Feedforward neural control of toe walking in humans

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Running title:

Feedforward control of toe walking

Executive Summary:

Jakob Lorentzen PT, MSci (Health), PhD is Research Associate Professor at University of Copenhagen, Department of Neuroscience where he runs and supervises projects aiming to transfer knowledge from basic science into clinical practice.

Jakob was trained as a clinician but has for the past 10 years mainly been conducting research focusing on neurosciences, neurorehabilitation and Cerebral Palsy where he has been involved in several intervention studies focusing on how to improve cognitive and motor deficits after brain lesion.

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Jakob has authored or co-authored 25 papers in international peer-reviewed journals, numerous meeting-abstracts and book chapters for staff and scientists in neurorehabilitation.

Key points

Activation of ankle muscles at ground contact during toe walking is unaltered when sensory feedback is blocked or ground is suddenly dropped.

Responses in the soleus muscle to Transcranial Magnetic stimulation, but not peripheral nerve stimulation, are facilitated at ground contact during toe walking.

We argue that toe walking is supported by feedforward control at ground contact.

Abstract:

Toe walking requires careful control of the ankle muscles in order to absorb the impact of ground contact and maintain a stable position of the joint. The present study aimed to clarify the peripheral and central neural mechanisms involved.

Fifteen healthy adults walked on a treadmill (3.0 km/hr). Tibialis Anterior (TA) and Soleus (Sol) EMG, knee and ankle joint angles and gastrocnemius-soleus muscle fascicle lengths were recorded. Peripheral and central contributions to the EMG activity were assessed by afferent blockade, H-reflex testing, Transcranial Magnetic Brain Stimulation (TMS) and sudden unloading of the planter flexor muscle-tendon complex.

Sol EMG activity started prior to ground contact and remained high throughout stance. TA EMG activity, which is normally seen around ground contact during heel strike walking, was absent.

Although stretch of the Achilles tendon-muscle complex was observed after ground contact, this was not associated with lengthening of the ankle plantar flexor muscle fascicles. Sol EMG around ground contact was not affected by ischemic blockade of large diameter sensory afferents, or the sudden removal of ground support shortly after toe contact. Soleus motor evoked potentials elicited by TMS were facilitated immediately after ground contact, whereas Sol H-reflexes were not.

These findings indicate that at the crucial time of ankle stabilisation following ground contact, toe walking is governed by centrally mediated motor drive rather than sensory driven reflex mechanisms.

These findings have implications for our understanding of the control of human gait during voluntary toe walking.

Keywords: Ischemia, TMS, Ultrasound, Toe walking

Abbreviations: EMG, electromyography; TA, Tibialis anterior muscle; Sol, Soleus muscle.

Introduction

Human bipedal walking with the characteristic heel strike at ground contact evolved at least 3.5 million years ago (Harcourt-Smith & Aiello, 2004). We do not know whether our ancestors already at this time had the ability to walk on their toes rather than their heels, but it is a gait pattern which is commonly adapted in modern humans in an effort to make as little noise as possible when walking. For our ancestors this may have been relevant when hunting or escaping predators. When running and especially when sprinting the need for speed may cause us to switch from rearfoot to forefoot contact and elite runners can sustain running on their toes over long distances (Vaughan, 1984; Willems *et al.*, 2012). In classical ballet, standing and dancing on the toes (*en pointe*) is an integral part of the aesthetic expression, which takes years to perfect (Ahonen, 2012).

Toe walking is frequently associated with neurodevelopmental disorders, for example, cerebral palsy (CP)(Ruzbarsky *et al.*, 2016), but it is also observed in an idiopathic form with a prevalence of around 2% at the age of 5 years in typically developing (TD) children (Engstrom & Tedroff, 2012; Ruzbarsky *et al.*, 2016; Pomarino *et al.*, 2017). The causes of toe walking in children have not been clarified, but the belief that hyperactive reflexes are involved dominates current therapeutic strategies in the clinic (Tardieu *et al.*, 1989; Gross *et al.*, 2015; Kedem & Scher, 2015). However, several studies have failed to demonstrate enhanced sensory contribution to the muscle activity in toe walking children and an alternative theory, which puts emphasis on altered central control as an adaptation to demands of muscle and joint mechanics has been suggested (Berger *et al.*, 1982; Gough & Shortland, 2012; Willerslev-Olsen *et al.*, 2014).

These findings can be included as part of a broader and long standing discussion of the role of sensory feedback and central feedforward motor commands in the control of movement (Houk, 1988; Prochazka *et al.*, 2000; Hultborn, 2006; Nielsen, 2016). The idea of reflexes and voluntary movement as two separate entities, where hyperactive reflexes may disturb and interrupt voluntary motor efforts, is challenged to an increasing extent by a newer understanding of motor control, which puts emphasis on feedforward control that incorporates prediction of sensory feedback as a fundamental control measure (Shadmehr *et al.*, 2010; Franklin & Wolpert, 2011; Adams *et al.*, 2013; Wolpert & Flanagan, 2016). According to this paradigm, the nervous system establishes internal representations or models of the body and world through practice (Shadmehr *et al.*, 2010; Franklin & Wolpert, 2011;

Adams *et al.*, 2013; Wolpert & Flanagan, 2016). Using sensory feedback as error signals these internal models become increasingly precise in their prediction of the sensory consequences of movement (Shadmehr *et al.*, 2010; Franklin & Wolpert, 2011; Adams *et al.*, 2013; Wolpert & Flanagan, 2016). The internal model, prediction and feedback paradigm may also apply to toe walking where the nervous system has to precisely predict the sensory consequences of the impact with the ground in each step; given the complex dynamics of toe walking this is a challenging scenario.

Toe walking requires that the position of the ankle joint is maintained in a plantar flexed position throughout stance even though the full body weight is placed over the foot. Furthermore, the impact at ground contact with the foot in a plantar flexed position will also tend to stretch the plantar flexor tendon-muscle complex, which would be expected to elicit stretch reflexes in the ankle plantar flexors. How does the nervous system solve this challenge? Here, we explore systematically the extent to which muscles that stabilise the joint during the early stance phase of toe walking are activated through feed-forward or feed-back mechanisms. These experimental findings will allow a better understanding of the feed-forward versus feed-back control of normal toe walking and will form the basis of a better appreciation of the pathophysiological mechanisms that underlie involuntary to walking in children and adults with neurological disorders.

Methods and materials

Participants

Fifteen able-bodied participants aged 25-54 years (10 men; 5 women) participated in the study. The local ethics committee of the Greater Copenhagen area, Region H, granted approval of the study (H-16028528) and all participants provided written informed consent prior to participation. All experimental procedures conformed with the Declaration of Helsinki (except for registration in a database).

Experimental design

In the majority of experiments, participants were asked to walk barefoot on a treadmill at a speed of 3 km/h without support. In one experimental session, participants were, in addition, asked to walk barefoot over-ground in order to study the effect of sudden ground drop on

muscle activity. In all experimental sessions two minutes of data were sampled during normal walking in which participants made ground contact with the heel first (heel walking) and during toe walking in which participants were asked to make ground contact with the ball of their toes (Fig. 1). Participants were instructed not to allow the heel to make contact with the ground at any time in this latter task. Kinematic and electrophysiological (EMG) comparison of heel strike and toe strike walking revealed clear differences in the ankle dorsiflexor and plantar flexor EMG and Kinematic patterns through the gait cycle (Fig 1). During over-ground walking the EMG and Kinematic patterns were identical to those obtained during the two conditions of treadmill walking, indicating that treadmill walking provides a realistic assessment of typical human gait conditions.

In separate experimental sessions, we measured the following during heel and toe walking: 1) movement of muscle fascicles in the gastrocnemius and soleus muscles (n=10). 2) The effect on muscle activity and joint movements during block of transmission in large diameter afferents (n=7); 3) Modulation of Soleus motor evoked potentials (MEPs) and Soleus H-reflexes (n=8); 4) We analysed the Soleus EMG response during over ground walking to a sudden unexpected vertical drop (unloading) produced by downward motion of a force platform triggered by foot contact (n=6). Trials with toe and heel walking were randomized.

Motion analysis

In all experiments a motion analysis system (Qualisys, Gothenburg, Sweden) consisting of six infrared source cameras (Oqus120) was used to collect the 3D position of 14 mm reflective markers placed on both legs at the base of the little toe, the lateral malleolus, caput fibula and crista illiaca (resolution 3 megapixel). These data were used to calculate joint angles at the knee and ankle joint during gait. Additional markers were placed on the head of the participant and on ultrasound probes and magnetic coils to check for stability of the position of coils and probes throughout the experiments. It was ensured that neither ultrasound probes or magnetic coils moved more than 5 mm relative to the markers placed on the participant during any of the experiments. In some experiments, markers were also placed on the heel corresponding to the insertion of the Achilles tendon on the calcaneus bone in order to calculate changes in the length of the plantar flexor muscles and Achilles tendon during toe gait (see below).

Electromyographic (EMG) recording

EMG activity was recorded from the right leg using custom-made bipolar electrodes with small recording areas (9 mm^2) and a short bipolar inter-electrode distance (0.5 cm). The pairs of bipolar electrodes were placed on the skin over the Soleus (Sol) and Tibialis anterior (TA) muscles. The Sol electrodes were placed just distal to the heads of the gastrocnemius muscles. The TA electrodes were placed over the belly of the muscle. The skin was prepared by first brushing the skin softly with sandpaper (3M red dot; 3M, Glostrup, Denmark). EMG signals were amplified (x1000; Zerowire, Aurion, Italy) and sampled at 2000 Hz (Micro 1401 and Spike 2, Cambridge Electronic Design, UK), filtered (band-pass, 3 Hz–1000Hz), and stored on a PC for off-line analysis.

Achilles tendon tension measurements

Changes in tension of the Achilles tendon during toe and heel walking (Fig. 1) were measured in four participants with a buckle type gauge originally developed by Volker Dietz (Berger *et al.*, 1982). The gauge was fixed laterally at the tendon so that the tendon was pressed against the strain gauge bearing branch by a metal frame from the other side. Since the attachment of the gauge was painful and not acceptable for most participants, this measurement was only performed in four participants, who were able to walk with the same EMG activity pattern and kinematics with and without attachment of the gauge.

Ultrasound measurements

Two dimensional ultrasound imaging was used to monitor length changes of medial gastrocnemius (MG) and Sol muscle fibres in real time during heel and toe walking in 10 participants using the technique described by (Maganaris *et al.*, 1998). A 5 MHz B-mode ultrasound probe (Telemed, Vilnius, Lithuania) was secured using elastic, adhesive tape on the skin over the belly of the MG muscle along the longitudinal axis of the muscle. The dimensions of the probe were 10 x 2 x 2 cm and it weighed 95 g. The position of the ultrasound probe and the depth focus were adjusted so that fascicles in both the MG muscle and the underlying Sol muscle could be visualized in the same image (Fig. 2A). Images were recorded at 50 Hz. Motion analysis markers were placed on the probe in order to check for stability of recording. This ensured that muscle fascicle movements could be related only to ankle joint movement and muscle and tendon length changes (see below).

A second ultrasound probe was placed over the junction of the Achilles tendon and the MG muscle. This allowed visualization and measurement of the movement of the muscle-tendon junction (MTJ) during the gait phase (Fig. 2A) using a procedure similar to that described by (Kalsi *et al.*, 2016). The ultrasound images were imported into Matlab and the position of the MTJ was marked for each frame using custom built software (courtesy Glen Lichtwark, University of Queensland, Australia). Motion analysis markers placed on the ultrasound probe were used to reconstruct the 3D coordinates of the MTJ movement. An estimate of the length of the Triceps surae-tendon unit was calculated from changes in the knee and ankle joint movements. The Achilles tendon length was calculated from the distance between the MTJ and the insertion point of the Achilles tendon on the calcaneus.

Ischaemia

In seven participants, EMG activity and joint kinematics were recorded during 2 minutes of toe walking on the treadmill before the subject was seated and a blood pressure cuff was placed around the right thigh approximately 10 cm above the patella and inflated to 240 mmHg in order to block transmission in large diameter afferents. At regular intervals after inflation of the cuff, the soleus H-reflex was elicited, while the subject remained comfortably seated. The reflex was elicited by 1-ms electrical pulses (DH7A stimulator; Digitimer, UK) applied to the tibial nerve in the popliteal fossa using a spring-loaded ball electrode. The reference electrode (anode) was placed over the patella. When the H-reflex had diminished to less than 10% of its initial size (after 18-23 minutes of ischemia in the different participants), the subject was asked to walk for as long as possible with a similar walking pattern as before ischemia. All participants were able to walk for at least one minute with ischemia. When the subject failed to continue walking, the cuff was quickly deflated and the experiment was terminated.

Transcranial magnetic stimulation (TMS) and H-reflex testing during treadmill walking. In experiments on eight participants, TMS was applied through a figure of eight coil (loop diameter: 9 cm) over the leg area of the left motor cortex using a rapid magnetic stimulator (Magstim Rapid 2 stimulator; Magstim Company Ltd, Dyfed, UK). The coil

position and orientation over the scalp was systematically adjusted at the beginning of each experiment to find the optimal location to elicit a motor evoked potential (TMS MEP) in the Sol muscle. This was generally around 2 cm to the left of the vertex. In the beginning of each experiment the TMS MEP threshold was determined while the subject performed a plantar flexion while standing corresponding to approximately 15% of maximal voluntary effort using rectified and integrated Sol EMG activity as visual feedback. In subsequent measurements, a stimulus intensity of 1.2 x TMS MEP threshold was used. The coil was fixed with respect to the head by a harness (modified from Balgrist Tech, Zurich, Switzerland), that was worn throughout the experiment. A pressure-sensitive resistor placed under the heel or the forefoot of the right foot was used as a timing signal to trigger the magnetic stimulator. Magnetic stimuli were applied at different times (every 10 ms between 0 and 100 ms after ground contact and every 50 ms between 100 and 700 ms after ground contact) during either heel or toe walking. Magnetic stimuli were delivered every 2-3 strides until 15 TMS MEPs were elicited for each time in relation to ground contact.

In the same experimental session, but in separate trials, Sol H-reflexes were elicited during heel and toe walking triggered on ground contact similar to TMS. Electrical stimuli (1-ms pulses; DH7A stimulator, Digitimer, UK) were applied through a spring-loaded ball electrode securely fixed over the tibial nerve in the popliteal fossa. The anode was a metal plate, which was strapped to the leg just below the patella. The intensity of the stimulation was adjusted so that a small M-response was elicited together with the H-reflex. This M-response was used to monitor the stability of stimulation conditions. It was therefore not possible to adjust the H-reflex to the same size as the TMS MEPs and H-reflexes were therefore generally larger than the MEPs in most conditions. An additional stimulator was used to elicit maximal M-responses (Mmax) following supramaximal stimulation of the tibial nerve. The Mmax was used to monitor the stability of recording conditions at the different time intervals at which H-reflexes and TMS MEPs were measured. H-reflexes, M-responses and Mmax were measured at the same time intervals in relation to ground contact during heel and toe walking as the TMS MEPs. Similar to the TMS MEPs, the responses were elicited every 2-3 steps and a total of 15 responses were obtained for each stimulus interval following ground contact.

Unloading during over-ground walking

Six participants walked barefoot at a self-selected speed (~4–5 $km \cdot h^{-1}$) on a 10 m path over a robotic platform mounted flush in the floor of the laboratory. The robotic platform has 4 degrees of freedom and is composed of a force plate (OR6-5, Advanced Mechanical Technology, Watertown, MA) mounted on hydraulically actuated pistons (Klint *et al.*, 2009). After familiarisation, the participants' right foot touched down approximately centred on the platform. On random trials determined by a computer algorithm, the platform was dropped vertically by 8 cm with a constant acceleration and deceleration of 8 m/s^2. The movement of the platform was initiated either immediately at ground contact or at a latency of 400 ms corresponding to late stance as determined by the force plate. The latter latency was used primarily to demonstrate that unloading can indeed evoke EMG changes (Fig. 4C). The perturbations were presented randomly with a ratio of 1:5 between perturbed and non-perturbed (control) trials to prevent subject anticipation. Data were acquired until 10 trials of each perturbation were recorded. The onset of the platform movement was determined on the basis of the vertical component of the ground reaction force. The responses in the muscle activity to the perturbations were analyzed on the basis of the difference between the ensemble average of the control and the perturbed trials. The latency of the response was determined as the first deviation larger than 5 % and longer than 5 ms from the control EMG of the perturbed Sol EMG within 30-80 ms following the perturbation (Sinkjaer *et al.*, 2000; Af Klint *et al.*, 2009; Frisk *et al.*, 2017). To quantify the response, the relative difference of the area under the curve for the perturbed trials and the control was used.

Offline data analysis and statistics.

Signal processing and analysis were performed off line. All data were imported into Matlab (Mathworks, Massachusetts, USA) for further analysis.

All population average data are reported with standard deviations in the Result section, except in Fig. 5B-D where error bars designate standard error of the mean and Fig. 5E where 95 % confidence intervals are indicated.

In experiments involving ischemia and over-ground walking, Sol EMG was quantified by measuring the area of EMG activity in a 100-ms window after ground contact. Shapiro-Wilk was used to test that data were normally distributed. A paired Student’s t-test was used to compare the amount of EMG activity before and during ischemia and for over-ground

walking with and without drop of the force platform. A paired Student's t-test was also used to compare measurements during heel and toe walking.

Sol H-reflexes, TMS MEPs and Mmax were full-wave rectified before being averaged (n=8). The average amplitude of the responses was measured by setting cursors on either side of the responses in Signal 5.2 (Cambridge Electronic Design, UK). The excitability changes during stance phase of gait were compared between heel strike and toe strike walking and using the two conditions, the relative changes in central and peripheral excitability were estimated. Paired Student´s t-test was used for statistical evaluation of these comparisons. All statistical tests were performed with Sigmaplot 13.0 **(**SYSTAT Software, San Jose, CA, USA**)** for Windows.

Results

Sol EMG activity in relation to ground contact during toe walking

During normal heel walking, participants dorsiflexed the ankle in late swing and made ground contact with the heel of the foot (Fig. 1A-B; black lines). This event was marked by a large burst of TA EMG activity (Fig. 1E; black line). Sol EMG was, in contrast, absent at this time and only started increasing 100-200 after ground contact (Fig. 1D, black line). During toe walking Sol EMG activity was observed already prior to ground contact and was especially pronounced in the first part of stance (Fig. 1D; red line). The TA muscle was, in contrast, silent just preceding and at the time of ground contact during toe walking (Fig. 1E; red line). The Achilles tendon tension increased slowly in parallel with the Sol EMG activity in the stance phase during heel walking (Fig. 1F-black line), whereas it had increased already prior to ground contact during toe walking and remained large and relatively constant throughout the stance phase – again in parallel with the Sol EMG activity (Fig. 1F; red line).
Sol EMG activity was seen in all participants prior to ground contact during toe walking with an average onset of 85 $\pm$ 45 ms prior to ground contact. Shortly after ground contact, a burst of EMG activity was seen on top of the already existing EMG activity in 8 of the 15 participants (examples are marked in Fig. 1C and Fig. 2C). This EMG burst had a latency of 57 ms in relation to ground contact in this subject. For the eight participants, in whom this burst was observed, an average latency in relation to ground contact of 54.6 $\pm$ 9.2 ms was calculated. This latency is consistent with transmission in a relatively direct fast-conducting

spinal reflex pathway. A putative reflex origin of the reflex was further supported by the observation of a significant stretch of the plantar flexor muscle-tendon complex at the time of ground contact (Fig. 1B). The average position of the ankle joint was 125.3 $\pm$ 10.7 deg at ground contact during toe walking as compared to 101.7 $\pm$ 12.1 deg during heel walking ($p<0.001$). An average drop of the heel by 17.0 $\pm$ 4.1 deg was observed in the first 100 ms after ground contact during toe walking, thereby stretching the plantar flexor muscle-tendon complex. The average velocity of this stretch was 136 $\pm$ 30.0 deg/s, which is well above the velocity required to elicit stretch reflex activity in most able-bodied participants (Lorentzen *et al.*, 2010).

No change in muscle fascicle length in relation to ground contact during toe walking

To investigate whether the stretch of the plantar flexors at ground contact resulted in a stretch of muscle fibres in the plantar flexor muscle-tendon complex, we used 2D ultrasound to monitor movement of fascicles in the MG and Sol muscles during toe walking (Fig. 2B-E). These measurements were performed in 10 of the participants. Surprisingly, despite of the stretch of the muscle-tendon complex, fibres from neither of the muscles lengthened as a result of ground contact during toe walking (Fig. 2D-E). The length of the muscle fascicles remained unchanged during the first part of the stance phase and the fascicles only shortened just prior to push-off when the activity in the plantar flexor muscles peaked (Fig. 2B-E). We infer from this result that all of the stretch of the muscle-tendon complex resulting from ground contact consists of stretch of the Achilles tendon rather than the muscle fibres (Fig. 2F). For the population of the participants as a whole, the MG fascicle length shortened rather than lengthened by 0.17 $\pm$ 0.26 mm within the first 200 ms following ground contact. The average length of the MG muscle fascicles at ground contact during toe walking was 28.4 $\pm$ 6.9 mm. In contrast, at ground contact during heel walking in the same participants the length of the MG muscle fascicles was on average 36.6 + 11.0 mm ($n=10$; $p<0.01$).

No change in Sol EMG activity shortly after ground contact during toe walking when sensory feedback in large diameter afferents is blocked by ischaemia

To further investigate whether stretch reflex activity contributed to the Sol EMG activity in early stance phase we compared Sol EMG activity with and without ischaemic block of large diameter afferents (Nielsen *et al.*, 1992; Sinkjaer *et al.*, 2000). This experiment was performed in 7 participants. Data from one of these participants are illustrated in Fig. 3. EMG

and ankle joint position measurements were performed during toe walking prior to induction of ischemia (Fig. 3B-D, black traces) and then repeated 22 minutes after inflation of a blood pressure cuff placed around the thigh. At this time Sol H-reflexes were abolished, indicating that transmission in large diameter afferents was blocked by the ischaemia (Fig. 3A). The presence of M-responses simultaneously indicated that transmission in alpha motor axons was still intact despite the cuff inflation. This was confirmed by the participants' ability to walk on toes on the treadmill with almost the same cadence, step length and ankle joint movements as prior to ischemia (Fig. 3B-D, red lines). The subject used for the illustration in Fig. 3 did activate the soleus muscle earlier when walking with ischemia as compared to without ischemia. However, this was not a general finding across all subjects. EMG activation immediately prior to and after ground contact was not influenced by ischemia.

Quantification of the amount of Sol EMG activity within the initial 100 ms after ground contact showed no significant difference with and without ischemia for the population of participants (235+/- 43 μV.ms vs 245 +/- 36 μV.ms; n=7; p=0.65). This indicates that large diameter afferents do not contribute significantly to the Sol EMG activity observed after ground contact during toe walking. No significant differences in the position of the ankle joint at ground contact (122.2 +/- 6.3 deg/s with and 123.4 +/- 3.8 deg/s without ischemia; n= 7; p=0.37) were observed.

Sudden drop of ground support has no effect on Sol EMG activity immediately following ground contact during toe walking

Although large diameter stretch sensitive afferents do not appear to contribute to the Sol EMG activity and reflex-like EMG burst right after ground contact, there is a possibility that feedback from force sensitive afferents (i.e. Golgi tendon Ib afferents) may be involved. As illustrated in Fig. 1F there is a considerable load on the Achilles tendon at ground contact during toe walking and force sensitive afferents must therefore be assumed to be vigorously active (Stein *et al.*, 2000; Donelan & Pearson, 2004; Donelan *et al.*, 2009). Feedback from force sensitive afferents has also been shown to contribute to the Sol EMG activity *late* in stance during normal heel strike walking (Sinkjaer *et al.*, 2000; Grey *et al.*, 2007; Af Klint *et al.*, 2009). This is illustrated also in Fig. 4C for a subject who walked on toes over-ground. It

was confirmed that the same EMG and kinematic characteristics as described in Fig. 1 for toe and heel walking on a treadmill were observed during overground walking.

When a force platform placed in the ground was made to suddenly drop in late stance (400 ms after ground contact ~ 60 % of gait cycle) a significant reduction in Sol EMG activity was observed with a latency around 60 ms (Fig. 4C). This unload effect is likely to be caused by reduction of motoneuronal drive through spinal circuitries from force sensitive afferent activity (Grey *et al.*, 2007; Af Klint *et al.*, 2009). If force sensitive afferents similarly contribute to Sol EMG activity around and immediately after ground contact during toe walking (i.e. early stance phase), then, a similar reduction in Sol EMG activity would be expected when the platform is suddenly dropped right after ground contact. However, as shown in Fig. 4B this was not the case. The Sol EMG activity remained unaltered until around 120 ms after drop of the platform at which time increased EMG activity was observed. Similar observations were made in the other five participants in whom this experiment was performed. In none of the participants was any change in EMG activity observed within the initial 100 ms after ground contact when the platform was dropped (Fig. 4B; shaded area). In late stance by contrast an average reduction of Sol EMG activity of 15.5 +/- 6 % and an average latency of 55 +/- 11 ms was observed, consistent with previous findings (Af Klint *et al.*, 2009).

Evidence of increased corticospinal excitability immediately after ground contact during toe walking.

In order to investigate whether transmission in corticospinal pathways contributes to the Sol EMG activation after ground contact during toe walking, we compared the modulation of Sol H-reflexes elicited by stimulation of the tibial nerve (Fig. 5A) and Sol MEPs elicited by TMS (Fig. 5B). In addition, background Sol EMG activity and Sol M-responses were measured in order to monitor the stability of recording and stimulation conditions (Fig. 5C-D). This experiment was performed in eight participants and Fig. 5 illustrates average data from all eight participants. During normal heel walking both MEPs and H-reflexes were small or absent in the beginning of the stance phase, but in middle stance both responses increased in size parallel with the increase in background EMG activity (Fig. 5A-C; closed circles). During toe walking both MEPs and H-reflexes were large in the initial part of the stance phase immediately after ground contact (Fig. 5 A-B; open circles). However, the ratio of heel-strike and toe-strike of H-reflex magnitudes and TMS MEP magnitudes indicates that at

time points 70-200 ms after ground contact MEPs were significantly more facilitated during toe walking than the H-reflexes (Fig. 5E; compare red and grey shaded areas which indicate 95 % confidence intervals for each of the estimates). Thus, corticospinal excitability is increased during the early stance phase of toe walking.

Discussion

In this study, we have demonstrated that Sol EMG activity begins just prior to ground contact in preparation for landing during toe walking. In contrast, during heel walking there is TA activity and no Sol activity just prior to heel strike. An important question is whether EMG activity in the ankle plantar flexors during toe walking arises due to activation of either stretch or force sensitive afferent activity or whether it is supported by central feed-forward mechanisms. Initial examination of the raw EMG revealed in 8 of 15 participants a reflex-like burst of Sol EMG-activity in early stance during toe walking. The timing of this EMG burst is consistent with a spinal reflex increase in motoneurone excitation resulting from ground contact causing stretch of the plantar flexor muscle-tendon. This possibility was systematically investigated. Despite the stretch of the muscle-tendon complex, no movement of muscle fascicles was observed at ground contact. Furthermore, consistent with the plantar flexed approach of the foot to the ground in comparison to heel strike walking, the muscle fascicles during toe walking were shortened. Ischaemia, which blocked transmission in larger diameter afferents, did not change the Sol EMG activity during the early stance phase. This is strong evidence against there being a soleus EMG contribution from the monosynaptic Ia spinal stretch reflex pathway, although it cannot be excluded that participants changed strategy and used compensatory mechanisms to generate the muscle activity when sensory feedback was blocked during ischemia. It was therefore essential that additional experiments in which sudden drop of the supporting ground during toe walking also had no effect on the soleus EMG activity during the first 100 ms following ground contact. Taken together these observations strongly suggest that the EMG activity pattern observed immediately following ground contact during toe walking is due to feedforward control mechanisms and that sensory feedback mechanisms play either minimal or no part in muscle activation and the resulting stabilisation of the ankle and foot during the early stance phase of toe walking. This observation was strengthened by the observation that TMS of the corticospinal pathways elicited large MEPs in the soleus muscle immediately after ground

contact during toe walking. This indicates that corticospinal pathways are active and may be an important component of the presynaptic drive to ankle plantar flexor motoneurones at this point of the gait cycle.

We note that the experiment, in which the ground support was unexpectedly dropped by 8 cm when the subject made ground contact, is similar to work of Dyhre-Poulsen & Laursen (1984). They demonstrated that the EMG activity pattern when monkeys land on the ground from a drop jump, is pre-programmed rather than elicited by reflex activity from the landing (Dyhre-Poulsen & Laursen, 1984). This was shown through the creation of a false ground, which the monkeys would jump though before hitting the real ground below. The EMG activity was found to be timed to the expected landing rather than the real landing. We similarly observed that Sol EMG activity was unchanged at the time of expected ground impact when the ground was moved 8 cm lower than what the participants expected (Fig. 4). This is strong evidence that the Sol EMG activity prior to and at least within the initial 100 ms after ground contact is mediated by a feedforward motor command independent of the sensory feedback from the impact with the ground. It is a concern that participants may have changed their gait pattern because of the knowledge that the platform may drop at some point during the experimental session. However, we do not find it likely that this has influenced our results, since the participants reported that they were able to walk relaxed without fear of the drop of the platform. The drop of the platform was deliberately made sufficiently small for the participants to be able to continue walking with little disturbance of their gait. Importantly, our observation that the unexpected drop of the ground support later in the stance phase of the gait cycle produces a reduction in the Sol EMG (i.e at the time of foot push-off) - is important as it demonstrates that the drop of the platform does have a measurable effect when applied at a different time in the gait cycle (Fig. 4). This result is similar to earlier findings (Sinkjaer *et al.*, 2000; Af Klint *et al.*, 2009) and confirms that load related sensory feedback contributes to the EMG activity at this later period of the stance phase.

There was no movement of fascicles at the time of muscle stretch although the stretch of the muscle-tendon complex was sufficiently large (10 mm) and fast (>130 deg/s) to elicit stretch reflexes in resting conditions. The pre-programmed activation of the plantar flexors, which starts already 50-100 ms prior to ground contact during toe walking, appears to be of importance in increasing the stiffness of the muscle at the time of ground contact. This may

minimize the effect of the stretch, which is taken up fully by the tendon as calculations based on our ultrasound measurements indicate.

To our knowledge, this study is the first to investigate muscle and tendon length changes during toe walking. However, a number of studies have used ultrasound measurements to study changes in tendon and muscle fascicle length during heel walking (Fukunaga *et al.*, 2001; Lichtwark *et al.*, 2007; Lichtwark & Wilson, 2008; af Klint *et al.*, 2010; Kalsi *et al.*, 2016; Barber *et al.*, 2017). Similar to our findings during toe walking, it has been a general finding from these studies that there is only little change in muscle fascicle length in most of the stance phase also during heel walking (Fukunaga *et al.*, 2001; Lichtwark *et al.*, 2007; Lichtwark & Wilson, 2008; af Klint *et al.*, 2010; Kalsi *et al.*, 2016; Barber *et al.*, 2017). Although the ankle joint is increasingly dorsiflexed throughout the stance phase of heel walking, the simultaneous activation of the plantar flexor muscles prevents stretch of the fascicles and all of the lengthening of the muscle-tendon complex takes place in the tendon. Only towards the time of push-off is a shortening of muscle fascicles seen (Fukunaga *et al.*, 2001; Lichtwark *et al.*, 2007; Lichtwark & Wilson, 2008; af Klint *et al.*, 2010; Kalsi *et al.*, 2016; Barber *et al.*, 2017). This is very similar to what we observed here during toe walking except that all of the stretch of the muscle-tendon complex took place within the initial 100 ms instead over 400-500 ms during heel walking.

We further note that several participants such as the subject used for the illustration in Fig. 4 showed several bursts of EMG activity following the initial burst around 50 ms after ground contact. These bursts came at 100 ms intervals in these participants corresponding to a 10 Hz rhythmicity, which is reminiscent of physiological tremor (Schnitzler *et al.*, 2006). These bursts were also observed when the ground was suddenly removed suggesting that not only the first burst, but also the following bursts are centrally generated (Schnitzler *et al.*, 2006).

We cannot determine the exact central origin of the pre-programmed activation of the plantar flexor muscles from these experiments, but the observation that Sol TMS MEPs were more facilitated than H-reflexes during toe walking when compared at the same time points to heel walking, suggests that corticospinal excitability is increased during the early stance phase. However, we cannot fully exclude that the increase of the MEPs is explained by increased spinal motoneuronal excitability as reflected in the larger background Sol EMG activity, since the lack of increase of the H-reflex may possibly be explained by increased presynaptic inhibition of Ia afferents (Capaday & Stein, 1986; Faist *et al.*, 1996) or postsynaptic excitability changes in spinal interneurons, which have been shown to contribute

to the H-reflex size (Burke *et al.*, 1983; Marchand-Pauvert *et al.*, 2002). TMS MEPs are not only mediated by direct monosynaptic connections to the spinal motoneurones and we therefore also cannot rule out that the large size of the MEPs was explained by increased excitability of neurons in an indirect corticospinal pathway (Nielsen *et al.*, 1993; Petersen *et al.*, 2003). Since a significantly larger facilitation of MEPs than of H-reflexes was not observed until 70 ms after ground contact also opens the possibility that elicitation of a transcortical (stretch) reflex pathway may be involved (Christensen *et al.*, 2000). It should finally be pointed out that other central pathways (e.g. reticulospinal (Riddle *et al.*, 2009; Nonnekes *et al.*, 2015; Baker & Perez, 2017) and vestibulospinal (Cathers *et al.*, 2005; Iles *et al.*, 2007; Riddle *et al.*, 2009; Barthelemy *et al.*, 2015; Nonnekes *et al.*, 2015)) are also likely to contribute to pre-programmed activation of the muscles. It will require further specific experiments to address to what extent these different pathways contribute to the activation of the muscles.

The toe walking that we have described here in healthy adults shares a number of features with toe walking observed in typically developed children and children with CP and other neurological and neuro-developmental disorders (Romkes & Brunner, 2007; Schweizer *et al.*, 2013). As has also been reported in other studies there are only minor differences in the kinematics and EMG activity patterns when comparing involuntary (pathological) toe walking and deliberate voluntary toe walking (Berger *et al.*, 1982; Brunner & Romkes, 2008; Schweizer *et al.*, 2013). Note especially that the Achilles tendon tension parallels fully the tension reported for toe walking in children with CP (Berger *et al.*, 1982). This does not mean that the same mechanisms are responsible for generating the EMG activity in pathological obligatory toe walking and normal voluntary toe walking. However, it should be acknowledged that our observations are consistent with the hypothesis that toe walking in children with CP is a central compensatory adaptation that serves to secure efficient muscle activation, control of the ankle joint position and optimization of forward propulsion (Romkes & Brunner, 2007; Schmid *et al.*, 2013; Schweizer *et al.*, 2013). Feedback mechanisms appear to contribute less to gait in children with CP than in other children (Willerslev-Olsen *et al.*, 2014) and we hypothesise that the observations of a centrally pre-programmed control of the ankle joint at ground contact reported in the present study may also apply to toe walking in children with CP.

Conclusion

We have demonstrated that activation of ankle plantar flexors in relation to ground contact during toe walking is centrally generated and that it does not depend on sensory feedback from the ground impact. Increased corticospinal excitability immediately following ground contact in toe walking suggests that this central program may involve the corticospinal tract and primary motor cortex. These results are consistent with motor control theories that emphasize the significance of feedforward motor commands that integrate sensory information as predictive error codes in the control of normal and abnormal movement. We argue that the primary feedforward control of toe walking that we have demonstrated here should be considered as a potential mechanism and therefore a possible treatment target in the gait education of children whose obligatory toe walking results from underlying central nervous system pathology.

Additional information section

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These experiments were performed in the laboratory of JBN at the Department of Neuroscience, University of Copenhagen, except for the experiments on unloading which were performed in the laboratory of UK at the University of Aalborg.

The study was conceived and designed by JLO, MWO, SFF and JBN

All authors participated in the acquisition, analysis and interpretation of the data.

The first draft of the manuscript was written by JLO, MWO, SFF and JBN. All authors participated in revising it critically for important intellectual content.

All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons listed as authors qualify as authors and all those who qualify as authors have been listed.

Figures and legends

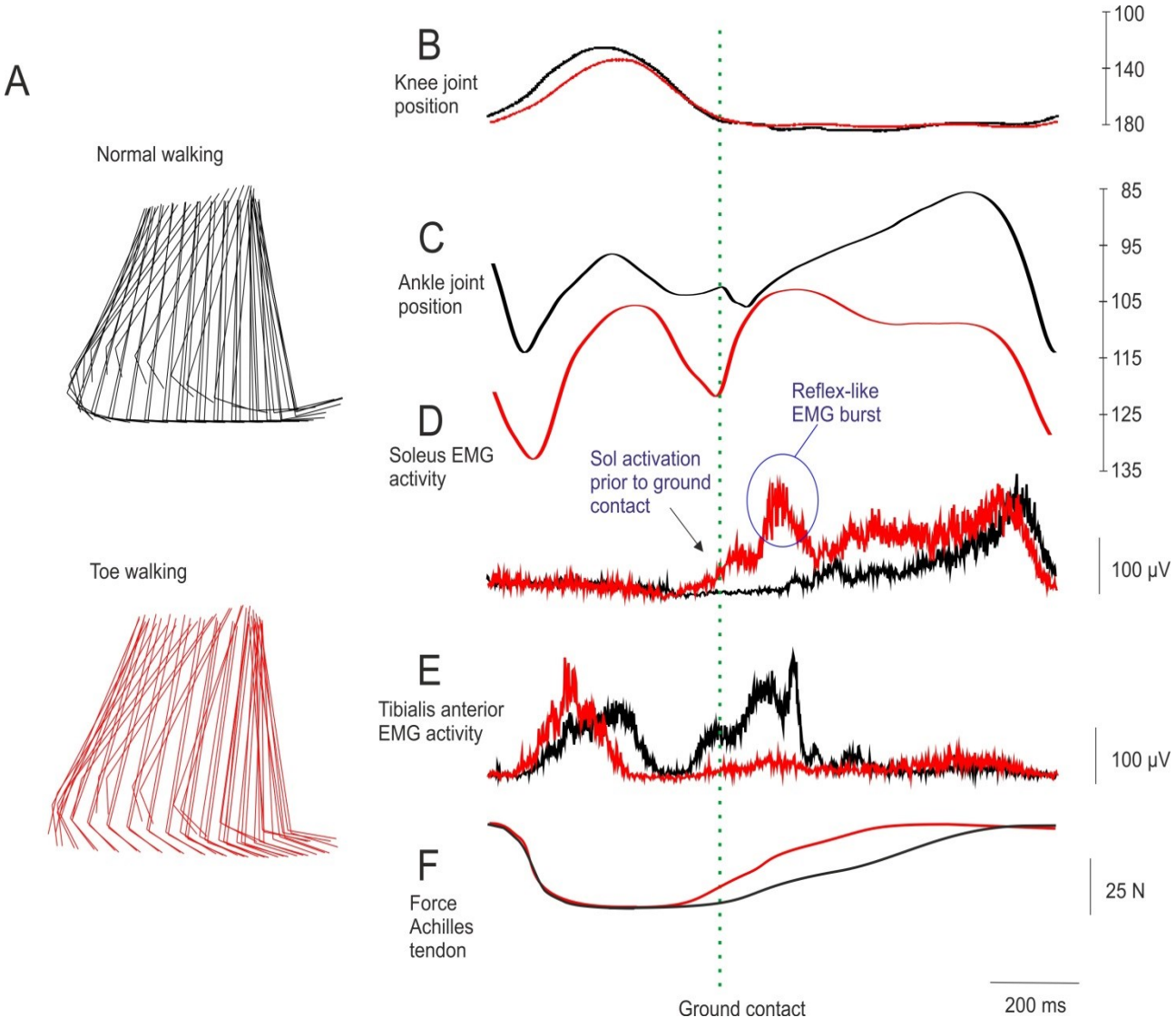

Figure 1. Comparison of kinematics and EMG activity during normal heel walking (black) and toe walking (red) in a single subject. A stick diagrams of the left and right limb positions in a full gait cycle obtained by 3-D motion analysis. B-F show averaged traces of knee (B) and ankle joint position (C), Sol EMG activity (D), Tibialis anterior EMG activity (E) and tension measured from the Achilles tendon (F). All traces were obtained by averaging the respective measurements triggered on ground contact (marked by green dashed vertical line). The averaging was performed for a 1 s period (time scale indicted by horizontal bar bottom right) covering one gait cycle. Scaling of measurements are indicated to the right as vertical bars in each graph.

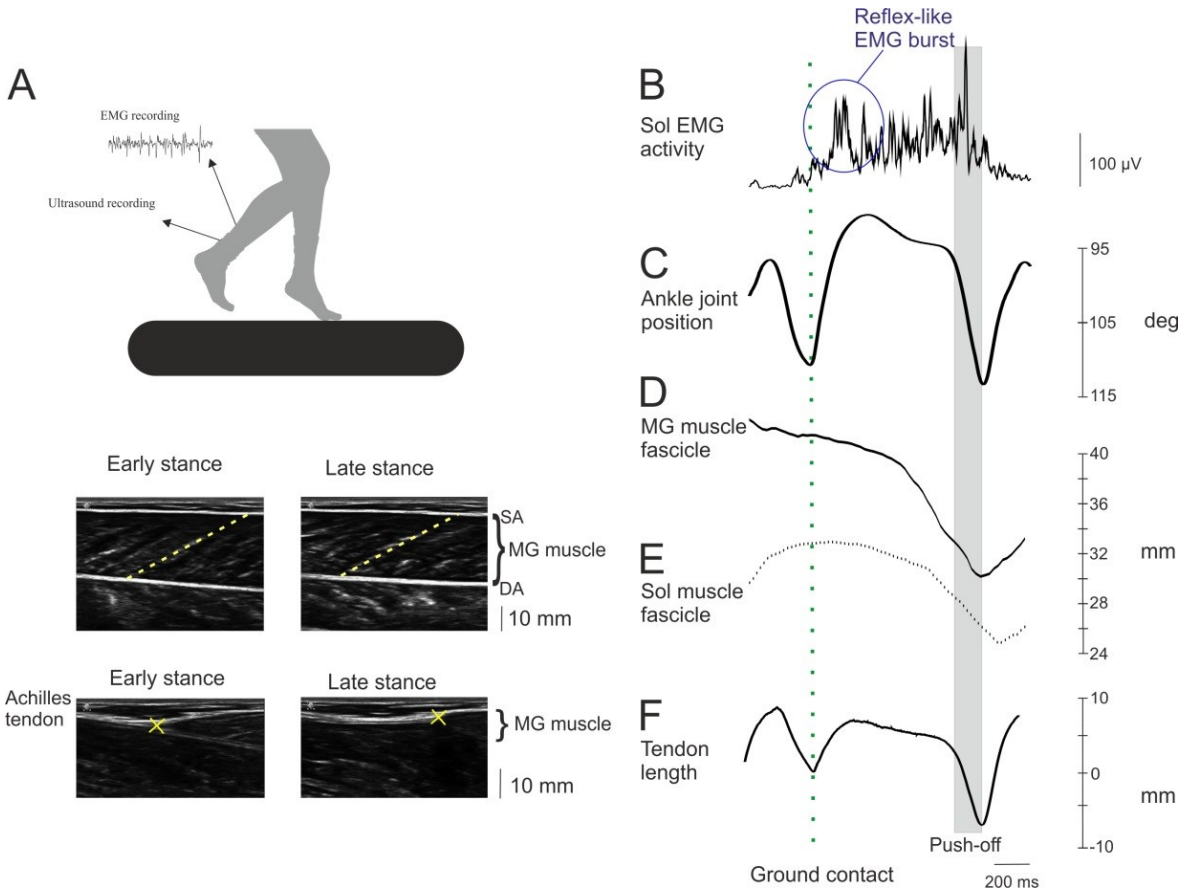

Figure. 2 Changes in muscle-tendon length during toe walking. Ultrasound (US) probes were placed over the belly of the MG muscle and the junction between the MG muscle and the Achilles tendon. Sol EMG activity and joint kinematics were measured simultaneously. Examples of US images from the two probes are shown in A for early and late stance. The upper row of images is from the probe placed over the MG muscle belly. The superficial (SA) and deep aponeuroses (DA) are clearly visible. A single MG muscle fascicle spanning from SA to DA has been marked by yellow dashed line in the two images. Note, that the images only represent the upper 50 % of the original US image, so that the Sol muscle is only partly visible below the MG muscle. For measurement of Sol muscle fascicles, the entire depth (70 mm) of the image was used. The lower row of images is from the probe placed over the junction between the MG muscle and the Achilles tendon. The junction has been marked in the images by a yellow cross. B-E show averaged traces (n=60) of Sol EMG activity in µV (B), ankle joint position in deg. (C), MG muscle fascicle length in mm (D) and the Sol muscle fascicle length in mm (E) triggered on ground contact (vertical dashed green line). The Achilles tendon length was calculated from the movement of the junction between the MG muscle and the Achilles tendon relative to the movement of the muscle-tendon complex as measured from markers placed on the heel, the US probe and the knee. The time axis is given by the horizontal line in the bottom right, whereas y-axes are indicated to the right of the respective traces.

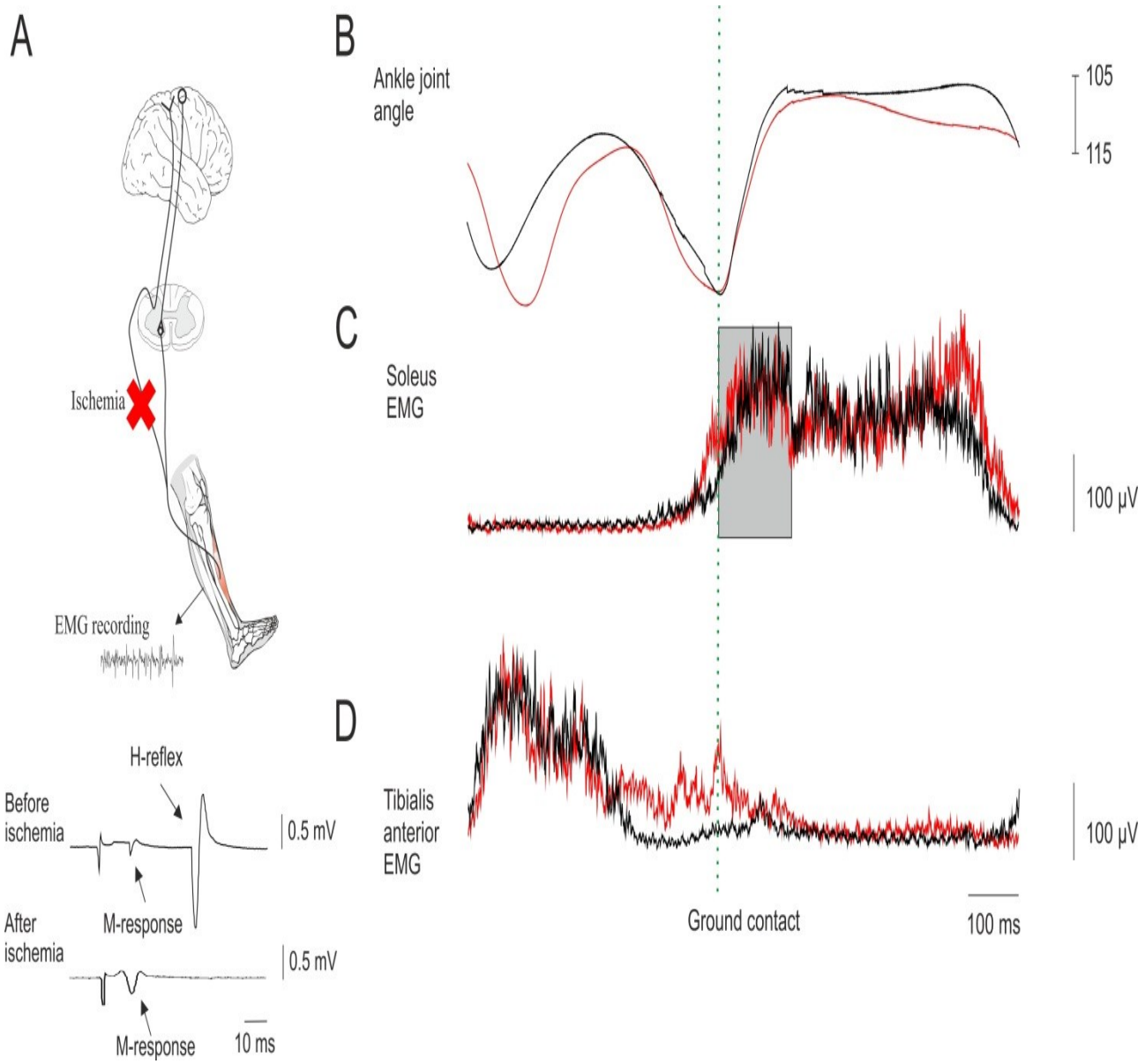

Figure 3. Toe walking with (red) and without (black) block of transmission in large diameter sensory fibres induced by ischemia. Ischemia was induced by inflating a blood pressure cuff placed around the thigh to 240 mmHg. Transmission in large diameter afferents was checked by stimulating the tibial nerve and recording Sol H-reflexes (A), before ischemia. 22 minutes after induction of ischemia H-reflexes had disappeared, while an M-response could still be elicited (A), after ischemia. B-D show averaged traces (n=45) of the ankle joint position (B), Sol EMG activity (C) and Tibialis anterior EMG activity (D) during toe walking before (black lines) and after ischemia (red lines). The averaging was triggered on ground contact (indicated by vertical dashed green line). The grey shaded box indicates the period of Sol EMG activity, which was quantified and compared with and without ischemia. The time axis is given by the horizontal line in the bottom right, whereas y-axes are indicated to the right of the respective traces.

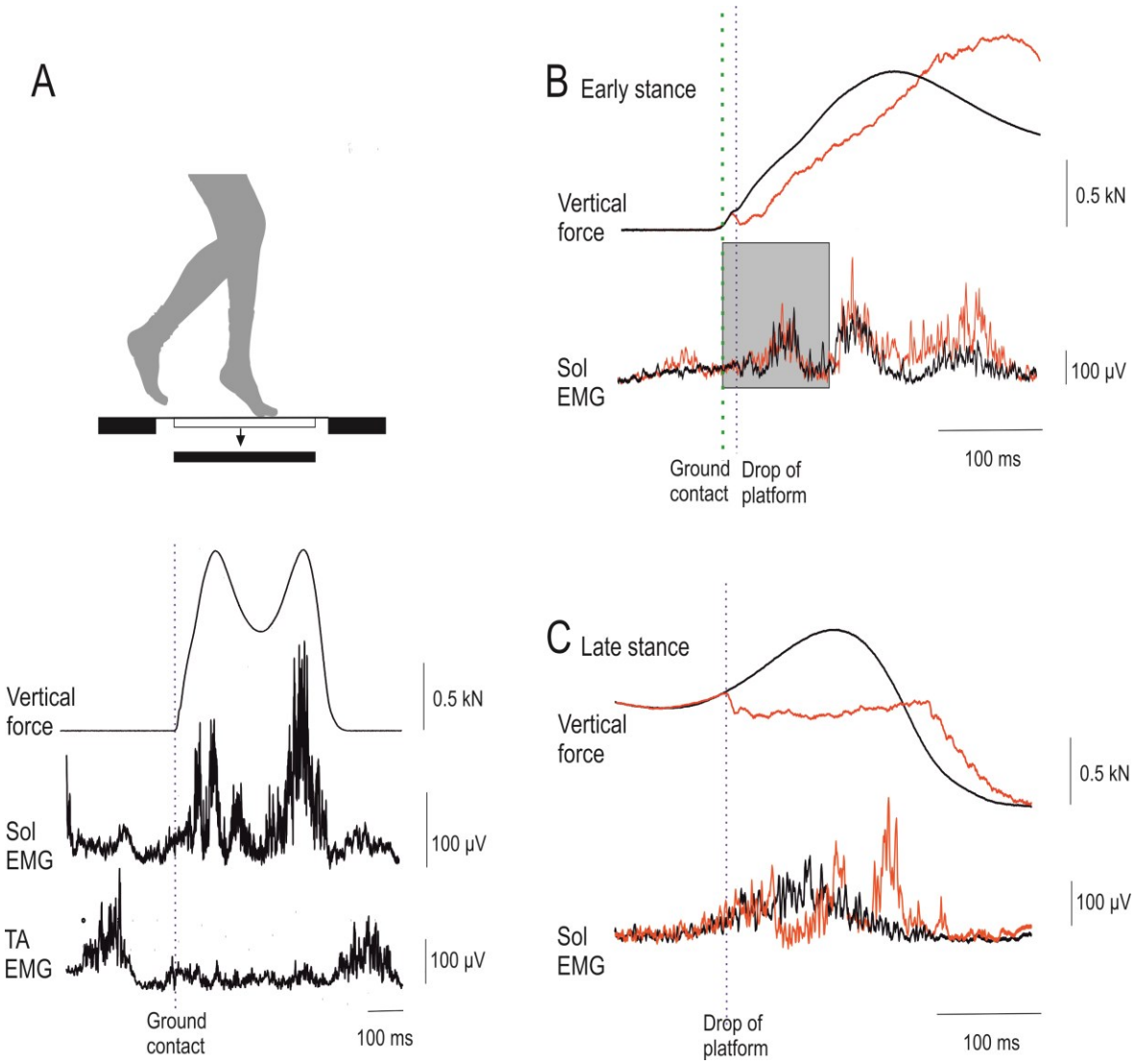

Figure. 4 Sudden drop in ground support. Participants were asked to walk barefoot on their toes over a force platform placed in the floor. A shows averaged traces (n=40) of the vertical force from the platform (upper traces), the sol EMG activity (middle traces) and the Tibialis anterior (TA) EMG activity (lower traces) during control steps without perturbations. X- and y-scale bars are given to the right and below the traces. B and C show averaged traces (n=10) of vertical force and Sol EMG activity in control steps (black lines) and steps in which the platform was suddenly dropped 8 cm at 0.8 g (red lines). The traces were triggered on ground contact (vertical, dashed green line). In B, the platform was dropped immediately when the subject made ground contact, whereas the drop was delayed by 400 ms so that it occurred in late stance in C. The time of the drop is indicated by the black, dashed vertical lines in B and C. The grey shaded box in B indicates the period of Sol EMG activity, which was quantified and compared with and without drop of the platform. X- and y-scale bars are indicated below and to the right of the individual traces.

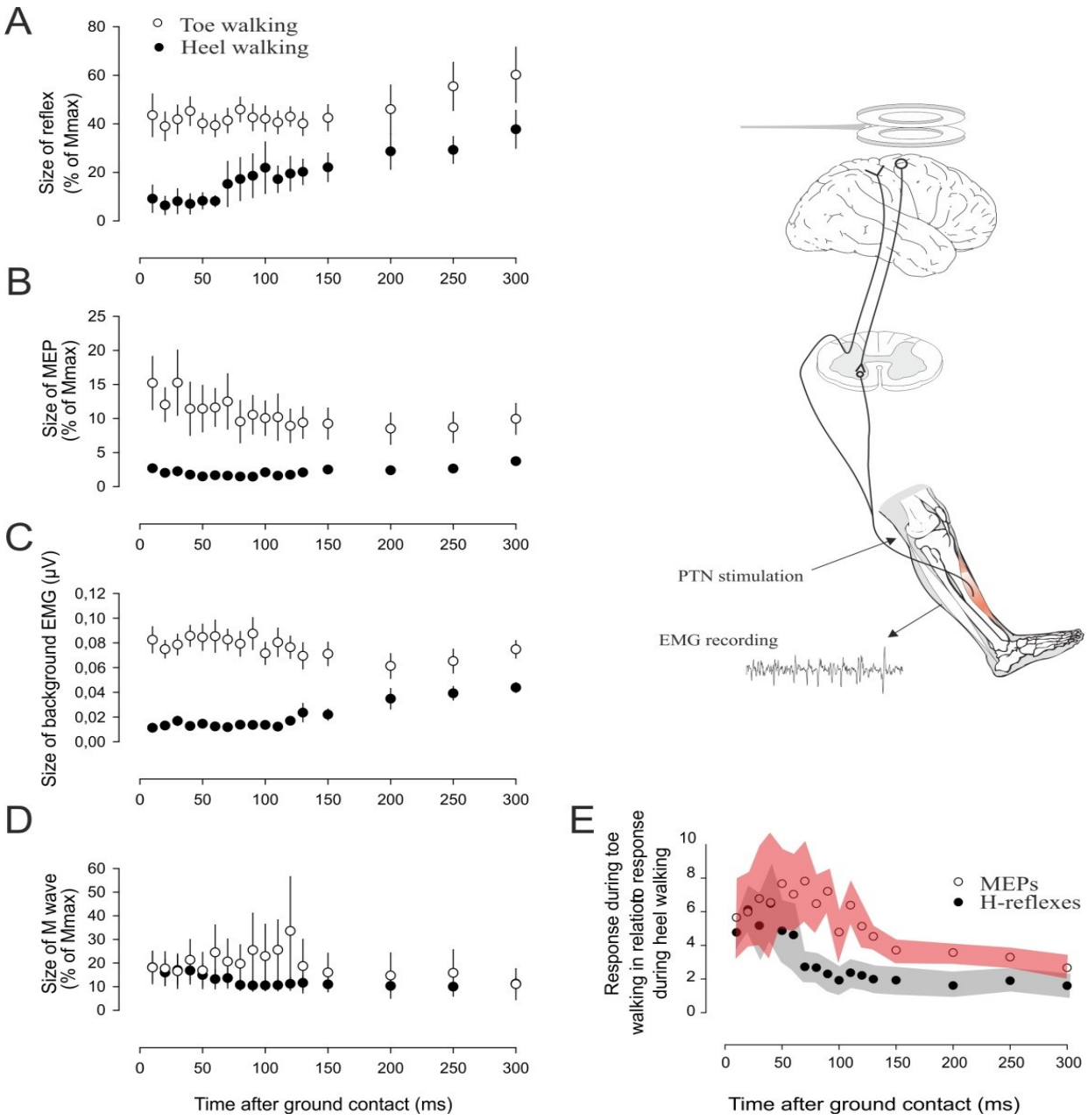

Figure 5. Modulation of soleus H-reflexes (A) and soleus MEPs elicited by TMS (B) during heel (closed circles) and toe walking (open circles). Background Soleus EMG activity is shown in C. The size of Soleus M-responses is shown in D. The size of the H-reflexes, MEPs and M-responses is expressed as a percentage of Mmax measured at the same time point. E shows the size of H-reflexes (closed circles) and MEPs (open circles) recorded during toe walking (open circles in A and B) divided by the size of the reflexes and MEPs recorded during heel walking (closed circles in A and B). The x-axis in all graphs is the time after ground contact in milliseconds. Data are population averages from all 8 investigated participants. Vertical bars in B-Dare one SEM. In E shaded red and grey areas indicate 95 % confidence intervals.

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