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REVIEW**Cutaneous and muscular afferents from the foot and sensory fusion processing: physiology and pathology in neuropathies**Guido Felicetti¹ | Philippe Thoumie^{2,3} | Manh-Cuong Do^{4,5} | Marco Schieppati⁶

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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

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

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 weight³⁻⁶. 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 reflexes¹⁰ 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, e.g., cutaneous,¹⁷ proprioceptive,¹⁸ vestibular.¹⁹ As a consequence, compensation processes²⁰ 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 pain²². 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), and 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 hand²⁶ 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, cutaneous 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,³⁹⁴⁰ because continuous motion of the retinal image is an effective stimulus for postural stabilisation.^{41 42 43} Body sway is reduced also when the brain receives additional information from light touching a solid frame with a finger tip or from the contact to the ground of a hand-held cane.^{44 45 46 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 touch⁴⁶. This suggests that the integration of the input for balance control is a time-consuming neural operation initiated by the haptic stimulus²⁶ at the interface finger-frame or hand-cane. Passive tactile cues to the skin of the lower limb or to 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 53 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 in itself, but is normally coordinated with supra postural tasks (see e.g.,^{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 (see⁶²). 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 & Zehr.⁶⁴ One may note that locomotion produces a continuous spatio-temporal change in the plantar pressures (and from foot dorsum when wearing shoes⁶⁵), 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, ordained 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, 70, 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 stance⁷⁴, 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 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 walking⁷⁶ (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 Sweden⁷⁹ (see⁸⁰). 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.^{88,89} 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 motoneurons to leg muscles by way of presynaptic inhibition.⁸⁹

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 contralaterally with respect to the stimulation site.⁹⁰ Conceivably, subjects perceive their body weight displaced towards 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.^{91,92} 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,⁹³ 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.^{94,95} A small raised edge placed underneath the boundary of the foot was shown to improve the reaction to unpredictable postural perturbations.⁹⁶ 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.^{97,98,99} Anyhow, in spite of a plethora of fine studies addressing this issue in healthy subjects and patients (e.g.,¹⁰⁰), the clinical effectiveness of mechanical stimulation by patterned insoles remains elusive.^{101,102}

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.¹⁰³

In an influential article, Proske & Gandevia¹⁰⁴ 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^{105,106} and the sensory inflow from the receptors of these active muscles must play a pre-eminent role in balance control.¹⁰⁷ The more so, because spindles are subject to centrifugal control, whereby the gamma motoneurons can enhance the spindle responsiveness to changes in muscle length by acting onto the intrafusal muscle fibres. Burke & Eklund¹⁰⁸ recorded the discharge of single nerve fibres from the spindles of the pretibial muscles. The spindle discharge frequency was not higher under standing 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.¹⁰⁹ 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. All in all, 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.¹¹⁰ The activation of these muscles increases with increasing postural demand^{111,112} as the foot shape changes.¹¹³ 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.¹¹⁴ 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.¹¹⁵ 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 ^{116,117} and full-blown stretch reflex responses are elicited by fast perturbations of stance. ¹¹⁶ 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. ^{118,119} 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 ^{120,121} (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. ¹²² 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. ¹²³ 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. ¹²⁴

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. ¹²⁵ Therefore, foot muscle afferents establish oligo-synaptic connections transmitting mixed effects to the triceps muscle motoneurons, 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 ¹²⁶ and that the H reflex is depressed during the early stance phase of gait. ¹²⁷ 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 help control the position of the upper body. ¹²⁸

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. ¹²⁹ Briefly, the spindle firing frequency diminished in the presence of vision by reduction of the efferent activity of the gamma-motoneurons, 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. ¹³⁰ 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.¹³¹ No wonder that fatigue of the neck muscles increases body sway during stance and worsens the perception of stability.¹³² The neck and the axial muscles represent a complex source of inputs appropriate for producing balance correcting responses to perturbations¹³³ 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.¹³⁴ Unilateral vibration of the erector spinae muscle during gait produces a deviation of the walking trajectory toward the opposite side as well.^{135, 136}

As expected, vision reduces the sway evoked by neck vibration during standing.¹³⁷ 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^{138, 139 140} (see¹⁴¹). A recent review by Jamal et al.¹⁴³ 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 published¹⁴³. Elderly subjects show significantly elevated threshold for high-frequency vibration of the foot sole^{144, 145, 146} or of internal malleolus.¹⁴⁴ 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 foam¹⁴⁷ discloses a decline in postural stability¹⁴⁸. Sway increases beyond 60 years of age or so¹⁴⁹, in particular when unhealthy conditions are present.^{150, 151, 152} A study by Machado et al.¹⁵³ showed that foot sensitivity diminishes with age, particularly at the heel. The reduced plantar sensitivity of the foot in the elderly, correlated with changes in the threshold of the skin receptors, affects the strength of the cutaneous postural reflexes as well.¹⁵⁴ 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.¹⁵⁵ 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.¹⁵⁶

3.5 | Sarcopenia

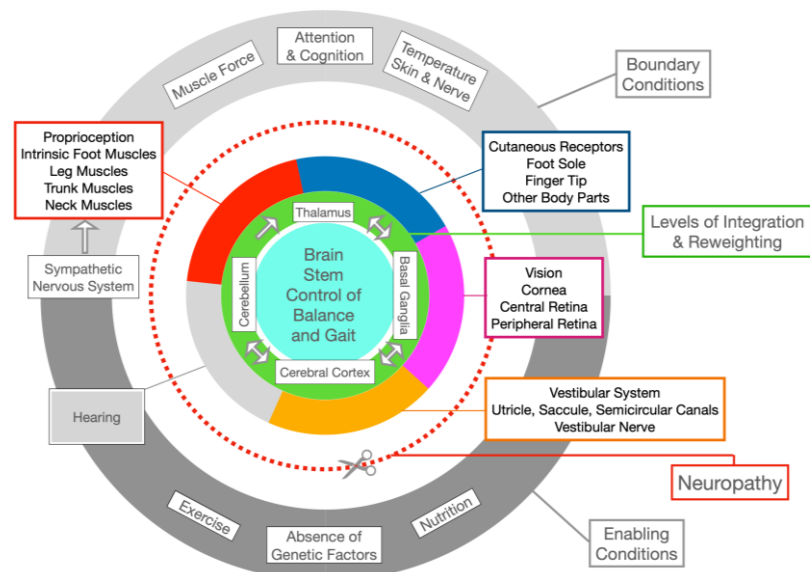
Certainly, in the old adult, muscle weakness is an issue. Sarcopenia designates the loss of muscle mass and strength that occurs with ageing and contributes to frailty and functional impairment in the elderly.¹⁵⁷ Loss of skeletal muscle innervation with structural changes in neuromuscular junction can accompany increased age. Muscle fibres can lose 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.¹⁵⁸ This event does not necessarily accompany physically fit ageing, where intense motor activity may facilitate axonal sprouting and reinnervation of denervated fibers.¹⁵⁹ 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^{160, 161, 162}). There is hope to soon elucidate the relevant molecular pathways.¹⁶³

The connections between muscle condition and balance function in older and younger subjects are addressed in a comprehensive review article.¹⁶⁴ Many studies have considered the control of balance under static and dynamic conditions in the elderly with an eye on their muscle status, but no firm conclusions have been reached, probably because of the complexity of the matter.¹⁶⁴ Muscle weakness certainly is a cause of insufficient production of muscle torques for standing and walking.¹⁶⁵ 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.¹⁶⁶ 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.¹⁶⁷

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.¹⁶⁸ 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).¹⁶⁹ 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 women¹⁷⁰ (see^{171,172} 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.

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)



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.¹⁷³

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.^{111,174} Nutritional deficiencies represent a frequent source of complex neuropathies,¹⁷⁵ and should be carefully considered because of the overlapping of the clinical picture with other disorders and with balance problems in the elderly.¹⁷⁶ Recent reviews have addressed the complex features of neuropathies, with a view on improving diagnosis and considering the possibility of counteracting their evolution.^{177,178,179,180} 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.^{181,182} 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, e.g.,¹⁸³). This is because muscles spindles, much as the typical extrafusal muscle fibres and their neuromuscular junctions as well,¹⁸⁴ receive sympathetic innervation potentially modulating their transduction properties.^{185,186,187} Whether sympathetic neuropathy can contribute to sarcopenia (3.5) is not settled, but is not beyond understanding.¹⁸⁸

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.¹⁸⁹ 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 skin²⁵ declines with age and neuropathy.^{145,154} 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.^{190,191} 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.¹⁹² 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 distal-most part of the lower limb adds to muscle weakness and to the diffuse sarcopenia frequently encountered in neuropathy,¹⁹³ leading to major problems in balance and gait, hence to impairment in the patient's mobility and independence (see¹⁹⁴).

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.¹⁹⁵ These patients often suffer from sensorimotor distal symmetric polyneuropathy starting in the feet, even if the upper limbs are not spared.^{196,197} 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.¹⁹⁸ 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.¹⁹⁹ The decrease in conduction velocity of the group II fibres¹⁹⁹ 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.^{198,199} The magnitude of changes in the neuromuscular properties of these patients are muscle dependent and reflect a length-dependent disease progression.²⁰⁰

It has been shown earlier and confirmed recently that these patients are generally less stable than healthy subjects, as detected by posturography.^{201, 202, 203} Even with vision, their postural stability is impaired, indicating incomplete compensation by vision of the loss of input from the feet.²⁰⁴ In a recent assessment centred on balance and falls, three fourths of multiple-faller patients had a diagnosis of neuropathy.²⁰⁵ 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.²⁰⁶ 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.²⁰⁷

In some diabetic patients, vision can be impaired as well. Both the retina and the cornea are involved in the neurodegenerative process.^{208, 209} Remarkably it has been shown that both motor unit loss and retinal dysfunction are early markers of subclinical neuropathy.²¹⁰ 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.²¹¹ This adds to the conclusion of previous ample studies on the risk of falling in a general population, in which multiple sensory impairment, i.e. vision, peripheral neuropathy and hearing problems²¹² were associated with higher probability of falls or balance dysfunction.²¹³ However, reduced muscle strength in diabetic patients is present before the clinical onset of neuropathy and is characterised by increased fatigability and reduced muscle twitch amplitude, without major changes in the pattern of motor unit firing, pointing to primary disruption of contractile function.²¹⁴ Muscle weakness impacts on the functional abilities of these patients and can lead to severely impaired balance reactions (see²¹⁵).

A high prevalence of vestibular dysfunction was found in diabetic patients, accompanying a neuropathy of long duration. After adjusting for peripheral neuropathy and retinopathy, the vestibular dysfunction appeared to contribute to the risk of falling.²¹⁶ 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.²¹⁷ 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.²¹⁸ 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.²¹⁹ The consequences of involvement of the central nervous system in diabetic and other neuropathies²²⁰ 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.^{221, 222} 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.^{120, 223, 224} 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),²²⁵ 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,^{226, 227} 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. The group II fibres are recruited during gait in response to a mild perturbation of the ankle angle in the patients with CMT1A,^{228, 229} suggesting that they can normally assist gait, possibly as part of the central co-activation of the alpha- and gamma-motoneurons. Li et al.²³⁰ 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.²³¹ A systematic review 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.²³² 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 ladder²³³. Unfortunately, the role of the foot deformity, which can have peculiar effects on the sensory inflow during stance and gait and complex tasks,^{114, 234} has not received much attention. This is particularly relevant because the onset of CMT disease is usually in childhood,²³⁵ a crucial period for the development of the gait networks and for the growth of the locomotor apparatus.^{236, 237}

Much as hereditary ataxias can affect fibres in the peripheral nerves (see^{238, 239}), the peripheral neuropathies can also be associated with white matter loss in the spinal tracts²⁴⁰ and higher brain centres.^{241, 242} 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),²⁴³ 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 than in patients with CMT1A and also larger than in patients with diabetes, with and without vision.²⁴⁴ 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.²⁴⁵ 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,²⁴⁶ 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,²⁴⁷ suggesting a differential sensitivity of the dorsal ganglion neurones to the responsible noxious agent²⁴⁸ (see also²⁴⁹ for the diabetic polyneuropathy). A peculiar form of progressive late-onset ganglionopathy of genetic origin with marked instability and high risk of falling,^{250, 251} the cerebellar ataxia with neuropathy and bilateral vestibular areflexia (CANVAS), has been under investigation for a number of years.²⁵²

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.²⁵³ Surgical decompression normally enhances balance and gait, but the improvement may not be immediate.²⁵⁴ 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,²⁵⁵ 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,²⁵⁶ 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 (e.g., ^{257, 258, 259}). 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. ²⁶⁰ 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, ²⁶¹ simple attention-requiring concurrent tasks can worsen balance control in patients with diabetes and neuropathy, ²⁶² 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 ²⁶³) 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. ^{264, 265} These effects (e.g., short-latency afferent inhibition, afferent facilitation, and long-latency afferent inhibition) have been attributed a role in cortical plasticity. ²⁶⁶ 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. ²⁶⁷ 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 ^{268, 269}). 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. ²⁷⁰

The reassuring news is that fibre regeneration in neuropathy is possible. ^{271, 272, 273, 274} Excluding pharmacological treatments, motion (physical activity) seems to be the first and foremost step in fostering regeneration. ^{178, 275, 276, 277, 278} No doubt, exercise, despite being itself a quite unspecific undertaking, should be recommended to aged people and neuropathic patients whenever possible. ²¹⁵ In particular, aside from general strength training, specific exercises centred on the muscles of the foot and around the ankle should be considered, ²⁷⁹ because postural stabilisation is degraded by reduction of muscle strength in the distal muscles. ²³³ 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, ²⁸⁰ and strengthening exercises may not be manifestly effective in adult patients with Charcot-Marie-Tooth disease, ²⁸¹ whereas adapted training can be helpful. ²⁸² Endurance and balance training seem to be effective in chemotherapy-induced peripheral neuropathies. ²⁸³

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 ²⁸⁴ into a broader and pragmatic vision.

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