Modulation of multisegmental monosynaptic responses in a variety of leg muscles during walking and running in humans

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Motor responses evoked by stimulating the spinal cord percutaneously between the T11 and T12 spinous processes were studied in eight human subjects during walking and running. Stimulation elicited responses bilaterally in the biceps femoris, vastus lateralis, rectus femoris, medial gastrocnemius, soleus, tibialis anterior, extensor digitorum brevis and flexor digitorum brevis. The evoked responses were consistent with activation of Ia afferent fibres through monosynaptic neural circuits since they were inhibited when a prior stimulus was given and during tendon vibration. Furthermore, the soleus motor responses were inhibited during the swing phase of walking as observed for the soleus H-reflex elicited by tibial nerve stimulation. Due to the anatomical site and the fibre composition of the peripheral nerves it is difficult to elicit H-reflex in leg muscles other than the soleus, especially during movement. In turn, the multisegmental monosynaptic responses (MMR) technique provides the opportunity to study modulation of monosynaptic reflexes for multiple muscles simultaneously. Phase-dependent modulation of the MMR amplitude throughout the duration of the gait cycle period was observed in all muscles studied. The MMR amplitude was large when the muscle was activated whereas it was generally reduced, or even suppressed, when the muscle was quiescent. However, during running, there was a systematic anticipatory increase in the amplitude of the MMR at the end of swing in all proximal and distal extensor muscles. The present findings therefore suggest that there is a general control scheme by which the transmission in the monosynaptic neural circuits is modulated in all leg muscles during stepping so as to meet the requirement of the motor task.

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Modulation of reflexes by the central nervous system is critical for successful movement. The stretch reflex has been shown to contribute up to 40–60% to the total torque produced around the target joint during static motor tasks (Toft *et al.* 1991; Mrachacz-Kersting & Sinkjaer, 2003). This implies that the central nervous system has to modulate the strength of muscle reflexes throughout the movement as required to perform the specific task, i.e. task- and phase-dependent reflex modulation (Capaday & Stein, 1986, 1987; Crenna & Frigo, 1987; Dyhre-Poulsen *et al.* 1991; Edamura *et al.* 1991; Sinkjaer *et al.* 1996; Lavoie *et al.* 1997; Faist *et al.* 1999; Schneider *et al.* 2000; Mrachacz-Kersting *et al.* 2004). The Hoffman (H)-reflex technique uses direct electrical stimulation to the motor nerve to evoke the short latency component of the stretch reflex in dynamic conditions (Andersen & Sinkjaer, 1999). The H-reflex bypasses the fusimotor regulation system as well as the mechanical stimulus on muscle spindles, and therefore directly assesses the central modulation of synaptic efficacy of afferent input from large-diameter fibres onto motor neurons (Schieppati, 1987). The amplitude of the soleus H-reflex is strongly modulated during human locomotion with high amplitude during the stance phase and suppression during the swing phase (Capaday & Stein, 1986; Simonsen & Dyhre-Poulsen, 1999). Furthermore, the soleus H-reflex

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amplitude is significantly lower during walking and running compared with standing (Edamura *et al.* 1991; Simonsen & Dyhre-Poulsen, 1999; Ferris *et al.* 2001). Such task- and phase-dependent changes of the input–output properties of the soleus H-reflex neural circuitry reflect an adaptive modulation of the functional connectivity within the spinal motor infrastructure to meet the biomechanical and physiological demands of locomotion (Stein & Capaday, 1988; Simonsen *et al.* 2002).

The neural control of locomotion conceivably requires the central nervous system to modulate reflex excitability not only in the soleus muscle, but in all leg muscles. Knowledge on the modulation of synaptic efficacy of proprioceptive afferents from multiple leg muscles would facilitate the understanding of the neural control properties of human locomotion and allow investigation of these systems following neurological disorders. For example, extensor and flexor muscles as well as proximal *versus* distal muscles respond very differently to a given neuromotor impairment (Harkema, 2001; Dietz & Muller, 2004; Courtine *et al.* 2005*b*). However, only a few muscles are accessible using the H-reflex technique and the H-reflex cannot be studied simultaneously in multiple muscles during walking (Dietz *et al.* 1990*b*; Toft *et al.* 1991; Faist *et al.* 1999; Christensen *et al.* 2001; Mrachacz-Kersting *et al.* 2004).

In this study, we show that percutaneous stimulation applied between T11 and T12 spinous processes elicit multisegmental monosynaptic responses (MMR) in multiple leg muscles bilaterally (Minassian *et al.* 2007). We used this methodology to study the modulation of the monosynaptic neural circuits from a number of flexor and extensor motor pools innervating proximal and distal leg muscles during locomotion. We investigated the modulation of MMR during walking and running to assess whether the task-dependent reflex modulation observed for the soleus monosynaptic neural circuit could be generalized to the other leg muscles.

Methods

Research participants

Eight individuals (3 females, 5 males) gave voluntary written consent to participate in the experiments. Their mean age was 29 years (range, 24–34 years), mean height was 1.75 m (range, 1.68–1.95 m) and mean body weight was 64 kg (range, 44–77 kg). The study was approved by the ethics committee of the University of California at Los Angeles (UCLA) and conformed to the *Declaration of Helsinki*.

Experimental procedure

We placed EMG electrodes on the leg muscles and recorded evoked responses to the percutaneous stimulation of the spinal cord at the T11–T12 level. We first elicited evoked responses with and without continuous Achilles tendon vibration while the individual was lying prone. We then elicited evoked responses while the individuals walked (3.5 km h^{-1}) and ran (8 km h^{-1}) on a motor-driven treadmill. We also evoked responses during standing before and after each walking or running bout. In five individuals, we measured the right soleus H-reflex during sitting at the end of the experimental session to evaluate the extent of crosstalk between soleus and tibialis anterior muscles.

Electromyography, goniometers and footswitches

Bipolar surface electrodes with an interelectrode distance of 2 cm were mounted over 16 leg muscles bilaterally (Harkema *et al.* 1997; Beres-Jones & Harkema, 2004). The electrodes were placed as follows: for the rectus femoris, vastus lateralis and biceps femoris muscles, the electrodes were positioned on the muscle belly, midway between the upper and lower muscle insertion; for the soleus, approximately 15 cm above the calcaneus over the gastrocnemius aponeurosis but below the muscle fibres of the gastrocnemius heads; for the tibialis anterior muscle about 12 cm below the caput fibulae; for the medial head of the gastrocnemius muscle, approximately 5 cm below the caput fibulae; for the extensor digitorum brevis, on the outer lateral aspect of the foot; for the flexor digitorum brevis, under the arch of the foot, on the muscle belly. Electrodes were connected to preamplifiers (Konigsberg Instruments, CA, USA) located close to the subjects. The EMG signals were then led through long shielded wires to preamplifiers (Konigsberg Instruments) with a frequency response between 20 Hz and 1 kHz. The set-up permitted the subjects to move freely on the treadmill. Foot–ground contact was detected by microswitches placed under the heel and forefoot of both feet. The hip, knee and ankle joint positions were measured in one subject with electromagnetic sensors (Skill Technologies Inc., Phoenix, AZ. USA).

Multisegmental monosynaptic responses (MMRs)

We placed the AgCl cathode (Lead-Lok Inc., pre-gelled, soft surface electrode) over the skin between T11 and T12 spinous processes and two 50 mm × 100 mm large anodes (UltraStim SN2040) bilaterally over the anterior spine of the iliac crest. The optimum site of stimulation was first located by a hand-held electrode. The site of stimulation was selected where the motor responses could be elicited in all the recorded muscles as symmetrically as possible. When the optimal site of stimulation was detected, the surface electrode was attached to the body. We observed that pressure applied to the cathode had a much greater effect on the MMR amplitude than lateral displacements. Therefore we secured a piece of foam

rubber over the cathode with a strong elastic band wrapped tightly around the body. A custom-built constant current stimulator produced the 1 ms square pulse. The stimulus intensity ranged from 9 mA to 66 mA and was determined by eliciting a response in all muscles and limiting the amplitude of right soleus to approximately 5 mV. The stimulus intensity was adjusted before each testing condition, i.e. sitting, standing, walking and running conditions. The sensation reported by the individuals was not pain, rather discomfort primarily due to contraction of the paraspinal muscles especially when lying prone.

A custom-written computer program controlled the electrical stimulator during walking and running (Dyhre-Poulsen *et al.* 1991). We recorded the duration of a step cycle as the time from a heel strike to the next heel strike and then divided the step cycle into 16 equal time bins. We then delayed the stimulus to be delivered into a selected bin. The procedure was repeated after a minimum of 4 s without stimulation. The stimuli were evenly distributed over the gait cycle into the 16 time bins ensuring approximately 12 stimulations per bin.

H-reflex measurements

We elicited the soleus H-reflex by stimulating the right tibial nerve with an AgCl cathode on the skin in the popliteal fossa and anode placed over the patella while the subjects were seated (Simonsen & Dyhre-Poulsen, 1999). The stimulation intensity during the soleus H-reflex was selected to evoke similar amplitudes that were observed for the soleus MMR during walking and running. During the stimulation of the tibial nerve, we measured the activity from the soleus H-reflex detected by the tibialis anterior electrodes. The assumption was that eliciting a soleus H-reflex should not result in tibialis anterior EMG activity and any activity detected from these electrodes would estimate the relative amount of crosstalk from the soleus muscle to the tibialis anterior muscle recording electrodes.

Signal processing

We sampled EMG, goniometer, stimulus synchronization pulse and footswitch data at 2000 Hz using a customized LabView programme. We analysed the data using a customized Matlab programme that detected those steps with a stimulus by the synchronization pulse generated by the stimulator. Left and right footswitches were used to define the step cycle as time from one heel strike to the consecutive heel strike and were used for left and right muscles, respectively. We calculated the step cycle duration from the preceding step. The step cycle duration (mean $\pm$ S.D.) was 1.12 ± 0.03 s for the walking condition and 0.76 ± 0.03 s for the running condition. For each step receiving a stimulus, we calculated the time from heel strike to the stimulus artefact onset and sorted them into the appropriate bin number (1–16). The duration of each time slice was approximately 70 ms (walking) and 48 ms (running). The MMRs were averaged for each bin, and the peak-to-peak amplitude (in millivolts) measured. In addition, the EMG (20–1000 Hz, fourth order Butterworth digital filters with no phase lag), hip, knee and ankle joint angle trajectories from the step preceding the stimulation were normalized to 2000 points and averaged.

Crosstalk estimation. Analysis of MMR modulation patterns during stepping recorded from the first three individuals studied suggested that MMRs recorded from the tibialis anterior muscle may have been contaminated by the high amplitude EMG activity generated by the soleus muscle. Therefore, to estimate the contribution of crosstalk we elicited the soleus H-reflex by stimulating the tibial nerve during sitting. We divided the amplitude of the activity recorded from the tibialis anterior electrodes by the amplitude recorded from the soleus electrodes. This percentage was subsequently used to correct the tibialis anterior MMR amplitude during walking and running. For each bin average, we subtracted from the tibialis anterior MMR amplitude the soleus MMR amplitude recorded during stepping multiplied by the calculated percentage from the H-reflex during sitting (Fig. 9*B*). The method used is based on the assumption that the amount of crosstalk increases linearly with the size of the soleus EMG amplitudes generated.

Results

Percutaneous stimulation of the spinal cord at the T11–T12 level evokes multisegmental monosynaptic responses (MMR) in leg muscles bilaterally

Previous observations from stimulating the cauda equina suggested that these motor responses are mediated via the monosynaptic connections of the large-diameter Ia afferent fibres onto motor neurons, a response equivalent to the soleus H-reflex (Minassian *et al.* 2007). Percutaneous stimulation between T11 and T12 spinous processes evoked responses in the leg muscles bilaterally as exemplified by one subject lying in the prone position (Fig. 1). The latency of the evoked response was longer in distal than proximal muscles (Table 1 and Fig. 1). The amplitude of the extensor digitorum brevis and flexor digitorum brevis muscles were lower than the other muscles with the T11–T12 cathode placement. We observed that with lower placement of the cathode during the prone position, the MMR amplitudes of the foot muscles were higher with a concomitant decrease in amplitude from the more proximal muscles.

We also tested the effects of a preceding stimulus and muscle vibration on the MMRs evoked by stimulating the lumbar segments of the spinal cord to assess whether they were consistent with neurophysiological characteristics of a monosynaptic reflex. Figure 2*A* shows the MMR in

Table 1. Latency of evoked responses (ms)

		Left		Right	
Muscle	Abbr.	Mean	S.D.	Mean	S.D.
Rectus femoris	RF	15.6	2.9	16.1	4.0
Vastus lateralis	VL	16.2	2.7	15.6	2.8
Biceps femoris	BF	17.6	1.7	18.0	1.5
Medial gastrocnemius	MG	23.6	2.6	21.7	2.4
Tibialis anterior	TA	24.3	2.8	23.1	2.3
Soleus	Sol	25.3	1.8	24.6	2.0
Extensor digitorum brevis	EDB	27.7	4.2	29.1	3.6
Flexor digitorum brevis	FDB	31.0	3.6	28.9	2.1

The mean and standard deviation (s.d) of the latency (ms) of motor responses evoked by percutaneous stimulation of the spinal cord at the T11/T12 level from all individuals ($n = 8$). The abbreviations (abbr.) used to designate the each muscle is indicated and used for all figures. The latencies measured in left and right muscles are separately reported. Muscles are vertically ordered according to their distance from the stimulating electrode, i.e. from proximal to distal muscles.

each muscle to two stimuli with a 50 ms interval from one individual in the prone position. In this individual the MMR to the second stimulation was eliminated. For all individuals, the amplitude following the second stimulus was significantly ($P < 0.05$, t test) lower in 12/16 muscles (Fig. 2*B*). MMRs in the left rectus femoris, vastus lateralis, flexor digitorum brevis and extensor digitorum muscles did not reach significance, most probably due to their low MMR amplitude. Figure 3 represents the average of 10 evoked MMRs from the left and right soleus muscles with and without continuous, bilateral vibration (70 Hz) applied to the Achilles tendon. In all individuals, the concurrent vibratory stimulation resulted in a significant depression (Wilcoxon test, $P < 0.01$) of the MMR amplitudes.

In addition, all the individuals studied demonstrated modulation of the soleus MMR during walking (Fig. 4) similar to that reported for the soleus H-reflex in previous studies (Capaday & Stein, 1986; Simonsen & Dyhre-Poulsen, 1999).

Modulation of MMR amplitude during walking and running

The patterns of EMG activity observed during walking and running were similar to those reported in previous studies on human gait (Nilsson *et al.* 1985; Simonsen & Dyhre-Poulsen, 1999; Hunt *et al.* 2001). Below are described the patterns of MMR modulation in the different studied muscles.

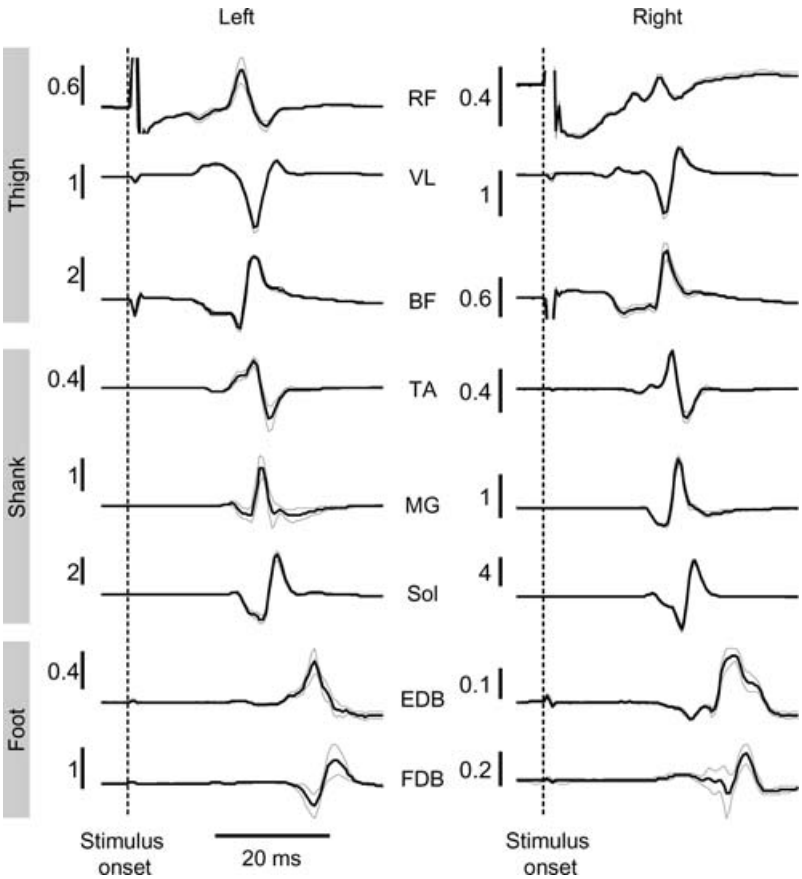

Figure 1. Motor responses evoked by percutaneous stimulation of the lumbar segments of the spinal cord at the T11–T12 level in the prone position
Each trace is the average ± S.D. of 10 MMRs recorded in the left and right leg muscles from one individual. Muscles are in order vertically according to their anatomical location, i.e. from proximal to distal. The vertical bars indicate the scale for the amplitude (mV) of the EMG signal. The vertical dotted line represents the onset of the stimulation. The horizontal bar at the bottom indicates the scale for time (ms).

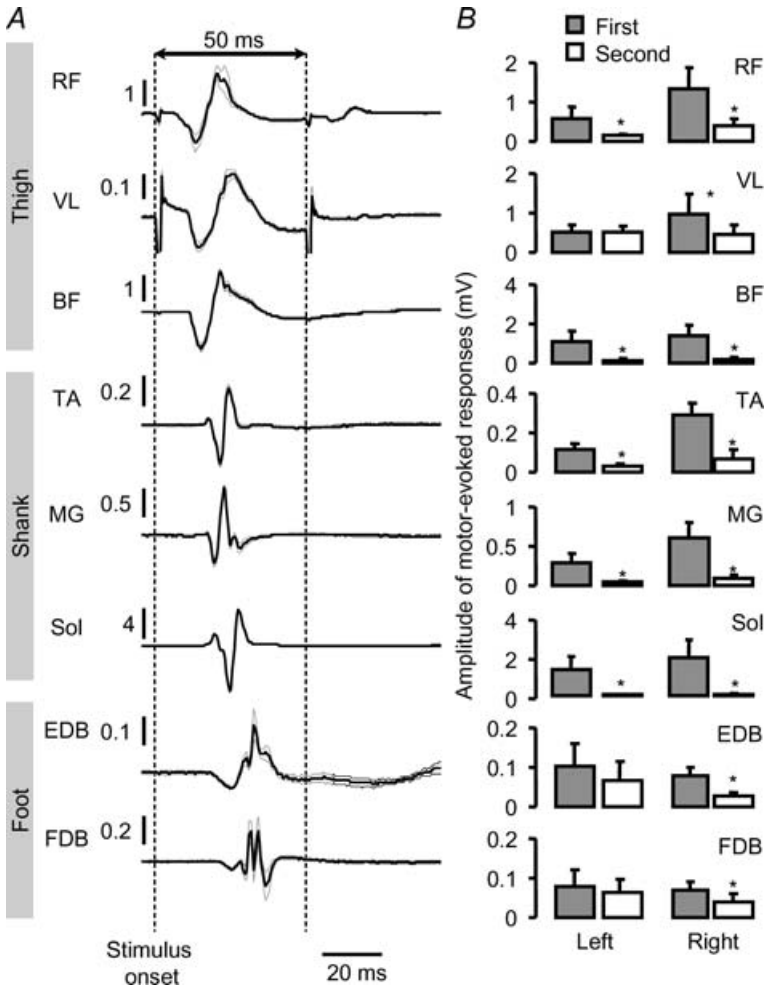

Figure 2. Comparison of the amplitude of motor responses evoked by two successive stimulations in the prone position
A, each trace is the average ± S.D. of 10 evoked motor responses to two successive electrical stimulations delivered with a 50 ms time interval recorded in the right leg muscles from one individual. The vertical dotted lines represent the stimuli onsets. *B*, mean (+ S.D.) amplitudes of the evoked motor responses to the first (filled bar) and second (open bar) stimulations are shown for the left and right muscles of all individuals ($n = 8$). *Significant decrease in the amplitude of the motor response to the second stimulus compared with the first stimulus.

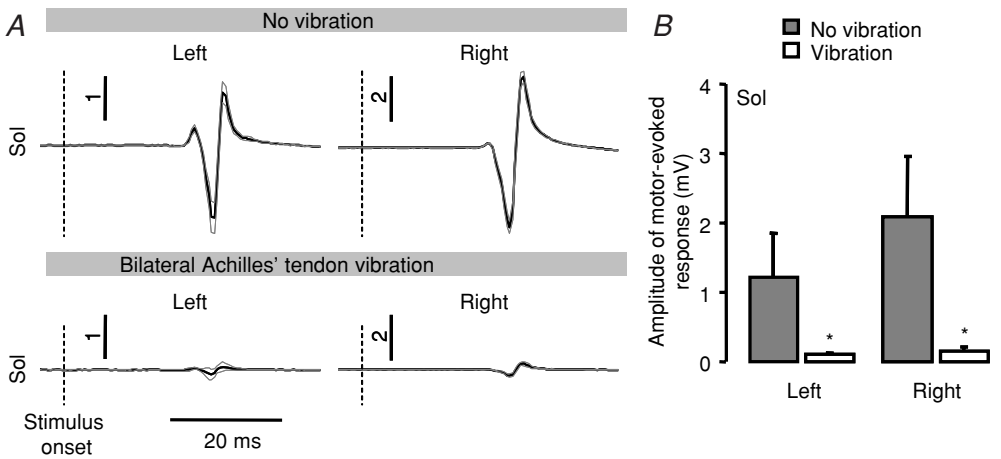

Figure 3. Effect of vibration on evoked responses in the soleus muscle
A, each trace is the average ± S.D. of 10 MMRs without vibration (upper traces) and with continuous, bilateral Achilles tendon vibration (lower traces) in the prone position. No vibration and vibration conditions are depicted with the same scale. The vertical dotted line represents the onset of the stimulation. The horizontal bar at the bottom indicates the scale for time (ms). *B*, mean (+ S.D.) amplitudes of the MMRs in the left and right soleus muscles without vibration (filled bar) and with vibration (open bar). *Significant decrease in the amplitude of the MMR with vibration compared with without vibration.

Shank muscles. Modulation of MMRs from the soleus, medial gastrocnemius and tibialis anterior muscles were observed in all individuals studied. The soleus and medial gastrocnemius MMRs were facilitated during stance and suppressed in swing during walking (Figs 5*A*, 6 and 8*A*) and running (Figs 5*B*, 7 and 8*B*). The facilitation of the MMR amplitude coincided with the EMG activity recorded in the same phase as the step immediately preceding the stimulation (Figs 6 and 7). For example, the onset of the MMR response occurred prior to heel contact during running as did the ankle extensor EMG activity.

The tibialis anterior MMR showed unexpected modulation patterns during walking (Figs 5*A*, 6 and 8*A*) when compared with previous studies (Christensen *et al.* 2001). The tibialis anterior MMR amplitude was higher than expected during the stance phase of walking (Fig. 9*B*, open circles) and coincided with the soleus MMR (Figs 5*A*, 6 and 8*A*). Many previous studies have identified crosstalk between antagonist muscles as a potential methodological problem when recording high-amplitude EMG. Therefore we evaluated the estimated per cent contribution from the soleus MMR amplitude to the tibialis anterior MMR amplitude using the ratio calculated from the soleus H-reflex sitting (see Methods *Crosstalk estimation* section for details, Fig. 9*A*). When we adjusted the amplitude of the tibialis anterior MMR using the estimated influence of crosstalk from the soleus MMR (Fig. 9*B*, filled circles), the tibialis anterior MMR amplitude was attenuated or even suppressed during mid- and late-stance. The modulation of the tibialis anterior MMR corrected amplitude also coincided with the background EMG activity during both walking (Fig. 9*C*) and running (Figs 8 and 9*D*).

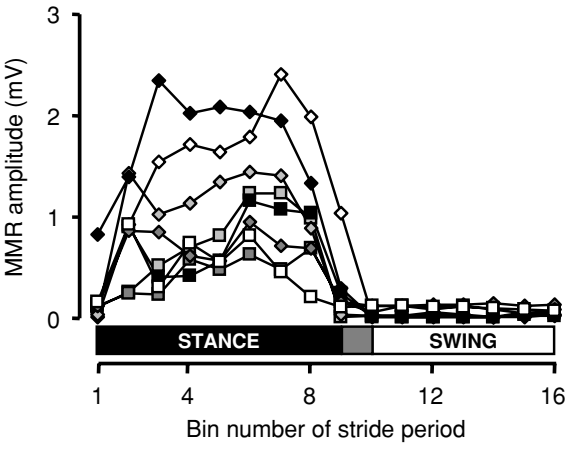

Figure 4. Mean amplitude of MMRs in the right soleus muscle during walking for all individuals
Each point represents the right soleus mean MMR amplitude (mV) for each of the 16 bins for 10 steps of walking (3.5 km h^{-1}) from all individuals. Each symbol designates an individual ($n = 8$). The horizontal bars indicate the stance and swing phase of gait. The shaded area shows the inter-subject variability in the timing of swing phase onset.

Thigh muscles. Biceps femoris MMRs were observed in all the individuals studied during walking and running. The biceps femoris MMR amplitude was facilitated during the swing phase and the beginning of the stance phase, and suppressed at the stance-to-swing transition during walking (Figs 5*A*, 6*B* and 8*A*) and running (Figs 5*B*, 7*B* and 8*B*). Vastus lateralis MMRs were evoked in the left side in 5/8 individuals and in the right side in 6/8 individuals during walking and running. In the individuals that generated a response, vastus lateralis MMRs during walking (Figs 5*A*, 6*B* and 8*A*) were elevated during the entire stance phase and terminal swing. EMG activity during walking (Fig. 6*A*) coincided with the modulation, except for during the mid-stance phase where it was quiescent. The vastus lateralis MMRs during running (Figs 5*B*, 7*B* and 8*B*) were elevated during terminal swing and initial stance phase, similar to the modulation pattern of the biceps femoris muscle. Rectus femoris MMRs were elicited in both legs in 4/8 individuals during walking (Fig. 8*A*) and running (Fig. 8*B*). In the individuals that generated a response, the rectus femoris MMRs occurred throughout the step cycle. However, the stimulus artefact was relatively high compared with the detectable amplitude of the response and complicated the analyses.

Foot muscles. MMRs in the extensor digitorum brevis and flexor digitorum brevis muscles were observed during walking and running in all the individuals studied. The amplitude of both extensor digitorum brevis and flexor digitorum brevis MMRs shows modulation during walking (Figs 5*A*, 6*B* and 8*A*) and running (Figs 5*B*, 7*B* and 8*B*) that co-varied with EMG activity (Figs 6*A* and 7*A*). Although modest motor responses were usually elicited in these foot muscles during standing (0.21 ± 0.1 mV for the extensor digitorum brevis muscle and 0.33 ± 0.2 mV for the flexor digitorum brevis muscle), the MMR amplitude substantially increased during walking (Figs 6 and 7).

Difference between walking and running

A critical difference between the modulation patterns of the MMR during running compared to walking was the anticipatory increase in the amplitude of the MMR at the end of the swing phase of gait in all proximal and distal extensor muscles (Fig. 8). The substantial increase in the size of the MMR contrasted with the concurrent modest or absent increase in the amplitude of the EMG activity of the homonymous muscle (Figs 5 and 6). Such anticipatory modulation of the MMR amplitude during walking and running, which has been reported previously for the soleus H-reflex (Capaday & Stein, 1987 their Fig. 3; Simonsen & Dyhre-Poulsen, 1999), was not observed during walking in the present study (see Fig. 7). On the contrary, the MMR amplitude increased only some 100–200 ms after heel strike during walking in ankle extensors muscles

whereas it anticipates by 50–150 ms the beginning of stance during running. This was consistently observed in all the subjects.

Discussion

The present investigation shows that multisegmental monosynaptic motor responses (MMR) can be evoked bilaterally and simultaneously in leg muscles by stimulating the spinal cord percutaneously at the low thoracic level during walking and running in humans. These motor responses have the neurophysiological characteristics of reflexes involving monosynaptic neural circuitry for extensors and flexors of the knee, ankle and foot. This MMR neurophysiological technique represents a novel tool to assess reflex modulation and neural control of movement in non-disabled human individuals and following neurological disorders.

Neural structures involved in the generation of the MMR

A number of studies have shown that electrical stimulation applied with epidural electrodes over the dorsal cord in animals (Gerasimenko *et al.* 2006) and humans (Guru *et al.* 1987; Struijk *et al.* 1993; Hunter & Ashby, 1994;

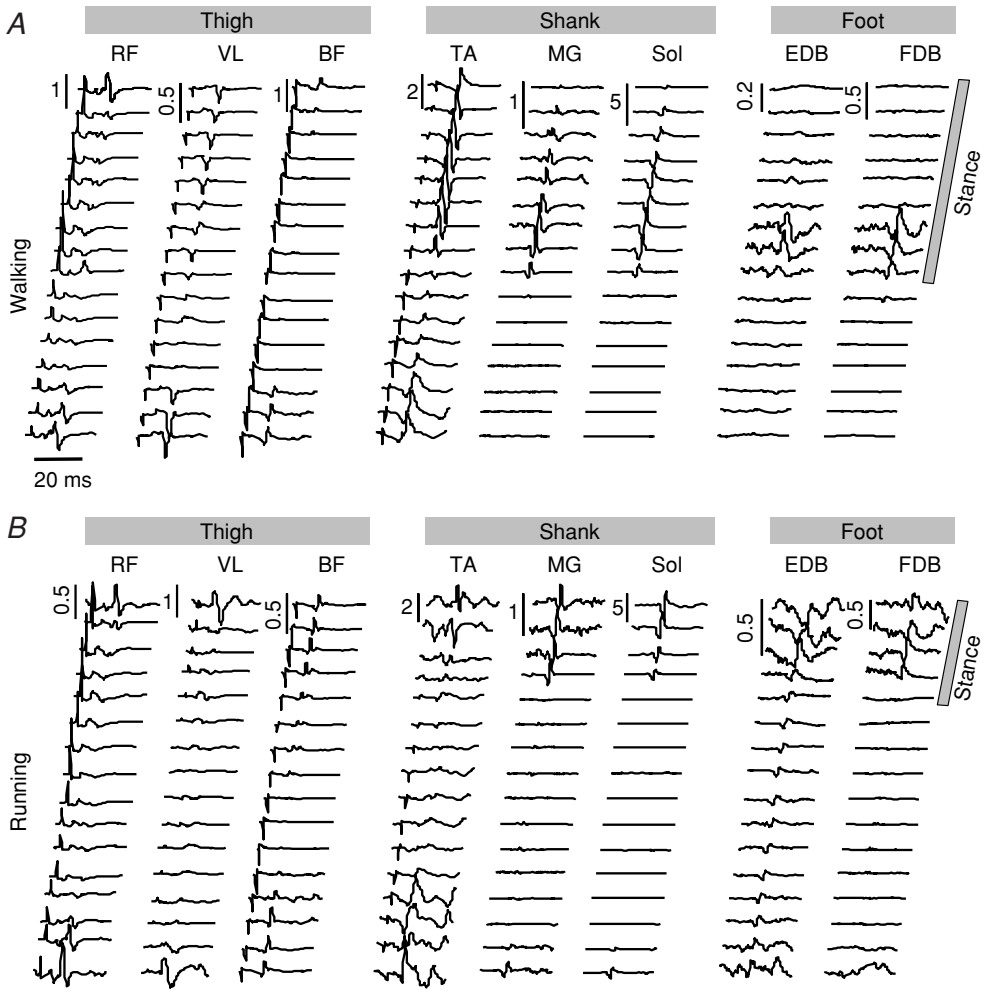

Figure 5. MMR modulation in the right leg muscles of one individual during walking at 3.5 km h^{-1} and running at 8 km h^{-1}

Each trace represents the averaged MMRs from 10 step cycles for each of the 16 bins during walking (*A*) and running (*B*) for the thigh (rectus femoris, RF; vastus lateralis, VL; biceps femoris, BF), shank (tibialis anterior, TA; medial gastrocnemius, MG; soleus, Sol) and foot (extensor digitorum brevis, EDB; flexor digitorum brevis, FDB) muscles of the right leg. For each muscle, the traces represent a complete step cycle and are in order vertically starting at the top with heel strike. The shaded bars at the right side of the figure indicate the stance phase. The vertical bars indicate the scale for the amplitude (mV) of the EMG signal. The horizontal bar at the bottom indicates the scale for time (ms).

Minassian *et al.* 2004, 2007) can activate primary afferents in the dorsal columns and dorsal roots to elicit monosynaptic facilitation of motoneurons. The MMRs evoked by percutaneous stimulation of the spinal cord at the T11–T12 level show the characteristics associated with monosynaptic circuitry of Ia afferents to the motoneurons, i.e. the same neural circuit as the Hoffman reflex. (i) The latency of the evoked responses gradually increased with the distance between the muscle and the stimulating electrode and corresponded to those expected by the length of the motor nerve (Fig. 1 and Table 1), i.e. as opposed to an increase in the central delay. (ii) The amplitudes of the motor responses from the muscles were strongly depressed when a conditioning stimulus was delivered 50 ms before the test stimulus (Fig. 2). This result is consistent with the excitability cycle of soleus H-reflex (Schieppati & Crenna, 1984). (iii) Concurrent vibration of the Achilles tendons that specifically activate primary endings of Ia fibres (Roll *et al.* 1989) inhibited the soleus MMR (Fig. 3). Post-activation depression, post-tetanic potentiation, vibration-induced occlusion of the reflex and presynaptic inhibition of the Ia afferents have been reported to result in inhibition of the H-reflex under continuous muscle vibration (Schieppati & Crenna, 1984; Schieppati, 1987; Hultborn *et al.* 1996). The vibration-induced depression of the MMR amplitude was also observed for the other studied muscles (data not shown). (iv) The soleus MMR amplitude during walking was dependent on the phase of the cycle period with higher amplitudes during stance and suppression during swing (Fig. 4). Similar modulation patterns of the soleus H-reflex during stepping have been reported in

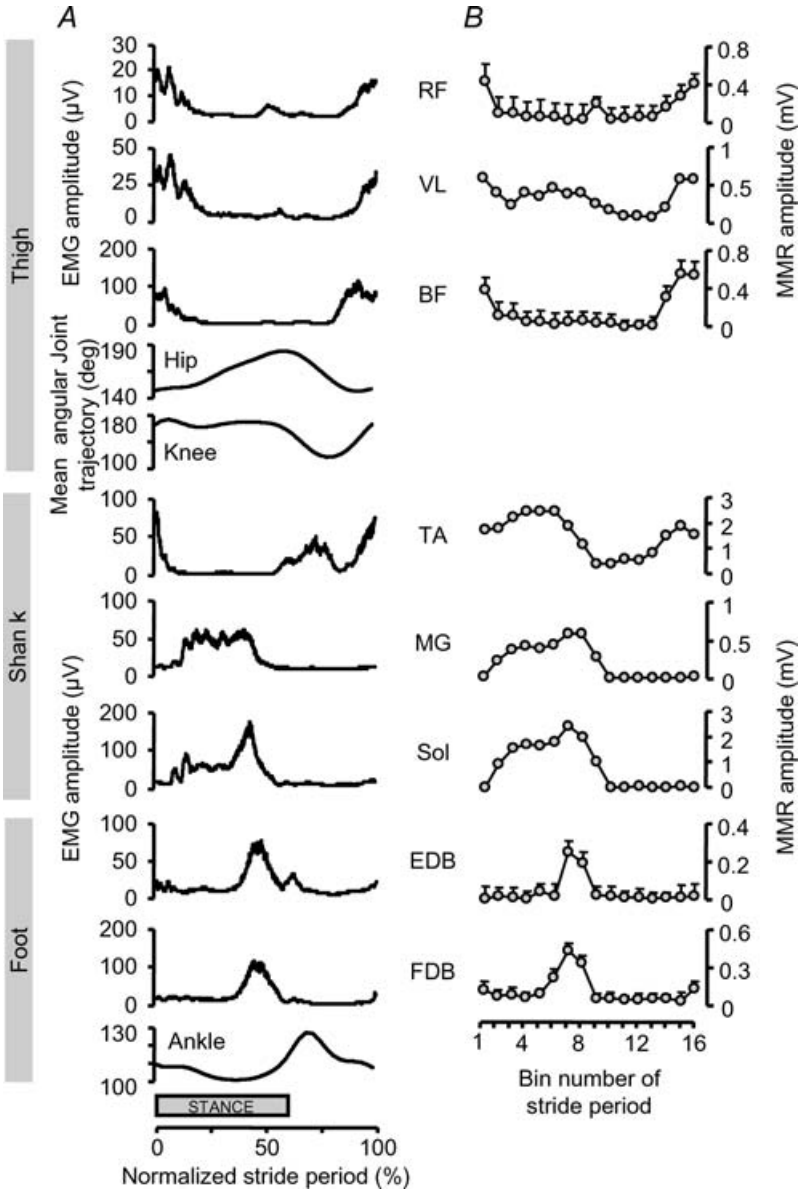

Figure 6. Mean EMG activity and MMR modulation in the right leg muscles from one individual during walking at 3.5 km h^{-1}
A, each trace represents the averaged rectified EMG activity (μV) and hip, knee and ankle joint angles from 100 step cycles preceding the stimuli during walking (3.5 km h^{-1}) for the thigh (rectus femoris, RF; vastus lateralis, VL; biceps femoris, BF), shank (tibialis anterior, TA; medial gastrocnemius, MG; soleus, Sol) and foot (extensor digitorum brevis, EDB; flexor digitorum brevis, FDB) muscles of the right leg. The horizontal bar at the bottom indicates the mean duration of the stance phase of gait. *B*, each point represents the mean + S.D. of the MMR amplitude (mV) during 10 steps for each of the 16 bins during walking from one individual.

previous investigations (Capaday & Stein, 1986; Simonsen & Dyhre-Poulsen, 1999). Since the MMR showed the same neurophysiological properties as the H-reflex (Schieppati, 1987), we concluded that percutaneous stimulation of the spinal cord at the low thoracic level elicits motor responses through activation of the monosynaptic neural circuit connecting Ia afferents to motor neurons. The large electrical field created by the stimulation probably activates the thicker Ia afferent fibres and the lumbar dorsal roots in a manner similar to epidural spinal cord stimulation (Minassian *et al.* 2004). The thicker fibres have the lowest threshold and the Ia fibres branch both at the spinal ganglion and when they enter in the spinal cord decreasing their threshold for nerve fibre activation (Struijk *et al.* 1992, 1993). Moreover, the multisegmental branches of spindle afferents are known to monosynaptically excite homonymous motor neurons (Mendell & Henneman, 1971; Rudomin, 2002; Gaunt *et al.* 2006). This would explain why relatively few changes in the MMR amplitude were observed when moving the stimulating electrode up or down by one vertebra (Minassian *et al*. 2007).

Methodological considerations

There are some methodological issue associated with the MMR techniques.

(i) The electrical stimulation was not selective for the muscle group since heteronymous facilitation

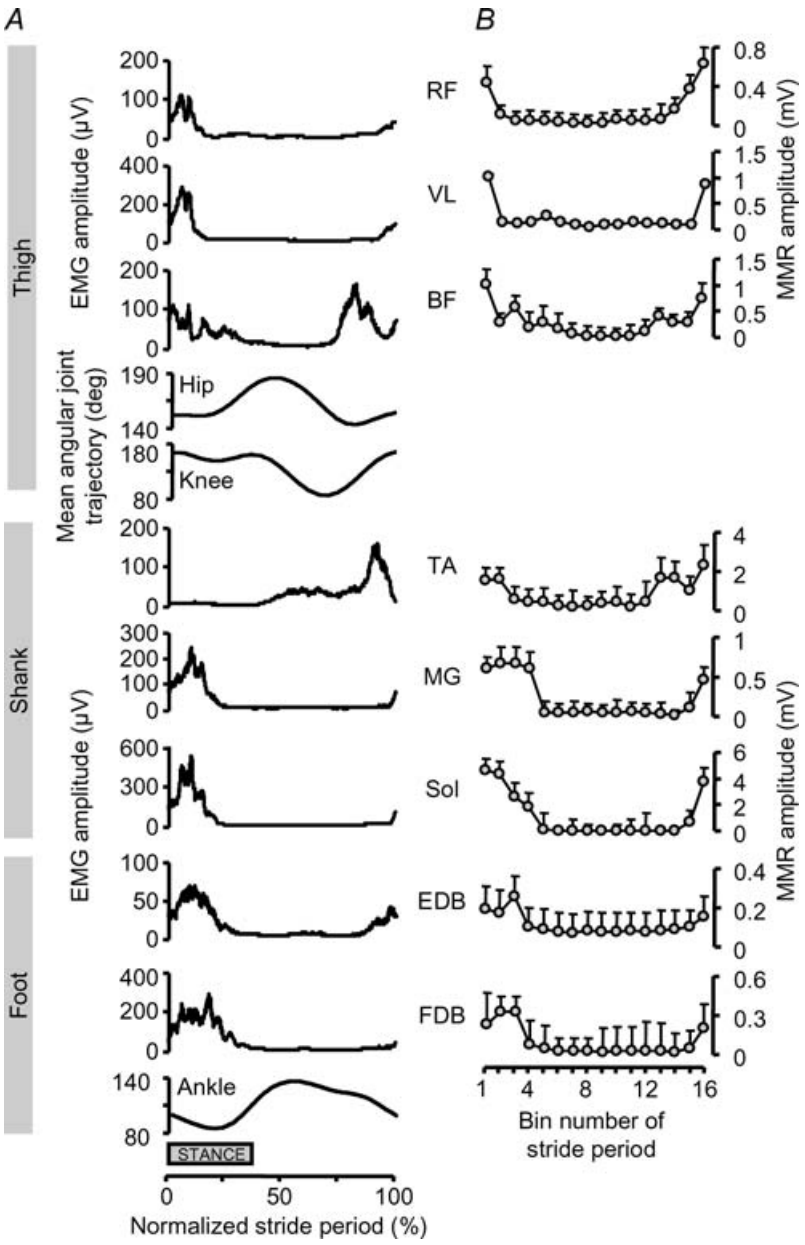

Figure 7. Mean EMG activity and MMR modulation in the right leg muscles from the same subject during running at 8 km h^{-1}
A, each trace represents the averaged rectified EMG activity (μV) and hip, knee and ankle joint angles from 100 step cycles preceding the stimuli during running (8.0 km h^{-1}) for the thigh (rectus femoris, RF; vastus lateralis, VL; biceps femoris, BF), shank (tibialis anterior, TA; medial gastrocnemius, MG; soleus, Sol) and foot (extensor digitorum brevis, EDB; flexor digitorum brevis, FDB) muscles of the right leg. The horizontal bar at the bottom indicates the mean duration of the stance phase of gait. *B*, each point represents the mean + S.D. of the MMR amplitude (mV) during 10 steps for each of the 16 bins during walking from one individual.

of motor neurons, which is substantial in humans (Pierrot-Deseilligny *et al.* 1981; Burke *et al.* 1984) compared with cats (Meunier *et al.* 1990; Capaday, 2002), could not be avoided. The MMRs were the sum of all the Ia-sensory volleys conveyed from a number of muscle afferents to a given motor neuron pool.

(ii) Contrary to the soleus H-reflex, stimulation of the spinal cord at the low thoracic level did not recruit motor nerves, and no M-waves were elicited to normalize reflex responses (Simonsen & Dyhre-Poulsen, 1999). Consequently we could not monitor the efficacy of the stimulation and therefore the variability of the evoked responses from the movement of the spine with respect to the stimulating electrode could not be assessed.

(iii) Activation of proximal and distal muscles required adjustments to the electrode position, i.e. to move the electrode one spinous process up or down, or to increase the stimulus intensity, notably in more corpulent subjects. It was difficult to obtain symmetrical responses in all muscles at the same time. This could be due to head position (Kennedy & Inglis, 2002) or side differences in the composition of the peripheral nerve fibres (Agduhr, 1934). We did prompt the individuals to keep their head position stable and monitored the position throughout the duration of the experiment. We consistently located the stimulating electrode between T11 and T12 spinous processes since this location allowed the study of reflex properties in a higher number of muscles. Future studies may require performing testing using two stimulus intensities or two electrode locations in order to fully investigate the property of the monosynaptic neural circuits for proximal and distal muscles simultaneously.

(iv) There was systematic contamination of the tibialis anterior EMG signal by the large motor responses elicited in calf muscles. Soleus H-reflex measurements were used as a method to correct tibialis anterior MMR for cross-talk (Fig. 9). Even though this method turned out efficient, results should be interpreted cautiously since

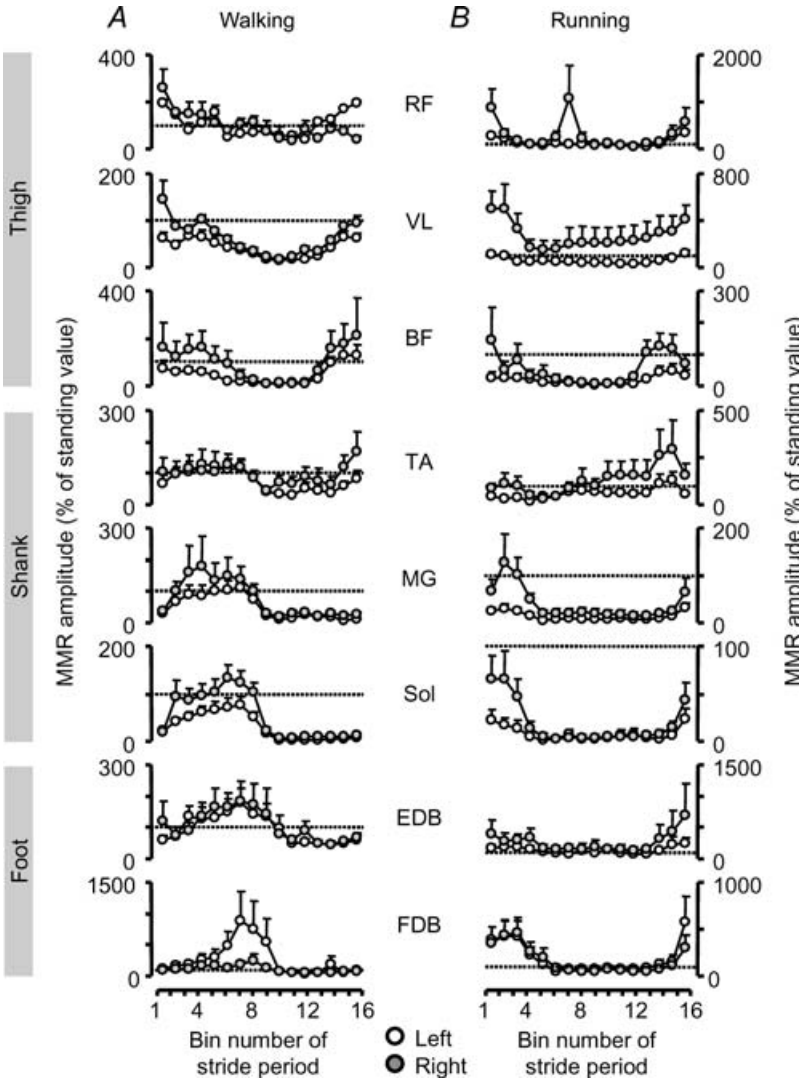

Figure 8. MMR modulation in the left and right leg muscles for all the subjects during walking and running
Each point represents the mean + S.D. of the MMR amplitude (mV) for each of the 16 bins during 10 steps of walking (*A*; 3.5 km h^{-1}) and running (*B*; 8.0 km h^{-1}) for the thigh (rectus femoris, RF; vastus lateralis, VL; biceps femoris, BF), shank (tibialis anterior, TA; medial gastrocnemius, MG; soleus, Sol), and foot (extensor digitorum brevis, EDB; flexor digitorum brevis, FDB) muscles of the left (open circles) and right (shaded circles) legs from all individuals ($n = 8$), except for the VL ($n = 5$ on the left side and $n = 6$ on the left side) and the RF ($n = 4$ on both sides). Each point represents the mean value of the mean MMR amplitude for a given bin. Bin number 1 is the first time slice after heel strike. Open and shaded circles depict MMR amplitude of left and right muscles, respectively. The amplitude of the MMR for walking and running was normalized to the MMR amplitude during standing for each individual (MMR amplitude, % of standing (dashed horizontal line)).

the resulting tibialis anterior MMR waves were of small amplitude following crosstalk removal, and occasionally of the same amplitude as the voluntary EMG signal. Alternative techniques should be used in future studies to investigate the properties of the MMR from the tibialis anterior muscle.

Adaptive modulation of the monosynaptic neural circuit during locomotion

In the present study, we examined the modulation of multisegmental monosynaptic response during walking and running by means of methods previously used in soleus H-reflex studies (Capaday & Stein, 1986; Dyhre-Poulsen *et al.* 1991). Phase-dependent modulation of the MMR amplitude throughout the duration of the gait cycle period was observed in the leg muscles studied. The MMR modulation pattern was specific to the motor task, i.e. it differed during walking compared with running. The amplitude of the reflex corresponded to the voluntary EMG activity of the corresponding muscle, and was generally reduced, or even suppressed, when the muscle was quiescent (Figs 5–8). For example, during walking, the motor responses from soleus, medial gastrocnemius, extensor digitorum brevis and flexor digitorum brevis were high during stance and inhibited during swing, whereas the rectus femoris, vastus lateralis and biceps femoris responses were large before heel strike and rapidly decreased over the duration of the stance phase (Fig. 8*A*). MMR of the tibialis anterior muscle was of larger amplitude during the swing phase and the early part of the stance phase (Fig. 9). Similar modulation patterns of H-reflex amplitude during walking have been reported for the soleus, medial gastrocnemius (Capaday & Stein, 1986; Simonsen & Dyhre-Poulsen, 1999), tibialis anterior (Petersen *et al.* 1999) and vastus lateralis (Dietz *et al.* 1990*b*) muscles although in a limited number of studies and subjects. To our knowledge, however, there was no information regarding H-reflex modulation of the biceps femoris, rectus femoris, extensor digitorum brevis and flexor digitorum brevis muscles during locomotion. Modulation of the short latency response to muscle stretch in the tibialis anterior, biceps femoris, rectus femoris and vastus lateralis muscles during walking (Dietz *et al.* 1990*a*; Faist *et al.* 1999; Christensen *et al.* 2001; Mrachacz-Kersting *et al.* 2004) and the modulation pattern of H-reflex during running (Capaday & Stein, 1987;

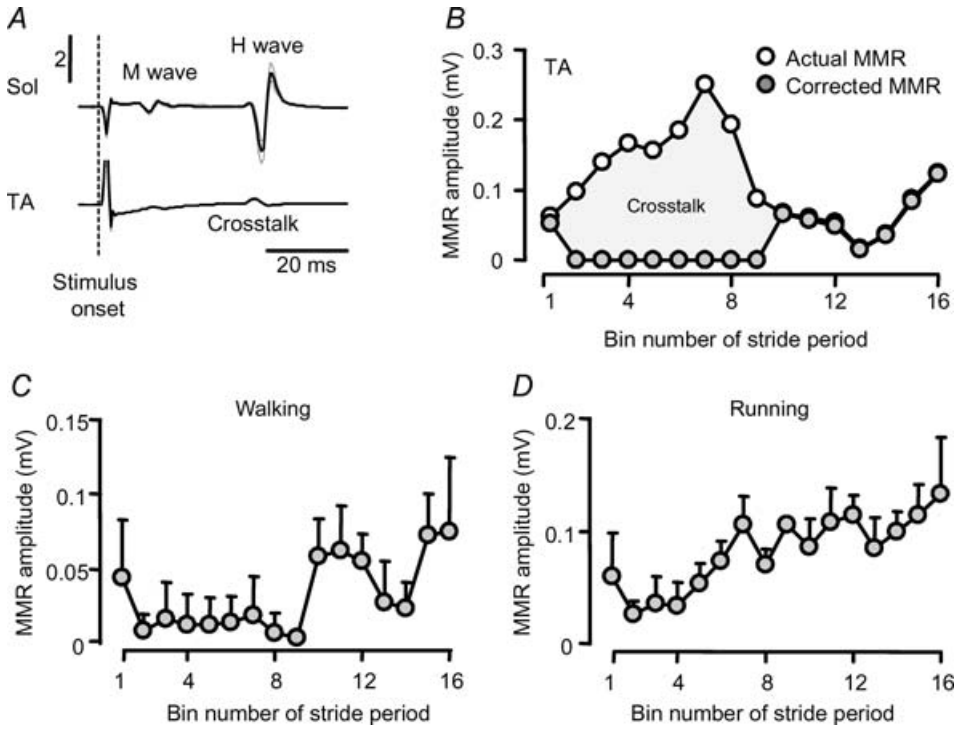

Figure 9. Evaluation of the crosstalk between the soleus and tibialis anterior muscles
A, each trace represents the average ± S.D. right soleus (Sol) and tibialis anterior (TA) EMG responses from 10 tibial nerve stimuli during sitting for one individual. *B*, each point represents the mean of the actual (open circles) and corrected (shaded circles) MMR amplitude (mV) for each of the 16 bins during 10 steps of walking (3.5 km h^{-1}) for the tibialis anterior (TA) muscle for the subject depicted in *A*. *C* and *D*, each point represents the mean + S.D. of the corrected MMR amplitude (mV) for each of the 16 bins during 10 steps of walking (*C*, 3.5 km h^{-1}) and running (*D*; 8.0 km h^{-1}) for the tibialis anterior (TA) for five individuals.

Simonsen & Dyhre-Poulsen, 1999) were similar to the MMR modulation patterns in our study. The present investigation thus confirmed that the amplitude of the electrically evoked monosynaptic reflex of the soleus muscle is substantially modulated over the course of the cycle period during stepping in humans, and extends this finding to flexor and extensor muscles of the proximal and distal parts of the leg during both walking and running.

Neural mechanisms

Previous studies showed that modulation of input–output properties of the monosynaptic neural circuits in leg muscles during stepping is a function of the general state of motor neuron excitation and depends upon pre-motoneuronal mechanisms mediated centrally (Schieppati, 1987). The reflex excitability was lower during walking than during a voluntary contraction of similar amplitude, and during standing (Capaday & Stein, 1986; Edamura *et al.* 1991; Simonsen *et al.* 1995; Lavoie *et al.* 1997; Simonsen & Dyhre-Poulsen, 1999). These differences are attributed to an increase in presynaptic inhibition of Ia fibre terminals during gait compared with voluntary contraction (Faist *et al.* 1996) and is supported by neurophysiological recordings in the cat (Gossard, 1996; Cote & Gossard, 2003). In the present study, both technical and ethical limitations prevent similar comparisons of reflex excitability during standing, walking and running conditions. It was not possible to elicit MMRs of similar amplitude while standing and walking in all muscles. In some cases the stimulus intensity had to be adjusted between walking and running conditions to maintain reasonable MMR amplitudes. Percutaneous stimulation of the spinal cord at the level of T11–T12 avoids the M-wave that is classically used in H-reflex studies to monitor variations in stimulation efficacy due to stimulating and recording electrode movements (Simonsen & Dyhre-Poulsen, 1999). A method to partially overcome this methodological problem when comparing walking and running was to normalize MMR amplitude recorded during locomotion to those during standing. The MMR generally was of smaller amplitude during walking and running than during standing; however, the EMG backgrounds were larger (Fig. 8). The MMRs in the flexor digitorum brevis muscle during walking and running, and the rectus femoris, vastus lateralis and extensor digitorum brevis muscles during running MMRs were higher during standing than during walking (Fig. 8) (Simonsen & Dyhre-Poulsen, 1999). Accordingly, the results of the present study are in agreement with the idea that monosynaptic reflex excitability of shank muscles are reduced during stepping compared with standing or a voluntary contraction (Capaday & Stein, 1986, 1987; Dietz *et al.* 1990*b*; Edamura *et al.* 1991; Faist *et al.* 1999; Simonsen & Dyhre-Poulsen, 1999). We observed a substantial anticipatory increase in the excitability of the MMRs in the extensor muscles approximately 50–100 ms prior to foot contact during running when the motor neuron output also increased, though modestly (Figs 6, 7 and 8). However, the MMR amplitudes increased about 200 ms after heel strike during walking. The present findings suggest that there is a general control scheme by which the transmission in the monosynaptic neural circuit is selectively adapted in all leg muscles to the phase and the motor task being performed in humans (Rudomin, 1999).

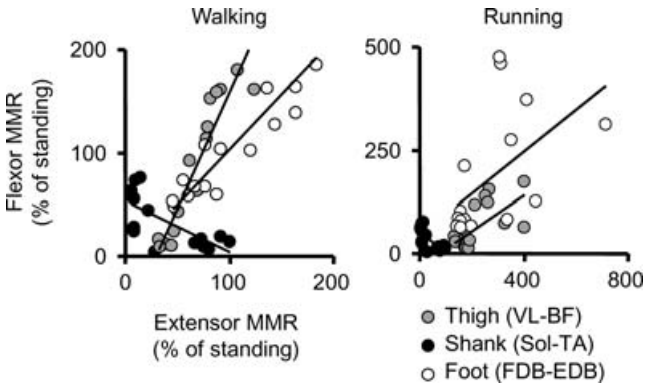

Figure 10. Relationship between MMR amplitude of antagonist muscles during walking and running
The mean amplitude of the MMR (all subjects) recorded in each bin for each pair of antagonist muscles of the leg joint is plotted one against each other, i.e. extensor *versus* flexor muscle. Left,walking; right, running.

The neural mechanisms presynaptically acting on the muscle spindle afferents are probably involved in monosynaptic reflex modulation during stepping (Menard *et al.* 1999). Nonetheless, modulation of Ia inhibitory interneurons, which convey reciprocal inhibition between antagonist muscles, also may contribute to the observed modulation of the soleus and tibialis anterior monosynaptic reflexes during gait (Lavoie *et al.* 1997; Petersen *et al.* 1999). The reflex modulation pattern of soleus and tibialis anterior muscles followed the classic pattern of reciprocal inhibition (Figs 8, 9 and 10) between antagonist muscles in a number of stepping conditions (Edamura *et al.* 1991). However, extensor and flexor muscles of the knee and the foot and the corresponding MMRs were co-activated during walking (Figs 5, 6, 8 and 10). In the walking cat, Ia inhibitory interneurons are activated from quadriceps afferents when the muscle is active (Pratt & Jordan, 1984; Enriquez-Denton *et al.* 2000). Such rhythmic modulation of inhibitory interneurons may help to reduce antagonistic muscle activity during walking. Similarly, we have shown that epidurally evoked monosynaptic responses are reciprocally modulated between extensor and flexor muscles of the thigh during continuous bipedal stepping in the rat (Gerasimenko *et al.* 2006). In turn, the co-contraction of thigh muscles, which is peculiar to

human bipedal gait (Capaday, 2002; Courtine *et al.* 2005*a*), implies that centrally produced reciprocal inhibition between proximal antagonist muscles (Jankowska, 1992) is depressed during human locomotion.

Functional considerations

Studying leg MMRs during movement provides insight into intermuscular coordination (Ferris *et al.* 2001) and the control of motoneuronal activation (Nielsen & Sinkjaer, 2002). For example, the co-activation of MMRs in proximal muscles as opposed to the reciprocal pattern between ankle antagonistic muscles suggests that muscle coordination during stepping is dependent upon the specific function of the muscle group. The reciprocal inhibitory pattern of stretch-related reflexes between extensor and flexor muscles of the ankle (Fig. 10) is a pre-requisite to the control of foot movement during walking, for example, inhibition of calf muscle stretch reflexes the end of stance allows foot dorsiflexion during swing (Stein & Capaday, 1988). Suppression of monosynaptic reflexes in a variety of muscles during stepping at specific phases of the movement, as reported in the present study, highlights the deep modulatory action of the central nervous system onto spinal neural circuits during movement execution. Central neural processes may substantially depress potent automated reflexes during gait according to the biomechanical demands of the task. For example, reflex responses were virtually absent in almost all muscles at the stance-to-swing transition during walking (Fig. 8*A*). On the other hand, high reflex excitability at specific parts of the step cycle period suggests that activation of leg muscles is at least partly generated through Ia afferent input during gait (Yakovenko *et al.* 2004). This hypothesis is documented for a number of muscles in the present study: (i) the rapid knee extension (Figs 6 and 7) during terminal swing activates velocity-sensitive biceps femoris stretch afferents (Prochazka *et al.* 1976) that probably contribute to the recruitment of the motoneurons (Faist *et al.* 1999), and help to slow the leg down before ground contact; (ii) the large MMR amplitude in the flexor digitorum brevis muscles during walking (Fig. 8) suggests that the powerful sensory volley generated by the toe dorsiflexion occurring at the end of stance participates in foot muscle activation (Schieppati *et al.* 1995), thereby preserving body stability at push off; (iii) as hypothesized in previous studies (Dietz *et al.* 1979; Capaday & Stein, 1987; Simonsen & Dyhre-Poulsen, 1999), the anticipatory increase in monosynaptic reflex excitability of proximal and distal extensor muscles at the end of the swing phase during running (Fig. 8*B*) suggests that spinal stretch reflex are important to attenuate impact forces at foot landing (Jefferson *et al.* 1990; Ferris *et al.* 2001). This neural control mechanism can be significant for antigravity muscles such as the vastus lateralis muscle (Farley & McMahon, 1992) with high MMR amplitude in the running condition (Fig. 8*B*).

Relevance for investigating neuromotor disorders

The neurophysiological method developed in the present study allows us to study simultaneously the properties of the monosynaptic neural circuit for extensor and flexor motor pools innervating both proximal and distal muscles of the leg. Extensor *versus* flexor muscles as well as proximal *versus* distal muscles could respond very differently to a given neurological impairment (Harkema, 2001; Dietz & Muller, 2004; Courtine *et al.* 2005*b*). Accordingly, simultaneous assessment of reflex properties in a variety of leg muscles during locomotion may provide significant insights into specific deficits of neuronal function following injury. Furthermore, recent studies showed that reflex function enhancement can contribute to the recovery of the motor activity following reduction in supraspinal control (Pearson, 2001; Edgerton *et al.* 2004). We recently have demonstrated using a similar methodology in the rat that the recovery of epidural stimulation-evoked hindlimb reflexes coincides with the reappearance of stepping ability following a complete mid-thoracic spinal cord transection injury in adult animals (Lavrov *et al.* 2006). The MMR technique provides the potential to investigate training-induced changes in the properties of leg muscle reflexes during motor execution and assess the functional plasticity of spinal sensorimotor pathways function following neurological impairments (Harkema, 2001; Dy *et al.* 2005).

Conclusions

In the present study, we describe a technique that allowed us to investigate the modulation of the monosynaptic neural circuit excitability in nearly all the muscles of both legs simultaneously under static and dynamic conditions in humans. Modulation of the MMR in the leg muscles during both walking and running revealed there is a general neural control scheme by which the functional connectivity is modulated in spinal sensorimotor pathways to meet the biomechanical and physiological demands of producing complex whole-body movement in humans. Future studies should take advantage of this methodology to assess reflex properties following neuromotor impairments and may be useful in assessing the effects of rehabilitation interventions to recover standing, walking and running.

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