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REVIEW

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Cutaneous and muscular afferents from the foot and sensory fusion processing: Physiology and pathology in neuropathies

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Abstract

The foot-sole cutaneous receptors (section 2), their function in stance control (sway minimisation, exploratory role) (2.1), and the modulation of their effects by gait pattern and intended behaviour (2.2) are reviewed. Experimental manipulations (anaesthesia, temperature) (2.3 and 2.4) have shown that information from foot sole has widespread influence on balance. Foot-sole stimulation (2.5) appears to be a promising approach for rehabilitation. Proprioceptive information (3) has a pre-eminent role in balance and gait. Reflex responses to balance perturbations are produced by both leg and foot muscle stretch (3.1) and show complex interactions with skin input at both spinal and supra-spinal levels (3.2), where sensory feedback is modulated by posture, locomotion and vision. Other muscles, notably of neck and trunk, contribute to kinaesthesia and sense of orientation in space (3.3). The effects of age-related decline of afferent input are variable under different foot-contact and visual conditions (3.4). Muscle force diminishes with age and sarcopenia, affecting intrinsic foot muscles relaying relevant feedback (3.5). In neuropathy (4), reduction in cutaneous sensation accompanies the diminished density of viable receptors (4.1). Loss of foot-sole input goes along with large-fibre dysfunction in intrinsic foot muscles. Diabetic patients have an elevated risk of falling, and vision and vestibular compensation strategies may be inadequate (4.2). From Charcot-Marie-Tooth 1A disease (4.3) we have become aware of the role of spindle group II fibres and of the anatomical feet conditions in balance control. Lastly (5) we touch on the effects of nerve stimulation onto cortical and spinal excitability, which may participate in plasticity processes, and on exercise interventions to reduce the impact of neuropathy.

KEYWORDS
ageing, balance, central nervous system, cutaneous receptors, diabetes, exercise, foot sole, gait, intrinsic foot muscles, muscle spindles, peripheral neuropathy, reflexes, sarcopenia

1 | INTRODUCTION

Our bipedal posture is intrinsically unstable.[1,2] Gait consists in a continuous series of downward accelerations and active braking of the body weight.[3-6] No wonder falls are a problem. Fusion of sensory information, continuous check of balance, descending control of the spinal pattern generators by brain stem centres and cortical areas and appropriate recruitment of locomotor and postural muscles enable effective stance and locomotor tasks.[7] Proper orchestration of balance and walking activities protects us from toppling over when smooth progression is perturbed by sudden or anticipated changes in our environment.[8]

Information from the interface with the surrounding world is all too relevant for producing congruous motor activity. Sensory input from all the moving body parts constitutes a continuous flow of detailed messages correlated to those originating from the ground and objects we come in contact with.[9] All these inputs operate through short- or long-latency reflexes[10] or by conveying to the brain messages able to modulate the excitability of the neural circuits controlling balance and gait.[11] Vision displays the details of the environment and tells us whether the trajectory is appropriate or complications materialise ahead of us, and permits prediction and planning of sidestep strategies.[12,13]

Here we wish to build upon old consolidated notions and briefly mention recent findings on the function of the receptors influencing the control of balance and gait and body orientation in space, having in mind ageing people and patients with peripheral neuropathies of various nature. Neuropathy is a quite complex condition that affects balance and gait by altering the transmission of the action potentials in the nerve fibres. Not only that, because neurones in the dorsal root ganglia can be affected together with the axons travelling in the long spinal tracts. The degenerative disorder can also damage the nerve fibres originating in the vestibular receptors[14,15] and in the eye,[16] thereby presenting a further threat to balance and a serious risk factor for falls. Adaptation to loss of one or more sensory inputs can occur, for example, cutaneous,[17] proprioceptive,[18] vestibular.[19] As a consequence, compensation processes[20] can interfere with the control of balance and gait.

2 | SKIN RECEPTORS OF THE FOOT SOLE

The notion that sensory information from the feet is not negligible in modulating posture and locomotion has been established for many years.[21] Cutaneous receptors detect and code a wide range of mechanical stimuli. Low-threshold receptors code for pressure, vibration, light touch, texture as well as displacement of an object on the skin or vice versa. High-threshold receptors code for pain.[22] The former are innervated by large myelinated fibres, the latter (not considered here) by small myelinated and unmyelinated fibres with low conduction velocity. A recent review summarises the general anatomy of the skin receptors and their transduction properties in response to adequate mechanical stimuli.[23] Receptors may be fast-adapting, ceasing to fire in spite of a steady stimulus with a restricted (FA type I) or larger receptive field (FAII), or slowly-adapting (SAI and SAII, respectively).[24] The skin receptors have a different distribution in the glabrous skin of the hand (with small receptive fields in a higher proportion distally) compared to the foot (where they are more uniformly distributed),[25] according to the distinct roles of hand[26] and foot.

Another review article, centred on microneurographic recordings from sensory fibres from the skin of the foot sole, provides a detailed analysis of the receptive field distribution and density of these fibres.[27] About 60% of all recorded fibres originate in fast-adapting receptors with small receptive fields. The large percentage of fast-adapting receptors suggests that dynamic as opposed to static stimuli trigger the necessary information about the relationship of the foot with its support surface. Interestingly, in the fast- compared to slow-adapting receptors there is a better match between the firing of the nerve fibres and the stimulus perception,[28] pointing to a potential role of the fast-adapting receptors in the subjective perception of body sway amplitude.[29,30] Microneurographic recording from the tibial nerve at the ankle is likely to offer further information on the role of the receptors of the foot sole in the control of stance and gait.[31]

2.1 | Is there a role for the continuous oscillation of the body during quiet stance?

Body sway during normal standing is not just an effect of 'inadequate' balance control mechanisms. Kiemel et al[32] noted that minimisation of muscle activity rather than of body sway *per se* is the main task of the postural control system during quiet stance. Independently of the underpinning mechanisms,[33] sway is a source of crucial information and in stance healthy individuals sway continually. Carpenter et al[34] suggested that the postural sway may be exploited to ensure that continuous dynamic inputs are provided by multiple sensory systems. In its spatial 'exploration', the body acquires sensory information from fast-adapting receptors from the foot sole (and from different distributed sources) in order to develop a better representation of where the body is in space.[35] Conversely, slowly-adapting receptors may not serve exploration, but rather signal sharp or intense persistent stimuli, such as during the stance phase of gait.[36] Over time, not all receptors located in the skin of the foot sole may be firing, even when the foot is in contact with the support base, because they might be adapted if the mechanical stimulus is unchanging. The scope of the postural sway would be to allow the recruitment of new 'silent' receptors, as and when the previously firing fast-adapting receptors become adapted during still stance. Of course, the exploratory role would depend on the distance between the feet. This plays a substantial role, because sway increases when standing in tandem position (or under a single-leg stance condition), where the narrow base of support requires the development of a continuous stabilising torque about the ankles produced by leg and foot muscles.[37,38] In this case, the input from the foot sole varies much more and would be accompanied by a larger proprioceptive input from the recruited muscles.

As it happens, sway can and does diminish when vision and/or touch subserve complementary sensory inflow,[39,40] because continuous motion of the retinal image is an effective stimulus for postural stabilisation.[41-43] Body sway is reduced also when the brain receives additional information from light touching a solid frame with a fingertip or from the contact to the ground of a hand-held cane.[44-47] Since this is true even when touch may not be mechanically stabilising, as when the force exerted by finger or cane is below or close to 1 Newton,[48] appropriately allocated sensory integration processes initiated by the light-touch feedback would explain the effect. Similar stabilising effects of the input from fingertip touch have been documented when sighted and blind subjects lightly touched the ground with a cane, and the time course of stabilisation process has been described.[49] The non-negligible time-interval (of the order of a second) from ground contact by the cane to reduction of leg muscle activity and body sway is also similar to that following the index-finger light touch.[46] This suggests that the integration of the input for balance control is a time-consuming neural operation initiated by the haptic stimulus[26] at the interface finger-frame or hand-cane. Passive tactile cues to the skin of the lower limb or of the shoulder,[50] again exerting no mechanical effect, also enhance postural stability in older people and patients with neuropathy,[51] proving that the postural control process easily adapts to passive cutaneous information from various parts of the body.

It would not be surprising if the 'exploration' would be centrally controlled in order to avoid a random input, which would be not easily exploited by the brain and require continuous unsupervised corrections. In this light, the hypothesis has been supported by several experimental observations that control of body sway during quiet stance relies on predictive, anticipatory control of postural muscle length rather than on postural muscle tone or stretch reflexes.[52-54] Possibly, the input from the foot sole is weighted by the descending control driving the anticipatory postural activities.[55] Clearly, postural sway is not an end it itself, but is normally coordinated with supra postural tasks (see for example,[56,57]).

2.2 | Cutaneous input and gait

Standing does not occupy a large proportion of our time, but we assume this posture very often during our daily life activities. The sensory inflow from the foot sole plays a crucial role in detecting the effects of the postural changes and affects the activity of the postural muscles of the leg.[58,59] Not only of those muscles, though, because inputs from foot cutaneous mechanoreceptors produce widespread, task-dependent, reflex actions on multiple muscles in the ipsilateral and contralateral legs.[60] This information is up-weighted when a critical task like gait initiation is planned.[61]

Stimulation of the nerves carrying information from the foot skin has been extensively used. The reflexes evoked by sural stimulation are modulated with a presumably functional purpose by the locomotor activity as well (see[62]). A modulation of a cutaneous reflex from the skin of the foot dorsum (by stimulation of the superficial peroneal nerve), dependent on the task of avoiding an obstacle,[63] occurs during locomotion and is stronger when vision is experimentally degraded. A most remarkable synthesis of the effects of cutaneous input from discrete regions of the foot during walking can be found in Pearcey and Zehr.[64] One may note that locomotion produces a continuous spatio-temporal change in the plantar pressures (and from foot dorsum when wearing shoes[65]), thereby continuously varying the foot areas from which skin receptors are activated.[65,66] For instance, remarkable changes in the plantar pressure occur between straight and curved walking,[67] potentially informing the brain on how to adapt the body motion to the complex condition of steering while walking.[68] The concurrent activation of the intrinsic foot muscles and of other postural muscles must provide a complex, presumably meaningful afferent discharge to be integrated by the centres responsible for the control of balance and gait. These inputs would contribute to fine-tuning the activity of the leg muscles for progression and of the trunk muscles for producing the centripetal force.[69-71]

2.3 | Foot sole anaesthesia

Foot sole anaesthesia decreases the activity of the ipsilateral soleus and diminishes the vertical ground reaction force below the insensitive foot during balance recovery from an induced fall.[72,73] Therefore, the plantar sensation is relevant in the maintenance of stance,[74] in particular under critical balance conditions or in the absence of vision. Mildren et al[75] found that the perceptual threshold increases after anaesthesia. By reducing skin feedback, particularly around the region of the heel, and asking the subjects to voluntarily perform a feet-position matching task with eyes closed for assessing joint position sense, the ankle of the anaesthetised foot was felt relatively more dorsiflexed when the ankle angles were actually equal, suggesting that the posterior heel-region signals the magnitude of the skin stretch. A lidocaine block of all the nerve branches supplying the skin of foot and ankle did not modify the amplitude of the soleus stretch reflexes elicited by an imposed dorsiflexion of the foot during the stance phase of walking[76] (see Section 3.1), as if joint position sense and short-latency motoneurone reflex excitability would be differently affected by the cutaneous input from the heel.

2.4 | Foot sole temperature

The above findings complement experiments with cooling of the foot sole.[77] The threshold for vibratory sensitivity increases with cooling,[77] supporting the notion that skin temperature modulates the afferent discharge from the foot sole.[78] Four times as many falls in January than May have been reported in Sweden[79] (see[80]). Even by accounting for stumbles on snow or ice, falls were two times more frequent in cold weather. Cooling the foot (or leg) may be blamed for many falls, more so in the elderly or in neuropathic patients. However, cooling the foot sole may not be sufficient to increase sway during quiet stance to any major extent in healthy subjects.[81,82] Controlled cooling has also scarce effects on anticipatory and compensatory balance responses to perturbations.[83] These findings can be explained by the relatively modest effects of cutaneous input from the foot sole and on the central reweighting of different inputs to compensate for the cold-induced loss of plantar cutaneous sensation.[84,85] On the other hand, the sensitivity threshold decreases as the temperature increases.[86] Active (after treadmill walking) or passive warming (by an infrared radiator) the foot sole lowers the vibration perception thresholds.[87]

2.5 | Enhanced cutaneous information from the foot sole

A non-painful stimulation to the sural nerve, which innervates the lateral aspect of foot and heel, or to the tibial nerve at the ankle at about the motor threshold elicit reflex actions on many active muscles of the lower limbs.[58,60] These effects are partly spread to the contralateral limb as well, have a short latency (however longer than that of the monosynaptic reflex), can be facilitatory or inhibitory, and are task-modulated (standing, sitting, reclining). They may differ depending on the muscle and the motor units, emphasising a widespread and complex influence. The modulatory effects suggest that the inputs from the foot may be gated by the motor command to play different functional roles. For example, the foot cutaneous input and the descending volley from the motor cortex converge at spinal level and affect the firing motoneurones to leg muscles by way of presynaptic inhibition.[88]

Direct mechanical stimulation of the foot sole delivered to different areas of the skin of the foot sole produce marked postural effects. These are ‘meaningful’, because moderate body tilts are produced, oriented contra-laterally with respect to the stimulation site.[89] Conceivably, subjects perceive their body weight displaced toward the stimulated foot and shift the body to the opposite side to make the CoP even. Again, in several studies vibratory stimulations to the foot sole have been administered by instrumented insoles, and reduced sway and gait variability have been observed.[90,91] A simple mechanical stimulation by means of a thin object placed underneath the forefoot, on the force plate upon which subjects stand, produces a reduction in body sway area and improvement in recovering balance following a perturbation,[92] as if additional information would represent a further reference. Others have recently confirmed that mechanical facilitation of sensation of the plantar soles enhances postural stability.[93,94] A small raised edge placed underneath the boundary of the foot was shown to improve the reaction to unpredictable postural perturbations.[95] Changing the texture of a shoe-insert from smooth to clearly perceptible textured material can alter lower leg muscle activity during walking, suggesting that the sensory feedback from cutaneous receptors of the plantar surface of the foot improves dynamic balance control.[96-98] Anyhow, in spite of a plethora of fine studies addressing this issue in healthy subjects and patients (e.g., [99]), the clinical effectiveness of mechanical stimulation by patterned insoles remains elusive.[100,101]

One would argue that a certain thickness underneath the foot sole and the toes would not only produce a deformation of the receptive field of the cutaneous receptors, but would also modify, albeit minimally, the length of the plantar muscles of the foot, thereby recruiting stretch-sensitive muscle receptors. This adds to, but does not cancel the purely cutaneous input, as shown by the anaesthesia experiments mentioned above. Hence, both cutaneous and proprioceptive muscle inputs cooperate in sending the brain and spinal cord combined information crucial for postural control. In this light, Jean-Pierre Roll and coworkers posited that tactile and proprioceptive information from foot soles and leg postural muscles is centrally integrated to subserve balance control.[102]

In an influential article, Proske and Gandevia[103] noted that the discharge of skin receptors contributes to movement sensation and stated that ‘receptors involved in proprioception are located in skin’, in addition to more conventional locations. That standpoint represents the best link to the following sections of this brief overview.

3 | PROPRIOCEPTION AND THE INTRINSIC MUSCLES OF THE FOOT

Foot muscles possess quite a number of spindles[104,105] and the sensory inflow from the receptors of these active muscles must play a preeminent role in balance control.[106] The more so, because spindles are subject to centrifugal control, whereby the gamma motoneurones can enhance the spindle responsiveness to changes in muscle length by acting onto the intrafusal muscle fibres. Burke and Eklund[107] recorded the discharge of single nerve fibres from the spindles of the pretibial muscles. The spindle discharge frequency was not higher understanding than supine condition, but increased when the muscles were active, as during body backward sway (producing contraction of the pretibial muscles in order to shift the centre of feet pressure toward the heels). The afferent input from the intrinsic foot muscles has been also addressed recently.[108] In this case as well, many spindles were silent at rest, but during stance their discharge was modulated by changes in the position of the centre of foot pressure. Overall, it is evident that the muscle spindles contribute significant information about the displacement, anyhow modest, of the standing body.

Foot muscles act as a group to provide dynamic support of the longitudinal arch of the foot during quiet standing as well as during gait, where they concur to body propulsion in the last phase of the stance period.[109] The activation of these muscles increases with increasing postural demand[110,111] as the foot shape changes.[112] During stance, changes in the foot architecture may produce ‘internal’ foot muscle deformation, and affect spindle discharge from the foot intrinsic muscles. This can originate a significant input, when the information about the foot dorsi- or plantar-flexor muscles may not accurately code for the ankle angle due to the foot compliance.[113] Further, internal changes in muscle length occur normally during body sway, out of phase with the ankle angle. This occurrence has been shown for the triceps muscle,[52,54] but may hold for the intrinsic foot muscles as well (see 2.1). Individual differences in foot compliance are common, and could be responsible for the ample variability across subjects detected in posturography measures. During walking, the action of the intrinsic foot muscles is largely specific and separable from that of the extrinsic foot muscles.[114] Thus, these muscles contribute to locomotion in unique and likely irreplaceable ways, and must be coordinated in a highly controlled synergy.

3.1 | Postural responses to electrically- or perturbation-elicited proprioceptive input from the foot

Years ago, we and others have shown that the intrinsic muscles of the foot are the site of clear-cut reflex responses. The H reflex can be elicited in these muscles by electrical stimulation of the tibial nerve[115,116] and full-blown stretch reflex responses are elicited by fast perturbations of stance.[115] The flexor digitorum brevis is the site of short- and medium-latency responses to toe-up rotation of the platform upon which the subject stands. This action adds to and supports the well-known reflex response elicited in the triceps surae muscles when the body reacts to such a perturbation.[117,118] In passing, the concurrent recording from muscles placed at a different distance from the spinal cord (foot and calf) allowed to identify the receptors and estimate the conduction velocity of the fibres responsible for the short- (group Ia spindle afferents) and the medium-latency (group II spindle afferents) reflex response to stretch[119,120] (see 4.3).

3.2 | Interactions between cutaneous and proprioceptive inputs and their central integration

There is ample possibility for interaction of proprioceptive and cutaneous input at the spinal as well as at higher levels. Skin afferents from the foot have multi-synaptic reflex connections with the motoneurone pools directed to the leg muscles.[59] These influences have a well-defined distribution[60] and are depressed by standing.[121] Reflexes in the erectores spinae muscles are evoked by stimulation of the sural nerve and are modulated by postural tasks, indicating that meaningful responses are produced in these muscles by cutaneous receptors of the foot.[122] Anaesthesia of the entire contact surface of the foot sole modifies the amplitude and distribution of the body reaction to a balance perturbation in the frontal plane.[123]

A simple example of an interaction between skin and muscle inputs, likely occurring at spinal level, is the inhibitory effect on the triceps surae activity exerted by the foot sole. Electrical stimulation of the tibial nerve at the ankle, aimed at activating the proprioceptive fibres from the foot muscles, normally induces a short-lasting facilitation of the tonic activity of the triceps surae. This is preceded by inhibition under quiet stance or when a firm surface is pressed against the foot sole under reclining condition.[124] Therefore, foot muscle afferents establish oligo-synaptic connections transmitting mixed effects to the triceps muscle motoneurones, while the foot sole continuous mechanical stimulation discloses a short-latency inhibitory action. In this light, it comes as no surprise that H-reflex amplitude is larger under prone than standing condition[125] and that the H reflex is depressed during the early stance phase of gait.[126] Overall, the cutaneous input from the foot produces a modulation of the excitability of the monosynaptic reflex of the leg postural muscles during stance, possibly for avoiding excessive responses elicited by a toe-up perturbation that would produce a backward body thrust. Simultaneously, the muscles of the trunk receive information that helps control the position of the upper body.[127]

The multi-sensory integration for posture and balance has received substantial attention in the exhaustive synthesis by Peterka,[55] which highlights the variable weight attributed to the sensory inflow depending on the current behavioural conditions. A recent finding represents a straightforward case of a high-level reweighting of proprioception by vision. The firing of spindles of leg and foot relaxed muscles was recorded by microneurography during passive foot plantar- and dorsiflexion movements, while the subjects could see their foot or not.[128] Briefly, the spindle firing frequency diminished in the presence of vision by reduction of the efferent activity of the gamma-motoneurones, possibly in order to attenuate the spindle firing when an additional, complementary information reaches the brain.

3.3 | The proprioceptive input from different body parts affects balance and gait and is modulated by vision

The distribution of the muscle spindles is tremendously different across the muscles of our body. Of course, the spindle number is proportional to the muscle mass. However, when a regression is built of spindle number against muscle mass, the muscle with the greatest upward offset from the average distribution is the longissimus capitis of the neck, and that with the greatest negative deviation is the digastricus.[129] While the paucity of spindles in the latter is easily explained by the protective role of the digastricus muscle in the jaw-opening reflex, where there is no need of spindle feedback and controlled development of force, the former must have its purpose in the need of detailed information about head and trunk position during dynamic tasks.[130] No wonder that fatigue of the neck muscles increases body sway during stance and worsens the perception of stability.[131] The neck and the axial muscles represent a complex source of inputs appropriate for producing balance correcting responses to perturbations[132] and modifying our orientation in space during a locomotor task. Selective spindle afferent fibres activation by unilateral vibration of the neck sterno-mastoideus muscle induces ample deviations of the gait path (eyes-closed) toward the side opposite to stimulation.[133] Unilateral vibration of the erector spinae muscle during gait produces a deviation of the walking trajectory toward the opposite side as well.[134,135]

As expected, vision reduces the sway evoked by neck vibration during standing.[136] This occurs also when vision precedes the vibratory stimulation, while no-vision before vibration enhances the vibration-induced destabilisation. Hence, a finite time period must elapse before the visual reference is fully established. In a study on proprioceptive-visual integration, Kabbaligere et al[7] noted that the postural response to combined stimulation (leg proprioception by vibration and vision by motion of a virtual scene) depends on the weight allotted to each cue, in turn contingent on its reliability. Moreover, neck muscle proprioception and vestibular stimulation interact at different brain levels and contribute to the subject's representation of space[137-139] (see[140]). A recent review by Jamal et al[141] summarises and discusses the findings of neck vibration on postural orientation and spatial perception.

3.4 | Foot sensitivity in the elderly

A review on balance and gait changes associated with ageing has been recently published.[142] Elderly subjects show significantly elevated threshold for high-frequency vibration of the foot sole[143-145] or of internal malleolus.[143] However, healthy ageing may not be necessarily accompanied by major increases in body sway during stance when vision is available, although absence of vision or standing on foam[146] discloses a decline in postural stability.[147] Sway increases beyond 60 years of age or so,[148] in particular when unhealthy conditions are present.[149-151] A study by Machado et al[152] showed that foot sensitivity diminishes with age, particularly at the heel. The reduced plantar sensitivity of the foot in the elderlies, correlated with changes in the threshold of the skin receptors, affects the strength of the cutaneous postural reflexes as well.[153] Critical information about the tibio-tarsal angle originates also from the proprioceptors (muscle spindles, see below) of the leg muscles about the ankle and by the retinacula of the ankle joint as well, which are endowed with receptors and nerve fibres.[154] Interestingly, a recent report shows that acuity of proprioception at the ankle does not diminish in healthy ageing, as tested by psychophysical methods under controlled conditions, taking into account the history of the leg muscle contractions and relaxations.[155]

3.5 | Sarcopenia

Certainly, in the old adult, muscle weakness is an issue. Sarcopenia designates the loss of muscle mass and strength that occurs with ageing and contributes to frailty and functional impairment in the elderly.[156] Loss of skeletal muscle innervation with structural changes in neuromuscular junction can accompany increased age. Muscle fibres can loose their pristine innervation by retraction of the terminal parts of their motor axons and may be innervated by the remaining healthy axons. However this compensatory process may fail with age, and an attenuation of motor unit growth would ensue, with no compensation for lost skeletal muscle innervation.[157] This event does not necessarily accompany physically fit ageing, where intense motor activity may facilitate axonal sprouting and reinnervation of denervated fibres.[158] As a side note, animal studies have established that ageing results in the loss of fast-twitch motor units, but the reinnervation process in humans is not simple (see[159-161]). There is hope to soon elucidate the relevant molecular pathways.[162]

The connections between muscle condition and balance function in older and younger subjects are addressed in a comprehensive review article.[163] Many studies have considered the control of balance under static and dynamic conditions in the elderlies with an eye on their muscle status, but no firm conclusions have been reached, probably because of the complexity of the matter.[163] Muscle weakness certainly is a cause of insufficient production of muscle torques for standing and walking.[164] However, physical activity practice does not seem to give an edge to either young or elderly healthy subjects when standing quietly on a firm surface or on foam.[165] On the other hand, a recent study on a large cohort of subjects has found that sarcopenia markedly increases the risk of postural dysfunction in middle-age adults.[166]

Whether sarcopenia in the elderly directly affects the spindle sensitivity is another question. Intriguingly, in the mouse, the capsule surrounding the muscle spindles undergoes thickening with ageing, probably modifying their transduction properties.[167] Some time ago, the hypothesis had been put forward that muscle weakness per se impairs the joint position sense and the control of stance, as deduced from the disproportionate increase in sway in the weaker subjects on closing the eyes (for an equal sway amplitude eyes-open).[168] Apparently, vision information compensated for an impaired sensibility of the muscle spindles receptors. This might indirectly explain the more favourable outcome on stance control of interventions aimed at strengthening the muscles than training postural capacities by balance exercises in sarcopenia women[169] (see[170,171] for a general discussion on this matter and other interventions).

Figure 1 is an attempt to summarise some of the issues mentioned so far, as an introduction to Section 4.

4 | HINTS FROM NEUROPATHIES

A clinical-epidemiological study addressed the association of decreased sensation of the foot skin assessed by monofilament technique with mortality, in a large cohort of general adult population (including but not limited to diabetic or neuropathic patients). The authors' conclusion was that peripheral neuropathy, which is not uncommon in the general population, is associated with excess risk of all-cause mortality.[172]

Clinical evaluation allocates patients into motor, sensitive or mixed neuropathy. Interestingly, a simple test based on the measure of the limits of equilibrium is able to discriminate between motor and sensory neuropathies, dependent on the exerted force necessary to reach the limits of stability.[110,173] Nutritional deficiencies represent a frequent source of complex neuropathies,[174] and should be carefully considered because of the overlapping of the clinical picture with other disorders and with balance problems in the elderly.[175] Recent reviews have addressed the complex features of neuropathies, with a view on improving diagnosis and considering the possibility of counteracting their evolution.[176-179] Overall, nerve fibre degeneration (demyelination or axonopathy or both) would be the consequence of a diffuse nerve ischaemia produced by a microvascular disease, the effects of which range from nerve fibre loss to foot ulcers (in a detrimental feedback loop between the two), to retinopathy and to autonomic neuropathy.[180,181] In connection with the latter, autonomic neuropathy would not be inconsequential as far as proprioception is concerned (in addition to the protean ailments accompanying autonomic failure, for example, [182]). This is because muscles spindles, much as the typical extrafusal muscle fibres and their neuromuscular junctions as well,[183] receive sympathetic innervation potentially modulating their transduction properties.[184-186] Whether sympathetic neuropathy can contribute to sarcopenia (3.5) is not settled, but is not beyond understanding.[187]

4.1 | Skin and muscle nerve fibres in the foot are affected by neuropathy

The density and the anatomy of Meissner corpuscles has been quantified from skin biopsies obtained from patients with neuropathy.[188]

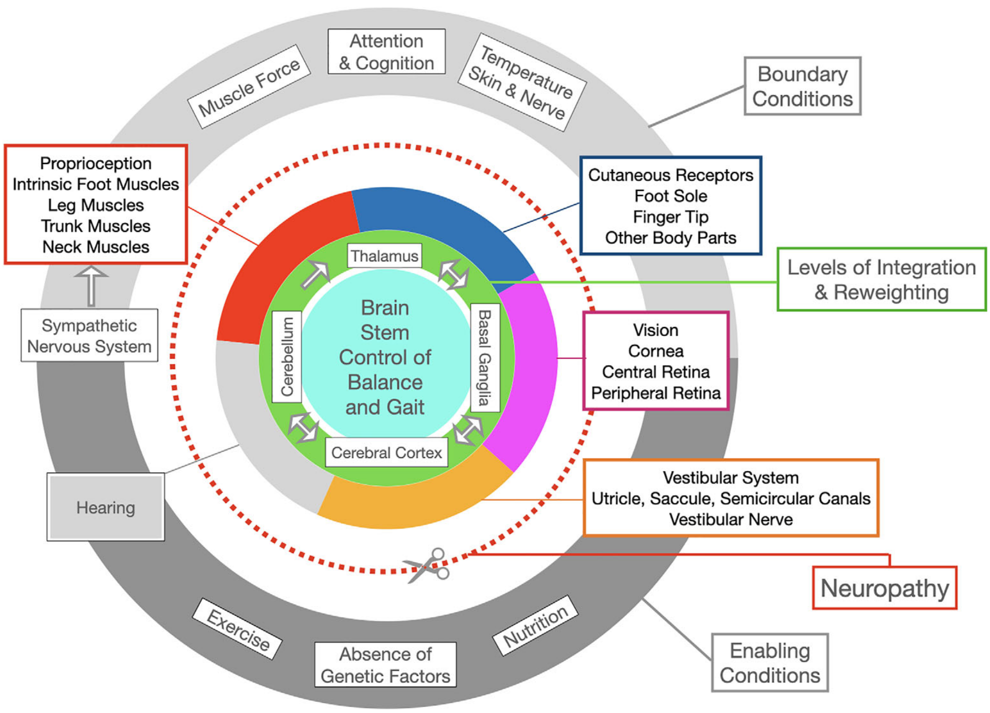

FIGURE 1 The highly simplified scheme lists some of the receptors responsible for conveying to the brain relevant inputs for balance control. All of them are briefly considered in this article (except Hearing), but skin and muscle receptors have received more attention. Neuropathy can lead to degeneration (the red dotted-line circle) of all mentioned receptors and fibres in the nerves and ascending tracts, and prevents information from accessing the brain centres (green) devoted to integration and reweighting of the sensory information (including the thalamus, basal ganglia, cerebellum and several cortical areas). The innermost turquoise circle denotes the brain stem centres which contain the nuclei orchestrating balance and gait control processes. Central pathways are omitted despite being mentioned in text. Some flow of information is indicated by arrows as in the 'Levels of Integration & Reweighting', but not shown in every relevant case to avoid intricacy. The outermost ring would point to several conditions and factors that affect transduction, firing, impulse conduction and effectiveness of motor action (top part) and integrity of the conditions enabling overall safe control of balance and gait (lower part)

Within the neuropathy but not the healthy subjects' cohort, there was an association between the number of intact receptors and the detection threshold. This is in keeping with numerous findings showing, as mentioned above, that sensitivity of the plantar skin[25] declines with age and neuropathy.[144,153] On the motor side, remarkably, the volume of the intrinsic foot muscles is much reduced in patients with diabetic neuropathy, and their atrophy is related to the clinical severity.[189,190] In a recent retrospective study in a large number of patients with proven small-fibre neuropathy with loss of skin fibres, evaluation by electrodiagnostic tests of denervation in the foot muscles revealed large-fibre dysfunction.[191] Hence, neuropathy disrupts both skin *and* muscle input and likely disorganises their coordinated effects on balance at spinal level. Since information from foot skin and muscle normally affects the balance control centres that supervise balance and locomotion, and modulates the excitability of many related muscles as mentioned above (3.1, 3.2, 3.3), the effect of the loss of these fibres must be extremely relevant for balance control. The nerve fibre dysfunction in the distalmost part of the lower limb adds to muscle weakness and to the diffuse sarcopenia frequently encountered in neuropathy,[192] leading to major problems in balance and gait, hence to impairment in the patient's mobility and independence (see[193]).

4.2 | Balance and falls in diabetic patients

In a study on a large cohort of patients with type 2 diabetes, two-thirds were found to have evidence for some variety of neuropathy, even if symptoms appeared in less than half of them.[194] These patients often suffer from sensorimotor distal symmetric polyneuropathy starting in the feet, even if the upper limbs are not spared.[195,196] The degenerative process affects both the large and the small-diameter myelinated fibres originating in the skin and muscles, both in type 1 and type 2 diabetes.[197] The conduction velocity of the fibres in the spindle group Ia and group II fibres of the foot and leg muscles is diminished in diabetes and the medium-latency response to foot and leg muscles stretch produced by balance perturbation are delayed.[198] The decrease in conduction velocity of the group II fibres[198] contributes to postural unsteadiness of these patients, supporting the view that the spindle group II fibres may normally play a major role in standing stability. The conduction velocity of the motor nerves is diminished as well.[197,198] The magnitude of changes in the neuromuscular properties of these patients are muscle dependent and reflect a length-dependent disease progression.[164]

It has been shown earlier and confirmed recently that these patients are generally less stable than healthy subjects, as detected by posturography.[199-201] Even with vision, their postural stability is impaired, indicating incomplete compensation by vision of the loss of input from the feet.[202] In a recent assessment centred on balance and falls, three fourths of multiple-faller patients had a diagnosis of neuropathy.[203] These exhibited objectively increased body sway with or without vision, standing on solid ground or foam, and walking speed was slower than in patients who did not fall. In this regard, it has been found in a study that recruited patients of different age groups that the tactile pressure sensitivity threshold increases significantly across the entire foot sole with age, with the larger loss of sensitivity at the heel than at the forefoot.[204] This probably explains part of their gait problems such as a reduced ankle flexion at the stance phase and higher loads at the push-off phase.[205]

In some diabetic patients, vision can be impaired as well. Both the retina and the cornea are involved in the neurodegenerative process.[206,207] Remarkably it has been shown that both motor unit loss and retinal dysfunction are early markers of subclinical neuropathy.[208] Combined effect of poor visual acuity, kinaesthetic sense, slow walking speed and potential cognitive impairment are to be blamed for the increased fall risk beyond peripheral neuropathy itself.[209] This adds to the conclusion of previous ample studies on the risk of falling in a general population, in which multiple sensory impairment, that is, vision, peripheral neuropathy and hearing problems[210] were associated with higher probability of falls or balance dysfunction.[211] However, reduced muscle strength in diabetic patients is present before the clinical onset of neuropathy and is characterised by increased fatiguability and reduced muscle twitch amplitude, without major changes in the pattern of motor unit firing, pointing to primary disruption of contractile function.[212] Muscle weakness impacts on the functional abilities of these patients and can lead to severely impaired balance reactions (see[213]).

A high prevalence of vestibular dysfunction was found in diabetic patients, accompanying a peripheral neuropathy of long duration. After adjusting for peripheral neuropathy and retinopathy, the vestibular dysfunction appeared to contribute to the risk of falling.[214] This adds to the effects of somatosensory loss, especially because somatosensory loss can result in increased vestibulo-spinal sensitivity, which normally compensates the severity of the peripheral neuropathy, as shown by increased postural sensitivity to galvanic vestibular stimulation.[215] It is known that the labyrinth modulates the muscle synergy that corrects the effects of balance perturbations and that a vestibular deficit reduces the activation of leg and trunk muscles.[216] Higher centres, including the cerebellum, integrate sensory input from multiple systems including the vestibular, visual, proprioceptive and somatosensory, and co-process information from the motor efference copy as well.[217] The consequences of involvement of the central nervous system in diabetic and other neuropathies[218] may not have received the necessary attention in the framework of balance control.

4.3 | Other neuropathies and balance

A loss of the large-diameter (group Ia) spindle afferent fibres in the hereditary CMT1A disease is responsible for the disappearance of the monosynaptic reflex and of the short-latency reflex response to a perturbation-induced triceps stretch. Oddly enough, this major loss does not worsen the body sway to highly abnormal values during quiet stance, contrary to what occurs in diabetic patients with neuropathy.[219,220] Further, in patients with CMT1A, postural perturbations delivered by a movable support base elicit in the foot and leg muscles full blown but delayed medium-latency responses. These are mediated by the small-diameter myelinated spindle fibres (group II fibres), normally conducting the action potentials at about half the velocity of the large fibres.[119,221,222] Together with the above mentioned observation that the H reflex is decreased during stance in healthy subjects, this suggests that the group Ia spindle afferent fibres may not be essential for transmitting relevant information for the control of quiet stance. Since the diabetic neuropathy affects both large- and smaller-diameter fibres and body sway is increased in these patients, as noted above (4.2),[223] much of the control of quiet stance must be exerted by the smaller-diameter group II fibres. Alterations in body sway both while standing and in the stance phase of gait are larger in the diabetic than CMT1A patients,[224,225] indicating that static and dynamic control of balance and gait worsen when the neuropathy affects the smaller-diameter group II fibres in addition to the large fibres. These group II fibres are recruited during gait in response to a mild perturbation of the ankle angle in the patients with CMT1A,[226,227] suggesting that they can normally assist gait, possibly as part of the central co-activation of the alpha- and gamma-motoneurones. Li et al[228] have recently proposed a model, inclusive of the process of adaptation to the neuropathy, with the aim of explaining the relationship between postural stability and the input from the smaller and larger spindle fibres.

Gait is certainly severely affected in neuropathies, partly due to the muscle weakness or sensory loss, partly to the adaptation strategies such as reduced walking speed.[229] A systematic review that considered young patients with mixed sub-types of CMT disease showed reduced walking speed and short stride length, and highlighted the need for further studies[230] In a large number of mildly affected young adults, whose walking velocity on level ground was similar to that of healthy peers, kinematics and kinetics became clearly abnormal, as a sign of muscle weakness, when patients climbed a ladder.[231] Unfortunately, the role of the foot deformity, which can have peculiar effects on the sensory inflow during stance and gait and complex tasks,[113,232] has not received much attention. This is particularly relevant because the onset of CMT disease is usually in childhood,[233] a crucial period for the development of the gait networks and for the growth of the locomotor apparatus.[234,235]

Much as hereditary ataxias can affect fibres in the peripheral nerves (see[236,237]), the peripheral neuropathies can also be associated with white matter loss in the spinal tracts[238] and higher brain centres.[239,240] These severe complications may be responsible for major problems in balance and gait. Another group of peripheral nerve disease is represented by ganglionopathies (or sensory neurone diseases, SND),[241] often associated with immune-mediated conditions, vitamin intoxication or deficiency, neurotoxic drugs, and cancer. The loss of the sensory neurones in the dorsal root ganglia leads to degeneration of both the peripheral axons and their central projections. In these patients, body sway is much larger that in patients with CMT1A and also larger than in patients with diabetes, with and without vision.[242] This occurs even if muscle force is preserved. In SND, the somatosensory evoked potentials are undetectable, while cervical magnetic resonance imaging shows a diffuse hyper-intensity in the posterior columns in all the patients.[243] Again, such large degeneration of centripetal spinal cord tract would imply a major loss of input to the brain stem centres controlling balance, thereby explaining the abnormal control of standing and of the responses to perturbations. When a patient with a dorsal root ganglionopathy that produced total sensory loss in the lower limbs received postural perturbations by various displacements of the support base,[244] no short-latency responses were elicited. Later responses in the legs occurred, likely produced by hip, trunk and neck proprioceptive inputs, exploited by central compensatory mechanisms. In passing, in some of these patients, deep reflexes (tendon tap and H reflex) are paradoxically preserved and associated with complete loss of cutaneous afferent path,[245] suggesting a differential sensitivity of the dorsal ganglion neurones to the responsible noxious agent[246] (see also[247] for the diabetic polyneuropathy). A peculiar form of progressive late-onset ganglionopathy of genetic origin with marked instability and high risk of falling,[248,249] the cerebellar ataxia with neuropathy and bilateral vestibular areflexia (CANVAS), has been under investigation for a number of years.[250]

Cervical spondylosis is another not uncommon condition that produces major balance impairment. Most patients show increased body sway, larger in cervical spondylosis with myelopathy than without.[251] Surgical decompression normally enhances balance and gait, but the improvement may not be immediate.[252] In the chronic inflammatory demyelinating polyradiculoneuropathy, affecting both sensory and motor fibres and both distal and proximal nerve segments, body sway is much larger than in healthy subjects, and varies from a mainly ankle to a mainly hip strategy,[253] probably owing to the large extension of the sensory and motor impairment. The poor trunk control in these conditions resembles that observed in spinal cord injury,[254] where abnormal transmission of the somatosensory information to supra-spinal centres and of the descending commands to lower cord levels are accountable for ataxia.

5 | CONCLUSIONS AND PERSPECTIVES

Voluntary and automatic movements are unimaginable without appropriate control of balance. Safe balance is the final shared responsibility of our senses and of their central integration. In turn, the brain can provide proper control of balance if the motor pathways and the muscles themselves are functioning correctly. The quality of static and dynamic balance is the expression of the functioning of complex and diverse neural processes. Conveniently, we can rely with confidence on accurate and effective methodologies for recording and analysing balance and gait (eg, [255-257]). In neuropathies, one or more senses can be weakened. The combined action of their impoverishment can produce unfortunate consequences. The critical role of close attention to the task, as shown by Lajoie et al[258] in a subject with massive loss of sensory fibres below the neck, can hardly compensate for the loss of sensory input. Attention is clearly an issue even in less deteriorated conditions. While in normal young subjects a dual-task may have a limited effect on gait,[259] simple attention-requiring concurrent tasks can worsen balance control in patients with diabetes and neuropathy,[260] an indication of the subtlety and frailness of standing and walking.

Even if the short-term effect of a sensory volley produced by electrical stimulation of a peripheral nerve (either cutaneous or muscular[261]) reaching the sensorimotor cortex is far beyond the scope of this short article, we would like to remind that this mere direct input plays a remarkable role in modifying the cortical excitability.[262,263] These effects (e.g., short-latency afferent inhibition, afferent facilitation, and long-latency afferent inhibition) have been attributed a role in cortical plasticity.[264] Further, a recent study has shown that a conditioning, prolonged stimulation of the cutaneous nerves that innervate the foot sole can increase the spinal excitability by reducing the activity of the spinal circuits underpinning the presynaptic inhibition, as tested by the H reflex.[265] In this light, the loss of sensation from the lower limbs in neuropathies might have far reaching, still uncharted consequences in the capacity of the nervous system to adapt to this loss and to the presumably altered plasticity phenomena (see[218,240]). Conversely, it has been shown that activation of the somatosensory cortex by transcranial direct-current stimulation improves somatosensory function in the elderly, as tested by changes in the threshold to foot-sole vibratory stimulation while standing.[266]

The reassuring news is that fibre regeneration in neuropathy is possible.[267-270] Excluding pharmacological treatments, motion (physical activity) seems to be the first and foremost step in fostering regeneration.[177,271-273] No doubt, exercise, despite being itself a quite unspecific undertaking, should be recommended to aged people and neuropathic patients whenever possible.[213] In particular, aside from general strength training, specific exercises centred on the muscles of the foot and around the ankle should be considered,[274] because postural stabilisation is degraded by reduction of muscle strength in the distal muscles.[231] However, treatment should depend on the disease and the impairments. For instance, it is not clear whether exercise can be helpful in children with ataxia,[275] and strengthening exercises may not be manifestly effective in adult patients with Charcot-Marie-Tooth disease,[276] whereas adapted training can be helpful.[277] Endurance and balance training seem to be effective in chemotherapy-induced peripheral neuropathies.[278]

As a final observation, there are considerable technical and methodological challenges in conducting static and dynamic balance studies in healthy young and ageing subjects, not to speak of the effects onto the higher centres by the sensory inputs related to balance and locomotion, of their integration and of the elaboration of brain responses appropriate to the context. To a very large degree, the findings obtained in patients with sensory loss can help understand the normal function of the cutaneous and proprioceptive receptors during standing and walking, and of the motor impairments linked to motor nerve fibre loss and sarcopenia. Apparent inconsistencies in past and recent therapeutic approaches need to be harmonised with new pathophysiological findings[279] into a broader and pragmatic vision.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Guido Felicetti, Philippe Thoumie, Manh-Cuong Do, and Marco Schieppati contributed to the conception of this manuscript. Marco Schieppati contributed to literature collection, manuscript preparation and writing. Guido Felicetti, Philippe Thoumie, Manh-Cuong Do, and Marco Schieppati contributed to the manuscript revision. All authors have read and agreed on the manuscript.

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REFERENCES

1. Hwang S, Agada P, Kiemel T, Jeka JJ. Identification of the unstable human postural control system. *Front Syst Neurosci*. 2016;10:22. https://doi.org/10.3389/fnsys.2016.00022.
2. Ivanenko Y, Gurfinkel VS. Human postural control. *Front Neurosci*. 2018;12:171. https://doi.org/10.3389/fnins.2018.00171.
3. Do MC, Breniere Y, Brenguier P. A biomechanical study of balance recovery during the fall forward. *J Biomech*. 1982;15:933-939. https://doi.org/10.1016/0021-9290(82)90011-2.
4. Duysens J, Clarac F, Cruse H. Load-regulating mechanisms in gait and posture: comparative aspects. *Physiol Rev*. 2000;80:83-133. https://doi.org/10.1152/physrev.2000.80.1.83.
5. Honeine JL, Schieppati M, Gagey O, Do MC. The functional role of the triceps surae muscle during human locomotion. *PLoS One*. 2013;8:e52943. https://doi.org/10.1371/journal.pone.0052943.
6. Honeine JL, Schieppati M, Gagey O, Do MC. By counteracting gravity, triceps surae sets both kinematics and kinetics of gait. *Physiol Rep*. 2014;2:e00229. https://doi.org/10.1002/phy2.229.
7. Kabbaligere R, Lee BC, Layne CS. Balancing sensory inputs: sensory reweighting of ankle proprioception and vision during a bipedal posture task. *Gait Posture*. 2017;52:244-250. https://doi.org/10.1016/j.gaitpost.2016.12.009.
8. Schillings AM, van Wezel BM, Mulder T, Duysens J. Muscular responses and movement strategies during stumbling over obstacles. *J Neurophysiol*. 2000;83:2093-2102. https://doi.org/10.1152/jn.2000.83.4.2093.
9. Dietz V, Müller R, Colombo G. Locomotor activity in spinal man: significance of afferent input from joint and load receptors. *Brain*. 2002;125:2626-2634. https://doi.org/10.1093/brain/awf273.
10. Sinkjaer T, Andersen JB, Ladouceur M, Christensen LO, Nielsen JB. Major role for sensory feedback in soleus EMG activity in the stance phase of walking in man. *J Physiol*. 2000;523:817-827. https://doi.org/10.1111/j.1469-7793.2000.00817.x.
11. Brooke JD. Somatosensory paths proceeding to spinal cord and brain – centripetal and centrifugal control for human movement. *Can J Physiol Pharmacol*. 2004;82:723-731. https://doi.org/10.1139/y04-045.
12. Patla AE, Prentice SD, Robinson C, Neufeld J. Visual control of locomotion: strategies for changing direction and for going over obstacles. *J Exp Psychol Hum Percept Perform*. 1991;17:603-634. https://doi.org/10.1037//0096-1523.17.3.603.
13. Nakamura T. Quantitative analysis of gait in the visually impaired. *Disabil Rehabil*. 1997;19:194-1977. https://doi.org/10.3109/09638289709166526.
14. Buetti B, Luxon LM. Vestibular involvement in peripheral neuropathy: a review. *Int J Audiol*. 2014;53:353-359. https://doi.org/10.3109/14992027.2014.885121.
15. Holmes S, Male AJ, Ramdharry G, et al. Vestibular dysfunction: a frequent problem for adults with mitochondrial disease. *J Neurol Neurosurg Psychiatry*. 2019;90:838-841. https://doi.org/10.1136/jnnp-2018-319267.
16. Mermeklieva EA. Pattern electroretinography and retinal changes in patients with diabetes mellitus type 2. *Neurophysiol Clin*. 2019;49:209-215. https://doi.org/10.1016/j.neucli.2019.04.002.
17. Stål F, Fransson PA, Magnusson M, Karlberg M. Effects of hypothermic anesthesia of the feet on vibration-induced body sway and adaptation. *J Vestib Res*. 2003;13:39-52.
18. Vinti M, Couillandre A, Thoumie P. Does somatosensory loss induce adaptation of the gait initiation process? *Neurosci Lett*. 2010;480:178-181. https://doi.org/10.1016/j.neulet.2010.06.017.
19. Tighilet B, Bordiga P, Cassel R, Chabbert C. Peripheral vestibular plasticity vs central compensation: evidence and questions. *J Neurol*. 2019;266(suppl 1):27-32. https://doi.org/10.1007/s00415-019-09388-9.
20. Bringoux L, Scotto Di Cesare C, Borel L, Macaluso T, Sarlegna FR. Do visual and vestibular inputs compensate for somatosensory loss in the perception of spatial orientation? Insights from a deafferented patient. *Front Hum Neurosci*. 2016;10:181. https://doi.org/10.3389/fnhum.2016.00181.
21. Inglis JT, Kennedy PM, Wells C, Chua R. The role of cutaneous receptors in the foot. *Adv Exp Med Biol*. 2002;508:111-117. https://doi.org/10.1007/978-1-4615-0713-0_14.
22. Gross F, Üçeyler N. Mechanisms of small nerve fiber pathology. *Neurosci Lett*. 2020;737:135316. https://doi.org/10.1016/j.neulet.2020.135316.
23. Delmas P, Hao J, Rodat-Despoix L. Molecular mechanisms of mechanotransduction in mammalian sensory neurons. *Nat Rev Neurosci*. 2011;12:139-153. https://doi.org/10.1038/nrn2993.
24. Strzalkowski NDJ, Ali RA, Bent LR. The firing characteristics of foot sole cutaneous mechanoreceptor afferents in response to vibration stimuli. *J Neurophysiol*. 2017;118:1931-1942. https://doi.org/10.1152/jn.00647.2016.
25. Kennedy PM, Inglis JT. Distribution and behaviour of glabrous cutaneous receptors in the human foot sole. *J Physiol*. 2002;538:995-1002. https://doi.org/10.1113/jphysiol.2001.013087.
26. Yau JM, Kim SS, Thakur PH, Bensmaia SJ. Feeling form: the neural basis of haptic shape perception. *J Neurophysiol*. 2016;115:631-642. https://doi.org/10.1152/jn.00598.2015.
27. Strzalkowski NDJ, Peters RM, Inglis JT, Bent LR. Cutaneous afferent innervation of the human foot sole: what can we learn from single-unit recordings? *J Neurophysiol*. 2018;120:1233-1246. https://doi.org/10.1152/jn.00848.2017.
28. Strzalkowski ND, Mildren RL, Bent LR. Thresholds of cutaneous afferents related to perceptual threshold across the human foot sole. *J Neurophysiol*. 2015;114:2144-2151. https://doi.org/10.1152/jn.00524.2015.
29. Schieppati M, Tacchini E, Nardone A, Tarantola J, Corna S. Subjective perception of body sway. *J Neurol Neurosurg Psychiatry*. 1999;66:313-322. https://doi.org/10.1136/jnnp.66.3.313.
30. Fujiwara K, Asai H, Miyaguchi A, Toyama H, Kunita K, Inoue K. Perceived standing position after reduction of foot-pressure sensation by cooling the sole. *Percept Mot Skills*. 2003;96:381-399. https://doi.org/10.2466/pms.2003.96.2.381.
31. Knellwolf TP, Burton AR, Hammam E, Macefield VG. Microneurography from the posterior tibial nerve: a novel method of recording activity from the foot in freely standing humans. *J Neurophysiol*. 2018;120:953-959. https://doi.org/10.1152/jn.00937.2017.
32. Kiemel T, Zhang YF, Jeka JJ. Identification of neural feedback for upright stance in humans: stabilization rather than sway minimization.

J Neurosci. 2011;31:15144-15153. https://doi.org/10.1523/JNEUROSCI.1013-11.2011.

33. Morasso P. Centre of pressure versus centre of mass stabilization strategies: the tightrope balancing case. *R Soc Open Sci*. 2020;7:200111. https://doi.org/10.1098/rsos.200111.
34. Carpenter MG, Murnaghan CD, Inglis JT. Shifting the balance: evidence of an exploratory role for postural sway. *Neuroscience*. 2010;171:196-204. https://doi.org/10.1016/j.neuroscience.2010.08.030.
35. Murnaghan CD, Horslen BC, Inglis JT, Carpenter MG. Exploratory behavior during stance persists with visual feedback. *Neuroscience*. 2011;195:54-59. https://doi.org/10.1016/j.neuroscience.2011.08.020.
36. Nurse MA, Nigg BM. The effect of changes in foot sensation on plantar pressure and muscle activity. *Clin Biomech (Bristol, Avon)*. 2001;16:719-727. https://doi.org/10.1016/s0268-0033(01)00090-0.
37. Sozzi S, Honeine JL, Do MC, Schieppati M. Leg muscle activity during tandem stance and the control of body balance in the frontal plane. *Clin Neurophysiol*. 2013;124:1175-1186. https://doi.org/10.1016/j.clinph.2012.12.001.
38. Kelly LA, Kuitunen S, Racinais S, Cresswell AG. Recruitment of the plantar intrinsic foot muscles with increasing postural demand. *Clin Biomech (Bristol, Avon)*. 2012;27:46-51. https://doi.org/10.1016/j.clinbiomech.2011.07.013.
39. Edwards AS. Body sway and vision. *J Exp Psychol*. 1946;36:526-535. https://doi.org/10.1037/h0059909.
40. Jeka JJ. Light touch contact as a balance aid. *Phys Ther*. 1997;77:476-487. https://doi.org/10.1093/ptj/77.5.476.
41. Paulus WM, Straube A, Brandt T. Visual stabilization of posture. Physiological stimulus characteristics and clinical aspects. *Brain*. 1984;107:1143-1163. https://doi.org/10.1093/brain/107.4.1143.
42. Schmid M, Casabianca L, Bottaro A, Schieppati M. Graded changes in balancing behavior as a function of visual acuity. *Neuroscience*. 2008;153:1079-1091. https://doi.org/10.1016/j.neuroscience.2008.03.024.
43. Horiuchi K, Ishihara M, Imanaka K. The essential role of optical flow in the peripheral visual field for stable quiet standing: evidence from the use of a head-mounted display. *PLoS One*. 2017;12:e0184552. https://doi.org/10.1371/journal.pone.0184552.
44. Clapp S, Wing AM. Light touch contribution to balance in normal bipedal stance. *Exp Brain Res*. 1999;125:521-524. https://doi.org/10.1007/s002210050711.
45. Sozzi S, Do MC, Monti A, Schieppati M. Sensorimotor integration during stance: processing time of active or passive addition or withdrawal of visual or haptic information. *Neuroscience*. 2012;212:59-76. https://doi.org/10.1016/j.neuroscience.2012.03.044.
46. Honeine JL, Crisafulli O, Sozzi S, Schieppati M. Processing time of addition or withdrawal of single or combined balance-stabilizing haptic and visual information. *J Neurophysiol*. 2015;114:3097-3110. https://doi.org/10.1152/jn.00618.2015.
47. Sozzi S, Crisafulli O, Schieppati M. Haptic cues for balance: use of a cane provides immediate body stabilization. *Front Neurosci*. 2017;11:705. https://doi.org/10.3389/fnins.2017.00705.
48. Kouzaki M, Masani K. Reduced postural sway during quiet standing by light touch is due to finger tactile feedback but not mechanical support. *Exp Brain Res*. 2008;188:153-158. https://doi.org/10.1007/s00221-008-1426-5.
49. Sozzi S, Decortes F, Schmid M, Crisafulli O, Schieppati M. Balance in blind subjects: cane and fingertip touch induce similar extent and promptness of stance stabilization. *Front Neurosci*. 2018;12:639. https://doi.org/10.3389/fnins.2018.00639.
50. Rogers MW, Wardman DL, Lord SR, Fitzpatrick RC. Passive tactile sensory input improves stability during standing. *Exp Brain Res*. 2001;136:514-522. https://doi.org/10.1007/s002210000615.
51. Menz HB, Lord SR, Fitzpatrick RC. A tactile stimulus applied to the leg improves postural stability in young, old and neuropathic subjects. *Neurosci Lett*. 2006;406:23-26. https://doi.org/10.1016/j.neulet.2006.07.014.
52. Loram ID, Maganaris CN, Lakie M. Active, non-spring-like muscle movements in human postural sway: how might paradoxical changes in muscle length be produced? *J Physiol*. 2005;564:281-293. https://doi.org/10.1113/jphysiol.2004.073437.
53. Morasso PG, Schieppati M. Can muscle stiffness alone stabilize upright standing? *J Neurophysiol*. 1999;82:1622-1626. https://doi.org/10.1152/jn.1999.82.3.1622.
54. Loram ID, Maganaris CN, Lakie M. Paradoxical muscle movement in human standing. *J Physiol*. 2004;556:683-689. https://doi.org/10.1113/jphysiol.2004.062398.
55. Peterka RJ. Sensory integration for human balance control. *Handb Clin Neurol*. 2018;159:27-42. https://doi.org/10.1016/B978-0-444-63916-5.00002-1.
56. Smart LJ Jr, Mobley BS, Otten EW, Smith DL, Amin MR. Not just standing there: the use of postural coordination to aid visual tasks. *Hum Mov Sci*. 2004;22:769-780. https://doi.org/10.1016/j.humov.2004.02.003.
57. Bonnet CT. Positive relations between vision and posture in the fixation task performed upright. *Motor Control*. 2019;6:1-16. https://doi.org/10.1123/mc.2018-0094.
58. Aniss AM, Gandevia SC, Burke D. Reflex responses in active muscles elicited by stimulation of low-threshold afferents from the human foot. *J Neurophysiol*. 1992;67:1375-1384. https://doi.org/10.1152/jn.1992.67.5.1375.
59. Fallon JB, Bent LR, McNulty PA, Macefield VG. Evidence for strong synaptic coupling between single tactile afferents from the sole of the foot and motoneurons supplying leg muscles. *J Neurophysiol*. 2005;94:3795-3804. https://doi.org/10.1152/jn.00359.2005.
60. Burke D, Dickson HG, Skuse NF. Task-dependent changes in the responses to low-threshold cutaneous afferent volleys in the human lower limb. *J Physiol*. 1991;432:445-458. https://doi.org/10.1113/jphysiol.1991.sp018393.
61. Mouchnino L, Fontan A, Tandonnet C, et al. Facilitation of cutaneous inputs during the planning phase of gait initiation. *J Neurophysiol*. 2015;114:301-308. https://doi.org/10.1152/jn.00668.2014.
62. Duysens J, Bastiaanse CM, Smits-Engelsman BC, Dietz V. Gait acts as a gate for reflexes from the foot. *Can J Physiol Pharmacol*. 2004;82:715-722. https://doi.org/10.1139/y04-071.
63. Marigold DS, Chang AJ, Lajoie K. Cutaneous reflex modulation during obstacle avoidance under conditions of normal and degraded visual input. *Exp Brain Res*. 2017;235:2483-2493. https://doi.org/10.1007/s00221-017-4976-6.
64. Pearcey GEP, Zehr EP. We are upright-walking cats: human limbs as sensory antennae during locomotion. *Physiology (Bethesda)*. 2019;34:354-364. https://doi.org/10.1152/physiol.00008.2019.
65. Klarner T, Pearcey GEP, Sun Y, et al. Beyond the bottom of the foot: topographic Organization of the Foot Dorsum in walking. *Med Sci Sports Exerc*. 2017;49:2439-2450. https://doi.org/10.1249/MSS.0000000000001389.
66. Godi M, Turcato AM, Schieppati M, Nardone A. Test-retest reliability of an insole plantar pressure system to assess gait along linear and curved trajectories. *J Neuroeng Rehabil*. 2014;11:95. https://doi.org/10.1186/1743-0003-11-95.
67. Zehr EP, Nakajima T, Barss T, et al. Cutaneous stimulation of discrete regions of the sole during locomotion produces "sensory steering" of the foot. *BMC Sports Sci Med Rehabil*. 2014;6:33. https://doi.org/10.1186/2052-1847-6-33.
68. Turcato AM, Godi M, Giordano A, Schieppati M, Nardone A. The generation of centripetal force when walking in a circle: insight from the distribution of ground reaction forces recorded by plantar

insoles. *J Neuroeng Rehabil*. 2015;12:4. https://doi.org/10.1186/1743-0003-12-4.
69. Courtine G, Schieppati M. Human walking along a curved path. I. Body trajectory, segment orientation and the effect of vision. *Eur J Neurosci*. 2003;18:177-190. https://doi.org/10.1046/j.1460-9568.2003.02736.x.
70. Courtine G, Schieppati M. Tuning of a basic coordination pattern constructs straight-ahead and curved walking in humans. *J Neurophysiol*. 2004;91:1524-1535. https://doi.org/10.1152/jn.00817.2003.
71. Courtine G, Papaxanthis C, Schieppati M. Coordinated modulation of locomotor muscle synergies constructs straight-ahead and curvilinear walking in humans. *Exp Brain Res*. 2006;170:320-335. https://doi.org/10.1007/s00221-005-0215-7.
72. Do MC, Bussel B, Breniere Y. Influence of plantar cutaneous afferents on early compensatory reactions to forward fall. *Exp Brain Res*. 1990;79:319-324. https://doi.org/10.1007/BF00608241.
73. Thoumie P, Do MC. Changes in motor activity and biomechanics during balance recovery following cutaneous and muscular deafferentation. *Exp Brain Res*. 1996;110:289-297. https://doi.org/10.1007/BF00228559.
74. Meyer PF, Oddsson LI, De Luca CJ. The role of plantar cutaneous sensation in unperturbed stance. *Exp Brain Res*. 2004;156:505-512. https://doi.org/10.1007/s00221-003-1804-y.
75. Mildren RL, Hare CM, Bent LR. Cutaneous afferent feedback from the posterior ankle contributes to proprioception. *Neurosci Lett*. 2017;636:145-150. https://doi.org/10.1016/j.neulet.2016.10.058.
76. Mazzaro N, Grey MJ, do Nascimento OF, Sinkjaer T. Afferent-mediated modulation of the soleus muscle activity during the stance phase of human walking. *Exp Brain Res*. 2006;173:713-723. https://doi.org/10.1007/s00221-006-0451-5.
77. Asai H, Fujiwara K, Toyama H, Yamashina T, Nara I, Tachino K. The influence of foot soles cooling on standing postural control. In: Brandt TH, Paulus W, Bles W, Dieterich M, Krafezyk S, Straube A, eds. *Disorders of Posture and Gait*. Stuttgart: Thieme; 1990:198-201.
78. Lowrey CR, Strzalkowski ND, Bent LR. Cooling reduces the cutaneous afferent firing response to vibratory stimuli in glabrous skin of the human foot sole. *J Neurophysiol*. 2013;109:839-850. https://doi.org/10.1152/jn.00381.2012.
79. Öberg G. *Skadade fotgängare – Fokus på drift och underhåll vid analys av sjukvårdsregistrerade skadade i STRADA [Injured pedestrians – Focus on operation and maintenance in the analysis of healthcare registered injuries in STRADA]*. 2011. https://www.diva-portal.org/smash/get/diva2:670581/FULLTEXT01.pdf.
80. Elvik R, Bjørnskau T. Risk of pedestrian falls in Oslo, Norway: relation to age, gender and walking surface condition. *J Transp Heal*. 2019;12:359-370.
81. Billot M, Handrigan GA, Simoneau M, Corbeil P, Teasdale N. Short term alteration of balance control after a reduction of plantar mechanoreceptor sensation through cooling. *Neurosci Lett*. 2013;535:40-44. https://doi.org/10.1016/j.neulet.2012.11.022.
82. Hoch MC, Russell DM. Plantar cooling does not affect standing balance: a systematic review and meta-analysis. *Gait Posture*. 2016;43:1-8. https://doi.org/10.1016/j.gaitpost.2015.10.011.
83. Germano AM, Schmidt D, Milani TL. Effects of hypothermically reduced plantar skin inputs on anticipatory and compensatory balance responses. *BMC Neurosci*. 2016;17:41. https://doi.org/10.1186/s12868-016-0279-2.
84. Glasser S, Collings R, Paton J, Marsden J. Effect of experimentally reduced distal sensation on postural response to hip abductor/ankle evertor muscle vibration. *Gait Posture*. 2015;42:193-198. https://doi.org/10.1016/j.gaitpost.2015.05.009.
85. Ferguson OW, Polskaia N, Tokuno CD. The effects of foot cooling on postural muscle responses to an unexpected loss of balance. *Hum Mov Sci*. 2017;54:240-247. https://doi.org/10.1016/j.humov.2017.05.008.
86. Schlee G, Sterzing T, Milani TL. Foot sole skin temperature affects plantar foot sensitivity. *Clin Neurophysiol*. 2009;120:1548-1551. https://doi.org/10.1016/j.clinph.2009.06.010.
87. Schmidt D, Germano AMC, Milani TL. Effects of active and passive warming of the foot sole on vibration perception thresholds. *Clin Neurophysiol Pract*. 2016;2:38-43. https://doi.org/10.1016/j.cnp.2016.12.005.
88. Iles JF. Evidence for cutaneous and corticospinal modulation of presynaptic inhibition of Ia afferents from the human lower limb. *J Physiol*. 1996;491:197-207. https://doi.org/10.1113/jphysiol.1996.sp021207.
89. Kavounoudias A, Roll R, Roll JP. Foot sole and ankle muscle inputs contribute jointly to human erect posture regulation. *J Physiol*. 2001;532:869-878. https://doi.org/10.1111/j.1469-7793.2001.0869e.x.
90. Lipsitz LA, Lough M, Niemi J, Travison T, Howlett H, Manor B. A shoe insole delivering subsensory vibratory noise improves balance and gait in healthy elderly people. *Arch Phys Med Rehabil*. 2015;96:432-439. https://doi.org/10.1016/j.apmr.2014.10.004.
91. Chen WM, Li JW, Geng X, Wang C, Chen L, Ma X. The potential influence of stochastic resonance vibrations on neuromuscular strategies and center of pressure sway during single-leg stance. *Clin Biomech (Bristol, Avon)*. 2020;77:105069. https://doi.org/10.1016/j.clinbiomech.2020.105069.
92. Wang Y, Watanabe K, Chen L. Effect of plantar cutaneous inputs on center of pressure during quiet stance in older adults. *J Exerc Sci Fit*. 2016;14:24-28. https://doi.org/10.1016/j.jesf.2016.02.001.
93. Tramontano M, Piermaria J, Morone G, Reali A, Vergara M, Tamburella F. Postural changes during exteroceptive thin plantar stimulation: the effect of prolonged use and different plantar localizations. *Front Syst Neurosci*. 2019;13:49. https://doi.org/10.3389/fnsys.2019.00049.
94. Viseux F, Barbier F, Parreira R, Lemaire A, Villeneuve P, Leteneur S. Less than one millimeter under the great toe is enough to change balance ability in elite women handball players. *J Hum Kinet*. 2019;69:69-77. https://doi.org/10.2478/hukin-2019-0024.
95. Maki BE, Perry SD, Norrie RG, McIlroy WE. Effect of facilitation of sensation from plantar foot-surface boundaries on postural stabilization in young and older adults. *J Gerontol A Biol Sci Med Sci*. 1999;54:M281-M287. https://doi.org/10.1093/gerona/54.6.m281.
96. Palluel E, Nougier V, Olivier I. Do spike insoles enhance postural stability and plantar-surface cutaneous sensitivity in the elderly? *Age (Dordr)*. 2008;30:53-61. https://doi.org/10.1007/s11357-008-9047-2.
97. Viseux F, Lemaire A, Barbier F, Charpentier P, Leteneur S, Villeneuve P. How can the stimulation of plantar cutaneous receptors improve postural control? Review and clinical commentary. *Neurophysiol Clin*. 2019;49:263-268. https://doi.org/10.1016/j.neucli.2018.12.006.
98. Nurse MA, Hulliger M, Wakeling JM, Nigg BM, Stefanyshyn DJ. Changing the texture of footwear can alter gait patterns. *J Electromyogr Kinesiol*. 2005;15:496-506. https://doi.org/10.1016/j.jelekin.2004.12.003.
99. Robb KA, Perry SD. Textured foot orthotics on dynamic stability and turning performance in Parkinson's disease. *J Mot Behav*. 2020;52:396-403. https://doi.org/10.1080/00222895.2019.1639609.
100. Alfuth M. Textured and stimulating insoles for balance and gait impairments in patients with multiple sclerosis and Parkinson's disease: a systematic review and meta-analysis. *Gait Posture*. 2017;51:132-141. https://doi.org/10.1016/j.gaitpost.2016.10.007.
101. Paton J, Hatton AL, Rome K, Kent B. Effects of foot and ankle devices on balance, gait and falls in adults with sensory perception loss: a systematic review. *JBI Database Syst Rev Implement Rep*. 2016;14:127-162. https://doi.org/10.11124/JBISRIR-2016-003229.

102. Kavounoudias A, Roll JP, Anton JL, Nazarian B, Roth M, Roll R. Proprio-tactile integration for kinesthetic perception: an fMRI study. *Neuropsychologia*. 2008;46:567-575. https://doi.org/10.1016/j.neuropsychologia.2007.10.002.
103. Proske U, Gandevia SC. The proprioceptive senses: their roles in signaling body shape, body position and movement, and muscle force. *Physiol Rev*. 2012;92:1651-1697. https://doi.org/10.1152/physrev.00048.2011.
104. Matthews PBC. The structures of the receptors. In Davson E, Greenfield ADM, Wittam R, Brindley GS (ed.), *Mammalian Muscle Receptors and their Central Actions*. Monographs of the Physiological Society, Number 23. London: Edward Arnold LTD; 1972.
105. Macefield VG, Knellwolf TP. Functional properties of human muscle spindles. *J Neurophysiol*. 2018;120:452-467. https://doi.org/10.1152/jn.00071.2018.
106. McKeon PO, Hertel J, Bramble D, Davis I. The foot core system: a new paradigm for understanding intrinsic foot muscle function. *Br J Sports Med*. 2015;49:290. https://doi.org/10.1136/bjsports-2013-092690.
107. Burke D, Eklund G. Muscle spindle activity in man during standing. *Acta Physiol Scand*. 1977;100:187-199. https://doi.org/10.1111/j.1748-1716.1977.tb05936.x.
108. Knellwolf TP, Burton AR, Hammam E, Macefield VG. Firing properties of muscle spindles supplying the intrinsic foot muscles of humans in unloaded and freestanding conditions. *J Neurophysiol*. 2019;121:74-84. https://doi.org/10.1152/jn.00539.2018.
109. Farris DJ, Kelly LA, Cresswell AG, Lichtwark GA. The functional importance of human foot muscles for bipedal locomotion. *Proc Natl Acad Sci U S A*. 2019;116:1645-1650. https://doi.org/10.1073/pnas.1812820116.
110. Schieppati M, Hugon M, Grasso M, Nardone A, Galante M. The limits of equilibrium in young and elderly normal subjects and in parkinsonians. *Electroencephalogr Clin Neurophysiol*. 1994;93:286-298. https://doi.org/10.1016/0168-5597(94)90031-0.
111. Farris DJ, Birch J, Kelly L. Foot stiffening during the push-off phase of human walking is linked to active muscle contraction, and not the windlass mechanism. *J R Soc Interface*. 2020;17:20200208. https://doi.org/10.1098/rsif.2020.0208.
112. Wright WG, Ivanenko YP, Gurfinkel VS. Foot anatomy specialization for postural sensation and control. *J Neurophysiol*. 2012;107:1513-1521. https://doi.org/10.1152/jn.00256.2011.
113. Gurfinkel VS, Ivanenko YP, Levik YS. The contribution of foot deformation to the changes of muscular length and angle in the ankle joint during standing in man. *Physiol Res*. 1994;43:371-377.
114. Zelik KE, La Scaleia V, Ivanenko YP, Lacquaniti F. Coordination of intrinsic and extrinsic foot muscles during walking. *Eur J Appl Physiol*. 2015;115:691-701. https://doi.org/10.1007/s00421-014-3056-x.
115. Schieppati M, Nardone A, Siliotto R, Grasso M. Early and late stretch responses of human foot muscles induced by perturbation of stance. *Exp Brain Res*. 1995;105:411-422. https://doi.org/10.1007/BF00233041.
116. Ellrich J, Steffens H, Treede RD, Schomburg ED. The Hoffmann reflex of human plantar foot muscles. *Muscle Nerve*. 1998;21:732-738. https://doi.org/10.1002/(sici)1097-4598(199806)21:6<732::aid-mus4>3.0.co;2-8.
117. Nardone A, Corrà T, Schieppati M. Different activations of the soleus and gastrocnemii muscles in response to various types of stance perturbation in man. *Exp Brain Res*. 1990;80:323-332. https://doi.org/10.1007/BF00228159.
118. Corna S, Galante M, Grasso M, Nardone A, Schieppati M. Unilateral displacement of lower limb evokes bilateral EMG responses in leg and foot muscles in standing humans. *Exp Brain Res*. 1996;109:83-91. https://doi.org/10.1007/BF00228629.
119. Nardone A, Schieppati M. Medium-latency response to muscle stretch in human lower limb: estimation of conduction velocity of group II fibres and central delay. *Neurosci Lett*. 1998;249:29-32.
120. Schieppati M, Nardone A. Medium-latency stretch reflexes of foot and leg muscles analysed by cooling the lower limb in standing humans. *J Physiol*. 1997;503:691-698. https://doi.org/10.1111/j.1469-7793.1997.691bg.x.
121. Nakajima T, Sakamoto M, Tazoe T, Endoh T, Komiyama T. Location specificity of plantar cutaneous reflexes involving lower limb muscles in humans. *Exp Brain Res*. 2006;175:514-525. https://doi.org/10.1007/s00221-006-0568-6.
122. Clair JM, Okuma Y, Misiaszek JE, Collins DF. Reflex pathways connect receptors in the human lower leg to the erector spinae muscles of the lower back. *Exp Brain Res*. 2009;196:217-227. https://doi.org/10.1007/s00221-009-1849-7.
123. Meyer PF, Oddsson LI, De Luca CJ. Reduced plantar sensitivity alters postural responses to lateral perturbations of balance. *Exp Brain Res*. 2004;157:526-536. https://doi.org/10.1007/s00221-004-1868-3.
124. Abbruzzese M, Rubino V, Schieppati M. Task-dependent effects evoked by foot muscle afferents on leg muscle activity in humans. *Electroencephalogr Clin Neurophysiol*. 1996;101:339-348. https://doi.org/10.1016/0924-980x(96)95682-9.
125. Bove M, Trompetto C, Abbruzzese G, Schieppati M. The posture-related interaction between Ia-afferent and descending input on the spinal reflex excitability in humans. *Neurosci Lett*. 2006;397:301-306.
126. Crenna P, Frigo C. Excitability of the soleus H-reflex arc during walking and stepping in man. *Exp Brain Res*. 1987;66:49-60. https://doi.org/10.1007/BF00236201.
127. Thompson C, Bélanger M, Fung J. Effects of plantar cutaneo-muscular and tendon vibration on posture and balance during quiet and perturbed stance. *Hum Mov Sci*. 2011;30:153-171. https://doi.org/10.1016/j.humov.2010.04.002.
128. Ackerley R, Chancel M, Aimonetti JM, Ribot-Ciscar E, Kavounoudias A. Seeing your foot move changes muscle proprioceptive feedback. *eNeuro*. 2019;6:ENEURO.0341-18.2019. https://doi.org/10.1523/ENEURO.0341-18.2019.
129. Banks R. Muscle spindles and tendon organs. *Elsevier Reference Module in Biomedical Sciences*. Amsterdam, Netherlands: Elsevier; 2018. http://www.sciencedirect.com/science/article/pii/B9780128012383994893.
130. Liu JX, Thornell LE, Pedrosa-Domellöf F. Muscle spindles in the deep muscles of the human neck: a morphological and immunocytochemical study. *J Histochem Cytochem*. 2003;51:175-186. https://doi.org/10.1177/002215540305100206.
131. Schieppati M, Nardone A, Schmid M. Neck muscle fatigue affects postural control in man. *Neuroscience*. 2003;121:277-285. https://doi.org/10.1016/s0306-4522(03)00439-1.
132. Bloem BR, Allum JH, Carpenter MG, Honegger F. Is lower leg proprioception essential for triggering human automatic postural responses? *Exp Brain Res*. 2000;130:375-391. https://doi.org/10.1007/s002219900259.
133. Bove M, Diverio M, Pozzo T, Schieppati M. Neck muscle vibration disrupts steering of locomotion. *J Appl Physiol (1985)*. 2001;91:581-588. https://doi.org/10.1152/jappl.2001.91.2.581.
134. Schmid M, De Nunzio AM, Schieppati M. Trunk muscle proprioceptive input assists steering of locomotion. *Neurosci Lett*. 2005;384:127-132. https://doi.org/10.1016/j.neulet.2005.04.059.
135. Courtine G, De Nunzio AM, Schmid M, Beretta MV, Schieppati M. Stance- and locomotion-dependent processing of vibration-induced proprioceptive inflow from multiple muscles in humans. *J Neurophysiol*. 2007;97:772-779. https://doi.org/10.1152/jn.00764.2006.
136. Bove M, Fenoggio C, Tacchino A, Pelosin E, Schieppati M. Interaction between vision and neck proprioception in the control of stance. *Neuroscience*. 2009;164:1601-1608. https://doi.org/10.1016/j.neuroscience.2009.09.053.

137. Karnath HO. Subjective body orientation in neglect and the interactive contribution of neck muscle proprioception and vestibular stimulation. *Brain*. 1994;117:1001-1012. https://doi.org/10.1093/brain/117.5.1001.
138. Bove M, Brichetto G, Abbruzzese G, Marchese R, Schieppati M. Neck proprioception and spatial orientation in cervical dystonia. *Brain*. 2004;127:2764-2778. https://doi.org/10.1093/brain/awh291.
139. Magnusson M, Andersson G, Gomez S, et al. Cervical muscle afferents play a dominant role over vestibular afferents during bilateral vibration of neck muscles. *J Vestib Res*. 2006;16:127-136.
140. Pettorossi VE, Schieppati M. Neck proprioception shapes body orientation and perception of motion. *Front Hum Neurosci*. 2014;8:895. https://doi.org/10.3389/fnhum.2014.00895.
141. Jamal K, Leplaideur S, Leblanche F, Moulinet Raillon A, Honoré T, Bonan I. The effects of neck muscle vibration on postural orientation and spatial perception: a systematic review. *Neurophysiol Clin*. 2020;50:227-267. https://doi.org/10.1016/j.neucli.2019.10.003.
142. Osoba MY, Rao AK, Agrawal SK, Lalwani AK. Balance and gait in the elderly: a contemporary review. *Laryngoscope Investig Otolaryngol*. 2019;4:143-153. https://doi.org/10.1002/lio2.252.
143. Deshpande N, Metter EJ, Ling S, Conwit R, Ferrucci L. Physiological correlates of age-related decline in vibrotactile sensitivity. *Neurobiol Aging*. 2008;29:765-773. https://doi.org/10.1016/j.neurobiolaging.2006.12.002.
144. Viseux FJF. The sensory role of the sole of the foot: review and update on clinical perspectives. *Neurophysiol Clin*. 2020;50:55-68. https://doi.org/10.1016/j.neucli.2019.12.003.
145. Era P, Jokela J, Suominen H, Heikkinen E. Correlates of vibrotactile thresholds in men of different ages. *Acta Neurol Scand*. 1986;74:210-217. https://doi.org/10.1111/j.1600-0404.1986.tb07857.x.
146. Patel M, Fransson PA, Johansson R, Magnusson M. Foam posturography: standing on foam is not equivalent to standing with decreased rapidly adapting mechanoreceptive sensation. *Exp Brain Res*. 2011;208:519-527. https://doi.org/10.1007/s00221-010-2498-6.
147. Teasdale N, Stelmach GE, Breunig A. Postural sway characteristics of the elderly under normal and altered visual and support surface conditions. *J Gerontol*. 1991;46:B238-B244. https://doi.org/10.1093/geronj/46.6.b238.
148. Abrahamová D, Hlavacka F. Age-related changes of human balance during quiet stance. *Physiol Res*. 2008;57:957-964.
149. Lord SR, Clark RD, Webster IW. Postural stability and associated physiological factors in a population of aged persons. *J Gerontol*. 1991;46:M69-M76. https://doi.org/10.1093/geronj/46.3.m69.
150. Schieppati M., Grasso M., Siliotto R., Nardone A. Effect of age, chronic diseases and parkinsonism on postural control. In: Stelmach GE, Hömberg V (eds). *Sensorimotor Impairment in the Elderly. NATO ASI Series (Series D: Behavioural and Social Sciences)*, 1993;75:355–373.Springer, Dordrecht. https://doi.org/10.1007/978-94-011-1976-4_22.
151. Anson E, Bigelow RT, Swenor B, et al. Loss of peripheral sensory function explains much of the increase in postural sway in healthy older adults. *Front Aging Neurosci*. 2017;9:202. https://doi.org/10.3389/fnagi.2017.00202.
152. Machado ÁS, Bombach GD, Duysens J, Carpes FP. Differences in foot sensitivity and plantar pressure between young adults and elderly. *Arch Gerontol Geriatr*. 2016;63:67-71. https://doi.org/10.1016/j.archger.2015.11.005.
153. Peters RM, McKeown MD, Carpenter MG, Inglis JT. Losing touch: age-related changes in plantar skin sensitivity, lower limb cutaneous reflex strength, and postural stability in older adults. *J Neurophysiol*. 2016;116:1848-1858. https://doi.org/10.1152/jn.00339.2016.
154. Stecco C, Macchi V, Porzionato A, et al. The ankle retinacula: morphological evidence of the proprioceptive role of the fascial system. *Cells Tissues Organs*. 2010;192:200-210. https://doi.org/10.1159/000290225.
155. Djajadikarta ZJ, Gandevia SC, Taylor JL. Age has no effect on ankle proprioception when movement history is controlled. *J Appl Physiol (1985)*. 2020;128:1365-1372. https://doi.org/10.1152/japplphysiol.00741.2019.
156. Cruz-Jentoft AJ, Sayer AA. Sarcopenia. *Lancet*. 2019;393:2636-2646. https://doi.org/10.1016/S0140-6736(19)31138-9 Erratum in: Lancet. 2019;393:2590.
157. Piasecki M, Ireland A, Piasecki J, et al. Failure to expand the motor unit size to compensate for declining motor unit numbers distinguishes sarcopenic from non-sarcopenic older men. *J Physiol*. 2018;596:1627-1637. https://doi.org/10.1113/JP275520.
158. Piasecki M, Ireland A, Piasecki J, et al. Long-term endurance and power training may facilitate motor unit size expansion to compensate for declining motor unit numbers in older age. *Front Physiol*. 2019;10:449. https://doi.org/10.3389/fphys.2019.00449.
159. Ciciliot S, Rossi AC, Dyar KA, Blaauw B, Schiaffino S. Muscle type and fiber type specificity in muscle wasting. *Int J Biochem Cell Biol*. 2013;45:2191-2199. https://doi.org/10.1016/j.biocel.2013.05.016.
160. Murgia M, Toniolo L, Nagaraj N, et al. Single muscle fiber proteomics reveals fiber-type-specific features of human muscle aging. *Cell Rep*. 2017;19:2396-2409. https://doi.org/10.1016/j.celrep.2017.05.054.
161. Machek SB. Mechanisms of sarcopenia: motor unit remodelling and muscle fibre type shifts with ageing. *J Physiol*. 2018;596:3467-3468. https://doi.org/10.1113/JP276586.
162. Wiedmer P, Jung T, Castro JP, et al. Sarcopenia – molecular mechanisms and open questions. *Ageing Res Rev*. 2020;65:101200. https://doi.org/10.1016/j.arr.2020.101200.
163. Paillard T. Relationship between muscle function, muscle typology and postural performance according to different postural conditions in young and older adults. *Front Physiol*. 2017;8:585. https://doi.org/10.3389/fphys.2017.00585.
164. Allen MD, Doherty TJ, Rice CL, Kimpinski K. Physiology in medicine: neuromuscular consequences of diabetic neuropathy. *J Appl Physiol (1985)*. 2016;121:1-6. https://doi.org/10.1152/japplphysiol.00733.2015.
165. Maitre J, Paillard TP. Influence of the plantar cutaneous information in postural regulation depending on the age and the physical activity status. *Front Hum Neurosci*. 2016;10:409. https://doi.org/10.3389/fnhum.2016.00409.
166. Kim AY, Lee JK, Kim SH, Choi J, Song JJ, Chae SW. Is postural dysfunction related to sarcopenia? A population-based study. *PLoS One*. 2020;15:e0232135. https://doi.org/10.1371/journal.pone.0232135.
167. Fan C, Stecco C, Fede C, et al. Effect of age on the muscle spindle in triceps surae in mouse. 59. P3, p. 40. In: Carraro U (ed). Thirty Years of Translational Research in Mobility Medicine: Collection of Abstracts of the 2020 Padua Muscle Days. *Eur J Transl Myol*. 2020;30:8826-8847. https://doi.org/10.4081/ejtm.2019.8826.
168. Butler AA, Lord SR, Rogers MW, Fitzpatrick RC. Muscle weakness impairs the proprioceptive control of human standing. *Brain Res*. 2008;1242:244-251. https://doi.org/10.1016/j.brainres.2008.03.094.
169. Piastra G, Perasso L, Lucarini S, et al. Effects of two types of 9-month adapted physical activity program on muscle mass, muscle strength, and balance in moderate sarcopenic older women. *Biomed Res Int*. 2018;2018:5095673. https://doi.org/10.1155/2018/5095673.
170. Lesinski M, Hortobágyi T, Muehlbauer T, Gollhofer A, Granacher U. Effects of balance training on balance performance in healthy older adults: a systematic review and meta-analysis. *Sports Med*. 2015;45:1721-1738. https://doi.org/10.1007/s40279-015-0375-y Erratum in: *Sports Med*. 2016;46:457.
171. Paillard T. Acute and chronic neuromuscular electrical stimulation and postural balance: a review. *Eur J Appl Physiol*. 2020;120:1475-1488. https://doi.org/10.1007/s00421-020-04383-9.

172. Hicks CW, Wang D, Matsushita K, Windham G, Selvin E. Peripheral neuropathy and all-cause and cardiovascular mortality in U.S. adults : a prospective cohort study. *Ann Intern Med*. 2020. https://doi.org/10.7326/M20-1340 [Epub ahead of print].
173. Gomes Paiva AF, Thoumie P, Missaoui B. How far do stabilometric and clinical parameters correlate in peripheral neuropathies? *Gait Posture*. 2017;52:11-14. https://doi.org/10.1016/j.gaitpost.2016.11.010.
174. Gwathmey KG, Grogan J. Nutritional neuropathies. *Muscle Nerve*. 2020;62:13-29. https://doi.org/10.1002/mus.26783.
175. Cangussu LM, Nahas-Neto J, Orsatti CL, et al. Effect of isolated vitamin D supplementation on the rate of falls and postural balance in postmenopausal women fallers: a randomized, double-blind, placebo-controlled trial. *Menopause*. 2016;23:267-274. https://doi.org/10.1097/GME.0000000000000525.
176. Merkies IS, Faber CG, Lauria G. Advances in diagnostics and outcome measures in peripheral neuropathies. *Neurosci Lett*. 2015;596:3-13. https://doi.org/10.1016/j.neulet.2015.02.038.
177. Ramdharry G. Peripheral nerve disease. *Handb Clin Neurol*. 2018;159:403-415. https://doi.org/10.1016/B978-0-444-63916-5.00026-4.
178. Freeman R, Gewandter JS, Faber CG, et al. Idiopathic distal sensory polyneuropathy: ACTTION diagnostic criteria. *Neurology*. 2020;95:1005-1014. https://doi.org/10.1212/WNL.0000000000010988.
179. Kazamel M, Stino AM, Smith AG. Metabolic syndrome and peripheral neuropathy. *Muscle Nerve*. 2020. https://doi.org/10.1002/mus.27086 Epub ahead of print.
180. Edmonds M. Vascular disease in the lower limb in type 1 diabetes. *Cardiovasc Endocrinol Metab*. 2019;8:39-46. https://doi.org/10.1097/XCE.0000000000000168.
181. Tesfaye S. Recent advances in the management of diabetic distal symmetrical polyneuropathy. *J Diabetes Investig*. 2011;2:33-42. https://doi.org/10.1111/j.2040-1124.2010.00083.x.
182. Patel K, Horak H, Tiryaki E. Diabetic neuropathies. *Muscle Nerve*. 2021;63:22-30. https://doi.org/10.1002/mus.27014.
183. Khan MM, Lustrino D, Silveira WA, et al. Sympathetic innervation controls homeostasis of neuromuscular junctions in health and disease. *Proc Natl Acad Sci U S A*. 2016;113:746-750. https://doi.org/10.1073/pnas.1524272113 Erratum in: PNAS, 2017;114:E5277. http://doi.org/10.1073/pnas.1708559114.
184. Barker D, Saito M. Autonomic innervation of receptors and muscle fibres in cat skeletal muscle. *Proc R Soc Lond B Biol Sci*. 1981;212:317-332. https://doi.org/10.1098/rspb.1981.0042.
185. Passatore M, Deriu F, Grassi C, Roatta S. A comparative study of changes operated by sympathetic nervous system activation on spindle afferent discharge and on tonic vibration reflex in rabbit jaw muscles. *J Auton Nerv Syst*. 1996;57:163-167. https://doi.org/10.1016/0165-1838(95)00074-7.
186. Radovanovic D, Peikert K, Lindström M, Domellöf FP. Sympathetic innervation of human muscle spindles. *J Anat*. 2015;226:542-548. https://doi.org/10.1111/joa.12309.
187. Rodrigues ACZ, Wang ZM, Messi ML, et al. Heart and neural crest derivative 2-induced preservation of sympathetic neurons attenuates sarcopenia with aging. *J Cachexia Sarcopenia Muscle*. 2020. https://doi.org/10.1002/jcsm.12644 Epub ahead of print.
188. Kennedy WR, Selim MM, Brink TS, et al. A new device to quantify tactile sensation in neuropathy. *Neurology*. 2011;76:1642-1649. https://doi.org/10.1212/WNL.0b013e318219fadd.
189. Andersen H, Gjerstad MD, Jakobsen J. Atrophy of foot muscles: a measure of diabetic neuropathy. *Diabetes Care*. 2004;27:2382-2385. https://doi.org/10.2337/diacare.27.10.2382.
190. Henderson AD, Johnson AW, Rasmussen LG, et al. Early-stage diabetic neuropathy reduces foot strength and intrinsic but not extrinsic foot muscle size. *J Diabetes Res*. 2020;2020:9536362-9536369. https://doi.org/10.1155/2020/9536362.
191. Parikh P, Polston D, Li Y. Prevalence of denervation in the intrinsic foot muscles in patients with distal predominantly small fiber neuropathy. *Muscle Nerve*. 2020;61:595-599. https://doi.org/10.1002/mus.26829.
192. Yang Q, Zhang Y, Zeng Q, et al. Correlation between diabetic peripheral neuropathy and sarcopenia in patients with type 2 diabetes mellitus and diabetic foot disease: a cross-sectional study. *Diabetes Metab Syndr Obes*. 2020;13:377-386. https://doi.org/10.2147/DMSO.S237362.
193. Bianchi L, Volpato S. Muscle dysfunction in type 2 diabetes: a major threat to patient's mobility and independence. *Acta Diabetol*. 2016;53:879-889. https://doi.org/10.1007/s00592-016-0880-y.
194. Kraiwong R, Vongsirinavarat M, Hiengkaew V, von Heideken Wågert P. Effect of sensory impairment on balance performance and lower limb muscle strength in older adults with type 2 diabetes. *Ann Rehabil Med*. 2019;43:497-508. https://doi.org/10.5535/arm.2019.43.4.497.
195. Lamontagne A, Buchthal F. Electrophysiological studies in diabetic neuropathy. *J Neurol Neurosurg Psychiatry*. 1970;33:442-452. https://doi.org/10.1136/jnnp.33.4.442.
196. Papanas N, Maltezos E. The diabetic hand: a forgotten complication? *J Diabetes Complications*. 2010;24:154-162. https://doi.org/10.1016/j.jdiacomp.2008.12.009.
197. Løseth S, Stålberg EV, Lindal S, Olsen E, Jorde R, Mellgren SI. Small and large fiber neuropathy in those with type 1 and type 2 diabetes: a 5-year follow-up study. *J Peripher Nerv Syst*. 2016;21(1):15-21. https://doi.org/10.1111/jns.12154 PMID: 26663481.
198. Nardone A, Schieppati M. Group II spindle fibres and afferent control of stance. Clues from diabetic neuropathy. *Clin Neurophysiol*. 2004;115:779-789. https://doi.org/10.1016/j.clinph.2003.11.007.
199. Simoneau GG, Ulbrecht JS, Derr JA, Becker MB, Cavanagh PR. Postural instability in patients with diabetic sensory neuropathy. *Diabetes Care*. 1994;17:1411-1421. https://doi.org/10.2337/diacare.17.12.1411.
200. Bergin PS, Bronstein AM, Murray NM, Sancovic S, Zeppenfeld DK. Body sway and vibration perception thresholds in normal aging and in patients with polyneuropathy. *J Neurol Neurosurg Psychiatry*. 1995;58:335-340. https://doi.org/10.1136/jnnp.58.3.335.
201. Bonnet C, Carello C, Turvey MT. Diabetes and postural stability: review and hypotheses. *J Mot Behav*. 2009;41:172-190. https://doi.org/10.3200/JMBR.41.2.172-192.
202. Boucher P, Teasdale N, Courtemanche R, Bard C, Fleury M. Postural stability in diabetic polyneuropathy. *Diabetes Care*. 1995;18:638-645. https://doi.org/10.2337/diacare.18.5.638.
203. Wettasinghe AH, Dissanayake DWN, Allet L, Katulanda P, Lord SR. Falls in older people with diabetes: identification of simple screening measures and explanatory risk factors. *Prim Care Diabetes*. 2020;14:723-728. https://doi.org/10.1016/j.pcd.2020.05.006.
204. Kimura K, Endo Y. Age-related changes in the tactile pressure sensitivity threshold in the sole of the foot in diabetic patients. *J Phys Ther Sci*. 2018;30:917-920. https://doi.org/10.1589/jpts.30.917.
205. Sacco IC, Hamamoto AN, Gomes AA, Onodera AN, Hirata RP, Hennig EM. Role of ankle mobility in foot rollover during gait in individuals with diabetic neuropathy. *Clin Biomech (Bristol, Avon)*. 2009;24:687-692. https://doi.org/10.1016/j.clinbiomech.2009.05.003.
206. Simó R, Frontoni S. Neuropathic damage in the diabetic eye: clinical implications. *Curr Opin Pharmacol*. 2020;55:1-7. https://doi.org/10.1016/j.coph.2020.08.013.
207. Hafner J, Pollreisz A, Egner B, Pablik E, Schmidt-Erfurth U. Presence of peripheral lesions and correlation to macular perfusion, oxygenation and neurodegeneration in early type II diabetic retinal disease. *Retina*. 2020;40:1964-1971. https://doi.org/10.1097/IAE.0000000000002704.
208. Picconi F, Mataluni G, Ziccardi L, et al. Association between early neuroretinal dysfunction and peripheral motor unit loss in patients

with type 1 diabetes mellitus. *J Diabetes Res*. 2018;2018:9763507-9763509. https://doi.org/10.1155/2018/9763507.
209. Hewston P, Deshpande N. Falls and balance impairments in older adults with type 2 diabetes: thinking beyond diabetic peripheral neuropathy. *Can J Diabetes*. 2016;40:6-9. https://doi.org/10.1016/j.jcjd.2015.08.005.
210. Carpenter MG, Campos JL. The effects of hearing loss on balance: a critical review. *Ear Hear*. 2020;41(suppl 1):107S-119S. https://doi.org/10.1097/AUD.0000000000000929.
211. Wilson SJ, Garner JC, Loprinzi PD. The influence of multiple sensory impairments on functional balance and difficulty with falls among U.S. adults. *Prev Med*. 2016;87:41-46. https://doi.org/10.1016/j.ypmed.2016.02.023.
212. Senefeld JW, Keenan KG, Ryan KS, D'Astice SE, Negro F, Hunter SK. Greater fatigability and motor unit discharge variability in human type 2 diabetes. *Physiol Rep*. 2020;8:e14503. https://doi.org/10.14814/phy2.14503.
213. Ramdharry GM. Rehabilitation in practice: management of lower motor neuron weakness. *Clin Rehabil*. 2010;24:387-397. https://doi.org/10.1177/0269215509357848.
214. Agrawal Y, Carey JP, Della Santina CC, Schubert MC, Minor LB. Diabetes, vestibular dysfunction, and falls: analyses from the National Health and Nutrition Examination Survey. *Otol Neurotol*. 2010;31:1445-1450. https://doi.org/10.1097/MAO.0b013e3181f2f035.
215. Hlavačka F, Horak FB. Somatosensory influence on postural response to galvanic vestibular stimulation. *Physiol Res*. 2006;55(suppl 1):S121-S127.
216. Allum JH, Honegger F, Schicks H. The influence of a bilateral peripheral vestibular deficit on postural synergies. *J Vestib Res*. 1994;4:49-70.
217. Baumann O, Borra RJ, Bower JM, et al. Consensus paper: the role of the cerebellum in perceptual processes. *Cerebellum*. 2015;14:197-220. https://doi.org/10.1007/s12311-014-0627-7.
218. Ferris JK, Inglis JT, Madden KM, Boyd LA. Brain and body: a review of central nervous system contributions to movement impairments in diabetes. *Diabetes*. 2020;69:3-11. https://doi.org/10.2337/db19-0321.
219. Nardone A, Tarantola J, Miscio G, Pisano F, Schenone A, Schieppati M. Loss of large-diameter spindle afferent fibres is not detrimental to the control of body sway during upright stance: evidence from neuropathy. *Exp Brain Res*. 2000;135:155-162. https://doi.org/10.1007/s002210000513.
220. van der Linden MH, van der Linden SC, Hendricks HT, van Engelen BG, Geurts AC. Postural instability in Charcot-Marie-tooth type 1A patients is strongly associated with reduced somatosensation. *Gait Posture*. 2010;31:483-438. https://doi.org/10.1016/j.gaitpost.2010.02.005.
221. Simonetta-Moreau M, Marque P, Marchand-Pauvert V, Pierrot-Deseilligny E. The pattern of excitation of human lower limb motoneurones by probable group II muscle afferents. *J Physiol*. 1999;517:287-300. https://doi.org/10.1111/j.1469-7793.1999.0287z.x.
222. Behse F, Buchthal F. Normal sensory conduction in the nerves of the leg in man. *J Neurol Neurosurg Psychiatry*. 1971;34:404-414. https://doi.org/10.1136/jnnp.34.4.404.
223. Kars HJ, Hijmans JM, Geertzen JH, Zijlstra W. The effect of reduced somatosensation on standing balance: a systematic review. *J Diabetes Sci Technol*. 2009;3:931-943. https://doi.org/10.1177/193229680900300441.
224. Nardone A, Corna S, Turcato AM, Schieppati M. Afferent control of walking: are there distinct deficits associated to loss of fibres of different diameter? *Clin Neurophysiol*. 2014;125:327-335. https://doi.org/10.1016/j.clinph.2013.07.007.
225. Tozza S, Aceto MG, Pisciotta C, et al. Postural instability in Charcot-Marie-tooth 1A disease. *Gait Posture*. 2016;49:353-357. https://doi.org/10.1016/j.gaitpost.2016.07.183.
226. Mazzaro N, Grey MJ, Sinkjaer T, Andersen JB, Pareyson D, Schieppati M. Lack of on-going adaptations in the soleus muscle activity during walking in patients affected by large-fiber neuropathy. *J Neurophysiol*. 2005;93:3075-3085. https://doi.org/10.1152/jn.01071.2004.
227. Grey MJ, Ladouceur M, Andersen JB, Nielsen JB, Sinkjaer T. Group II muscle afferents probably contribute to the medium latency soleus stretch reflex during walking in humans. *J Physiol*. 2001;534:925-933. https://doi.org/10.1111/j.1469-7793.2001.00925.x.
228. Li L, Zhang S, Dobson J. The contribution of small and large sensory afferents to postural control in patients with peripheral neuropathy. *J Sport Health Sci*. 2019;8:218-227. https://doi.org/10.1016/j.jshs.2018.09.010.
229. Wuehr M, Schniepp R, Schlick C, et al. Sensory loss and walking speed related factors for gait alterations in patients with peripheral neuropathy. *Gait Posture*. 2014;39:852-858. https://doi.org/10.1016/j.gaitpost.2013.11.013.
230. Kennedy RA, Carroll K, McGinley JL. Gait in children and adolescents with Charcot-Marie-tooth disease: a systematic review. *J Peripher Nerv Syst*. 2016;21:317-328. https://doi.org/10.1111/jns.12183.
231. Lencioni T, Piscosquito G, Rabuffetti M, et al. Electromyographic and biomechanical analysis of step negotiation in Charcot Marie tooth subjects whose level walk is not impaired. *Gait Posture*. 2018;62:497-504. https://doi.org/10.1016/j.gaitpost.2018.04.014.
232. Estilow T, Glanzman AM, Burns J, et al. Balance impairment in pediatric Charcot-Marie-tooth disease. *Muscle Nerve*. 2019;60:242-249. https://doi.org/10.1002/mus.26500.
233. Thomas PK. Overview of Charcot-Marie-tooth disease type 1A. *Ann N Y Acad Sci*. 1999;883:1-5.
234. Ivanenko YP, Dominici N, Cappellini G, et al. Changes in the spinal segmental motor output for stepping during development from infant to adult. *J Neurosci*. 2013;33:3025-3036. https://doi.org/10.1523/JNEUROSCI.2722-12.2013.
235. Dewolf AH, Sylos-Labini F, Cappellini G, Lacquaniti F, Ivanenko Y. Emergence of different gaits in infancy: relationship between developing neural circuitries and changing biomechanics. *Front Bioeng Biotechnol*. 2020;8:473. https://doi.org/10.3389/fbioe.2020.00473.
236. Anheim M, Tranchant C, Koenig M. The autosomal recessive cerebellar ataxias. *N Engl J Med*. 2012;366:636-646. https://doi.org/10.1056/NEJMra1006610.
237. Berciano J, García A, Infante J. Peripheral nerve involvement in hereditary cerebellar and multisystem degenerative disorders. *Handb Clin Neurol*. 2013;115:907-932. https://doi.org/10.1016/B978-0-444-52902-2.00051-5.
238. Selvarajah D, Wilkinson ID, Emery CJ, et al. Early involvement of the spinal cord in diabetic peripheral neuropathy. *Diabetes Care*. 2006;29:2664-2669. https://doi.org/10.2337/dc06-0650.
239. Tesfaye S, Selvarajah D, Gandhi R, et al. Diabetic peripheral neuropathy may not be as its name suggests: evidence from magnetic resonance imaging. *Pain*. 2016;157(suppl 1):S72-S80. https://doi.org/10.1097/j.pain.0000000000000465.
240. Selvarajah D, Wilkinson ID, Fang F, et al. Structural and functional abnormalities of the primary somatosensory cortex in diabetic peripheral neuropathy: a multimodal MRI study. *Diabetes*. 2019;68:796-806. https://doi.org/10.2337/db18-0509.
241. Sghirlanzoni A, Pareyson D, Lauria G. Sensory neuron diseases. *Lancet Neurol*. 2005;4:349-361. https://doi.org/10.1016/S1474-4422(05)70096-X.
242. Nardone A, Galante M, Pareyson D, Schieppati M. Balance control in sensory neuron disease. *Clin Neurophysiol*. 2007;118:538-550. https://doi.org/10.1016/j.clinph.2006.11.012.
243. Lauria G, Pareyson D, Sghirlanzoni A. Neurophysiological diagnosis of acquired sensory ganglionopathies. *Eur Neurol*. 2003;50:146-152. https://doi.org/10.1159/000073055.

244. Bloem BR, Allum JH, Carpenter MG, Verschuuren JJ, Honegger F. Triggering of balance corrections and compensatory strategies in a patient with total leg proprioceptive loss. *Exp Brain Res*. 2002;142: 91-107. https://doi.org/10.1007/s00221-001-0926-3.
245. Burke D, Halmagyi GM. Normal tendon reflexes despite absent sensory nerve action potentials in CANVAS: a neurophysiological study. *J Neurol Sci*. 2018;387:75-79. https://doi.org/10.1016/j.jns.2018.01.023.
246. Lallemend F, Ernfors P. Molecular interactions underlying the specification of sensory neurons. *Trends Neurosci*. 2012;35:373-381. https://doi.org/10.1016/j.tins.2012.03.006.
247. Zochodne DW. Sensory neurodegeneration in diabetes: beyond glucotoxicity. *Int Rev Neurobiol*. 2016;127:151-180. https://doi.org/10.1016/bs.irn.2016.03.007.
248. Cazzato D, Bella ED, Dacci P, Mariotti C, Lauria G. Cerebellar ataxia, neuropathy, and vestibular areflexia syndrome: a slowly progressive disorder with stereotypical presentation. *J Neurol*. 2016;263:245-249. https://doi.org/10.1007/s00415-015-7951-9.
249. Cortese A, Simone R, Sullivan R, et al. Biallelic expansion of an intronic repeat in RFC1 is a common cause of late-onset ataxia. *Nat Genet*. 2019;51:649-658. https://doi.org/10.1038/s41588-019-0372-4.
250. Dupré M, Hermann R, Froment TC. Update on cerebellar Ataxia with neuropathy and bilateral vestibular areflexia syndrome (CANVAS). *Cerebellum*. 2020. https://doi.org/10.1007/s12311-020-01192-w Epub ahead of print.
251. Nardone A, Galante M, Grasso M, Schieppati M. Stance ataxia and delayed leg muscle responses to postural perturbations in cervical spondylotic myelopathy. *J Rehabil Med*. 2008;40:539-547. https://doi.org/10.2340/16501977-0214.
252. Haddas R, Ju KL, Boah A, Kosztowski T, Derman PB. The effect of surgical decompression on functional balance testing in patients with cervical spondylotic myelopathy. *Clin Spine Surg*. 2019;32:369-376. https://doi.org/10.1097/BSD.0000000000000889.
253. Rinalduzzi S, Serafini M, Capozza M, et al. Stance postural strategies in patients with chronic inflammatory demyelinating Polyradiculoneuropathy. *PLoS One*. 2016;11:e0151629. https://doi.org/10.1371/journal.pone.0151629.
254. Milosevic M, Masani K, Kuipers MJ, et al. Trunk control impairment is responsible for postural instability during quiet sitting in individuals with cervical spinal cord injury. *Clin Biomech (Bristol, Avon)*. 2015;30:507-512. https://doi.org/10.1016/j.clinbiomech.2015.03.002.
255. Frigo C, Crenna P. Multichannel SEMG in clinical gait analysis: a review and state-of-the-art. *Clin Biomech (Bristol, Avon)*. 2009;24: 236-245. https://doi.org/10.1016/j.clinbiomech.2008.07.012.
256. Paillard T, Noé F. Techniques and methods for testing the postural function in healthy and pathological subjects. *Biomed Res Int*. 2015; 2015:891390. https://doi.org/10.1155/2015/891390.
257. Drăgulinescu A, Drăgulinescu AM, Zincă G, Bucur D, Feieş V, Neagu DM. Smart socks and in-shoe systems: state-of-the-art for two popular technologies for foot motion analysis, sports, and medical applications. *Sensors (Basel)*. 2020;20:4316. https://doi.org/10.3390/s20154316.
258. Lajoie Y, Teasdale N, Cole JD, et al. Gait of a deafferented subject without large myelinated sensory fibers below the neck. *Neurology*. 1996;47:109-115. https://doi.org/10.1212/wnl.47.1.109.
259. Penati R, Schieppati M, Nardone A. Cognitive performance during gait is worsened by overground but enhanced by treadmill walking. *Gait Posture*. 2020;76:182-187. https://doi.org/10.1016/j.gaitpost.2019.12.006.
260. Omana H, Madou E, Montero-Odasso M, Payne M, Viana R, Hunter S. The effect of dual-task testing on balance and gait performance in adults with type 1 or type 2 diabetes mellitus: a systematic review. *Curr Diabetes Rev*. 2020. Epub ahead of print;16. https://doi.org/10.2174/1573399816999201001203652.
261. Pilurzi G, Ginatempo F, Mercante B, et al. Role of cutaneous and proprioceptive inputs in sensorimotor integration and plasticity occurring in the facial primary motor cortex. *J Physiol*. 2020;598: 839-851. https://doi.org/10.1113/JP278877.
262. Ridding MC, Rothwell JC. Afferent input and cortical organisation: a study with magnetic stimulation. *Exp Brain Res*. 1999;126:536-544. https://doi.org/10.1007/s002210050762.
263. Tokimura H, Di Lazzaro V, Tokimura Y, et al. Short latency inhibition of human hand motor cortex by somatosensory input from the hand. *J Physiol*. 2000;523:503-513. https://doi.org/10.1111/j.1469-7793.2000.t01-1-00503.x Erratum in: *J Physiol*. 2000;524:942.
264. Brown KE, Neva JL, Feldman SJ, Staines WR, Boyd LA. Sensorimotor integration in healthy aging: baseline differences and response to sensory training. *Exp Gerontol*. 2018;112:1-8. https://doi.org/10.1016/j.exger.2018.08.004.
265. Pearcey GEP, Zehr EP. Repeated and patterned stimulation of cutaneous reflex pathways amplifies spinal cord excitability. *J Neurophysiol*. 2020; 124:342-351. https://doi.org/10.1152/jn.00072.2020.
266. Zhou J, Lo OY, Lipsitz LA, Zhang J, Fang J, Manor B. Transcranial direct current stimulation enhances foot sole somatosensation when standing in older adults. *Exp Brain Res*. 2018;236:795-802. https://doi.org/10.1007/s00221-018-5178-6.
267. Lauria G, Lombardi R. Skin biopsy in painful and immune-mediated neuropathies. *J Peripher Nerv Syst*. 2012;17(Suppl 3):38-45. https://doi.org/10.1111/j.1529-8027.2012.00430.x.
268. Zochodne DW. Reversing neuropathic deficits. *J Peripher Nerv Syst*. 2012;17(suppl 2):4-9. https://doi.org/10.1111/j.1529-8027.2012.00388.x.
269. Bönhof GJ, Strom A, Püttgen S, et al. Patterns of cutaneous nerve fibre loss and regeneration in type 2 diabetes with painful and painless polyneuropathy. *Diabetologia*. 2017;60:2495-2503. https://doi.org/10.1007/s00125-017-4438-5.
270. Lien BV, Brown NJ, Ransom SC, et al. Enhancing peripheral nerve regeneration with neurotrophic factors and bioengineered scaffolds: a basic science and clinical perspective. *J Peripher Nerv Syst*. 2020; 25:320-334. https://doi.org/10.1111/jns.12414.
271. Missaoui B, Thoumie P. Balance training in ataxic neuropathies. Effects on balance and gait parameters. *Gait Posture*. 2013;38:471-476. https://doi.org/10.1016/j.gaitpost.2013.01.017.
272. Busse M, Ramdharry G. Targeting sedentary behaviour in neurological disease. *Pract Neurol*. 2020;20:187-188. https://doi.org/10.1136/practneurol-2019-002491.
273. Mahalakshmi B, Maurya N, Lee SD, Bharath Kumar V. Possible neuroprotective mechanisms of physical exercise in neurodegeneration. *Int J Mol Sci*. 2020;21:5895. https://doi.org/10.3390/ijms21165895.
274. Sartor CD, Hasue RH, Cacciari LP, et al. Effects of strengthening, stretching and functional training on foot function in patients with diabetic neuropathy: results of a randomized controlled trial. *BMC Musculoskelet Disord*. 2014;15:137. https://doi.org/10.1186/1471-2474-15-137.
275. Hartley H, Cassidy E, Bunn L, et al. Exercise and physical therapy interventions for children with Ataxia: a systematic review. *Cerebellum*. 2019;18:951-968. https://doi.org/10.1007/s12311-019-01063-z.
276. Sman AD, Hackett D, Fiatarone Singh M, Fornusek C, Menezes MP, Burns J. Systematic review of exercise for Charcot-Marie-tooth disease. *J Peripher Nerv Syst*. 2015;20:347-362. https://doi.org/10.1111/jns.12116.
277. Mori L, Signori A, Prada V, et al. Schenone a; TreSPE study group. Treadmill training in patients affected by Charcot-Marie-tooth neuropathy: results of a multicenter, prospective, randomized, single-blind, controlled study. *Eur J Neurol*. 2020;27:280-287. https://doi.org/10.1111/ene.14074.

278. Kneis S, Wehrle A, Müller J, et al. It's never too late – balance and endurance training improves functional performance, quality of life, and alleviates neuropathic symptoms in cancer survivors suffering from chemotherapy-induced peripheral neuropathy: results of a randomized controlled trial. *BMC Cancer*. 2019;19:414. https://doi.org/10.1186/s12885-019-5522-7.
279. Kobayashi M, Zochodne DW. Diabetic polyneuropathy: bridging the translational gap. *J Peripher Nerv Syst*. 2020;25:66-75. https://doi.org/10.1111/jns.12392.

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