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## The effects of peripheral nerve impairments on postural control and mobility among people with peripheral neuropathy

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THE EFFECTS OF PERIPHERAL NERVE IMPAIRMENTS ON POSTURAL CONTROL  
AND MOBILITY AMONG PEOPLE WITH PERIPHERAL NEUROPATHY

A Dissertation

Submitted to the Graduate Faculty of the  
Louisiana State University and  
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in partial fulfillment of the  
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in

The School of Kinesiology

by  
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B.S., Shanghai University of Sport, 2009  
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## **ABSTRACT**

Approximately 20 million Americans are suffering Peripheral Neuropathy (PN). It is estimated that the prevalence of all-cause PN is about 2.4% in the entire adult population, whereas over 8-10% in the population segment over the age of 55 (Martyn & Hughes, 1997). Peripheral Neuropathy leads to a high risk of falling, resulting from the deficits of postural control caused by the impaired peripheral nerves, especially the degenerative somatosensory system. To date, there is no effective medical treatment for the disease but pain managements. The deficits of postural control decrease the life quality of this population.

The degeneration of peripheral nerves reduces sensory inputs from the somatosensory system to central nervous system via spinal reflexive loop, which should provide valuable real-time information for balance correction. Therefore, it is necessary to investigate how PN affects the somatosensory system regarding postural control. Besides that, people with PN may develop a compensatory mechanism which could be reinforced by exercise training, ultimately to improve balance and mobility in their daily life. The neuroplasticity may occur within somatosensory system by relying on relative intact sensory resources. Hence, unveiling the compensatory mechanism in people with PN may help in understanding (a) essential sensations or function of peripheral nerves to postural control, (b) effective strategy of physical treatments for people with PN, and (c) task-dependent sensory information requirements.

Therefore, this dissertation discussed the roles of foot sole sensation, ankle proprioception, and stretch reflex on balance as well as gait among people with PN. Furthermore, the discussion of the coupling between small and large afferent reflexive loops may spot the compensatory mechanism in people with PN.



# **CHAPTER 1. POSTURAL CONTROL IN LOMOTION**

## **Postural Stability in Standing and Walking**

Postural control is defined as the act of maintaining, achieving or restoring a state of balance during any posture or activity (Pollock, Durward, Rowe, & Paul, 2000). The postural control system involves the complex organization from related peripheral sensory receptors, mediated by the central nervous system (CNS), to the musculoskeletal system. The structure of the human body is an inherently unstable system that requires a neuromuscular control system to maintain balance. A real time interaction between postural control system and external system is required during standing and walking. This interaction involves not only the relative success of maintaining an equilibrium position but also the appropriateness and efficiency of movement strategies used to achieve that equilibrium position (Horak, 1987). Balance is a generic term describing the dynamics of body posture to prevent falling which is related to the inertial forces acting on the body and the inertial characteristics of body segments (Winter, 1995). The goal of postural control is to maintain balance which is governed by the neuromuscular control of the Center of Mass (COM) position in relation to the base of support.

### **Postural Stability in Standing**

The COM is a point equivalent to the total body mass in the global reference system and is the weighted average of the COM of each body segment in a three dimensional space. While standing, the classic definition of postural stability is the ability to maintain an upright posture and to keep the vertical projection of the COM within the limits of the base of support (Karlsson & Frykberg, 2000). Since the COM is difficult to determine, Center of Pressure (COP) is used in most literature to study the postural control. The COP is the point location of the vertical ground reaction force vector. It reflects a weighted average of all the pressures over the surface of the

area while the feet are in contact with the ground which is correlated but not identical to the COM. The projection of the sway of COM on the ground can be measured by the sway of COP. The “sway” of COP is not exactly the same as the behavior of COM but mainly results from ankle movements during postural control. The COP trajectory in anterior-posterior (A/P) direction reflects ankle plantar/dorsiflexion which represents the neuromuscular control of the ankle during postural control. In standing, the difference between COP and COM is proportional to the horizontal acceleration of the COM (Geursen, Altena, & Massen, 1976). Additionally, there is a negative correlation between COP-COM and the acceleration of COM (Winter, 1995). When COP is ahead of COM, the acceleration is backward, but it is reverse when COP is behind COM. This relationship also applies to medial-lateral (M/L) direction directions. The COP is not identical with COM, but it would reflect the behavior of the COM while standing.

Compared to the COM, the COP is easier to determine by a force plate. It not only reflects the proprieties of COM excursions but also exhibits properties of postural stability used in the control of equilibrium (Blaszczyk, Lowe, & Hansen, 1994; Maki, 1986; Prieto, Myklebust, & Myklebust, 1993). As a traditional measure of postural stability, COP is frequently used in medical diagnostics and postural control studies. Its related measures can generally predict the risk of falling even though most falls occur during locomotor tasks rather than during standing tasks. Relative COP measures are reliable to assess postural stability, including the displacement of COP, 95% area, velocity at A/P and M/L directions, and plantar pressure distribution. Postural stability is commonly assessed by relative outcomes of COP and plantar pressure distribution in standing (Thorbahn & Newton, 1996). The stance width, standing posture (i.e., unipedal vs. bipedal), and visual cues can influence results (i.e., balance performance increases with increased stance width (Henry, Fung, & Horak, 2001). In Sheldon’s study, inability to control body sway

in the elderly has been evidenced as a major causation of their postural instability (Sheldon, 1963). Therefore, the risk of falls can be predicted by postural instability which is assessed by the relevant COP measures in standing.

### Postural Control in Walking

Postural stability during walking is different than during standing. However, postural control in walking is not only concerned on how a single stride is generated, but also on how movements are controlled from one stride to the next. COP is not well suited to address the fundamental control task of walking: maintaining dynamic stability. In fact, human gait is typically analyzed by normalizing and averaging data from a number of continuous strides. The stability is quantified by various aspects of locomotor variability (Holt, Jeng, Ratcliffe, & Hamill, 1995; Winter, 1989; Yack & Berger, 1993). One indicator of instability in walking is the increased variability of stride time over a long period of walking (Hausdorff, Peng, Ladin, Wei, & Goldberger, 1995). The control capacity of lateral balance in gait can also be assessed by variability of step width (Bauby & Kuo, 2000; Hausdorff et al., 1995). However, the variability of step length, step width, stride time and the relative angle at the joints during the gait are speed dependent which is the “U” shape relationship between variability and gait speed (England & Granata, 2007; Hausdorff et al., 1995). In the “U” shape, the lowest variability of step width is observed at self-paced speed (Bauby & Kuo, 2000; Hausdorff et al., 1995). Moreover, increased variability has been associated with increased fall risk in the elderly (Maki, 1997) and older adults with degenerative neurological disorders (DeMott, Richardson, Thies, & Ashton-Miller, 2007; Hausdorff, Cudkowicz, Firtion, Wei, & Goldberger, 2004).

The definition of local dynamic stability, which refers to the sensitivity of the system to infinitesimal perturbations, was raised by Dingwell (2001). It is the parameter quantified from

the mean divergence over time of locally perturbed trajectories in state space which is parameterized as a double exponential process (Kang & Dingwell, 2006). Local dynamic stability quantifies very small perturbations continuously in real time which is the natural fluctuation during locomotion and needs to be adjusted at least within the current stride by the locomotor control system (Cavanagh & Sternad, 2001). Local stability measures different aspects of locomotor control with traditional measures of variability, which could quantify the large perturbations during continuous strides.

However, these measures are considered to reflect the control ability of walking rather than directly predicting falls. Functional mobility tests are the clinical measures to predict falls in elderly people. Physical performance and control ability in gait can be evaluated by functional mobility tests, including 6-Minute Walk test (6MW) and Timed Up-and-Go test (TUG), as the non-linear dynamic analysis for the evaluation of stability during walking. They are reliable measures for people with neurological deficits (i.e., elderly people and people with Peripheral Neuropathy (Manor, Doherty, & Li, 2008).

The 6MW is a well-established measure of aerobic capacity in elders with cardiorespiratory and peripheral vascular disease (Enright, 2003). Since around the 1960s, the “12-Minute Walk” was popular as a quick and easy fitness test. Although there are a full range of functional test, objective walking test are usually better than the self-report test (i.e., how many flights of stairs can you climb or how many blocks can you walk?). 6MW was recommended by American Thoracic Society Pulmonary Function Standards Committee, because it is easier to administer, better tolerated, and better reflects activities of daily living than other walk tests (Solway, Brooks, Lacasse, & Thomas, 2001). 6MW is self-paced and reported no untoward events (Enright & Sherrill, 1998; Roomi et al., 1996), and it is safe for participants who may

have a history of instable angina or had a heart attack during previous month. The normal range of distance is  $631 \pm 93$  m and 84 m greater in males than females among healthy elderly people (above 50 years old) (Troosters, Gosselink, & Decramer, 1999). Height, weight, sex and age independently contribute to the walking distance in healthy populations and explains the 66% of variance within the measurement (Troosters et al., 1999). Moreover, arthritis and other musculoskeletal diseases also decrease the distance of 6MW. Caution needs to be used when interpreting low distance in 6MW because it is nonspecific and nondiagnostic. It may result from the deficits of pulmonary function, cardiac function, ankle stability, muscle strength, nutritional status, orthopedic function, and cognitive function. For example, in people with diabetes, the walking distance may be influenced by foot pain (Novak, Burger, Marincek, & Meh, 2004). In general, improvements of cardiorespiratory function will lead to increased distance of 6MW. The 6MW is a useful measurement of functional capacity targeted at people with at least moderately severe mobility impairment.

The TUG test is a reliable and valid test for quantifying functional mobility and has been recommended as a screening tool to identify older people who are at risk of falling (Kenny, Rubenstein, Martin, & Tinetti, 2001; Podsiadlo & Richardson, 1991). Mathias and his associates devised a “Get-Up and Go” test (Mathias, Nayak, & Isaacs, 1986). Participants were videotaped while rising from a chair, standing still momentarily, walking toward a wall, then turning to return to the chair. Balance function was evaluated with a five-point scale by a group of observers from different medical backgrounds. Although there was agreement among observers on the subjective scoring of the clinical test, and a good correlation with laboratory test, this measure was not reliable because of the unknown reliability of raters. The “Get-Up and Go” test has been modified by Podsiadlo and Richardson to one with an objective evaluation using the

average time over three trails (Podsiadlo & Richardson, 1991). The “Timed Up-and-Go” test requires participants to stand up, walk 3m, turn, walk back, and sit down. The cutoff value of greater than 30s would be predicting functional dependence among older adults (Mathias et al., 1986); while in community-dwelling elderly people, taking longer than 14s to complete the test could be categorized as a high risk of fall (Shumway-Cook, Brauer, & Woollacott, 2000). The TUG consists of basic daily movements along with its various complicated components, which includes the interactions between sensory input, central processing and neuromuscular function (Nordin, Rosendahl, & Lundin-Olsson, 2006; Podsiadlo & Richardson, 1991). TUG is a simple screening test, which is a sensitive and specific measure of probability for falls among older adults.

Postural stability in standing, dynamic stability in walking, and functional mobility indicate different aspects of postural control and they are all highly correlated with the risk of fall. Unlike the postural stability in standing with concern about the relative position between COM and base of support, dynamic stability in walking is more concerned with the stable gait pattern among continuous strides. Moreover, functional mobility tests comprehensively reflect the ability of independence and risk of falls in daily life among elderly people. Together with the functional mobility test, postural stability in standing and walking reflects the overall capability of postural control in daily life.

### **Neuromuscular Consideration of Postural Control**

The elderly are prone to many chronic illnesses or neurological disorders which may cause balance problems during locomotion. The common underlying chronic diseases are hypertension, diabetes mellitus, arthritis, and heart diseases. In people with Peripheral Neuropathy, the deficits of balance are mainly caused by reduced sensory information at lower

extremities (Simmons, Richardson, & Pozos, 1997) . The dysfunction of CNS in Parkinson patients is considered as the main cause of their balance problems (Ashburn, Stack, Pickering, & Ward, 2001). Additionally, chronic ankle instability can also lead to postural stability alterations (Freeman, 1965).

The role of muscle strength in postural control has been investigated among community-dwelling older adults. Muscle strength is considered as an important factor in postural control. The effect of strength training on balance improvement among elderly people is contradicted in different studies. A 12-week strength training can improve balance and gait velocity in community-dwelling elderly people (Topp, Mikesky, Wigglesworth, Holt, & Edwards, 1993). However, in Buchner's study (1997), the effect of a 24-36 weeks strength and endurance training on balance improvement is weak in community-living older adults (Buchner et al., 1997). The different observations may be due to the different instruments: elastic tubing and weigh machines. Muscle strength is correlated with balance, but the nervous system may also play an important role.

The nervous system collects and processes the information from external and internal environments in postural control. After receiving the stimulations or signals from the nervous system, the muscular system generates the necessary amount of force output to maintain balanced movements. The functional role of the nervous system is categorized into three parts: stimulation collection, (Sensory receptors); pathway of signal, (Sensory and Motor nerves); and controller of information processing and decision making, (CNS). The whole system is responsible for the interaction between the body and external environments in the balance detection and correction.

Visual, vestibular and somatosensory systems provide sensory information in balance control (Manchester, Woollacott, Zederbauer-Hylton, & Marin, 1989). The contributions of sensory activity in postural control are accomplished in two fundamentally different ways. Sensory activities may provide the errors between current posture and upright position at unexpected perturbations and also these activities may trigger the pre-programmed motoneuronal drive in the CNS. Multiple sensations (three sensory systems above) contribute to the sensory activity for maintaining balance at all times (Manchester et al., 1989). However, different sensory systems or different sensations within one sensory system, are weighted differently in locomotion, depending on tasks (Diener & Dichgans, 1988; Mergner & Rosemeier, 1998; Peterka & Benolken, 1995; Simoneau, Ulbrecht, Derr, & Cavanagh, 1995). For example, in quiet standing with eyes open and feet apart with a fist width, the somatosensory system and visual system could provide sufficient sensory information to maintain balance as well as to trigger stretch reflexes of balance correction (Timmann, Belting, Schwarz, & Diener, 1994). When balance test is conducted on a flexible platform, the vestibular system would be involved more to provide the information of how far from the upright position (Lacour & Borel, 1993). The relationship among those three sensory systems is dynamic and changing with demands of sensory perception.

The somatosensory system includes the tactile and proprioceptive systems. The proprioceptive system includes muscle spindle receptors and Golgi Tendon Organ (GTO), which monitor the changes of length, velocity and loading of muscles. Proprioception contributes to detect joint position and sense joint motion (Hijmans, Geertzen, Dijkstra, & Postema, 2007; McKeon & Hertel, 2007). The tactile system is involved with sensations of foot sole cutaneous sensation and vibration (Bray, Cragg, Macknight, & Mills, 1999). Somatosensation influences



static stability in standing and dynamic stability by mediating the gait patterns at ankle, knee and hip joints as well as the activities of tibialis anterior muscle during walking (Erickson, Oliver, Baldini, & Bach, 2004). The roles of these two sub-systems in balance control are not very clear, but there is evidence showed that lower extremity proprioception at the distal end is not required for the balance correction (Bloem, Allum, Carpenter, Verschuuren, & Honegger, 2002) .

In somatosensory system, large fibers that are responsible for primary muscle spindles and the GTO, and small fibers are responsible for innervations of the cutaneous receptors (eg. Merkel's cell, Pacinian corpuscles, Meissner's corpuscles, and Ruffini endings in the skin) (Nardone, Galante, Pareyson, & Schieppati, 2007; Nardone, Grasso, & Schieppati, 2006). Furthermore, the Meissner's and Pacinian corpuscles (fasting-adapting receptors) are both responsible for vibrotactile sensitivity (Nardone et al., 2000). It suggests that Merkel's cells and Ruffini endings (slow adapting receptors) are responsible for touch and pressure sensitivity (Perry, McIlroy, & Maki, 2000).

In those studies, the impairments of somatosensory system are determined by Semmes-Weinstein monofilaments (SW), vibration perception threshold (VPT), and joint movement perception threshold (JMPT). The higher thresholds in the three tests indicate the severity of impairments in somatosensory system. In SW and VPT tests, testing spots could be at Big Toe (BT), 1st & 5th Metatarsal (M1 & M5), Middle Heel (MH) and Heel (HL) as well as other interested spots. In SW test, different sizes of monofilaments provide different amounts of force, when the monofilaments touch the testing spots with bended angle of 90 °. Instead of applying different amounts of force, in VPT test, different frequencies of vibration are applied to the testing spots to get the vibration threshold. Joint movement perception test will be discussed later.

Ankle proprioception has been described as “a specialized variation of the sensory modality of touch which encompasses the sensations of joint movement (kinesthesia) and joint position (joint position sense)” (Lephart, Kocher, Fu, Borsa, & Harner, 1992). This afferent sensory information mechanism depends upon various peripheral mechanoreceptors respond to mechanical deformation by initiating action potentials that are conducted to and processed by the CNS (Grigg, 1994). Combined with other sensory inputs, the results of gathered and processed information are conscious awareness of joint position and motion, unconscious joint stabilization through protective spinal-mediated reflexes and the maintenance of posture and balance (Lephart, Pincivero, & Rozzi, 1998). As a result, an individual is able to perceive both movement (Kinesthesia) and position (joint position sense) of a joint. The integration of muscle stiffness around the joints and joints stabilization via spinal-mediated reflexes is considered to correlate to postural control in standing rather than the ankle proprioception alone (Loram & Lakie, 2002; Morasso & Sanguineti, 2002).

There is a high correlation between joint stability and ankle proprioception which is assessed by ankle proprioception test with broad sensory input at joints (Fu & Hui-Chan, 2005; Jerosch & Prymka, 1996). In these studies, the ankle proprioception test is conducted by the reposition tests at the ankle with its motion of inversion and version in passive and active modes. Participants start from maximum inversion and the targeted positions are set at: 10 ° eversion, 0 ° subtalar neutral, and 15 ° inversion in active and passive modes by Biodex 3 isokinetic dynamometer (Biodex Medical System, Inc, Shirley, NY, USA). The absolute values of the three tails for each test position are averaged to create a representative index for the assessment of active ankle proprioception (AAP) and passive ankle proprioception (PAP) for each limb (Bernier & Perrin, 1998). These tests are a comprehensive assessment of multiple sensory inputs

at ankle joints with no influence from one altered sensory input at ankle lateral ligament (Konradsen, Ravn, & Sorensen, 1993) which has been used as a broad ankle proprioception assessment among unilateral functional ankle instability population and elderly population (Lee & Lin, 2008).

In addition, primary and secondary afferents in soleus muscle spindles are involved within stretch reflex for balance correction which is a component of central motor command (Clarac, Cattaert, & Le Ray, 2000). Primary and secondary afferents in muscle spindle are responsible for different functions. Primary afferent is mainly responsible for extensor muscle and secondary afferent is responsible for producing flexor reflex effects. They both contribute to stretch reflex in standing and walking (Clarac et al., 2000; Grey, Ladouceur, Andersen, Nielsen, & Sinkjær, 2001; Schieppati & Nardone, 1999, 2004). Primary afferent in muscle spindle is not a determinant factor of body sway in standing (Nardone et al., 2000). In gait, motor response to perturbation is evoked by secondary afferent via spinal pathway (Dietz, Quintern, & Berger, 1985). Primary and secondary afferents are the sensory receptors and sending the sensory information of muscle to CNS.

The sensory information is processed at the spinal cord to trigger a corresponding reflex and motor action. It also goes up to the cerebellum for more complex processing. Stretch reflex arc is the connection between afferents in muscle spindle to the  $\alpha$ -motoneuron, which contributes to motor response of balance correction and muscle stiffness in human locomotion (Hoffer & Andreassen, 1981; Sinkjaer, Andersen, & Larsen, 1996). The amplitude of stimulation would be modified by interneuron in the spinal cord. The sensitivity and excitation of interneuron are modulated by a high level of CNS. In gait, the reflex at soleus muscle provides the inhibition of

muscles at the ankle during the swing phase, whereas it provides the excitation in stance phase. However, the central mechanism behind the modulations of reflexes is still unknown.

Hoffmann reflex is a common tool to estimate the function of stretch reflex (Akazawa, Aldridge, Steeves, & Stein, 1982; Aldridge & Stein, 1982). The profile of H-reflex and stretch reflex are parallel, and they share similar modulation in the walking cat experiment (Akazawa et al., 1982). Furthermore, although the H-reflex and stretch reflex are not identical, their functions are both dependent on the synaptic connections between the primary afferent and the  $\alpha$ -motoneuron (Burke, 1983). Similar to stretch reflex, the latency of H-reflex reflects the efficacy of the synaptic transmission between the afferents and  $\alpha$ -motoneurons while the amplitude of H-reflex indicates the excitation level of  $\alpha$ -motoneuron. The latency and amplitude of H-reflex would be modified by the sensitivity and threshold of excitability of the interneuron within reflex arc as well as by central control mechanisms (Capaday & Stein, 1986). H-reflex is widely used to investigate central adaptive neuroplasticity in exercise intervention studies (Zehr, 2002). To the extent that H-reflex is less dependent on the peripheral sensory effects of muscle spinal, it would provide a better measure of the entire reflex arc.

Sensory systems provide valuable feedback in postural control. Muscle strength is correlated with balance, but the nervous system is also important. The weighing of three sensory systems is task dependent in postural control. The sensory receptors located in somatosensory system, evaluated by SW, VPT, and JMPT tests, are responsible for the corresponding stimulation from external environments. The stretch reflex could be triggered by the stimulation from muscle spindle in somatosensory system where the function of the reflex arc could be assessed by the latency and magnitude of Hoffmann reflex.

## Mechanism of Postural Control in Standing and Walking

The regulation of postural stability involves passive control and active control in quiet standing and walking (Winter, 1995; Winter, Patla, Prince, Ishac, & Gielo-Perczak, 1998).

Passive control refers to the stiffness and kinematic proprieties created by anatomical structures as well as gravity which is considered to be a mechanical model built by inherent human structures. Active control refers to neural control under a real-time interaction with external environments which requires energy (Bauby & Kuo, 2000).

Passive control mainly explains the stability of the ankle in A/L direction and at the hip joint in M/L direction. The postural stability is accomplished by the stiffness of muscles and tendons surrounding the joints (Winter, 1995). Passive control in humans is imitated by pendulum mechanic model in standing as well as the rigid mechanic model in walking (McGeer, 1990). Passive control partially explains the decline in postural stability after muscle fatigue in lower extremities. Moreover, it also could partially explain the consistent ability of postural control under different tasks. However, without active control, passive control is insufficient for stabilization and maintaining balance in humans while standing and walking (Garcia, Chatterjee, Ruina, & Coleman, 1998; Morasso & Schieppati, 1999).

Active control (Neural control) refers to sensory-motor system actively controls in the body against dynamic instability in locomotor tasks. It is responsible for postural detection and correction which involves interactions between sensory input, central processing, neuromuscular function, and cognitive function (Bauby & Kuo, 2000; Qu & Nussbaum, 2009). With sensory input, the motor systems perform a remarkable analysis for each movement to maintain balance. The dysfunction of active control could lead to postural instability in standing and walking. For example, blocking visual cue in standing causes poor balance performance (Yardley & Redfern,

2001). People with peripheral neuropathy, who have impaired sensory nerves, have a high risk of falling (Richardson & Hurvitz, 1995). In walking, the importance of active control is evidenced in the M/L direction (Bauby & Kuo, 2000).

Motor behavior is achieved by active control ranging from feedforward to feedback control (Seidler, Noll, & Thiers, 2004). Feedforward control is accomplished with an internal pre-programmed model for the anticipation without the online use of sensory information during the action (Kawato, 1999). Feedback control, in contrast, involves modification of the ongoing movement using the information from sensory receptors. Consequently, such process allows for a high degree of accuracy in the error detection and correction, but it is necessarily slow. Optimal postural control is a combination of both feedforward and feedback processes (Desmurget & Grafton, 2000).

In standing, the goal of maintaining balance is to keep the upright body from falling. It is achieved by the detection of errors in the upright position and balance correction carried out by the motor system. Hellebrandt (1938) introduced the concept of the stretch reflex strategy, or ‘geotropic reflex’, where the shift of the COM constantly stimulated stretch afferents of muscles which then contracted reflexively (Hellebrandt, 1938). This strategy was questioned since the angular motion at the ankle was less than necessary to elicit a stretch reflex (Kelton & Wright, 1949). Subsequent studies support a theory of central organization program in postural control. In the new concept, balance correction is not aimed to regulate the ankle angle or muscle length but a more global parameter such as the position of the COM (Dietz, Gollhofer, Kleiber, & Trippel, 1992). Thus, the system strategy replaces the stretch reflex strategy whose role is then limited to coping with perturbations not predicted by the ongoing central program.

Two popular theories of postural control in the gait are passive dynamic walking (PDW) and central pattern generator (CPG). PDW and CPG have different emphasis. PDW develops from a simple mechanical model, and the stability of this model would be enhanced by feedback and feedforward control. Nonetheless, CPG focuses on the mechanism of neural control in walking.

Passive dynamic theory is based on a classic two-legged mechanic model in which the motion is generated by gravity and inertia (McGeer, 1990). The two-legged model is performed with a natural dynamic by walking on split-belt treadmills with a shallow slope which is comparable to human walking. Human walking is explained by this model with the additional active control. The importance of active control is highlighted in the lateral balance maintained in the gait (Bauby & Kuo, 2000). Two-legged machine with feedforward as the controller process and feedback control for error correction is a more stable model than pure feedback or feedforward control (Kuo, 2002). Under the frame of passive dynamic walking theory, walking is subjected to segment and joint stiffness and a series reflex of the human body. It requires an active interaction between the body and external environments by feedforward control at gait generation and feedback control for balance correction.

Central Pattern Generator explains gait control from the neuromuscular aspects. Walking as a rhythmic movement, is pre-programmed at the upper level of the spinal cord (Duysens & Van de Crommert, 1998). Although sensory input is important in the standing phase for balance correction, it is less important in the swing phase (Sinkjær, Andersen, Ladouceur, Christensen, & Nielsen, 2004). The studies of decerebrate cats suggest that quadruped locomotion could occur without feedback control (Armstrong 1986). Rhythmic movements like walking can be performed in the absence of descending or afferent inputs which has been supported by

decerebrate cat studies (Grillner & Zangger, 1979; Pearson & Rossignol, 1991). Nonetheless, bipedal gait is generally presumed to require some levels of feedback control as well as the CNS modulation (Reisman, Wityk, Silver, & Bastian, 2007). CPG is trying to explain the control mechanism of gait control especially the mechanism mediated by the nervous system.

Passive & active control and feedback & feedforward control are generally applied to postural control in all locomotion. The postural control theories in standing are trying to explain the detection of upright posture and how to trigger the series reflexes by a marker indicating postural instability. In walking, the theories focus on how to explain the generation of continuous gait cycles. In brief, control theories in standing focus on balance detection, and the theories in walking focus on gait generation.

Postural control mainly refers to the detection of the sway of COM based on sensory inputs and the information process by CNS, and the correction of COM by motor response in order to prevent the body from falling. The performance of postural control can be assessed by postural stability in standing, functional mobility, and dynamic stability in walking. Maintaining balance requires passive control (i.e., the muscle strength and the stiffness of ligaments) and the active control with an optimal combination of feedback and feedforward control. Therefore, somatosensation and the central modulation are important in balance. Although the central mechanism of postural control is not very clear, stretch reflex is identified as a simple feedback control loop modulated by the conjunction between the somatosensation and central modulation.

#### The Effect of Somatosensation and Stretch Reflex on Postural Control

Both Lord et al. (1991) and Anacker and DiFabio (1992) reported on the primary role of somatosensory function to maintain balance in the aged population (Anacker & Di Fabio, 1992; Lord, Clark, & Webster, 1991). These studies induced different experimental manipulations to



reduce the somatosensation in healthy participants and then investigated the effects of reduced somatosensation in postural control during standing and walking. The attempts to reduce the function of the somatosensory system in healthy participants include the use of soft or moving supporting surfaces, ischemic injection, mechanical vibratory stimuli of achilles tendons, and inflated blood pressure cuffs at the ankle or thigh (Anacker & Di Fabio, 1992; Horak, Nashner, & Diener, 1990; Lord et al., 1991; Mauritz & Dietz, 1980; Teasdale, Stelmach, & Breunig, 1991). In those studies, the impairments of the somatosensory system may be determined by the vibration perception threshold (VPT), Semmes-Weinstein monofilaments (SW), and joint movement perception threshold (JMPT). Experimentally reduced somatosensation leads to postural instability in elderly population, but it doesn't affect the postural stability in healthy young populations as much.

In standing, the primary muscle spindle and GTO responsible for the proprioception are not playing a key role in postural control compared to cutaneous receptors which are responsible for foot sole sensation (Nardone et al., 2007; Nardone et al., 2006). Furthermore, the Meissner's and Pacinian corpuscles (fasting-adapting receptors) are both responsible for the vibrotactile sensitivity which is less involved in standing balance control (Nardone et al., 2007; Nardone et al., 2006; Nardone et al., 2000). However, Merkel's cells and Ruffini endings (slow adapting receptors), which are responsible for the touch and pressure (tactile) sensitivity, play a key role in standing balance control (Perry et al., 2000). These evidences further confirmed the importance of tactile sensation in standing.

#### The Role of Foot Sole Sensation in Postural Control

In standing, people rely on foot sole sensation to provide feedback information for maintaining balance and balance correction (Kars, Hijmans, Geertzen, & Zijlstra, 2009). Foot

sole sensation in healthy people was experimentally reduced by having them stand on a soft supporting surface (i.e., the surface made by the foam and sand). This led to decreased postural stability (McKeon & Hertel, 2007; Wu & Chiang, 1997). The contribution of plantar cutaneous afferents to balance control is largely evidenced by previous studies. Feedback from foot sole sensation, among other sensory information, is vitally important for balance control.

Foot sole sensation, which includes tactile and vibration sensations, provides valuable information for postural control. Foot sole sensitivity is reported to be correlated with plantar pressure distribution which directly stimulates the receptors on the foot sole and is modified by the CNS in conjunction with afferent information (Nurse & Nigg, 2001). Regional plantar pressures change after altering the sensory input in the foot sole in healthy people while standing (Chen, Nigg, Hulliger, & de Koning, 1995; Nurse & Nigg, 2001). Reduced sensitivity of the entire foot sole by anesthetizing the receptors leads to an alternation in plantar pressure distribution in healthy people (Meyer, Oddsson, & De Luca, 2004). Based on the previous studies, the foot sole sensation plays an important role of plantar pressure distribution in standing.

Many studies investigated the effect of acutely reduced foot sole sensation on the plantar pressure distribution in the gait of healthy people by inducing insensitivity on the whole, fore or rear foot (Caselli, Pham, Giurini, Armstrong, & Veves, 2002; Chen et al., 1995; Eils et al., 2004; Eils et al., 2002; Nurse & Nigg, 2001). Reduced vibration sensitivity threshold at the hallux has been linked to reduced pressure in the same region among healthy people in walking (Caselli et al., 2002). It has been proven that reduced sensation in the whole foot sole leads to decreased peak pressure at the big toe and the heel, along with the COP shifts loading to central forefoot, lateral forefoot, and lateral midfoot in walking (Eils et al., 2004; Eils et al., 2002). These studies

suggest that reduced foot sole sensation changes plantar pressure distribution which implies the importance of foot sole sensation in postural control during walking.

However, recent research, using a local anesthetic solution, puts forward a new concept that plantar pressure distribution in gait is not affected by targeted reduced foot sole sensation (Höhne, Stark, & Brüggemann, 2009). In Hohne's study, targeted plantar sensory afferent was effectively reduced among healthy people using intradermal injections of anesthetic solutions, but plantar pressure distribution in walking did not significantly change. These inconsistent findings may be explained by the different distributions of manipulated insensitive areas at the foot sole (Höhne et al., 2009; Kars et al., 2009). Unlike the previous studies, Hohne and his associates reduced the sensitivity at different spots of the foot sole, rather than a whole area of forefoot, rear foot or whole foot. Moreover, this observation may suggest walking is less dependent on feedback but more on feed forward control as in the case in the Central Pattern Generator (Rossignol, Dubuc, & Gossard, 2006) .

Reduced foot sole sensation leads to a cautious walking pattern, including a slower walking speed, a smaller step length and a wider step width in healthy people and people with Peripheral Neuropathy disease (Manor & Li, 2009; Tsai & Lin, 2012). However, reduced foot sole sensation doesn't influence the dynamic stability in walking (England & Granata, 2007; Höhne, Stark, Brüggemann, & Arampatzis, 2011). During walking, minimal movement of balance correction is evoked by motor responses to a sudden interference from external environments (Lam, Anderschitz, & Dietz, 2006). This observation implies feedback control may be not necessary for maintaining dynamic stability while walking but only works when the external environment becomes challenged. Therefore, these studies suggest that the foot sole sensation may not play an important role in postural control during walking.

The strong evidences in previous studies show the importance of foot sole sensation in balance control during standing. Similarly, reduced foot sole sensation may cause different basic characteristics of gait pattern in walking. However, the correlation between dynamic stability and foot sole sensation is contradicted. In walking, the effects of foot sole sensation on plantar pressure distribution are not clear yet. Further study is needed.

#### The Role of Ankle Proprioception in Postural Control

The role of ankle proprioception in postural control is controversial. There is no direct evidence that proves reduced ankle proprioception decreases postural stability during standing and walking. This may be because of the difficulty in experimentally isolating articular mechanoreceptors from other sensory receptors in muscles and skin. Additionally, reduced function of articular mechanoreceptors would be compensated by the interaction among the other types of sensory receptors. For example, the muscle spindle, that monitors the muscle length and rate of changes in length, could compensate for the reduced function of the articular mechanoreceptors. In another word, the effects of articular sensory receptors are weak in postural control in walking.

Two papers have been published to determine the role of the articular input at the ankle in postural control. Hertel investigated the effect of isolated joint-afferent reduction on postural control by anesthetizing the anterior talofibular ligament and lateral joint capsule (Hertel, Guskiewicz, Kahler, & Perrin, 1996). Singlepostural control assessments were conducted under eyes-open and eyes-closed conditions using a fixed support surface and a slowly rotating support surface (plantar flexion-dorsiflexion and inversion-eversion). Postural control was measured by the COP and the amount of movements around the average COP location. The alterations of the average COP location were not significant under the fixed or rotating surface conditions. The

author suggested that an adaptive mechanism occurred after anesthesia to compensate for the loss of afferent inputs from the lateral ankle. Another study, using a more dynamic approach, investigated the effect of anterior talofibular ligament anesthesia on multiaxial-platform stability (De Carlo & Talbot, 1986). Nevertheless, postural stability didn't decrease as expected, but a significant increase of stability was observed after loss of sensitivity at the anterior talofibular ligament. These results indicate a lack of importance of the articular sensory input in postural control which may be due to the insensitive measures of stability.

The stability of the ankle joint is important for postural control in standing and walking, and it is associated with the stiffness of surrounding muscles and ligaments as well as ankle joint proprioception (Morasso & Sanguineti, 2002; Winter et al., 1998; Winter, Patla, Rietdyk, & Ishac, 2001). There are three potential components which would contribute to instability of ankle joints: a decrease in muscular strength of the ankle evertors, an increase in lateral ligamentous laxity, and proprioceptive deficits resulting from a disruption in the integrity of the joint mechanoreceptors (Freeman, 1965; Garn & Newton, 1988; Lentell, Katzman, & Walters, 1990; Tropp, 1986). Since the stiffness of muscles and ligaments around the ankle joint alone cannot achieve the joint stabilization (Morasso & Sanguineti, 2002), proprioception is believed to be an important factor of functional joint stability (Irrgang, Whitney, & Cox, 1994; Morasso & Sanguineti, 2002). Therefore, ankle proprioception could influence the functional stability of ankle joints, and, in turn, ankle proprioception may influence postural stability in standing and walking.

Based on these results, the function of single sensory input from muscles or ligaments at the ankle in postural control is not very important. However, ankle proprioception tests with broad assessment at the ankle show a correlation between ankle proprioception and joint

instability (Fu & Hui-Chan, 2005; Jerosch & Prymka, 1996). There is no direct evidence showing the importance of ankle proprioception during postural control, but in Lee's study, with the 12 week biomechanical ankle platform system (BAPS) training, the ankle proprioception and postural stability in standing improved among unilateral functional ankle instability populations (Lee & Lin, 2008).

To sum up, ankle proprioception as well as ankle stiffness would be considered important for ankle joint stability. Although the effects of articular mechanoreceptors, which are responsible for the ankle proprioception, are not clear, ankle proprioception assessed with reposition tests is correlated with postural control.

#### The Effect of Stretch Reflex on Postural Control

The monosynaptic stretch reflex, as a simple feedback loop of sensory–motor organization, is modified by the CNS and other peripheral sensory inputs (Clarac et al., 2000). The sensory feedback from somatosensory system is important for postural control, but the knowledge of how the afferent information contributes to the control mechanism is still limited. However, there is the evidence showing afferent-mediated feedback reflex (stretch reflex) is used by the CNS in control of the gait when unexpected stretching of the ankle extensors is imposed (Matthews, 1991; Sinkjaer et al., 1996).

By stretching the soleus muscle during seated posture, stretch reflex has two bursts with different latencies: short latency and long latency. The one with short latency has an onset latency of approximately 40ms and is attributed to monosynaptic excitation of spinal motoneurons from the large diameter group I afferent fibers (Matthews, 1991; Taylor, Stein, & Murphy, 1985). The long latency, with approximately 70ms, is mediated by II afferent fibers

(Schieppati & Nardone, 1997). The small diameter myelinated II afferent fibers originate from the secondary endings and may contribute to flexor reflex effects (Schieppati & Nardone, 1999).

In standing, both types of afferents in muscles contribute to balance control in healthy people. Unlike walking, the comparable importance of these two types of afferents is only observed during stance phase. Additionally, ischemia primary afferents in muscle spindle do not influence walking. This suggests that overall, I afferents are not that important in walking (Grey et al., 2001). In contrast, the long latency component of the stretch reflex contributes to the amplitude of the soleus muscle activity during stance phase in the gait cycle (Mazzaro, Grey, do Nascimento, & Sinkjær, 2006). These studies demonstrate primary and secondary afferents contribute to feedback mechanisms in postural control during standing and walking.

The primary and secondary afferents in muscle spindle are the sensory receptors responsible for the innervations of stretch reflex in soleus muscle. At certain posture, stretching the soleus muscle produces two bursts. The one with short latency (primary I afferents) is important in standing but not in walking. The one with long latency (II afferents) influences the soleus muscle activity in standing and walking. Although the stretch reflex reflects the adaptation of the central mechanism, it is affected by other peripheral sensory inputs. This makes the Hoffmann reflex a better assessment to investigate the central mechanism of afferent mediated feedback control.

The regulation of motoneuron activity is obtained through supraspinal as well as sensory inputs namely in the spinal reflex pathway. A submaximal stimulation produces a characteristic Hoffmann reflex which is the result of the motoneuron discharge evoked by the activation from the muscle spindles (H reflex) as well as a direct depolarization of  $\alpha$ -motoneurons' axons by increasing the stimulus intensity (M wave) (Maffiuletti et al., 2001). H-reflex reflects changes in

synaptic efficacy between the muscle afferents and the  $\alpha$ -motoneurons which is modulated in the CNS by changes in the sensitivity or the threshold of reflex arc. The ratio between the maximum amplitudes of the H reflex response ( $H_{\max}$ ) and motor wave ( $M_{\max}$ ) is commonly used as an index for estimating the level of reflex excitability of the motor pool ( $H_{\max}$ -to  $M_{\max}$  ratio). The ratio depends on the facilitation of the transmission between I fibers and the  $\alpha$ -motoneurons (Schieppati, 1987). The Hoffmann reflex test provides a better measure of stretch reflex arc due to less influence of the activities of sensory receptors and motions. Hoffmann test reflects the function of the stretch-reflex arc as well as the modulation by the central mechanism.

Capaday and Stein's study shows different activities of the soleus H-reflex in standing and walking. Large magnitudes of H-reflexes are fairly stable during standing with the control of position required to maintain a stable posture (Capaday & Stein, 1986). However, the amplitude of H-reflex is changing in walking with small reflexes in swing phase and large reflexes in stance phase. The different modulations of H-reflex suggest different neural control mechanisms in standing and walking. Walking requires a certain amount of compliance (Houk, 1976) whereas standing may require a more rigid control of the ankle position. In walking, the small amplitudes of reflex are partly due to the dorsiflexion required for the soleus muscle to flex. The strong modulation of H reflex during walking is not simply a passive effect of the  $\alpha$ -motoneuron excitation level which involves additional central mechanism control. In standing, the magnitude of H-reflex is maintaining at a comparable high level, but there is less modulation of H-reflex. Similar activities of H-reflex are observed in the stance phase during walking. This implies the importance of stretch reflex and feedback control in postural control during walking. In swing phase, small magnitude of H-reflex indicates feedback control is less involved. Different modulations of the H reflex in standing and walking indicate the different control mechanisms



suggesting the CNS is more involved with postural control in walking rather than in standing (Scaglioni et al., 2002).

H-index is a measure to investigate the entire loop of stretch reflex arc which is modulated by peripheral sensory information and CNS in people with PN. H-index is calculated as  $\left[\frac{Height\ (cm)}{\Delta t_H - \Delta t_M}\right]^2 * 2$  (Scaglioni et al., 2002). In general, the conduction velocity of the reflex arc is assessed by sensory nerve conduction velocity and motor nerve conduction velocity separately rather than being studied as a function of entire loop. In fact, the conduction velocity of motor nerve and sensory nerve correlates with different aspects of postural control. Impaired motor nerve conduction velocity is correlated with the force output (Metter, Conwit, Metter, Pacheco, & Tobin, 1998), whereas impaired sensory nerve conduction velocity is correlated with the body sway area in quiet standing and the walking speed in gait (Nardone et al., 2000). The H-index is believed to associated with modulation in the CNS (Scaglioni et al., 2002).

Stretch reflex is triggered by sensory receptors (primary I and secondary afferents) in the muscle spindle. In a stretch reflex, primary I afferents may contribute to the contraction of agonist muscle and secondary afferents may produce the relaxation of antagonist muscle in the corresponding movement. The reflex arc is a simple feedback loop with the modulation of CNS. Soleus H-reflex is an objective measure of stretch reflex in soleus muscle. The relevant measures of H-reflex are commonly used as the tool to investigate the changes in CNS.

#### Neural Adaptive Strategy of Reduced Somatosensation in Postural Control

Postural control is a complex, dynamic process that involves neuromuscular coordination, biomechanical interactions, and multiple sensory feedback loops. Various types of sensory receptors located at labyrinthine, visual, muscular and cutaneous organs contribute to postural stabilization as well as the basis for body posture representation (Horak, Bergera, Menapace, &

Schuster, 1996; Lestienne & Gurfinkel, 1988; Mergner & Rosemeier, 1998). By experimental manipulation, blocking one of the sensory receptors may change the mechanisms of postural control. Sensory receptors located in muscles, skin, and tendons of the lower extremities, as well as the receptors involved with vestibular system and visual system (Bronstein & Buckwell, 1997; Eklund, 1972; Kavounoudias, Roll, & Roll, 1998; Lund & Broberg, 1983). Multiple sensations weigh differently in postural control during standing and walking (Kavounoudias, Roll, & Roll, 2001). However, some evidences show the feedback information is redundant and blocking one sensory channel may not influence the postural stability in standing and walking as expected (Diener & Dichgans, 1988; Horak et al., 1990; Kornilova et al., 2004).

It is well known that intact participants actively seek out alternative sources of sensory information in destabilizing environments caused by reduced sensory inputs (Curthoys & Halmagyi, 1995; Merabet & Pascual-Leone, 2009; Nashner, 1982). Compensation strategies are adaptations of reweighing multisensation. The process of sensory re-weighting (inter-modality) is termed so because of strong coupling of one stimulus with postural sway (up-weighting) in conjunction with weak coupling with another stimulus (down-weighting) (Oie, Kiemel, & Jeka, 2002; Peterka, 2002).

Several studies have investigated the organization of sensory input for postural control. When visual information is unavailable, but the somatosensory and vestibular information is available and accurate, then the individual will rely primarily on the somatosensory input and only secondarily on the vestibular input (Merabet & Pascual-Leone, 2009). People with loss of vestibular function show postural instability in the absence of visual input and disturbed somatosensory input. Accordingly, when visual input is not available and somatosensory

information is inaccurate, individuals will rely predominantly on the vestibular input (Horak et al., 1990) .

An intact somatosensory system provides the most accurate sensory information to assist postural control (Manchester et al., 1989). When this function declines with aging or experimental manipulation, the adaptation may compensate for the loss in postural control. The causes of reduced somatosensation by aging and experimental manipulation are different which may lead to different compensatory strategies.

Experimentally reduced somatosensation in a healthy young population causes an acute adaptation of reweighting multisensation by increasing the sensitivity of the vestibular system to maintain the appropriate postural control in locomotion (Horak & Hlavacka, 2001). The manipulation of the lower limbs is the vascular ischemia, the anesthesia or cooling, as well as the reduction of sensory information input by compliant contact surface. In standing, Andrea's study suggests when sensory input is sufficient from the somatosensory system, the somatosensation will compensate for the loss of postural control caused by visual blocking in healthy young populations (Preszner-Domjan et al., 2012). Moreover, an additional 10-minute manual stimulation on plantar mechanoreceptors can partially compensate for postural control in the absence of visual cue and reduced somatosensation by standing on a compliant surface (Preszner-Domjan et al., 2012). These studies suggest that reweighting multisensation is an effective way of compensating for the absence of visual and reduced somatosensation to maintain a stable posture in healthy young adults.

In the elderly population, postural stability in standing was decreased under conditions where peripheral vision was occluded and the somatosensation was limited (only foveal vision and vestibular input remaining) (Manchester et al., 1989). The ability of older the adults to

balance was impaired under conditions of reduced or conflicting sensory information. When confronted with functionally inappropriate visual and/or somatosensory inputs, half of the older group lost balance (Woollacott, Shumway-Cook, & Nashner, 1986). In most instances, however, the older participants were able to maintain stability with conflicting stimuli but not under conditions with reduced sensory inputs.

Fall-prone older adults are believed to have impaired function of the reweighing sensory process, a decline in the adaptive use of changing or conflicting sensory inputs for estimating body dynamics. In Allison's study, the sensory inputs are intact in fall-prone older adults, and they display clear evidence of intra- and inter-sensory reweighting to both vision and touch motion stimuli in standing. With sufficiently intact peripheral sensations, fall-prone older adults demonstrated the same pattern of adaptive gain change as healthy older and younger adults (Jeka et al., 2006). These data suggest that, with small amplitude vision and touch stimuli, the sensory reweighting adaptation process remains intact in healthy and fall-prone older adults with intact peripheral sensory system. The cause of high risk of falling may be due to the slow information processing in the CNS.

It has been suggested that loss of sensory feedback is not critical for maintaining stable locomotor patterns during undisturbed walking (Dingwell & Cavanagh, 2001). In Hohne's study, plantar cutaneous sensation was reduced by multiple injections of anesthetic solution in an experimental group which left foot and ankle proprioception and intrinsic foot muscles unaffected. The study aimed to investigate the influence of loss of foot sole sensation on dynamic stability and its influence on the afferent feedback correction and predictive control in perturbed walking. Better body stable position was observed in the experimental group than the control group at first perturbation indicating better feedback correction occurring as an acute

adaptation. This could be explained by the increased vestibular sensitivity or an acceleration of the processing of the afferent information in the CNS in the experimental group. There was no difference between the two groups in the recovery time at the next two perturbations indicating the predictive control was not influenced by loss of plantar cutaneous sensation. Loss of plantar cutaneous sensation doesn't influence the dynamic stability during walking in healthy young populations even during perturbed walking (Höhne et al., 2011). Combined with another study, these results suggest somatosensation affects the central mechanism in gait less, and it is not as important in gait as in standing.

Sensory reweighing is thought of as the compensatory strategy to the reduced sensory inputs in postural control. Reduced somatosensation is not leading to postural instability in healthy young and elderly people, but it does decrease the postural stability in fall-prone adults. However, with intact visual and vestibular sensations, the same patterns of reweighing sensation after reduced somatosensation are displayed in standing among healthy young, elderly, and fall-prone older adults. Therefore, the postural instability in fall-prone adults may be due to the decline of the ability to process information in the CNS in standing. In walking, reduced somatosensation changes the basic characteristics of gait pattern, but the dynamic stability is unaffected among healthy young and elderly people. Moreover, the loss of sensory input doesn't influence dynamic stability in pretreated walking in healthy young people.

The function of somatosensory system and stretch reflex loop are important for postural control. However, differential effects of somatosensation are observed in postural stability during standing and walking. Additionally, activities of H-reflex display different patterns in standing and walking. These observations imply the importance of sensory input as well as feedback control in standing but not in walking. In standing, the patterns of sensory reweighing are similar

in the healthy population, but the ability of sensory processing in the CNS may have a deficit in fall-prone people. In walking, sensory reweighing may be the reason for no effect of reduced somatosensation on dynamic stability. However, less dependence on feedback control may be a better explanation.

### **The Effect of PN on Postural Control and Neural Adaptation**

#### **Peripheral Neuropathy**

According to the 108th US Congress report in 2005 (Specter, 2005), approximately 20 million Americans are suffering Peripheral Neuropathy (PN). 27% is caused by diabetes, and 33% of people with PN do not have a cause. This is termed as “idiopathic” (Gordon Smith & Robinson Singleton, 2006; Hamza et al., 2000). The prevalence of all-cause PN is estimated to be 2.4% in the entire adult population as compared to over 8-10% in the population segment over the age of 55 (Martyn & Hughes, 1997). Peripheral neuropathy is a general term for the family of severely debilitating, progressive diseases that target the peripheral nervous system (PNS) (Boulton, Malik, Arezzo, & Sosenko, 2004). More than 100 types of peripheral neuropathy have been identified (Boulton, Gries, & Jervell, 1998) giving rise to a wide array of signs, symptoms, and complications. The most common form of peripheral neuropathy, termed “chronic diffuse polyneuropathy,” primarily targets the peripheral sensory system.

PN is a disorder that arises progressively from damages to the distal end of the peripheral nervous system to the entire foot, ankle, lower leg, and in some cases, the upper extremities (Boulton et al., 2004). In fact, chronic damage to the sensory nerve system accounts for over 85% of documented PN cases (Padua et al., 2005). It has profound effect on sensation though progressive deterioration from distal sensory nerves especially during the early stages of PN. With sever PN disease, it leads to painful sensations, reduced somatosensation and slow

conduction velocities in sensory (sural) and motor (peroneal) nerves (Behse, Buchthal, & Carlsen, 1977).

The majority of diagnosed PN are acquired secondary to pre-existing illness. The most common of “co-morbidities” include systemic disease, infections, and or autoimmune disorders (Boulton et al., 2004). Additionally, specific causes of PN include “diabetes mellitus (DM), alcoholism, nutritional deficiencies (e.g., thiamine, B12), infections (e.g. HIV, Lyme disease), malignancies (e.g., bronchogenic carcinoma, renal cell carcinoma, lymphoma, multiple myeloma), trauma from external agents or injury, and autoimmune diseases (e.g., systemic lupus erythematosus, Sjogren’s syndrome, Rheumatoid arthritis)” (Mold, Vesely, Keyl, Schenk, & Roberts, 2004).

PN most frequently occurs as a comorbid condition with both type I and type II DM. In fact, “diabetic peripheral neuropathy” (DPN) constitutes 27% of all diagnosed PN patients (Mold et al., 2004). More specifically, 30% of type I diabetics, and 36% of type II diabetics, develop DPN (Harris, Eastman, & Cowie, 1993). The second largest sub-group of PN cases is idiopathic. Despite ample evaluations, no cause is found for one third of individuals with diagnosed PN. The percentage of idiopathic PN cases is likely much higher in the actual population than the one presented in current research (Mold et al., 2004).

Specific to sensory nerve impairments, nerve conduction velocity is a typical clinic evaluation which is used in combination with self-reported pain or numbness of the feet (Richardson, 2002). Nerve conduction velocity is an accurate measure of large-diameter, myelinated nerve function in terms of both the velocity (NCV) and amplitude of conducting action potentials. The standard sensory NCV test is assessed by the sural, or short saphenous nerve, because it supplies innervation to the skin along the posterior aspect of the lower legs,

ankles, and feet (Umphred, 2001). In patients with DPN in DM, NCV along the sural nerve diminishes approximately 0.5 m/s each year (Claus, Mustafa, Vogel, Herz, & Neundörfer, 1993). Average sural NCV decline is from 48.3 to 44.4 m/s, or 3.9 m/s every ten years in patients diagnosed with type II DM (Jarmuzewska & Ghidoni, 2000). The NCV of the sural nerve has been linked to impaired glycemic control (Tkac & Bril, 1998), abnormal sensation (Løseth, Lindal, Ståberg, & Mellgren, 2006), and decreased quality of life (Padua et al., 2002) in this population. Although it requires further studies to investigate if NCV is the determinant measure differential PN from other population, nerve conduction testing is considered to be a valuable method for detecting and monitoring DPN.

NCV is limited to large-diameter nerves, and it may not predict the degeneration of small unmyelinated fibers ( $< 7 \mu\text{m}$ ) in PN. Small-diameter nerves likely occurs prior to larger fiber involvement in the earliest stages of the disorder (Lacomis, Giuliani, Steen, & Powell, 1997). Patients had an 89% reduction of intra-epidermal nerve fiber density associated with the sural nerve in skin biopsy tests — only 50% of these patients had abnormal nerve conduction velocity (Periquet et al., 1999). Therefore, small-fiber involvement is at least to some degree independent of large-fiber involvement. However, the skin biopsy test cannot be widely employed because of the limitation of instrumentation and the complex histological techniques, as well as the expensive cost (Lacomis, 2002).

In addition to the slow NCV, there are symptoms caused by impairments to nerve systems in people with PN. These symptoms may be marked differently depending upon the patient's age, the cause of PN, and the time of day. Nevertheless, these symptoms would be classified by positive and negative symptoms of paraesthesia, or abnormal sensation. Positive symptoms arise spontaneously as a response to stimuli, painful (i.e., prickling, tingling, burning,



throbbing, allodynia, etc.), and non-painful (stiff, asleep, prickling, tingling, etc.) (Apfel et al., 2001). Positive symptoms are regularly worse at night and after long periods of weight-bearing activity. In contrast, negative symptoms are reduced responses to stimuli and are often described as numbness or “feet feel dead” (Boulton et al., 2004). Moreover, leg cramps and restless legs syndrome are also reported in this population (Holland et al., 1998).

PN is a chronic disease at the peripheral nerve system which progressively degenerates from distal to proximal in the lower extremities. Most people diagnosed PN have pre-existing diseases and impaired sensory nerve systems. The population of PN is underestimated because of the variation of PN, the limitation of clinical diagnose tools, and difficulty of describing the symptoms.

#### The Effects of PN on Postural Control

The effect of PN on muscle strength is inconclusive. Strength loss can be observed in severe cases of PN. However, it is only indirectly associated with the disease. This weakness may be caused by disuse to avoid pain or fear of falling. In Anderson and colleague’s study, maximal isokinetic muscle strength was significantly reduced at ankle extensors (17%), ankle flexors (14%), and knee flexors (14%) in neuropathic DM patients compared to non-neuropathic DM patients (Andersen, Nielsen, Mogensen, & Jakobsen, 2004). However, Resnick reported no difference of lower extremity strength in two similar groups of individuals (Resnick et al., 2002). Further, maximal strength decline was reported in symptomatic DPN patients but not in asymptomatic DPN patients or non-neuropathic DM patients (Andreassen, Jakobsen, & Andersen, 2006). The confliction has therefore suggested that strength losses in PN may be associated with indirect causes such as physical inactivity (Boulton et al., 2004) rather than by be a direct result of PN.

Balance deteriorates with the severity of the disease in people with PN (Geurts, Mulder, Nienhuis, Mars, & Rijken, 1992; Kavounoudias et al., 1998; Meyer et al., 2004; Rogers, Wardman, Lord, & Fitzpatrick, 2001). The resulting deficits in proprioceptive and cutaneous afferent feedback lead to well-documented increased postural sway in those patients during standing (Cavanagh, Derr, Ulbrecht, Maser, & Orchard, 1992; Simoneau, Ulbrecht, Derr, Becker, & Cavanagh, 1994). Poor postural stability is evidenced in people with Neuropathy by the exaggerated COP outcomes such as 95% area of COP and velocity of COP movement (Kars et al., 2009). Reduced functional gait performance, documented by 6MW and TUG tests in people with PN, highly correlates with standing balance but not with leg strength (Manor & Li, 2009). These evidences indicate deficits of postural stability among PN are due to sensory loss rather than strength weakness.

PN patients walk with a cautious gait and significantly decreased speed (Dingwell & Cavanagh, 2001; Menz, Lord, St George, & Fitzpatrick, 2004; Richardson, Thies, DeMott, & Ashton-Miller, 2004), step lengths (Richardson et al., 2004), ankle moments, ankle powers, and ground reaction forces in the AP and vertical directions (Mueller, Minor, Sahrman, Schaaf, & Strube, 1994). Individuals with PN exhibit similar walking alterations to those healthy individuals with experimentally reduced plantar cutaneous sensation. Additionally, patients walk with significantly increased double support time (Courtemanche et al., 1996) and mean step width (Richardson et al., 2004). Compared to individuals with experimentally reduced sensation, PN patients are more consistent on those measures (Eils et al., 2004). Indeed, this difference suggests that PN does not selectively affect plantar cutaneous receptors alone but rather impairs all peripheral sensory systems and is accompanied by significant reductions in physical activity (Sinkjær et al., 2004).

People with PN are 15 times more likely to experience an injury while walking than age matched participants with intact sensation (Cavanagh, Derr, Ulbrecht, Maser, & Orchard, 2009). The predictive factors that have been linked to increased fall risk are the relative measures of dynamic stability in walking (i.e. variability of stride-to-stride, step lengths and step widths) (Maki, 1997). However, increased measures of variability in people with PN are due to their slow walking speeds but not directly related to sensory loss (Dingwell & Cavanagh, 2001). Falls are mainly caused by perturbations during walking rather than in stable walking among PN population (DeMott et al., 2007; Stolze et al., 2004). These evidences suggest sensory information is not important for dynamic stability in gait unless there is perturbation for balance correction.

#### Potential Adaptation in PN during Standing and Walking

People with PN may have adapted for reduced somatosensation in postural control. Greater sensitivity of vestibular and vibrating sensations in standing was observed in people with PN compared to an age matched healthy population (Horak & Hlavacka, 2001). Although attention was distracted, additional vibrating stimulation at foot sole improved standing balance in participants with neuropathy compared to healthy age-matched control group (Hijmans, Geertzen, Zijlstra, Hof, & Postema, 2008). In Menz's study, tactile stimulation was applied either to the skin of the ankle, calf or knee among young individuals, healthy older adults, and older individuals with PN under eyes open/closed conditions. With the additional simulation, the PN group displayed the greatest amount of reduction of sway in both conditions (see Figure 1.1) (Menz, Lord, & Fitzpatrick, 2006). These studies indicate adaptations within the nervous system (i.e., sensory reweighing) may compensate for the impaired postural stability caused by PN.

Moreover, the mechanism of this adaptation could provide a window of effective treatment of postural instability in PN.

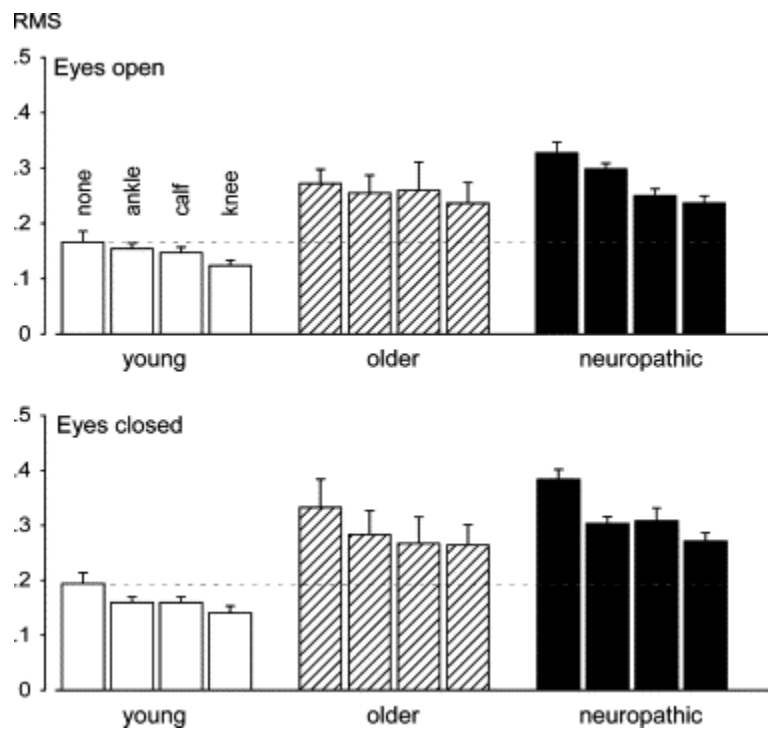


Figure 1.1. Mean (S.E.) Sway in the Three Subject Groups for the Four Stimulus Conditions

In gait, a distinctive strategy and an earlier leg EMG activity were observed in the PN group compared to the age-matched control group (Bunday & Bronstein, 2009). Bunday investigated the locomotor adaptation and aftereffects in people with reduced somatosensation caused by PN. PN and control groups were asked to walk five times from a fixed pathway to a moving pathway as a BEFORE trail. After 15 practice trails, another five trails were completed as AFTER trails. The results (see Figure 1.2 for details) show a clear separation in consequent aftereffects in PN group, but not in control group, which indicates the PN group developed distinctive strategies to negotiate the moving pathway resulting in different aftereffects. In addition, the PN group displayed earlier leg EMG activity after first trial than the control group. The different adaptive motor performance suggests that people with PN adopted a different feed-forward compensatory strategy at central level to the sensory loss on postural control.

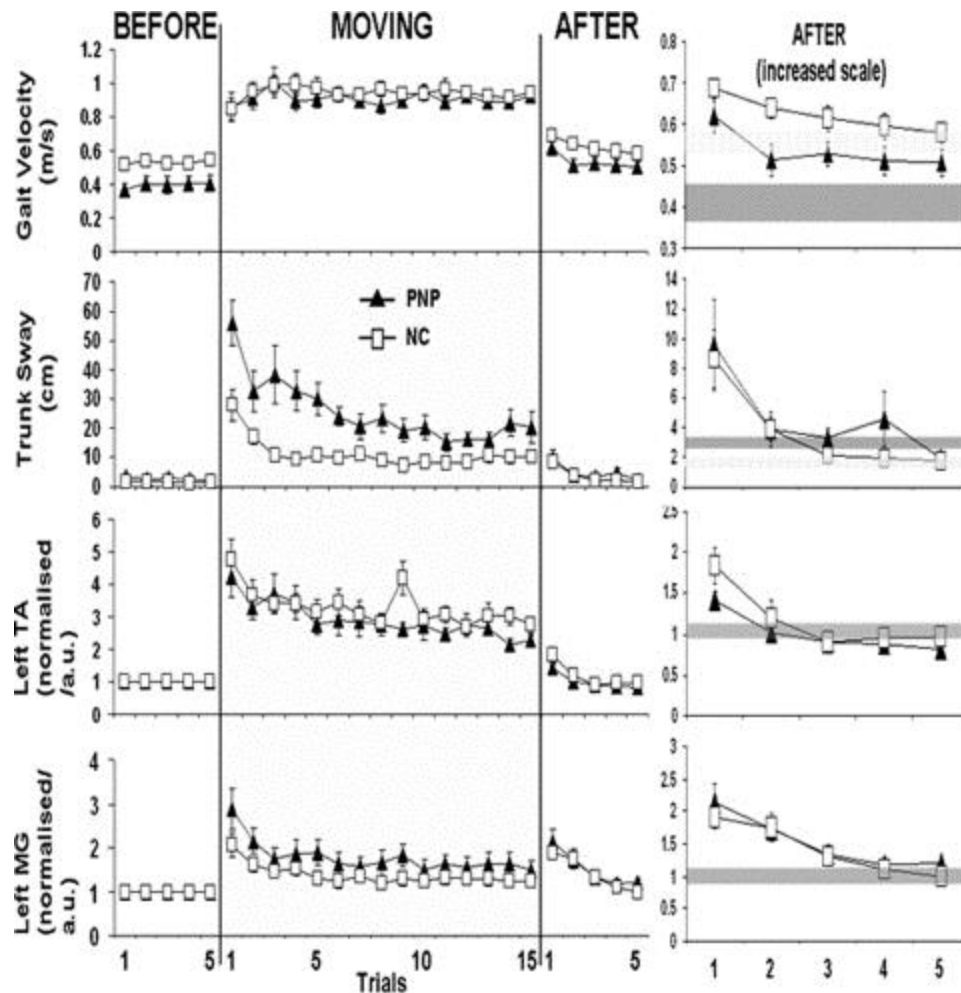


Figure 1.2. Mean ( $\pm$ SE) Data for Conditions BEFORE, MOVING, and AFTER for all Normal Control (NC;  $\square$ ) and Peripheral Neuropathy Patients (PNP;  $\blacktriangle$ ). Numbers along the horizontal axis represent trial numbers. A change from stationary to moving or moving to stationary is represented by a vertical black line. Top to bottom: gait velocity, trunk sway, normalized left TA, and normalized left MG. Note the aftereffect as increased trunk forward sway, gait velocity, left TA and MG particularly in the AFTER *trial 1*. The gray shaded areas represents mean  $\pm$  2SD of the BEFORE data for controls and PNP groups, respectively.

#### Medical Treatments on PN

There is no optimal medical treatment for PN, and most treatments are aimed at reducing the severity of pain. Chinese acupuncture was reported as a safe and effective therapy for the long-term management of painful DPN (Abuaisha, Costanzi, & Boulton, 1998). 6 courses of acupuncture over 10 weeks improved the symptoms (i.e., pain, numbness) in 77% of participants. Among the patients with the follow-up 18-52 weeks of therapy, 67% were able to stop or

reduced medications without the symptoms getting worse. However, acupuncture is to some degree dependent on the skill level of the physician and the situation of patient which is not reliable among different physicians. Therefore, this treatment cannot be widely used. Similarly, one year after decompression surgery, the percentages of patients with balance improvement varied from 36% to 89% in different studies (Aszmann, Kress, & Dellon, 2000; Dellon, 1992; Valdivia, Dellon, Weinand, & Maloney, 2005). The inconsistent results may be due to the different surgical procedures and surgeons. Nevertheless, the reliability of surgical treatment needs further studies to confirm. Besides that, most medications are specific to the pain, rather than the impaired sensory nerve in people with PN (Torrance, Smith, Watson, & Bennett, 2007). Therefore, there is no optimal treatment among the ones above to improve balance and sensitivity at lower extremities.

It has been reported that concentrated exercise involving balance training improves postural stability in people with PN. A 3-week course of concentrated exercise for balance and standing strength benefited participants with DPN with improved balance and functional reach performance. However, this improvement was not observed in the age matched control group (Richardson, Sandman, & Vela, 2001). Shorter finger and foot reaction times to visual stimuli, less sway, greater leg strength, and reduced fall risk were observed after a 6-week program of stretching, balance and strength exercises of the lower limbs in people PN (Morrison, Colberg, Mariano, Parson, & Vinik, 2010). A 24-week Taichi practice reversed the decline of foot sole sensation caused by PN and improved the patients' performance on TUG and 6MW tests (Li & Manor, 2010). Moreover, increased conduction velocity was observed after Taichi and Yoga training in this population (Hung et al., 2009; Malhotra et al., 2002).

So far, the reason for these improvements is not clear. Given that adaptation of PN may potentially compensate for deficits in postural control, it is believed that concentrated exercises are associated with the enhancements of that adaptation which most likely occurs in the central nervous system. This is a reasonable hypothesis to explain the significantly increased postural stability as well as the reverse of foot insensitivity and the slow NCV in people with PN. To be more specific, these exercises may strengthen the ability of sensory reweighing strategy (i.e., relying on more accurate sensations in visual and vestibular systems) or central adaptive mechanism (i.e., improvement of the ability to process the conflicting sensory inputs).

The adaptation in the CNS may play a key role in the improvements of postural stability with additional stimulations and/or after certain types of training in people with PN. Although there is no optimal effective medical treatment of PN, some concentrated exercises do improve the postural stability. These exercises may improve the ability of sensory reweighing and/or central processing. These mechanisms of adaptation and compensation to PN are still not clear and need further studies.

Peripheral Neuropathy leads to a high risk of falling resulting from dysfunctional postural control caused by impaired sensory nerves of PN. As a result of the complex pathology, most medical treatments are aimed at reducing pain rather than curing the disease or reducing the risk of falling among this population. Fortunately, concentrated exercises show a positive effect on balance enhancements and even reverse of sensory loss at the foot sole and slow NCV. It is considered to correlate with the adaptation to reduced sensory inputs for postural control in people with PN. Although the mechanisms are not clear, it is a potential strategy to develop physical treatment to postural instability and risk of falling in patients with PN. Therefore, it is interesting to investigate the mechanism of the adaptation caused by PN.

## **Outline of Dissertation**

Chapter 1 has provided relevant background information regarding PN and its effects on established markers of postural control. Plantar pressure sensation (PPS) provides most accurate and important real-time feedback during standing and walking and acutely reduced PPS affects postural control. However, previous studies suggest COP relevant measures corresponding to the chronic loss of PPS are inconsistent with the resulting behaviors from acutely reduced PPS in postural control. Therefore, the effect of chronic PPS loss on postural control remains unknown. Chapter 2 investigates the effect of chronic PPS on plantar pressure distribution in standing and walking. This study provides insights into differential control mechanisms between standing and walking. People with PN may develop an adaptive neural control mechanism of standing to compensate the chronic PPS loss. During walking, postural control doesn't require the intact PPS, which implies that the feedforward control may be the determinative mechanism of postural control in gait. The study suggests the physical dysfunction caused by PN may be compensated by the neuroplasticity at the peripheral or central nervous level.

Stretch reflex could be triggered by sensory receptors and modulated by the CNS accordingly. The reflexive loop is considered to play an important role in postural control. People with PN, especially with impaired sensory inputs of small-afferent fibers (SAF) reflexive loop, maybe dependent more on the large-afferent fibers (LAF) reflexive loop to maintain balance in standing. Consequently, the function of reflexive loop should be examined in people with PN. Nevertheless, no reliable measure of stretch reflex has been proven in people with PN, except the measure of presynaptic inhibition. Therefore, Chapter 3 presents a reliability study investigating the measures of H-reflex as well as the ankle proprioception in people with PN. The results provide the fundamental reliable measures for next project. Chapter 4 examines the



influence of LAF reflexive loop on postural control when SAF reflexive loop is impaired in PN. People with PN depend more on the LAF reflexive loop and ankle proprioception for postural control when the SAF reflexive loop or its sensory receptors are impaired. The studies outlined in Chapters 2, 3, and 4 have increased our knowledge of the influence of PN on standing and walking. They also provide a foundation for future research within these areas. Chapter 5 concludes this dissertation by providing a focused discussion related to key results, limitation, and future studies of related research.

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## **CHAPTER 2. THE DIFFERENTIAL EFFECTS OF FOOT SOLE SENSORY ON PLANTAR PRESSURE DISTRIBUTION BETWEEN BALANCE AND GAIT**

### **Abstract<sup>1</sup>**

Foot sole tactile sensation provides valuable feedback to the central nervous system. Acutely reduced foot sensation changes plantar pressure distribution in standing and gait; however, the effect of chronic foot sole sensory impairment on plantar pressure distribution is unclear. **PURPOSE:** This study aims to examine the effects of Peripheral Neuropathy (PN) induced chronic sensory loss on plantar pressure distribution in walking and standing. **METHODS:** Foot sole sensitivity was tested at the five sites: hallux (BT), 1<sup>st</sup> metatarsal (M1), 5<sup>th</sup> metatarsal (M5), mid-foot (MF) and Heel (HL). Relative peak pressures (RPP) of the five sites were collected during a 20-sec walking on a treadmill at 0.45 m/s and a 30-sec quiet standing with eyes open. Five-way MANOVA was used to examine the influence of sensitivity of each site on overall plantar pressure distribution for standing and walking separately. Tukey's test was used to examine the significant associations. **RESULTS:** In standing, the sensitivity of BT affected average RPP at BT significantly ( $P < .05$ ), where RPP associated with insensitive BT ( $8.1\% \pm 5.7\%$ ) was greater than with sensitive BT ( $4.5\% \pm 4.9\%$ ). Furthermore, the RPP at HL was greater for insensitive MF ( $36.1\% \pm 17.9\%$ ) compared with sensitive MF ( $23.6\% \pm 7.4\%$ ) ( $P < .05$ ). No pressure distribution changes were observed in walking. **CONCLUSIONS:** Feedback from foot sole tactile sensation in gait is not as significant as in standing, showing standing balance control relies more on feedback control mechanism while gait control relies more on feed forward control mechanism.

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## **Introduction**

According to the 108th Congress report (Specter, 2005), approximately 20 million Americans were suffering Peripheral Neuropathy (PN). PN is a disorder which arises from damage to the peripheral nervous system. Chronic damage to the sensory motor system accounts for over 85% of documented PN cases (Padua et al., 2005). The consequence of the chronic damage to the sensory motor system is the reduced tactile sensation at the sole of the foot. PN related foot sole tactile sensation reduction is likely to cause gait instability and balance problems. Gait and balance deteriorate with increased severity of the disease (Geurts et al., 1992; Kavounoudias et al., 1998; Meyer et al., 2004; Rogers et al., 2001). Reduced functional gait performance, documented by 6 min walking and time-up-to-go tests in people with PN, highly correlates with standing balance but not with leg strength (Manor & Li, 2009). These evidences suggest that gait instability among PN sufferers could be mainly due to balance impairments resulting from reduced foot tactile sensation than weakness, as in other aging populations.

Large fibers, like the innervations for the primary muscle spindles and the Golgi tendon organs, are less significant in postural control compared with the small fibers that innervate the cutaneous receptors (eg. Merkel's cell, Pacinian corpuscles, Meissner's corpuscles, and Ruffini endings in the skin) (Nardone et al., 2007; Nardone et al., 2006). Merkel's cells and Ruffini endings (slow adapting receptors), responsible for touch and pressure sensitivity, are more important in standing balance control than the Meissner's and Pacinian corpuscles (fasting-adapting receptors), responsible for the vibrotactile sensitivity (Nardone et al., 2006; Nardone et al., 2000; Perry et al., 2000; Shaffer & Harrison, 2007). Moreover, foot sole tactile sensation could also be involved with gait pattern control at lower limb joints as well as the activities of

tibialis anterior muscles (Meyer et al., 2004). These evidences further confirm the importance of cutaneous sensation in maintaining postural and gait stability.

Plantar pressure directly stimulates the receptors on foot sole and the distribution of plantar pressure is modified by the central nervous system in conjunction with afferent information. Foot sole sensitivity was also reported to correlate with plantar pressure distribution (Nurse & Nigg, 2001). In healthy individuals, regional plantar pressures change in response to alterations in the sensory input on the foot sole during walking and standing (Chen et al., 1995; Nurse & Nigg, 2001). However, neuropathy patients with reduced cutaneous sensation have different plantar pressure distributions compared to healthy individuals (Caselli et al., 2002; Chen et al., 1995). This suggests that reduced plantar pressure sensitivity contributes to balance deficiencies in PN population (Meyer et al., 2004). To date, little is known about the influence of reduced sensitivity on plantar pressure.

Many studies investigated the effect of acutely reduced sensation on the plantar pressure distribution on the plantar pressure distribution in healthy people by inducing insensitivity on the whole, fore, or rear foot. A reduced vibration sensitivity threshold at the hallux has been linked to reduced pressure in the same region among healthy people in walking and running (Caselli et al., 2002; Chen et al., 1995; Eils et al., 2004; Eils et al., 2002; Nurse & Nigg, 1999, 2001). It has been shown that reduced sensation in the whole foot surface leads to decreased peak pressure at the hallux and heel. Further to that, Elis's study has shown that center of pressure (COP) shifts the load to the central forefoot, lateral forefoot and lateral mid-foot when walking (Eils et al., 2004; Hähne et al., 2009). A more recent study, however, suggested that plantar pressure distribution during walking was not affected by the targeted reduced cutaneous sensation. (Hähne et al., 2009). These inconsistent findings may be explained by different distribution of

reduced sensation areas (Höhne et al., 2009; Kars et al., 2009). Unevenly distributed sensory loss caused by the neuropathy may have a more complicated influence on pressure distribution. This cannot be simulated by acute sensory reduction. Therefore, the effects of chronic reduction in foot sole sensation on gait and standing are unclear.

This aim of this study was to investigate the effect of foot sole cutaneous sensitivity on plantar pressure distribution in standing and walking. It is hypothesized that (i) loss of foot sole tactile sensation would affect plantar pressure distribution during standing and walking; and (ii) the pressure would increase under the site with reduced sensitivity; and (iii) insensitivity-induced pressure re-distribution would be different in standing and walking. Relative of peak pressure (RPP) of each of the following five sites: hallux (BT), 1st metatarsal (M1), 5<sup>th</sup> metatarsal (M5), mid-foot (MF) and heel (HL).

## **Methods**

### **Participants**

Twenty-four elderly PN sufferers (Idiopathic, seven male, 17 female) participated in the study, with an average age of ( $\pm$  standard deviation)  $73.0 \pm 6.9$  years, height of  $167.8 \pm 9.4$  cm and body mass of  $79.2 \pm 18.4$  kg.

All participants were previously diagnosed by neurologists before participating in the current study. The project was approved by the local Intramural Review Board, and written consent was obtained from the participants prior to participation.

### **Experimental Protocol**

A foot sole sensitivity test was conducted with a 5.07 gauge Semmes-Weinstein monofilament (North Coast Medical. Inc, Morgan Hill, CA, US), which has high diagnostic specificity and is useful in detecting advanced cases of PN (Kamei et al., 2005). There were five

regions of interest in this study: BT, M1, M5, MF and HL. Each site was tested three times in random order, following methods by Manor's method (2008). The monofilament was pressed to each site with sufficient force to produce a bowing at a 90° angle for at least 1s. When tested, the participants were lying on their back and unable to see the testing process. They were instructed to respond with a "yes" and the correct name of the sites when pressure was felt. A site was determined as insensitive if it could not be correctly identified in two out of three times. This pressure threshold test proved to be reliable in the PN population (Manor et al., 2008).

After entering the laboratory, all participants had 10 min rest prior to the plantar pressure test. Participants wore the same brand and type shoes to avoid the influence of different shoes on the pressure distribution during standing and walking tasks. Plantar pressure distribution data were stored and analyzed using FScan software (FScan, South Boston, MA, US). Walking was conducted on a treadmill at 0.45 m/s for 20 seconds, and standing data were collected as the patients were standing for 30 seconds with eyes open (Manor et al., 2008; Taraldsen et al., 2011). Peak pressure distribution data were stored and analyzed using FScan software (FScan, South Boston, MA, US). Foot sole was divided into 12 different regions including BT, M1, M5, MF and HL. Peak pressure data were averaged over the duration of testing, and used to calculate the relative peak pressure for each of the five sites for both walking and standing conditions. Relative peak pressure was calculated by dividing the pressure at the site of interest by the sum of peak pressures of the 12 regions of a one single foot during the entire data collection period, and then multiplying by 100%. The relative peak pressure (RPP) data were then analyzed separately for the sensitive and insensitive groups of sites in both walking and standing condition. Relative peak pressures at five of the 12 examined regions (BT, M1, M5, MF and HL) were calculated for each participant for the entire data collection session.



## Data Analysis

Five-way MANOVA was used to examine the association between the dependent variables (the combined RPP of five sites, BT, M1, M5, MF and HL) and the independent variables (the sensitivity of each of five sites) for standing and walking separately. Wilk's Lambda in multivariate analysis was used for statistical testing (Everitt & Dunn, 1991). Significant associations were examined further using Post Hoc Tukey's test. The test helped to locate different RPP distribution caused by the sensitive foot sole locations.

It was not our interest to examine the interaction between independent variables, because the sensitivity of each one of the five sites was independent of all other sites. Therefore, the results of interaction among independent variables were not reported in this paper.

Data were processed by SAS statistic software (Version 9.2 SAS Institute Inc., Cary, NC, USA) and analyzed based on five plantar regions for sensory score and RPP over entire foot sole. Significant level was set at .05 for all analysis results.

## Results

### Foot Sole Sensation

All PN participants were tested using 5.07 gauge monofilaments on the five sites, BT, M1, M5, MF and HL. The overall correct sensory responses were 132 out of 240, accounting for 55% of all the responses. Most sensitive sites (altogether 38) were observed from MF, whereas 18, 23, 29 and 24 sensitive sites were observed from BT, M1, M5 and HL respectively. The differences were not statistically significant.

### Plantar Pressure Distribution

Relative peak pressure of the five tested sites was analyzed according to the sensitivity of each site and then processed separately for standing and walking conditions. No significant

sensitivity effects were observed on the pressure distribution during walking. However, significant effects of sensitivity on plantar pressure distribution over BT and MF were observed during standing.

The effects of BT sensitivity on pressure distribution among the five tested sites were analyzed separately for standing and walking (see Figure 2.1 A. and C. for detailed information). The sensitivity of BT affected average RPP at BT significantly ( $p < .05$ ). RPP associated with insensitive BT ( $8.1\% \pm 5.7\%$ ) was greater than with sensitive BT ( $4.5\% \pm 4.9\%$ ). However, the sensitivity of BT had no significant effect on RPP of other four sites, M1, M5, MF and HL.

As shown in Figure 2.1 B. and D., the sensitivity of MF influenced the plantar pressure distribution significantly ( $p < .05$ ). RPP at HL was greater for insensitive MF ( $36.1\% \pm 17.9\%$ ) compared with sensitive MF ( $23.6\% \pm 7.4\%$ ,  $p < .05$ ).

### **Discussion**

The purpose of this study was to examine the effects of chronic sensory loss due to peripheral neuropathy (PN) on plantar pressure distribution during walking and standing. The effects of sensory loss at BT, M1, M5, MF and HL on plantar pressure distribution were examined. The findings showed that plantar pressure distribution changes as a result of insensitivity were significant during standing but not during walking status. Insensitive BT was related to greater pressure on BT in standing and insensitive MF was related to greater pressure at HL in standing. No change was observed in pressure distribution resulting from sensory loss in other sites during standing and all five sites during walking.

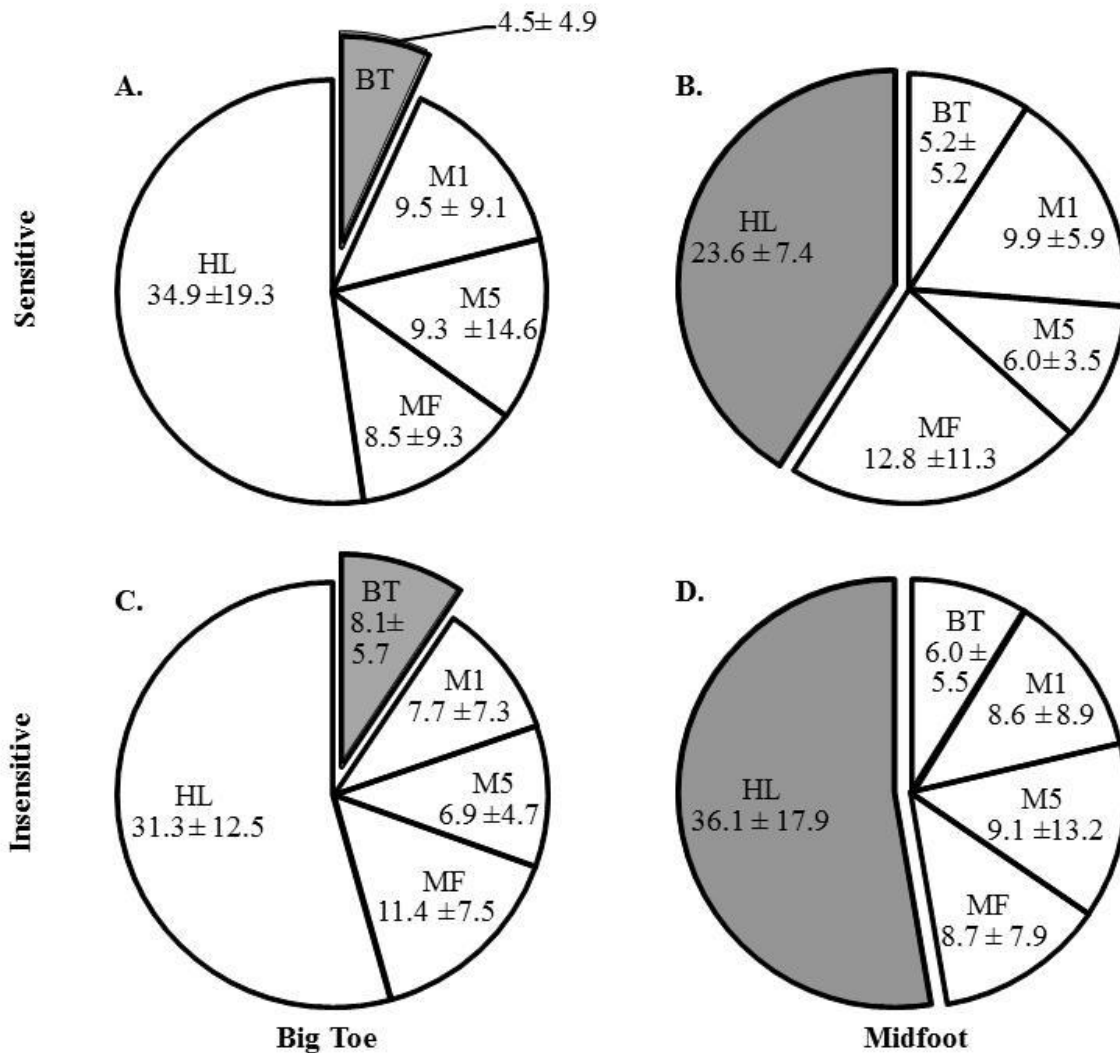


Figure 2.1. The Sensitivity of Hallux (BT) and Midfoot (MF) Effects on Plantar Pressure Distribution Significantly during Standing. The relative peak pressure of the five tested sites (BT, MF, M1 – first metatarsal, M5 – fifth metatarsal, and HL – Heel) are presented here for four different situations, respectively. Left column shows BT sensitivity impairment led to different overall plantar pressure distributions ( $p < .05$ ), where insensitive BT caused greater pressure under BT ( $p < .05$ ). Right column presents the differential effects of MF sensitivity ( $p < .05$ ) on overall plantar pressure distributions where insensitive MF caused greater pressure under HL ( $p < .05$ ). The gray area in charts A & C (B & D) signify the significant differences.

Our results indicate that the effect of reduced foot sole sensation on plantar pressure distribution was specific to standing, but not to walking. Meyer reported that the center of pressure (COP) moved toward the lateral mid-foot after exposing the whole foot to ice in healthy individuals (Meyer et al., 2004). Contrary to these findings, the present study indicates that the

effect of insensitive regions at BT and MF led to greater pressure at BT and HL, respectively.. These differences could be explained by the use of acute sensory reduction in previous studies vs. the chronic loss in our participants. Furthermore, ice immersion induced sensory loss is uniform across the foot sole while disease induced insensitivity is unevenly located at different foot sole regions.

Peripheral Neuropathy individuals rely on foot sole tactile sensation to provide feedback for maintaining balance and body sway correction (Kars et al., 2009). The poor postural stability was shown by the increased area of COP and velocity of COP movement (Kars et al., 2009). However, the role of foot cutaneous sensation to maintain balance in healthy people is moderate (Meyer et al., 2004). Our observations that foot sole tactile sensation influences plantar pressure distribution in standing suggests that cutaneous input plays an important role in balance control during standing for PN sufferers. Our observations that foot sole tactile sensation influences plantar pressure distribution in standing suggests that cutaneous input plays an important role in balance control in standing for PN sufferers. Feedback from foot sole sensation, among other sensory information, is vitally important for balance control among this population.

The effect of foot sole tactile sensation on plantar pressure distribution was not observed in walking. The present study confirmed Hohne's findings, where injections of anesthetic were used in healthy individual, but plantar pressure distribution during walking did not significantly change (Höhne et al., 2009). However, this observation is not consistent with two other studies using ice-induced sensory loss on healthy people. Nurse and Nigg (2001) reduced the sensitivity on whole, fore and rear foot sole separately by ice immersion. The general tendency in their study was load shifting away from the insensitive area to the sensitive area during walking. In another study, ice-induced whole foot surface sensory reduction led to decreased peak pressure at

the hallux and heel, and load shifted from heel and toes to central and lateral forefoot and lateral mid-foot in walking (Eils et al., 2004). One possible explanation may be that ice-induced intervention created an evenly distributed foot sensation on whole, fore and rear foot, causing a heterogeneous foot sole sensitivity loss. In the present study, as in Hohne's, the distribution of foot sensitivity was uneven, suggesting that evenly distributed acute sensory loss could not mimic long-term foot sensory loss. Another possible explanation is that the ice-induced intervention may influence joint mobility or force capacities. In our observation, PN induced foot sole sensation loss did not affect plantar pressure distribution in walking. This may be because walking is less dependent on feedback but more on feed forward control, just like the case in Central pattern generator (Rossignol et al., 2006).

In our study, foot sole sensation affected plantar pressure distribution in standing but not in walking, which indicates cutaneous input plays a lesser role in walking among people with PN. Previous studies of spinal and decerebrated cats suggested that quadruped locomotion could occur without feedback control (Armstrong, 1986). Rhythmic movements, such as walking could be performed in the absence of descending or afferent inputs, which has been supported by decerebrate and spinal cat studies (Grillner & Zangger, 1979; Pearson & Rossignol, 1991); Bipedal gait is generally presumed to require some level of cerebral control (Reisman et al., 2007). In some studies, minimal movement was observed to have been evoked by motor responses caused by sudden interference from the external environment (Lam et al., 2006). This implies that feedback control was not a necessary factor to maintain gait but only worked when the external environment become challenging. The task of 20s walking at .45m/s on the treadmill may not match up with normal walking speed and 30s quiet standing in the present study was not challenging. Besides, there were no unexpected disturbances or errors that required movement

correction in walking (Rossignol et al., 2006; Zehr, 2002). In agreement with previous studies, our observations suggest that peripheral feedback (foot cutaneous sensory information) did not influence foot pressure distribution and walking was mainly modulated by feed forward control rather than by feedback control.

There are potential limitations when interpreting the observations reported here. First, the walking conditions we used here cannot be generalized beyond slow treadmill walking. Most PN patients walk much slower than the general population with unstable gait. Although treadmills with safety harnesses, as we employed in this project, provided them a safety environment, it was different from the environments of the home or community where most people navigate when they walk. Second, it is possible that longer standing or walking time could provide us with a more stable data set. However, considering the restrictions in physical capability of elderly people with PN and the testing equipments, the test design had minimize risk and be manageable. Previous research showed that these testing protocols produce reliable data with our data. Finally, we did not examine the influence of the body weight distribution, between the two feet, on plantar pressure distribution within each foot due to the limitation of our equipment. It is possible that patients could have asymmetrical weight distribution due to asymmetrical sensory or strength loss, pain and other factors. This is unlikely because peripheral neuropathy usually induces symmetrical deterioration of sensation and pain at the feet and legs (Thomas, 1997).

Our observations show that insensitivity of the hallux and mid-foot leads to increased relative pressure at the hallux and heel, respectively, during standing. The plantar pressure redistribution could be a compensatory mechanism for the long-term sensory loss due to PN. Interestingly, long-term foot sole sensory loss affects plantar pressure distribution in standing but

not in walking. The different effects suggest that standing rely more on tactile sensation feedback more than walking, and walking is dominated by feed forward control.

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## **CHAPTER 3. RELIABILITY OF NERVE FUNCTION ASSESSMENTS FOR PEOPLE WITH PERIPHERAL NEUROPATHY**

### **Abstract**

Examining degenerative sensory and reflexive activity among people with peripheral neuropathy (PN) is important for clinical examinations and understanding relevant neural impairments. However, other than the test of presynaptic inhibition, the reliability of other related tests is largely unknown. The purpose of this project was to examine the test-retest reliability of lower extremity sensory and reflexive measures in people with PN. Twelve participants (8 women, 4 men, age =  $72.5 \pm 9.2$  years) diagnosed with PN were assessed on two occasions at least 7 days apart. Plantar sensitivity, H-reflex, and active and passive ankle proprioception (AAP and PAP) were tested. Paired student's t-test and Intraclass correlation coefficients (ICC) were used for statistical analysis. Significant difference was observed in AAP at 0° position ( $P = .04$ ). No other significant differences were observed. Moderate to high reliability was observed at measures of Plantar sensitivity (.92), peak to peak H (.71) and M (.84) waves, latency between H and M (.78), H-index (.85), AAP (.62) and PAP index (.60). Low reliability was observed of other parameters. The measures of  $H_{\max}$ ,  $M_{\max}$ , latency, H-index, plantar sensitivity, and AAP & PAP indices of proprioception tests can be measured reliably for further study in this population.

### **Introduction**

Peripheral Neuropathy (PN) is a neurodegenerative disease that damages the peripheral nervous system (Martyn & Hughes, 1997). People with PN often exhibit uncomfortable sensations, such as numbness and pain in the lower extremities associated with a reduction of nerve conduction velocity. PN-related neurological abnormalities are believed to decrease the ability of balance control (Padua et al., 2005; Richardson & Hurvitz, 1995), and diminish

functional mobility, which are both linked to survival (Era, Heikkinen, Gause-Nilsson, & Schroll, 2002; Studenski et al., 2011) and fall risk (Pajala et al., 2008; Van Kan et al., 2009) in older adults. In people with PN, nerve conduction velocity is a typical clinic evaluation, combined with self-report of pain or numbness in the feet (Richardson, 2002). Although these assessments pathologically examine the peripheral nervous system, they hardly explain the postural instability and improvement in neurological function (i.e., foot sole sensation and nerve conduction velocity) after exercise training in the PN population. Therefore, it is necessary to seek reliable evaluations of neuroplasticity changes within this population.

Reliable measures of neurological function may explain the effectiveness of physical treatments within this population. Many clinical studies demonstrated the effectiveness of certain exercise training on postural control improvements, but little is known about the mechanism. A 3-week training for balance and strength benefited participants with diabetic PN resulting in increased postural control and functional reach performance (Richardson et al., 2001). Similarly, shorter finger and foot reaction time to visual stimuli, less sway, greater leg strength, and reduced fall risk were observed in people with PN after 6-week stretching, balance and strength exercises for lower limbs (Morrison et al., 2010). Also, Tai Chi training improves the functional mobility and postural control in people with PN and people with reduced sensation (Tsang, Wong, Fu, & Hui-Chan, 2004). Furthermore, Tai Chi has been reported to reverse the symptom of foot insensitivity in people with PN (Li & Manor, 2010). Most likely, the better postural control and the reverse of the symptom maybe not because of the regeneration of the peripheral nerves but the improved neurological function of the peripheral nervous system. Therefore, to establish reliable measures of the peripheral nervous system in people with PN further research is necessary.

Foot sole sensation and ankle proprioception, along with Hoffman reflex (H-reflex) should be considered for functional assessments of peripheral nervous system within this population. The regulation of motoneuron activity is obtained through supraspinal as well as sensory inputs, namely in the spinal reflex pathway. To some extent, tactile sensitivity, proprioception, and ultimately the function of reflex arc that send information to the CNS are all affecting postural control. The monosynaptic stretch reflex, as a simple feedback loop of sensory–motor organization, would be modified by the peripheral sensory inputs in addition to central nervous system modulation (Clarac et al., 2000). H-reflex test provides a good measure of stretch reflex pathway. It would reflect any changes in synaptic efficacy between the muscle afferents and the  $\alpha$ -motoneurons. Its function would be modulated by the central mechanism and the modulation is accompanied by changes in both reflex sensitivity and reflex threshold (Scaglioni et al., 2002).

The magnitude of H-reflex can be measured through the maximum amplitudes of H- ( $H_{\max}$ ) and M-waves ( $M_{\max}$ ).  $H_{\max}$  to  $M_{\max}$  ratio represents the level of excitation of  $\alpha$ -motoneuron as well as the modulation by CNS (Schieppati, 1987). Besides that, H-index is also an important diagnostic tool in neurological impairments by providing an estimate measure of conduction velocity of an entire reflex arc (Aiello, Rosati, Serra, & Manca, 1981). H-reflex measurements have been used in a wide variety of settings in the healthy aging population. In a clinical population, presynaptic inhibition, examined by H-reflex, has proved to be a reliable measure in patients with diabetic peripheral neuropathy. It refers to the modulation of the Ia afferent impulses by the action of GABAergic interneurons before it reaches a synapse (Misiaszek, 2003; Palmer & Hong, 2012; Pierrot-Deseilligny, 2005); However,  $H_{\max}$  to  $M_{\max}$  ratio as well as H-index have not yet been shown to be reliable measures for people with PN.

Measuring the role of somatosensation in regards to postural control could also help in localizing an effective treatment strategy for postural control impairments. Reduced somatosensation at the lower extremity would impair postural control in people with PN (Eils et al., 2004; Geurts et al., 1992; Nardone et al., 2007). Foot sole tactile sensation may be appropriate measures for this population due to the disease distal to proximal progression starting from the toes and foot soles. It is widely accepted that 5.07 monofilament is a reliable assessment of foot tactile sensation for PN population.

Ankle proprioception is defined as “a specialized variation of the sensory modality of touch, which encompasses the sensations of joint movement (kinesthesia) and joint position (joint position sense)” (Lephart et al., 1992). The afferent sensory feedback are from various peripheral mechanoreceptors in the surrounding skin, muscles, tendons, ligaments and joints (Grigg, 1994). It is believed that the importance of ankle proprioception on ankle stability is critical for maintaining balance (Freeman, 1965; Glencross & Thornton, 1981; Lentell et al., 1995). The deficits of ankle joint position sense are considered to be a major the factor in falling in people with PN (Richardson & Hurvitz, 1995). Nonetheless, Szczerba’s study questioned the reliability of measures at isolated position in motion with ankle inversion and eversion among healthy subjects (Szczerba, Bernier, Perrin, & Gansneder, 1995). Later, in Lee’s study, averages of measures at three isolated positions were created as indices for active and passive ankle joint proprioception separately. The indices of active and passive ankle joint proprioception are reliable in people with unilateral functional ankle instability (Lee & Lin, 2008). Further study to test the reliability of these protocols is necessary for the PN population.

The purpose of this study was to assess the test-retest reliability of foot sole tactile sensation, ankle joint proprioception, and H-reflex among people with PN, so that reliable

measures can be incorporated to perhaps further understand the effectiveness of intervention study in people with PN.

## **Methods**

Sixteen people diagnosed with peripheral neuropathy volunteered for the project. Participants signed informed consent forms, as approved by local Institutional Review Board, after all of their questions were answered satisfactorily at the first visit.

### **Protocol**

The measurements of interest for this study were the latencies between H- and M-wave, the magnitudes of peak-to-peak H- and M-wave ( $H_{\max}$  and  $M_{\max}$ ), five-point monofilament test for plantar pressure sensitivity, and active (AAP) and passive (PAP) ankle joint proprioception indices for proprioception. Data were collected in the order of anthropometrics, the nerve function test, plantar pressure sensitivity and the passive and active ankle reposition tests with ample rest time between sections. All measurements were collected on two separate occasions with at least 7 days in between.

### **H-Reflex Test**

The test was performed with the participants lying prone on an examination table with their feet hanging slightly off of the edge. Special attention was given to maintaining the same position throughout the entire test. Two 20 mm in diameter recording electrodes (EL503, Vinyl 1-13/8", BIOPAC Systems, Inc. Goleta, CA, USA) were placed in parallel to the orientation of muscle fibers at the belly of right lateral gastrocnemius with inter-electrodes center distance of 20 mm. The reference electrode was placed on the Achilles tendon. Abrasion of the skin was performed at the fixation sites with alcohol gauze to reduce impedance.

H- and M-wave were elicited by 1 ms square-wave stimulating the tibial nerve of right popliteal foss using a bipolar constant voltage stimulator (BSLSTMA with the MP30, BIOPAC Inc., Goleta, CA, USA). Stimulation intensity was increased progressively from 0 volts until an involuntary twitch at the leg was visible. The electromyographic (EMG) signals were amplified and recorded by the MP36R Data Acquisition and Analysis Systems (BIOPAC Systems, Inc., Goleta, CA, USA). To obtain  $H_{max}$ , the stimulus intensity was increased until no further increase of peak-to-peak H-wave amplitude. After determining the  $H_{max}$ , the test was repeated consecutively 3 times with a 30s break between each trial. The latency between H- and M-wave, a period between the onsets of H- and M-wave were recorded 9 times with greater stimulation, at which H- and M-wave could be seen concurrently. The intensity of stimulation was then increased gradually to achieve the M-wave plateau ( $M_{max}$ ). Then, the  $M_{max}$  was collected three times.

The average  $H_{max}$  and  $M_{max}$  of three trials were used for further calculations and statistical analysis.  $H_{max}$  to  $M_{max}$  ratio was determined by dividing the average of  $H_{max}$  by the average of the  $M_{max}$ . The average of 9 latencies recorded was used for reliability analysis and the calculation of H-index,  $H\text{-index} = \left[ \frac{Height (cm)}{\Delta t_H - \Delta t_M} \right]^2 * 2$  (Scaglioni et al., 2002).

#### Plantar Pressure Sensitivity Test

Participants were laying supine on an examination table with feet hanging slightly off the edge of the table while sensitivity was assessed using a 5.07 gauge Semmes-Weinstein monofilament (North Coast Medical. Inc, Morgan Hill, CA, USA). Testing sites included the Heel (HL), bases of the first (M1) and fifth (M5) metatarsal, mid-foot (MF) and hallux (BT). Testing details can be found in our previous publication (Li & Manor, 2010).

## Ankle Proprioception Test

Active (AAP) and passive (PAP) ankle proprioception were assessed using Biodex 3 dynamometer and the Biodex Advantage Software Package (Biodex Medical System, Inc, Shirley, NY, USA). Participants sat in the Biodex chair with the back of the chair positioned at 70° and participants legs parallel with the ground. After participant's right foot was properly aligned with the axis of dynamometer, the right foot was then placed into the ankle Inversion / Eversion attachment and fastened securely by a Velcro strap with the weight of the limb supported by an additional attachment placed under the thigh. The range of motion was set before active and passive reposition tasks for safety consideration. The testing protocols of active and passive reposition tests consisted of localizing three target positions: 15° of inversion, 0° subtalar neutral, 10° of eversion (Birmingham, 2000). Prior to test, each participant received a practice test followed by a 1-minute rest period. Participants started from maximal inversion for all passive and active reposition tests. The order of target position was randomized and each position was tested three times with a practice session followed by a testing session.

For active ankle reposition the participant voluntarily moved their testing foot until it came to a stop at the target position. The participant will hear an audible signal from the dynamometer when they reach the target position during practice. During the test session, the participants actively moves his/hers ankle joint to each test position in the same order as during the practice session but without the audible signal. Participants were requested to use a hand-held switch to make a trigger signal when they felt they have moved the ankle joint to each of the pre-selected test positions.

Passive ankle reposition was also tested in the same manor except that the attachment was set to move the foot at 2°/s though the tests. The participant's foot was first passively



moved by the dynamometer from each individual maximal inversion range-of-motion into the three testing positions at 2°/s. The order of the target positions presented were randomized. In the practice session, the dynamometer was stopped at each target position for 10 s, with each participant instructed to concentrate on the position of the ankle joint. In the test session, the foot was passively moved just as it was in the practice session. In order to avoid the possible timing-prediction learning effects (e.g., at the angular velocity of 2°/s, it takes 5 s to move from 0° to 10°eversion), the participant does not know the actual velocity setting for the passive reposition test.

Joint reposition tests recorded absolute degrees of error between the preselected angle and the repositioned angle three times for each target position. The average of three trials represented the result of reposition test at each testing position.

#### Data Analysis

Statistical analysis was performed by the statistical package PSS 17.0 (SPSS Inc., Chicago, Illinois). Differences between sessions were analyzed using a Paired Student t-test. Intraclass correlation coefficients (ICC) model 1.1 was chosen to examine the consistency of participant performance across testing sessions as measured by a single rater (Shrout & Fleiss, 1979). 95% confidence intervals of ICC's were also computed. ICC values below .60 were considered poor and above .80 as highly reliable. Between .60 and .80 was deemed moderate (Shrout & Fleiss, 1979).

### **Results**

We have only successfully induced H-reflex among twelve of our participants. The following report includes observations from these twelve participants (8 women, 4 men, age:  $72.5 \pm 9.2$  years, height:  $163.0 \pm 11.9$  cm, and body mass:  $78.0 \pm 21.0$  kg). Causes of PN

included diabetes (n=2), trauma (n=1), and idiopathic (n=9). Duration of PN was  $10.0 \pm 1.7$  (Mean  $\pm$  S.D.) years. For each test measure, the mean, standard error and the associated p-value from the student's t-test are presented in Table 1. Significant difference was observed in the Active 0° reposition test ( $P = .04$ ). No other significant difference between testing sessions was observed for either active or passive reposition. Intraclass correlation coefficients (ICC) with 95% confidence intervals are also presented in Table 3.1.

Table 3.1. Mean and S.D., Test-retest Reliability Scores

Measures	# of Trials	Test		Re-Test		P-value	ICC (1,1)	95% CI
		Mean	S.D.	Mean	S.D.			
M <sub>max</sub> (mV)	3	3.90	1.10	4.32	0.74	0.44	0.84 <sup>†</sup>	[.55, .95]
H <sub>max</sub> (mV)	3	0.55	0.22	0.58	0.34	0.89	0.71 <sup>†</sup>	[.30, .91]
Latency (ms)	9	30.10	1.08	29.60	0.91	0.94	0.78 <sup>†</sup>	[.40, .93]
H <sub>max</sub> /M <sub>max</sub>		0.45	0.24	0.14	0.05	0.20	0.09	[-.47, .61]
H-index	9	61.21	4.52	61.00	4.07	0.44	0.85 <sup>†</sup>	[.53, .96]
Plantar Sensitivity	3	2.83	0.61	2.83	0.55	1.00	0.92 <sup>†</sup>	[.75, .98]
Active -15 °	3	11.83	3.26	8.91	2.55	0.51	0.61 <sup>†</sup>	[.10, .87]
Active 0 °	3	8.16	1.51	11.64	2.06	0.04 <sup>*</sup>	0.39	[-.19, .77]
Active 10 °	3	8.73	1.11	8.94	1.69	0.57	0.45	[-.11, .80]
Passive -15 °	3	6.20	1.75	4.82	0.66	0.62	0.34	[-.25, .75]
Passive 0 °	3	5.57	1.22	5.63	1.01	0.68	0.41	[.17, .78]
Passive 10 °	3	6.27	0.85	6.20	1.42	0.73	0.48	[-.08, .73]
AAP		8.45	6.22	9.58	6.05	0.48	0.62 <sup>†</sup>	[.13, .87]
PAP		5.34	3.68	5.42	2.83	0.93	0.60 <sup>†</sup>	[.09, .86]

- ❖ Table 3.1 includes the Mean and Standard Error of Mean for measures that were of interest for this study. Intraclass correlation coefficients with 95% confidence intervals are also provided.
- ❖ <sup>†</sup> indicates the moderate or high reliability.
- ❖ \* indicates the significant difference between two testing occasions.

Low reliability (.09) observed for the ratio of H<sub>max</sub> to M<sub>max</sub> although H<sub>max</sub> and M<sub>max</sub> were measured moderately or highly reliable, ICC = .71 and .84, respectively. Moderate reliability was also observed for latency (.78) and H-index (.85). Plantar sensitivity measures via a 5.07 gauge Semmes-Weinstein monofilament were highly reliable (.92). Reliability of active ankle reposition for target locations -15° (.61) was moderate and 10° (.45) was poor.

Active ankle reposition for target location 0° did show a significant difference ( $P < .05$ ), and it exhibited poor reliability (.39). Also, poor reliability was observed for all passive ankle reposition target positions: the target location 0° (.41), -15° (.34) and 10° (.48). AAP and PAP indices were moderately reliable with ICC = .62 and .60, respectively.

## **Discussion**

H<sub>max</sub> was considered as a variable response in participants; thus requiring multiple trials to obtain a stable mean (Christie A, Kamen G, Boucher JP, Inglis JG, & Gabriel DA, 2010; Palmieri RM, Hoffman MA, & Ingersoll CD, 2002). We failed to induce H-wave among four participants, which is consistent with the literature. It has been observed that H-wave cannot be elicited in everyone in the healthy older adult population (Scaglioni et al., 2002).

H<sub>max</sub> to M<sub>max</sub> Ratio, active ankle reposition at target locations 0° and 10°, and all target positions in passive ankle reposition test exhibited low reliability. Moderate reliability was observed for H<sub>max</sub>, latency, H-index, active ankle reposition for target locations -15°, and both AAP & PAP indices. Only M<sub>max</sub> and plantar sensitivity were highly reliable. The measures with moderate and high reliability will provide the information about the sensations and the nerve function in people with PN for further study.

The means of H<sub>max</sub> and M<sub>max</sub> from both testing sessions were lower than that reported by Scaglioni, et al. (2002) when they examined healthy older adults. Similarly, their observation of H-index is greater than our observations. The lower scores observed here may be explained by the effects of peripheral neuropathy. The symptom of peripheral neuropathy includes the slow sensory nerve conduction velocity. It may partially be due to adaptations in CNS, which need a further study to confirm.

The poor reliability of  $H_{\max}/M_{\max}$  ratio was unexpected. The ratio between the amplitudes of the maximum reflex response ( $H_{\max}$ ) and maximum direct motor wave ( $M_{\max}$ ) is commonly used for estimating the level of reflex excitability of the motor pool ( $H_{\max}$  to  $M_{\max}$  ratio). The magnitude of the ratio depends on the facilitation of the transmission between the Ia fibers and the  $\alpha$ -motoneurons (Schieppati, 1987). The ratio represents the level of excitation of  $\alpha$ -motoneuron as well as the modulation by CNS (interneuron inhabitation). Previous studies showed this ratio is highly reliable under different testing postures in healthy population and, in turn, it has been widely used for a variety of nerve function studies. In this study, poor reliability of  $H_{\max}/M_{\max}$  ratio is possibly due to the changed proprieties caused by PN, which may suggest there are adaptations or changes within neural system of people with PN. Therefore,  $H_{\max}/M_{\max}$  ratio is not a reliable measure for people with PN. Nonetheless, both latency and H-index were reliably measured as we expected. In addition, the latency and  $H_{\max}$  are used as measures of the neural system in PN population (Bertelsmann, Heimans, van Rooy, & Visser, 1986; Valk, Nauta, Strijers, & Bertelsmann, 1992). The H-reflex is considered as a measure of the monosynaptic arc and its amplitude is a measure of excitability of the motoneurons. Latency and  $H_{\max}$  would provide useful information to reflect the function of monosynaptic arc from the soleus muscle (Schieppati, 1987).

In the seated position, the stretch of soleus muscle leads to two bursts. The one with short latency has an onset of approximately 40ms and is attributed to monosynaptic excitation of spinal motoneurons from the large diameter group I afferent fibers (Matthews, 1991; Taylor et al., 1985). The long latency of approximately 70ms is mediated by group II afferent fibers (Schieppati & Nardone, 1997). The advantage of this measure could evaluate the primary I and II fibers in muscles separately. However, the stimulation by stretch muscle is hard to control

and it could be influenced by the function of sensory receptors as well as the muscle activity. H-reflex is more controllable and less affected by peripheral sensory information than stretch reflex. Thus, the measures of H-reflex are better at reflecting the overall function of stretch reflex loop. In addition to the reliable parameter presynaptic inhibition identified by Plamer's study for the diabetic PN population (Palmer & Hong, 2012), we have also added H-index as reliable parameters that can be tested among the same population.

Typically, the conduction velocity of reflex arc is assessed by sensory nerve conduction velocity and motor nerve conduction velocity separately rather than being studied as a function of an entire loop. The impaired motor nerve conduction velocity is correlated with the force output (Metter et al., 1998), where the estimated conduction velocity of group II spindle sensory fibers is correlated with sway area (Nardone et al., 2007). Similar, faster postural reflexes are associated with better postural control and mobility in older persons with chronic stroke (Marigold et al., 2005). Besides, H-index is believed to be associated with modulation in the central nervous system (Scaglioni et al., 2002). Therefore H-index is more suitable to reflect the dysfunction and neuroplasticity changes in people with PN regarding to postural control. The plantar sensitivity measure observed here is reliable to evaluate the tactile sensation of people with PN, and is consistent with the previous reliability study (Manor et al., 2008).

AAP and APP indices are reliable indicators of the active and passive ankle reposition in people with PN which is the same as those reported for people with ankle instability (Lee & Lin, 2008). However, the isolated measures of proprioception tests were not as reliable as the indices, except active -15 °reposition, which were observed to have moderate reliability. These results are consistent with the observations in Szczerba's study (Szczerba et al., 1995). Ankle

proprioception is a comprehensive measure because of multiple sensory inputs at ankle joints with no influence from one altered sensory input at ankle lateral ligaments (Konradsen et al., 1993). Also, the reposition test may indicate ankle stability as well as the muscle stiffness around the ankle joint (Lee & Lin, 2008). The integrity of the stiffness of muscles around joints and joint stabilization via spinal-mediated reflexes is considered to correlate with postural control in standing rather than ankle proprioception alone (Loram & Lakie, 2002; Morasso & Sanguineti, 2002). Therefore, AAP and APP indices would represent the function of ankle proprioception in regard to postural control (Bernier & Perrin, 1998), and they are reliable measures in persons with PN.

In conclusion, the measures of  $H_{\max}$ ,  $M_{\max}$ , latency and the H-index, plantar sensitivity, and AAP & PAP indices of proprioception tests can be measured reliably for people with all-caused PN. These measures could be implemented to better assess progressions of the impairments, and / or potential improvements during different intervention strategies for people with peripheral neuropathy. Our future study will utilize these reliable measures and focus on investigating the relationships between multiple sensory resources, and postural & gait control in people with PN.

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## **CHAPTER 4. H-INDEX IS IMPORTANT FOR POSTURAL CONTROL WITH IMPAIRED FOOT SOLE SENSATION IN PEOPLE WITH PERIPHERAL NEUROPATHY**

### **Abstract**

People with Peripheral Neuropathy (PN), especially those with impaired sensory input through the small-afferent fibers (SAF) reflexive loop, might depend more on the large-afferent fibers (LAF) reflexive loop for postural control. Purpose: This part of the study examined whether the function of the LAF reflexive loop, assessed by H-reflex and ankle proprioception, influences postural control when the SAF reflexive loop is impaired, indicated by reduced foot sole sensation. Methods: Thirty-three participants (8 women, 5 men) diagnosed with PN and twelve age-matched healthy people (7 women, 5 men) were recruited. Age, height, body mass, cause, and duration of diagnosed PN were recorded. The measures of interest for this study were H-index of the H-reflex test, indices of the active (AAP) and passive (PAP) ankle proprioception test, score on the five-point monofilament test for plantar pressure sensitivity (PPS), average sway velocity ( $V_{AVG}$ ) and sway area ( $A_{95}$ ) in the balance test with eyes closed, walking distance in the 6-minute walk test (6MW), and time of the timed up-and-go test (TUG). Results: Compared to the control group, the PN group demonstrated reduced PPS ( $2.00 \pm 1.87$  vs.  $4.25 \pm 1.22$ ,  $P = .0018$ ), lower H-index ( $63.63 \pm 10.85$  vs.  $76.43 \pm 15.99$ ,  $P = .0272$ ) greater  $V_{AVG}$  ( $3.51 \pm 2.08$  vs.  $1.56 \pm 0.56$  cm/s,  $P = .0060$ ), greater  $A_{95}$  ( $10.02 \pm 10.10$  vs.  $2.48 \pm 1.50$  cm<sup>2</sup>,  $P = .0203$ ), lower 6MW ( $442.2 \pm 93.0$  vs.  $525.3 \pm 68.2$  m,  $P = .0187$ ), and lower TUG ( $9.40 \pm 1.64$  vs.  $6.48 \pm 1.27$  s,  $P = .0001$ ). Significant correlation was observed between PAP and 6MW ( $R^2 = 0.46$ ,  $P = .0146$ ), as well as TUG ( $R^2 = 0.24$ ,  $P = .0421$ ), in the PN group. Significant correlation was also observed between  $V_{AVG}$  and H-index in the PN group ( $R^2 = .32$ ,  $P = .04$ ). Significant group dependent regression was observed between H-index and  $V_{AVG}$  ( $F_{1, 23} = 9.59$ ,  $p < .05$ ). No

significant group difference, correlation, or group dependent regression was observed.

Conclusion: Postural control depends more on the LAF reflexive loop when the SAF reflexive loop is impaired.

## **Introduction**

The prevalence of all-cause PN is estimated to be 2.4% in the entire adult population and over 8-10% in people over the age of 55 (Martyn & Hughes, 1997). The health care cost of Diabetic PN in the United States was estimated to be between \$4.6 and \$13.7 billion (Gordois, Scuffham, Shearer, Oglesby, & Tobian, 2003). PN is a neurodegenerative disease that damages the peripheral nervous system from distal to proximal areas (Martyn & Hughes, 1997). People with PN often exhibit an impaired somatosensory system (numbness, pain, and tingling in the lower extremities) and a reduction of nerve conduction velocity (CV) (Richardson, 2002). PN-related neurological abnormalities can inhibit postural control (Padua et al., 2005; Richardson & Hurvitz, 1995) and diminish functional mobility (Manor & Li, 2009), both of which are important outcomes linked to patient survival (Era et al., 2002; Studenski et al., 2011) and fall risk (Pajala et al., 2008; Van Kan et al., 2009) in older adults.

Postural control disparities have been observed among individuals with PN (Nardone et al., 2006). Postural instability could be partially due to deficits in SAF and their corresponding sensory input (Nardone et al., 2007). LAF, innervating primary muscle spindles and the Golgi tendon organs, has been considered less important in postural control than the small fibers that innervate the cutaneous receptors and secondary muscle spindles (Nardone et al., 2007; Nardone et al., 2006). Cutaneous sensory receptors that are responsible for touch and pressure sensitivity, and secondary muscle spindles that are responsible for muscle length changes, have been more commonly tied to postural control while standing than primary muscle spindles and the Golgi

tendon organs, which are responsible for proprioception and vibration at the joints and muscles (Mazzaro et al., 2006; Nardone et al., 2007; Nardone et al., 2006; Nardone et al., 2000; Perry et al., 2000; Shaffer & Harrison, 2007).

As sensory receptors are stimulated, nerve impulses propagate along the reflex arc in the spinal cord to cause corresponding muscular activity. The stretch reflex is the connection between afferents in muscle spindles to the  $\alpha$ -motoneuron, which contributes to motor response during balance correction (Hoffer & Andreassen, 1981; Sinkjaer et al., 1996). By stretching the soleus muscle in the seated posture, the stretch reflex features two bursts with different latencies. The Moderate Latency component of the stretch reflex (MLR), with an approximate onset latency of 70ms, mediated by SAF (Schieppati & Nardone, 1997), contributes more to postural control while standing and to the stance phase in the gait cycle; the Short Latency component of the stretch reflex (SLR), with an approximate onset latency of 40ms, is innervated by LAF (Grey et al., 2001; Matthews, 1991; Taylor et al., 1985). Most likely, MLR is the reflexive response of secondary muscle spindles to a mechanical stimulus, while SLR is the reflexive response of primary muscle spindles. The inhibition of SLR by ischemia primary muscle spindle has no influence on the stance phase of walking (Mazzaro et al., 2006). On the other hand, SLR, by itself, is not determinant to maintain postural control while standing still (Nardone & Schieppati, 2004). Therefore, the function of LAF and the sensory receptors they innervate are secondary to the SAF and the sensory receptors they innervate during postural control.

People actively seek out alternative sources of sensory information in destabilizing environments created by diminished sensory input (Curthoys & Halmagyi, 1995; Merabet & Pascual-Leone, 2009; Nashner, 1981). For people with PN, reduced cutaneous sensation could alter plantar pressure distribution when standing; as a result, they need a different strategy for

postural control that takes advantage of the sensation in their relatively intact foot sole. To some extent, improvements in balance provided by additional vibratory stimulation on the skin might be due in part to increased proprioceptive inputs. Furthermore, much evidence indicates the use of sensory reweighting in PN patients to improve postural control. Consequently, with reduced plantar pressure sensation, people with PN are likely to depend more on the large reflexive group and its corresponding sensory inputs.

Therefore, in this study, we investigated whether postural control depends more on the LAF reflexive loop, as assessed by the Hoffmann reflex test, and the sensory receptors they innervate, as assessed by the ankle proprioception test, in people with PN and reduced sensory inputs from the SAF reflexive loop, as assessed by the plantar pressure sensitivity test. The Hoffmann reflex is a common tool for estimating the function of the stretch reflex arc (Capaday & Stein, 1986; Zehr, 2002) in people with fewer peripheral sensory inputs. We also investigated the correlation between ankle proprioception, balance, and mobility in people with PN and reduced plantar pressure sensitivity. We proposed the following hypotheses: i) With reduced plantar pressure sensation, the PN group will exhibit lower performance in H-reflex, ankle proprioception, standing balance, and mobility; ii) The measures of H-reflex and ankle proprioception will correlate with standing balance and mobility in people with PN but not in the control group; iii) Standing balance will depend more on the performance of the H-index (transmission time of the signals in the reflex arc) and ankle proprioception for people with PN than for the control group.

## **Methods**

Twenty-three participants (16 women, 7 men) diagnosed with PN and twelve age-matched healthy people (7 women, 5 men) were recruited. Ten people from the PN group were

not satisfied with the participation criteria and were excluded from statistical analysis. After all questions were answered satisfactorily, participants signed the consent forms before any tests were conducted. This project was approved by the local Institutional Review Board.

## Procedures

Age, height, body mass, causation, and duration of diagnosed PN were recorded. The measures of interest were H-index in the H-reflex test, indices of the active and passive ankle proprioception test, score on the five-point monofilament test for plantar pressure sensitivity, average sway velocity in the balance test with eyes closed, walking distance in the 6-minute walk test, and time of the timed up-and-go test. Participants were permitted to rest after each test.

## Plantar Pressure Sensitivity Test

Participants were asked to lay supine on an examination table with their feet hanging slightly off the end of the table. Plantar pressure sensitivity was assessed using a 5.07 gauge Semmes-Weinstein monofilament (North Coast Medical, Inc., Morgan Hill, CA, USA). Testing sites included the heel (HL), bases of the first (M1) and fifth (M5) metatarsal, mid-foot (MF), and hallux (BT) on the right foot. Details of the test can be found in our previous publication (Li & Manor, 2010).

## H-index Test

The Hoffmann reflex test was performed on the right leg while the participants lay prone on an examination table with their feet hanging slightly off the end. Special attention was given to maintain the position of the participant throughout the test. Two recording electrodes (20 mm in diameters, EL503, Vinyl 1-13/8", BIOPAC Systems, Inc., Goleta, CA, USA) were placed parallel to the orientation of muscle fibers of the lateral gastrocnemius and 20 mm apart

(center to center). The reference electrode was placed on the Achilles tendon. Fixation sites were wiped with alcohol gauze to reduce impedance.

The tibial nerve of the right popliteal foss was stimulated by a 1 ms square-wave using a bipolar constant voltage stimulator (BSLSTMA with the MP30, BIOPAC, Inc., Goleta, CA, USA). Stimulation intensity was increased progressively from 0 volts until an involuntary twitch in the leg was visible. The electromyographic signals were amplified and recorded by the MP36R Data Acquisition and Analysis Systems (BIOPAC Systems, Inc., Goleta, CA, USA). The stimulus intensity was increased until H-wave and M-wave could be seen concurrently. The period between the onsets of H- and M-wave was recorded nine times. The average of nine latencies was used for the calculation of H-index ( $H\text{-index} = \left[ \frac{\text{Height (cm)}}{\Delta t_H - \Delta t_M} \right]^2 * 2$ ) (Scaglioni et al., 2002). H-index is a reliable measure for people with PN (Zhang, Holmes, & Li, 2014).

#### Ankle Proprioception Test

Ankle proprioception test was conducted using a Biodex 3 dynamometer and the Biodex Advantage Software Package (Biodex Medical System, Inc., Shirley, NY, USA) following the protocols detailed in our previous study (Zhang et al., 2014). Participants sat in a Biodex chair reclined at 70° with legs parallel to the ground. The right ankle joint was properly aligned with the axis of the dynamometer, and the right foot was fastened securely by a Velcro strap to the ankle Inversion/Eversion attachment. The weight of the limb was supported by an additional attachment placed under the thigh. The testing protocols of active and passive reposition tests consisted of localizing three target positions: 15° of inversion, 0° subtalar neutral, 10° of eversion (Birmingham, 2000). Prior to testing, participants were allowed to practice. During the reposition test, participants started from maximal inversion. The order of



target position was randomized, and each position was tested three times, each time following a practice session.

During the practice session of the active ankle reposition test, the participant voluntarily moved the testing foot from the maximal inversion toward the target position. The participant would hear an audible signal from the dynamometer when the target position was reached. During the test session, the participant actively moved the testing foot to each test position in the same order as the practice session, this time without the audible signal. The participants were asked to use a hand-held switch to trigger a signal when they felt they had reached the target ankle joint positions.

Passive ankle reposition was examined in the same manner except that the attachment moved the foot at  $2^{\circ}/s$  from maximal inversion to the target position during the practice session. The participant did not know the actual velocity setting of the passive reposition test. The dynamometer was stopped at each target position for 10 s, during which time each participant was instructed to concentrate on the position of the ankle joint. During the test session, the testing foot was passively moved just as it has been during the practice session. Participants were asked to trigger the hand-held switch when they felt they had reached the target position. The angle between the preselected position and the resulting position was recorded as an error in degree. The average degree of error across three trials represented the result of the ankle proprioception tests.

#### Functional Mobility Test

The 6-minute walk (6MW, distance in meters) and timed up-and-go (TUG, time in seconds) test were used to measure functional mobility (Manor et al., 2008). The tests followed the standard procedures outline in our previous paper. In the 6MW test, two cones were set 30

meters apart in a hallway. Participants were required to walk from one cone to another, making a turn around each cone, as many times as possible in 6 minutes. They were permitted walking assistance if needed.

### Balance Test

Participants completed one 30-second balance trial with eyes closed. Standing balance was assessed on a force platform (AccuSway, AMTI, Watertown, MA, USA). Participants stood on the force platform in a normal pose, facing forward with their heels about one fist apart.

Center of pressure (COP) was sampled at 50 Hz.  $V_{AVG}$  and  $A_{95}$  were calculated.

### Statistical Analysis

Statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, NC). Descriptive statistics were used to summarize all variables. Independent t-tests examined potential differences among group demographics. Group differences in PPS, H-index,  $A_{95}$ ,  $V_{AVG}$ , 6MW, TUG, PAP, and AAP were examined using One-way MANOVA. Univariate analysis of variance and post hoc analyses were conducted when necessary. Pearson correlation analyses were performed to analyze further correlation among the outcome variables between both groups. Accordingly, for each group, we analyzed covariance to examine dependent regressions between the two different outcome variables. Alpha value was set at .05.

## Results

The results for 13 of the 23 PN participants are presented here. Participants who were unable to finish the 6MW test (2 people), failed to induce H-reflex (5 people), and had no plantar pressure sensitivity impairment (3 people) were excluded. The results for 12 participants in the control group are presented for comparison. The only significant difference between the two groups was a history of PN; age (PN:  $73.0 \pm 8.0$ ; Control:  $70.5 \pm 9.5$  years), height (PN:  $165.3 \pm$

10.3; Control:  $167.7 \pm 8.8$  cm), and body mass (PN:  $79.4 \pm 20.65$ ; Control:  $71.97 \pm 14.37$  kg) were similar between the two groups.

Table 4.1. Demographics and Outcome Variables for PN and Control Groups

	PN (N=13)		Control (N=12)		P value	Effect Size
	Mean	S.D.	Mean	S.D.		
PPS	2.00	$\pm 1.87$	4.25	$\pm 1.22$	.0018*	.35
H-index	63.63	$\pm 10.85$	76.43	$\pm 15.99$	.0272*	.20
V <sub>AVG</sub> (cm/sec)	3.51	$\pm 2.08$	1.56	$\pm 0.56$	.0060*	.30
A <sub>95</sub> (cm <sup>2</sup> )	10.02	$\pm 10.10$	2.48	$\pm 1.50$	.0203*	.30
6MW (m)	442.2	$\pm 93.0$	525.3	$\pm 68.2$	.0187*	.22
TUG (sec)	9.40	$\pm 1.64$	6.48	$\pm 1.27$	<.0001*	.46
PAP	6.50	$\pm 3.53$	3.91	$\pm 1.43$	.027	.20
AAP	7.67	$\pm 5.26$	5.59	$\pm 2.76$	.235	

\*Indicates a significant difference between the two groups at level of .05.

Significant Wilks' Lambda was observed between the two groups. As shown in Table 4.1, The PN group demonstrated lower plantar pressure sensitivity ( $2.00 \pm 1.87$  vs.  $4.25 \pm 1.22$ ,  $P = .0018$ ) and a lower H-index ( $63.63 \pm 10.85$  vs.  $76.43 \pm 15.99$ ,  $P = .0272$ ) than the control group. In the functional performance tests, significant differences were observed between the two groups. The PN group exhibited greater V<sub>AVG</sub> ( $3.51 \pm 2.08$  vs.  $1.56 \pm 0.56$  cm/s,  $P = .0060$ ), greater A<sub>95</sub> ( $10.02 \pm 10.10$  vs.  $2.48 \pm 1.50$  cm<sup>2</sup>,  $P = .0203$ ), lower 6MW ( $442.2 \pm 93.0$  vs.  $525.3 \pm 68.2$  m,  $P = .0187$ ), and lower TUG ( $9.40 \pm 1.64$  vs.  $6.48 \pm 1.27$  s,  $P = .0001$ ).

Significant correlation was observed between PAP and 6MW ( $R^2 = 0.46$ ,  $P = .0146$ ), as well as TUG ( $R^2 = 0.24$ ,  $P = .0421$ ), in the PN group, but not in the control group (6MW:  $R^2 = 0.01$ ,  $P = .7742$ ; TUG:  $R^2 = 0.24$ ,  $P = .1297$ ) (see Figure 4.1). Also, significant correlation was found between V<sub>AVG</sub> and H-index in the PN group ( $R^2 = .32$ ,  $P = .04$ ), but not in the control group ( $R^2 = .10$ ,  $P = .30$ ) (see Figure 4.2). No significant correlation was observed between H-index or PPS and the other outcomes in either group.

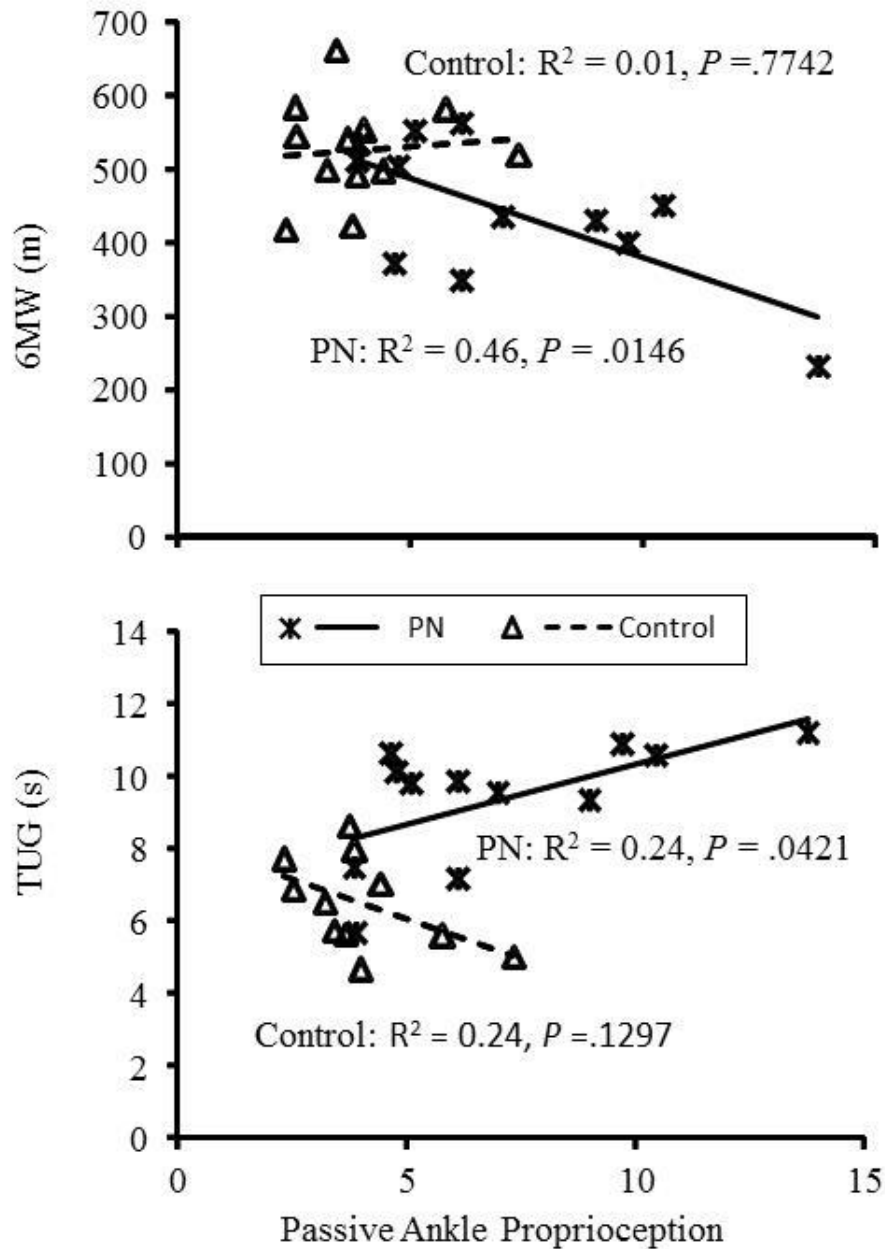


Figure 4.1. Correlations between Passive Ankle Proprioception and Functional Mobility. Relationships between PAP in relation 6MW (top panel) and TUG (lower panel) are displayed here. Notice that the significant correlations between PAP and 6MW, as well as TUG, in the PN group are absent in the control group.

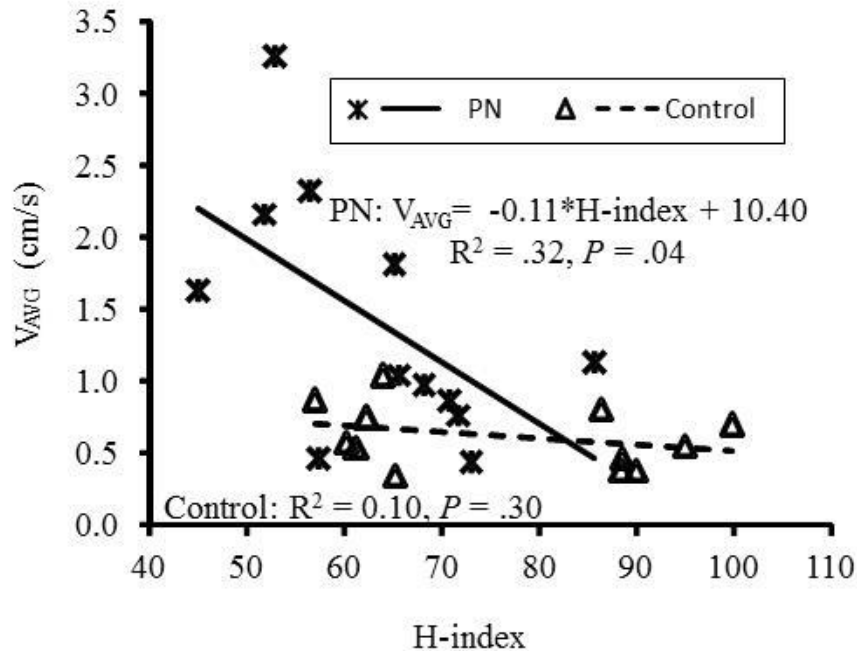


Figure 4.2. Regression Lines between  $V_{AVG}$  and H-index with Raw Data from both Groups. Covariation between  $V_{AVG}$  and H-index are significantly different between the groups, suggesting that the influence of H-index on  $V_{AVG}$  were different in the two groups. The  $R^2$ -value and equation of regression line for the PN group are listed above the curve, indicating a significant negative relationship between  $V_{AVG}$  and H-index. The  $R^2$ -value for the control group is listed below the curve; there is no regression line because the regression was not statistically significant.

Significant group-dependent regression was observed between H-index and  $V_{AVG}$  ( $F_{1, 23} = 9.59, p < .05$ ). In the PN group,  $V_{AVG}$  decreased as H-index increased. However, no significant relationship between  $V_{AVG}$  and H-index emerged from the control group (see Figure 4.2). No other significant group dependent regression was detected between PAP and 6MW/ TUG.

### Discussion

The PN group exhibited exaggerated body sway, greater sway velocity, and reduced mobility compared to the control group. Lower H-index values were expected in the PN group, for reduced sensory nerve conduction velocity is typical in this group, accounting for a large portion of the H-reflex arc. Poor performance in passive ankle repositioning in the PN group indicates impaired ankle proprioception. However, this group's active ankle repositioning was

similar to the control group, an unexpected finding.  $V_{AVG}$  and H-index were significantly related in the PN group, but not in the control group. The group-dependent relationship between  $V_{AVG}$  and H-index suggests that in the PN group, balance depended more on H-index than in the control group.

The results for  $A_{95}$ ,  $V_{AVG}$ , 6MW, TUG and PPS are consistent with previous studies (Manor et al., 2008; Manor & Li, 2009). For H-index, our healthy control group ( $76.43 \pm 15.99$ ) was similar to the elderly group ( $75.19 \pm 10.26$ ) reported by Scaglioni in 2002. No previous studies had reported H-index in people with PN (Scaglioni et al., 2002). For ankle proprioception assuring inversion and eversion, Van den Bosch reported no effect of PN on the detection threshold of ankle position at the seated position with audio cues (Van den Bosch, Gilsing, Lee, Richardson, & Ashton-Miller, 1995). This result conflicts with our finding that people with PN had lower PAP than the control group. Most likely, the inconsistency is due to different settings during the ankle proprioception test.

H-index is the normalized time course between the onset of the M wave and the onset of the H wave relative to an individual's height. It represents the transmission time of the large-diameter peripheral nerve (sensory and motor) and the synapses in the spinal cord (Knikou, 2008), which is more standard and controllable than the latency of the mechanically induced stretch reflex. Therefore, H-index is a more appropriate measure of postural control than the conduction velocity of either sensory or motor nerves. In addition, H-index significantly correlates with balance measures, further confirming the appropriateness of H-index for measuring postural control. Furthermore, the significant group-dependent regression between H-index and  $V_{AVG}$  suggests that standing balance depended on the function of H-index in the PN group, but not in the control group.

The deficits of postural control in people with PN primarily result from an impaired sensory system, rather than weakness, which is the primary cause in other aging populations (Manor & Li 2009). Previous studies have tried to establish a correlation between balance measures and time frame of impulses along the LAF (nerve conduction velocity), SAF (estimated group II muscle spindle CV in stretch reflex) (Nardone et al., 2006), and postural reflex (reaction time after a mechanical stimulus in the muscle) in people with PN (Morrison et al., 2010). Interestingly, there is no documented correlation between balance and the sensory nerve CV, particularly the CV of LAF. In the current study, H-index, representing the transmission time of the LAF reflexive loop, significantly correlates with  $V_{AVG}$ . Perhaps H-index better represents the duration of the stretch reflex than the elements of this loop.

Although the function of SAF is more important when standing still (Nardone et al., 2006), correlations between the log function of body sway and estimated CV of the tibial SAF were observed in the participating groups of PN and control. Nevertheless, another study suggested that the conduction velocity of the sural nerve could mediate postural control while standing in people with PN (Nardone et al., 2007). Perhaps balance depends on the coupling of the SAF and LAF reflexive loops. Even though the SAF reflexive loop plays a larger role, when it is impaired, people with PN will depend more on the LAF reflexive loop and its associated sensory inputs for postural control. Some intervention studies have shown that exercise can improve the function of the LAF reflexive loop in athletes and elderly adults (Gruber et al., 2007; Guan & Koceja, 2011). Maybe physical therapy that targets balance deficits in people with PN could improve the function of the LAF reflexive loop and ankle proprioception.

The LAF and SAF reflexive loops share the responsibility for postural control and balance while standing. With impaired plantar pressure sensation, people with PN tend to rely

more on the time course of the LAF reflex loop and ankle proprioception in postural control than people with intact plantar pressure sensation. These results suggest that exercise targeting the LAF reflexive loop may improve standing balance and that exercise targeting ankle proprioception may improve the functional mobility of people with PN.

The key difference between the active reposition and passive reposition tests is likely the kind of information used to calibrate the final position (Paillard & Brouchon, 1968). Unlike self-induced movement, passively moving to the final position might depend more on information from muscle spindles, such as changes in muscle length and muscle velocity. During passive movement, people with PN might have limited or inaccurate information from muscle spindles because of an impaired somatosensory system, whereas the control group might receive relatively normal information from muscle spindles for joint sensation. During active movement, PN patients can freely move their feet, generating sufficient muscle spindle activity to gain accurate information; indeed, AAP results for the PN group and the control group were similar.

The significant correlation between PAP and functional mobility in PN may not only indicate a relationship between proprioception and functional mobility but also suggests the importance of ankle joint stability to postural control while walking (Diener, Dichgans, Guschlbauer, & Mau, 1984; Fu & Hui-Chan, 2005; Jerosch & Prymka, 1996). Previous studies have shown that the proprioception from a single muscle, tendon, ligament around ankle joint does not influence standing or walking posture (Hertel et al., 1996; Konradsen et al., 1993; Lephart et al., 1998). The broader assessment of ankle proprioception demonstrate that the comprehensive function of the ankle joint, including ankle proprioception and stability, is important to postural control (Lee & Lin, 2008). People with PN tend to walk or move slowly to compensate for deficits in postural control. Functional mobility does not correlate with strength



but with standing balance in PN patients (Manor & Li, 2009), suggesting that decreased moving or walking speed is primarily due to PN-related sensory impairment. The association between PAP and functional mobility in people with PN suggests that ankle proprioception maybe an active sensation responsible for postural control for walking and other functional movements.

In this study, we did not examine the CV of the SAF reflexive loop. However, the impaired plantar pressure sensation indicates the dysfunction of sensory receptors in the SAF reflexive loop. Besides, this study only compared PN individuals with reduced plantar pressure sensation to a control group, for few people with PN have intact plantar pressure sensation. Also, we used healthy participants for the control group because they were virtually guaranteed to have relatively intact SAF and sensory receptors.

People with PN depend more on the LAF reflexive loop and ankle proprioception for postural control when the SAF reflexive loop or its sensory receptors are impaired. Similarly, ankle joint proprioception and joint stability are more crucial to walking in people with PN than people without PN. This study suggests that interventions aimed at improving LAF and ankle proprioception could be effective treatments for people with PN.

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## **CHAPTER 5. DISCUSSION**

### **Key Results**

Chapter 2 examined the differential effects of plantar pressure sensitivity on gait and balance in people with PN. The chronic loss of plantar sensation affects plantar pressure distribution while standing but not while walking. Extending this line of research, the influences of ankle proprioception and reflexive loop on balance and gait need to be identified. Chapter 3 demonstrated the reliability of the measures for assessing ankle proprioception and the LAF reflexive loop in people with PN. Given their high reliability, these measures were used in subsequent testing. Using similar protocols, Chapter 4 explored whether PN individuals relied more on ankle proprioception and the LAF reflexive loop for postural control than the age-matched healthy control group. Despite significant correlations between ankle proprioception and functional mobility in PN individuals, H-index predicts balance performance in the PN group and control group differently. The following discussion reiterates the key results from these tests and explores several insights by examining the combined results of this dissertation. This chapter concludes with limitations of this study and recommendations for future research.

### **Summary of the Results**

In people with PN, an insensitive foot sole at hallux and heel will affect plantar pressure distribution while standing. However, plantar sensation does not affect plantar pressure distribution while walking.

Indices of ankle proprioception are more reliable than measures of isolated target positions. In the Hoffmann reflex test, H-index is reliable for people with PN. However, the  $H_{\max}$ -to- $M_{\max}$  ratio is not reliable.

People with PN exhibited lower H-index, passive ankle proprioception, plantar sensation, functional mobility, and balance than the control group, but both groups had similar active ankle proprioception. Among individuals with PN, the distance of 6MW increased with better passive ankle proprioception. The time of TUG decreased with better passive ankle proprioception. Also, a greater H-index was associated with better balance control. Moreover, the prediction of H-index influence on balance was different between the two groups.

### **Implications of Key Results**

#### **Neuroplasticity in People with PN**

The correlation between H-index and balance was observed in the PN group but not in the control group. When a person is standing still, the somatosensory system provides sufficient sensory information to maintain balance as well as to trigger reflexes for balance correction (Timmann et al., 1994). H-reflexes are fairly high and stable when standing upright, confirming the requirement of position control to maintain a stable posture (Capaday & Stein, 1986). H-index, representing the estimated time course of the LAF reflexive loop, is important for balance performance when the SAF reflexive loop or PPS is impaired (see Chapter 1). Most likely, the function of the LAF reflexive loop correlates with balance performance only in persons with an impaired SAF reflexive loop or impaired sensory receptors.

In general, time course of a peripheral nerve is assessed by measuring the sensory nerve and motor CV separately, rather than the entire loop. Deficits in postural control in persons with PN primarily result from impaired sensory nerves, rather than muscle weakness, which is the primary cause in other aging populations. Interestingly, correlation between the sensory nerve CV and balance in persons with PN has not been documented. Nevertheless, one study suggested that the conduction velocity of the sural nerve might mediate balance control when a person with

PN is standing still (Nardone et al., 2007). To some extent, the observations in Chapter 4 are inconsistent with the findings of previous studies. Some have suggested that the estimated CV of the SAF reflexive loop contributes more to standing balance in all people, whether suffering from PN or fully healthy (Nardone et al., 2006). Perhaps when the SAF reflexive loop or its sensory receptors are impaired, people rely more on the LAF reflexive loop and its innervated sensory receptors.

Group-dependent regression between H-index and  $V_{AVG}$  could be explained by neuroplasticity in the PN group, likely stemming from sensory reweighting and neural adaptation to impaired PPS. According to the results of Chapter 2 and Chapter 4, PPS, ankle proprioception, and H-index were not essential for standing and walking in healthy older adults, but they did influence postural control in the PN group. When PPS was impaired, individuals with PN depended on the LAF reflexive loop for balance performance (see Chapter 4). Ankle vibration threshold has also been shown to correlate with body sway in people with axonal neuropathy (Bergin, Bronstein, Murray, Sancovic, & Zeppenfeld, 1995). People with PN seem to depend more on the LAF reflexive loop and ankle vibration threshold when the SAF reflexive loop or its corresponding sensory inputs are impaired.

Sensory re-weighting (inter-modality) occurs because the strong coupling of one stimulus with postural sway (up-weighting) compensates for the weak coupling of another stimulus (down-weighting) (Oie et al., 2002; Peterka, 2002). In this way, the LAF reflexive loop and its sensory receptors (up-weighting) take on some of the responsibility of the SAF reflexive loop and its sensory receptors (down-weighting).

Group-dependent regression was not observed between the LAF reflexive loop/PAP and functional mobility in the PN group. This finding suggests that neuroplasticity did affect mobility.



In young and healthy populations, experimentally reduced plantar sensation did not significantly influence dynamic stability during the act of walking or even during perturbed walking (Dingwell & Cavanagh, 2001; Höhne et al., 2011). For people with PN, feed-forward gait compensatory strategies were observed in response to peripheral sensory loss (Bunday & Bronstein, 2009).

#### Feedforward and Feedback Control in Standing and Walking

Falling, a challenge to postural control during human locomotion, is a threat to the quality of life in an aging population. Falling can be caused by weak or injured anatomical structures (muscular and skeletal) and neural deficits. In people with PN, balance deficits primarily results from reduced sensory information in the lower extremities (Simmons et al., 1997). Muscle strength is considered an important factor in postural control, but the effect of strength training on balance improvement among elderly people has been inconsistent in different studies (Buchner et al., 1997; Topp et al., 1993). However, lower extremity strength has not been found to be lower in PN patients than in healthy people of corresponding age or to correlate with balance issues (Manor & Li, 2009). The main mechanism responsible for the deterioration of postural control during the act of standing among people with PN is an impaired somatosensory system.

Chronic PPS loss alters plantar pressure distribution when standing, but not when walking at a self-preferred pace. To some extent, deficits in somatosensation caused by PN do not influence postural control in walking as much as they do in standing. According to the literature, reduced foot sole sensation leads to a cautious walking pattern, including a slower walking speed, a smaller step length, and a wider step width, in healthy people and people with PN alike (Manor & Li, 2009; Tsai & Lin, 2012). However, reduced foot sole sensation does not

influence the dynamic stability of walking (England & Granata, 2007; Hähne et al., 2011). During the act of walking, minimal movement for balance correction is evoked by motor responses to sudden interference from external environments (Lam et al., 2006). This observation implies that feedback control might not be necessary for maintaining that stability while walking, except when the external environment presents a challenge.

The consideration of postural control when walking is different from postural control when standing. In the former, postural control is concerned not only with each single stride but also with the movements that link one stride to the next. COP is not well suited to address the fundamental control task of walking: maintaining dynamic stability. In fact, human gait is typically analyzed by normalizing and averaging data from a number of continuous strides. The stability is quantified by various aspects of locomotor variability (Holt et al., 1995; Winter, 1989; Yack & Berger, 1993). The variability of step length, step width, stride time, and relative angle at the joints are speed dependent, producing the “U” shape relationship between variability and gait speed (England & Granata, 2007; Hausdorff et al., 1995). In the “U” shape, the lowest variability was observed for self-preferred pace on step width (Bauby & Kuo, 2000; Hausdorff et al., 1995). Therefore, people with PN could walk at a self-preferred pace to gain better dynamic stability, leading to fewer influences from an impaired somatosensory system on postural control.

The reason for the correlation between passive ankle proprioception and functional mobility in the PN group is unclear. In the literature, the role of ankle proprioception in postural control is controversial, and no direct evidence has shown that reduced ankle proprioception decreases postural stability when standing and walking (De Carlo & Talbot, 1986; Hertel et al., 1996). This lack of evidence might be due to the difficulty in experimentally isolating articular mechanoreceptors from other sensory receptors in the muscles. Additionally, the reduced

function of articular mechanoreceptors could be compensated by the other types of sensory receptors.

Ankle joint stability is important for postural control when standing and walking, and it is associated with the stiffness of surrounding muscles and ligaments as well as ankle joint proprioception (Morasso & Sanguineti, 2002; Winter et al., 1998; Winter et al., 2001). The stiffness of muscles and ligaments around the ankle joint alone cannot achieve stabilize the joint (Morasso & Sanguineti, 2002); proprioception is believed to be an important factor in this function (Irrgang et al., 1994; Morasso & Sanguineti, 2002). The measures of ankle proprioception presented in Chapter 4 are a comprehensive assessment of multiple sensory inputs at the ankle joint without the influence of any altered sensory inputs in the ankle lateral ligament (Konradsen et al., 1993); these assessment measures have been used to diagnose ankle stability and proprioception among people with unilateral functional ankle instability and the elderly (Lee & Lin, 2008). Most likely, the correlation between PAP and functional mobility indicates the importance of ankle stability in walking.

In the PN group with impaired PPS, the correlation between H-index and standing balance was observed, but not in functional mobility tests. Capaday and Stein's study showed that walking involves modulation of the soleus H-reflex (Capaday & Stein, 1986). The amplitude of the H-reflex changes with different phases in walking, from small during the swing phase to large during the stance phase. The spontaneous reflex increases and decreases during the stance and swing phases, as well as the onset of muscle activity before latency of the H-reflex, suggest that this process is pre-programmed by the CNS rather than the peripheral sensory inputs. Therefore, the time course of the reflex arc from the primary muscle spindle to the  $\alpha$ -motoneurons might not be important to functional mobility.

Perhaps standing is dominated by feedback control, while walking is dominated by feed forward control. This assertion is supported by popular theories of balance control, the different requirements of sensory information to maintain balance, and adaptations that occur in response to reduced sensory information from the lower extremities. The studies presented in this dissertation support the hypothesis that standing is dominated by feedback control, requiring more sensory activity to maintain posture, and that walking is dominated by feed forward control, relying less on sensory activity to maintain posture.

### **Limitations**

The research outlined in this dissertation features several methodological issues that potentially limit the generalization of the findings. One major issue is related to sampling bias. For instance, the PN group sample was relatively high functioning, perhaps limiting the conclusions to a small portion of the PN population. Individuals with PN were recruited based on the following factors: (a) physician diagnosis of PN, (b) severe loss of plantar pressure sensation, (c) the ability to finish a six-minute walk, and (d) presence of an H-reflex response. The first two criteria assured the presence of PN-related sensory impairments, and the third criteria assured the safe completion of the ground and treadmill walking trials. The absence of the H-reflex response is likely not limited to individuals with PN; it might not always be present in healthy individuals. The reason for this absence is unknown. Although the conclusions of this study might not apply to people with PN who did not meet the above criteria, the relative homogeneity of the included participants lends validity to the findings.

The second limitation is the lack of SAF assessments of people with PN in Chapter 4. Indeed, the clinical assessments of SAF could improve the methodology and further confirm the impairment of the SAF reflexive loop. However, in reality, skin biopsies are likely inappropriate

for behavioral studies. First, no evidence suggests that diminished density of free nerve endings correlates with postural control in standing and walking. Second, the questions addressed in this study focused on the role of the LAF reflexive loop when the SAF reflexive loop is impaired, and the SAF reflexive loop includes its innervated sensory receptors. Reduced PPS indicates a dysfunctioning SAF reflexive loop, or at least points to an impaired sensory end of the loop.

### **Future Studies**

#### **Neuroplasticity in People with PN**

Scholars have suggested that the physical dysfunction caused by PN might be compensated by neuroplasticity in the central nervous system. Conversely, investigating the influence of central neuroplasticity on physical performance might point to compensatory strategies that could improve PN-related deficits of postural control (e.g., a specific exercise targeting the influential components of the central nervous system). Previous studies have demonstrated that these adaptations occur at different sites of the central nervous system: (a) spinal adaptations (Bove, Trompetto, Abbruzzese, & Schieppati, 2006), (b) supraspinal adaptations (Lalonde & Strazielle, 2007; Visser & Bloem, 2005), and (c) adaptations in the cerebellum (Manor, Newton, Abduljalil, & Novak, 2012). However, most of those adaptations have not been shown to influence physical performance in the PN population. Future research could try to identify the essential components of central neural adaptation that relate to postural control in this clinical population.

At the spinal level, extracted outcomes of H-reflex are widely used to probe neural adaptation after exercise in both young and aging populations (Schieppati, 1987; Zehr, 2002). However, most of those outcomes have not been established as reliable measures in the PN population, except for presynaptic inhibition and H-index (see Chapter 3). Hence, scholars

should seek reliable evaluations that show improvement of neurological function at the spinal level within this population. Similarly, reliable measures are important to the study of supraspinal adaptations (Lalonde & Strazielle, 2007; Visser & Bloem, 2005) and adaptations in the cerebellum as they relate to postural control.

#### Intervention Study in People with PN

The findings of this dissertation suggest that the improved function of the LAF reflexive loop might benefit postural control in PN individuals with an impaired SAF reflexive loop.

Taichi training has been shown to improve H-reflex in the elderly population (Guan & Kocaja, 2011). A 3-week concentrated exercise plan targeting balance and standing strength improved balance and reach performance in participants with DPN (Richardson et al., 2001). Shorter finger and foot reaction times to visual stimuli, lower sway, greater leg strength, and reduced fall risk were observed after six weeks of stretching, balance, and strength exercises for lower limbs in people with PN (Morrison et al., 2010). A 24-week Taichi course reversed the decline of foot sole sensation caused by PN and improved performance on TUG and 6MW tests (Li & Manor, 2010). Moreover, increased conduction velocity was observed after Taichi and Yoga training in this population (Hung et al., 2009; Malhotra et al., 2002).

So far, the mechanism for these improvements in people with PN is not clear. Given that adaptation in people with PN might compensate for deficits in postural control, exercise could help enhance neural adaptation at the spinal and supraspinal level. These exercises might facilitate sensory reweighting (i.e., relying on more accurate sensations in the LAF reflexive loop and the visual and vestibular systems) or the central adaptive mechanism (i.e., improving the ability to process conflicting sensory inputs). Future research could help design effective training program and explore the mechanism of adaptation in people with balance disorders.

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## **VITA**

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