Modification of cutaneous reflexes during visually guided walking

Casey R. Ruff, Andreas B. Miller, Mona L. Delva, Kim Lajoie, and Daniel S. Marigold

Department of Biomedical Physiology and Kinesiology, Simon Fraser University, Burnaby, British Columbia, Canada

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Ruff CR, Miller AB, Delva ML, Lajoie K, Marigold DS. Modification of cutaneous reflexes during visually guided walking. J Neurophysiol 111: 379–393, 2014. First published October 23, 2013; doi:10.1152/jn.01076.2012.—Although it has become apparent that cutaneous reflexes can be adjusted based on the phase and context of the locomotor task, it is not clear to what extent these reflexes are regulated when locomotion is modified under visual guidance. To address this, we compared the amplitude of cutaneous reflexes while subjects performed walking tasks that required precise foot placement. In one experiment, subjects walked overground and across a horizontal ladder with narrow raised rungs. In another experiment, subjects walked and stepped onto a series of flat targets, which required different levels of precision (large vs. narrow targets). The superficial peroneal or tibial nerve was electrically stimulated in multiple phases of the gait cycle in each condition and experiment. Reflexes between 50 and 120 ms poststimulation were sorted into 10 equal phase bins, and the amplitudes were then averaged. In each experiment, differences in cutaneous reflexes between conditions occurred predominantly during swing phase when preparation for precise foot placement was necessary. For instance, large excitatory cutaneous reflexes in ipsilateral tibialis anterior were present in the ladder condition and when stepping on narrow targets compared with inhibitory responses in the other conditions, regardless of the nerve stimulated. In the ladder experiments, additional effects of walking condition were evident during stance phase when subjects had to balance on the narrow ladder rungs and may be related to threat and/or the unstable foot-surface interaction. Taken together, these results suggest that cutaneous reflexes are modified when visual feedback regarding the terrain is critical for successful walking.

locomotion; vision; context-dependent reflex modulation; precision walking; cutaneous afferents

Sensory feedback from muscle, joint, and skin receptors is important during locomotion as it facilitates the modulation of ongoing muscle activity, plays a role in phase transitions of the step cycle, and contributes to corrective responses following a perturbation (Rossignol et al. 2006; Zehr and Stein 1999). Cutaneous input, for example, provides important details, on a step-by-step basis, regarding the terrain an individual encounters while walking (Bouyer and Rossignol 2003; Eils et al. 2004; Rossignol et al. 2006). This information appears particularly relevant under demanding situations. Indeed, denervation of a cat’s cutaneous nerves supplying the hind feet results in larger deficits when walking across the rungs of a horizontal ladder compared with normal ground (Bouyer and Rossignol 2003). In addition, excitation of cutaneous afferents can elicit complex reflexive responses geared to counteract a perturbation, such as tripping on an obstruction (Haridas et al. 2008). Furthermore, cutaneous feedback contributes to the scaling of corrective reflexive responses triggered by support surface translations during walking (Bolton and Misiaszek 2009). Interestingly, cutaneous afferents also have the capacity to modulate spinal reflexes (i.e., H-reflex and flexion reflex) in people with spinal cord injury (Knikou 2010).

Research on cutaneous reflexes, using mechanical or electrical stimulation in cats and humans, has demonstrated several fundamental findings. Specifically, the amplitudes of cutaneous reflexes are modulated depending on the phase of the gait cycle, a concept known as phase-dependent modulation, and different reactions involving many muscles across multiple joints are elicited depending on the nerve stimulated, referred to as local sign (Duyens et al. 1990; Forssberg 1979; van Wezel et al. 1997; Yang and Stein 1990; Zehr et al. 1997; Zehr and Stein 1999). For instance, Zehr et al. (1997) have shown that stimulation of the tibial nerve (a mixed nerve transmitting input from the plantar foot surface) generates a placing reaction (i.e., ankle plantar flexion) in late swing phase and generates ankle dorsiflexion in the stance to swing transition while walking. In contrast, stimulation of the superficial peroneal (SP) nerve (a cutaneous nerve at the level of the ankle transmitting input from the foot dorsum) elicits a stumble corrective response in early swing phase, as illustrated by ankle plantar flexion and knee flexion (Zehr et al. 1997). Cutaneous reflexes elicited during locomotion are also context dependent (Haridas et al. 2005, 2006, 2008). Specifically, the amplitude of cutaneous reflexes elicited by SP nerve stimulation increases in several lower limb muscles when a subject’s arms are constrained and the uncertainty of waist-pull perturbations are present (i.e., greater postural threat or instability) compared with when arm motion is not restricted (Haridas et al. 2005).

Taken together, the evidence above suggests that the major roles of cutaneous afferents from the foot are in the control of foot placement, particularly when foot placement is constrained during walking, and in the corrective responses to perturbations.

Vision is critical for planning where to place the foot when walking over irregular terrain and provides information regarding characteristics of the terrain, the context of the task, and possible threats in the environment. This information can be used in a predictive manner to modify nonvisual afferent feedback to allow for a smooth locomotor pattern. Importantly, cortical activity is altered during visually guided tasks. For example, discharge activity increases in neurons of the motor and posterior parietal cortices when cats step over obstacles and walk across a horizontal ladder compared with walking on flat ground (Andujar et al. 2010; Beloozerova and Sirotà 1993, 2003; Beloozerova et al. 2010; Drew et al. 2008). Lesions and pharmacological inactivation of these cortical areas result in locomotor deficits, predominantly under these visually demanding conditions compared with flat ground (Beloozerova...
and Sirota 1993; Friel et al. 2007; Lajoie and Drew 2007). However, it is not yet clear to what extent cutaneous reflexes can be modified when visual feedback regarding the detailed nature of the terrain is critical for step progression. An interaction between supraspinal centers and cutaneous pathways must exist for visual feedback to adjust transmission of cutaneous input. In reduced cat preparations, there is spatial convergence of corticospinal and rubrospinal pathways with cutaneous afferents onto motoneurons innervating the hindlimbs (Fleshman et al. 1988; Pinter et al. 1982).

In intact walking cats, Bretzner and Drew (2005) have shown that stimuli applied to the motor cortex result in facilitation and depression of hindlimb cutaneous reflexes depending on the nerve and the phase of stimulation. Conversely, cutaneous afferents modify the discharge pattern of reticulospinal and motor cortex neurons (Drew et al. 1996; Marple-Horvat and Armstrong 1999; Palmer et al. 1985). Interestingly, responses in motor cortex neurons were larger around foot placement when cats walked on a horizontal ladder (Marple-Horvat and Armstrong 1999).

In humans, several studies demonstrate how the cortex can influence cutaneous reflexes. First, transcranial magnetic stimulation (TMS) to the motor cortex paired with electrical stimulation of the sural nerve (a pure sensory nerve transmitting input from the lateral margin of the foot) results in facilitation of cutaneous reflexes during the swing phase of walking (Christensen et al. 1999; Pijnappels et al. 1998). Second, cutaneous reflex amplitude during walking can be reduced when electrical stimulation of the nerve is self-induced compared with when evoked by a computer (Baken et al. 2006).

Third, the size of TMS induced motor evoked potentials (MEPs) in muscles surrounding the ankle joint changes when stepping to targets on a treadmill compared with normal treadmill walking (Schubert et al. 1999). Given these effects, we hypothesize that increasing the visuomotor challenge of a walking task modifies the amplitude of cutaneous reflexes.

In the present study, we compare the amplitude of tibial and SP nerve evoked cutaneous reflexes while subjects perform walking tasks that require precise foot placement and, consequently, visual guidance (Hollands and Marple-Horvat 2001).

In one experiment, subjects walked overground and across a horizontal ladder secured within a walkway. The ladder was constructed with a series of four equally spaced rungs. Rungs were 122 cm long and made of 10 cm wide × 10 cm high cedar planks and spaced 71 cm apart from each of the midpoints (see Fig. 1). Space between rungs was filled with solid panels that were flush to the surrounding floor. Rungs sat securely within a recessed edge, such that the tops of the rungs were ~3.5 cm above the floor. Subjects were instructed to step using the ball of the foot as the primary contact surface in this condition. Note that the width of the rungs made a normal heel-to-toe motion of the foot difficult. The order of the overground and ladder conditions was counterbalanced across subjects such that one-half of the subjects began the experiment with the overground condition, and the remainder started with the ladder condition. Subjects wore a full-body harness anchored to an overhead ceiling-mounted trolley system via a dynamic rock-climbing rope to reduce the chance of injury in the event of a fall during the walking tasks.

**Stepping stone experiments.** Ten subjects (7 men, 3 women; mean ± SD age = 25.2 ± 3.9 yr) underwent electrical stimulation of the SP nerve during walking, and 10 subjects (6 men, 4 women; mean ± SD age = 23.1 ± 3.7 yr) underwent electrical stimulation of the tibial nerve. All but one subject (in the SP nerve experiment) was right leg dominant. Three subjects participated in both of these experiments.

Subjects walked a distance of ~6 m in two different conditions with and without electrical stimulation of the tibial or SP nerve. In one (large target) condition, subjects walked across a series of four flat targets (15 × 30 cm; see Fig. 1). The size of these targets allowed subjects to place their entire foot inside and walk in a normal heel-to-toe manner. In the other (narrow target) condition, subjects walked across a series of four targets (30 × 10 cm; see Fig. 1) similar to the ladder rungs, but flat. Subjects were instructed to step using the ball of the foot as the primary contact surface in this condition to match the constraints imposed in the ladder condition of the other experiment. Thus the primary difference between this and the ladder condition was the raised (and thus more threatening/less stable) ladder rung. The order of the large and narrow target conditions was counterbalanced across subjects such that one-half of the subjects began the experiment with the large target condition, and the remainder started with the narrow target condition.

**Muscle, kinematic, and gait cycle timing data.** In each experiment, muscle activity was recorded with a MA300 EMG system (Motion Lab Systems, Baton Rouge, LA) at 2,000 Hz, and bilaterally, from the tibialis anterior (TA), medial gastrocnemius (MG), vastus lateralis (VL) and biceps femoris (BF). Foot contact of the right leg (i.e., stimulated) was determined using two foot switches, which were attached to the plantar surface of the foot under the head of the second metatarsal and under the calcaneus. On the right leg, infrared emitting diodes were placed facing laterally at the head of the fifth metatarsal, the midcalcaneus, the lateral malleolus, and head of the fibula (or halfway between the head of the fibula and the lateral malleolus). Kinematic data were collected at 200 Hz with an Optotrak Certus camera system (Northern Digital, Waterloo, Ontario, Canada). EMG, kinematic, and foot switch data were synchronized using LabVIEW software.

**Electrical nerve stimulation.** The right SP or tibial nerve at the ankle was electrically stimulated using a Digitimer constant current stimulator (model: DS7A, Digitimer, Hertfordshire, UK) attached to disposable bipolar silver/silver-chloride electrodes (GS27, Bio-Medical Instruments, Warren, MI). Stimulation was applied in trains of
5 × 1.0 ms pulses at 300 Hz and at a current of 2.5 × the subject’s radiating threshold (RT) (Bagna and Bouyer 2011; Haridas et al. 2005; Zehr et al. 1997). The RT was defined as the point at which a sensation spread across the dermatome distal to the electrode. This threshold was tested while subjects were seated and again while standing. In the ladder experiment, this resulted in an average applied current of 8.2 ± 4.3 mA (range = 4.3–16.9 mA) and 9.4 ± 2.8 mA (range = 6.8–13.7 mA) for the tibial and SP nerves, respectively. In the stepping stone experiment, this resulted in an average applied current of 7.8 ± 1.8 mA (range = 5.7–11 mA) and 8.9 ± 1.6 mA (range = 6.8–11.8 mA) for the tibial and SP nerves, respectively.

For the tibial nerve, stimulation was delivered between the Achilles tendon and the medial malleolus. For the SP nerve, stimulation was delivered at the talar-navicular junction. Stimulation was manually triggered, once per walking trial, by an experimenter via LabVIEW software and applied randomly across a predefined gait cycle. Specifically, electrical nerve stimulation was delivered between toe-off from the first ladder rung or target (depending on the experiment) to toe-off from the third ladder rung or target (see Fig. 1). Stimulation was delivered in a similar range for the overground condition of the ladder experiment. A total of 30 nonstimulation walking trials were also recorded. Ten occurred at the beginning of each walking condition, and the remaining 20 were randomly interspersed amongst 108 stimulation trials per condition. Between the conditions, the RT was reassessed. If the threshold was different, current was increased or decreased accordingly to maintain the 2.5 × RT value. This seldom occurred, and when it did the RT was on average only 0.1 mA different, suggesting that the RT remained stable throughout testing.

**Data analysis.** To process cutaneous reflexes we used a MATLAB routine developed and described in detail by Bagna and Bouyer (2011). Briefly, EMG data were rectified and low-pass filtered using a nine-point moving average filter. The EMG signal was then divided into different gait cycles based on the toe-offs, as determined by the foot switch data (or kinematic data in one subject). Toe-off was used instead of heel contact to retain cross-comparability between the overground and ladder conditions and the large and narrow target conditions. In the ladder condition, heel contact was less discernible due to the small width of the ladder rung and nature of the foot-rung interaction. This was also the case for the narrow target condition due to the imposed stepping constraint.
Next, the EMG of stimulated and nonstimulated trials were identified, separated, and normalized to the duration of the predefined gait cycle. All nonstimulated trials were subtracted from each stimulated trial (Fig. 2). Note that we used all 30 nonstimulated trials compared with only 10 by Bagna and Bouyer (2011). This produced 30 difference signals (Fig. 2B) for each stimulation trial. Subsequently, a confidence index value (CIV) was calculated for each sample between 40 and 200 ms poststimulation, which measured the agreement among the difference signals by counting the proportion that were positive and negative (Bagna and Bouyer 2011). The sum of this proportion provides a CIV at each point in time of the signal. For each sample k from 40 to 200 ms, the CIV is calculated based on the following formula:

$$CIV(k) = \frac{\sum_{i=1}^{N} [\Delta S_i(k) > 0]}{N}$$

where N equals the number of subtracted gait cycles and \(\Delta S_i(1 \leq i \leq N)\) represents the difference signals, and 0 \(\leq CIV \leq 1\).

A CIV of 1 indicates that 100% of the difference signals agree that the stimulated signal is above the nonstimulated (control) EMG activity. In contrast, a CIV of 0 indicates that 100% of the difference signals agree that the stimulated signal is below the nonstimulated EMG activity. A cutaneous reflex response was identified when greater than 85% (or >25/30) of difference signals had the same sign. Thus a CIV \(\geq 0.85\) represented an excitatory cutaneous reflex, and a CIV \(\leq 0.15\) represented an inhibitory cutaneous reflex. Reflex onset latency is the point in time when the CIV reaches these values. Figure 2 illustrates this process for a representative stimulation trial of one subject.

Cutaneous reflex amplitude was calculated by dividing the reflex area by the reflex duration. The minimum duration for a significant reflex response was determined based on false positives associated with running the nonstimulation trials through the routine (Bagna and Bouyer 2011). Only cutaneous reflexes that were longer than this duration, which varied based on the muscle of interest, were analyzed. Cutaneous reflexes occurring between 50 and 120 ms poststimulation were then sorted into 10 bins, each spanning 10% of the gait cycle (i.e., bin 1 = 1–10%, bin 2 = 11–20%, etc.). The average reflex amplitude of each bin was then calculated, and amplitude normalized to the maximum EMG activity from the mean nonstimulated trials in the overground or large target conditions in the ladder and stepping stone experiments, respectively. Each muscle and subject was processed separately. The MATLAB routine also determined mean background EMG activity from nonstimulated trials at the same onset and duration of each reflex (Bagna and Bouyer 2011). Background EMG activity was separated into phase bins, and amplitude normalized similar to the cutaneous reflexes.

From the kinematic data we calculated ankle joint angle throughout the gait cycle. Ankle joint angle was subsequently time normalized and amplitude normalized to the maximum plantar flexion angle during the gait cycle. The kinematic data were also used as a backup for determining foot contact events in case the foot switches failed or were too noisy in a given trial.

**Statistical analysis.** We log-transformed the cutaneous reflex amplitude data for the statistical analysis due to the fact that these data are not normally distributed (Duyssens et al. 1996; Hoogkamer et al. 2012). Separate two-way repeated-measures ANOVAs (phase \(\times\) condition) were performed for each muscle to compare cutaneous reflex amplitude data for the statistical analysis due to the fact that these data are not normally distributed (Duyssens et al. 1996; Hoogkamer et al. 2012). Separate two-way repeated-measures ANOVAs (phase \(\times\) condition) were performed for each muscle to compare cutaneous reflex amplitude data for the statistical analysis due to the fact that these data are not normally distributed (Duyssens et al. 1996; Hoogkamer et al. 2012).
amplitude across phase (bins 1–10) and condition (overground and ladder or large targets and narrow targets, depending on the experiment). If warranted, Tukey’s post hoc tests were used for significant main effects. Preplanned contrasts comparing the two conditions across each of the 10 phase bins were performed when a significant interaction was found. Background EMG amplitude was compared in a similar manner. In addition, we performed linear regression to determine the relationship between cutaneous reflex and background EMG amplitude during the two conditions of both experiments for each nerve-muscle combination. Cutaneous reflexes during walking are typically evoked while on a treadmill. The results in the overground walking condition in our study can be compared with the results of these studies to determine similarities. Thus we also analyzed this condition separately. Specifically, significant differences from zero for cutaneous reflex amplitudes were determined using t-tests for each phase bin in the overground walking condition of the ladder experiment. This method is similar to previous work (e.g., van Wezel et al. 1997). All statistical analyses were performed using JMP 10 software, and the significance criterion was set with an alpha level of 0.05.

RESULTS
In the ladder experiments, the mean ± SD number of electrical stimuli per phase bin in the overground and ladder conditions across subjects for the tibial nerve was 10.3 ± 1.8 and 9.9 ± 1.8, respectively, and for the SP nerve was 10.7 ± 2.5 and 10.4 ± 2.3, respectively. In the stepping stone experiments, the mean ± SD number of electrical stimuli per phase bin in the large and narrow target conditions across subjects for the tibial nerve was 10.2 ± 2.5 and 10.5 ± 2.3, respectively, and for the SP nerve was 10.5 ± 3.2 and 10.3 ± 3.0, respectively. Thus manual triggering of the electrical nerve stimulation was successful in equally distributing stimuli across the gait cycle.

Cutaneous reflexes were evident following electrical stimulation to both the tibial and SP nerves in each experiment. The average onset latencies of these reflexes ranged from 81 to 91 ms across all muscles and conditions.

Ladder experiment: tibial nerve stimulation. Cutaneous reflex amplitude (bars) and background muscle activity (lines) across the phases in the overground walking condition are illustrated in Fig. 3 for comparison with previous treadmill walking studies. Reflexes were present in each muscle of the ipsilateral (iTA, iVL, iMG, iBF; Fig. 3A) and contralateral (cTA, cMG, cVL, cBF; Fig. 3B) legs and depended on the phase of the gait cycle (P < 0.05). Reflex amplitudes in iTA were high in early and late stance. Similar reflex facilitation was evident during stance in iVL and iBF. In contrast, iMG reflexes were facilitated during swing. In each ipsilateral muscle, reflexes were not significantly different from zero when background EMG was at, or close to, its peak. Cutaneous reflexes in contralateral muscles were evident in both stance and swing phase, regardless of background activity.

The horizontal ladder imposed constraints on the walking pattern, which may explain the small difference in gait speed between the conditions (overground = 1.55 ± 0.20 m/s vs. ladder = 1.38 ± 0.17 m/s). Furthermore, the ipsilateral ankle was more plantar flexed (i.e., closer to 1.0 in Fig. 4F) during swing phase and midstance.

Figure 4 shows group mean normalized reflex amplitude (bars) and normalized background EMG activity (line) in the overground and ladder conditions for tibial nerve stimulation. Note that only muscles that demonstrated significant differences between walking conditions are shown. Cutaneous reflex amplitude of iTA was significantly different between the overground and ladder conditions across phase bins (condition × phase interaction: F9,151 = 4.8, P < 0.0001). Reflex amplitude during phases 2–4 (corresponding to mid- to late ipsilateral swing) and phase 9 (corresponding to late ipsilateral stance) was greater while walking on the ladder compared with overground. In phase 5 (swing-to-stance transition), there was a reduction in the excitatory response in the ladder condition compared with overground. Cutaneous reflex amplitude of the other ipsilateral ankle muscle, iMG, was also significantly different between the overground and ladder conditions across phase bins (condition × phase interaction: F9,150 = 2.7, P = 0.006). Specifically, a large inhibitory reflex was present in midswing (phase 3) in the ladder condition compared with reflex facilitation overground (although background activity was very low in the overground condition in this phase, thereby reducing the likelihood of reflex suppression). A similar reflex response was seen in midstance (phase 7), whereas there was a greater inhibitory reflex in the ladder condition in phase 8. The only other ipsilateral muscle that demonstrated a significant condition × phase interaction was iBF (F9,138 = 2.5, P = 0.013). Post hoc contrasts showed that cutaneous reflex amplitude was greater while walking on the ladder in early swing (phase 2), but reduced such that inhibition was evident in early stance (phase 6) compared with overground.

There were fewer effects of condition in contralateral muscles (Fig. 4). A large excitatory cutaneous reflex overground in cMG was replaced by an inhibitory reflex on the ladder during midswing (phase 3; condition × phase interaction: F9,141 = 4.2, P < 0.0001) of the ipsilateral leg (corresponding to midstance of the contralateral limb). In cVL, cutaneous reflex amplitude was reduced on the ladder compared with overground during late ipsilateral/early contralateral stance (phase 9; condition × phase interaction: F9,149 = 2.1, P = 0.030).

In muscles where there was a significant difference in cutaneous reflex amplitude between walking conditions, we also found differences in background muscle activity (Fig. 4). Specifically, there was a significant condition × phase interaction for iTA background activity (F9,152 = 12.4, P < 0.0001). Contrasts showed that background activity was lower in phases 3 and 4, but greater in phases 6 and 9, in the ladder condition compared with overground. Background iMG muscle activity in phases 1–5 was greater when stepping on the ladder rungs (condition × phase interaction: F9,150 = 8.2, P < 0.0001). In cMG, background muscle activity was greater while walking on the ladder in phases 6–10 (condition × phase interaction: F9,143 = 12.5, P < 0.0001). There were no significant differences in background muscle activity based on condition in iBF or cVL (P > 0.05).

Stepping stone experiment: tibial nerve stimulation. In this experiment, the requirement to step with the ball of the foot in the narrow target condition led to greater ankle plantar flexion during ipsilateral swing phase. Despite this finding, gait speed was well matched between walking conditions (large targets = 1.55 ± 0.19 m/s vs. narrow targets = 1.51 ± 0.16 m/s).

Figure 5 illustrates the group mean normalized reflex amplitude (bars) and normalized background activity (lines) in the large target (gray) and narrow target (black) conditions in this
Fig. 3. Tibial nerve evoked cutaneous reflex amplitude (bars) and background muscle activity (lines) of all ipsilateral (i; A) and contralateral (c; B) muscles for the overground walking condition of the ladder experiment (means ± SE). Note that the gait cycle spans from ipsilateral toe-off to subsequent ipsilateral toe-off, such that swing phase occurs in phase bins 1–4 (and into early bin 5). Each phase bin spans 10% of the gait cycle (i.e., bin 1 = 1–10%, bin 2 = 11–20%, etc.). Foot contact occurred at a phase of 41.9 ± 3.0%. *Significant cutaneous reflex amplitude differences from zero based on t-tests (P < 0.05). BF, biceps femoris; MG, medial gastrocnemius; TA, tibialis anterior; VL, vastus lateralis.

experiment. Striking differences in cutaneous reflex amplitude between conditions were evident during ipsilateral swing phase at a time when the ankle was in greater plantar flexion in the narrow target condition due to the precision required to perform the task. Specifically, the large suppressive iTA cutaneous reflex responses while walking across the large targets were absent in phases 3 and 4, and instead, replaced with small excitatory responses while walking across the narrow targets ($F_{9,138} = 3.6, P = 0.0005$). A two-way ANOVA also showed that the iMG reflex amplitude was significantly different between conditions in a phase-dependent manner (condition × phase interaction: $F_{9,139} = 2.9, P = 0.003$). In contrast, however, there were large inhibitory cutaneous reflex responses when walking across the narrow targets in the same phases compared with the facilitation seen while walking across the large targets.

Based on two-way ANOVAs there were no significant effects of condition for iBF, cVL, or cMG ($P > 0.05$), despite finding differences between conditions in the ladder experiment for these muscles. There were also no effects of walking condition on cutaneous reflex amplitude in the remaining muscles ($P > 0.05$).

An analysis of background muscle activity revealed a significant condition × phase interaction for iTA ($F_{9,137} = 4.3, P < 0.0001$). Background activity was reduced in phases 3 and 4 when subjects had to step on the narrow targets relative to the large targets (Fig. 5A). In phases 2–5 and 8, iMG background activity was greater in the narrow target condition (condition ×
phase interaction: $F_{9,130} = 6.2, P < 0.0001$). There were no effects of condition on the background muscle activity in iBF or cVL ($P > 0.05$). However, cMG background activity was greater in the narrow target condition in phases 8–10 (condition $\times$ phase interaction: $F_{9,143} = 11.5, P < 0.0001$).

**Ladder experiment: SP nerve stimulation.** Normalized cutaneous reflex amplitude (bars) and background muscle activity (lines) across the phases in the overground walking condition are illustrated in Fig. 6. Reflexes were present in the majority of muscles of the ipsilateral and contralateral legs following SP nerve stimulation ($P < 0.05$). Responses in iTA were heavily suppressed in late swing phase, whereas in iVL and iBF strong facilitation was present. Despite the presence of excitatory and inhibitory iMG reflexes, large intersubject variability prevented these responses from being significantly different from zero. Significant reflexes were largely absent in cTA and cVL.

Changes in ipsilateral ankle joint angle were identical to the other ladder experiment. Greater ankle plantar flexion was observed during swing and midstance phases (Fig. 7F). Again, there was a minor difference in gait speed between walking conditions (overground = $1.57 \pm 0.14$ m/s vs. ladder = $1.40 \pm 0.08$ m/s), likely due to the constraints associated with the ladder.

The amplitude of cutaneous reflexes elicited by SP nerve stimulation varied depending on the walking condition and phase of the gait cycle in several muscles. Figure 7 shows group mean normalized reflex amplitude (bars) and normalized background activity (lines) in the overground (gray) and ladder (black) conditions. There was a significant condition $\times$ phase interaction for iTA ($F_{9,154} = 4.0, P = 0.0001$). As illustrated in Fig. 7A, reflex amplitude was larger early in ipsilateral swing (phase 2) and toward late stance (phase 9) when subjects had to step on the ladder rungs. In phases 3 and 4, the large inhibitory reflex responses overground gave way to excitatory reflexes in the ladder condition. In iMG, responses changed from being facilitated during ipsilateral swing phase to being suppressed during early to midstance phase in both walking conditions (see Fig. 7B). However, there were noticeable differences between conditions ($F_{9,163} = 2.0, P = 0.038$). In particular, there was a large amplitude excitatory reflex in the
Fig. 5. Tibial nerve evoked cutaneous reflex amplitude (bars) and background muscle activity (lines) across the gait cycle in the large target (gray lines/bars) and narrow target (black lines/bars) walking conditions (means ± SE). Only ipsilateral (i) and contralateral (c) muscles that demonstrated differences in reflex amplitude between walking conditions in the ladder experiment are shown for this experiment. A: iTA; B: iMG; C: iBF; D: cMG; E: cVL. Muscle abbreviations are the same as in Fig. 3. Note that the gait cycle spans from ipsilateral toe-off to subsequent ipsilateral toe-off such that swing phase occurs in phases 1–4 (and into early bin 5). Foot contact occurred at a phase of 42.9 ± 6.7% for the large target condition and 46.8 ± 6.2% for the narrow target condition. *Significant differences in cutaneous reflex amplitude between walking conditions (post hoc tests, P < 0.05). **Significant differences in background muscle activity between walking conditions (post hoc tests, P < 0.05). F: ankle joint angles are time normalized to the gait cycle and amplitude normalized to maximum ankle plantar flexion angle. Dashed lines represents SE.

swing-to-stance transition (phase 5) while on the ladder compared with a small inhibitory response in the overground condition. In midstance (phase 8), there was a greater inhibitory cutaneous reflex response while on the ladder.

Walking condition also influenced thigh muscle cutaneous reflex amplitude. Specifically, there was a significant condition × phase interaction for both iVL (F\(_{9,165} = 3.0, P = 0.003\)) and iBF (F\(_{9,161} = 2.2, P = 0.025\)). At a time when iVL would be involved in extending the leg and in the loading response (phases 4 and 5; swing-to-stance transition), post hoc tests demonstrated that reflex amplitude was significantly reduced, or the response switched to inhibition, on the ladder relative to overground (Fig. 7C). iBF reflex amplitude was substantially larger on the ladder during mid- to late stance (phases 8 and 9).

On the contralateral limb, cTA demonstrated a significant condition × phase interaction (F\(_{9,158} = 2.0, P = 0.042\)). Specifically, reflex amplitude was greater while on the ladder in late contralateral stance (phase 4; corresponding to late ipsilateral swing). However, there was no effect of walking condition on the remaining muscles (P > 0.05).

Ipsilateral ankle background muscle activity in this experiment depended on the walking condition and phase (iTA: F\(_{9,154} = 8.8, P < 0.0001\); iMG: F\(_{9,161} = 9.1, P < 0.0001\). Differences were evident in phases 2–4, 8, and 9 for iTA and phases 1–5 for iMG (Fig. 7, A and B, line graphs). There were also significant interactions for iVL (F\(_{9,164} = 2.5, P = 0.010\), iBF (F\(_{9,160} = 2.0, P = 0.039\), and cTA (F\(_{9,158} = 7.0, P < 0.0001\). Post hoc tests showed that differences were present in phases 6–8 for iVL, phases 1 and 7–9 for iBF, and phases 7–9 for cTA. In iVL and iBF, these differences manifested as greater background activity while walking in the ladder condition, whereas the opposite was true for cTA (Fig. 7, C, D, and E).

There were no effects of walking condition on the background muscle activity of cBF or cVL (P > 0.05); however, there was a significant interaction for cMG (F\(_{9,157} = 14.8, P < 0.0001\)) such that differences were present in phases 4 and 6–10 (results not shown on figure).

Stepping stone experiment: SP nerve stimulation. The ipsilateral ankle joint angle exhibited greater plantar flexion in swing and midstance phases in the narrow target condition due to
the precision requirement of the task (Fig. 8F). This was similar to the other stepping stone experiment. Again, gait speed was well matched between walking conditions (large targets = 1.39 ± 0.08 m/s vs. narrow targets = 1.37 ± 0.11 m/s).

The cutaneous reflex amplitude of several leg muscles changed as a function of the two walking conditions in a phase-dependent manner. Figure 8 illustrates group mean normalized reflex amplitude (bars) and normalized background activity (lines) in the large target (gray) and narrow target (black) conditions for SP nerve stimulation. Differences in the amplitude of cutaneous reflexes between the narrow and large target conditions were present only during ipsilateral swing phase and into the swing-to-stance transition (iTA): $F_{9,138} = 3.6, P = 0.0005$; iMG: $F_{9,117} = 4.5, P < 0.0001$). For iTA (Fig. 8A), there were excitatory cutaneous reflexes in the narrow target condition during mid- and late ipsilateral swing (phases 3 and 4) compared with large inhibitory responses in the large target condition. In contrast, iMG cutaneous reflex responses (Fig. 8B) were inhibitory in the narrow target condition from midswing to the swing-to-stance transition (phases 3–5), while, albeit small, responses in the large target condition were excitatory.

A two-way ANOVA indicated a significant condition $\times$ phase interaction for iVL ($F_{9,144} = 4.2, P < 0.0001$), where post hoc contrasts revealed greater reflex amplitude in the narrow target condition in phase 4 (corresponding to late
ipsilateral swing). Differences in phase 5 almost reached significance ($P = 0.054$). In iBF, there was also a significant condition $\times$ phase interaction ($F_{9,139} = 3.0, P = 0.003$). Post hoc contrasts indicated that the reflex response was inhibitory in the narrow target condition in midipsilateral swing (phase 3) compared with excitatory in the large target condition.

Unlike the ladder experiment, there were no effects of walking condition on cTA in this experiment (no interaction: $F_{9,139} = 1.2, P = 0.276$; no condition main effect: $F_{1,136} = 0.04, P = 0.842$). The opposite finding was found for cMG. In the ladder experiment, there were no effects of walking condition. In this experiment, however, there was a condition main effect ($F_{1,137} = 4.4, P = 0.039$) such that cutaneous reflex amplitude was lower in the narrow compared with the large target condition. These results are not shown in Fig. 8, as we have restricted the presentation of muscles to those where there was a significant interaction in the ladder experiment (see Fig. 7). There were also no effects of walking condition in cBF and cVL ($P > 0.05$).

Background muscle activity in muscles with differences in cutaneous reflex amplitude between walking conditions (Fig. 8) depended on the muscle in question and the phase of the gait cycle. For instance, background muscle activity of iBF remained similar between walking conditions (no interaction: $F_{9,138} = 1.3, P = 0.265$; no condition main effect: $F_{1,136} = 2.0, P = 0.156$). In contrast, iVL ($F_{9,142} = 3.4, P = 0.0009$), iTA ($F_{9,139} = 9.1, P < 0.0001$), and iMG ($F_{9,120} = 20.0, P < 0.0001$) each exhibited significant condition $\times$ phase interactions. As illustrated in Fig. 8, post hoc tests indicated differences in background muscle activity in phases 1–5 for iMG, phases 3 and 4 for iTA, and phases 7 and 10 for iVL.

In cMG, background activity was larger in phases 7–9 in the narrow target condition relative to the large target condition (condition $\times$ phase interaction: $F_{9,142} = 16.1, P < 0.0001$; results not shown in figure). Background muscle activity in cTA was greater while walking on the large targets in similar phases (Fig. 8; condition $\times$ phase interaction: $F_{9,137} = 4.8, P < 0.0001$).
Relationship between background EMG activity and cutaneous reflex amplitude. We found significant linear regressions between background EMG activity and SP/tibial nerve cutaneous reflex amplitude in both experiments. However, the $r^2$ values were very low, explaining less than 25% of the variance with a few exceptions (see Table 1). Many of the significant regressions demonstrated negative slopes, indicating that reflex amplitude decreased with greater background EMG activity. It is also clear from qualitative observation that reflex amplitude did not closely follow the background activity (see Figs. 4, 5, 7, and 8). Furthermore, there were several instances where the sign of the slope was opposite between the two different walking conditions (e.g., overground vs. ladder).

**DISCUSSION**

The nervous system must integrate the input it receives from vision with vestibular and somatosensory sources to accurately estimate the state of the body and limbs, and to adjust to the nature of the ground terrain for smooth and efficient locomotion. In the present study, we were interested in the interaction between visual and cutaneous feedback. Specifically, we sought to determine whether increasing the need to visually guide foot placement while walking alters the amplitude of cutaneous reflexes elicited by electrical stimulation of the tibial and SP nerves, which transmit cutaneous feedback from the plantar and dorsal foot surfaces, respectively. We found that cutaneous reflex amplitude was modulated, in a phase-dependent manner, between overground walking and walking across a horizontal ladder that required subjects to use precision foot placement and accommodate different terrain (i.e., narrow, raised ladder rungs). Furthermore, we discovered that cutaneous reflex amplitude was modulated based on the stepping constraints associated with walking across a series of flat targets. These results extend the understanding of context- and task-dependent modulation of cutaneous reflexes (Burke et al. 1991; Duyssens et al. 1993; Haridas et al. 2005; Hoogkamer et al. 2012; Lamont and Zehr 2006) to visually guided walking.
reflex activity was facilitated in early and midswing phase. For iMG, we found that reflex responses are often reported (e.g., Baken et al. 2006; Haridas et al. 2005; Hoogkamer et al. 2012). Of note, however, is that this suppression was evident in the large target condition of the stepping stone experiment (see Fig. 5). For iTA, we found that reflex activity was facilitated in early and midswing phase. This is relatively similar to previous research on the treadmill, which demonstrated facilitation more toward late swing (Zehr et al. 1997). Furthermore, reflex activity in iVL was facilitated during midswing and midstance phases (Fig. 3), as also shown by Zehr et al. (1997). There were also similarities for the reflex responses in contralateral muscles. For instance, reflex activity in cTA was facilitated during stance (corresponding to ipsilateral swing), as previously reported (van Wezel et al. 1997). However, we failed to find the typical suppressed reflex response in iBF during late swing (van Wezel et al. 1997).

Comparison of cutaneous reflexes elicited on normal ground with those during treadmill walking. The overground condition in our ladder experiment provides an opportunity to compare cutaneous reflex modulation between treadmill walking, which most research studies use, and normal overground walking. While gait speed is constrained to ~1.1 m/s when using a treadmill (Bagna and Bouyer 2011; Baken et al. 2006; Duyssens et al. 1990; Haridas et al. 2005; Hoogkamer et al. 2012; van Wezel et al. 1997; Zehr et al. 1997), our subjects walked slightly faster between 1.4 and 1.6 m/s. Nevertheless, there are several similarities in the pattern of cutaneous reflex modulation between overground and treadmill walking. With tibial nerve stimulation (Fig. 3) we observed the typical large excitatory reflex activity of iTA in late stance (van Wezel et al. 1997; Yang and Stein 1990; Zehr et al. 1997). Although van Wezel et al. (1997) and Yang and Stein (1990) also report strong suppression in this muscle during late swing and the swing-to-stance transition, only 5/10 of our subjects showed this pattern, which explains why the reflex amplitude was not significantly different from zero. Intersubject differences in reflex responses are often reported (e.g., Baken et al. 2006; Hoogkamer et al. 2012). Of note, however, is that this suppression was evident in the large target condition of the stepping stone experiment (see Fig. 5). For iMG, we found that reflex activity was facilitated in early and midswing phase.

### Table 1. Results of linear regression analysis comparing the relationship between background EMG activity and reflex amplitude in the ladder (overground and ladder conditions) and stepping stone (narrow and large target conditions) experiments

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Condition</th>
<th>Slope</th>
<th>Y-intercept</th>
<th>r²</th>
<th>Slope</th>
<th>Y-intercept</th>
<th>r²</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cBF</td>
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<td>0.30†</td>
<td>0.44</td>
<td>0.04</td>
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<td>NS</td>
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<td>NS</td>
<td></td>
<td>1.51</td>
<td>-0.09</td>
<td>0.36†</td>
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</tbody>
</table>

SP, superficial peroneal; c, contralateral; i, ipsilateral; BF, biceps femoris; MG, medial gastrocnemius; TA, tibialis anterior; VL, vastus lateralis; NS, not significant. Significant r² values: *P < 0.05, †P < 0.01.

This is relatively similar to previous research on the treadmill, which demonstrated facilitation more toward late swing (Zehr et al. 1997). Furthermore, reflex activity in iVL was facilitated during midswing and midstance phases (Fig. 3), as also shown by Zehr et al. (1997). There were also similarities for the reflex responses in contralateral muscles. For instance, reflex activity in cTA was facilitated during stance (corresponding to ipsilateral swing), as previously reported (van Wezel et al. 1997). However, we failed to find the typical suppressed reflex response in iBF during late swing (van Wezel et al. 1997).

Cutaneous reflex responses of the ipsilateral thigh muscles were highly comparable to treadmill walking for SP nerve stimulation (van Wezel et al. 1997; Zehr et al. 1997). Specifically, we found iVL reflex activity was facilitated in mid- to late swing phase (although we also show facilitated activity during mid- to late stance that has not been reported previously). In addition, iBF reflex activity was facilitated throughout swing phase and also during mid- to late stance. Cutaneous reflex responses in iTA demonstrated only minor similarities between overground walking in our experiment and previous treadmill studies. In particular, we found strong suppression in late swing phase (van Wezel et al. 1997; Zehr et al. 1997), but not the typical suppression seen in the stance-to-swing transition and into early swing phase (Zehr et al. 1997). In iMG there was evidence of reflex suppression in early stance, but it did
not reach significance. During treadmill walking iMG reflex activity is normally suppressed in early and midstance and facilitated in late swing (Zehr et al. 1997).

Taken together, the patterns of cutaneous reflex modulation are relatively similar between overground and treadmill walking. Importantly, this suggests that cutaneous reflex modulation is robust across experimental paradigms, such that the findings from treadmill studies can be extended to normal overground walking situations. Differences in stimulation intensity, analysis techniques, gait speed, optic flow patterns and constraints associated with a treadmill may account for the minor discrepancies between these paradigms.

**Precision and terrain requirements modify cutaneous reflexes while walking.** Walking on the horizontal ladder and narrow flat targets required greater foot placement precision relative to the overground and large target conditions, respectively. In both cases strong gaze and foot coupling is required (Hollands and Marple-Horvat 2001). The difference in precision led to changes in ankle joint trajectory during swing phase. Specifically, we saw increased ankle plantar flexion (as illustrated by the joint angle deviation between ~10–40% of the gait cycle in Figs. 4, 5, 7, and 8), which resembles increased wrist plantar flexion seen in cats when walking on a ladder (Beloozerova et al. 2010) and is similar to preshaping of the hand while reaching to objects of different sizes (Jakobson and Goodale 1991). Interestingly, reflex differences between conditions in each of our experiments were most prevalent during the swing phase. For instance, large inhibitory iTA reflex responses while walking overground were replaced by excitatory responses when walking across the ladder and in the narrow target conditions in response to tibial and SP nerve stimulation. On the other hand, large inhibitory iMG reflex responses in the ladder and narrow target conditions were present in similar swing phases compared with relatively small excitatory responses in the other conditions. Together, this would facilitate ankle dorsiflexion to prevent tripping on the ground or ladder rungs. Most reflex responses in the conditions of the two experiments requiring greater precision (i.e., ladder and narrow targets) were similar during swing phase. However, for SP nerve stimulation there was clear facilitation of iMG responses in the ladder condition, whereas there were inhibitory responses in the same muscle in the narrow target condition. The ladder rungs may require more plantar flexion (“grasping”) than the flat narrow targets, which could explain this difference.

The ladder rungs also decreased stability (and increased task difficulty) because there was less foot-surface contact due to the small rung width and elevated construction. Therefore, improper foot placement while walking on the ladder rungs would increase the risk of ankle injury and/or tripping. Consequently, ladder walking may be perceived as more threatening. While many differences in reflex amplitude between conditions in the ladder and the stepping stone experiments were present during swing phase, the additional changes during ipsilateral stance when walking on the ladder could be attributed to a change in threat or decreased stability. In response to SP nerve stimulation, we found a substantially greater inhibitory reflex on the ladder during mid- to late stance (phase 8) in iMG relative to the overground condition (Fig. 7B). This reflex response was also seen following tibial nerve stimulation and could serve to decrease forward acceleration (Jansen et al. 2012). It also occurred when the ankle was in a more plantar flexed posture compared with overground walking (~70–80% of gait cycle; Fig. 7F). An increase in iTA reflex amplitude on the ladder in late stance, coupled with increased reflex amplitude in iTA (seen following both tibial and SP nerve stimulation), may facilitate a lift-off withdrawal action. This would replace the typical push-off seen on normal ground, which would be inappropriate given the nature of the ladder rungs. Ultimately, we found no generalized increase or decrease in cutaneous reflex amplitude with the ladder condition, suggesting a functional modification by the nervous system to accommodate the nature of the terrain (Haridas et al. 2005).

Changes in the amplitude of cutaneous reflexes have previously been attributed to walking in conditions associated with greater postural threat, suggesting a degree of context-dependent modulation (Haridas et al. 2005, 2006, 2008). For example, Haridas et al. (2008) demonstrated that a mechanical perturbation to the foot dorsum during walking with increased postural threat (i.e., arms crossed plus perturbation condition) led to larger cutaneous reflex amplitude in cMG and less suppression in iTA when evoked by electrical stimulation of the SP nerve. In contrast, increased threat appears to reduce H-reflex gain. Llewellyn et al. (1990) found attenuated soleus H-reflexes (~40% with respect to background activity) when walking on a narrow, elevated beam compared with regular treadmill walking. This task was somewhat similar to ours in that the narrow beam was more visually demanding due to the restriction in foot placement.

**Possible neuronal mechanisms.** The question arises as to what are the neuronal mechanisms responsible for the changes in cutaneous reflex amplitude during the visually guided walking tasks. Differences between walking conditions may have resulted from fluctuations in motoneuron pool excitability within the spinal cord, reflected by changes in background EMG activity. However, there are several reasons why changes in motoneuron pool excitability cannot explain our findings. First, there were several instances where there was no difference in background EMG activity between conditions in a particular phase, yet the amplitudes of cutaneous reflexes were significantly altered. Second, $r^2$ values from the linear regression between reflex amplitude and background EMG activity were very small, explaining less than 25% of the variance in most cases. Although cutaneous reflex amplitude is known to vary with background EMG activity during standing, little correlation during walking has been found in other studies (Duyens et al. 1993; Komiymama et al. 2000; Lamont and Zehr 2006; van Wezel et al. 1997). Third, the slopes of the regressions were often negative, suggesting that cutaneous reflex amplitude was greater with reduced background activity. This is opposite to the concept of automatic gain compensation, which argues that reflex activity would be larger with greater background EMG activity (Matthews 1986).

In humans, TMS induced TA MEPs are modulated during walking, suggesting a corticospinal influence on muscle activity (Schubert et al. 1997). This is further supported by the work of Petersen et al. (2001), who reported a suppression of ongoing TA muscle activity during swing phase using subthreshold TMS, which likely activates inhibitory cortical interneurons. Visual feedback regarding the environment, which is processed in extrastriate visual areas, can alter the excitability of cortical regions giving rise to descending tracts (Drew et
al. 2008). In fact, neurons from multiple brain regions discharge rhythmically when cats step from rung to rung on a horizontal ladder, including the motor and posterior parietal cortices (Amos et al. 1990; Belozerova and Sirota 1993, 2003) and the cerebellum (Marple-Horvat and Criado 1999). A similar effect of visual feedback on corticospinal neurons is also likely in humans. When precise foot placement was required during treadmill walking, Schubert et al. (1999) demonstrated that TMS-induced TA and MG MEPs were modulated, in a phase-dependent manner, compared with normal treadmill walking.

There is evidence to suggest that a transcortical pathway mediates cutaneous reflexes during walking. Electrical stimulation of the sural nerve facilitates TA muscle responses evoked by TMS during swing phase when the applied magnetic stimulation is timed to when the cutaneous input reaches the cortex (Christensen et al. 1999; Pijnappels et al. 1998). Evidence based on the differential effects of TMS vs. intracranial electrical stimulation also supports this notion. TMS, but not transcortical electrical stimulation, is sensitive to cortical excitability, and sural nerve stimulation only facilitated MEPs following TMS (Christensen et al. 1999; Nielsen et al. 1997). A similar transcortical loop appears to be responsible for mediating ankle stretch reflexes, as demonstrated by repetitive TMS to the motor cortex and subsequent suppression of the late TA stretch reflex component elicited during the stance phase of walking (Zuur et al. 2009). In the present study, we observed substantial modulation of this muscle (and its antagonist) during swing phase, a time when the leg must be properly controlled to step on the narrow ladder rungs or targets. Furthermore, our cutaneous reflex onset latencies (~85 ms) were sufficiently long as to act via a cortical route (Nielsen et al. 1997). Therefore, the impact of cutaneous input on cortical regions may be affected by modified cortical excitability during visually guided walking.

Changes in cortical discharge activity, particularly during swing, may also act to phasically modulate the excitability of the spinal circuits onto which cutaneous afferents impinge (Bretzner and Drew 2005). Presynaptic inhibition (such as that from primary afferent depolarization) onto cutaneous afferents can originate from brain stem or cortical centers (Andersen et al. 1964; Seki et al. 2003). In the monkey, for instance, Seki et al. (2003) have shown cortically induced presynaptic inhibition of cutaneous afferents onto interneurons in the spinal cord just before and during voluntary wrist movements. Unfortunately, our experiments do not address the specific mechanisms of the cutaneous reflex modulation directly, and thus further research is warranted.

Conclusion. On the basis of our results and the visually guided nature of the walking tasks, visual input appears to predictively gate incoming cutaneous feedback such that the gain of cutaneous reflexes is modulated depending on constraints associated with foot placement. Specifically, precision requirements and the nature of the terrain can modify cutaneous reflexes elicited during walking. Further research should examine how the quality of visual feedback, such as following the development of eye disease, influences cutaneous reflexes.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES


