Parallel facilitatory reflex pathways from the foot and hip to flexors and extensors in the injured human spinal cord

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Abstract

Spinal integration of sensory signals associated with hip position, muscle loading, and cutaneous sensation of the foot contributes to movement regulation. The exact interactive effects of these sensory signals under controlled dynamic conditions are unknown. The purpose of the present study was to establish the effects of combined plantar cutaneous afferent excitation and hip movement on the Hoffmann (H) and flexion reflexes in people with a spinal cord injury (SCI). The flexion and H-reflexes were elicited through stimulation of the right sural (at non-nociceptive levels) and posterior tibial nerves respectively. Reflex responses were recorded from the ipsilateral tibialis anterior (TA) (flexion reflex) and soleus (H-reflex) muscles. The plantar cutaneous afferents were stimulated at three times the perceptual threshold (200 Hz, 24-ms pulse train) at conditioning–test intervals that ranged from 3 to 90 ms. Sinusoidal movements were imposed to the right hip joint at 0.2 Hz with subjects supine. Control and conditioned reflexes were recorded as the hip moved in flexion and extension. Leg muscle activity and sagittal-plane joint torques were recorded. We found that excitation of plantar cutaneous afferents facilitated the soleus H-reflex and the long latency flexion reflex during hip extension. In contrast, the short latency flexion reflex was depressed by plantar cutaneous stimulation during hip flexion. Oscillatory joint forces were present during the transition phase of the hip movement from flexion to extension when stimuli were delivered during hip flexion. Hip-mediated input interacts with feedback from the foot sole to facilitate extensor and flexor reflex activity during the extension phase of movement. The interactive effects of these sensory signals may be a feature of impaired gait, but when they are appropriately excited, they may contribute to locomotion recovery in these patients.

Keywords

H-reflex; Flexion reflex; Locomotion; Reflex circuits; Rehabilitation; Sensorimotor integration

Introduction

Spinal integration of sensory signals is necessary for movement regulation and is especially important for the recovery of walking in people with a spinal cord lesion. Although locomotion

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can be induced without any sensory input from the periphery (Grillner and Zangger, 1979), extensive studies in lower vertebrates and humans have demonstrated that sensory signals associated with afferents that register hip position, muscle loading, and cutaneous sensation from the foot sole have specific regulatory effects on locomotion (Whelan, 1996;Rossignol et al., 2006). An improved understanding of the physiologic processing of these sensory signals in human spinal cord injury (SCI) is important to the design and implementation of therapeutic interventions for locomotor rehabilitation. In particular, the sensory feedback from plantar cutaneous afferents is expected to have a powerful effect on locomotor reflex function. To this end, the purpose of this study was to identify the combined neuromodulatory effects of plantar cutaneous and hip sensory feedback on spinal reflexes in people with clinically incomplete SCI.

In this context, electrical stimulation of cutaneomuscular afferents from the plantar or pure sensory nerves has demonstrated the existence of complex synaptic actions on active ankle muscles (Aniss et al., 1992;Zehr et al., 1997). For example, a short latency inhibitory pathway from plantar cutaneous afferents to ankle extensors following low-threshold stimulation to the posterior tibial nerve is enabled in spinal intact subjects when the foot sole contacts a surface (Abbruzzese et al., 1996). Excitation of cutaneous afferents arising from the sural nerve or foot sole induces long-lasting facilitation of the ipsilateral extensor motoneurons in the cat (Schieppati and Crenna, 1984) and human (Fallon et al., 2005) and induces crossed inhibitory postsynaptic potentials in the knee and ankle extensors (Edgley and Aggelopoulos, 2006). These effects may be related to the postulated action of plantar cutaneous afferents on the presynaptic inhibition acting on Ia afferent terminals (Iles, 1996), to their interaction with the machinery of reciprocal innervation (Rossi and Mazzocchio, 1988), and to their actions on Ib inhibitory pathways during which soleus exerts facilitation (instead of inhibition) to quadriceps when the triceps surae muscle is contracting (Pierrot-Deseilligny et al., 1981,1982). Following SCI, the reflex excitability of many pathways is altered (Hultborn, 2003), resulting in changes in reflex function that impact motor control and movement.

The spinal reflex effects from cutaneous afferents of the foot sole have also been implicated in the reflex regulation of locomotion, particularly with low-threshold afferents from the foot to reinforce stance (Aniss et al., 1992). The contribution of low-threshold plantar afferents to walking is clearly seen in cases where cutaneous input from the hind paws of spinalized cats is absent, resulting in an inability of the cats to be trained to step or walk. Preservation of minimal cutaneous input, however, is sufficient to allow re-education of the spinal cord to step. This loss in training ability is correlated to a reorganization of the plantar flexors activation patterns that is also attributed to the removal of plantar cutaneous input (Bouyer and Rossignol, 2003a,b). Similar effects have been reported for people with a sensory polyneuropathy of the feet, where a large variability in the step cycle duration and associated gait impairment are associated with a loss of reflex action of low-threshold cutaneous afferents (Van Wezel et al., 1997). In this respect, when foot sole stimulation is used as a conditioning stimulus it can depress soleus H-reflex excitability during assisted walking of people with a chronic SCI, resulting in a more normalized soleus H-reflex modulation pattern during walking (Fung and Barbeau, 1994).

A second sensory signal that is critical to locomotor reflex function is the hip position, which substantially affects the locomotor rhythm in both animals and humans. Evidence from studies conducted in lower vertebrates (Andersson and Grillner, 1983;Kriellaars et al., 1994;Hiebert et al., 1996;Lam and Pearson, 2001) suggest that this input accesses circuits responsible for walking contributing to phase transition and swing initiation. Blocking of the knee joint during human walking fails to alter the soleus H-reflex modulation pattern (Schneider et al., 2000), while pronounced hip extension enhances the swing phase during assisted walking in human SCI (Dietz et al., 1998,2002). Further, sensory signals mediating static hip angle and sensation

from the foot sole interact and induce a hip-dependent graded facilitation of the soleus H-reflex and tibialis anterior (TA) non-nociceptive flexion reflex in people with intact or injured spinal cord at rest (Knikou and Rymer, 2002;Knikou, 2005;Knikou et al., 2006b).

Accordingly, the current experiments were conducted to establish the combined effects of plantar cutaneous and hip-mediated sensory feedback on the soleus H- and TA flexion reflexes under well-controlled dynamic conditions in people with chronic incomplete SCI. Specifically, reflex conditioning effects were investigated during imposed sinusoidal hip movements. Muscle responses and forces exerted at the leg joints associated with the imposed sinusoidal hip movements were concurrently established. We hypothesized that hip movement would alter the conditioning effects of foot cutaneous afferents on H- and TA flexion reflex pathways, consistent with the reflex regulation of locomotion.

Materials and methods

Subjects

Experiments were conducted after a full institutional review board (IRB) approval of the experimental protocol (Northwestern University, IRB No. 1236-001) and according to the 1964 Declaration of Helsinki and Belmont Report. Written informed consent from each subject was obtained before testing. Eight subjects with lesions ranging from cervical (C) C5–8 to thoracic (T) T3–11 spinal segments participated in the study. Subject characteristics are summarized in Table 1.

All subjects participated in two tests that were conducted on different days. In the first test, we investigated the effects of plantar cutaneous afferent excitation on the soleus H-reflex, while in the second test we established the effects on the TA flexion reflex. Both tests were conducted during imposed hip movements. The hip range of movement (ROM) during both experimental trials is indicated in Table 1. Different hip ROMs were used for each subject, based largely on day-to-day as well as subject-to-subject differences in passive ROM, muscle tone, and spasms. In particular, the hip flexion range was limited in some subjects by an increased hip adductor tone.

Experimental apparatus and imposed sinusoidal hip movements

With subjects' supine, the right leg was secured in a leg brace with single-axis torque transducers (Himmelstein Inc., Hoffman Estates, IL, USA) aligned with the axes of rotation of the knee and ankle joints. The leg brace was affixed to the motor head of a Biodex system (Biodex Medical Systems Inc., Shirley, NY) that also measured the hip torque. The brace's footplate had a clamp to hold the fore-foot and a strap to secure the heel. The hip–knee and knee–ankle links of the brace were adjustable to accommodate each subject's leg length. The pelvis was secured to the seat with a strap.

After the leg brace was secured, the hip's center of rotation was aligned with the center of the Biodex motor head unit and sinusoidal movements at the hip in the sagittal plane were imposed. Hip movements were controlled by the Biodex system using the Researcher's Toolkit pattern files. The hip was moved through 10 full cycles of flexion and extension at 0.2 Hz (i.e., each hip movement cycle lasted 5 s). Although the movement was relatively slow, it allowed testing under dynamic hip conditions and resulted in similar hip positions during all conditioning paradigms. The ankle and knee joints were set at 20° of plantar flexion and 30° of flexion, respectively.

In all tests, surface electromyograms (EMGs) were recorded from the right TA, soleus (SOL), medialis gastrocnemius (MG), medial hamstrings (MH), vastus medialis (VM), and rectus femoris (RF) muscles in all subjects using differential bipolar electrodes (DE-2.1; DelSys, MA,

USA). All electrodes were placed following standard procedures. EMG signals were band pass filtered (20–250 Hz) before being sampled at 2 kHz using a data acquisition card (National Instruments, Austin, TX) and customized acquisition programs (LabVIEW software, National Instruments), and saved for further analysis.

Stimulation and recording protocols of the spinal reflexes

The TA flexion reflex was elicited and recorded according to procedures identical to those previously employed in the same SCI subjects (Knikou, 2007b;Knikou et al., 2006b). Briefly, the flexion reflex was evoked following sural nerve stimulation by a 30-ms train of 1-ms pulses delivered at 300 Hz using a constant current stimulator (DS7A, Digitimer, UK), and recorded from the TA muscle. For each subject, the stimulus delivered to the sural nerve was increased progressively, and the response was monitored to observe its sensitivity to the stimulus intensity strength. The stimulus intensity required to induce the initial EMG activity in the TA was identified as the reflex threshold (RT). Reflex responses were categorized as short reflex loop (SRL) responses when their latency was less than 100 ms or long reflex loop (LRL) responses when their latency was beyond 120 ms (Spaich et al., 2004;Knikou and Conway, 2005). During testing, the sural nerve was stimulated at 1.5 times the RT and ranged from 12 to 45 mA (32 ±13.7) across subjects. At these intensities, limb movement or pain were not evoked.

The soleus H-reflex was elicited and recorded according to procedures identical to those previously employed in the same SCI subjects (Knikou, 2005;Knikou et al., 2006a). Briefly, the H-reflexes were elicited on the ascending part of the recruitment curve by stimulation of the posterior tibial nerve using a single pulse of 1 ms that were 15–30% of the maximal M-wave (Mmax), and the corresponding M-waves were monitored online for each stimulus. H-reflexes were recorded from the right soleus muscle via a single differential electrode (Delsys Inc., Boston, USA) having established the correct site of stimulation by using a stainless steel monopolar electrode as a probe (see more details in Knikou et al., 2006a).

Plantar cutaneous afferent conditioning stimulation

Plantar skin stimulation was identical to that previously employed in the same SCI subjects (Knikou et al., 2006b;Knikou, 2007a). Cutaneous afferents were excited with a pulse train of 24 ms at 200 Hz delivered through two Ag-AgCl surface electrodes placed transversely across the 1st and 3rd metatarsals. The conditioning stimulation was delivered at 3 times the perceptual threshold (PT) in all subjects. Although the cutaneous excitation threshold may be decreased in people with SCI, on the basis that tactile units remain intact after chronic SCI (Thomas and Westling, 1995) transmission of plantar cutaneous sensation was not regarded as problematic in the current study and the excitation threshold was used as a tool to normalize the level of the conditioning stimulation across subjects. This stimulation intensity did not elicit any movement of the intrinsic foot muscles and no pain was reported, verifying that the conditioning afferent volley excited mostly large cutaneous afferents of the foot sole.

The conditioning pulse train preceded the soleus H-reflex and TA flexion reflex at different conditioning–test (C–T) intervals, measured as the time between the end of the pulse train delivered to the foot sole and the beginning of the pulse train or single pulse delivered to the sural or posterior tibial nerves, respectively. The different C–T intervals were delivered in random order and ranged from 3 to 90 ms (3, 6, 9, 15, 30, 60, and 90 ms) in order to observe short and long latency effects on both spinal reflexes.

Experimental protocol

In each subject, two control reflexes (10 repeated responses without plantar cutaneous excitation during hip flexion or extension; Ho[homonymous]) were recorded randomly with the conditioned reflexes (H-reflex preceded by foot sole stimulation at short and long C–T intervals

while the hip was moving in flexion or in extension). The control and conditioned reflexes were elicited only once in every movement cycle of the leg. Stimuli were sent at each of the 10 cycles either at mid-flexion (2.5 s) or mid-extension (0 s) depending on the test condition. The M-wave size was continually monitored to ensure stability in the stimulation procedures and especially to maintain a constant Ia afferent volley. M-wave amplitude constituted the intra-subject criterion for accepting the conditioned H-reflexes during hip movement. When the M-wave of the conditioned H-reflex was different from the M-wave of the control reflex (both reflexes recorded during hip movement), the stimulus intensity was adjusted so that the sizes of the M-waves of both reflexes were similar. Experimental data were rejected when a significant difference between the M-wave of the conditioned and Ho^{homonymous} reflexes was established. The same procedure was employed for the TA flexion reflex recordings during hip movement, and the control flexion reflex during hip movement was identified as SRL^{homonymous} or LRL^{homonymous}, respectively.

In each experimental session, surface EMG and joint torques were also collected during imposed hip movements (10 cycles) without stimulation of the sural or posterior tibial nerves. The data collected during the hip movement cycle with quiescent muscles were used as a measure of the combined effects of inertia, gravity, and the passive resistance of the limb and instrumented leg brace.

Data analysis

The soleus H-reflex and TA flexion reflex were full wave rectified and their sizes were measured as the area under the corresponding waveforms. The rectified area of the flexion reflexes was measured from the onset latency and the point in time during which the response fell below 1.5 standard deviations of the baseline EMG activity. The reflexes recorded at each C–T interval as the hip moved in flexion or extension were expressed as a percent of the mean size of the control reflex collected with the hip in the same movement direction (e.g., flexion or extension, Ho^{homonymous} or SRL^{homonymous}; LRL^{homonymous}). A one-way analysis of variance (ANOVA) along with post hoc Bonferroni tests were applied to the experimental data for each subject and reflex (flexion or H-reflex) separately to determine whether the conditioned reflexes were statistically significant different from the control reflex, and whether the conditioned reflexes varied across C–T intervals. Having established statistically significant differences between the control and conditioned reflexes, the average size of each subject's conditioned flexion or H-reflex was then grouped based on the C–T interval and the hip movement direction and a one-way ANOVA with repeated measures was applied to the data to determine changes in the size of the conditioned reflexes across the C–T intervals investigated for the subject group. This analysis was performed separately for tests conducted during hip flexion and extension. A two-way ANOVA and/or a paired *t*-test was also conducted on the pool data so to establish statistically significant differences between the conditioned reflexes recorded during hip extension and hip flexion.

For each subject, the M-waves of the control and conditioned H-reflexes were expressed as a percentage of the maximal M-wave. A one-way ANOVA with post hoc Bonferroni tests was used to test for differences between the M-waves of the reflexes recorded under control conditions and during limb movement. When significant differences were encountered the trial was rejected.

For each subject, the TA and SOL activities were measured from the rectified EMG recordings 100 ms before sural or posterior tibial nerve stimulation, and 200–250 ms after nerve stimulation in order to identify different underlying muscle activation levels across the test conditions. For both cases, the mean rectified EMG was computed for a period of 50 ms. This calculation was conducted separately for conditioned reflexes elicited during mid-flexion and mid-extension of the hip. Then, the pre- and post-stimulus TA and SOL EMG activities during

hip flexion were compared to the EMG activity during hip extension using a paired *t*-test. The average pre- and post-stimulus TA and SOL EMG activities from each subject were grouped based on the phase of the movement when the stimulus was delivered (flexion or extension) and a three-way ANOVA with repeated measures was applied to that data.

The pattern of muscle responses produced by the sinusoidal oscillation at the hip was characterized for each subject to establish the effects of peripheral nerve and/or plantar afferents stimulation on the reflex response produced by the hip movement. The timing and duration of the muscle responses were measured when nerve or cutaneous afferents were either stimulated or not. For each subject and trial, the EMG data from each muscle were band pass filtered (20–500 Hz, Butterworth 2nd order filters with no phase lag), full-wave rectified, smoothed and averaged over the 10 consecutive hip movement cycles. Then, the average EMG signal for each muscle was normalized using the average integrated area under its rectified curve and the resultant normalized EMG was plotted as a function of time.

The joint torque data produced by the imposed sinusoidal hip oscillations were used to determine the net reflexive effects at the hip, knee, and ankle. A movement cycle without any EMG activity was used to estimate the effects of passive movement, inertia, and gravity on the joint torques of the leg and brace. In order to obtain the reflex torques, the respective joint torques from the "no-EMG" trial were aligned with individual torques from the active trials, based on the hip position data, and the difference was calculated. This difference was the torque response attributed to the reflexive movement and was filtered with a 2nd-order, 2-Hz low pass Butterworth filter. The average of the filtered data from all trials from each subject and particular test condition are reported as the torque response for the particular joint and subject. In all statistical tests, significant differences were established at 95% of confidence level. Results are presented as mean values along with the standard error of the mean (SEM).

Results

Combined effects of foot sole stimulation and hip movement on the TA flexion reflex

The effects of low-threshold plantar cutaneous afferent excitation on the TA flexion reflex depended on the direction of the imposed hip movement. Representative examples of these effects are illustrated for two subjects (S7 and S10) in Fig. 1. The LRL TA responses were substantially facilitated at the C–T interval of 90 ms in both subjects during hip extension (top traces of Fig. 1). In contrast, plantar conditioning during hip flexion depressed the SRL TA response in subject 7, while the LRL was not affected (bottom traces of Fig. 1).

One-way ANOVA showed that plantar cutaneous afferent excitation during imposed hip extension resulted in a significant facilitation of the LRL flexion reflex in all subjects (data from each subject are not illustrated). For each C–T interval, the average size (all subjects tested) of the TA LRL responses during hip extension or flexion is illustrated in Fig. 2A. During hip extension, the conditioned TA LRL response reached overall amplitude of $140\pm21\%$ and $143\pm24.7\%$ ($P<0.05$) of the $LRL^{homonymous}$ at C–T intervals of 9 and 90 ms, respectively. A one-way ANOVA along with post hoc Bonferroni tests revealed that the facilitation of the conditioned TA LRL responses during hip extension did not change significantly ($F_{6, 47} = 0.061$, $P=0.99$) across C–T intervals. In contrast, excitation of low-threshold plantar cutaneous afferents did not induce significant effects on the TA LRL responses during hip flexion at any of the C–T interval tested ($P>0.05$) (Fig. 2A). A two-way ANOVA conducted between the conditioned LRL flexion reflexes from all subjects recorded during hip extension and hip flexion at all C–T intervals revealed that the conditioned LRL flexion reflexes during hip flexion were significantly different from the conditioned reflexes recorded during hip extension ($F_{1,5} = 6.99$, $P=0.03$).

The SRL TA response was observed in 5 of the 8 subjects during hip extension, and for all subjects, the reflex was not significantly modulated by stimulation of the foot sole at either short or long C–T intervals (single subject one-way ANOVA, $P>0.05$). The average size (all subjects tested) of the SRL TA flexion reflex during hip extension is shown in Fig. 2B. In contrast, the SRL TA responses were observed in 7 out of 8 subjects during hip flexion and were depressed with foot sole stimulation at the longer C–T intervals tested (e.g., 30, 60, and 90 ms) (Fig. 2B). A two-way ANOVA along with post hoc Bonferroni tests revealed that there were significant effects due to limb movement only during hip flexion and for the C–T intervals of 30 to 90 ms ($P<0.05$). Overall, during hip extension, the conditioned LRL TA responses were facilitated while the associated conditioned SRL TA responses were similar to control reflex values. The opposite effect was observed during hip flexion (compare Figs. 2A and B). The hip-phase-dependent modulation of the flexion reflex following excitation of plantar cutaneous afferents coincided with no changes in TA background activity. A three-way ANOVA revealed that there were no significant main effects due to limb movement (flexion/ extension, $P =0.39$), C–T interval (9 to 90 ms, $P=0.37$), and timing of stimulus (pre- and post-stimulus, $P =0.2$) on the TA activity during sinusoidal leg movement (see Fig. 2C).

In general, the underlying leg muscle activity measured during the imposed hip movement with conditioning–test stimuli was similar to trials with only the flexion reflex stimuli. A constant behavior of muscle responses was observed across C–T intervals, which coincided mostly with the stimulus timing. One exception to the association of the EMG with the stimuli was an activation of the MH during flexion of the hip in trials when stimuli were delivered during hip extension (Fig. 3), consistent with stretch reflex activation of the MH. Similar to the EMGs, the underlying torque responses during the conditioning–test recordings were similar to those for sural nerve stimulation alone. The torque data are summarized for conditioned TA flexion reflex recordings during hip extension and flexion in Fig. 4A for the longest C–T interval tested (i.e., 90 ms). When the leg moved from mid- to peak extension, the torques at the hip were mostly flexor for stimuli sent at mid-extension (Fig. 4Ai), and extensor for stimuli sent at mid-flexion (Fig. 4Aii). Further, an oscillatory spasmodic activity at the hip was present during the transition phase of the hip from flexion to extension and was only observed when stimuli were delivered during hip flexion. This spasmodic response appeared to be associated with the timing of the sural stimulation and not with the conditioning stimulus from the plantar cutaneous afferents since the effect was also observed with no conditioning stimulus (Fig. 4B). The flexor and extensor torques at the hip coincided with a similar behavior of the torque responses at the ankle joint, while in this trial, the torques at the knee joint were rejected. For comparison, the torque data for unconditioned flexion reflexes are indicated in Fig. 4B. It is apparent that the torque responses across the lower limb joints with sural stimulation alone were generally similar to those observed during the reflex conditioning trials.

Combined effects of foot sole stimulation and hip movement on the soleus H-reflex

Plantar cutaneous afferent excitation produced significant changes in the soleus H-reflex that were hip-phase-dependent. Fig. 5A shows the waveform averages of the soleus H-reflexes following excitation of plantar cutaneous afferents at 9 and 90 ms C–T intervals for one subject (S4) superimposed on the control H-reflex ($Ho^{homonymous}$), both recorded during hip extension. It is clear that excitation of plantar skin facilitated the soleus H-reflex.

One-way ANOVA (single subject) between the control and the conditioned H-reflexes revealed that excitation of plantar cutaneous afferents had significant effects during hip extension but not during hip flexion. A summary of changes (all subjects tested) in the conditioned H-reflex following excitation of low-threshold plantar sole stimulation for all C–T intervals during hip flexion and extension is illustrated in Fig. 5B. One-way ANOVA showed that the overall conditioned soleus H-reflex (all subjects tested) varied significantly with changes in the C–T

interval during hip extension. Excitation of plantar cutaneous afferents with the hip in mid-extension resulted in a significant facilitation of the soleus H-reflex at the C–T interval of 6 ms. At 6 ms, the conditioned H-reflex reached an amplitude of $130\pm 15\%$ of $Ho^{homonymous}$. Similarly, the H-reflex was significantly facilitated at C–T intervals of 9 and 15 ms, but reduced to control reflex values at 30 and 60 ms. Reflex facilitation re-emerged during the longest C–T interval (i.e., 90 ms). Thus, it is apparent that plantar cutaneous input induced an early followed by a late soleus H-reflex facilitation during hip extension. In contrast, excitation of plantar cutaneous afferents induced no significant effects on the amplitude of the soleus H-reflex at either short or long C–T intervals (one-way ANOVA, $F_{6, 35} = 0.534$, $P=0.78$) during hip flexion. A paired t-test showed that the overall conditioned reflexes during hip extension were statistically significant different compared to those observed during hip flexion (Tst=−3.9, df=31, $P<0.05$).

The modulation of the soleus H-reflex following excitation of plantar skin afferents during hip movement occurred with no significant changes on the SOL pre- and post-stimulus EMG activity. A summary of the SOL EMG activity (all subjects tested) before and after posterior tibial nerve stimulation during hip flexion and extension for all C–T intervals is indicated in Fig. 5C. A three-way ANOVA for repeated measures showed no significant differences between pre- and post-stimulus SOL EMG activity during hip flexion and extension across C–T intervals (flexion/extension, P =0.813; pre- and post-stimulus, P=0.167; C–T interval, P=0.074), suggesting that the hip-phase-dependent reflex modulation during cutaneous plantar stimulation was not due to simple changes in the underlying soleus motoneuronal excitability.

The H-reflex and plantar cutaneous stimuli did not appear to affect the underlying reflex response to imposed hip movements. The hip, knee, and ankle reflexive torques when the soleus H-reflex was conditioned with plantar cutaneous afferent excitation at 90 ms during hip extension and flexion are illustrated in Fig. 6A. At the hip joint, flexor torques were observed when the leg moved from mid- to peak extension, while during the transition phase of the leg from peak flexion to mid-extension a spasmodic oscillatory behavior of this joint was apparent when the hip was flexed. The hip flexor torques coincided mostly with extensor torques at the knee and ankle. For comparison we also illustrate the joint torques observed following soleus H-reflex elicitation without the conditioning stimulation ($Ho^{homonymous}$) (Fig. 6B). It is apparent that the torque responses across the lower limb joints were similar to those observed during the reflex conditioning trials. Similarly, most EMG responses coincided with the timing of the stimulus, with stimulus-independent activity observed only in the MH and the VM, a behavior that was observed across C–T intervals (data not shown graphically).

Comparing the joint torque responses following stimulation of a mixed peripheral nerve (posterior tibial) (Fig. 4) or a pure cutaneous nerve (sural) (Fig. 6) during imposed sinusoidal hip movements, it is apparent that the ankle joint torques were manifested in a similar pattern regardless the combination of stimuli. However, this was not the case for the hip joint torques, which were in extension upon sural nerve stimulation and flexion upon posterior tibial nerve stimulation when the hip moved from mid-extension to mid-flexion, suggesting that flexion reflex stimulus affected the response to hip movement.

Discussion

The main finding of this study was that in SCI subjects, plantar cutaneous stimulation induced a long-lasting facilitation of the soleus H- and TA flexion reflexes during hip extension that occurred with stable ongoing background activity of the involved muscles. The reflex modulation pattern was largely dependent on the phase of the hip movement such that during hip flexion no significant effects on the monosynaptic H-reflex were observed, while the early component of the flexion reflex (SRL) was depressed. These observations are consistent with

the modulation of reflex pathways by afferent systems that have been implicated in the reflex regulation of locomotion. Consequently, these results have implications in the reflex control of gait in people with SCI and emphasize the importance of sensory feedback in locomotor rehabilitation.

Contribution of feedback from the foot sole and hip to spinal reflex circuits and locomotor-related neuronal pathways

Plantar cutaneous conditioning stimulation facilitated the LRL TA flexion reflex responses and the soleus H-reflex during imposed hip extension, indicating a mixed effect on flexor and extensor reflex pathways. Specifically, the TA LRL flexion response was facilitated during hip extension when the foot sole was stimulated, but no effects on the LRL were observed during hip flexion (Fig. 2A). Further, the SRL TA response was depressed during hip flexion at C–T intervals that varied from 30 to 90 ms (Fig. 2B), supporting further the involvement of different interneuronal circuits in the expression of the flexion reflex components (Knikou and Conway, 2005). Similarly, the soleus H-reflex displayed an early followed by a late conditioning effect during hip extension (Fig. 5B) but was not affected by foot sole stimulation at either short or long C–T intervals during hip flexion. Thus, the conditioning effect of cutaneous afferents from the foot sole on both spinal reflexes during hip extension was facilitatory.

The sensitivity of spinal reflexes to convergent feedback from hip proprioceptors and plantar cutaneous afferents suggests that locomotor reflexes may be involved, since these same afferent sources have modulatory effects on locomotor activity (Rossignol et al., 2006). If we then assume that locomotor-related pathways were involved in the modulation of the spinal reflexes in this study, one might anticipate that facilitation of extensor reflex pathways by cutaneous afferents during hip extension would have been accompanied by an inhibition of the flexor reflex pathways. In this respect, it has been postulated that skin afferent input is capable of blocking the onset of swing phase and inducing extensor muscle activity (Schomburg et al., 1998;Duysens and Pearson, 1976). Thus, the lack of observing a differential effect on flexor and extensor reflex pathways by plantar conditioning stimulation during hip extension might be attributed to the loss of spinal inhibitory mechanisms as a result of the SCI (Knikou, 2005,2007a;Hultborn, 2003).

The facilitatory effects of the plantar cutaneous afferents on the TA flexion reflex during hip extension is inconsistent with the general increase in the response during swing and suppression during the transition phase from swing to stance observed in spinal-intact subjects (Yang and Stein, 1990). Similarly, a phase-dependent modulation and reversal of cutaneous reflexes is observed in spinal cats during fictive locomotion (Duysens et al., 1990;Schmidt et al., 1989;Moschovakis et al., 1991;Degtyarenko et al., 1996). Cutaneous afferents innervating the ankle and the foot-pad skin enhance and prolong stance and can increase the extensor burst by as much as 100% (Duysens and Pearson, 1976). However, the conditioning effects of the plantar cutaneous afferents on the TA flexion reflex were facilitatory during the hip extension phase of the cyclic movement in the current study, contradicting the decrease in flexion reflexes typically observed during stance. The difference may be related to a lower level of activity in the spinal locomotor generator in the supine subjects in the current study.

The joint torque oscillations observed during the transition phase from flexion to extension when either conditioning or test stimuli were delivered during hip flexion (Fig. 6) could be potentially interpreted to indicate that spinal locomotor pathways were activated by the stimulation. We have previously observed a similar behavior when group Ia afferents (but not Ib afferents) from the common peroneal nerve or flexion reflex afferents were excited during imposed hip movements in the same SCI subjects (Knikou et al., 2006a;Knikou, 2007b). In those cases, oscillatory activity was observed during hip extension and flexion, but its

amplitude was half of that observed here (compare Fig. 4 with Fig. 6 in Knikou et al., 2006a). This oscillatory rhythmic activity resembles the one seen during fast paw shake following stimulation of specific skin sites described in animals (Pearson and Rossignol, 1991) and also resembles clonus of the leg in humans (Beres-Jones et al., 2003), with the latter proposed to be mediated by a spinal stepping generator.

Sensory feedback associated with hip position and cutaneous sensation from the foot sole is known to contribute to gait regulation. The long latency TA flexion reflex is strongly modulated by hip position in the acute spinal cat (Grillner and Rossignol, 1978), while imposed flexion at the hip during fictive locomotion in L-DOPA-treated spinal cats shortens the flexor burst duration when applied near the end of the flexor bursts (Andersson and Grillner, 1983;Lam and Pearson, 2001). Analogously, afferents originating from the foot sole delay the initiation of swing and inhibit long latency flexion reflexes promoting stance (Duysens and Pearson, 1976;Conway et al., 1995). Although specific afferents or neuronal pathways have not been identified in humans, hip-mediated sensory signals affect the walking pattern of spinal injured people by enhancing the swing phase (Dietz et al., 1998,2002), while input from the foot sole acting either in isolation or in combination with input from the hip affect reflexly mediated motor behavior (Knikou and Conway, 2001;Knikou, 2007a;Knikou et al., 2006b).

It is likely that during our experiments, spinal locomotor-related circuits participated in the modulation of the spinal reflexes, but in the absence of limb loading and upright posture of the SCI subjects, the effects of sensorimotor reflex conditioning resulted in an exaggerated or fragmented expression of the locomotor-related muscle activation. To conclude, it is suggested that sensory feedback from the hip and plantar cutaneous afferents contribute to locomotor reflexes and likely contribute to the locomotor recovery of people with SCI following treadmill walking training. However, demonstration of these same reflex pathways remains to be tested during treadmill walking or step training.

Possible neuronal mechanisms

The imposed sinusoidal hip motion was delivered without a stop in either flexion or extension, providing an ongoing signal reflecting hip proprioception. Thus, proprioceptive hip muscle afferents sensitive to stretch and to dynamic changes of muscle length (i.e., primary and secondary muscle spindle afferents) interacted with low-threshold plantar cutaneous afferents to mediate the observed reflex modulation. Given that both spinal reflexes and conditioning stimulation were delivered at non-nociceptive levels, low-threshold sensory afferents were implicated in the reflex responses. Significant evidence suggests that hip proprioceptors interact with segmental Ia and Ib inhibitory interneurons (Knikou, 2005;Knikou et al., 2006b), thereby affecting motor output of the injured human spinal cord.

Ipsilateral and contralateral sural nerve stimulation has been reported to decrease presynaptic inhibition of soleus Ia afferent terminals in spinal intact subjects (Delwaide et al., 1981;Iles, 1996), a phenomenon that has been described in people with clinically complete SCI (Roby-Brami and Bussel, 1992). In this respect, cutaneous stimuli can reduce the level of presynaptic inhibition of group I afferents during fictive stepping in the cat (Menard et al., 2002;Enriquez-Denton et al., 2002) without changing the pattern of phase-dependent modulation (Menard et al., 2002). Similarly, input from the foot sole influences alpha motoneuronal excitability through segmental inhibitory inter-neuronal circuits (Pierrot-Deseilligny et al., 1982;Rossi and Mazzocchio, 1988;Iles, 1996). Further, the presynaptic inhibition acting on soleus Ia afferent is abolished following static hip angle changes in spinal-intact and spinal-injured subjects (Knikou, 2005,2006), while the stepping generator itself does not presynaptically inhibit the soleus H-reflex during the extension phase of locomotor activity (Misiaszek et al., 2000), suggesting a pre-motoneuronal reflex regulation by hip muscle and plantar cutaneous afferents. Nonetheless, current findings might be related to the recruitment of excitatory interneurons or

dis-facilitation of inhibitory interneurons projecting to excitatory interneurons in group I and flexion reflex afferents. However, given the indirect nature of the current experiments, a specific neuronal mechanism cannot be assigned.

Functional implications

The present study provides evidence that actions of plantar cutaneous afferents on the soleus H-reflex and TA flexion reflex are modulated by hip movement in a phase-dependent manner. Both reflexes were facilitated during hip extension. Hip-mediated sensory feedback is known to shape the walking pattern of the injured human spinal cord and to account for phase transitions and swing phase initiation in spinal cats during fictive locomotion. It is suggested that hip proprioceptors might contribute to the recovery of walking in people with a SCI by adjusting extensor and flexor spinal reflexes through cutaneous afferent pathways. This is partially supported by findings in spinal cats during locomotion training, where skin input that signals ground contact is modified by step training (Côte and Gossard, 2004). Further research is thus needed to establish the interactive effects of hip proprioceptors and plantar cutaneous afferents on spinal reflexes before and after locomotor training in human SCI so that sensorimotor reflex conditioning systems may be developed to enhance locomotor training and thus promote recovery of walking in people with a sensorimotor incomplete SCI.

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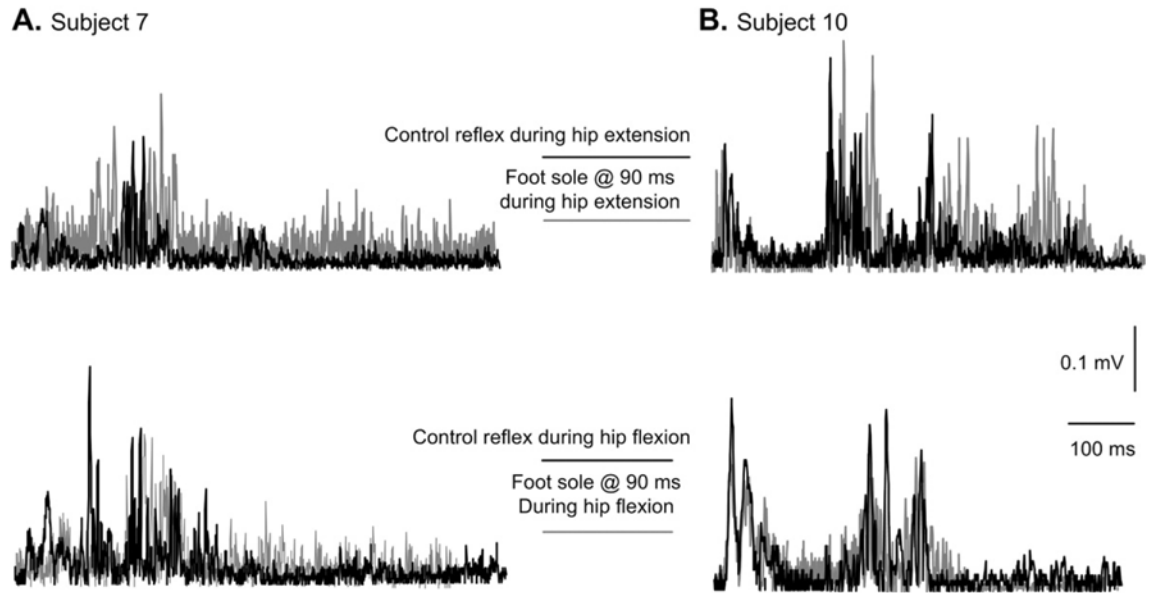
A. Subject 7

B. Subject 10

Control reflex during hip extension

Foot sole @ 90 ms
during hip extension

0.1 mV

Control reflex during hip flexion

100 ms

Foot sole @ 90 ms
During hip flexion

Fig 1.
For two subjects (S7 and S10) the average (*n*=10) control TA flexion reflexes (black lines) recorded during hip extension (upper traces) and during hip flexion (lower traces) are illustrated superimposed on the TA flexion reflexes conditioned by plantar cutaneous afferents at a conditioning–test interval of 90 ms (grey lines). It is clear that in both subjects, excitation of plantar cutaneous afferents during hip extension facilitated the long reflex loop (LRL) TA flexion reflex. In contrast, during hip flexion the LRL TA flexion reflex was not affected by the conditioning stimulus, while the short reflex loop (SRL) response was depressed in subject 7. In subject 10, no significant changes in the amplitude of the SRL TA response were noted following reflex conditioning during hip flexion.
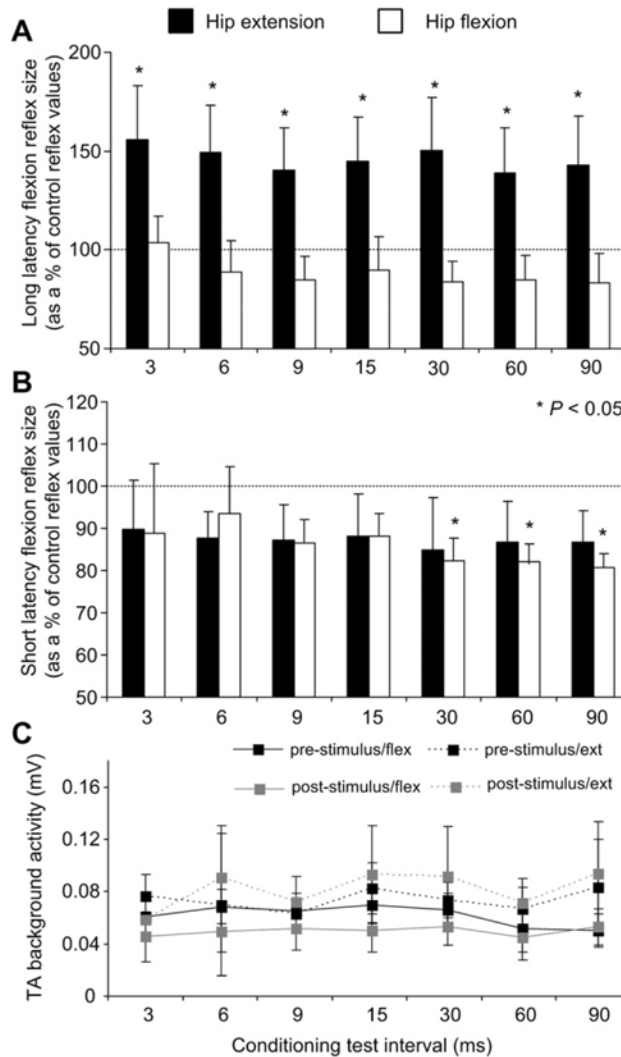
Fig 2.
(A) Effects of plantar sole conditioning stimulation on the TA long reflex loop (LRL) response during hip extension and hip flexion. Data represent the overall mean size (all subjects tested) of the conditioned TA flexion reflex expressed as a percentage of the associated control reflex (LRL[homonymous]) and grouped according to the conditioning–test (C–T) interval and hip movement. (B) Average size (all subjects tested) of the TA short reflex loop (SRL) response as a percentage of the associated control flexion reflex (SLR[homonymous]) during hip extension and flexion. (C) Overall amplitude (all subjects tested) of the pre-and post-stimulus TA background activity during hip flexion and extension is illustrated for all C–T intervals. See text for more details on the statistical analysis. Error bars in all graphs designate the standard error of the mean and asterisks the cases of statistically significant differences between the conditioned and the control reflexes across the C–T intervals at 95% of confidence level.
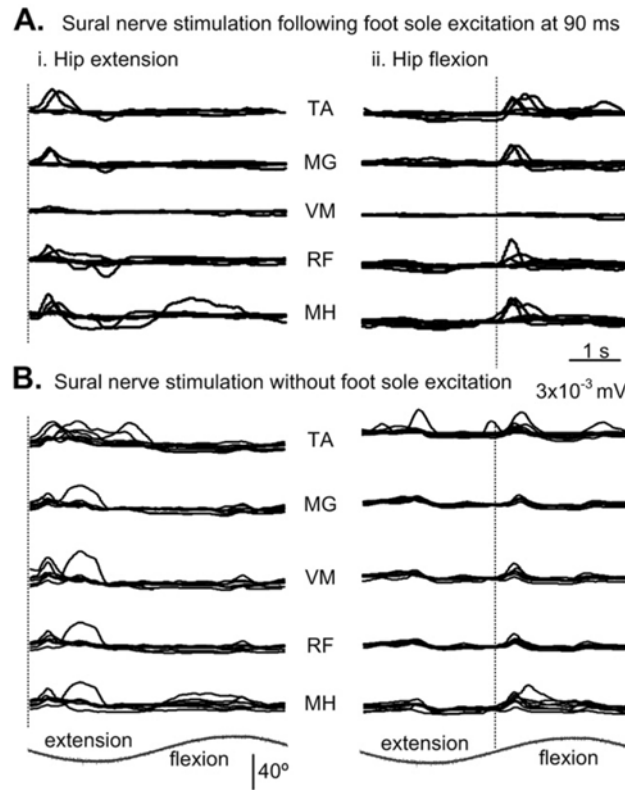
Fig 3.
Normalized average muscle responses when the TA flexion reflex was conditioned by low-threshold plantar cutaneous afferent stimulation at the conditioning–test interval of 90 ms (A) and when the conditioning stimulus was not present (B) during hip extension and flexion. Bottom traces indicate the sinusoidal motion at the hip joint, as recorded by the Biodex system. The dotted lines indicate the position of the hip (0 s for mid-extension and 2.5 s for mid-flexion) during which stimuli (sural nerve and/or combined sural nerve and foot sole) were delivered.
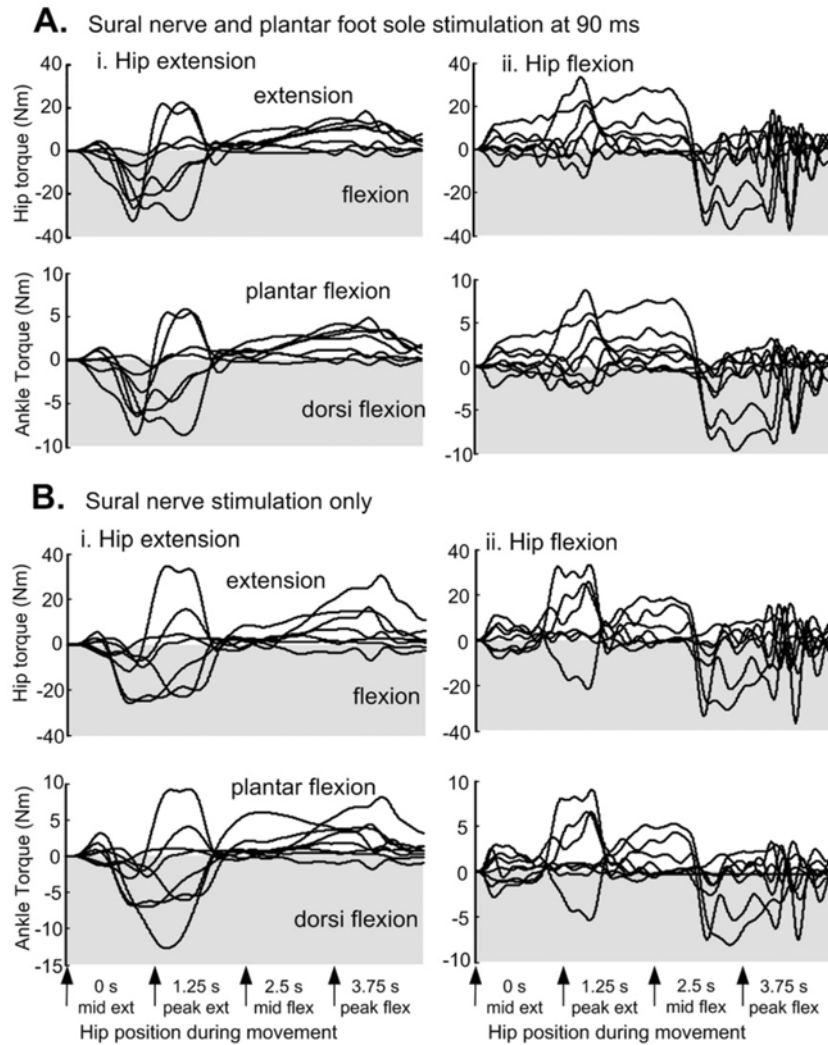
Fig 4.
The reflexive joint torques (Nm) at the hip and ankle are indicated for cases when the TA flexion reflex was conditioned by plantar sole stimulation at 90 ms during hip extension and flexion (A), and when the conditioning stimulus was not present (B). Each waveform represents the average of 10 consecutive hip movement cycles (each cycle lasted 5 s). Arrows at the bottom of the figure indicate the position of the hip during a hip sinusoidal movement cycle (mid-extension at 0 s, peak extension at 1.25 s, mid-flexion at 2.5 s, and peak flexion at 3.75 s). For extension trials stimuli were delivered at 0 s and for flexion trials at 2.5 s. Torques above zero designate extension and those below zero designate flexion. Oscillatory torques at the hip and ankle were mostly observed during the transition phase of the hip from flexion to extension, and only when stimuli were delivered during hip flexion.
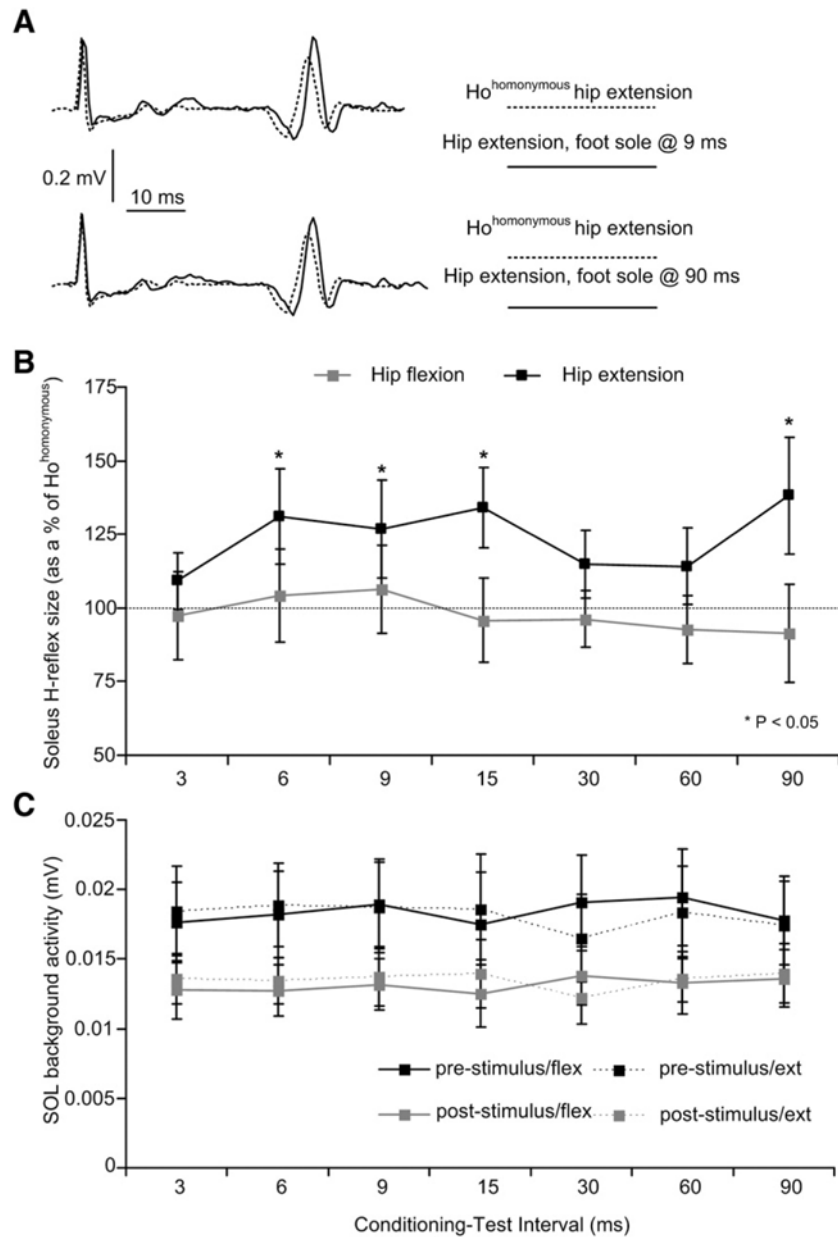
Fig 5.
(A) The average H-reflex (*n*=10) recorded under control conditions (Ho[homonymous]; dashed lines) and during conditioning of the soleus H-reflex with stimulation of low-threshold cutaneous afferents of the foot sole at the conditioning–test (C–T) intervals of 9 and 90 ms (solid lines) during hip extension are presented. It is clear that during hip extension plantar sole stimulation resulted in a significant soleus H-reflex facilitation. Note that the increment in H-reflex amplitude occurs without significant changes in the M-wave. (B) Effects of variation of the C–T interval on the soleus H-reflex during hip extension and hip flexion. Data represent the overall mean (all subjects tested) of the conditioned soleus H-reflex expressed as a percentage of the associated control reflex (Ho[homonymous]) and grouped according to the C–T interval and hip movement direction. Asterisks indicate cases of statistically significant differences between the control and the conditioned reflex. (C) Overall mean amplitude of the

pre- and post-stimulus SOL background EMG activity for conditioned H-reflexes elicited during hip extension and flexion is indicated for each C–T interval.
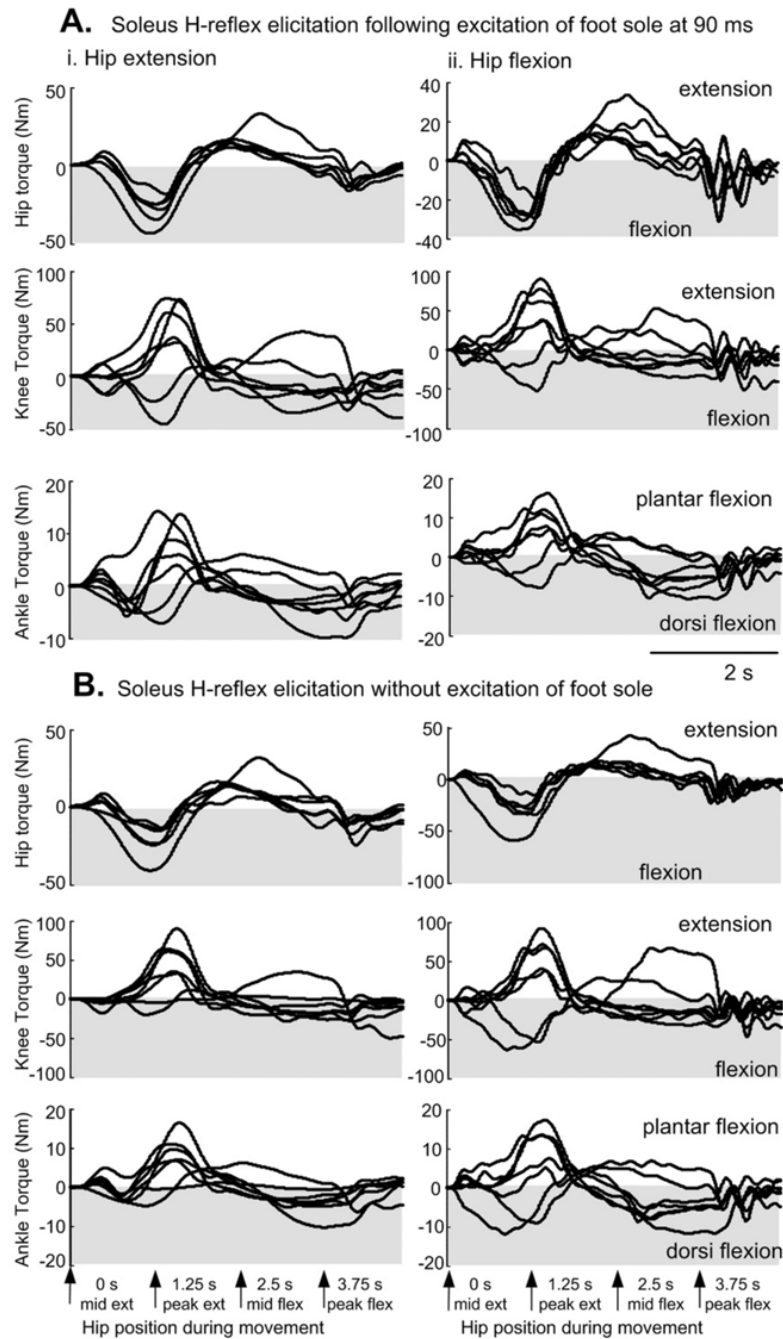
A. Soleus H-reflex elicitation following excitation of foot sole at 90 ms

i. Hip extension

ii. Hip flexion

B. Soleus H-reflex elicitation without excitation of foot sole

Fig 6.
Hip, knee, and ankle reflexive torques (Nm) when the soleus H-reflex was conditioned by plantar sole stimulation at 90 ms during hip extension and flexion (A), and when the conditioning stimulus was not present (B). Each waveform represents the average of 10 consecutive hip movement cycles. Arrows at the bottom of the figure indicate the position of the hip during a hip sinusoidal movement cycle (mid-extension at 0 s, peak extension at 1.25 s, mid-flexion at 2.5 s, and peak flexion at 3.75 s). For extension trials, stimuli were delivered at 0 s and for flexion trials at 2.5 s. Torques above zero designate extension and those below zero designate flexion. Oscillatory joint responses were mostly observed during the transition

phase of the hip from peak flexion to extension but only when stimuli were delivered during hip flexion.

Table 1

Summarized characteristics of SCI subjects[a]

S#	Gender	Age (years)	Post-injury (months)	Ashworth score	ASIA	Lesion level	Sensation	Medication per day	Hip ROM	
									H-reflex	Flexion reflex
S1	M	25	99	1	C	C5	Intact	–	40°	43°
S3	M	29	39	0	C	C5	Intact	–	50°	45°
S4	M	47	81	2	C	C6	Intact	Baclofen 60 mg	55°	55°
S5	M	22	48	2	C	T11	Intact	–	60°	65°
S7	F	61	53	0	C	T9	Intact	–	60°	57°
S10	M	52	213	1	C	C5	No sensation of cold/warm	Baclofen 30 mg	48°	55°
S11	M	52	189	3	C	C5	No sensation of cold/warm	–	50°	60°
S12	M	36	39	2	B	T8	Intact	Baclofen pump	60°	58°

[a] Spasticity at the ankle was scaled according to the Ashworth (1964) score. Lesion completeness was classified according to the American Spinal Injury Association (ASIA) impairment scale (Maynard et al., 1997) with ASIA C representing a sensory and motor incomplete lesion where more than half of the muscles below the injury level have a strength of less than 3 (out of 5), and ASIA B representing sensory incomplete but motor complete spinal cord lesion. S#: subject number; F: female; M: male; ROM: range of sinusoidal hip movement.