KG.** Inhibition of flexor burst generation by loading ankle extensor muscles in walking cats. *Brain Res* 187: 321–332, 1980.
- 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.
- Edgerton VR, Courtine G, Gerasimenko YP, Lavrov I, Ichiyama RM, Fong AJ, Cai LL, Otsoshi CK, Tillakaratne NJ, Burdick JW, Roy RR.** Training locomotor networks. *Brain Res Rev* 57: 241–254, 2008.
- Eklund G, Hagbarth K-E.** Normal variability of tonic vibration reflexes in man. *Exp Neurol* 16: 80–92, 1966.
- Feldman AG, Orlovsky GN.** Activity of interneurons mediating reciprocal Ia inhibition during locomotion. *Brain Res* 84: 181–194, 1975.
- Forssberg H, Grillner S, Halbertsma J, Rossignol S.** The locomotion of the low spinal cat. II. Interlimb coordination. *Acta Physiol Scand* 108: 283–295, 1980.
- Glasauer S, Schneider E, Grasso R, Ivanenko YP.** Space–time relativity in self-motion reproduction. *J Neurophysiol* 97: 451–461, 2007.
- Goldberger ME.** Spared-root deafferentation of a cat's hindlimb: hierarchical regulation of pathways mediating recovery of motor behavior. *Exp Brain Res* 73: 329–342, 1988.
- Goltz F, Freusberg A.** Über die Funktionen des Lendenmarkes des Hundes. *Pflügers Physiol* 8: 460, 1874.
- Gregory JE, Wood SA, Proske U.** An investigation into mechanisms of reflex reinforcement by the Jendrassik maneuver. *Exp Brain Res* 138: 366–374, 2001.
- Grillner S.** Control of locomotion in bipeds, tetrapods, and fish. In: *Handbook of Physiology. The Nervous System. Motor Control*. Bethesda, MD: Am. Physiol. Soc., 1981, sect. 1, vol. II, pt. 2, p. 1179–1236.
- Grillner S.** Biological pattern generation: the cellular and computational logic of networks in motion. *Neuron* 52: 751–766, 2006.
- Grillner S, Zangger P.** On the central generation of locomotion in the low spinal cord. *Exp Brain Res* 34: 241–261, 1979.
- Gurfinkel VS, Ivanenko YP.** Low-threshold reactions of human muscles at rest. *Hum Physiol* 13: 317–323, 1987.
- Gurfinkel VS, Lebedev MA, Levik YS.** Effects of reversal in the human equilibrium regulation system. *Neurofiziologia* 24: 297–304, 1993.
- 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.
- Gurfinkel VS, Levik YS, Lebedev MA.** Immediate and remote postactivation effects in the human motor system. *Neurofiziologia* 21: 247–253, 1989.
- Hultborn H.** State-dependent modulation of sensory feedback. *J Physiol* 533: 5–13, 2001.
- Ivanenko YP, Cappellini G, Poppele RE, Lacquaniti F.** Spatiotemporal organization of alpha-motoneuron activity in the human spinal cord during different gaits and gait transitions. *Eur J Neurosci* 27: 3351–3368, 2008.
- Ivanenko YP, Grasso R, Macellari V, Lacquaniti F.** Control of foot trajectory in human locomotion: role of ground contact forces in simulated reduced gravity. *J Neurophysiol* 87: 3070–3089, 2002.
- Ivanenko YP, Poppele RE, Lacquaniti F.** Spinal cord maps of spatiotemporal alpha-motoneuron activation in humans walking at different speeds. *J Neurophysiol* 95: 602–618, 2006a.
- Ivanenko YP, Poppele RE, Lacquaniti F.** Distributed neural networks for controlling human locomotion: lessons from normal and SCI subjects. *Brain Res Bull* 78: 13–21, 2009.
- Ivanenko YP, Wright WG, Gurfinkel VS, Horak F, Cordo P.** Interaction of involuntary post-contraction activity with locomotor movements. *Exp Brain Res* 169: 255–260, 2006b.
- Jordan LM, Liu J, Hedlund PB, Akay T, Pearson KG.** Descending command systems for the initiation of locomotion in mammals. *Brain Res Rev* 57: 183–191, 2008.
- Kiehn O.** Locomotor circuits in the mammalian spinal cord. *Annu Rev Neurosci* 29: 279–306, 2006.
- Kohnstamm O.** Demonstration einer katatonieartigen Erscheinung beim Gesunden (Katatonusversuch). *Neurol Zentral Bl* 34S: 290–291, 1915.
- Kremer E, Lev-Tov A.** Localization of the spinal network associated with generation of hindlimb locomotion in the neonatal rat and organization of its transverse coupling system. *J Neurophysiol* 77: 1155–1170, 1997.
- Landau WM, Struppeler A, Mehls O.** A comparative electromyographic study of the reactions to passive movement in parkinsonism and in normal subjects. *Neurology* 16: 34–48, 1966.
- Lavrov I, Courtine G, Dy CJ, van den Brand R, Fong AJ, Gerasimenko Y, Zhong H, Roy RR, Edgerton VR.** Facilitation of stepping with epidural stimulation in spinal rats: role of sensory input. *J Neurosci* 28: 7774–7780, 2008.
- McLean DL, Masino MA, Koh IY, Lindquist WB, Fetcho JR.** Continuous shifts in the active set of spinal interneurons during changes in locomotor speed. *Nat Neurosci* 11: 1419–1429, 2008.
- Minassian K, Persy J, Rattay F, Pinter MM, Kern H, Dimitrijevic MR.** Human lumbar cord circuitries can be activated by extrinsic tonic input to generate locomotor-like activity. *Hum Mov Sci* 26: 275–295, 2007.
- Mochon S, McMahon TA.** Ballistic walking. *J Biomech* 13: 49–57, 1980.
- Molinari M.** Plasticity properties of CPG circuits in humans: impact on gait recovery. *Brain Res Bull* 78: 22–25, 2009.
- Mori S, Sakamoto T, Ohta Y, Takakusaki K, Matsuyama K.** Site-specific postural and locomotor changes evoked in awake, freely moving intact cats by stimulating the brainstem. *Brain Res* 505: 66–74, 1989.
- Orlovsky GN, Deliagina TG, Grillner S.** *Neural Control of Locomotion. From Mollusc to Man*. Oxford, UK: Oxford Univ. Press, 1999.
- Pearson KG.** Generating the walking gait: role of sensory feedback. *Prog Brain Res* 143: 123–129, 2004.
- Pearson KG, Rossignol S.** Fictive motor patterns in chronic spinal cats. *J Neurophysiol* 66: 1874–1887, 1991.
- Poppele RE, Bosco G.** Sophisticated spinal contributions to motor control. *Trends Neurosci* 26: 269–276, 2003.
- Roaf HE, Sherrington CS.** Further remarks on the spinal mammalian preparation. *Q J Physiol* 3: 209–211, 1910.
- Roll JP, Gilhodes JC, Tardy-Gervet MF.** Effect perceptifs et moteurs des vibrations musculaires antagonistes. *Arch Ital Biol* 118: 51–71, 1980.
- Rossignol S, Dubuc R, Gossard JP.** Dynamic sensorimotor interactions in locomotion. *Physiol Rev* 86: 89–154, 2006.
- Rybak IA, Shevtsova NA, Lafreniere-Roula M, McCrear DA.** Modelling spinal circuitry involved in locomotor pattern generation: insights from deletions during fictive locomotion. *J Physiol* 577: 617–639, 2006.
- Safranov VA.** Regulation of muscle tone. *Biophysics* 15(6): 1103–1111, 1970.
- Shapkova EY, Schomburg ED.** Two types of motor modulation underlying human stepping evoked by spinal cord electrical stimulation (SCES). *Acta Physiol Pharmacol Bulg* 26: 155–157, 2001.
- Shik ML.** Action of the brainstem locomotor region on spinal stepping generators via propriospinal pathways. In: *Spinal Cord Reconstruction*, edited by Kao CC, Bunge RP, Reier RJ. New York: Raven Press, 1983, p. 421–434.
- Sinkjaer T, Andersen JB, Ladouceur M, Christensen LO, Nielsen JB.** Major role for sensory feedback in soleus EMG activity in the stance phase of walking in man. *J Physiol* 523: 817–827, 2000.
- 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.
- 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.
- 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.
- Winter DA.** Biomechanics of normal and pathological gait: implications for understanding human locomotor control. *J Mot Behav* 21: 337–355, 1989.
- Winter DA, Yack HJ.** EMG profiles during normal human walking: stride-to-stride and inter-subject variability. *Electroencephalogr Clin Neurophysiol* 67: 402–411, 1987.
- Yang JF, Lam T, Pang MY, 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.
- Yang JF, Lamont EV, Pang MY.** Split-belt treadmill stepping in infants suggests autonomous pattern generators for the left and right leg in humans. *J Neurosci* 25: 6869–6876, 2005.
- Zehr EP.** Neural control of rhythmic human movement: the common core hypothesis. *Exerc Sport Sci Rev* 33: 54–60, 2005.
- Zehr EP, Komiyama T, Stein RB.** Cutaneous reflexes during human gait: electromyographic and kinematic responses to electrical stimulation. *J Neurophysiol* 77: 3311–3325, 1997.